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Publication information: *Journal of Hepatology* (ISSN 0168-8278). For 2018, volumes 68 and 69 are scheduled for publication. Subscription prices are available upon request from the Publisher or from the Elsevier Customer Service Department nearest you or from this journal's website (http://www.elsevier.com/locate/jhep). Further information is available on this journal and other Elsevier products through Elsevier's website: (http://www.elsevier.com). Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis. Issues are sent by standard mail (surface within Europe, air delivery outside Europe). Priority rates are available upon request. Claims for missing issues should be made within six months of the date of dispatch.

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Acknowledgements

The European Association for the Study of the Liver thanks all the abstract reviewers for their time and effort and appreciates their contribution towards the success of the International Liver Congress™ 2018.

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VOLUME **68**, SUPPLEMENT **1**, PAGES **S1–S926**

Abstracts of The International Liver Congress™ 2018 – 53rd annual meeting of the European Association for the Study of the Liver April 11–15, 2018, Paris, France

Publication of this Abstract Book is supported by the European Association of the Study of the Liver

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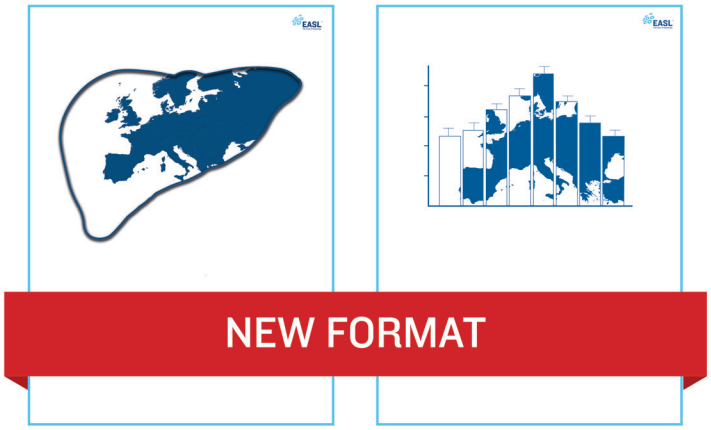

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Thursday, 12 April 2018

General session I and opening ceremony

GS-001

Epidemiology, predictors and outcomes of multi drug resistant bacterial infections in patients with cirrhosis across the world. Final results of the "Global study"

S. Piano[1], V. Singh[2], P. Caraceni[3], R. Maiwall[4], C. Alessandria[5], J. Fernandez[6], E. Soares[7], D.J. Kim[8], S.E. Kim[9], M. Marino[10], J. Vorobioff[11], R. de Cassia Ribeiro Barea[12], M. Merli[13], L. Elkrief[14], V.M.V. Blasco[15], A. Krag[16], S. Singh[17], L.A. Lesmana[18], C. Toledo[19], S. Marciano[20], V. Xavier[21], F. Wong[22], N. Intagliata[23], L. Rabinowich[24], L.A. Colombato[25], S.G. Kim[26], A. Gerbes[27], F. Durand[28], J.P. Roblero[29], K. Bhamidimarri[30], T.D. Boyer[31], M. Maevskaya[32], E.L. Fassio[33], H.S. Kim[34], J.-S. Hwang[35], A. Gadano[20], S.K. Sarin[36], P. Angeli[37].
[1]University of Padova, University and General Hospital of Padova, Padova, Italy; [2]Postgraduate Institute of Medical Education and Research, Chandigarh, India; [3]University of Bologna, Bologna, Italy; [4]Institute of Liver and Biliary Sciences (ILBS), New Delhi, India; [5]University Hospital of Turin, Turin, Italy; [6]Hospital Clinic of Barcelona, Liver Unit, Barcelona, Spain; [7]Gastrocenter-Unicamp, Campinas, Brazil; [8]Hallym University College of Medicine, Chuncheon, Korea, Rep. of South; [9]Hallym University Sacred Heart Hospital, Korea, Rep. of South; [10]Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina; [11]Universidad Nacional de Rosario, Rosario, Argentina; [12]Faculty of Medicine of Bahia, Campo Grande, Brazil; [13]Sapienza University of Rome, Department of Clinical Medicine, Rome, Italy; [14]University Hospital of Geneva, Geneva, Switzerland; [15]Hospital Vall d'Hebron, Liver Unit, Barcelona, Spain; [16]Odense University Hospital, Odense, Denmark; [17]Shri Ramachandra Bhanj Medical College, Orissa, India; [18]Digestive Disease and Oncology Centre (DDOC)-Medistra Hospital, Jakarta, Indonesia; [19]Hospital Valdivia, Universidad Australe de Chile, Valdivia, Chile; [20]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [21]Ghent University Hospital, Ghent, Belgium; [22]University of Toronto, Toronto, Canada; [23]University of Virginia, Charlottesville, United States; [24]Tel-Aviv Medical Center, Tel-Aviv, Israel; [25]Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [26]Soonchunhyang University – Bucheon Hospital, Bucheon, Korea, Rep. of South; [27]University of Munich, Munich, Germany; [28]Hospital Beaujon, Clichy, France; [29]Universidad de Chile, Santiago, Chile; [30]University of Miami Miller School of Medicine, Miami, United States; [31]University of Arizona, Tucson, United States; [32]First Moscow State Medical University, Moscow, Russian Federation; [33]Hospital Nacional Alejandro Posadas, Buenos Aires, Argentina; [34]Hallym University College of Medicine, Kangdong, Korea, Rep. of South; [35]Keimyung University Dongsan Medical Center, Daegu, Korea, Rep. of South; [36]Institute of Liver and Biliary Sciences, Department of Hepatology, Vasant kunj, India; [37]University of Padova, Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine – DIMED, Padova, Italy
Email: pangeli@unipd.it

Background and Aims: Bacterial infections are common and life-threatening in patients with cirrhosis. However, the epidemiology and the outcome of bacterial infections across the world is poorly known. Thus, the International Club of Ascites promoted this multicenter intercontinental study aimed to investigate the epidemiology and the outcome of bacterial/fungal infections in hospitalized patients with cirrhosis across the world.
Method: Hospitalized patients with cirrhosis and bacterial infection were prospectively included at 46 centers across the world. Demographic, clinical, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. Patients were followed till death, transplantation or discharge. Multi drug resistant (MDR) bacteria were defined as bacteria resistant to at least one antibiotic in >2 classes
Results: From October 2015 to September 2016, 1302 patients were included, 25% from North or South America, 32% from Asia and 43% from Europe. The most common infections were SBP (27%), UTI (22%) and pneumonia (19%). 740 patients (57%) had at least 1 positive culture and 959 microorganisms were isolated (58% Gram neg; 38% Gram pos; 4% Fungi). The global prevalence of MDR across the world was 34% (95% CI = 31–37%). Independent risk factors for MDR infections were an infection in Asia (OR = 2.79; p = 0.017), particularly in India (OR = 7.94; p < 0.001) or in South America (OR = 2.23; p = 0.053), the use of antibiotics in the previous 3 months before the hospitalization (OR = 1.92; p = 0.001), the category of infection (nosocomial [OR = 2.65; p < 0.001] and healthcare associated [1.62; p = 0.032])and the site of infection (pneumonia [OR = 3.20;p < 0.001], UTI [OR = 2.48; p < 0.001] and skin and soft tissue infection [OR = 2.92; p = 0.004]). Infections due to MDR bacteria were associated with a lower rate of response to empirical antibiotic treatment (40 *vs.* 68%; p < 0.001), a higher incidence of shock (27 *vs.* 15%; p < 0.001) and new organ failures (42 *vs.* 31%; p = 0.001), a lower rate of resolution of infection (82 *vs.* 72%; p = 0.003), and a higher in-hospital mortality (31 *vs.* 21%; p = 0.004) than those due to non-MDR bacteria.
Conclusion: The relevant differences in the etiology of bacterial/fungal infections across the world, particularly as regard to prevalence of MDR bacteria, highlight the need to develop different empirical antibiotic strategies across different continents and countries. In addition, while waiting for new antibiotics, any effort should be done to reduce the spread of MDR bacteria in cirrhosis.

GS-002

Cenicriviroc treatment for adults with non-alcoholic steatohepatitis: Year 2 analysis of the Phase 2b CENTAUR study

V. Ratziu[1], A. Sanyal[2], S. Francque[3], W. Sun, V. Wong[4], R. Loomba[5], Z. Goodman[6], E. Lefebvre[7], G. Aithal[8], S. Harrison[9], M. Abdelmalek[10], S. Friedman[11], F. Tacke[12]. *[1]Hôpital Pitié Salpêtrière and Université Pierre et Marie Curie, Hôpital Pitié Salpêtrière and Université Pierre et Marie Curie, Paris, France; [2]Virginia Commonwealth University, Department of Gastroenterology, Richmond, United States; [3]UZA, Gastroenterology Hepatology, Edegem, Belgium; [4]The Chinese University of Hong Kong, Department of Medicine and Therapeutics; [5]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States; [6]Inova Fairfax Medical Campus, Center for Liver Diseases; [7]Allergan plc; [8]Nottingham University Hospitals, NIHR Nottingham Biomedical Research Centre, [9]Radcliffe Dept. of Medicine, University of Oxford, Oxford, United Kingdom; [10]Duke University, Department of Medicine, Division of Gastroenterology & Hepatology; [11]Icahn School of Medicine at Mount Sinai, Division of Liver Diseases; [12]University Hospital Aachen, Department of Medicine III*
Email: vratziu@teaser.fr

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Background: Cenicriviroc (CVC) is an oral CCR2/5 antagonist under treatment evaluation for liver fibrosis in adults with non-alcoholic steatohepatitis (NASH). CVC had significant antifibrotic benefit over placebo (PBO) at the 1 year (Y1) primary endpoint; herein, we report year 2 (Y2) data of the Phase 2b CENTAUR study (NCT02217475).
Method: Adults with histologically-confirmed NASH, non–alcoholic fatty liver disease activity score (NAS) ≥ 4, and liver fibrosis (NASH Clinical Research Network stage 1–3) were randomized 2:1:1 to CVC 150 mg once daily or PBO. Arms A and C received CVC or PBO, respectively, for 2 years; Arm B received PBO in Y1 and crossed over to CVC in Y2. Fibrosis, NASH, and NAS status were assessed in liver biopsies at baseline (BL), Y1, and Y2 by a central pathologist. All analyses were prespecified.
Results: 289 adults were randomized: 52% diabetes, mean BMI 34 kg/m^2, and 67% fibrosis stage 2–3 (F2-3). 242 subjects continued after Y1 (121, 61, and 60 per Arm A, B, and C); 213 had paired BL and Y2 biopsies, with missing data for 42, 12, and 16 subjects per arm. For Y1 PBO nonresponders (i.e., those who did not achieve ≥1-stage fibrosis improvement and no worsening of NASH at Y1), fibrosis improvement without worsening of NASH was seen in subjects crossing over to CVC vs. remaining on PBO (24% [10/41] in Arm B vs. 17% [6/35] in Arm C; p = 0.36), while 16/41 (39%) on CVC and 10/35 (29%) on PBO achieved ≥1-stage fibrosis reduction. Over 2 years, a similar proportion on CVC or PBO achieved ≥1-stage fibrosis improvement and no worsening of NASH (15% [15/99] in Arm A vs. 17% [9/54] in Arm C); however, a greater proportion on CVC achieved ≥2-stage fibrosis improvement and no worsening of NASH (11% [7/65] in Arm A vs. 3% [1/34] in Arm C). For those with biopsies at BL, Y1, and Y2, a greater proportion on CVC achieving ≥1-stage fibrosis improvement at Y1 maintained benefit at Y2 (60% [18/30] in Arm A vs. 30% [3/10] in Arm C); in CVC subjects with BL F3 that improved, upto 86% (12/14) maintained benefit at Y2. Greater reductions in hs-CRP and fibrinogen, but no effect on NASH or liver enzymes were observed with CVC. Adverse events were comparable for CVC and PBO and no deaths occurred.
Conclusion: CVC was well tolerated and provided antifibrotic activity in adults with NASH and liver fibrosis, confirming the Year 1 primary endpoint. A majority of subjects achieving ≥1-stage fibrosis improvement at Year 1 maintained benefit at Year 2 with CVC, with greater effect in those with advanced fibrosis.

GS-003
Sorafenib with versus without concurrent conventional transarterial chemoembolization (*c*TACE) in patients with advanced hepatocellular carcinoma (HCC): Results from a multicenter, open-label, randomized, controlled phase III STAH trial

J.-W. Park[1], Y.J. Kim[2], D.Y. Kim[3], S.H. Bae[4], S.W. Paik[5], Y.-J. Lee[6], D. Lee[7], H.C. Lee[8], S.Y. Han[9], J.Y. Cheong[10], O.S. Kwon[11], J.E. Yeon[12], B.H. Kim[1], J.-S. Hwang[13]. *[1]National Cancer Center, Korea; [2]Seoul National University Hospital; [3]Severance Hospital; [4]The Catholic University of Korea, Seoul St. Mary's Hospital; [5]Samsung Medical Center; [6]Inje University Busan Paik Hospital; [7]SNU Boramae Medical Center; [8]Asan Medical Center; [9]Dong-A University Hospital; [10]Ajou University Hospital; [11]Gachon University Gil Medical Center; [12]Korea University Guro Hospital; [13]Keimyung University Dongsan Medical Center*
Email: jwpark@ncc.re.kr

Background and Aims: Sorafenib is the standard first-line therapy for patients (pts) with advanced HCC (aHCC). *c*TACE is an effective treatment for unresectable HCC. A previous phase II study revealed that sorafenib combined with concurrent *c*TACE (SOR+T) tended to improve outcomes. Herein, we present the results from an investigator-initiated phase III trial that evaluated the effects of SOR+T in pts with aHCC.
Method: Pts were randomly assigned (1:1) into one of two arms, to receive sorafenib with *c*TACE (Arm C) or without *c*TACE (Arm S) according to modified International Union Against Cancer tumor stage, extent of vascular invasion, Child-Pugh score and serum alpha fetoprotein level. All eligible pts received 800 mg sorafenib within 3 days (Arm S and C) and *c*TACE within 7-21 days after randomization, and repeating *c*TACE on demand (Arm C). The study continued until progression or unacceptable toxicities were observed. The primary endpoint was overall survival (OS), and secondary endpoints included time to progression (TTP), progression-free survival (PFS), tumor response rate (TRR), and safety profile.
Results: Between January 2013 and December 2015, 339 pts were enrolled from 13 hospitals in South Korea, and the last pt completed the trial on June 2017. Pts baseline characteristics were well balanced. For Arm C and S, respectively, median OS was 12.8 vs. 10.8 months (m) (hazard ratio [HR], 0.91; 95% confidence interval [CI] 0.69–1.21; p = 0.290); median TTP was 5.3 vs. 3.5 m (HR, 0.67; 95% CI, 0.53–0.85; p = 0.003); median PFS was 5.2 vs. 3.6 m (HR, 0.73; 95% CI, 0.59–0.91; p = 0.01); TRR was 60.6% vs. 47.3% (p = 0.005).
For Arm C and S, respectively, serious adverse events (AE) were 33.3% vs. 19.8% (p = 0.006), and grade ≥ 3 AE were increased alanine aminotransferase (20.3% vs. 3.6%), hyperbilirubinemia (11.8% vs. 3.0%), ascites (11.8% vs. 4.2%), thrombocytopenia (7.2% vs. 1.2%), anorexia (7.2% vs. 1.2%), hyponatremia (5.2% vs. 0%) (p < 0.05); hand-foot skin reaction (10.5% vs. 11.4%), encephalopathy (5.2% vs. 1.2%) and diarrhea (5.2% vs. 4.2%).
Subgroup analysis showed a survival benefit in pts (46.4%) of Arm C who received ≥2 *c*TACE sessions when compared to pts in Arm S (18.6 vs. 10.8 m; HR, 0.58; 95% CI, 0.40-0.82; p = 0.006).
Conclusion: SOR+T therapy did not improve OS versus sorafenib alone in pts with aHCC. However, SOR+T therapy significantly improved TTP, PFS, and TRR, and a survival benefit was observed in the pts who received SOR+T ≥2 *c*TACE sessions.

GS-004
Integrative molecular classification of extrahepatic cholangiocarcinoma

R. Montal[1,2], W.Q. Leow[2], C. Montironi[1], L. Bassaganyas[1], A. Moeini[1], D. Sia[2], R. Pinyol[1], L. Cabellos[1], J. Peix[1], M. Maeda[2], P. Tabrizian[2], B. Minguez[3], T. Pawlik[4], I. Labgaa[5], L. Roberts[6], M. Sole[1], M.I. Fiel[2], S. Thung[2], S. Roayaie[7], A. Villanueva[2], M. Schwartz[2], J.M. Llovet[1,2,8]. *[1]Liver Cancer Translational Research Laboratory, Barcelona Clinic Liver Cancer (BCLC) Group, Liver Unit, IDIBAPS-Hospital Clínic, CIBERehd, University of Barcelona, Barcelona, Spain; [2]Liver Cancer Program, Divisions of Liver Diseases and RM Transplant Institute, Tisch Cancer Institute, Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, United States; [3]Liver Unit, Department of Internal Medicine. Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut of Research (VHIR), CIBERehd, Universitat Autonoma de Barcelona, Barcelona, Spain; [4]Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center, Columbus, United States; [5]Centre Hospitalier Universitaire Vaudois, Department of Visceral Surgery, Lausanne, Switzerland; [6]Miles and Shirley Fiterman Center for Digestive Diseases, College of Medicine, Mayo Clinic, Rochester, United States; [7]Department of Surgery, White Plains Hospital, White Plains, United States; [8]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain*
Email: romontal@clinic.cat

Background and Aims: Cholangiocarcinoma (CCA) is a malignancy of the biliary tree that can be divided into intrahepatic (iCCA) or extrahepatic (eCCA), with differences in pathogenesis and clinical management. There are no effective systemic molecular therapies for eCCA and no comprehensive molecular profiling of this cancer has been performed in western patients. Thus, understanding the main molecular classes and drivers of this tumor will lead to a more precise therapeutic approach.
Method: A total of 189 FFPE primary eCCA treated by resection were retrospectively collected at seven international centers from 1995 to 2015. Median survival of the cohort was of 48.5mo. Whole gene-expression profiling (Affymetrix) was performed and data was

submitted to unsupervised clustering by NMF consensus. Clusters were characterized by Gene Set Enrichment Analysis and Ingenuity Pathway Analysis and correlated with clinico-pathological data. Screening of most prevalent somatic mutations and copy number aberrations is currently ongoing.
Results: We have identified four distinct molecular subtypes of eCCA (NMF cophenetic coefficient = 0.995). Tumors classified within the *metabolic class* *(18.7%) were enriched in gene signatures defining bile- and fatty-acid ($p < 0.001$) metabolism and presented over-expression of classic hepatocyte markers with HNF4A as the major activated upstream transcription factor ($p < 0.001$). The *proliferation class* (22.5%) was associated with papillary histology ($p < 0.01$) and presented enrichment of MYC ($p < 0.001$) and mTOR ($p < 0.05$) signaling, as well as iCCA proliferation subclass ($p < 0.001$). The *mesenchymal class* (47.3%) was associated with signatures defining epithelial-mesenchymal transition ($p < 0.001$) and stromal activation ($p < 0.001$), which was in accordance with higher desmoplasia at pathological study ($p < 0.05$). Moreover, tumors belonging to the mesenchymal class were significantly associated with poor prognosis in terms of OS (median survival 33.2 vs 55.5mo, HR = 2.02, p = 0.022). Finally, tumors classified as *immune class* (11.5%) were characterized by enrichment of PD-1 signaling ($p < 0.01$) and presented increased tumor-infiltrating lymphocytes when compared to the other three subtypes ($p < 0.001$).
Conclusion: Transcriptome-based classification of eCCA identifies four distinct molecular subtypes (metabolic, proliferation, mesenchymal and immune) that correlate with clinico-pathological characteristics. These molecular findings enhance the understanding of this cancer and pave the way for more precise therapeutics.

GS-005
Final results of a multicenter, open-label phase 2b clinical trial to assess safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection

H. Wedemeyer[1], P. Bogomolov[2], A. Blank[3,4], L. Allweiss[5,6], M. Dandri-Petersen[5,6], B. Bremer[1], N. Voronkova[2], K. Schöneweis[4,7], A. Pathil[8], J. Burhenne[3,4], M. Haag[9,10], M. Schwab[9,10], W.-E. Haefeli[3,4], J.S.Z. Wiesch[6,11], A. Alexandrov[12], S. Urban[4,7]. *[1]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [2]Moscow Regional Research Clinical Institute, Hepatology Department, Moscow, Russian Federation; [3]Heidelberg University Hospital, Department of clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany; [4]German Center for Infection Research (DZIF), Heidelberg Partner Site, Heidelberg, Germany; [5]University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany; [6]German Center for Infection Research (DZIF), Lübeck-Borstel Partner Site, Hamburg, Germany; [7]University Hospital Heidelberg, Department of Infectious Diseases, Molecular Virology, Heidelberg, Germany; [8]Heidelberg University Hospital, Internal Medicine IV, Gastroenterology and Hepatology, Heidelberg, Germany; [9]IKP Stuttgart, Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Germany; [10]German Center for Infection Research (DZIF), Tübingen Partner Site; [11]University Medical Center Hamburg-Eppendorf, Department of Internal Medicine, Infectious Diseases Unit, Hamburg, Germany; [12]MYR GmbH, Bad Homburg, Germany*
Email: Katrin.Schoeneweis@med.uni-heidelberg.de

Background and Aims: Currently there is no approved drug for hepatitis D virus (HDV) infection. Myrcludex B (MyrB) is a first-in-class entry inhibitor blocking the HBV/HDV receptor NTCP. We previously reported end-of-treatment data of a Phase 2 clinical trial in chronic HDV infection (Wedemeyer et al.; Hepatology 2017, DOI: 10.1002/hep.29500). Here we present follow up data after stopping MyrB therapy.
Methods: 120 patients with chronic Hepatitis D were randomized in four treatment arms. Treatment with TDF 245 mg/day started not less than 12w prior to MyrB. MyrB was administered s.c. once daily at 2 (A), 5 (B) or 10 mg (C) for 24w followed by a 24w period continuing TDF. Patients in arm D received TDF alone. The primary endpoint was HDV RNA reduction by 2log or negativity.
Results: At abstract submission, virology data from 41 patients who completed the week 12 of follow up, and ALT data from 94 patients are available. **Safety:** MyrB was very well tolerated. Apart from bile acids increase, no specific AE pattern could be identified for MyrB. After MyrB cessation, two hepatitis exacerbations after stopping MyrB were reported as SAEs. The ALT flairs were not associated with bilirubin increases and resolved without intervention. Bile acid levels returned to baseline at the follow up week 1. **Efficacy:** At end of treatment, the primary endpoint was reached by 46.4%, 46.8%, 76.6%, and 3.3% of patients of arms A, B, C, and D. Median HDV RNA declined by −1.75 log, −1.60 log, −2.70 log and −0.18 log. Plasma HDV RNA decline correlated with intrahepatic decrease of HDV RNA replication. ALT normalization was achieved in 42.8%, 50%, 40% and 6.6%. Mean liver stiffness values significantly declined in all MyrB groups from baseline to treatment week 24 but not in the control group.
At follow up week 12, an HDV RNA relapse occurred in 60%, 80% and 83% of HDV RNA responders. Median HDV RNA increased by 1.26 log, 0.62 log, 1.85 log, 0 log in arms A, B, and C and D. HDV RNA levels remained −0.77 log, −1.27 log, −0.99 log, and 0 log below BL levels. Median ALT increased from 44.0 U/l, 40.5 U/l, 43.0 U/l and 76.0 U/l to 79 U/l, 63 U/l, 93 U/l and 64 U/l.
Conclusion: Myrcludex B shows a dose-dependent antiviral efficacy against HDV associated with improvements of biochemical activity and liver stiffness. Sustained HDV control after 24 weeks of therapy is possible in single patients but longer treatment durations or even maintenance therapy need to be investigated in future trials.

GS-006
Efficacy and safety of 8 weeks of elbasvir/grazoprevir in HCV GT4-infected treatment-naïve participants

T. Asselah[1], S. Pol[2], C. Hezode[3], V. Loustaud-Ratti[4], V. Leroy[5], S.N.S. Ahmed[6], V. Ozenne[7], J.-P. Bronowicki[8], D. Larrey[9], A. Tran[10], L. Alric[11], E. Nguyen-Khac[12], M. Robertson[13], G. Hanna[13], D. Brown[13], E. Asante-Appiah[13], S. Ludmerer[13], M. Su[13], P. Hwang[14], S. Klopfer[13], F. Dutko[13], A. Guidoum[15], K. Hagen[16], B. Haber[17], R. Talwani[13], L. Serfaty[18]. *[1]Hôpital Beaujon, Clichy, France; [2]Assistance Publique-Hôpitaux de Paris, Paris, France; [3]A.P.H. Paris, Hopital Henri Mondor, Paris; [4]CHU Limoges, Limoges Cédex, France; [5]C.H.U. Grenoble Alpes, Grenoble, France; [6]Centre Hospitalier Régional d' Orléans, Orléans, France; [7]Hopital Saint Antoine, Paris, France; [8]Centre Hospitalier Universitaire, Vandoeuvre-lès-Nancy, France; [9]Hôpital Saint Eloi, Montpellier School of Medicine, Montpellier, France; [10]Hopital l'Archet 2, Nice Cedex 3, France; [11]C.H.U. de Toulouse, Hopital de Purpan, Toulouse, France; [12]Amiens University Hospital, France; [13]Merck & Co., Inc., Kenilworth, NJ, United States; [14]Merck & Co., Inc., UG1C-46, North Wales, PA, United States; [15]MSD France, Courbevoie, France; [16]MSD Sweden, Stockholm, Sweden; [17]Merck and Co, Merck, North Wales, United States; [18]APHP and INSERM UMR_S 938 Universite Pierre & Marie Curie, Paris, France*
Email: barbara.haber@merck.com

Background and Aims: Approximately 15–20% of HCV infections worldwide are due to genotype 4 (GT4). HCV GT4 is endemic in the Middle East and Africa, and increasing in prevalence in Europe as a result of immigration and injecting drug use. Shorter DAA treatment durations may expand access and facilitate treatment of more people infected with HCV GT4, in particular, those actively injecting drugs. Currently, a minimum of 12 weeks of the fixed-dose combination of elbasvir (EBR) 50 mg and grazoprevir (GZR) 100 mg once daily is approved for treatment of chronic HCV GT4 infection.
Methods: Protocol MK-5172-096 is a phase 4 study evaluating 8 or 12 weeks of EBR/GZR across multiple subgroups of HCV GT4 infected participants in France where 2 of the 4 study arms are to include 75 treatment-naïve participants with stage 0–2 fibrosis (FibroScan® score <8.0 kPa or demonstration of stage F0-F2 fibrosis from liver

biopsy specimen) randomized 2:1 to receive 8 or 12 weeks of EBR/GZR. Here we report interim results from those who received 8 weeks of EBR/GZR (target n = 50). The primary efficacy endpoint is sustained virologic response 12 weeks after the end of therapy (SVR12), defined as HCV RNA < 15IU/ml as measured by COBAS® AmpliPrep/COBAS® Taqman® HCV test (v. 2.0). HCV GT4 subtyping was determined by HCV NS5B miniamplicon sequence analysis.

Results: To date, 31 GT4 participants have been enrolled in the 8-week treatment arm and their demographics and baseline characteristics are summarized in the Table. Of the participants with available data, 18/18 had HCV RNA <15 IU/ml at the end of the 8-week treatment with EBR/GZR and 12/12 participants had no detectable HCV RNA at follow up week 4 (SVR4). There were no treatment discontinuations due to adverse events or serious adverse events.

Demographics and Baseline Characteristics		All patients (n = 31)
Sex, n (%)	Female	16 (52%)
	Male	15 (48%)
Race (self-reported), n (%)	White	17 (55%)
	Black	10 (32%)
	Asian	1 (3%)
	Not disclosed	3 (10%)
Age, years, mean (range)	54 (29–80)	
Baseline HCV RNA, n (%)	<800,000 IU/ml	9 (29%)
	>800,000 IU/ml	22 (71%)
	<2,000,000 IU/ml	19 (61%)
	>2,000,000 U/ml	12 (39%)
Fibrosis Stage	F0-F1 (by biopsy or FibroScan® score <7.0 kPA)	28 (90%)
	F2 (by biopsy or FibroScan® score > 7.0 and <8.0 kPa	3 (10%)
Samples with Completed NS5B Sequencing for GT4 Subtype Analysis, n (%); GT4 subtype, (n)	17 (55%)	4a (5), 4c (2), 4d (3), 4f (3), 4k (2), 4r (1), 4t (1)

Conclusion: Preliminary data suggest that 8 weeks of EBR/GZR may be effective, safe and well tolerated in treatment-naïve HCV GT4-infected individuals with minimal fibrosis. Interim results including SVR12 data from all enrolled participants receiving 8 weeks of EBR/GZR will be presented.

Autoimmune and cholestasis 1

PS-001

Estimated risk reduction of mortality and transplantation with bezafibrate in patients with PBC and inadequate response to UDCA: application of the UK-PBC and Global PBC risk scores to the BEZURSO trial

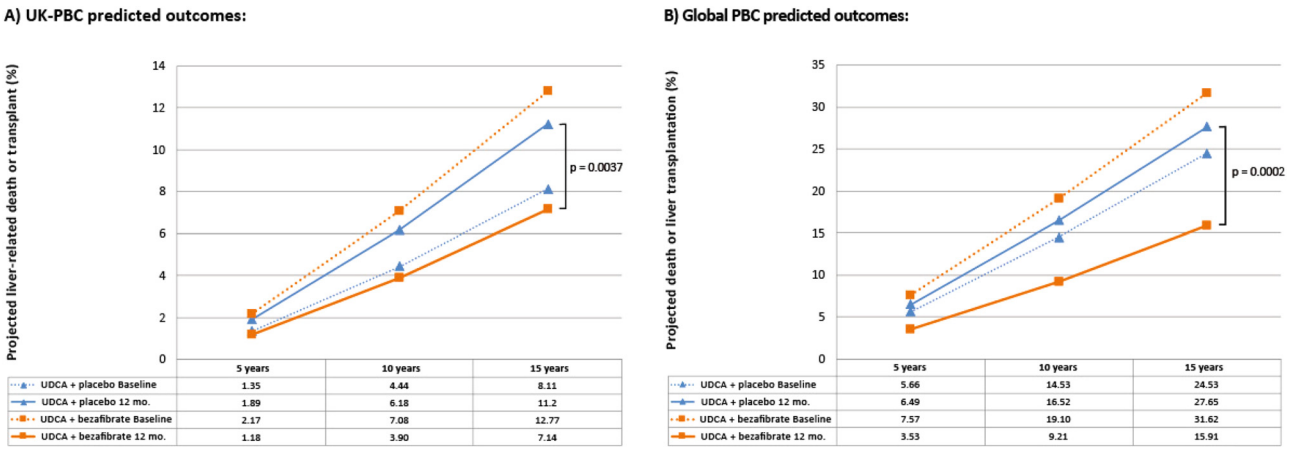
C. Corpechot[1,2], A. Rousseau[3], O. Chazouillères[1,2], L.G. Antonia[4], F. Habersetzer[5], P. Mathurin[6], O. Goria[7], P. Pascal[8], A.M. Franza[9], C. Silvain[10], A. Abergel[11], M.D. Gratien[12], D. Larrey[13], R. Olivier[14], J.-P. Bronowicki[15], J. Boursier[16], V. De Ledinghen[17], A. Heurgue-Berlot[18], E. Nguyen-Khac[19], F. Zoulim[20], O.-H. Isabelle[21], J.-P. Zarski[22], N. Gisèle[23], G. Farid[1], F.-H. Admane[3], T. Simon[3], R. Poupon[1,2]. *[1]Saint-Antoine Hospital, Assistance Publique – Hôpitaux de Paris, Reference Center for Inflammatory Biliary Diseases and Autoimmune Hepatitis, Paris, France; [2]Pierre and Marie Curie Paris 6 University, Inserm UMR_S938, Paris, France; [3]Saint-Antoine Hospital, Assistance Publique – Hôpitaux de Paris, Department of Clinical Pharmacology and Clinical Research Platform of East of Paris, Paris, France; [4]Rennes University Hospital, Hepatology, Rennes, France; [5]Strasbourg University Hospital, Hepatology, Strasbourg, France; [6]Lille University Hospital, Hepatology, Lille, France; [7]Rouen University Hospital, Hepatology, Rouen, France; [8]Orléans Hospital, Hepatology, Orléans, France; [9]Dijon University Hospital, Hepatology, Dijon, France; [10]Poitiers University Hospital, Hepatology, Poitiers, France; [11]Clermont-Ferrand University Hospital, Hepatology, Clermont-Ferrand, France; [12]Limoges University Hospital, Hepatology, Paris, France; [13]Montpellier University Hospital, Hepatology, Montpellier, France; [14]Beaujon University Hospital, Hepatology, Clichy, France; [15]Nancy University Hospital, Hepatology, Nancy, France; [16]Angers University Hospital, Hepatology, Angers, France; [17]Bordeaux University Hospital, Hepatology, Bordeaux, France; [18]Reims University Hospital, Hepatology, Reims; [19]Amiens University Hospital, Hepatology, Amiens, France; [20]Lyon University Hospital, Hepatology, Lyon, France; [21]Caen University Hospital, Hepatology, Caen, France; [22]Grenoble University Hospital, Hepatology, Grenoble; [23]Jean Verdier University Hospital, Hepatology, Bondy, France*
Email: christophe.corpechot@aphp.fr

Background and Aims: BEZURSO is the first ever placebo-controlled trial of a fibrate (i.e. an agonist of the peroxisome proliferator-activated receptor alpha) for the treatment of primary biliary cholangitis (PBC). It was a 24-month phase 3 study assessing the efficacy of bezafibrate (BZF) 400 mg daily in association with standard of care ursodeoxycholic acid (UDCA) in PBC patients with an inadequate response to UDCA. The trial reached the primary endpoint, which was a complete biochemical response at 24 months defined by normal levels of total bilirubin, alkaline phosphatases, transaminases, albumin and prothrombin index. However, the study duration was too short to observe a difference in liver-related complications or death. The UK-PBC and Global PBC risk scores are validated prognostic models based on data from >6,000 UDCA-treated patients with PBC. The aim of the present study was to assess the predicted reduction in the risk of death or liver transplantation (LT) of patients in BEZURSO using the UK-PBC and Global PBC risk scores.

Method: A total of 100 patients with an inadequate response to UDCA were randomized to receive BZF (n = 50) or placebo (n = 50), in association with UDCA, for 24 months. Baseline, Month 12, and Month 24 data were entered into the UK-PBC and Global PBC risk score calculations, to assess the risk of an endpoint (liver-related death or LT for UK-PBC score; death or LT for Global PBC score) at 5, 10, and 15 years in the two groups.

Results: The UK-PBC predicted changes in the risk of events from baseline following 12 months of treatment was on average −34.5% (IQR: −49.4%; −7.6%) in the BZF group and +25.4% (−10.9%; +57.9%) in the placebo group ($p < 0.0001$). The Global PBC predicted changes in this risk was −41.3% (−50.0%; −22.5%) in the BZF group and +15.4% (−4.6%; +51.2%) in the placebo group ($p < 0.0001$). Similar results were obtained after 24 months of treatment. Figure 1 shows the UK-PBC (A) and Global PBC (B) predicted percentages of events at 5, 10, and 15 years according to treatment group and time point (baseline vs. Month 12). While the percent risk did not differ within groups at baseline, it was significantly lower in the BZF group than in the placebo group after 12 months of treatment in both models ($p = 0.0037$ and $p = 0.0002$, respectively). Similar results were obtained after 24 months of treatment.

Conclusion: Compared to placebo and UDCA, BZF and UDCA combined treatment was associated with a significant reduction in estimated risk of LT and (liver-related vs. all-cause) mortality with both UK-PBC and Global PBC risk scores.



	5 years	10 years	15 years
UDCA + placebo Baseline	1.35	4.44	8.11
UDCA + placebo 12 mo.	1.89	6.18	11.2
UDCA + bezafibrate Baseline	2.17	7.08	12.77
UDCA + bezafibrate 12 mo.	1.18	3.90	7.14

	5 years	10 years	15 years
UDCA + placebo Baseline	5.66	14.53	24.53
UDCA + placebo 12 mo.	6.49	16.52	27.65
UDCA + bezafibrate Baseline	7.57	19.10	31.62
UDCA + bezafibrate 12 mo.	3.53	9.21	15.91

Figure 1: Estimated percent risk of events with UK-PBC and Global PBC prognostic models.

PS-002

Are the Globe and UK-PBC scores also effective for predicting risk in patients treated with bezafibrate in addition to ursodeoxycholic acid?: A validation study in Japan

A. Tanaka[1], A. Komori[2], M. Abe[3], M. Inao[4], T. Namisaki[5], N. Hashimoto[6], K. Kawata[7], A. Takahashi[8], M. Ninomiya[9], A. Honda[10], K. Jong-Hon[11], M. Arakawa[12], S. Yamagiwa[13], S. Joshita[14], K. Sato[15], A. Kaneko[16], K. Kikuchi[17], J. Itakura[18], T. Nomura[19], K. Kakisaka[20], T. Masaki[19], Y. Matsuzaki[21], H. Ohira[8], S. Mochida[22], H. Yoshiji[5], H. Takikawa[1]. *[1]Teikyo University School of Medicine, Department of Medicine; [2]National Hospital Organization Nagasaki Medical Center, Clinical Research Center; [3]Ehime University Graduate School of Medicine, Gastroenterology and Metabology; [4]Saitama Medical University, Department of Gastroenterology and Hepatology; [5]Nara Medical University, Third Department of Internal Medicine; [6]Tokyo Teishin Hospital, Department of Gastroenterology; [7]Hamamatsu University School of Medicine, Department of Internal Medicine II; [8]Fukushima Medical University School of Medicine, Department of Gastroenterology; [9]Tohoku University Hospital, Division of Gastroenterology; [10]Tokyo Medical University Ibaraki Medical Center, Department of Gastroenterology and Hepatology; [11]Teine-Keijinkai Hospital, Center for Gastroenterology; [12]Oita University Faculty of Medicine, Department of Gastroenterology; [13]Niigata University Medical & Dental Hospital, Division of Gastroenterology and Hepatology; [14]Shinshu University School of Medicine, Department of Medicine; [15]Gunma University Hospital, Department of Endoscopy and Endoscopic Surgery; [16]NTT West Osaka Hospital, Department of Gastroenterology; [17]Teikyo University Mizonoguchi Hospital, Fourth Department of Internal Medicine; [18]Musashino Red Cross Hospital, Department of Gastroenterology and Hepatology; [19]Kagawa University School of Medicine, Department of Gastroenterology and Neurology; [20]Iwate Medical University, Division of Hepatology, Department of Internal medicine; [21]Tokyo Medical University Ibaraki Medical Center, Department of Gastroenterology; [22]Saitama Medical University, Department of Gastroenterology and Hepatology*
Email: a-tanaka@med.teikyo-u.ac.jp

Background and Aims: It is crucial to stratify the risk for progression in patients with primary biliary cholangitis (PBC). Although the Globe and UK-PBC scores have been established for this purpose, these are not validated in patients treated with other drugs in addition to ursodeoxycholic acid (UDCA). We have used bezafibrate (BF) for patients who were refractory to UDCA in Japan, and herein performed a validation study of these scores in Japanese patients treated with UDCA and/or BF.
Method: We took advantage of a large-scale retrospective database in Japan consisting of 9,919 patients with PBC diagnosed between 1985 and 2014. We selected patients for the current study according the following criteria: (1) treated with UDCA and/or BF, (2) followed up at least 2 years after initiating treatment, and (3) biochemical treatment responses at 1 year of treatment and outcomes were clearly recorded. When patients were consecutively treated with both UDCA and BF, the treatment response at baseline and at 1 year of the secondary added drug was used for calculating the scores.
Results: We identified 727 patients who met the above criteria (M/F = 109/618, 58.4 ± 11.3 yo at diagnosis). Among them, 542, 183 and 3 patients were treated with UDCA only (74.5%), UDCA + BF (25.2%), and BF only (0.4%). Observation period was 8.3 ± 5.5 years. Liver transplantation (LT)-free survival rates at 5-, 10- and 15-years was 98.0%, 95.5% and 89.3%, respectively. The average estimated LT-free survival rates at 5-, 10- and 15-years using the Globe score were 81.9%, 62.9% and 47.5%, respectively, which were significantly lower than the real outcomes at each point ($p < 0.001$). AUROC of the Globe score was 0.811 for LT-free survival. Meanwhile, the estimated LT-free survival rates using the UK-PBC score were 96.9%, 91.8% and 86.6%, respectively, which were significantly lower as well ($p < 0.05$). AUROC of the UK-PBC score for LT-free survival was 0.899.
Conclusion: The risk predictive values of the Globe and UK-PBC scores were diminished when BF was additionally used for patients who were refractory to UDCA, while performance of the UK-PBC score was better. It is warranted to develop a new scoring system for predicting outcomes in patients treated with a new drug such as obeticholic acid in addition to UDCA.

PS-003

Sub-cutaneously delivered mesenchymal stromal cells and down-regulation of activated vascular endothelium – a novel, clinically ready, therapeutic approach to treating cholestatic liver disease

V. Vigneswara[1], N.-T. Luu[1], M. Alfaifi[1], L. O'flynn[2], C. Baan[3], M. Hoogduijn[3], M. Gargesha[4], D. Roy[4], S. Elliman[2], G. Hirschfield[1], P. Newsome[1]. *[1]National Institute for Health Research Birmingham Biomedical Research Centre at University Hospitals Birmingham NHS Foundation Trust and the University of Birmingham, United Kingdom; [2]Orbsen Therapeutics; [3]Erasmus Medical Center; [4]BioInVision*
Email: p.n.newsome@bham.ac.uk

Background and Aims: Human mesenchymal stromal cells represent a potential novel therapy for inflammatory liver diseases. We set out to define the mechanism of action, and specifically remote effects, of MSC in a murine pre-clinical model of PSC.
Method: Umbilical cord (UC) derived MSC (OrbCel™) were injected intravenously (IV) or subcutaneously (SC) into 6–7 week old male Mdr2$^{(-/-)}$ mice (FVB/N background) and subsequent impact on liver damage was determined by liver histology, serum analysis and FACS

analysis of liver digest. Bio-distribution of Q-dot labelled MSC was determined by whole mouse cryo-imaging. Effect of MSC or MSC-conditioned media (CM) on adhesion of peripheral blood mononuclear cells (PBMC) to hepatic sinusoidal endothelial cells (HSEC) over flow conditions were studied. HSEC activation markers (VCAM/ICAM) were studied *in vitro* and *in vivo* after MSC/MSC-CM treatment.
Results: MSC administered SC were as effective as IV, versus control (Con), in reducing liver injury *in vivo* with reductions in serum ALT (SC 493 iu vs Con 707 iu; $p < 0.05$) and bile acids (SC 38 mmol/l vs Con 75 mmol/l; $p < 0.05$). Numbers of CD4 and CD8 cells infiltrating the liver were also reduced after SC MSC administration. There was also an increase in the M2/M1 macrophage ratio after SC administration (SC 0.97 vs Con 0.71; $p < 0.05$). A cryo-imaging seven day time-course indicated MSC were cleared rapidly with no migration of SC administered cells. MSC and MSC-CM pre-treatment of HSEC reduced subsequent adhesion and trans-migration of PBMC under conditions of sinusoidal flow. In addition, this was associated with reduced expression of activation markers VCAM and ICAM on HSEC (flow cytometry and confocal fluorescent staining – Figure 1). SC MSC-treated Mdr2$^{(-/-)}$ mice demonstrated reduced VCAM/ICAM expression at the gene and protein level versus Con mice. MSC-CM also reduced senescence and increased proliferation of biliary epithelial cells *in vitro*.

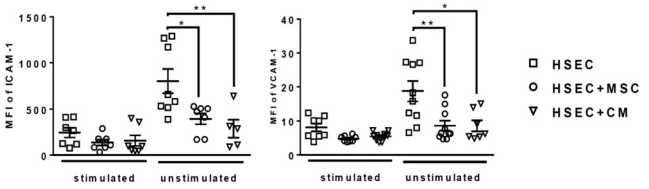


Figure 1: VCAM/ICAM expression on HSEC after treatment with MSC or MSC CM.

Conclusion: Remote sub-cutaneous MSC administration demonstrates a retained potent anti-inflammatory action in murine model of cholestatic liver injury. This effect is mediated through secreted factors that down-regulate endothelial cell activation reducing inflammatory cell ingress to the liver. MSC are cleared rapidly after infusion with no hepatic homing and induce significant M2 polarisation of hepatic monocytes.

PS-004
The gut-liver axis is essential for disease progression in the Mdr2−/− mouse model of primary sclerosing cholangitis

L. Liao[1,2], K.M. Schneider[1], M. Frissen[1], T. Strowig[3], H.-U. Marschall[4], A. Wahlström[5], G. Eric[3], A. Mohs[1], P. Jin[1], J. Jung[1], J. Reissing[1], H. Sun[1], C. Elfers[1], V. Bieghs[1], F.J. Cubero[6], C. Trautwein[1]. [1]*University Hospital, Department of Internal Medicine III, Aachen, Germany;* [2]*Renji Hospital, Shanghai Jiao Tong University, Department of Pain Management, Shanghai, China;* [3]*Helmholtz Centre for Infection Research, Braunschweig, Germany;* [4]*University of Gothenburg, Wallenberg Laboratory, Gothenburg;* [5]*University of Gothenburg, Wallenberg Laboratory, Gothenburg, Sweden;* [6]*Complutense University School of Medicine, Department of Immunology, Madrid, Spain*
Email: liaolijunxiao@gmail.com

Background and Aims: Primary sclerosing cholangitis (PSC) is strongly associated with inflammatory bowel disease. The gut-liver axis plays a critical role in PSC onset and progression. However, the functional implications of intestinal microbiota and inflammasome mediated innate immune response for PSC is unclear. Here, we investigated gut-liver crosstalk and NLRP3 inflammasome activation in the murine Mdr2 knockout (Mdr2$^{-/-}$) model resembling PSC.
Method: Mdr2$^{-/-}$, WT control mice, Mdr2$^{-/-}$/Casp8$^{\Delta hepa}$ and Mdr2$^{-/-}$/Casp8$^{f/f}$ were housed for 8w or 52w. Only male mice were used in this study. The relevance of Mdr2 deletion on liver injury as well as gut microbiota and bile acid profile were studied. NLRP3 inflammasome and caspase activation in the gut-liver axis were comprehensively analyzed. Pan-caspase inhibitor (IDN-7314) was treat to block caspase activation, and the effect of IND-7314 on gut-liver axis was detected.
Results: Mdr2$^{-/-}$ mice displayed significantly increased serum transaminases and liver peridutular inflammation compared to WT mice. Mdr2$^{-/-}$ liver was characteristic presenting a strong induction of apoptotic cell death, progressive bile duct proliferation and periportal fibrosis development over time (52 weeks). The abnormal bile acid composition in Mdr2$^{-/-}$ mice was associated with an altered intestinal microbiota composition. This was linked to an impaired intestinal barrier, including colonic mucus layers, reduction of tight junction expression and increased permeability evidenced by an in-vivo FITC-dextran assay. Intestinal dysbiosis in Mdr2$^{-/-}$ mice urged increased translocation of endotoxin and bacterial, further augmented the hepatic innate immune response. Mechanistically, enhanced hepatic NLRP3 inflammasome activation via caspase-1 triggered macrophage and neutrophil infiltration and caspase-3, -8 and -9 mediated apoptotic cell death. However, by introducing Mdr2$^{-/-}$/Casp8$^{\Delta hepa}$ animals the Mdr2$^{-/-}$ phenotype could not be rescued indicating that hepatocytic caspase-8 activation is a downstream consequence and dispensable for the inflammatory response. Strikingly, a pan-caspase (IDN-7314) dampened inflammasome activation and ameliorated liver injury, periportal inflammation, serum bile acid profile as well as intestinal dysbiosis.
Conclusion: Our data demonstrate that Mdr2 associated cholestasis triggers intestinal dysbiosis, with translocation of endotoxin and bacterial in the portal vein and subsequent NLRP3 inflammasome activation, which contributes to higher liver injury. This process can be blocked by pancaspase, but not hepatocytic caspase-8 inhibition.

PS-005
Immunomodulatory mechanisms of the novel therapeutic bile acid 24-nor-ursodeoxycholic acid

C.I. Zhu[1], N. Boucheron[2], C.D. Fuchs[1], H. Baazim[3], A. Lercher[3], E. Halilbasic[4], M. Tardelli[5], A. Bergthaler[3], W. Ellmeier[2], M. Trauner[6]. [1]*Medical University of Vienna, Division of Gastroenterology & Hepatology, Internal Medicine III, Wien, Austria;* [2]*Medical University of Vienna, Institute of Immunology, Center for Pathophysiology, Infectiology and Immunology, Vienna, Austria;* [3]*CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna, Austria;* [4]*Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria;* [5]*Medical University of Vienna, Division of Gastroenterology & Hepatology, Internal Medicine III, Vienna, Austria;* [6]*Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria*
Email: michael.trauner@meduniwien.ac.at

Background and Aims: Primary sclerosing cholangitis (PSC) is a progressive immune-mediated liver disease, currently lacking effective medical therapy. In a recent European multicenter phase II clinical study for primary sclerosing cholangitis (PSC), nor-ursodeoxycholic acid (*nor*UDCA), a side chain-shortened derivative of UDCA improved cholestasis irrespective of previous response to UDCA. However, potential immunomodulatory mechanisms of *nor*UDCA are still poorly understood. Since CD8 T-cell trafficking along the gut-liver axis is an important pathophysiological factor in PSC, we aimed to explore how *nor*UDCA impacts on CD8 T-cell immunity.
Method: The potential modulatory effects of *nor*UDCA on CD8 T-cell immunity were assessed in vitro by proliferation and differentiation assays as well as in vivo, in lymphocytic choriomeningitis virus (LCMV) model of CD8 T-cell driven hepatic immunopathology and in Mdr2 (Abcb4) KO mouse model of PSC.
Results: In vitro, *nor*UDCA but not UDCA reduced CD8 T-cell proliferation and lymphoblast formation by 53% compared to untreated controls ($p < 0.05$). Mechanistically, mTOR(Ser2448) phosphorylation of CD8 T-cells was suppressed by *nor*UDCA by 40% ($p <$

0.005). In line, *nor*UDCA reduced mTORC1 and mTORC2 kinase activities as reflected by lower phosphorylation level of P70 S6 Kinase (Thr421/Ser424) and AKT(Ser473) by 41% ($p < 0.05$) and 53% ($p < 0.05$), respectively. Additionally, *nor*UDCA strongly reduced mean fluorescence intensity of mTOR dependent Granzyme B and IFNγ by 73% and 56%. Moreover, similar to rapamycin, glycolysis but not oxidative phosphorylation in activated CD8 T-cells was inhibited by *nor*UDCA as shown by a reduction in extracellular acidification rate without a change in oxygen consumption rate. In vivo, *nor*UDCA ameliorated hepatic injury and inflammation induced by LCMV as shown by lower ALT (*nor*UDCA + LCMV 88U/L vs LCMV 209.6U/L, $p < 0.005$) and decreased liver expression of Granzyme B by 41% ($p < 0.005$) and Cxcl10 by 40% ($p < 0.005$). Supporting our in vitro finding, *nor*UDCA remarkably reduced CD8 effector T-cell frequency in the liver of LCMV infected mice. Notably, this reduction led to improved control of inflammation without compromising quality of viral-specific CD8 T-cell immunity. Additionally, *nor*UDCA (but again not UDCA) had similar impact on reducing liver CD8 T-cell number in Mdr2 KO mice.

Conclusion: Overall, we unraveled novel anti-inflammatory mechanisms of *nor*UDCA impacting mTOR signaling and distinct from UDCA, indicating that *nor*UDCA may represent a promising immunometabolic drug for treatment of T-cell based inflammatory liver diseases.

PS-006

Autoantibodies against Huntingtin-interacting protein 1-related protein are superior to conventinal autoantibodies in diagnosing autoimmune hepatitis in adults

R. Taubert[1], N.T. Baerlecken[2], C. Lalanne[3], L. Muratori[3], M.P. Manns[1], T. Witte[2], E. Jaeckel[4]. *[1]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]Hannover Medical School, Clinical Immunology, Hannover, Germany; [3]University of Bologna, Medical and Surgical Sciences, Bologna, Italy; [4]Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany*
Email: taubert.richard@mh-hannover.de

Background and Aims: Autoantibodies are key parameters in the diagnostic of autoimmune hepatitis (AIH) among those with chronic liver diseases. However, conventional autoantibodies such as anti-nuclear (ANA), anti-smooth muscle (SMA), anti-liver kidney microsomal antibodies (LKM) and antibodies against soluble liver antigen (SLA) either lack high sensitivity or high specificity. We screened for alternative autoantibodies with a better clinical performance.

Method: Antibodies against Huntingtin-interacting protein 1-related protein (HIP1R) were identified via a protein macroarray in patients with AIH. Next, antibodies against a HIP1R fragment, measured with an ELISA, were compared to conventional autoantibodies in three independent adult cohorts: a training and internal validation cohort from Hannover/Germany and an external validation cohort from Bologna/Italy. In total 208 AIH samples (untreated: n = 164; under therapy: n = 44), 350 samples with other chronic liver diseases and 46 healthy controls were analyzed.

Results: Patients with untreated AIH (type I and II) had the highest anti-HIP1R antibody concentrations compared to non-AIH liver diseases and healthy controls ($p < 0.001$). Baseline anti-HIP1R concentrations in AIH patients decreased to background levels of non-AIH liver diseases during therapy.

With the receiver operating characteristic the optimal cut-off for the distinction between untreated AIH and other liver diseases was identified (52.7 arbitrary units; AUC: 0.86; 95% confidence interval: 0.81–0.91). With this cut-off anti-HIP1R antibodies (OR: 12.8; 6.9–23.7) achieved a significantly higher sensitivity (0.77; 0.67–0.85) compared to SMA, LKM and SLA, a significantly higher specificity (0.80; 0.72–0.85) compared to ANA and SMA and the highest overall accuracy [0.79 (0.73–0.83); ANA: 0.71 (0.65–0.77); SMA: 0.57 (0.51–0.63), LKM: 0.64 (0.58–0.70); SLA: 0.64 (0.58–0.70)] for the diagnosis of untreated AIH in the retrospective training cohort from Hannover (n = 251).

Comparable results [anti-HIP1R: OR: 7.2 (3.5–14.9); sensitivity: 0.71 (0.56–0.83); specificity: 0.75 (0.68–0.81)] with a significantly higher overall accuracy (0.74; 0.68–0.79) than ANA and SMA were found in the prospective validation cohort from Hannover (n = 238). In the external validation cohort with only untreated AIH (n = 25) from Bologna, anti-HIP1R antibodies achieved the highest sensitivity (0.89; 0.68–0.97) from all tested autoantibodies.

Diagnostic anti-HIP1R concentrations were even found in 85% (11/13) of patients with untreated AIH negative for classical autoantibodies.

Conclusion: Anti-HIP1R autoantibodies seem superior to conventional autoantibodies (ANA, SMA, LKM) by a better clinical prediction of AIH and by a simpler ELISA assay compared to the demanding immunofluorescence titration on rodent tissue section.

PS-007

Intestine-specific deletion of Abcg5/g8 leads to hepatobiliary cholesterol overload: pathophysiology of biliary lipid secretion

R. Charlotte, B. Annika, M. Krawczyk, F. Lammert, S.N. Weber. *Saarland University Medical Center, Department of Medicien II, Homburg, Germany*
Email: susanne.weber@uks.eu

Intestine-specific deletion of *Abcg5/g8* leads to hepatobiliary cholesterol overload.

Charlotte Rebholz, Annika Bohner, Marcin Krawczyk, Frank Lammert, Susanne N. Weber.

Background and Aims: Gallstone disease is one of the most common disorders worldwide and is primarily caused by cholesterol supersaturation of bile. Cholesterol is secreted into bile by the ATP-dependent hepatobiliary sterol transporter ABCG5/G8, which also transports phytosterols and is expressed in liver and small intestine. Our aim now was to determine the role of intestinal ABCG5/G8 on biliary lipid secretion and cholesterol homeostasis, using mice in which the transporter is inactivated in the intestine but functional in the liver.

Methods: Using BAC-based recombineering, we generated conditional *Abcg5/g8* knock-out mice allowing tissue-specific deletion of the first 2 exons of *Abcg5* and the first exon of *Abcg8*, respectively, by cre-mediated recombination. *Abcg5/g8* fl/fl mice were crossed to *Villin*-cre mice expressing cre in the intestine under the control of the *Villin* promoter (*Abcg5/g8-Vil*). Hepatic bile was collected via cannulation of the common bile duct, and bile flow and biliary lipid secretion rates were measured in the first hour of an acute bile fistula in *Abcg5/g8-Vil* mice and controls.

Results: All animals developed normal, were fertile, and showed no macroscopic abnormalities. Total bile flow remained stable for three hours and did not differ between the strains. In hepatic bile from the intestine-specific *Abcg5/g8* knock-out mice, total lipid (1.1 ± 0.1 vs. 1.5 ± 0.1 g/dl) and bile acid concentrations (69.5 ± 3.3 vs. 78.4 ± 1.5 mole%) were significantly ($p < 0.05$) reduced as compared to controls. The mean cholesterol saturation index (CSI) exceeded 1 in knock-out mice only (2.1 ± 0.3 vs. 0.9 ± 0.1, $p < 0.05$). In the first hour of the acute bile fistula, cholesterol secretion rates were significantly higher ($0.30 + 0.07x$ vs. $0.15 + 0.03x$ μmol/h/100 g), and phosphatidylcholine secretion rates were significantly lower in *Abcg5/g8-Vil* mice than in controls. Upon feeding lithogenic diet (15% butter fat, 1% cholesterol, 0.5% cholic acid) for 12 weeks, 89% of *Abcg5/g8-Vil* mice vs. 58% of wild-type controls developed gross fatty liver disease, and 65% vs. 44% presented with cholesterol monohydrate crystals and gallstones, respectively. CSIs were ≥1 in both groups (2.4 ± 0.8 vs. 1.9 ± 0.2; $p < 0.05$).

Conclusions: Our results show that the intestine-specific deletion of *Abcg5/g8* leads to hepatobiliary overload and consecutive hypersecretion of cholesterol, resulting in marked cholesterol supersaturation of bile in the conditional knock-out mice without dietary

challenge. This is accompanied by decreased bile acid, phosphatidylcholine and total lipid concentrations. Further studies are needed to determine the adaptive responses to the selective lack of cholesterol and phytosterol efflux in the intestine.

PS-008

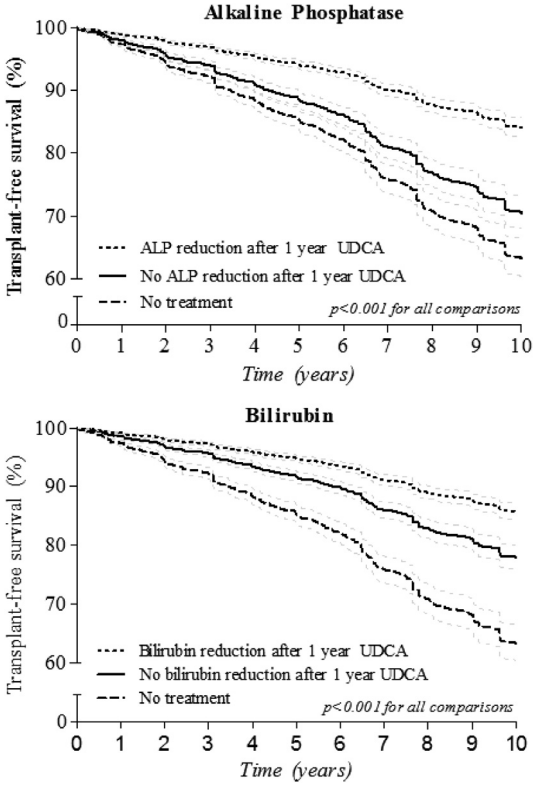
Ursodeoxycholic acid treatment is associated with prolonged transplant-free survival in primary biliary cholangitis – even in patients without biochemical improvements

M. Harms[1], H. Van Buuren[1], W.J. Lammers[1], C. Corpechot[2], D. Thorburn[3], P. Invernizzi[4], H. Janssen[5], P.M. Battezzati[6], F. Nevens[7], K. Lindor[8,9], A. Floreani[10], C. Ponsioen[11], M.J. Mayo[12], A. Pares[13], A.L. Mason[14], K.V. Kowdley[15], G. Hirschfield[16], B. Hansen[1,5], A. Van der Meer[1]. *[1]Erasmus University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; [2]Hôpital Saint-Antoine, APHP, Centre de Référence des Maladies Inflammatoires des Voies Biliaires, Paris, France; [3]The Royal Free Hospital, he Sheila Sherlock Liver Centre, and UCL Institute of Liver and Digestive Health, London, United Kingdom; [4]University of Milan-Bicocca, Division of Gastroenterology and Program for Autoimmune Liver Diseases, International Center for Digestive Health, Department of Medicine and Surgery, Milan, Italy; [5]Toronto General Hospital, Toronto Centre for Liver Disease, Francis Family Liver Clinic, Toronto, Canada; [6]Università degli Studi di Milano, Department of Health Sciences, Milan, Italy; [7]University Hospitals Leuven, KULeuven, Hepatology, Leuven, Belgium; [8]Mayo Clinic, Gastroenterology and Hepatology, Rochester, United States; [9]Arizona State University, College of Health Solutions, Phoenix, United States; [10]University of Padua, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; [11]Academic Medical Center, Gastroenterology and Hepatology, Amsterdam, Netherlands; [12]UT Southwestern Medical Center, Digestive and Liver Diseases, Dallas, United States; [13]University of Barcelona, Liver Unit, Hospital Clínic, CIBERehd, IDIBAPS, Barcelona; [14]University of Alberta, 14 Divison of Gastroenterology and Hepatology, Edmonton, Canada; [15]Swedish Medical Center, Liver Care Network and Organ Care Research, Seattle, United States; [16]University of Birmingham, NIHR Biomedical Research Unit and Centre for Liver Research, Birmingham, United Kingdom*
Email: m.h.harms@erasmusmc.nl

Background and Aims: Treatment with ursodeoxycholic acid (UDCA) is associated with a prolonged liver transplant (LT) free survival in primary biliary cholangitis (PBC). The effect of UDCA is primarily evaluated through improvements in alkaline phosphatase (ALP) and/or bilirubin. In this study, we aimed to assess the association between UDCA and LT-free survival among PBC patients without improvements of these surrogate markers after 1 year of treatment.

Method: An international cohort study including PBC patients from 14 large hepatology centers was performed. The association between UDCA therapy and LT-free survival was assessed with Cox survival analyses and inverse probability of treatment weighting, and was adjusted for sex, age, year of diagnosis, and baseline biochemistry including ALP, total bilirubin, albumin, platelet count, aspartate aminotransferase and alanine aminotransferase.

Results: We included 3902 patients with PBC, who were followed for a median of 7.8 (IQR 4.1–12.1) years. Mean age was 54.3 (SD 11.9) years, 3552 (94%) were female, and 3529 (90.4%) received UDCA treatment. In the overall cohort, UDCA was associated with a reduced risk of LT/death (adjusted HR 0.46, 95%CI 0.40–0.52, $p < 0.0001$) as opposed to no treatment. 624/3529 (17.7%) UDCA-treated patients showed no reduction in ALP after 1 year of UDCA. In these patients, UDCA was independently associated with a significantly lower risk of LT/death (adjusted HR 0.61, 95%CI 0.46–0.81, $p = 0.0008$). In patients who did show a reduction of ALP after 1 year (n = 2905, 83.3%), the adjusted HR was 0.37 (95%CI 0.31–0.44, $p < 0.0001$). In the 1484/3529 (42.1%) UDCA-treated patients that experienced no reduction of bilirubin after 1 year of treatment, UDCA was also associated with a significantly reduced risk of LT/death (adjusted HR 0.55, 95%CI 0.45–0.67, $p < 0.0001$), as opposed to a HR of 0.34 (95%CI 0.27–0.41, $p < 0.0001$) for patients that did show a reduction of bilirubin. In 337/3529 (9.5%) treated patients with neither ALP nor bilirubin improvement, UDCA treatment still showed a trend towards a lower risk of LT/death (HR 0.76, 95%CI 0.55–1.07, $p = 0.113$).



Conclusion: UDCA therapy was independently associated with a prolonged LT-free survival among PBC patients. Although the association was strongest in case of a biochemical improvement, it remained in those without any reduction of the commonly used surrogate markers. This finding supports the hypothesis that UDCA might have additional mechanisms of action.

Cirrhosis and its complications: Experimental and pathophysiology

PS-009

Stem cells as a new therapeutic strategy for portal hypertension and cirrhosis

A. Fernández-Iglesias[1,2], G. Pietrosi[3], M. Pampalone[4], O. Parolini[5], G. Vizzini[3], P.G. Conaldi[3], A. Luca[3], J. Bosch[2,1,6], J. Gracia-Sancho[1,2,6]. *[1]IDIBAPS Biomedical Research Institute, Liver Vascular Biology Research Group, Barcelona, Spain; [2]CIBEREHD, Madrid, Spain; [3]Mediterranean Institute for Transplantation and Advanced Specialized Therapies, IRCCS-ISMETT, Palermo, Italy; [4]Ri.MED Foundation, Palermo, Italy; [5]Centro di Ricerca "E. Menni", Fondazione Poliambulanza- Istituto Ospedaliero, Brescia, Italy; [6]Inselspital - University of Bern, Hepatology, Bern, Switzerland*
Email: jordi.gracia@idibaps.org

Background and Aims: Liver cirrhosis still represents a serious health problem; indeed lack of treatments to promote its regression

requires the development of new therapies including pluripotent stem cells transplantation. We herein aimed at characterizing the effects of human-placenta derived stem cells in a pre-clinical model of cirrhosis.

Method: Mesenchymal (hMSCs) and epithelial (hAECs) stem cells were isolated from human amnion membranes. Cirrhotic rats (CCl_4 inhalation) received 4×10^6 hMSCs, 4×10^6 hAECs, or vehicle (NaCl 0.9%) (i.p.; n = 10). After 2 weeks the following parameters were analysed: (a) stem cells engraftment by human mitochondria detection; (b) hemodynamic: mean arterial pressure (MAP), portal pressure (PP), portal blood flow (PBF) and hepatic vascular resistance (HVR); (c) liver microcirculatory function as response to acetylcholine; (d) hepatic cellular phenotype (fibrosis and hepatic stellate cells [HSC], inflammatory and endothelial phenotypes).

Results: Livers from stem cells-transplanted cirrhotic animals showed positivity to human mitochondria. Interestingly, cirrhotic rats receiving stem cell therapy had significantly lower PP than vehicle animals (15.4 ± 0.7 mmHg Veh vs. 12.8 ± 0.7 hMSCS (−17%); 12.3 ± 1.0 hAECs (−20%); $p < 0.01$), without changes in PBF, thus indicating decreased HVR. This was associated with a marked amelioration in liver microcirculatory dysfunction (+166% hMSCS, p = 0.023/+109% hAECs, p = 0.083). Blood tests showed improvement in the hMSCs group (Bilirubin −85% p = 0.03; Albumin +18% p = 0.04; AST −40% p = 0.08), without changes in the hAECs group.

The underlying mechanisms for the amelioration in portal pressure and liver microcirculatory dysfunction were mainly associated with a marked de-activation of HSC; hMSCs: −90% αSMA, −60% PDGFRβ, −77% TGFβ, −50% TIMP1, −68% col1a1 and −80% desmin. hAECs: −75% αSMA, −32% PDGFRβ, −30% TIMP2, −50% col1a1, without changes in desmin. Hepatic fibrosis was not changed, however hMSCs treatment improved the hepatic inflammatory [−65% MCP-1, −74% TNFα] and endothelial phenotypes [−80% CD31, −87% ET-1]. All $p < 0.05$.

Conclusion: The present pre-clinical study demonstrates for the first time the effectiveness, and the mechanism of action, of transplantation of human pluripotent stem cells as a treatment for advanced cirrhosis and portal hypertension. The results obtained open the possibility of evaluating the possible beneficial effects of human stem cells in patients with chronic liver disease.

PS-010

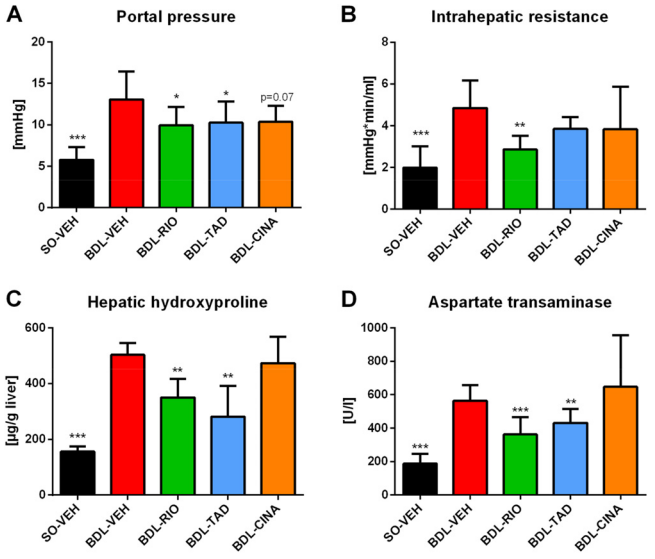
Targeting the nitric-oxide downstream pathway in bile-duct ligated rats to improve portal hypertension and liver fibrosis

K. Brusilovskaya[1,2], P. Königshofer[1,2], D. Lampach[1,2], A. Szodl[1,2], P. Supper[1,2], M. Trauner[1], T. Reiberger[1,2], P. Schwabl[1,2]. [1]*Medical University of Vienna, Div. of Gastroenterology and Hepatology, Dept. of Internal Medicine III, Vienna, Austria;* [2]*Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Vienna, Austria*
Email: philipp.schwabl@meduniwien.ac.at

Background and Aims: In cirrhotic livers the distorted nitric-oxide (NO) pathway worsens portal hypertension. We aimed to improve intrahepatic vasodilation and portal hypertension in cirrhotic rats by targeting the NO downstream pathway: soluble guanylate cyclase (sGC) – cyclic guanosine monophosphate (cGMP) – phosphodiesterase 5 (PDE5).

Method: 46 rats underwent bile-duct ligation (BDL) or sham operation. One week after surgery, animals received bidaily gavage of sGC-stimulator riociguat (RIO, 0.5 mg/kg), sGC-activator cinaciguat (CINA, 1 mg/kg), PFE5-inhibitor tadalafil (TAD, 1.5 mg/kg) or vehicle (VEH) for three weeks, respectively. Subsequently mean arterial pressure (MAP), heart rate (HR), portal pressure (PP), splanchnic blood flow, portal venous blood flow (PVBF) and intrahepatic resistance (PP/PVBF) were assessed and serum transaminases measured. Degree of hepatic fibrosis was quantified using chrome aniline blue (CAB) staining, hepatic hydroxyproline (HP) content and collagen expression. Intrahepatic cGMP levels and degree of inflammation (IL6, MCP-1) were assessed by PCR.

Results: BDL-VEH controls presented with portal hypertension (PP: 13.1 ± 3.3 mmHg) and liver cirrhosis. All treatments increased hepatic cGMP levels, especially RIO (+3.4-fold; p = 0.006). Both, RIO (9.9 ± 2.2 mmHg; p = 0.021) and TAD (10.2 ± 2.5 mmHg; p = 0.050) treated animals had significantly lower PP than BDL-VEH rats, whereas MAP and HR were not affected. In line, intrahepatic resistance decreased significantly in BDL-RIO animals (4.85 ± 1.3 vs. 2.86 ± 0.6; p = 0.005). Furthermore, livers of RIO (HP: 350 ± 66 vs. 503 ± 43 µg/g; p = 0.003/CAB: 2.1 ± 0.8 vs 4.2 ± 1.6%; p = 0.011) and TAD (HP: 281 ± 111 vs. 503 ± 43 µg/g; p = 0.003) treated rats had significantly less fibrosis compared to BDL-VEH controls. Hepatic collagen expression decreased by 50% in both groups. Significantly reduced levels of transaminases AST (RIO: −35%; TAD: −23%) and ALT (RIO: −32%; TAD: −27%) as well as less IL6 expression (RIO: −56%) indicated anti-inflammatory effects. In contrast, BDL-CINA rats suffered from toxic side effects. They presented with significant weight loss, increased lactate levels and a drop in MAP, without ameliorating hepatic hemodynamics, liver fibrosis or inflammation.



Conclusion: Increasing cGMP availability reduces intrahepatic resistance, decreases portal pressure and further improves liver fibrosis. sGC stimulators may be a potential treatment option for cirrhotic portal hypertension. Yet, pharmacokinetics in cirrhosis still need to be explored.

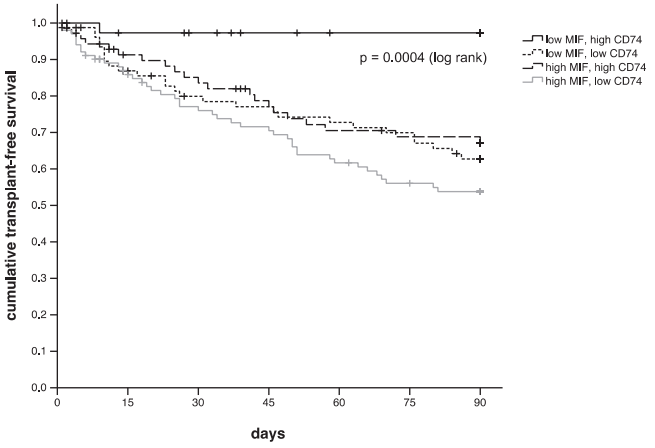
PS-011

Serum concentrations of Macrophage Migration Inhibitory Factor (MIF) and its soluble receptor CD74 predict transplant-free short-term survival in patients with acute decompensation of liver cirrhosis

T. Wirtz[1], N. Köse[2], B. Irina[1], B. Christina[3], P. Fischer[4], S. Stengel[2], Z.H. Wolfgang[3], K. Ingo[3], J. Bernhagen[5], C. Trautwein[4], A. Stallmach[2], M.-L. Berres[4], T. Bruns[2]. [1]*RWTH Aachen University Hospital, Medical Department III, Aachen, Germany;* [2]*Jena University Hospital, Department of Internal Medicine IV;* [3]*RWTH Aachen University Hospital, Institue of Human Genetics, Aachen, Germany;* [4]*RWTH Aachen University Hospital, Medical Department III;* [5]*University Hospital Munich, Institute for Stroke and Dementia Research*
Email: thwirtz@ukaachen.de

Background and Aims: Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine with chemokine-like functions and an important regulator of innate immune responses in different inflammatory diseases. We hypothesized that serum concentrations of MIF may indicate patients at risk of acute-on-chronic liver failure (ACLF) – a highly inflammatory multiple organ failure syndrome in decompensated cirrhosis.

Method: Concentrations of MIF and the shed form of its receptor (soluble CD74) were determined in sera from 292 German patients hospitalized for decompensation of cirrhosis with ascites, of which 78 (27%) had ACLF. Short-term mortality was prospectively assessed 90 days after inclusion. The MIF promoter polymorphisms G/C −173 and $(CATT)_{5-8}$ −794 were determined in DNA isolated from EDTA-blood using taqman genotyping PCR assays or fragment length analysis respectively.
Results: Although serum concentrations of MIF and sCD74 did not correlate with liver function parameters or ACLF, higher MIF (optimum cut-off >2300 pg/ml) and lower concentrations of sCD74 (optimum cut-off <66.5 ng/ml) both indicated poorer 90-days transplant-free survival in univariate Cox regression analyses (unadjusted HR 2.01 [1.26–3.22]; P = 0.004 for MIF; HR 0.59 [0.38–0.92]; P = 0.02 for sCD74) and after adjustment in multivariate models (Figure 1). Higher MIF concentrations correlated with higher surrogates of systemic inflammation (white blood cells, C-reactive protein). The investigated MIF promoter variants showed an association with sCD74 levels but did not correlate with short-term outcome.



Conclusion: Serum concentrations of Macrophage Migration Inhibitory Factor (MIF) and its soluble receptor CD74 increased 90-days transplant-free survival in patients with acute decompensation of cirrhosis. As this effect was independent of the investigated genetic predispositions and liver function but rather reflected systemic inflammation, MIF and sCD74 represent promising prognostic markers beyond classical scoring systems in patients at risk of ACLF.

PS-012
Oxidized albumin present in patients with decompensated cirrhosis triggers the inflammatory response in peripheral leukocytes through the p38 MAP kinase pathway

J.A. Quiles[1], M. Casulleras[1], K. Oettl[2], E. Titos[1,3], R. Flores-Costa[1], C. Lopez-Vicario[1], M. Duran-Güell[1], M. Pavesi[4], R.E. Stauber[5], V. Arroyo[4], J. Clària[1]. *[1]Hospital Clinic, Department of Biochemistry and Molecular Genetics; [2]Institute of Physiological Chemistry, Medical University of Graz, Center of Physiological Medicine, Graz, Austria; [3]CIBERehd; [4]EF-CLIF, Barcelona, Spain; [5]Division of Gastroenterology and Hepatology, Medical University of Graz, Department of Internal Medicine, Graz, Austria*
Email: jclaria@clinic.ub.es

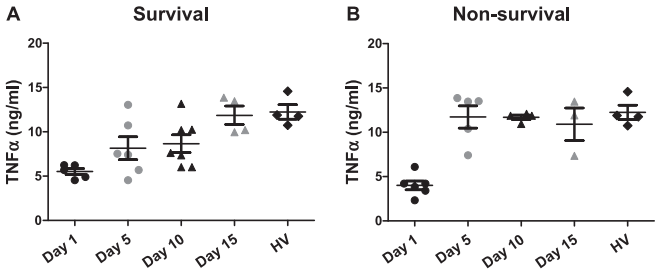
Background and Aims: Recent findings suggest that systemic inflammation characterized by increased levels of cytokines and oxidative stress plays a major role in the pathogenesis of ACLF in patients with decompensated cirrhosis. However, the endogenous factors triggering exacerbated inflammation in these patients remain unknown. Oxidation of circulating albumin to non-mercaptalbumin 1 (HNA1) and 2 (HNA2) is a common finding in cirrhosis. HNA1 and HNA2 have reduced binding capacity, lack the ability to effectively remove circulating toxic substances and are useful markers of oxidative stress in cirrhosis. Here, we examined whether in addition to these properties, HNA1 and HNA2 have the ability to activate innate immune cells and therefore to act as triggers of systemic inflammation in decompensated cirrhosis.
Method: The study included 48 healthy volunteers (HV), 41 patients with compensated cirrhosis and 153 patients with decompensated cirrhosis of whom 72 had ACLF. Levels and post-translational modifications of HNA1 and HNA2 were determined by HPLC and LC-qTOF/MS, respectively. Cell assays were performed in leukocytes, PBMCs and PMNs. Cytokine and eicosanoid levels in cell supernatants were measured by bead-based multiplex assays and LC-MS/MS, respectively. Gene expression was determined by real-time PCR. Kinase signaling pathways were determined by Proteome Profiler Human Phospho-Kinase Array Kit and validated by western blot.
Results: Plasma HNA1 and HNA2 levels increased in parallel with the severity of the disease and correlated very closely with markers of systemic inflammation (i.e. IL-6, IL-1β, TNF-alpha and IL-8) in patients with decompensated cirrhosis. Incubation of leukocytes with HNA1, which was characterized as a cysteinylated form of albumin, at concentrations in the range detected in patients with decompensated cirrhosis, resulted in increased IL-1beta, IL-6 and TNF-alpha mRNA and protein expression and enhanced release of eicosanoids (PGE_2, $PGF_{2\alpha}$, TXB_2 and LTB_4). Analysis of the Phospho-Kinase Array results revealed that HNA1 actions on leukocytes were associated with phosphorylation of the p38 MAP kinase.
Conclusion: Oxidized plasma albumin triggers inflammation in peripheral immune cells, providing a rationale for the removal and replacement of these oxidized albumin forms to efficiently prevent the development of organ failures in patients with decompensated cirrhosis.

PS-013
Lessons from ATTIRE feasibility study: differential inflammatory response profiles following treatment with albumin correlate with 6 months survival

N. Becares[1], S. Harmala[2], L. China[1], S.S. Skene[3], K. Bennett[3], Z. Shabir[3], A. O'brien[1]. *[1]University College London, Division of Medicine, London, United Kingdom; [2]University College London, Institute of Health Informatics, London, United Kingdom; [3]University College London, Comprehensive Clinical Trials Unit, London, United Kingdom*
Email: nbecares@gmail.com

Background and Aims: Infection is the most common cause of death in advanced liver disease secondary to immune suppression. We previously identified that circulating prostaglandin E2 (PGE2) was partly responsible for mediating immune suppression in acute decompensation/Acute-on-chronic liver failure (AD/ACLF) patients. Furthermore, albumin antagonised PGE2 effects and our single arm ATTIRE (Albumin to prevent infection in chronic liver failure) feasibility study of 79 patients at 10 sites demonstrated that 20% Human Albumin Solution (HAS) infusions improved immune function in AD/ACLF. Bacterial infections in AD/ACLF worsen 1 year mortality irrespective of liver disease severity and we therefore hypothesized that patients demonstrating a greater improvement in immune function following HAS would correlate with improved outcome.
Method: Immune function was assessed *ex-vivo* by treating human monocyte-derived macrophages (MDMs) with plasma samples randomly selected from the ATTIRE feasibility cohort corresponding to days 1 (pre-treatment), 5, 10 and 15 (end of trial) (n = 4–7) of participation, and measuring lipopolysaccharide-induced Tumour Necrosis Factor-alpha (TNFa) and Interleukin-10 production by ELISA. Plasma samples were divided *a priori* into two groups: those who died or survived during 6 months follow up at local NHS sites.
Results: There were no differences in clinical characteristics between groups pre-treatment; however, non-survivors developed increased nosocomial infections (36.7% vs 27.8%) and substantially

more renal dysfunction (26.7% vs 0%) during trial period. Our *ex-vivo* assay demonstrated worse immune function pre-treatment (day 1) in non-survivors (Fig. B) but unexpectedly showed a greater improvement at day 5 compared to survivors, with TNFa production reaching healthy levels (Fig. A). Moreover, PGE2 receptor antagonists improved immune function over the effect of HAS, irrespective of group (Fig. A,B). Lastly, non-survivors displayed significantly higher circulating C Reactive Protein (CRP) levels throughout trial period, consistent with an overall "hyper-inflammatory" phenotype.



Conclusion: Immune function was restored following HAS infusion to healthy levels by discharge in both survivors and non-survivors. Counter-intuitively, a more rapid improvement in immune function was associated with worse clinical outcome which was mirrored by a hyper-inflammatory phenotype in non-survivors, according to CRP levels. We have previously demonstrated lipid mediators profiling defined hyper/hypo-inflammatory profiles in AD/ACLF. This work is currently associative and future studies will investigate underlying molecular mechanisms and whether immune effects of HAS differ according to inflammatory profile.

PS-014

Acute-on-chronic liver failure is characterised by hepatocyte gasdermin D cleavage and release of the pro-inflammatory Damage Associated Molecular Pattern (DAMP) IL-α

U. Soffientini[1,2], N. Beaton[2], A. Habtesion[2], E. Weiss[3,4], V. Paradis[4], A. Nadar[2], N. Davies[2], R. Williams[1], S. Chokshi[1], R. Moreau[3,4], R. Jalan[2], G. Mehta[1,2]. [1]*Institute of Hepatology, Foundation for Liver Research, London, United Kingdom;* [2]*Institute for Liver and Digestive Health, UCL, London, United Kingdom;* [3]*INSERM, Centre de Recherche sur l'Inflammation, Paris, France;* [4]*Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France*
Email: gautam.mehta@ucl.ac.uk

Background and Aims: Acute-on-chronic liver failure (ACLF) displays systemic inflammation and non-apoptotic hepatocyte cell death. Gasdermin D (GSDMD) is a mediator of pyroptotic cell death. Upon cleavage, GSDMD forms pores in the cell membrane leading to cell death and release of DAMPs, such as IL-1α. The aim of this study was to determine if GSDMD cleavage and hepatocyte IL-1α release are features of ACLF in rodent models.
Method: Cirrhosis was induced in male C57BL mice by CCl4 gavage (0.5 ml/kg), and ACLF by LPS injection (2 mg/kg i.p). For validation experiments, cirrhosis was induced bile duct ligation (BDL) in Sprague-Dawley rats, and ACLF by LPS injection (0.03 mg/kg i.p). Experiments were terminated at baseline (control) or 4 hours (ACLF) following LPS injection (n = 7/group). Plasma ALT, creatinine and brain tissue water content were measured by standard techniques. GSDMD cleavage was assessed by Western blot (ratio cleaved:full-length). IL-1α expression was assessed by immunohistochemistry and ELISA. In vitro experiments were conducted on HepG2 cells, and immunofluorescence was performed using standard techniques.
Results: CCl4 + LPS mice show features of ACLF following LPS injection, with increased plasma ALT, creatinine and brain water at 4 hours compared to control. No positive immunostaining for IL-1α was seen at baseline, but following LPS multiple IL-1α positive hepatocytes are visible, consistent with cleavage of pro-IL-1α. A significant increase in hepatic mature IL-1α is noted in the CCL4 + LPS group at 4 hours compared to control (13.7 ± 3.5 *vs* 3.3 ± 0.3 pg/ml, $p < 0.05$). Importantly, no significant change in hepatic TNF-α or IL-1β was seen. A similar increase in mature IL-1α is seen in BDL + LPS at 4 hours compared to BDL control (21.7 ± 6.9 *vs* 0.2 ± 0.1 pg/ml, $p < 0.01$). Cleavage of hepatic GSDMD is seen in CCl4 + LPS at 4 hours compared to control (ratio: 7.7 ± 1.2 *vs* 2.1 ± 0.3, $p < 0.01$). Experiments in HepG2 cells demonstrate exposure to LPS in vitro also leads to GSDMD cleavage. Additionally, immunofluorescence demonstrates cytoplasmic IL-1α expression, which is reduced following LPS, consistent with GSDMD-mediated pore formation and IL-1α release.

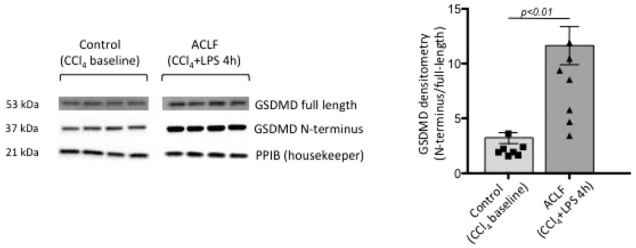


Figure: GSDMD cleavage in liver from control (CCl4 at baseline) and ACLF (CCl4+LPS) mice (n=7/group), presented as representative western blot *(left panel)* and densitometry of N-terminus:full-length GSDMD *(right panel)*.
Bar chart data are mean (SEM). Values compared with unpaired t-test.

Conclusion: This study demonstrates, for the first time, that ACLF is characterized by hepatocyte GSDMD cleavage, pore formation and release of the pro-inflammatory DAMP IL-1α. These findings suggest pyroptotic hepatocyte death as a key mechanism in ACLF, and support GSDMD and IL-1α as potential therapeutic targets in ACLF.

PS-015

Gut microbiome is profoundly altered in acute-on-chronic liver failure as evaluated by quantitative metagenomics. Relationship with liver cirrhosis severity

C. Sole[1,2,3], M. Llopis[2], E. Solà[2,4,5], K. Da Silva[6], S. Guilly[7], E. Le-Chatelier[6], P. Huelin[2,5,8], R. Moreira[2], M. Carol[2,9], G. De Prada[2,10], S. Ehrlich[6], I. Graupera[2,5,10], L. Napoleone[10,11,12,13], E. Pose[2,5,10], A. Juanola[10], N. Fabrellas[2,5,9], J. Doré[7], D. Ehrlich[7], P. Ginès[2,10,14]. [1]*Hospital Clinic Barcelona, Liver Unit;* [2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona;* [3]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Spain;* [4]*hospital Clinic Barcelona, Liver Unit, Barcelona;* [5]*centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Spain;* [6]*INRA (Institut national de la recherche agronomique), Unité MetaGenoPolis (MGP), Centre de recherche de Jouy-en-Josas, France;* [7]*iNRA (Institut national de la recherche agronomique), Unité MetaGenoPolis (MGP), Centre de recherche de Jouy-en-Josas, France;* [8]*Hospital Clinic Barcelona, Liver Unit;* [9]*Faculty of Medicine and Health Sciences, Universitat de Barcelona, Barcelona;* [10]*Hospital Clinic Barcelona, Liver Unit, Barcelona;* [11]*IDIBAPS, Barcelona, Spain;* [12]*University of Barcelona, Faculty of Medicine and Health Sciences, Barcelona, Spain;* [13]*CIBEReHD, Barcelona, Spain;* [14]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEReHD), Barcelona, Spain*
Email: csolem@clinic.ub.es

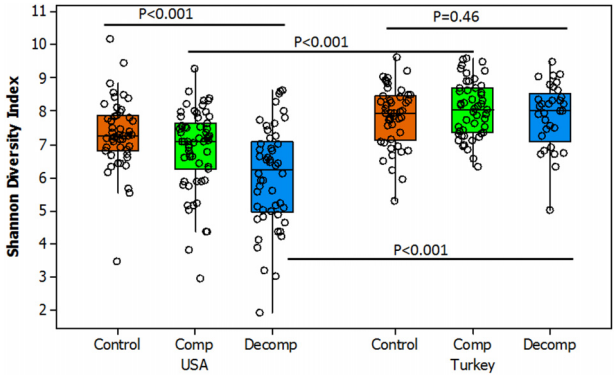
Background: Alterations in gut microbiome are common in human chronic diseases. Previous studies in patients with cirrhosis have shown a decreased gut microbial richness compared to healthy subjects. ACLF is the most severe clinical form of cirrhosis and is frequently associated with bacterial infections arising from endogenous flora. There is lack of information about gut microbiome alterations in ACLF using quantitative metagenomics.
Aims: To investigate the alterations in gut microbiome in a large series of patients with cirrhosis encompassing the whole spectrum of disease, from compensated (C), to acutely decompensated (AD) without ACLF, and ACLF.

Method: Stool samples were collected prospectively from 200 patients with cirrhosis: 35 C, 89 AD, and 76 ACLF. DNA extraction was performed using the Ion Proton sequencer for metagenomics characterization of complex microbial communities' composition. Microbial genes were grouped into clusters, denoted as metagenomic species (MGS), on the basis of their abundance profiles. Data was analyzed using non-parametric tests (Kruskal Wallis test or Dunn test), and Spearmans' correlations ($p < 0.01$).
Results: Overall, there was a significant loss of gene richness that correlated with disease stages. Gene richness was particularly low in patients with ACLF, independently of whether ACLF was present at hospital admission or developed during hospitalization. Reduced gene richness in ACLF appeared to be unrelated to antibiotic therapy. Two-hundred-and-ninety of the 1158 MGS detected contrasted between at least one disease stage. Interestingly, 44 MGS contrasted between AD and ACLF. The number of organ failures and MELD and Child-Pugh scores correlated positively with 3 MGS, basically from taxa that belong to *Enterococcus*. Unexpectedly, disease severity and organ failure also correlated with the finding of human DNA in stools.
Conclusion: Cirrhosis is characterized by marked alterations in gut microbiome that correlate with disease stage. Gene richness is strikingly reduced in the setting of ACLF. Enterococcus species correlate with disease severity, particularly with ACLF. The significance of the finding of homo sapiens DNA in stool samples of patients with cirrhosis, is uncertain but could be a marker of gut inflammation associated with disease severity, as shown by findings in inflammatory bowel disease.

PS-016
Diet affects gut microbiota and modulates hospitalization risk differentially in an international cirrhosis cohort

J.S. Bajaj[1], R. Idilman[2], L. Mabudian[3], M. Hood[3], A. Fagan[4], D. Turan[2], F. Karakaya[2], M. White[4], E. Gavis[4], D. Heuman[4], P. Hylemon[4], R. Atalay[5], R. Brown[3], M. Sikaroodi[3], P. Gillevet[3]. *[1]Virginia Commonwealth University and McGuire VAMC, Gastroenterology, Hepatology and Nutrition, Richmond, United States; [2]Ankara University School of Medicine, Gastroenterology, Ankara, Turkey; [3]George Mason University, Microbiome Analysis Center, Manassas, United States; [4]Virginia Commonwealth University and McGuire VAMC; [5]Middle East Technical University, Bioinformatics, Ankara, Turkey*
Email: jasmohan.bajaj@vcuhealth.org

Background and Aims: The relative ranking of cirrhosis-related deaths differs between high/middle-income countries. Gut microbiome is affected in cirrhosis and related to diet. However, analysis of differing dietary habits on gut microbiota and clinical outcomes is unclear.
Method: Outpatient compensated/decompensated cirrhotics and controls from Turkey and USA underwent dietary and stool microbiota analysis. Cirrhotics were followed till 90-day hospitalizations. Shannon diversity and multi-variable determinants of microbial diversity and hospitalizations were studied within/between groups.
Results: 296 subjects (157 USA:48 ctrls, 59 comp, 50 decomp, 139 Turkey:46 ctrls, 50 comp, 43 decomp) were included. Cirrhotics between cohorts had similar MELD scores (Table). American cirrhotics had more men, greater rifaximin/lactulose use and higher hepatitis C/alcohol etiologies. Coffee intake was higher in Americans while tea, fermented milk and chocolate intake were higher in Turkey ($p < 0.01$). The entire Turkish cohort had a significantly higher diversity than Americans, which did not change between their controls and cirrhotics (Figure). In contrast, diversity changed in the US-based cohort and was the lowest in decompensated patients. Coffee, tea, vegetable, chocolate and fermented milk intake predicted a higher diversity while MELD score, lactulose use and carbonated beverage use predicted a lower microbial diversity. The Turkish cohort had a lower risk of 90-day hospitalizations (Table). Coffee/tea and chocolate predicted lower 90-day hospitalization risk independent of cirrhosis severity (OR lactulose 3.84, MELD 1.15, coffee/tea 0.39, chocolate 0.33).



	USA (n = 157)				Turkey (n = 139)			
	All	Ctrl (n = 48)	Comp (n = 59)	Decomp (n = 50)	All	Control (n = 46)	Comp (n = 50)	Decomp (n = 43)
Age†		62 ± 14	61 ± 8	61 ± 7		42 ± 8	60 ± 10	60 ± 12*
Males†	121	27	48	46*	79	23	29	27
MELD		–	8.7 ± 2.9	12.6 ± 5.3*		–	8.4 ± 2.4	11.2 ± 3.5*
PPI Use	55	10	19	26*	46	8	17	31
Lactulose†	38	0	0	38	9	0	0	19
Rifaximin†	31	0	0	31	5	0	0	8
All-cause 90-day hospitalizations	29	0	9	20*	12	0	5	7*
Liver-related 90-day hospitalization	25	0	6	19*	10	0	3	7

†$p < 0.05$ between USA and Turkey, *$p < 0.05$ within same population

Conclusion: In this study of cirrhotic patients and healthy controls from USA and Turkey, a Mediterranean diet, along with coffee, tea and chocolate intake, is associated with a higher microbial diversity and an independently lower risk of 90-day hospitalizations.

Clinical management of hepatocellular carcinoma

PS-017
Personalized T cell therapy against HBV-related hepatocellularcarcinoma

A. Tan[1], T. Krishnamoorthy[2], N. Yang[3], D. Low[4], Y.L. Tham[1], A. Khakpoor[1], E. Felinska[1], V. Oei[1], R. Giri[1], Z.Z. Ho[5], H.K. Tan[2], R. Kumar[2], W. Hwang[6], E. Guccione[7], W.C. Chow[6], A. Bertoletti[1,3]. *[1]Duke-NUS Medical School, Emerging Infectious Diseases, Singapore, Singapore; [2]Singapore General Hospital, Department of Gastroenterology & Hepatology, Singapore, Singapore; [3]Singapore Institute for Clinical Sciences (SICS), Singapore, Singapore; [4]Institute of Molecular and Cell Biology (IMCB), Singapore, Singapore; [5]Lion TCR Pte. Ltd., Singapore, Singapore; [6]Singapore General Hospital, Department of Haematology, Singapore; [7]Institute of Molecular and Cell Biology, Agency for Science, Technology and Research, Singapore*
Email: anthony.tan@duke-nus.edu.sg

Background and Aims: Short HBV-DNA fragments are frequently integrated in HBV-related hepatocellularcarcinoma (HCC). We hypothesized that the HBV transcriptomic profile detected in HCC can guide the correct selection of HBV-specific T cell receptors (TCR) used to engineer T cells for HCC targeted immunotherapy in patients.

Method: HBV-DNA integrants in HCC cell lines were characterized using targeted re-sequencing of the HBV transcriptome and HBV-specific Nanostring probes. TCRs specific for different HBV epitopes was introduced in lymphocytes through mRNA electroporation. These cells were tested in vitro for HCC recognition or adoptively transferred in a liver transplanted patient with HBV-related HCC metastases in the lungs. Clinical parameters and imaging of HCC were evaluated longitudinally.
Results: We first test whether short integrated HBV fragments can produce HBV epitopes recognized by CD8 T cells. Expression of short specific HBV regions was characterized in natural HBV-related HCC lines negative for serological markers of HBV infection. We demonstrated the functional presentation of the HBV epitope encoded within the integrated sequences. We then analyzed the profile of integrated HBV-DNA fragments in the primary HCC of a liver transplant patient with HBsAg negative HCC relapses in the lungs. We detected the presence of mRNA coding for a short region of the HBV envelope and we engineered the patient's lymphocytes with a HBV-specific TCR specific for this region. Multiple adoptive transfers of engineered HBV-specific TCR T cells were performed over a 6 months period as a therapy for HCC relapses. No therapy-related adverse events were observed. CT imaging performed before and during therapy showed an objective positive response with a volumetric reduction of nearly all lung lesions detected without new lesions in the lung or liver till date.
Conclusion: HCC cells serologically negative for HBV-antigen can be lysed in vitro by T cells engineered with HBV-TCR specific for HBV epitopes originating from short HBV-DNA fragments detected in the HCC. Thus HBV DNA integration profile of tumour cells can guide personalized T cell adoptive immunotherapy of patients with HBV-related HCC. Therapy with T cells engineered with HBV-specific TCRs selected with this criteria demonstrated objective signs of clinical effectiveness.

PS-018
Role of 99mTc-Macroaggregated Albumin SPECT/CT based dosimetry in predicting survival and tumor response of patients with locally advanced and inoperable hepatocellular carcinoma (HCC) treated by selective intra-arterial radiation therapy (SIRT) with yttrium-90 resin microspheres, a cohort from SARAH study

A.-L. Hermann[1], A. Dieudonné[2], R. Maxime[1], S. Manuel[2], P. Helena[3], C. Gilles[3], C. Laurent[4], L. Rachida[2], V. Vilgrain[1], S.T. Group[5]. *[1]Hôpital Beaujon, Radiology, Clichy, France; [2]Hôpital Beaujon, Nuclear Medicine, Clichy, France; [3]Hôpital Européen Georges Pompidou, URC-Biostatistical Unit, Paris Cedex 15, France; [4]Hôpital Beaujon, Hepatology, Clichy, France; [5]Hôpital Beaujon, Radiology, Paris, France*
Email: annelaure.hermann@gmail.com

Background and Aims: To assess the role of 99mTc-MAA SPECT/CT based dosimetry in predicting survival and tumour response of patients with locally advanced and inoperable HCC treated by SIRT with yttrium-90 resin microspheres.
Method: Among the 184 patients from the SARAH trial who received SIRT, 121 and 109 were included in the survival and tumour response analysis respectively, according to available dosimetric/tumour response data. All exams (baseline CT, MAA-SPECT/CT and Y90 SPECT/PET) were centralized and reviewed. Tumour-absorbed-dose was computed using MAA-SPECT/CT. Visual agreement between MAA and baseline CT, and between MAA and Y90 imaging were assessed with a 3-points scale (good, acceptable, and poor). Overall survival (OS) was evaluated using Kaplan-Meier tests. Tumour response was assessed on follow-up CT performed 6 months after the treatment, using RECIST 1.1. The predictive role of tumour-absorbed-dose on OS and tumour response was assessed.
Results: Median OS of the entire cohort was 9.3 months (95% CI 6.7–10.7). The median tumour-absorbed-dose was 112.2 Gy (IQR 67.8–220.0). Patients who received ≥100 Gy (n = 67) had significantly longer survival (median 14.1 months (95% CI 9.6–18.6) vs. 6.1 months (95% CI 4.9–6.8) in patients receiving <100 Gy, p < 0.0001). Among them, those with a good visual agreement (n = 24) had the longest median OS (24.9 months 95% CI 9.6–33.9). Objective response (OR) and disease control (DC) rates were 20.5% and 63.7%. DC was significantly associated with higher tumour-absorbed dose (median 121.4 Gy (IQR 86.0–189.8) vs. 85.1 Gy (IQR 58.4–164.3) in non-DC patients, p = 0.0204), while OR was not (median 133.4 Gy (IQR 76.2–238.1) vs. 103.6 Gy (IQR 72.0–174.7) in non-OR patients, p = 0.2). Among DC patients who received ≥100 Gy, those with a good visual agreement (m = 31 treatments) had the highest DC rate (70.5%).
Conclusion: Tumour-absorbed dose computed on MAA-SPECT/CT is significantly associated with overall survival and disease control. The best OS and DC rates were observed in patients who had both ≥100 Gy and good visual CT-MAA-Y90 agreement.

PS-019
Pattern of progression determines post-progression survival in patients with hepatocellular carcinoma treated with Radioembolization

C. Jordan[1], M. de la Torre[1], A.C. Gardini[2], J.I. Bilbao[3], M. Rodriguez-Fraile[4], L.S. Rodriguez[4], D. D'avola[5], M. Iñarrairaegui[5], J.I. Herrero[5], J. Quiroga[5], B. Sangro[5]. *[1]Liver Unit, Pamplona, Spain; [2]Medical Oncology, Meloda, Italy; [3]Radiology, Pamplona, Spain; [4]Nuclear Medicine, Pamplona, Spain; [5]Liver unit and CIBEREHD, Pamplona, Spain*
Email: mdalaez@unav.es

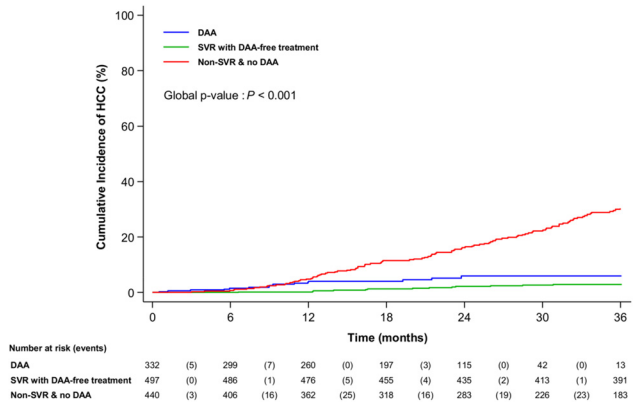
Background and Aims: In patients with hepatocellular carcinoma (HCC) treated with sorafenib, post-progression survival (PPS) is influenced by multiple variables, including the pattern of disease progression. Our objective was to assess the influence of patterns of progression in the PPS in patients with HCC treated with radioembolization (RE).
Method: Patients treated with RE between 1998 and 2015 were identified and those in BCLC-A stage with a nodule <5 cm or BCLC-C with metastasis to the lymph nodes were excluded. Patients were classified in 4 groups according to the pattern of progression: growth of treated lesions (gTL), growth of untreated lesions (gUTL), new intrahepatic disease (nIHD) or new extrahepatic lesions or vascular invasion (nEHD). Overall survival (OS, time from RE until death or last follow-up visit) and PPS (time from progression until death or last follow-up visit) were plotted using Kaplan-Meier method and compared by log-rank test. PPS and OS are expressed as median [95%CI]. A Cox regression was built to verify if pattern of progression was an independent prognostic factor.
Results: Out of 113 patients treated with RE that met the inclusion criteria, 77 had disease progression after a median follow-up of 14 months. Patterns of progression were gTL (n = 19), gUTL (n = 9), nIHL (n = 23) or nEHD (n = 26). OS in the entire cohort was 15.0 months [11.35–18.65] and PPS was 6.0 months [2.79–9.20]. PPS was similar in patients with nIHD (5.0 months [2.74–7.25]) or nEHD (4.0 months [1.20–6.79]), p = 0.42. Likewise, PPS was similar in patients with gTL (9 months [7.04–10.95]) or gUTL (15.0 months [12.34–17.65]), p = 0.74. Patients with growth of treated or untreated hepatic lesions (gHL) had a PPS of 12 months [7.10–16.89] that was significantly longer than the 4 months [2.20–5.79] of patients with new lesions inside or outside the liver (nL), p = 0.019. This classification of pattern of progression retained an independent prognostic value for PPS (HR: 2.96 95%CI: 1.6–5.47) in a multivariate model adjusted by ALBI grade and neutrophil to lymphocyte ratio. Time to progression in the gTL group (14.0 months [6.97–21.03] was significantly longer than that in the nEHD group (5.0 months [1.80–8.99]; p = 0.018) and the nIHD group (4.0 months [2.17–5.83], p = 0.48), while it was lowest for the gUTL group (2.0 months [0–4.77].
Conclusion: In a cohort of patients with HCC treated with RE, progression in the form of new intra- or extra-hepatic lesions was an independent prognostic factor of PPS.

PS-020

Lower compliance to prior HCC surveillance and liver function impairment explain the apparent higher HCC incidence under direct antivirals in HCV compensated cirrhotic patients: the French multicenter prospective ANRS CO12 CirVir cohort experience

P. Nahon[1], L. Richard[2], B. Valerie[1], C. Carole[3], M. Patrick[4], D. Guyader[5], P. Stanislas[6], D. Larrey[7], R. Francoise[2], E. Audureau[2]. *[1]APHP, Jean Verdier Hospital, Hepatology, Bondy, France; [2]APHP, Henri Mondor Hospital, Biostaisitcs, Créteil, France; [3]ANRS, Paris, France; [4]Hôpital Beaujon, Hépatologie; [5]Rennes Hospital, Hepatology, Renns, France; [6]APHP, Cochin Hospital, Hepatology, Paris, France; [7]Montpellier Hospital, Hepatology, Montpellier, France*
Email: pierre.nahon@jvr.aphp.fr

Background and Aims: This study aimed to accurately assess the incidence of HCC under and following DAAs therapy in patients with compensated cirrhosis included in the French prospective multicentre ANRS CO12 CirVir cohort as well as possible confounders.
Method: Data were collected from 1269 patients with compensated biopsy-proven HCV-cirrhosis recruited between 2006 and 2012 in 35 centres and currently prospectively followed-up, including clinical and biological features at baseline and achievement of a sustained virological response (SVR) during the study period. Patients were classified into 3 groups: patients who experienced DAAs (DAAs group, n = 332, T0 = date of DAAs treatment), patients who achieved SVR following interferon-based regimen (SVR-inf group, n = 497, T0 = date of interferon therapy treatment allowing SVR), non-SVR patients who never experienced DAAs (non-SVR group, n = 440, T0 = inclusion).
Results: During a median follow-up of 67.5 months, 749 (59%) patients achieved SVR. As compared to SVR-inf group, DAA patients were older (59.2 yrs vs 55.5 yrs, p < 0.0001), had higher rates of diabetes (24.9% vs 16.3%, p = 0.002), higher rates of baseline endoscopic portal hypertension (17.3% vs 35.5%, p < 0.0001) and lower platelet count (132/mm^3 vs 156/mm^3, p < 0.0001) and although compensated had a more impaired liver function [prothrombin time: 85% vs 91%, albuminemia: 40.2 g/l vs 43 g/l, bilirubin: 13 µmol/l vs 10 µmol/l, all p < 0.0001). During follow-up (fu), 200 (15.7%) patients developed HCC [DAAs group: 15 (4.5%), fu = 21.2 months), SVR-inf group: 30 (6.0%), fu = 63.0 months), non-SVR group: 155 (35.2%), fu = 42.5 months), p < 0.0001 for fu]. Corresponding HCC 3 yrs-cumulative incidences (CumI) were 6.0% vs 2.9% vs 30.3% respectively (global p < 0.0001, DAAs vs SVR-inf: HR = 2.46 [1.18; 5.11], P = 0.01, see Figure). Median rates of performed screening procedures were 81% in patients who developed HCC under DAAs vs 100% in the two other groups (p < 0.0001). In multivariate analysis DAAs intake was not associated with a higher risk of HCC occurrence. To account for indication biases and characteristics of patients, we used IPTW method. This approach confirmed the absence of deleterious effect of DAAs on HCC occurrence.



Conclusion: Although characterized by a shorter follow-up, compensated HCV cirrhotic patients experiencing DAAs have a lower HCC incidence as compared to non-SVR patients. An initial two-fold increase is observed as compared with patients who achieved SVR following interferon-based regimen, but can be explained by the phenotype of patients receiving DAAs encompassing older age, higher rates of comorbidities, impaired liver function and lower compliance to HCC surveillance prior to DAAs intake. These results do not support alarming reports suggesting higher risk of HCC following DAAs therapy.

PS-021

Post-treatment liver stiffness measurement is not useful to predict hepatocellular carcinoma in HCV patients who achieve SVR

S. Shili[1], S. Giovanna[2], J. Foucher[1], V. Anne[2], H. Jean-Baptiste[1], M. Francois[2], F. Chermak[1], P.-H. Bernard[1], V. De Ledinghen[1,3], C. Hezode[2,4]. *[1]Haut Leveque Hospital CHU Bordeaux, Hepatology, France; [2]CHU Créteil, Hepatology, France; [3]University of Bordeaux, France; [4]University of Créteil, France*
Email: sarah.shili@chu-bordeaux.fr

Background and Aims: The risk of development of hepatocellular carcinoma (HCC) persists in HCV patients who achieve a sustained virological response (SVR) after direct acting antiviral (DAA) treatment. Some predictors have been determined but the impact of the liver stiffness measurement (LSM) evolution between baseline and the post-treatment period on the occurrence of HCC is unknown. The aim of this study was to prospectively assess the role of LSM and its evolution for predicting the risk of HCC in HCV patients with SVR after DAA therapy.
Method: Patients were included in two French centers between May 2008 and November 2016. All consecutive patients treated with DAA and without prior history of HCC were included. LSM was assessed with the FibroScan® device before treatment and at least once during follow-up (12–24 and/or 48 weeks after the end of treatment). Delta-LSM was defined as LSM during follow-up – LSM at baseline. Patients were screened every six months for HCC using ultrasound and HCC occurrence during and after the treatment were considered.
Results: 849 patients (male 52.3%; median age: 61 years; genotype 3 14.7%; diabetes 15.9%; LSM ≥ 12 kPa 41.9%) were included. 799 of them (94.1%) achieved SVR. Median [Q1-Q3] LSM (kPa) was 10.9 [7.9–18]; 8.5 [5.5–16.6]; and 7.0 [5.0–13.9] at baseline, end of treatment, and the latest follow-up, respectively. Median decrease was −3.6 [−6.2- −1.1]kPa. For a median follow-up of 5 months [3–10], four patients died and 30 (3.5%) developed HCC in a median time of 5 [3–10] months. In the univariate analysis, delta LSM was associated with HCC (Hazard ratio [95% confidence interval] = 0.95 [0.91–0.99] per kPa, p = 0.01). In multivariate analysis, factors independently associated with the risk of HCC were age (1.05 [1.02–1.09] per year, p = 0.002), diabetes (3.03 [1.46–6.28], p = 0.003) and baseline LSM (1.05 [1.03–1.06] per kPa, p < 0.0001; HR = 2.5 [0.3–24] for patients with baseline LSM between 8 and 12 and HR = 14.0 [1.9–103.9] for patients with baseline LSM >12, compared to patients with baseline LSM < 8). After adjustment for baseline LSM, delta LSM was no longer associated with HCC (p = 0.50).
Conclusion: The risk of HCC is associated with age, diabetes and high LSM at baseline in patients with SVR after DAA. LSM decreases after SVR but its evolution is not independently associated with the risk of HCC. Post-treatment LSM should not be used to predict HCC in HCV patients with SVR.

PS-022

Efficacy and safety of REGORAFENIB in real life in the treatment of hepatocellular carcinoma. Multicenter experience

M. Fraile[1], M.T. Ferrer[2], A.M. Matilla[3], J.L. Lledó[4], B. Minguez[5], A. Hernandez[6], C. Perelló[7], J. Fernández-Castroagudín[8], C.R. de Lope[9], M.D.E. Aguilar[10], S. Montoliu[11], M. Sala[12], M. Romero-Gutiérrez[13], S. Pascual[14], J.J. Urquijo[15], D.E.M. Arraez[16], M.J.B. Rodriguez[17], M. Varela[1]. [1]*Hospital Universitario Central de Asturias, Liver Unit, Oviedo, Spain;* [2]*Hospital Universitario Virgen del Rocío, Liver Unit, Sevilla, Spain;* [3]*Hospital General Universitario Gregorio Marañón, Liver Unit, Madrid, Spain;* [4]*Hospital Universitario Ramón y Cajal., Liver Unit, Madrid, Spain;* [5]*Hospital Universitari Vall d'Hebron., Liver Unit, Barcelona, Spain;* [6]*Hospital General Universitario de Ciudad Real. Liver Unit, Ciudad Real, Spain;* [7]*Hospital Universitario Puerta de Hierro. Majadahonda, Liver Unit, Majadahonda, Madrid, Spain;* [8]*Complexo Hospitalario Universitario de Santiago, Liver Unit, Santiago de Compostela, Spain;* [9]*Hospital Universitario Marqués de Valdecilla., Liver Unit, Santander, Spain;* [10]*Hospital Virgen de las Nieves., Liver Unit, Granada, Spain;* [11]*Hospital Universitari de Tarragona Joan XXIII, Liver Unit, Tarragona, Spain;* [12]*Hospital Universitari Germans Trias i Pujol. Badalona, Liver Unit, Badalona, Barcelona, Spain;* [13]*Complejo Hospitalario Universitario de Toledo., Liver Unit, Toledo, Spain;* [14]*Hospital General Universitario de Alicante., Liver Unit, Alicante, Spain;* [15]*Hospital General Universitario de Valencia., Liver Unit, Valencia, Spain;* [16]*Hospital Universitario de Canarias, Liver Unit, Santa Cruz de Tenerife, Spain;* [17]*Hospital de Jerez, Liver Unit, Jerez de la Frontera, Cádiz, Spain*
Email: maria.varela.calvo@gmail.com

Background and Aims: Regorafenib (REGO) improves survival of hepatocellular carcinoma (HCC) in 2nd line after sorafenib (SOR). Patients with dermatological adverse effects >grade 2 in the first 60 days with SOR (DAE60) have greater survival (Reig et al., J Hepatol 2014). Finally, appearance of hand-foot syndrome (HFS) with REGO has a positive impact on survival (Merle et al., ILCA Congress 2017). AIMS: (1) to describe applicability, adverse effects (AE) and radiological response at 3 months of REGO in real life; (2) to asess if DAE60 with SOR is predictor of HFS with REGO.
Method: 65 patients (17 centres) were prospectively recruited: 58 with REGO indicated after SOR (group A); 3 after SOR and nivolumab (3rd line) (group B); 4 in post-transplant setting (group C).
Results: GROUP A: applicability 83%: 7 hasn't received REGO for symptomatic progression, 3 for lack of authorization. In the remaining 48: median age 64 yr, 79%men, etiology (%): 27 alcohol, 46 HCV, 10 HBV, 8 NAFLD. At diagnosis all were asymptomatic, Child A 89%, BCLC 0/A 39.6%, BCLC-B 39.6%, BCLC-C 20.8%. Tolerance to SOR estimated by final dose: full dose 70.8%, 600 mg 4.2%, 400 mg 25%. Median duration of REGO 3 months ($P_{25}P_{75}$ 1-6). 45.8% had DAE60, associated with non-significant greater survival from the start of SOR: mean 42.9 (95% CI 30.4–55.5) vs 28 months (95% CI 19.5–37.2), p = 0.052. The sensitivity, specificity, positive predictive value and negative predictive value of DAE60 to predict HFS with REGO were 89%, 80%, 73% and 92% respectively. Initial radiological evaluation was available in 28 cases: 35.7% (n = 10) presented absence of progression. Median survival from the start of SOR (SOR + REGO) was 15 months (P_{25}-P_{75} 10–22) and from diagnosis of HCC 28.4 months (P_{25}-P_{75} 20–43). Absence of symptoms at the beginning of SOR was the only predictor of higher survival: ECOG PS 0(n = 54) median 21 months, mean 41.9 (IC95% 26.1–57.7) vs ECOG PS 1(n = 4), mean 6.7 months (IC95% 0.0–14.8), p = 0.026. GROUP B: applicability 33%, scarce number of patients and short follow-up to draw conclusions. GROUP C: the most frequent AEs were asthenia, anorexia and diarrhea. None with HFS in the post-transplant setting.
Conclusions: In real life, REGO delays initial radiological progression of HCC in more than a third of patients. Absence of DAE60 with SOR predicts absence of HFS with REGO in 92% of cases, which can be useful when we have alternative 2nd line treatments.

PS-023

Pathological characteristics and early post-hepatic-resection outcome of patients with hepatocellular carcinoma occurred after hepatitis C treatment with new direct-acting antivirals: a multicenter cohort study

A. Vitale[1], F.P. Russo[1], C. Sposito[2], A. Cucchetti[3], G.B.L. Sandri[4], S. Gruttadauria[5], S. DI Sandro[6], D. Ghinolfi[7], D. Nicolini[8], F. Trevisani[3]. [1]*Department of Surgery, Oncology and Gastroenterology, University of Padua, Padua, Italy;* [2]*General Surgery and Liver Transplantation Unit, University of Milan and Istituto Nazionale Tumori (National Cancer Institute), IRCCS, Italy;* [3]*Department of Medical and Surgical Science, Semeiotica Medica, University of Bologna, Bologna, Italy;* [4]*Division of General Surgery and Liver Transplantation, San Camillo Hospital, Rome, Italy, Rome, Italy;* [5]*Mediterranean Institute for Transplantation and Specialization Therapies (IRCCS-ISMETT), Palermo, Italy;* [6]*Division of General Surgery and Abdominal Transplantation, ASST Grande Ospedale Metropolitano Niguarda, 20162 Milan, Italy;* [7]*Hepatobiliary Surgery and Liver Transplantation, University of Pisa Medical School Hospital, Italy;* [8]*Hepato-Biliary and Abdominal Transplantation Surgery, Polytechnic University of Marche, A.O.U. "Ospedali Riuniti", Ancona, Italy*
Email: alessandro.vitale@unipd.it

Background and Aims: There are no studies evaluating the pathological characteristics of recurrent or naïve hepatocellular carcinoma (HCC) occurring after anti-hepatitis-C (HCV) therapy with direct-acting antivirals (DAAs). Moreover, the early postoperative outcome of these HCC patients after hepatic resection is unknown.
Method: Prospectively collected data from 420 consecutive patients with HCC and HCV cirrhosis undergoing liver resection in 18 Italian hepato-biliary surgical units between January 2014 and December 2016 were analysed. Seventy-seven patients (18.3%) who develop recurrent or de novo HCC after DAAs therapy represented the study group, while the remaining 343 HCC patients formed the control group. The aim of this study was to compare these two groups in terms of pathological characteristics (primary endpoint) and early postoperative outcome (secondary endpoint). Inverse probability of treatment weighting (IPTW) was used to balance the preoperative characteristics of the two groups for the evaluation of the secondary endpoint.
Results: Primary endpoint (pathological characteristics): the study group showed significantly smaller tumors than the control group (25 mm vs. 35 mm), while no significant differences were found in terms of numbers of nodules, grading, micro and macro vascular invasion, and satellitosis. De novo/recurrent HCC and sustained viral response at resection variables did not influence this result.
Secondary endpoint (early postoperative outcome): after IPTW, the 2 groups became well-balanced for most baseline characteristics including patient's age, performance status, comorbidities, tumor radiological features, alpha-fetoprotein level, severity of underlying liver disease, and extension of liver resection. Patients in the study group showed a significantly lower incidence of severe (Clavien score >2) complications (3.4% vs. 9.3%) and early (within 6 months) postoperative mortality (2.0% vs 5.4%) than those in the control group. SVR patients in the study group (71%) reached a 0% postoperative mortality.
Conclusion: DAAs therapy doesn't seem to modify the biological aggressiveness of recurrent or de novo HCCs undergoing liver resection. Conversely, DAAs therapy significantly improves the early postoperative outcome of these patients. This benefit may be expected after all loco-regional therapies for HCC.

PS-024

Hepatic safety and biomarker assessments in sorafenib-experienced patients with advanced hepatocellular carcinoma treated with nivolumab in the CheckMate-040 study

T. Meyer[1], I. Melero[2,3], T. Yau[4], C. Hsu[5], M. Kudo[6], S.-P. Choo[7], J. Trojan[8], T. Welling[9], Y.-K. Kang[10], W. Yeo[11], A. Chopra[12], A. Baakili[13], C.D. Cruz[13], H. Zhao[13], J. Neely[13], T. Crocenzi[14], A. El-Khoureiry[15], B. Sangro[16]. [1]*Royal Free Hospital, London, United Kingdom;* [2]*Clinica Universidad de Navarra and CIBERONC, Pamplona, Spain;* [3]*Center for Applied Medical Research (CIMA), Pamplona, Spain;* [4]*University of Hong Kong, Hong Kong, Hong Kong;* [5]*National Taiwan University Hospital, Taipei, Taiwan;* [6]*Kindai University Faculty of Medicine, Osaka, Japan;* [7]*National Cancer Center, Singapore, Singapore;* [8]*Goethe University Hospital and Cancer Center, Frankfurt, Germany;* [9]*NYU Langone Health, New York, United States;* [10]*Asan Medical Center, University of Ulsan, Seoul, Korea, Rep. of South;* [11]*Chinese University of Hong Kong, Hong Kong, Hong Kong;* [12]*Johns Hopkins Singapore International Medical Centre, Singapore, Singapore;* [13]*Bristol-Myers Squibb, Princeton, United States;* [14]*Providence Cancer Center, Portland, United States;* [15]*USC Norris Comprehensive Cancer Center, Los Angeles, United States;* [16]*Clinica Universidad de Navarra and CIBEREHD, Pamplona, Spain*
Email: t.meyer@ucl.ac.uk

Background and Aims: The majority of patients (pts) with advanced HCC (aHCC) progress on sorafenib (sor) therapy. Nivolumab (NIVO) is a fully human anti–PD-1 IgG4 mAb that demonstrated durable responses, manageable safety, and long-term survival in pts with aHCC in CheckMate-040 (El-Khoueiry AB, Sangro B, et al. *Lancet* 2017). Here we present updated hepatic safety and biomarker analyses in sor-experienced (sor-exp) pts with aHCC in CheckMate-040.

Method: Sor-exp pts with or without chronic viral hepatitis received NIVO 3 mg/kg Q2W in the dose-expansion phase (EXP) regardless of PD-L1 status. Primary endpoint was objective response rate (ORR) reported by blinded independent central review using RECIST v1.1 (EXP). Secondary endpoints included overall survival (OS), disease control rate (DCR), and safety. Exploratory analyses of on-treatment HCV and HBV viral kinetics and alpha-fetoprotein (AFP) levels were performed.

Results: Median duration of follow-up was 14.9 mo in sor-exp pts (N = 145), 132 (91%) of whom had progressed on sor. Baseline Child-Pugh scores of 5 or 6 and extrahepatic metastases were observed in 99% and 71% of pts, respectively. The ORR with NIVO was 14%; the DCR was 56%; median OS was 15.6 mo. Any-grade and grade 3–4 hepatic treatment-related AEs (TRAEs) occurred in 12 (8%) and 5 (3%) pts, respectively; 100% of grade 3–4 hepatic TRAEs resolved. Frequencies of grade 3–4 treatment-related ALT/AST elevations were 2–3%. No drug-related deaths due to hepatic AEs occurred, and no new safety signals were observed. Among HBV-infected pts, 8% (3 of 38) had a >1 log decrease in HBsAg, and 12% (5 of 41) had a >1 log increase in HBV DNA. HBV DNA increases did not result in changes in hepatic parameters or serious AEs. Among HCV-infected pts, 30% (8 of 27) had a >1 log decrease in HCV RNA. Median baseline AFP in responders (165 µg/L) and nonresponders (85 µg/L) was similar ($p = 0.5898$). For pts with baseline AFP ≥10 µg/L, on-treatment AFP declines >1 log occurred in 94% of responders and 10% of nonresponders. Updated data will be presented.

Conclusion: NIVO demonstrated long-term survival and objective responses across etiologies in sor-exp pts with aHCC. The manageable safety profile of NIVO, including immune-mediated and hepatic AEs, was consistent with other tumor types in which NIVO is approved. NIVO had limited impact on viral kinetics in HBV and HCV-infected pts. Responses occurred irrespective of baseline AFP levels, and AFP declines were associated with response.

HBV Cure: Pre-clinical studies

PS-025

Combinatorial RNAi/vaccination therapy for chronic hepatitis B achieves long-term functional cure in preclinical mouse model

T. Michler[1], A. Kosinska[1], T. Bunse[1], M. Heikenwälder[2], D. Grimm[2], S. Milstein[3], L. Sepp-Lorenzino[3], U. Protzer[1]. [1]*Virology, Technische Universität/Helmholtz Zentrum München;* [2]*Department of Infectious Diseases/Virology, Heidelberg University;* [3]*Alnylam Pharmaceuticals, Cambridge*
Email: thomas.michler@tum.de

Background and Aims: Hepatitis B Virus (HBV) persistence was found to correlate with a failure to develop an efficient virus-specific T cell response due to high HBV antigen load. We evaluated the capacity of stabilized, liver-targeted siRNAs to (i) suppress HBV gene expression, (ii) allow recovery of HBV-specific B- and T cell responses spontaneously or (iii) after therapeutic vaccination.

Method: High viremic HBV-transgenic or C57/Bl6 mice transduced with an Adeno-Associated Virus (AAV)-HBV vector were treated with nucleoside analogue Entecavir (ETV), shRNA-expressing AAV (AAV-shHBV) or *N*-Acetylgalactosamine (GalNAc)-conjugated siRNAs. B and T cell immunity were monitored following therapeutic vaccination with a HBV core (HBc) and surface (HBs) protein prime vaccination and a Modified Vaccinia Ankara virus (MVA)-boost immunization (TherVacB).

Results: RNAi by monthly s.c. injections of 3 mg/kg GalNAc-siRNA or 1×10^{11} geq AAV-shHBV i.v. suppressed serum HBsAg and HBV DNA by 2–3 $\log_{10}$ and HBeAg by >1 $\log_{10}$. ETV reduced viremia by 4 $\log_{10}$ but antigen levels remained unchanged. TherVacB induced HBV-specific B-cell immunity and CD4 T cell responses independent of antigen levels, but HBV-specific CD8 T cell responses were only seen in animals with reduced antigen levels after RNAi. Induction of CD8 T cell responses coincided with suppression of HBV replication in the liver to levels undetectable by Southern blot or PCR. To evaluate if the combinatorial RNAi/vaccination therapy could achieve long-term control of HBV replication and functional cure, C57/Bl6 mice were transduced with 2×10^{11} geq AAV-HBV to establish high-titer, persistent HBV replication. 3 monthly doses of GalNAc-siRNAs followed by therapeutic vaccination using TherVacB reduced HBsAg and HBeAg to levels below the detection limit by 5 and 4 $\log_{10}$, respectively, and triggered seroconversion to anti-HBs and anti-HBe. Control of HBV replication was maintained for >5 months after the last siRNA dose. Mild, but long-term ALT elevation was observed after start of vaccination lasting until the siRNA effect had ceased. This suggests that by reducing antigen expression, siRNA therapy could mitigate killing of hepatocytes by CD8 T cells and thereby could attenuate liver damage.

Conclusion: We developed a combinatorial RNAi/therapeutic vaccination therapy for hepatitis B that is achieving long-term functional HBV cure in a preclinical mouse model, suggesting potential for clinical translation.

PS-026

Novel and potent HBV capsid modulator reduces HBeAg and cccDNA in core site directed T109I mutant in HepNTCP cells

L. Bassit[1], B. Cox[1], S.K. Ono[2], K. Verma[1], J. Yoon[1], F. Amblard[1], R.F. Schinazi[1]. [1]*Center for AIDS Research, Emory University School of Medicine, Atlanta, GA, USA, Pediatrics: Laboratory of Biochemical and Pharmacology;* [2]*University of São Paulo School of Medicine, Gastroenterology, Sao Paulo, Brazil*
Email: rschina@emory.edu

Background and Aims: A major barrier towards eradication of HBV in chronically infected individuals is elimination of cccDNA, which is not addressed by existing antiviral agents. Safe, potent agents that

destabilize cccDNA even in the presence of potential emergence of resistant variants, in combination with existing antiviral agents could confer a functional cure or eradication of HBV. We evaluated the ability of our novel, potent HBV capsid effector GLP-26 to block cccDNA formation and HBeAg production in HepNTCP-DL cells transfected with HBV wild type or HBV core T109I mutant. T109I mutant is present in ~1.2% of genotype B sequences and has shown resistance to both NV-010-001 and BAY 41–4109 capsid effectors (*Klumpp et al., PNAS 2015*).

Method: HepNTCP-DL cells were transfected 18 hr prior addition of antiviral drugs for 3-days, and total nucleic acid was purified, and cccDNA was amplified by real-time-PCR. HBeAg antigen production was measured by EIA. Additionally, drug-drug combination of GLP26 with ETV was also performed in HepAD38 cells and the effect on HBV DNA replication and other viral associated parameters were determined.

Results: Both GLP-26 or GLS4 reduced secreted HBeAg in HepNTCP-DL cells transfected with HBV wild type, with EC_{50} values of 0.7 and 1.7 µM, respectively. The core T109I mutant was more susceptible to inhibition of HBeAg production by GLP26 *versus* GLS4 when compared to wild type, with fold changes in EC_{50} values of 0.7 and 2.4, respectively. In addition, T109 mutant was also more susceptible to inhibition of cccDNA formation/amplification by GLP-26 *versus* GLS4, with 1.5 log reduction by GLP-26 *versus* no effect by GLS4. There was no effect on pgRNA or sRNA by both capsid effectors, whereas GLS4 but not GLP-26 reduced HBs antigen production in both wild type and T109I transfected cells. Combination of GLP-26 with ETV reduced cccDNA amplification of T109I mutant *versus* no effect by GLS4. Dual combination of GLP-26 with ETV resulted in a strong synergistic antiviral effect, with weighted average combination index value (CI_{wt}) of 0.4 in the HepAD38 system.

Conclusion: These data demonstrate that (1) GLP-26 and GLS4 demonstrate similar block on HBeAg production against wild-type virus, (2) GLP26, but not GLP4 is a potent inhibitor of cccDNA formation and HBeAg production against the mutant core T109I, and (3) GLP-26, but not GLS4 demonstrated synergistic activity with ETV in the HepAD38 system, reducing HBV DNA replication. These data underscore the utility of GLP-26 against drug-resistant variants of HBV, and its application in combination with existing antiviral agents. Together, combinations with GLP-26 could represent a tandem mechanism to block cccDNA formation towards a functional or sterilizing cure for HBV.

PS-027

Preclinical antiviral drug combination studies utilizing novel orally bioavailable investigational agents for chronic hepatitis B infection: AB-506, a next generation HBV capsid inhibitor, and AB-452, a HBV RNA destabilizer

N. Mani[1], A.H.L. Li[2], A. Ardzinski[1], L. Bailey[1], J.R. Phelps[2], R. Burns[2], T. Chiu[2], A.G. Cole[1], A. Cuconati[1], B.D. Dorsey[1], E. Evangelista[2], D. Gotchev[1], T.O. Harasym[2], A. Jarosz[2], S. Kadhim[2], A. Kondratowicz[2], S.G. Kultgen[1], K. Kwak[2], A.C.H. Lee[2], S. Majeski[2], K. Mcclintock[2], J. Pan[2], C. Pasetka[2], R. Rijnbrand[1], A. Shapiro[2], H.M. Steuer[1], K. Stever[1], S. Tang[2], X. Teng[2], M. Wong[2], M.J. Sofia[1]. [1]*Arbutus Biopharma Inc., Warminster, PA, United States;* [2]*Arbutus Biopharma Inc., Burnaby, BC, Canada*
Email: nmani@arbutusbio.com

Background and Aims: Chronic hepatitis B infection affects ~240 million people worldwide who are at risk of developing cirrhosis, liver failure, and hepatocellular carcinoma and, unfortunately, currently approved therapies have poor cure rates. Increasing cure rates will require a combination regimen that blocks viral replication, reduces antigen load, attenuates cccDNA formation, and activates host immune responses to control residual virus. We evaluated the anti-HBV activities of two novel orally administered agents, a HBV capsid inhibitor AB-506 and a HBV RNA destabilizer AB-452, in combination with approved nucleos(t)ide analogs (NA), entecavir (ETV), tenofovir disproxil fumarate (TDF), tenofovir alafenamide (TAF), as well as the investigational RNA interference agent, ARB-1467.

Methods: *In vitro* combination studies were conducted using three-dimensional modeling for antiviral drug-drug interactions (Prichard and Shipman1990) by measuring the reduction of rcDNA and HBsAg levels in HBV cell culture systems. Results were analyzed using MacSynergy II software to determine if a combination was additive, synergistic, or antagonistic. Cell viability was assessed using the CellTiter-Glo® reagent. *In vivo* antiviral activities were studied in a hydrodynamic injection (HDI) HBV mouse model. HBV markers were measured using bDNA, qPCR and ELISA assays.

Results: The *in vitro* dual combinations of AB-506 or AB-452 with approved NAs or ARB-1467 ranged from additive to moderately synergistic at reducing HBV rcDNA and HBsAg levels with no significant effects on cell viability. After a once-daily 7-day oral treatment period in HDI HBV mice, dual combinations of AB-506 + AB-452, AB-506 + TDF, and AB-452 + TDF demonstrated a strong antiviral activity with mean 1.4, 1.9, and 2.2 log reductions in serum HBV DNA *vs* the vehicle control, respectively, whereas the triple combination effected larger serum HBV DNA reductions, 2.8 log *vs* the vehicle control. All AB-506 and AB-452 treated groups demonstrated reductions in liver HBV DNA, with negligible reduction observed with TDF alone. Serum HBsAg reduction was detected in AB-452 treated groups, and when combined with AB-506 and/or TDF there was no adverse effect on the ability of AB-452 to reduce HBsAg.

Conclusion: These preclinical investigations suggest that these agents when combined have distinct but mechanistically compatible *in vitro* and *in vivo* antiviral activities and may feasibly be used in future combination therapeutic regimens.

PS-028

Combination treatment of a TLR7 agonist RO7020531and a capsid assembly modulator RO7049389 achieved sustainable viral loadsuppression and HBsAg loss in an AAV-HBV mouse model

L. Dai[1], Y. Yu[1], L. Gu[1], J. Zhao[1], L. Zhu[1], H. Yun[1], Y. Ji[1], W. Zhu[1], J. Young[2], L. Gao[1]. [1]*Roche Innovation Center Shanghai, Shanghai, China;* [2]*Roche Innovation Center Basel*
Email: lu.gao@roche.com

Background and Aims: The ideal endpoint of therapy for CHB patients is sustained viral suppression as evidenced by the loss of HBsAg with or without anti-HBs seroconversion. With existing HBV therapies (Peg IFN, nucleos(t)ides), HBsAg loss only occurs in approximately 3% of patients after 1 year of treatment. Here we evaluated the oral combination of two novel clinical Phase I molecules, a TLR7 agonist RO7020531 and a capsid assembly modulator RO7049389, in the AAV-HBV mouse model.

Method: In vivo efficacy of compounds was studied in a mouse model with a recombinant adeno associated virus carrying hepatitis B virus genome (AAV-HBV) for 6 weeks followed by a 6-week off-treatment period. The levels of HBV DNA, HBsAg, and HBeAg in mouse serum were measured by quantitative polymerase chain reaction (qPCR), HBsAg chemiluminescent immunoassay (CLIA), HBeAg CLIA kits, and a mouse IgG ELISA development kit, respectively. Germinal center B cell population in the spleen was analyzed by FACS analysis.

Results: In an AAV-HBV model, oral administration of the TLR7 agonist RO7020531 significantly reduced both HBV DNA and HBsAg levels with gradual rebound in these markers during a follow-up off-treatment period. Combining this TLR7 agonist with the approved nucleoside analog entecavir did not lead to greater HBsAg reduction. In striking contrast, however, the combination of RO7020531 and the capsid assembly modulator RO7049389, led to a dramatic reduction of HBsAg and HBV DNA with the levels declining to at or below the lower limit of quantification. Most importantly, during the off-treatment period, the effect on HBsAg was sustained, whereas HBV DNA rebound was minimum. Emergence of high levels of anti-HBs antibodies was also observed in a number of mice during the

off-treatment period. The combination therapy of TLR7 agonist and capsid assembly modulator was also associated with upregulated germinal center B cells in the spleen and increased level of anti-HBs antibody in the serum. In addition, HBeAg level in the combination group was reduced by more than 1-log, and similar to that in the monotherapy group of capsid assembly modulator.
Conclusion: In the AAV-HBV mouse model, the combination of the TLR7 agonist RO7020531 and the capsid assembly modulator RO7049389 demonstrated robust suppression of both HBsAg and HBV DNA levels and with the additional emergence of anti-HBs antibodies in several animals. These data highlight the merits of exploring this combination in the clinic as a potential means to achieve a functional cure for CHB infection.

PS-029

Durable inhibition of hepatitis B virus replication and antigenemia using a subcutaneously administered siRNA agent in preclinical models

A.C.H. Lee[1], J. Heyes[1], X. Ye[1], R. Holland[1], E.P. Thi[1], M. Wood[1], A. Judge[1], N.M. Snead[1], A. Martin[1], M.J. Sofia[2]. [1]*Arbutus Biopharma, Burnaby, Canada;* [2]*Arbutus Biopharma, Warminster, United States*
Email: alee@arbutusbio.com

Background and Aims: Developing a cure for chronic hepatitis B (CHB) must address multiple factors involved in viral persistence and likely will require combination of drugs with different modes of action. Reducing HBV proteins, particularly HBsAg, may abrogate viral suppression of immune function and facilitate reinvigoration of host defense. We have recently reported up to 2.7 log HBsAg reduction from ARB-1467 treatment in CHB patients regardless of HBeAg status and with favorable safety profile (AASLD 2017). Here we describe ARB-270729, a next-generation small interfering RNA (siRNA) therapeutic targeted to hepatocytes using a novel covalently conjugated N-acetylgalactosamine (GalNAc) moiety. ARB-270729 is a promising new agent to potentiate HBV cure and acts on multiple hepatitis B viral transcripts, enabling inhibition of HBV replication and suppression of all viral antigens.
Method: *In vitro* anti-HBV activity was studied in primary and immortalized hepatocyte culture systems and *in vivo* anti-HBV activity was studied in a tolerized mouse model of CHB, C57BL/6 mice infected with an adenovirus-associated virus (AAV) carrying a 1.2-fold overlength genome of genotype D.
Results: In comparison to lipid nanoparticle (LNP)-mediated intravenous delivery, GalNAc-conjugated subcutaneous delivery of the same reference siRNA required a 10-fold larger dose to achieve similar mean maximum inhibition of serum surface antigen (HBsAg) in AAV-HBV mice. However, HBsAg suppression in the LNP treatment group had fully resolved by Week 4 whereas the GalNAc treatment group nadir persisted from Week 2 through to Week 6. One dose of ARB-270729 was sufficient to achieve mean maximum HBsAg reductions of 1.1, 2.4 and 3.5 $\log_{10}$ at 1, 3 and 9 mg/kg, respectively, in AAV-HBV mice with baseline serum HBsAg 3.6 $\log_{10}$IU/ml. *In vivo* ARB-270729 suppression of HBsAg was also highly durable, with 83%, 89% and 99%, respectively, of the mean maximal effect remaining at Week 10 after a single dose. The GalNAc moiety is required for ARB-270729 activity; reduction of HBV RNA and HBsAg was completely blocked by asialofetuin competitive inhibition *in vitro*.
Conclusion: ARB-270729 is a next-generation siRNA agent possessing a well-defined mechanism of action as well as a different route of administration and more durable *in vivo* preclinical activity than earlier-generation siRNA agents for the treatment of chronic hepatitis B infection.

PS-030

Development of subcutaneously administered RNAi therapeutic ARO-HBV for chronic hepatitis B virus infection

C. Wooddell, R. Zhu, H. Hamilton, Q. Chu, H. Sternard, J. Schumacher, T. Schluep, M. Seefeld, Z. Li, B. Given. *Arrowhead Pharmaceuticals, Arrowhead Madison, Madison, United States*
Email: cwooddell@arrowheadpharma.com

Background and Aims: Chronic HBV (CHB) infection is a global health problem with high unmet medical need. HBV proteins, in conjunction with pregenomic RNA (pgRNA), replenish the virus and contribute to chronicity by interacting with the host immune system. RNA interference (RNAi) cleaves viral mRNA, reducing viral proteins and replication products.
Methods: The novel RNAi therapeutic ARO-HBV combines RNAi triggers in the S and X open reading frames, both ligand-targeted to hepatocytes, designed to reduce all HBV transcripts (including from host-integrated HBV DNA), to have broad genotype coverage and to avoid development of resistance. ARO-HBV was subcutaneously administered to mice expressing HBV RNA from a hydrodynamically injected 1.3 genome length HBV plasmid, either wild type or with a mutated binding site for the X trigger (HBV_{mut}) to simulate S transcripts produced from integrated HBV lacking a target site for the X trigger. HBV mRNA in liver and viral products in serum were measured: S antigen (HBsAg), e antigen (HBeAg) and HBV DNA. A combination index study was performed with entecavir. A pilot rat toxicity study was conducted with up to 300 mg/kg given on days 1, 8 and 15.
Results: A single injection of ARO-HBV (4.0 mg/kg) reduced HBsAg by 2.0 log, HBeAg by 1.1 log and serum HBV DNA by 1.3 log. Repeated injections of ARO-HBV (4 mg/kg every 3rd week x 3) reduced HBsAg (≥3.4 log), HBeAg (≥2.1 log) and HBV DNA (3.1 log), with multiple samples below LLOQ for HBsAg and HBeAg. Total HBV transcripts were reduced by 94% and precore/pgRNA transcripts by 89% at nadir following a single injection (4 mg/kg). S trigger alone gave 1.3 log less HBeAg reduction after 3 injections than the S plus X combination. The S trigger maintained full activity on RNA from HBV_{mut} (−3 logs HBsAg after single 3 mg/kg dose) despite a 10-fold excess of X trigger, which was inactive as monotherapy. ARO-HBV is synergistic with entecavir.

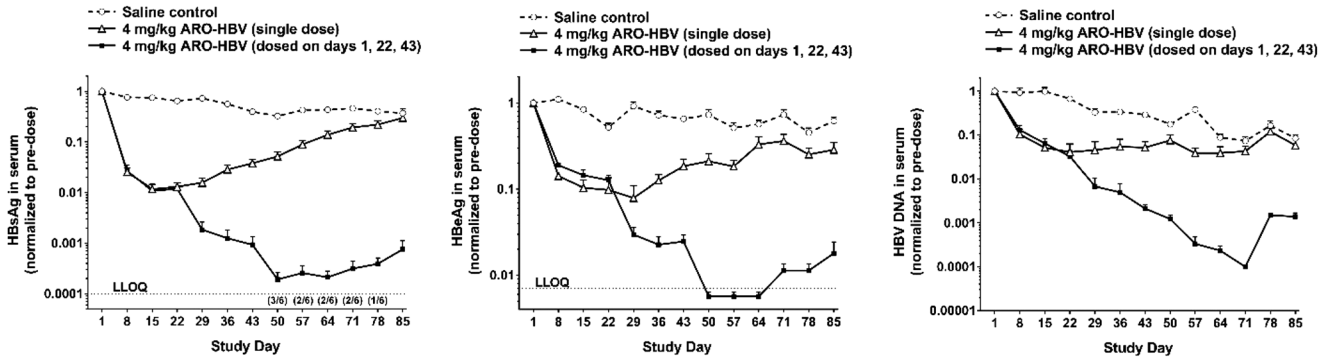
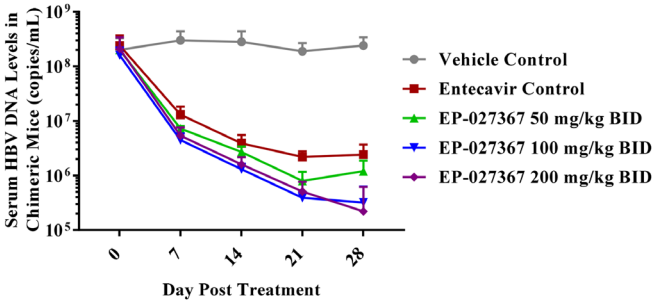


Figure: (abstract: PS-030): Single and multi-dose effects in pHBV-infected mice.

Based on clinical observations, clinical chemistries and histopathology evaluations, ARO-HBV was well tolerated, including when 900 mg/kg was given over 2 weeks.
Conclusion: ARO-HBV showed deep and prolonged reductions in viral antigens and HBV DNA, including in a model of integrated HBV DNA-derived HBsAg. It also appears to have low toxicity in rats. ARO-HBV is progressing to clinical trials in patients with CHB and is expected to synergize with other antiviral compounds.

PS-031
T cells grafted with HBV-specific T-cell receptors of high functional avidity achieve functional cure of HBV infection in humanized mice
K. Wisskirchen[1,2], J. Kah[2,3], A. Malo[1], L. Allweiss[2,3], K. Metzger[1], T. Volz[3], A. Krackhardt[4], M. Dandri-Petersen[2,3], U. Protzer[1,2]. *[1]Institute of Virology, Technical University of Munich/Helmholtz Zentrum München, Munich, Germany; [2]German Center for Infection Research (DZIF), Germany; [3]University Medical Center Hamburg-Eppendorf, 1st Department of Medicine; [4]3rd Medical Clinics, University Hospital rechts der Isar, Munich, Germany*
Email: protzer@tum.de
Background and Aims: Adoptive T-cell therapy of chronic hepatitis B or hepatitis B virus (HBV)-induced hepatocellular carcinoma intends to restore antiviral T-cell immunity to clear the infection or control tumor growth. We isolated HB-specific T-cell receptors (TCR) with high functional avidity to redirect T cells and aimed to test their potential to cure HBV infection *in vitro* and *in vivo*.
Method: We isolated a series of HLA-A*02 restricted TCRs specific for HBV S or core protein derived peptides from patients with acute and resolved HBV infection. Primary human T cells were genetically modified by retroviral transduction to express these HBV-specific TCRs. One S20- and C18-specific TCR each with high functional avidity were selected for further analysis. These HBV-specific TCRs recognized peptide of different HBV genotypes and presented on different HLA-A*02 subtypes common in areas with high HBV prevalence.
Results: Upon TCR grafting, $CD8^+$ as well as $CD4^+$ T cells became polyfunctional HBV-specific effector T cells recognizing even picomolar concentrations of cognate peptide. Upon antigen recognition, TCR-grafted T cells secreted IFN, TNF and interleukin-2, controlled HBV replication and effectively killed hepatoma cells with an integrated HBV genome. When co-cultured with HBV-infected cells, TCR-grafted T cells stopped viral replication, killed infected cells and eliminated viral antigens as well as cccDNA from the cell culture. TCRs mediated elimination of HBV when expressed on $CD8^+$ or $CD4^+$ T cells and also when grafted on T cells from patients with chronic hepatitis B. *In vivo*, TCR-redirected T cells targeted the liver when injected into HBV-infected humanized mice repopulated with HLA-A*02-matched primary human hepatocytes. After a single T cell injection, viremia and HBsAg dropped by more than 4–5 $\log_{10}$ to undetectable levels in 5/6 animals and HBeAg as well as cccDNA became negative. Alanine amino transferase levels peaked after 5 days and normalized thereafter. After three weeks, HBcAg staining in the liver had become negative. No HBV rebound was observed until the end of the experiment after 40 days.
Conclusion: Our experiments indicate that T cells stably transduced with TCRs of high functional avidity allow functional cure of HBV infection after a single injection causing limited liver injury. T-cell therapy of chronic hepatitis B and HBV-induced hepatocellular carcinoma thus is an interesting therapeutic approach that should be further evaluated.

PS-032
Discovery of a novel core inhibitor EP-027367 with potent antiviral activity both in vitro and in a humanized mouse model
M. Vaine[1], S. Clugston[1], J. Kass[1], X. Gao[1], H. Cao[1], W. Li[1], X. Peng[1], L. Jiang[1], K. Daniels[1], Y.-L. Qiu[1], Y.S. Or[1], K. Lin[2]. *[1]Enanta Pharmaceuticals; [2]Enanta Pharmaceuticals, Watertown, United States*
Email: mvaine@enanta.com
Background and Aims: Current therapies for hepatitis B virus (HBV) using nucleos(t)ides and IFN can effectively suppress viral replication but rarely lead to a functional cure, which necessitates the development of new antiviral drugs. Core inhibitors or capsid assembly modulators are a new class of HBV inhibitors which misdirect the assembly and function of the viral capsid. We have identified EP-027367 as a novel core inhibitor with a favorable antiviral, pharmacokinetic, and safety profile to treat HBV infection.
Method: The effect of EP-027367 on viral capsid assembly was determined *in vitro*. Its anti-HBV activities at different stages of the viral lifecycle were characterized in HepG2.2.15, HepAD38, HepDE19, HepaRG, and primary human hepatocytes. *In vivo* efficacy of EP-027367 was evaluated in a humanized mouse model consisting of uPA/SCID mice with livers repopulated by human hepatocytes and infected with a genotype C HBV.
Results: EP-027367 modulates HBV capsid assembly and blocks viral pgRNA encapsidation *in vitro*. It inhibits the production of HBV rcDNA with EC_{50}s of 20, 24 and 40 nM in HepG2.2.15, HepAD38, and HepDE19 cells, respectively. It is active across HBV genotypes A-H with potencies ranging from 7 to 50 nM and is not affected by known nucleos(t)ide resistant variants. Combinations of EP-027367 with other HBV inhibitors display additive to synergistic antiviral activity *in vitro*. Additionally, EP-027367 can prevent *de novo* infection of susceptible cell lines at sub-micromolar concentrations by inhibiting the formation of new cccDNA. In a human liver chimeric mouse model, EP-027367, given orally at 50, 100 and 200 mg/kg BID for 28 days, reduced HBV DNA level by 2.2, 2.7 and 3.0 logs from baseline, respectively.



Conclusion: EP-027367, a novel HBV core inhibitor with potent antiviral activities both *in vitro* and *in vivo*, represents a promising new therapeutic candidate for treating HBV infection.

Hepatitis C: Therapy

PS-033
Directly acting antiviral HCV therapy is safe and effective in patients with advanced cirrhosis: real world experience from the HCV-TARGET Cohort
E. Verna[1], G. Morelli[2], N. Terrault[3], A. Lok[4], J. Lim[5], A.M. DI Bisceglie[6], S. Zeuzem[7], C. Landis[8], G. Lutchman[9], M. Hassan[10], M.P. Manns[11], M. Vainorius[12], L. Akushevich[12], D.R. Nelson[2], M.W. Fried[12], R. Reddy[13]. *[1]Columbia University; [2]University of Florida; [3]University of California San Francisco; [4]University of Michigan; [5]Yale University; [6]Saint Louis University; [7]Goethe University Hospital; [8]University of Washington; [9]Stanford University; [10]University of Minnesota; [11]Hannover Medical School; [12]University of North Carolina Chapel Hill; [13]University of Pennsylvania*
Email: ev77@cumc.columbia.edu
Background and Aims: Direct-acting antiviral (DAA) HCV therapy is now being used in difficult to treat patient populations, including

decompensated cirrhosis. While high SVR rates have been reported in a limited number of clinical trials, we evaluated the real-world safety and effectiveness of DAAs in this population, and the impact on hepatic function.

Method: Patients with advanced cirrhosis enrolled in HCV-TARGET, who initiated HCV therapy with NS5A-containing DAAs, were included. Advanced cirrhosis was defined as cirrhosis and MELD score of ≥10, without prior liver transplantation (LT). Safety cohort (N = 473): Patients who started therapy prior to July 2017 and completed or discontinued therapy due to lack of efficacy, adverse event (AE), or death. Efficacy cohort (N = 386): Patients who started therapy by April 2017 with known virologic outcome who did not undergo LT during treatment or SVR12.

Results: In the safety cohort, mean age was 60 years, 67.2% male, 49.9% had failed prior antiviral therapy and 21.4% had failed prior all DAA regimens. The median MELD at treatment was 12 (range 10–39), with mean total bilirubin 1.6 (0.2–16.1), albumin 3.2 (1.0–4.7), platelets 82×10^3 (15–647), and creatinine 0.9 (0.4–12.7). 67% had a history of decompensating events. Genotype, MELD category, treatment regimen and SVR 12 rates are shown in the Table. At least one AE was reported in 74% of patients and 19.7% experienced SAEs. 13 patients in safety cohort died (5 on treatment and 8 in follow up) and 10 underwent liver transplant. At the time of SVR12, MELD had decreased by ≥2 points in 79 (39.9%), increased by ≥2 points in 33 (16.7%), and was unchanged in 86 (43.4%) patients.

Total Cohort	SOF/LDV +/− RBV (n = 309)	SOF/DCV +/− RBV (n = 75)	SOF/VEL +/− RBV (n = 69)	ELB/GRZ+/− RBV (n = 20)	ALL (n = 473)
GT 1 (n/%)	289 (94%)	11 (15%)	19 (28%)	20 (100%)	339 (72%)
GT 2	1 (0.3%)	15 (20%)	16 (23%)	0 (0%)	32 (7%)
G3	6 (2%)	48 (64%)	30 (44%)	0 (0%)	84 (18%)
G4/Other	13 (4%)	1 (1%)	4 (6%)	0 (0%)	18 (4%)
MELD					
10–15	258 (84%)	65 (87%)	57 (83%)	5 (25%)	385 (81%)
16–21	42 (14%)	7 (9%)	8 (12%)	1 (5%)	58 (12%)
>21	9 (3%)	3 (4%)	4 (6%)	14 (70%)	30 (6%)
With RBV	56(18%)	49 (65%)	37 (54%)	0 (0%)	142 (30%)
History of HCC	34 (11%)	12 (16%)	10 (15.0%)	1 (5.0%)	45 (14.3%)
History of Decomp events	205 (66%)	53 (71%)	47 (68%)	10 (50%)	315 (67%)
Discontinued due to AE	9 (3%)	4 (5%)	1 (1%)	1 (5%)	15 (3%)
Died	6 (2%)	5 (7%)	1 (1%)	1 (5%)	13 (3%)
Response*	(n = 260)	(n = 59)	(n = 51)	(n = 16)	(n = 386)
SVR 12	233 (90%)	50 (85%)	49 (96%)	16 (100%)	348 (90%)
Relapse	26	6	2	0	34
Non-response	1	3	0	0	4

*Efficacy cohort only.

Conclusion: In a large real world experience, NS5A-containing DAA therapy was effective in patients with advanced cirrhosis; adverse events were as previously observed in clinical trials in this population. Importantly, markers of hepatic function improved or remained unchanged in most at the time of SVR12. Long term follow up is ongoing to determine the degree and predictors of hepatic function recovery.

PS-034

8 weeks sofosbuvir/velpatasvir in genotype 3 patients with significant fibrosis: Highly effective amongst an OST cohort

A. Boyle[1,2], F. Marra[2,3], E. Peters[4], M. Heydtmann[5], H. Cairns[6], S. Datta[7], S. Barclay[8]. *[1]NHS Greater Glasgow and Clyde, Pharmacy Department; [2]University of Liverpool, Department of Molecular and Clinical Pharmacology; [3]NHS Greater Glasgow and Clyde, Pharmacy Dept; [4]NHS Greater Glasgow and Clyde, Brownlee Centre for Infectious Diseases; [5]NHS Greater Glasgow and Clyde, Royal Alexandra Hospital; [6]NHS Greater Glasgow and Clyde, Gartnavel General Hospital; [7]NHS Greater Glasgow and Clyde, Queen Elizabeth University Hospital, Glasgow; [8]NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary*
Email: alisonboyle2@nhs.net

Background and Aims: Twelve weeks of sofosbuvir/velpatasvir (SOF/VEL) is highly effective at treating genotype 3 (GT3) hepatitis C. A phase 2 trial reported high sustained viral response (SVR) rates in treatment-naïve non-cirrhotic patients, treated with 8 weeks of SOF/VEL (SVR 98.1% (52/53)). In order to maximise the number of patients potentially cured within a fixed treatment budget, we elected to treat non-cirrhotic GT3 patients eligible for treatment (F2/3) with 8 weeks of SOF/VEL. DAAs in our centres are dispensed from community pharmacies in line with patients' opiate substitution therapy (OST). Those still injecting or in early stages of recovery are prescribed methadone (and DAAs) as daily observed therapy (DOT), with more stable patients dispensed 2–3 x weekly or weekly. Patients not on OST are dispensed at 2 weekly intervals.

Method: By local treatment protocol, treatment-naive patients with F2 or F3 fibrosis (LSM > 6.9 kPa & <9.5 kPa and ≥9.5 kPa & <12.5 kPa respectively), were eligible for treatment with 8 weeks SOF/VEL. Such patients commencing treatment before October 1st 2017 were identified from the Scottish HCV database, and baseline data on age, gender, liver stiffness measurement (LSM), premature discontinuation and treatment response were obtained. Dispensing frequency was obtained from pharmacy records.

Results: Ninety-two patients (72 (78.3%) male), mean age 45.1 (IQR ± 6.1)) started 8 weeks SOF/VEL, prior to October 1st 2017. Median LSM was 8.5 kPa (IQR ± 2.3). 28 (30.4%) had F3 disease. Median baseline viral load was 5.63 log iu/ml (IQR ± 1.45), with 5 (5.4%) greater than 6 million iu/ml. 83 (90.2%) were on OST, including 39 (42.4%) on DOT. Six patients (6.5%) were treated in prison. To date, 84 (91%) patients have completed treatment, 3 (3.6%) prematurely. Intention to treat (ITT) SVR is 42/45 (93.3%). In non SVR patients, 1 was re-infected (with subsequent spontaneous clearance), 1 discontinued treatment at week 4, and one died following treatment completion. Modified intention to treat (mITT) SVR is 42/42 (100%). In DOT patients, ITT and mITT SVR to date are 13/14 (92.9%) and 14/14 (100%) respectively. Further SVR data will be presented.

Conclusion: Eight weeks of SOF/VEL is highly effective in GT3 infected patients with significant (F2/3) fibrosis. Patients on daily supervised OST have excellent SVR rates when given DAAs along with OST. Widespread adoption of 8 weeks treatment would reduce drug acquisition costs, and increase clinic treatment capacity, without sacrificing SVR. In settings with limited resources, such a strategy may help achieve the HCV elimination goals.

PS-035

Safety and efficacy of Sofosbuvir/Velpatasvir with and without Ribavirin in genotype 3HCV-infected patients with cirrhosis

M.B. Ferret[1,2], J. Pineda[3], J.L.C. Panero[4], M. Rodríguez[5], R.M. Morillas[6], J.M. Pascasio[2,7], A. Rivero[8,9], B. Mcnabb[10], G. Zhang[10], G. Camus[10], L. Stamm[10], D. Brainard[10], M. Subramanian[10], J.A. Carrión[11], R.J. Andrade[2,12,13], L.E.M. Amado[14], J. Turnés[15], S. Lens[2,16,17], M. Casado[18], R. Esteban[1,2]. *[1]Liver Unit, Hospital Universitari Vall d'Hebron, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; [2]CIBERehd; [3]Unit of Infectious Diseases and Microbiology, Hospital Universitario de Valme, Seville, Spain; [4]Department of Gastroenterology, Hospital Puerta de Hierro Majadahonda, Madrid, Spain; [5]Department of Hepatology, Hospital Central de Asturias, Oviedo, Spain; [6]Department of Hepatology, Hospital Germans Trias i Pujol, Badalona, Barcelona, Spain; [7]Hospital Virgen del Rocio de Sevilla, Sevilla, Spain; [8]Infectious Diseases Unit, Instituto Maimonides de Investigación Biomédica de Córdoba (IMIBIC), Cordoba, Spain; [9]Hospital Universitario Reina Sofía de Córdoba, Cordoba, Spain; [10]Gilead Sciences. Inc., Foster City, United States; [11]Liver Section, Gastroenterology Department, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain; [12]UGC de Ap Digestivo y Farmacología Clínica, Instituto de Investigación Biomédica de Málaga (IBIMA), Malaga, Spain; [13]Universidad de Málaga, Malaga,*

Spain; [14]Unit of Infectious Diseases, University Hospital Alvaro Cunqueiro, Vigo, Spain; [15]Complejo Hospitalario Universitario de Pontevedra, Instituto de Investigación Sanitaria Galicia Sur, Ponteverda, Spain; [16]Liver Unit, Hospital Clínic Barcelona, Barcelona, Spain; [17]IDIBAPS; [18]Hospital Torrecárdenas, Almeria, Spain
Email: brian.mcnabb@gilead.com

Background and Aims: The single tablet regimen of sofosbuvir/velpatasvir (SOF/VEL) is a highly effective and well-tolerated treatment for GT3 HCV-infected patients. In the Phase 3 ASTRAL-3 study, SOF/VEL for 12 weeks resulted in 95% of GT3 HCV-infected patients achieving SVR; patients with compensated cirrhosis had numerically lower SVR rates (91%) compared to those without cirrhosis (97%). This study evaluated the efficacy and safety of SOF/VEL ± RBV for 12 weeks in GT3 HCV-infected patients with cirrhosis.

Method: At 29 sites in Spain, patients with cirrhosis and chronic GT3 HCV infection who could be treatment – experienced but were NS5A-inhibitor naïve were randomized 1:1 to receive open-label SOF/VEL 400/100 mg daily for 12 weeks with or without weight-based RBV, stratified by prior treatment experience. Patients had cirrhosis defined by liver biopsy, Fibroscan >12.5 kPa, or combined Fibrotest >0.74 and APRI >2.0. HCV RNA was measured with the CAP/CTM HCV 2.0 assay with LLOQ = 15 IU/mL. The primary efficacy endpoint was SVR 12 weeks after treatment (SVR12). Evaluation for resistance associated substitutions (RASs) was performed by sequencing HCV NS5A and NS5B coding regions with a 15% cut-off. The primary safety endpoint was adverse events (AEs) leading to SOF/VEL discontinuation.

Results: A total of 204 GT3 HCV-infected patients with cirrhosis were randomized and treated. The mean (range) age was 51 (31–85); 79% were male, 88% were white, 27% were treatment-experienced, 57% had IL28B CC genotype, and 15% had HIV coinfection. The overall SVR12 rates (n/N; 95% CI) were 91% (92/101; 84–96%) for the SOF/VEL group and 96% (99/103; 90–99%) for the SOF/VEL + RBV group. Among SOF/VEL treated patients, there were 5 relapses, 1 on-treatment virologic failure, and 3 patients lost to follow-up (LTFU); for SOF/VEL + RBV treated patients, there were 2 relapses and 2 patients LTFU. SVR12 rates were 96% for both SOF/VEL and SOF/VEL + RBV treated patients with prior treatment experience. Baseline NS5A resistance associated substitutions (RASs) were present in 20% of patients (n = 40). Within this subgroup, SVR12 was 83% (15/18) among patients treated with SOF/VEL and 95% (21/22) among patients treated with SOF/VEL + RBV. One patient in each group discontinued SOF/VEL due to AEs (anxiety and dizziness in the SOF/VEL group and increased bilirubin in the SOF/VEL + RBV group). Common AEs (>10% of patients) were asthenia (12%) for SOF/VEL and asthenia (27%), headache (24%), and insomnia (12%) for SOF/VEL + RBV. No treatment-related serious AEs occurred in either group, and there were no deaths in this study.

Conclusion: GT3 HCV-infected patients with cirrhosis have high overall rates of SVR12 after treatment with SOF/VEL with or without RBV. Among those with baseline NS5A RASs and cirrhosis, the addition of RBV to 12 weeks of SOF/VEL led to numerically higher SVR rates.

PS-036

Scaling up HCV-DAA treatment in patients on opioid substitution therapy (OST) – does alcohol and cannabis diminish cure rates? Data from the German Hepatitis C-Registry (DHC-R)

S. Christensen[1], P. Buggisch[2], S. Mauss[3], K. Boeker[4], T. Müller[5], H. Klinker[6], T. Zimmermann[7], Y. Serfert[8], B. Weber[9], J. Reimer[10], H. Wedemeyer[11], D.H. C-Register[8]. *[1]CIM Münster, Münster, Germany; [2]Ifi-Institute for Interdisciplinary Medicine, Hamburg, Germany; [3]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; [4]Center of Hepatology, Hannover, Germany; [5]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [6]University Hospital Würzburg, Würzburg, Germany; [7]University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; [8]Leberstiftungs-GmbH Deutschland, Hannover, Germany; [9]Praxiszentrum Friedrichsplatz/Competence Center Addiction, Kassel, Germany; [10]Gesundheit Nord – Bremen Hospital Group, Bremen, Germany; [11]Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany*
Email: christensen@cim-ms.de

Background and Aims: People who inject drugs (PWID) are most affected by HCV infection. To reach the WHO goal of HCV eradication by 2030 DAA therapy has to be scaled up in these patients. We compared sustained virological response (SVR) rates and proportion of lost to follow up (LTFU) depending on alcohol and cannabis consumption in OST and non-OST patients starting DAA treatment between 2/2014 and 9/2015.

Method: The DHC-R is a national multicentre non-interventional real-world registry study. Non-OST patients were divided in patients with former/current drug use (non-OST/DU) and no drug use (non-OST/NDU). 7,747 chronic HCV patients started DAA therapy: 739 OST and 7,008 non-OST (1,500 non-OST/DU; 5,508 non-OST/NDU) patients. 528 OST and 5,582 non-OST patients had completed antiviral therapy and at least one follow-up documentation (Intention-to-treat (ITT) population).

Table 1: SVR rates and proportion of LTFU in non-OST/NDU, non-OST/DU and OST patients stratified by alcohol and cannabis consumption.

Baseline parameter	Lost to Follow Up (ITT), % (n/N)		
	Non-OST/NDU	Non-OST/DU	OST
alcohol consumption, yes	**3.0** (16/532)	8.8 (17/193)	12.4 (12/97)
>40g/d (m)/>30g/d (f)	7.4 (5/68)	9.5 (4/42)	14.8 (4/27)
≤40g/d (m)/≤30g/d (f)	**2.4** (11/464)	8.6 (13/151)	11.4 (8/70)
alcohol consumption, no	**3.2** (125/3,907)	8.5 (79/929)	9.2 (39/426)
cannabis consumption, yes	1.7 (1/57)	10.7 (11/103)	8.4 (7/83)
cannabis consumption, no	**3.2** (141/4,398)	8.3 (85/1,023)	10.6 (47/445)
Baseline parameter	**SVR rates (Intention-to-treat), % (n/N)**		
	Non-OST/NDU	**Non-OST/DU**	**OST**
alcohol consumption, yes	**91.2** (485/532)	83.4 (161/193)	83.5 (81/97)
>40g/d (m)/>30g/d (f)	85.3 (58/68)	78.6 (33/42)	85.2 (23/27)
≤40g/d (m)/≤30g/d (f)	**92.0** (427/464)	84.8 (128/151)	82.9 (58/70)
alcohol consumption, no	**92.4** (3,612/3,907)	86.5 /804/929)	86.2 (367/426)
cannabis consumption, yes	91.2 (52/57)	84.5 (87/103)	84.3 (70/83)
cannabis consumption, no	**92.3** (4,060/4,398)	86.2 (882/1023)	85.4 (380/445)
Baseline parameter	**SVR rates (Per-Protocol), % (n/N)**		
	Non-OST/NDU	**Non-OST/DU**	**OST**
alcohol consumption, yes	94.2 (484/514)	90.9 (159/175)	95.2 (79/83)
>40g/d (m)/>30g/d (f)	92.1 (58/63)	86.8 (33/38)	100 (23/23)
≤40g/d (m)/≤30g/d (f)	94.5 (426/451)	92.0 (126/137)	93.3 (56/60)
alcohol consumption, no	95.6 (3,598/3,763)	94.3 (796/844)	96.0 (362/377)
cannabis consumption, yes	92.9 (52/56)	94.4 (85/90)	93.3 (70/75)
cannabis consumption, no	95.5 (4,045/4,236)	93.7 (874/933)	96.4 (373/387)

Values highlighted in bold significantly differ from respective values of OST patients ($p<0.05$)
OST, opioid substitution therapy; DU, drug use; NDU, no drug use; SVR, sustained virological response

Results: Alcohol consumption was reported in 17.3% (128/739) of OST, in 17.1% (256/1,500) of non-OST/DU and in 11.3% (631/5,508) of non-OST/NDU patients. Among OST patients, 25% (32/128) consumed high amounts (>40 g alcohol/d (men)/>30 g/d (women)) of alcohol. In non-OST/DU, high amounts of alcohol were consumed in 22.2% (57/256). In non-OST/NDU, significantly less patients (13.9%, 88/631) consumed high amounts of alcohol when compared to OST patients ($p < 0.05$). Similarly, cannabis consumption was significantly higher in OST patients (18.8%, 139/739) than in non-OST/DU (9.4%, 141/1,500, $p < 0.05$) and non-OST/NDU patients (1.2%, 66/5,508, $p < 0.05$). In alcohol consuming patients, proportion of LTFU was significantly higher in OST (12/97) compared non-OST/NDU (16/532), but occurred mainly (8/97) after end of therapy (EOT). Therefore, the overall ITT SVR rate was significantly ($p < 0.05$) diminished in OST (85%) and non-OST/DU (86%) compared to non-OST/NDU patients (91%), but not in per protocol analysis (PP; OST 96%, non-OST/DU 94%,

NON-OST/NDU 95%). When stratified by alcohol consumption (yes/no) and moderate daily intake of alcohol (≤40 g/d (men)/≤30 g/d (women)), non-OST/NDU patients had significantly higher SVR rates than OST patients in ITT but not in PP analysis (Table 1). With respect to cannabis consumption, SVR rates did not differ between the three patient groups. Of note, relapse rates were lower in OST than in non-OST/DU and non-OST/NDU patients.

Conclusion: High SVR rates can be achieved in both OST and non-OST patients. Alcohol or cannabis consumption did not diminish cure rates in PP analysis. However, LTFU is more likely in patients with current or former drug use than in patients without drug history and in patients with high alcohol consumption, but occurred mainly after EOT, leaving a high chance for a cure in these patients.

PS-037

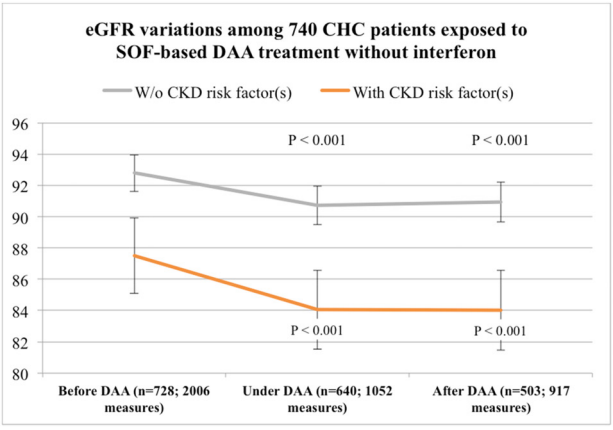
Estimated glomerular filtration rate variations and direct acting antivirals treatment for chronic hepatitis C: a retrospective longitudinal study

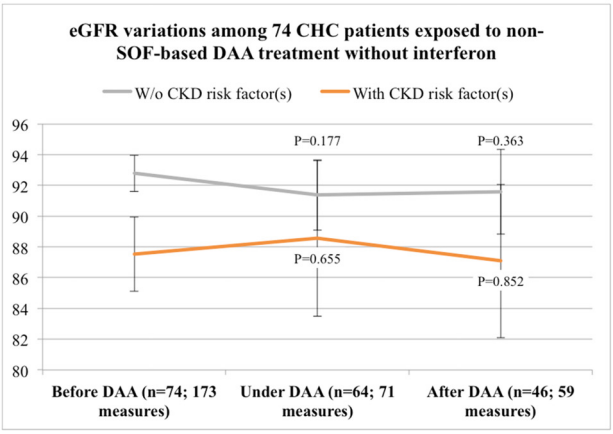
V. Mallet[1], L. Parlati[1], O. Dorval[1], L. Kramer[1], A. Hernvann[2], A.V. Pichard[1], C. Guerin[3], H. Fontaine[1], P. Sogni[1], S. Pol[4]. [1]*Assistance Publique – Hôpitaux de Paris (AP–HP), Cochin University Hospital, Hepatology Service, Paris, France;* [2]*Assistance Publique–Hôpitaux de Paris (AP–HP), Cochin University Hospital, Biochemestry Service, Paris, France;* [3]*Assistance Publique – Hôpitaux de Paris (AP–HP), Cochin University Hospital, Pharmacy Service, Paris, France;* [4]*Institut Cochin, Université Paris Descartes (UMR-S1016), CNRS (UMR 8104), Paris, France*
Email: vincent.mallet@cch.aphp.fr

Background: Nucleoside analogue treatment has been associated with renal toxicity. We evaluated the evolution of eGFR during and after DAA treatment for chronic hepatitis C (CHC).

Patients and Methods: We conducted a retrospective cohort study among consecutive and non-selected patients (n = 1131) who underwent direct acting antivirals (DAA) treatment for chronic hepatitis C (CHC) between 2013 and 2016. All serum creatinine measures, including those before DAA treatment, were retrieved from the biological database of the institution and merged in the patients' characteristics dataset. We selected patients with at least one creatinine measure. We excluded patients with HIV or HBV coinfections, patients with primary liver cancer or decompensated cirrhosis, patients with haematological malignancy, transplant recipients and patients under immunosuppressive therapy. Patients with a less than 30 ml/min/1.73 m2 estimated glomerular filtration rate (eGFR) on the first available creatinine measure were also excluded. Overall, the analyses included 4278 longitudinal eGFR measures assessed over a maximum 37 and 81 months post-treatment and total follow-up time period. We compared first and last measures with the pairwise T-test. We isolated the effect of DAA exposure on eGFR with a linear mixed model adapted for repeated measures allowing for the use of time-independent, here chronic kidney disease (CKD) risk factors, and – dependent, here DAA exposure, covariates.

Results: We selected 814 CHC patients treated with a sofosbuvir (SOF, n = 740) and a non-SOF (n = 74)-based regimen without interferon. Median age was 58 years, 40% had cirrhosis, 25% had CKD risk factors, including diabetes mellitus (9.8%) and high blood pressure (22.9%), and 96.5% had a baseline eGFR ≥ 60 ml/min/1.73 m^2. Median number of eGFR measures was 4 per patient and 784 (96.3%) patients had at least 2 eGFR measures. Mean eGFR decrease between first and last measure was 2.6 (p < 0.001) and 1.7 (p = 0.115) ml/min/1.73 m^2 for SOF and non-SOF patients. When all measures were taken into account, mean eGFR variations were −2.1 (95% confidence interval [CI] −2.70, −1.44; p < 0.001) and −1.8 (95% CI −2.6, −1.1; p < 0.001) and −3.5 (95% CI −4.7, −2.2; p < 0.001) and −3.5 (−4.8, −2.2; p < 0.001) ml/min/1.73 m^2 under and after SOF-based DAA treatment among patients with and without CKD risk factors, respectively. Other DAA combinations without SOF were not associated with eGFR variations.





Conclusion: SOF-based DAA treatment is associated with eGFR decrease among CHC patients, especially among those with CKD risk factors. Renal function should be monitored under and after SOF-based DAA treatment. The clinical implication(s) of these findings should be explored.

PS-038

Spontaneous clearance of HCV RNA after documented relapse following DAA-therapy: A case-control study

H. Kuriry[1], L. Krassenburg[1,2], M. Kuczynski[1], D. La[1], O. Cerocchi[1], D. Kaznowski[3], B. Hansen[1,2,4], H. Janssen[1], J. Feld[1]. [1]*University Health Network, Toronto, Toronto Centre for Liver Disease, Toronto, Canada;* [2]*Erasmus University Medical Center Rotterdam, Gastroenterology and Hepatology, Rotterdam, Netherlands;* [3]*Toronto General Hospital, Toronto Centre for Liver Disease, Toronto, Canada;* [4]*Management and Evaluation, University of Toronto, Institute of Health Policy, Toronto, Canada*
Email: h.kuriry@live.com

Background and Aims: Relapse after a course of therapy with direct-acting antivirals (DAAs) is rare (~3.5%) and usually results in recurrence of chronic hepatitis requiring retreatment. We have observed patients with documented relapse who spontaneously cleared infection without retreatment. Our aim is to compare clinical and virologic characteristics of patients with spontaneous clearance after relapse to those who achieved sustained virologic response (SVR) or relapsed without clearance.

Method: Clearers: CHC who relapsed with detectable HCV RNA 12 weeks after DAA therapy and then spontaneously resolved the infection within 6 months were compared to 2 control groups: "SVR" who had undetectable HCV RNA 12w post-treatment and "Relapse" who had detectable HCV RNA 12w after treatment without clearance. For each case, 2 SVR and 2 Relapse controls were randomly selected from the Toronto Centre for Liver Disease database. Demographic and laboratory data were compared between groups.

Results: Of 70 patients with documented relapse at SVR12, 10 (14%) spontaneously cleared infection without retreatment (Clearers). Baseline characteristics were similar between Clearers and Controls (Table 1). DAA regimens, use of ribavirin and treatment duration did not differ by group. Baseline and on-treatment liver enzymes and HCV RNA levels were similar, however at SVR12, despite detectable HCV RNA, Clearers had ALT values similar to those in the SVR group and significantly lower than in the relapse group (Table 1). Of the 10 Clearers, 9 had ALT values in the normal range at the time of relapse. HCV RNA levels were lower in the Clearers than Relapsers (4 log vs 6 log, p < .05). ALT levels remained low after the SVR12 time-point in Clearers. No Clearers had risk factors for reinfection.

		Relapse with Clearance (n = 10)	Relapser (n = 20)	SVR (n = 20)	p-Value
Age		60 (4)	60 (8)	60 (14)	0.97
Male		6 (60)	15 (75)	16 (80)	0.64
Fibrosis	Fibroscan	14.7 (9.4)	18.6 (16.5)	16 (9.5)	0.93
	FIB4	3.9 (2.9)	6.1 (3.2)	4.4 (3.2)	0.13
	Cirrhosis	5 (50)	15 (75)	14 (70)	0.45
Genotype	1	8 (80)	10 (50)	15 (75)	0.13
	2	0	2 (10)	0	
	3	1 (10)	7 (35)	5 (25)	
	4	0	1 (5)	0	
	6	1 (10)	0	0	
HCV RNA (log IU/mL)	Baseline	3.E6 (4.E6)	4.E6 (8.E6)	3.E6 (2.E6)	0.65
	Week 4	7.5E0 (8.7E0)	1.1E1 (1.6E1)	7.7E0 (1.3E1)	0.85
	SVR12	1.5E4 (3.9E4)	3.1E6 (7.1E6)	0	0.07
	Post SVR12	0	1.1E6 (1.0E6)		0.004
ALT (U/L)	Baseline	102 (62)	102 (63)	85 (112)	0.08
	SVR12	31 (30)	103 (68)	17 (8)	<.001
	Post SVR12	22 (5)	76 (41)	19 (7)	<.001

Mean(SD) or n(%).

Conclusion: Spontaneous clearance after documented relapse has not been described but occurred in over 14% of patients who relapsed after completed DAA therapy. Normal or near-normal liver enzymes despite detectable HCV RNA may identify patients likely to spontaneous clear after relapse. While the mechanisms for clearance remain obscure, the frequency of this observation highlights the need for confirmation of viremia prior to retreatment.

PS-039

NS5A resistance patterns and treatment outcomes in DAA-naive genotype 1a chronic hepatitis C patients with and without baseline resistance-associated substitutions

J. Dietz[1], J. Vermehren[1], S. Susser[1], K.-H. Peiffer[1], T. Welzel[1], K. Wursthorn[2], J. Petersen[2], H. Klinker[3], J.S.Z. Wiesch[4], H. Hinrichsen[5], T. Discher[6], L. Reinhardt[7], S. Mauss[8], M. Mueller-Schilling[9], C. Niederau[10], C. Neumann-Haefelin[11], R. Thimme[12], C. Berg[13], S. Zeuzem[1], C. Sarrazin[1,14]. *[1]Goethe University Hospital, Department of Internal Medicine I, Frankfurt am Main, Germany; [2]IFI-Institute for Interdisciplinary Medicine, Hamburg, Germany; [3]University Hospital Würzburg, Department of Internal Medicine II, Würzburg, Germany; [4]University Medical Center Hamburg-Eppendorf, Department of Internal Medicine I; [5]Practice of Gastroenterology, Kiel, Germany; [6]Justus Liebig University Gießen, Department of Medicine II, Gießen, Germany; [7]University Medical Center Göttigen, Department of Gastroenterology and Gastrointestinal Oncology, Göttingen, Germany; [8]Practice of Gastroenterology, Düsseldorf, Germany; [9]University Hospital Regensburg, Department of Internal Medicine I, Regensburg, Germany; [10]Katholisches Klinikum Oberhausen, St. Josef-Hospital, Oberhausen, Germany; [11]University Hospital Freiburg, Department of Medicine II, Freiburg, Germany; [12]University Hospital Freiburg, Department of Internal Medicine II, Freiburg, Germany; [13]University Hospital Tübingen, Department of Gastroenterology, Hepatology, and Infectiology, Tübingen, Germany; [14]St. Josefs-Hospital, Wiesbaden, Germany*
Email: julia.dietz@em.uni-frankfurt.de

Background and Aims: For patients with hepatitis C virus HCV genotype (GT) 1a infection who should be treated with grazoprevir (GZR) plus elbasvir (EBR), testing of NS5A resistance-associated variants (RASs) is recommended. In patients harboring RASs, SVR (sustained virologic response) rates were increased by the addition of ribavirin (RBV) and prolonging treatment to 16 weeks (wks.). Other regimens using sofosbuvir (SOF) plus ledipasvir (LDV) or velpatasvir (VEL) as well as paritaprevir, ombitasvir, dasabuvir (3D) and glecaprevir/pibrentasvir (G/P) are approved for GT1a as well. This study investigated the prevalence of EBR-specific RASs and the outcome of a DAA-based (direct acting antivirals) treatment in GT1a-infected patients according to the presence of RASs.
Method: In the European Resistance Database, we collected between October 2016 and May 2017, serum samples of 379 GT1a-infected and DAA-naïve patients, who were intended to receive GZR/EBR. Population sequencing was performed and NS5A RASs which conferred a >5-fold changed susceptibility to EBR were analysed and limited clinical and virological parameters were collected retrospectively.
Results: Overall, 82% of patients were treatment-naïve, 21% had a cirrhosis and EBR-specific RASs were detected in 6% of patients. A treatment based on a resistance analysis was started in 224/379 (59%) patients as yet and the median baseline viral load was 1.700.000 IU/mL. Patients without RASs (n = 210) were treated with GZR/EBR for 12 wks. (n = 122, 58%), GZR/EBR/RBV for 12/16 wks. (n = 17, 8%), LDV/SOF ± RBV (n = 46, 22%), G/P (n = 13, 6%), 3D/RBV (n = 10, 5%) and VEL/SOF (n = 2, 1%). Follow-up (FU) data was available for n = 83 patients and 99% achieved an SVR. In individuals with RASs (n = 14), Q30R/H (50%), Y93F/H (36%), L31M (21%) and M28T (14%) were detected. These patients received GZR/EBR/RBV for 16 wks. (n = 5, 37%), GZR/EBR for 16 wks. (n = 1, 7%), LDV/SOF (n = 3, 21%), VEL/SOF (n = 2, 14%), G/P (n = 1, 7%), 3D/RBV (n = 1, 7%) and SMV/SOF (n = 1, 7%). FU is completed in n = 5 individuals so far. All patients treated according to the guidelines achieved an SVR (n = 4/4, 100%) and one individual not treated appropriately did not receive RBV in addition to GZR/EBR and relapsed.
Conclusion: EBR-specific NS5A RASs were sparse in DAA-naïve patients with GT1a. A treatment based on a baseline resistance analysis according to the guidelines led to high SVR rates of ≥99% in patients with and without RASs.

PS-040

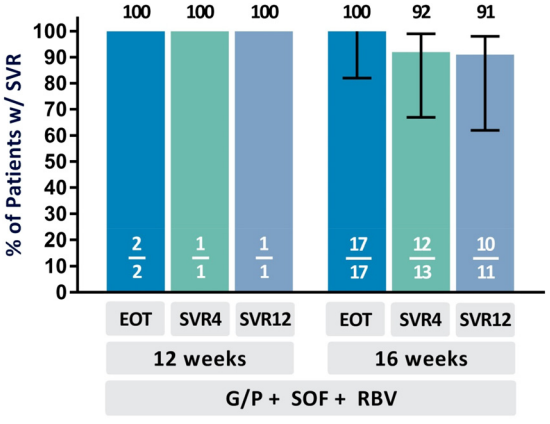
Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection

D. Wyles[1], O. Weiland[2], B. Yao[3], R. Reindollar[4], F. Weilert[5], J.-F. Dufour[6], S.C. Gordon[7], F. Poordad[8], A. Stoehr[9], A. Brown[10], S. Mauss[11], S. Samanta[12], T. Pilot-Matias[12], L.R. Jr[12], R. Trinh[12]. *[1]Denver Health Medical Center, Denver, United States; [2]Karolinska University Hospital Huddinge, Stockholm, Sweden; [3]AbbVie, North Chicago, United States; [4]Piedmont HealthCare, Statesville, NC, United States; [5]Waikato Hospital, Hamilton, New Zealand; [6]Inselspital, Bern, Switzerland; [7]Henry Ford Hospital, Detroit, MI, United States; [8]The Texas Liver Institute, San Antonio, TX, United States; [9]IFI Studien und Projekte Gmbh, Hamburg, Germany; [10]Imperial College Healthcare NHS Trust, London, United Kingdom; [11]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; [12]AbbVie, North Chicago, IL, United States*
Email: david.wyles@dhha.org

Background and Aims: Glecaprevir/pibrentasvir (G/P; glecaprevir identified by AbbVie and Enanta) has demonstrated high rates of sustained virologic response at posttreatment week 12 (SVR12) across all six major hepatitis C virus (HCV) genotypes (GT). Roughly 1% of patients treated with G/P in Phase II or III clinical trials, across all genotypes, had virologic failure. These patients were offered enrollment into a retreatment study, MAGELLAN-3.
Method: MAGELLAN-3 is an ongoing open-label, phase 3b trial to determine the efficacy and safety of G/P (300/120 mg once daily) + sofosbuvir (SOF; 400 mg once daily) + ribavirin (RBV; 1,000–

1,200 mg daily, divided into two doses) in patients who had virologic failure on G/P treatment in an AbbVie-sponsored clinical trial. Patients who had non-GT 3 infection, without cirrhosis, and were naïve to NS3/4A protease and NS5A inhibitors prior to failure with G/P, received 12 weeks of treatment; all others received 16 weeks. Efficacy (percentage of patients with SVR12), safety, and baseline resistance were assessed. Patients with at least end-of-treatment (EOT) data are reported here.

Results: Of 23 patients enrolled, 19 reached EOT; 2 patients were treated for 12 weeks (both reached EOT) and 21 were treated for 16 weeks (17 reached EOT). Overall, 30% (7/23), 9% (2/23), and 61% (14/23) of patients had HCV GT 1, 2, and 3 infection, respectively, and 30% (7/23) of patients had compensated cirrhosis. Twenty six percent (6/23) of patients had NS3/4A protease and/or NS5A inhibitor experience prior to their original G/P treatment; 39% (9/23) of patients had prior experience to other HCV treatment regimens. Twenty two percent (5/23) of patients had baseline resistance-associated substitutions (RAS) in NS3; the most common were at position D/Q168 (n = 4). All 23 patients had baseline RAS in NS5A (14 had multiple NS5A RAS); the most common were at position Q30 (n = 6) in GT1, and Y93 (n = 11) and A30 (n = 9) in GT3. One patient had virologic failure; currently available SVR12 rates are shown in the Figure. The retreatment regimen was well tolerated. One patient had a serious adverse event of cholelithiasis at treatment week 10. Complete efficacy and safety data will be presented at the conference.



EOT: HCV RNA below lower limit of quantification at end-of-treatment
SVR4/12: HCV RNA below lower limit of quantification at posttreatment week 4/12

Conclusion: Preliminary data show that retreatment with G/P + SOF + RBV for 12 or 16 weeks was well tolerated and has demonstrated a high rate of SVR12, regardless of HCV genotype or baseline resistance-associated substitutions.

Liver transplantation: Clinical

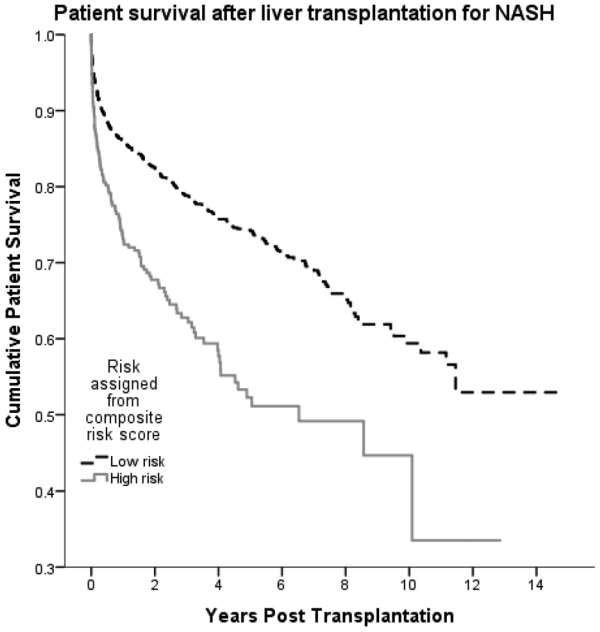
PS-041

Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in Europe

D. Haldar[1,2], B. Kern[3], J. Hodson[4], V. Karam[5], J. Fritz[3], R. Adam[5], B. Feurstein[3], W. Popp[3], H. Tilg[6], H. Zoller[6], P. Muiesan[2], S. Schneeberger[3], P. Newsome[1,4]. *[1]University of Birmingham, NIHR Birmingham Biomedical Research Centre, Centre for Liver Research, Birmingham, United Kingdom; [2]Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Liver Unit, Birmingham; [3]Innsbruck Medical University, Dept. of Visceral, Transplant and Thoracic Surgery, Innsbruck, Austria; [4]Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Institute of Translational Medicine, Birmingham; [5]Paul Brousse Hospital, Hepato-Biliary Center, Villejuif, France; [6]Innsbruck Medical University, Department of Internal Medicine, Gastroenterology, Hepatology & Endocrinology, Innsbruck*
Email: debashishaldar1983@gmail.com

Background and Aims: Non-alcoholic steatohepatitis (NASH) is an evermore-prevalent cause of liver disease in the western world. However, outcomes after liver transplantation (LT) for NASH are seldom reported. We aim to describe the relative frequency and analyse the outcomes of LT for NASH from a pan-European prospective database.

Method: We performed a retrospective cohort study of all adult patients (age > 18) who underwent primary LT for end stage liver disease between 1st January 2002 and 31st December 2016 using the European Liver Transplant Registry database. We compared data from patients transplanted for NASH to data from patients transplanted for other indications.



Kaplan-Meier survival curve describing cumulative patient survival after liver transplantation for NASH. Patients have been assigned to a risk group based on a composite score assigned to significant predictors of outcome in this cohort. The 5-year survival in the high-risk and low-risk group are 52% and 74% respectively (p<0.001).

Results: 68950 patients underwent a primary LT in the study period; NASH was the primary indication in 2741 patients (4.0%). The proportion of LTs done for patients with NASH has increased from 1.2% in 2002 to 8.7% in 2016. Patients with NASH undergoing LT are significantly older (median age 60 vs 55, $p < 0.001$) and of a greater body mass index (BMI) (32.6 ± 4.6 kg/m^2 vs 25.8 ± 4.4 kg/m^2, $p < 0.001$). A greater proportion of patients transplanted for NASH have concomitant HCC (39.1% vs 28.9%, $p < 0.001$). Patients with NASH receive organs from donors who are more likely to be male (62.3% vs 57.6%, $p < 0.001$) and of a greater body mass index (26.9 ± 4.8 kg/m^2 vs 25.5 ± 4.3 kg/m^2, $p < 0.001$). They also receive more donor organs after circulatory death (6.6% vs 2.6%, $p < 0.001$). Survival at 1 year

(84.3% vs 86.4%) and 5 years (71.3% vs 73.3%) after LT for NASH is marginally worse than for other indications (p = 0.005). However, on multivariable logistic regression, recipient (age, sex, BMI, blood group, presence of HCC) and donor (age, BMI, blood group, type of donor) factors are found to significantly affect post-transplant (PT) survival. On adjusting for these factors, NASH is not found to be an independent predictor of outcome (HR 1.07, p = 0.18). Graft survival is similar in patients transplanted for NASH compared to other indications other than HCV for which graft survival is comparatively poor. A multivariable analysis of the NASH cohort identifies recipient age, BMI, MELD, donor blood group and organ type to predict PT survival. A composite risk score (using the regression coefficient in significant variables) identifies a sub-cohort with poor 5-year survival after transplant (ROC AUC 0.636) (see image).

Conclusion: NASH is a growing indication for liver transplantation in Europe. It is not an independent predictor of PT survival, but patients are older, have a greater BMI, and have more likely to be transplanted with concomitant HCC. Predictive recipient and donor factors can be used to stratify potential transplantation risk and inform listing decisions.

PS-042

Liver transplantation in patients with multiple organ failures is feasible with good outcomes

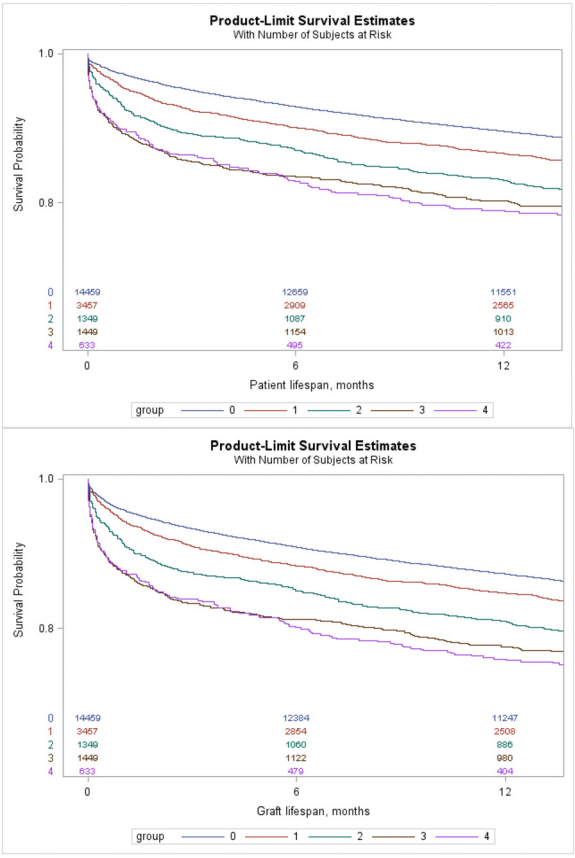
P.J. Thuluvath[1], A. Thuluvath[2], Y. Savva[3]. *[1]Mercy Medical Center & University of Maryland School of Medicine, Medicine, Baltimore, United States; [2]Johns Hopkins University, Medicine, Baltimore, United States; [3]Mercy Medical Center, Institute of Digestive Health & Liver Diseases, Baltimore, United States*
Email: thuluvath@gmail.com

Background and Aims: Patients who are transplanted within 30 days after listing for transplantation usually have very high MELD scores and many of these patients may have ACLF. There is a paucity of data on immediate and short-term outcomes of patients with multiple organ failures (OF) who undergo liver transplantation (LT).

Method: To examine the impact of OF on LT outcomes, we analyzed UNOS data from 2002 to 2016 of all adults who received LT within 30 days after listing for LT. We defined OF if patients were on dialysis, ventilator, life support or had stage 3 or 4 HE. Based on this, patients can have no OF or between 1 and 4 OF. Since organ failure is most likely to influence short and intermediate term outcomes, we analyzed only 30-day, 90-day and 1-year graft and patient survival. Kaplan-Meier estimator was used to construct survival curves and multivariate Cox proportional hazard regressions were used to study the association between the risk factors.

Results: During this period, 21,347 patients were transplanted within 30 days of listing. Of these 14,459 (68%) had no OF, 3,457 (16%) had one, 1,349 (6%) had two, 1,449 (7%) had three and 633 (3%) had four OF. The patient and graft survival outcomes of patients based on the number of OF are shown in Figures 1 & 2; 30-day and 90-day patient survival was highest without OF (97%, 95%) and lowest for those with 3 or 4 OF (89%, 86%). There was a progressive decline in survival with increasing number of OF. Multivariate Cox regression analysis for patient survival is shown in the table below. MELD score was not a predictor of mortality at 30 days and 90 days, when OF was included in the Cox regression, but the risk of death increased with increasing number of OF after adjustment for age, gender, race, BMI, etiology of liver disease, MELD, Karnofsky performance status scores (severe disability defined as 30% or less) and donor risk index (DRI). DRI and poor performance status were also strong independent predictors.

Conclusion: Our observations suggest that patients with multiple organ failures, when transplanted within 30 days of listing, have very good post-LT survival rates. Although the impact of OF is significant, survival outcomes are acceptable even with multiple OF.



	Predictor of Patient Mortality - Adjusted HR (from multivariate Cox regression)					
	30-day mortality	p-value	90-day mortality	p-value	1-year mortality	p-value
MELD score	1.01 (0.99–1.02)	0.3	1.00 (0.99–1.01)	0.27	1.01 (1.001–1.012)	0.03
KPS 30% or less	1.69 (1.35–2.11)	<0.01	1.49 (1.26–1.76)	<0.01	1.34 (1.19–1.51)	<0.01
Organ failure						
1	1.36 (1.07–1.72)	0.01	1.28 (1.07–1.53)	<0.01	1.19 (1.04–1.36)	0.01
2	1.68 (1.25–2.27)	<0.01	1.68 (1.33–2.12)	<0.01	1.50 (1.26–1.79)	<0.01
3	2.63 (2.02–3.41)	<0.01	2.35 (1.90–2.90)	<0.01	1.92 (1.62–2.28)	<0.01
4	2.20 (1.53–3.17)	<0.01	2.01 (1.49–2.72)	<0.01	1.87 (1.48–2.36)	<0.01
Donor Risk Index	1.26 (1.06–1.51)	0.01	1.40 (1.23–1.60)	<0.01	1.40 (1.27–1.54)	<0.01

PS-043

Evaluation of a pocket-sizedspectroscopy for extemporaneous macrosteatosis liver graft assessment

N. Golse[1], C. Cosse[2], M.-A. Allard[1], A. Laurenzi[1], M. Tedeschi[1], N. Guglielmo[1], B. Trechot[1], E.F. de Sevilla[1], C. Castro[1], M. Robert[3], G. Pittau[1], O. Ciacio[1], A. Sa Cunha[1], D. Castaing[1], D. Cherqui[1], R. Adam[1], D. Samuel[4], M. Sebagh[5], E. Vibert[1]. *[1]AP-HP Hôpital Paul-Brousse, Centre Hépato-BiliaireAP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire; [2]Faculty of Medicine Paris V, Paris, France; [3]Department of General Surgery and Bariatric Surgery, Edouard Herriot Hospital, Hospices Civils de Lyon; [4]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, F-94800, France, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France; [5]AP-HP Hôpital Paul-Brousse, Laboratoire Anatomie Pathologique, Villejuif, F-94800, France*
Email: nicolasgolse@me.com

Background and Aims: Liver macrosteatosis is a major predictor of graft dysfunction after liver transplantation (LT) and the impact on LT outcomes depends directly on the percentage of macrosteatosis.

However, the quantification of steatosis by frozen-section histological evaluation is not a reliable technique, and is often unavailable at night for logistical issues. Non-invasive imaging techniques are poorly correlated with permanent sections, so that decision for graft acceptance finally rests with the surgeon, by gross appearance. The goal of our study was to prospectively validate a non-invasive (=contact-free) pocket spectrometer (PS) giving an extemporaneous estimation of macrosteatosis and to ensure that we could obtain a reliable estimation.

Method: We evaluated a commercial PS (SCIO) never assessed for medical use. The gold standard for steatosis evaluation was the permanent section analysis. The PS communicated with a smartphone (Bluetooth connection) connected to internet (online database). A first stage (S1) of calibration was performed on 35 livers (macrosteatosis from 0% to 60%) and an algorithm was created, allowing a correlation between the estimation and the known values of graft steatosis. Then a second stage (S2) was carried out on 60 grafts (new cohort) during the procurement or after revascularization in the recipient to test the accuracy of the algorithm. The PS was placed at a distance <1.5 cm from the perfused liver (37°C).

Results: The algorithm established after S1 reached a coefficient of determination R2 = 0.811. The validation of this algorithm (S2) showed a Lin's concordance correlation coefficient of 0.89. After the creation of clinically relevant ranges of steatosis (0–20%, 21–40%, 41–60%), the Kappa score evaluating the inter-tests variability (pathologists vs PS) was of 0.77 ($p < 0.0001$). The liver graft weight, the donor body mass index and the scannographic liver-to-spleen attenuation ratio did not predict the macrosteatosis ($r < 0.5$).

Conclusion: Our study demonstrates that a PS allows a reliable and reproducible assessment of liver graft macrosteatosis. Its low cost and the immediacy of results may provide great value-added decision support, particularly when procurements are performed by unknown surgeons, to get an objective evaluation. This tool may avoid the travel of the surgical team in case of steatotic grafts, and avoid the prolonged cold ischaemia required by pathological examination in case of (potentially) marginal graft.

PS-044

Effect of longitudinal exposure to tacrolimus on chronic kidney disease occurrence at one year post liver transplantation

P. Maurel[1], V. Loustaud-Ratti[1], P. Carrier[1], E. Marie[1], A. Rousseau[2], M. Debette-Gratien[1], C. Silvain[3], X. Causse[4], L. Barbier[5], A. Prémaud[6], E. Salamé[5]. *[1]CHU Dupuytren, Limoges, France; [2]INSERM UMR 850, Limoges, France; [3]CHU la Miletrie, Poitiers; [4]CHU La Source, La Source, France; [5]CHU Trousseau, Chambray-Lès-Tours, France; [6]INSERM UMR 850, Limoges*
Email: paul_23_88@hotmail.fr

Background and Aims: Renal failure during the first year post-liver transplantation (LT) is predictive of mortality and increases health care costs. The nephrotoxic effects of calcineurin inhibitors are a major concern. Our aim was to study the relationship between tacrolimus (TAC) exposure and the risk of chronic kidney disease (CKD) in the first year post-LT.

Method: Retrospective data of consecutive patients transplanted in a single French Center (Tours University hospital, France as part of university hospital federation or FHU SUPORT) between 2011 and 2016 were collected. A joint model for longitudinal and time-to-event data were developed, using mixed effects models, to simultaneously analyse longitudinal exposure to tacrolimus (described using repeated residual concentrations) and risk of CKD within the first year post-LT. CKD was defined as a calculated glomerular filtration rate (eGFR) below 60 mL/minute/1.73 m2 (MDRD-4 formula), during three consecutive months. The effect of longitudinal exposure to tacrolimus, pre- and post-LT factors were investigated as potential predictors of CKD before M12 post-LT.

Results: Among 355 LT patients, 180 patients were studied after exclusion of LT for Acute Liver Failure, pré-LT dialysis, double kidney-LT and patients not receiving tacrolimus. CKD-free survival at one year was 74.5% and was not associated with tacrolimus longitudinal exposure within the observed exposure ranges. Pre-LT acute kidney injury (AKI) and post-LT eGFR at one month (<60 vs. ≥60 ml/min/1,73 m²) were statistically significant predictors of the hazard of CKD. By identifying two status within AKI, hepatorenal syndrome (HSR)-AKI and non HRS-AKI, only HRS-AKI remained predictive of CKD. HSR-AKI and eGFR at M1 under 60 ml/min significantly increased the risk of CKD (HR = 2.8; 95% confidence interval (CI):1.3–5.8 and HR = 4.4; 95%CI: 2.3–8.8, respectively).

Conclusion: Within the observed ranges of residual concentrations, the tacrolimus exposure was not significantly associated with post-LT CKD. This result is not so surprising as the different target concentrations of tacrolimus according to the post-LT delay are now well-defined and were respected in our population. On the other hand, HRS, classically considered as reversible, appears to be a key predictive factor of post-LT CKD, and the definition of non-reversibility criteria will be a new challenge.

PS-045

Donor specific antibodies after liver transplantation-still an underestimated risk?

K. Willuweit[1], A. Frey[1], P. Lisa[1], A. Heinold[2], P.A. Horn[2], G. Gerken[1], K. Herzer[1]. *[1]Department of Gastroenterology and Hepatology, Essen, [2]Institute for Transfusion Medicine*
Email: kerstin.herzer@uk-essen.de

Background and Aims: There is an ongoing controversy about the importance of donor specific antibodies (DSA), their prevalence and consequences for graft and patient survival after liver transplant (LT). Relative importance of antibody specificity and their strength (mean fluorescence intensity, MFI) remains to be elucidated. This analysis addresses the association of DSA with complications after LT and the relevance of antibody (AB) subspecies as well as MFI level.

Methods: Clinical and demographic data of 430 LT recipients were collected who are registered for aftercare at the LT unit of the University Hospital Essen. Antibody detection was performed using Luminex single antigen beads and a MFI value of more than 500 was considered positive. Statistical significance was analyzed by chi-quadrat test with Pearson approximation. A p-value less than 0.05 was considered statistically significant.

Results: Among all patients, 18.8% (81/430) were positive for DSA. Of these 81.5% (66/81) were HLA class II AB and 14.8% (12/81) HLA class I AB. HLA class II AB show a higher MFI (mean 4900 (600–20,600)) compared to HLA class I AB (mean XX (500–20,200)). Patients who developed DSA experienced more complications after LT (75.3%, 61/81) compared to DSA negative patients (72.8%, 254/349, $p = 0.67$). Cirrhosis after LT occurred significant more often in DSA positive patients than in patients without detectable DSA (18.5 vs. 8.8%, $p \leq 0.027$). Of the DSA positive patients 10% (8/81) developed de novo autoimmune hepatitis (dnAIH) while in DSA negative patients dnAIH occurred in only 4.3% (15/349, $p = 0.055$). Acute rejections (AR) were experienced by 24.7% (20/81) of the DSA positive patients compared to 16.6% (58/349, $p = 0.076$) of the DSA negative patients. We observed no significant difference in the frequency of complications with regard to either HLA class. Of HLA class II AB 50.1% (35/69) with an MFI >5,000 (p = ns) developed complications.

Conclusion: Patients who develop DSA after LT have a higher risk to experience complications withcirrhosis, dnAIH and AR being the most relevant. In particular, high-level HLA class II AB can be a predictor for complications. Therefore, detection of DSA and regular monitoring is important to maintain graft quality and survival. Furthermore, to specify risk factors for DSA development can influence the management of immunosuppression in order to prevent graft damage.

PS-046

Severe histological injury of common bile ducts in donation after circulatory death liver transplantation

F. Tinti[1,2], I. Umbro[1,2], S.G. Hubscher[3], J. Isaac[4], P. Onori[2], A. Franchitto[2], E. Gaudio[2], P. Muiesan[5], A.P. Mitterhofer[1]. *[1]Sapienza University of Rome, Department of Clinical Medicine, Nephrology Unit, Rome, Italy; [2]Sapienza University of Rome, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Rome, Italy; [3]Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Department of Cellular Pathology, Birmingham; [4]Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Liver Unit, Birmingham, United Kingdom; [5]Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Liver Unit, Birmingham, United Kingdom*
Email: francesca.tinti@uniroma1.it

Background and Aims: Within the model of donation after circulatory death (DCD), a more severe degree of ischaemia-reperfusion injury (IRI) is occurring, that seems to play a role on the pathogenesis of biliary complications.
Aim of the study was to assess the bile duct injury occurring in two different models of ischaemia, DCD and donation after brain death (DBD), in liver transplanted grafts.
Method: Bile duct injury was evaluated on histological samples of common bile duct retrieved after liver graft reperfusion, before biliary anastomosis.
Severity of donor bile duct injury was assessed and scored on the basis of Biliary epithelial cell loss, Mural stroma necrosis, Inflammation, Peribiliary vascular plexus damage, Arteriolonecrosis, Thrombosis, Periluminal and deep peribiliary glands damage.
Cholangiocyte apoptosis in periluminal and peribiliary glands was evaluated by quantitative terminal deoxy-nucleotidyl transferase dUTP-mediated nick-end labeling (TUNEL) analysis and cholangiocyte proliferation was studied by PCNA immunohistochemical expression in bile duct sections.
Results: Sixty-two patients had the bile duct sample available for histological evaluation (2014–2015). A significantly higher number of DCD patients presented necrosis >50% of the bile duct wall [DCD 14/28 (50%), DBD 9/34 (26.5%) p = 0.056], peribiliary vascular plexus damage [DCD 8/28 (29%), DBD 3/34 (9%); p = 0.053] and periluminal peribiliary gland damage [DCD 20/28 (71%), DBD 14/34 (41%); p = 0.016], defining the occurrence of severe histological injury, that was significantly more frequent in DCD liver transplant patients [15/28 (53.6%)] compared to DBD [7/34 (20.6%)] (p = 0.007). A significant increased apoptosis and decreased proliferation was evidenced in both periluminal (Tunel p = 0.029; PCNA p = 0.029) and deep PBGs (Tunel p = 0.002; PCNA p = 0.006) from bile duct sample with severe *histological injury.*
Conclusion: This study shows the early picture of microscopic damage at the level of the bile duct soon after reperfusion of liver graft during transplantation. Bile duct samples from DCD grafts expressed more severe injury at the histological level, defining the new feature of *severe histological injury*. Bile ducts with *severe histological injury* showed increased apoptosis and reduced proliferation as evaluated by Tunel assay and PCNA expression, both on periluminal and deep PBG. This study raises the hypothesis of a correlation between the occurrence of microscopic damage and the development of ischaemic biliary complications.
This study was supported by the ESOT Grant 2017.

PS-047

Prevalence of subclinical histological lesions and tolerance biomarkers in long-term adult liver transplant recipients considered for immunosuppression withdrawal

A. Sanchez-Fueyo[1], A. Douiri[1], M. Elstad[1], E. Kodela[1], J. Wall[1], E.B. Riani[2], G. Alexander[3], A. Marshall[4], M. Navasa[5], J. Ferguson[6], K.J. Simpson[7], A. Pascher[8], E. Jaeckel[9], P. Tachtatzis[10], F. Nevens[11], S. Masson[12]. *[1]King's College London, Institute of Liver Studies, London, United Kingdom; [2]Cliniques universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium; [3]Addenbrooke's Hospital, United Kingdom; [4]Royal Free Hospital, United Kingdom; [5]Hospital Clínic, Barcelona, Spain; [6]Queen Elizabeth Hospital, United Kingdom; [7]Royal Infirmary, United Kingdom; [8]Charité – Universitätsmedizin Berlin, Berlin, Germany; [9]Medizinische Hochschule Hannover, Hannover, Germany; [10]Leeds Teaching Hospitals NHS Trust, United Kingdom; [11]Leuven; [12]Hepatology, Newcastle*
Email: sanchez_fueyo@kcl.ac.uk

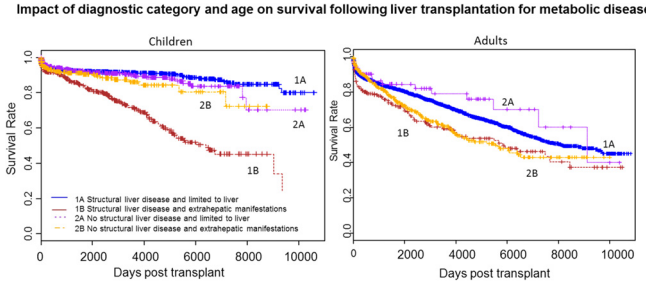
Background and Aims: LIFT is a multi-national prospective randomized controlled trial of immunosuppression withdrawal in adult liver transplantation initiated in 2015 in which a liver tissue transcriptional biomarker of tolerance is employed to stratify patients prior to immunosuppression weaning. Eligibility criteria, derived from a previous multi-center trial in which immunosuppression was successfully withdrawn in 40% of participants (Benitez et al. Hepatology 2013), include: >3 years post-transplant, normal liver function, no autoimmune or replicative viral liver disease, and absence of significant inflammatory/fibrotic lesions in a screening liver biopsy. We report here on the applicability of the trial and the estimated prevalence of operational tolerance.
Method: Between November 2015 and October 2017, 463 patients were screened and 127 were consented to participate in the trial and undergo a screening liver biopsy. Two central pathologists reviewed all biopsies. RNA was extracted from a cryopreserved portion of the biopsy cylinder and employed to assess the transcript levels of a previously described 5-gene signature of spontaneous operational tolerance (*IFNG, MIF, TFRC, CDHR2, PEBP1*).
Results: 108 biopsies were available for review: 59 met histological eligibility and 49 did not. In non-eligible patients the most frequent histological abnormalities were portal inflammation (74%), portal vein endotheliitis (49%), interface hepatitis (43%), bile duct lesions (43%), and fibrosis (75%; Ishak ≥3 in 20%). These abnormalities resulted in non-eligible patients exhibiting higher liver stiffness than those who were eligible (FibroScan 7 kPa versus 4; p = 0.001), despite being no differences in liver function tests between them. At the time of inclusion eligible patients were older (mean 62 years versus 58; p = 0.04), had a shorter post-transplant follow-up (mean 9.5 versus 11.3 years; p = 0.04), had higher Tacrolimus trough levels (mean 4.2 ng/mL versus 3.4; p = 0.04), and were more likely to have been transplanted for alcoholic liver disease (32% versus 14%; p = 0.03), than non-eligible patients. Overall 36% of patients had a positive biomarker profile (39% of eligible and 33% of non-eligible). Among the non-eligible group there were no significant differences between biomarker-positive and –negative patients.
Conclusion: A large proportion of adult stable liver transplant recipients exhibit potentially significant subclinical histological abnormalities. As a result, only a small proportion of them are eligible to participate in an immunosuppression withdrawal trial. Among patients meeting eligibility criteria, the proportion displaying a positive biomarker profile closely matches the estimated prevalence of operational tolerance.

PS-048

30 years of liver transplantation for metabolic disease in the United States

P. Mckiernan[1], J.E. Squires[1], R. Squires[2], G. Vockley[2], G.V. Mazariegos[3], Q. Sun[3], K. Soltys[3], A. Ganoza[3], R. Sindhi[3]. *[1]Children's Hospital of Pittsburgh, Division of Gastroenterology Hepatology and Nutrition, Pittsburgh, United States; [2]Children's Hospital of Pittsburgh, Division of medical genetics, Pittsburgh; [3]Children's Hospital of Pittsburgh, The Starzl Transplant Institute*
Email: patrick.mckiernan@chp.edu

Background and Aims: The indications for liver transplantation (LT) in metabolic disease (met) evolve as long-term outcomes are appreciated and new options develop. We reviewed the US experience with primary LT for metabolic disease in the Scientific Registry for Transplant Recipients (SRTR October 1987 to June 2017) to determine: (1) changes in indications with time, (2) long-term outcomes, and 3. factors predicting survival.
Method: Subjects were grouped by whether or not the primary defect caused structural liver disease (SLD) [categories 1 or 2 respectively] and whether or not the primary defect was confined to the liver [A or B respectively]. This resulted in 4 diagnostic categories. Indications and outcomes were compared over 3 consecutive 10 year eras, 1–3. Chi-square, t-test or Wilcoxon rank sum test were used as appropriate. Kaplan-Meier analysis or Cox proportional hazards were used to compare survivals.
Results: 6,048 underwent LT for met, 2406 [39.8%] being children. Compared to era 1, LT for met nearly doubled by era 3, from 603 to 1044 in children, and from 759 to 1617 among adults. Children experienced a six-fold increase in LT for non-SLD met in children, from 91/603 (15.1%) LT in era 1 to 578/1044 (55.4%) LT in era 3 ($p < 0.001$). Indications for LT remained relatively stable in adults. Living donor LT increased with eras from 5.6% to 7.6% in children, and 0–4.5% in adults. Fewer living donor LT were utilized in children with met compared with all other pediatric LT in the study period (179/1044, 7.6%, vs 1640/14125, 11.6%, $p < 0.001$). LT combined with transplantation of other organs was undertaken in 179/2406 children (8%) and 394/3642 (12%) adults ($p = 0.0001$) and was associated with reduced 10-year survival in children (87 vs 76%, $p < 0.001$) but not in adults (68% vs 62%, $p = 0.22$).
Outcomes improved with time. Latest 5-year patient survival were 94.4 and 81.5% in children and adults respectively, $p < 0.01$. Outcomes were worse in adults and in those with extrahepatic disease ($p < 0.01$, Figure] while SLD did not affect outcome. On multivariate analysis diagnostic category, inpatient status and transplant era significantly predicted outcome in all ages, with age at LT a predictor in adults and gender in childhood.



Conclusion: LT is increasingly utilized for phenotypic disease correction in children with excellent longterm survival.
Extrahepatic manifestations significantly impact longterm survival following LT for met at all ages.

NAFLD: Experimental and pathophysiology

PS-049

Acceleration of NASH in a mouse model provides novel insights on the mechanisms by which I148M PNPLA3 drives steatohepatitis

B. Banini[1], S. Cazanave[1,2], H.-K. Min[1], D. Kumar[1], P. Santhekadur[1], L. Wang[3,4], H.-P. Guan[3,5], M. Seneshaw[6], P. Bedossa[7], A. Oseini[6], F. Mirshahi[1], C. Alonso[8], S. Koduru[9], A. Sanyal[6]. *[1]Virginia Commonwealth University; [2]Glympse Bio, North Cambridge, United States; [3]MERCK Research Laboratories; [4]Morphic Therapeutic, Waltham, United States; [5]Quixgen Inc, New Brunswick, United States; [6]Virginia Commonwealth University, Richmond, United States; [7]Hôpitaux de Paris, Beaujon Hospital, Paris, France; [8]OWL Metabolomics, Parque Tecnológico de Bizkaia, Derio, Spain; [9]Pennsylvania State University, College of Medicine, Division of Plastic Surgery, Hershey, United States*
Email: arun.sanyal@vcuhealth.org

Background and Aims: The mechanisms by which $I^{148}M$ PNPLA3 mutation leads to NASH are unclear. The Diet-Induced Animal Model of NAFLD (DIAMOND) mouse develops steatosis and steatohepatitis with fibrosis after 4 and 16 weeks, respectively, on a Western diet (WD). The purpose of this study was to accelerate development of NASH in DIAMOND mice by liver-specific adenovirus-associated vector (AAV) delivery of human wild type (WT) or mutant (MT) PNPLA3 and to elucidate the underlying mechanisms.
Method: Three groups of mice, AAV-luciferase empty vector (AAV-LUC), AAV-WT and AAV-MT received chow diet (CD) or WD for 8 wks. Histology, gene (qPCR), protein (Western blot), lipidomic and transcriptomic (RNA seq) analyses were performed. ANOVA, chi-square for trend and Fisher Exact test were used for comparisons between groups.
Results: *Histology*: *All mice fed WD showed similar weight gain, insulin resistance and dyslipidemia regardless of AAV group. However, AAV-MT fed WD showed increased liver to body weight ratio when compared to all other groups, as well as increased ALT. On CD, all three groups had normal histology. On WD, AAV-LUC and AAV-WT both developed NAFL but AAV-WT had significantly less steatosis, triglyceride (TG) and diacylglycerol (DAG) than AAV-LUC ($p < 0.05$). NASH with fibrosis developed in 82% of AAV-MT mice compared to 35% of AAV-WT and 7% of AAV-LUC ($p < 0.01$ for all). *Lipidomics*: AAV-MT on WD (vs CD) had higher FFA, DAG, TG, ceramides, free cholesterol and multiple inflammatory eicosanoids (8-, 11-, 12-, 15-HETE) ($p < 0.05$); only DAG and eicosanoids were increased in AAV-MT vs AAV-LUC on WD. *Transcriptomics*: AAV-WT (vs AAV-LUC) on WD induced pathways related to inflammation. AAV-MT (vs AAV-WT) led to further activation of inflammatory pathways (multiple TLRs, CD14 and STAT3), as well as activation of LXR, FXR and mTOR. Metacore network analysis identified inflammation-innate immunity, iron transport and chemotaxis as the top pathways altered in AAV-MT compared to AAV-WT. *Cell-signaling*: Lipid metabolic targets increased in all groups on WD (ACC, FAS). ER stress markers (eif2α, ATF4, CHOP, GRP78, XBP-1) were significantly increased along with ASK1, p38MAPK and JNK in AAV-MT vs other groups on WD. Fibrogenic (procollagen 1, α-SMA) and oncogenic (pSTAT3/T705) signals were increased only in AAV-MT.
Conclusion: $I^{148}M$ PNPLA3 induces accumulation of multiple lipids and induces ER stress with inflammatory-fibrotic signaling to induce NASH with fibrosis.

PS-050

Novel link between gut-microbiome derived metabolite and shared gene-effects with hepatic steatosis and fibrosis in NAFLD

C. Caussy[1,2], C. Hsu[1], L. Min-Tzu[3], L. Amy[1], R. Bettencourt[1], V. Ajmera[1], B. Shirin[1], J. Hooker[3], S. Ethan[3], L. Richards[1], N. Schork[4], B. Schnabl[5], B. David[1,5], C. Sirlin[3], C. Chi-Hua[3], R. Loomba[6]. [1]*University of California, San Diego, NAFLD Research Center, La Jolla, United States;* [2]*University Lyon 1, Hospices Civils de Lyon;* [3]*University of California, Radiology, San Diego;* [4]*J. Craig Venter Institute, Human Biology;* [5]*University of California, Medicine, Gastroenterology, San Diego;* [6]*University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States*
Email: ccaussy@ucsd.edu

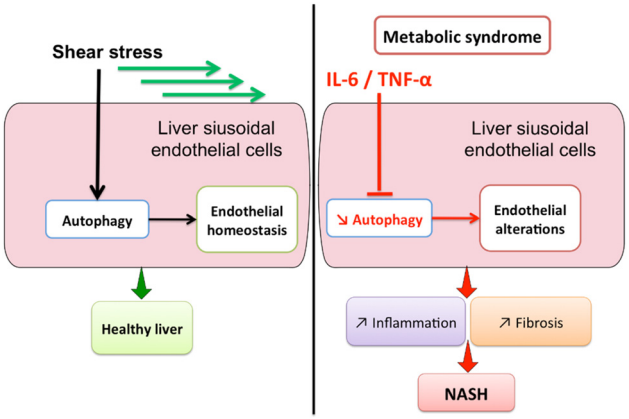
Background and Aims: Previous studies have shown that gut-microbiome is associated with NAFLD. We aimed to examine if serum metabolites especially those derived from the gut-microbiome have a shared gene-effect with hepatic steatosis and fibrosis.
Method: This is a cross-sectional analysis of a prospective discovery cohort including 156 well-characterized community-dwelling twins and families residing in Southern California with untargeted metabolome profiling assessment. Hepatic steatosis was assessed using magnetic-resonance-imaging proton-density-fat-fraction (MRI-PDFF) and fibrosis using MR-elastography (MRE). A twin AE model was used to estimate the shared gene-effect between metabolites and hepatic steatosis and fibrosis. The findings were validated in an independent prospective validation cohort of 156 participants with biopsy-proven NAFLD including shotgun metagenomics sequencing assessment in a subgroup of the cohort.
Results: The mean (±sd) age and BMI of the *discovery* cohort were 46.3 (±19.8) years and 26.6 (±6.0) kg/m2, respectively, and 36 subjects (23%) had NAFLD (MRI-PDFF ≥ 5%) and 28 subjects (18%) had hepatic fibrosis (MRE > 3 kPa). In the *discovery* cohort, 56 metabolites including 6 microbial metabolites had a significant shared gene-effect with both hepatic steatosis and fibrosis after adjustment for age, sex and ethnicity. In the *validation* cohort 6 metabolites were associated with advanced fibrosis. Among them, only one microbial metabolite, 3-(4-hydroxyphenyl)lactate, remained consistent and statistically significantly associated with liver fibrosis in the *discovery* and *validation* cohort (fold-change of higher-MRE versus lower-MRE:1.78,p < 0.001 and of advanced versus no advanced fibrosis:1.26, p = 0.037, respectively). The share genetic determination of 3-(4-hydroxyphenyl)lactate with hepatic steatosis was R_G:0.57,95%CI:0.27–0.80, p < 0.001 and with fibrosis was R_G:0.54,95%CI:0.036–1,p = 0.036. Pathway reconstruction linked 3-(4-hydroxyphenyl)lactate to several human gut-microbiome species. In the *validation* cohort, 3-(4-hydroxyphenyl)lactate was significantly correlated with the abundance of several gut-microbiome species including species previously reported as associated with advanced fibrosis.
Conclusion: Gut-microbiome-derived metabolite 3-(4-hydroxyphenyl)lactate shares gene-effect with hepatic steatosis and fibrosis and may be a biomarker of the severity of NAFLD.

PS-051

Defective autophagy in liver sinusoidal endothelial cells promotes non alcoholic steatohepatitis and fibrosis development

A. Hammoutene[1,2], J. Lasselin[1,2], A.-C. Vion[1,2], N. Colnot[3,4], V. Paradis[3,4,5], S. Lotersztajn[4,5], C. Boulanger[1,2], P.-E. Rautou[1,2,4,6]. [1]*INSERM U970, Paris Cardiovascular Research Center – PARCC, Paris, France;* [2]*Université Paris Descartes, Sorbonne Paris Cité, UMR-S970, Paris, France;* [3]*Service d'Anatomie Pathologique, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France;* [4]*Université Denis Diderot-Paris 7, Sorbonne Paris Cité, Paris, France;* [5]*UMR 1149 INSERM, Inflammation Research Center, Paris, France;* [6]*Service d'Hépatologie, DHU Unity, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France*
Email: amsadel@hotmail.com

Background and Aims: Autophagy is a cellular conserved process involved in the degradation of dysfunctional material. Nothing is known about the role of autophagy in liver sinusoidal endothelial cells (LSECs) in chronic liver diseases. Our aim was to analyze the potential implication of autophagy in LSECs in non-alcoholic steatohepatitis (NASH) and fibrosis.
Method: (a) Human samples: We quantified autophagic vacuoles in LSECs from patient without liver histological abnormalities, with simple steatosis or with NASH. **(b) Cultured LSECs:** We analyzed autophagic flux in transformed liver sinusoidal endothelial cells (TSECs) exposed to shear stress using chloroquine. We then tested the effect of IL-6, TNFα, MCP-1 and insulin (at concentrations present in the portal venous blood of patients with NASH) on autophagy in TSECs. **(c) Transgenic mice:** We analyzed the effect of a defect in endothelial autophagy on early stages of NASH, by using *Atg5$^{lox/lox}$-VECadherinCre^{+}* or *Atg7$^{lox/lox}$-VECadherinCre^{+}* mice, fed a high fat diet (HFD) for 16 weeks, and on advanced stages of liver fibrosis by treating *Atg5$^{lox/lox}$-VECadherinCre^{+}* mice with CCL4 (6 weeks).



Results: (a) Human samples: LSECs from patients with NASH contained twice less autophagic vacuoles than LSECs from patients without liver histological abnormalities or from patients with simple steatosis. **(b) Cultured LSECs:** TSECs exposed to shear stress exhibited an effective autophagic flux. IL-6 and TNFα decreased autophagy level (LC3II/GAPDH) in TSECs, but MCP-1 and insulin had no effect. **(c) Transgenic mice:** Compared to littermate controls, mice deficient in endothelial ATG5 fed a HFD had a more frequent nodular liver surface, a higher liver expression of inflammatory genes (*Mcp-1* and *Rantes*) and more liver fibrosis (increased liver gene expression of *Collagen1α2* and *Tgfβ1* and more Picrosirius staining). Similar results were obtained with mice deficient in ATG7 in endothelial cells. Mice deficient in ATG5 in endothelial cells treated with CCL4 had more liver fibrosis (more liver *Collagen1α2* and *Tgfβ1* mRNA, more Picrosirius staining).
Conclusion: Autophagy is defective in LSECs of patients with NASH. IL-6 and TNFα present in the portal blood of patients with NASH could be responsible for this defect. Autophagy defect in LSECs contributes to the development of liver inflammation and fibrosis at early and advanced stages of the disease. Stimulating endothelial autophagy could be an attractive strategy for NASH treatment.

PS-052

Modelling non-alcoholic fatty liver disease using human induced pluripotent stem cells

C.M. Morell[1], S. Tilson[1], M. Perrin[1], T. Gieseck[1], I. Geti[1], C. Rimland[1], F. Sampaziotis[1], L. Vallier[1,2]. [1]*Wellcome Trust – MRC Cambridge Stem Cell Institute, Surgery, United Kingdom;* [2]*Wellcome Trust Sanger Institute, United Kingdom*
Email: cmm94@cam.ac.uk

Background and Aims: The incidence of non-alcoholic fatty liver disease (NAFLD) in the western world has strongly increased in recent

years, while therapeutic interventions remain limited to liver transplant for end stage disease. Our understanding on NAFLD pathogenesis remains elusive due to the lack of a suitable tool to faithfully recapitulate the human pathology. Indeed, growing primary hepatic cells remains difficult while currently available culture systems do not capture tissue organization and cellular diversity. human Induced Pluripotent Stem Cells (hIPSC) provide an advantageous opportunity, since they retain the ability to self-renew and to differentiate into liver cells. Here, we aimed to take advantage of this unique system by developing a novel *in vitro* platform for NAFLD modeling that mimics the hepatic architecture by reproducing its multicellularity.

Method: We generated hepatocytes, cholangiocytes and macrophages from hIPSC, while the LX2 cell line was used to model stellate cells. The hepatic microenvironment was reproduced by co-culturing the cells in a 3D collagen matrix, taking advantage of fluorescent reporter cell lines to monitor cellular interactions. For each cell type, gene expression analyses, immunofluorescence and biochemical assays were performed to monitor key functions and markers. Free fatty acids were used to induce NAFLD phenotype.

Results: In the 3D environment, hepatocyte like cells (HLC) retained the expression of typical hepatocyte markers and functions, and their maturation improved with time in culture. Cholangiocytes preserved their biliary identity in the collagen matrix, while LX2 cells did not show an activated phenotype. Similarly, macrophage polarization was not influenced by the 3D environment. Interestingly, HLC spontaneously arranged around biliary structures without losing their functionality, while LX2 established contacts with HLC only after TGFβ treatment. Fatty acids treatment led to steatosis and lipotoxicity in HLC, and also interfered with CYP3A4 activity. The presence of non-parenchymal cells sustained fatty acid-induced hepatocyte damage.

Conclusion: Different hepatic cell types can be co-cultured in our novel 3D platform to model pathophysiological cellular interactions. We were able to mimic the mechanisms of hepatocytes steatosis and lipotoxicity, including the inflammatory and fibrotic response associated with NAFLD progression. Thus, our system represents an important step forward to model NAFLD *in vitro*.

PS-053

NLRP6 Inflammasome-mediated intestinal dysbiosis drives steatohepatitis and promotes HCC progression

K. Schneider[1], A. Mohs[1], L.S. Candels[1], C. Elfers[1], L. Lijun[1], V. Bieghs[1], E. Latz[2,3], I. Bergheim[4], T. Strowig[5], C. Trautwein[6]. [1]*University Hospital RWTH Aachen, Department of Medicine III, Aachen, Germany;* [2]*University Hospital Bonn, Institute of Innate Immunity, Bonn, Germany;* [3]*University of Massachusetts Medical School, Department of Infectious Diseases and Immunology, Worcester;* [4]*University Vienna, Department of Nutritional Sciences, Vienna, Austria;* [5]*Helmholtz Centre for Infection Research, Microbial Immune Regulation Research Group, Braunschweig, Germany;* [6]*University Hospital RWTH Aachen, Department of Medicine III, Aachen, Germany*
Email: kai.markus.schneider@gmail.com

Background and Aims: Today, the link between intestinal dysbiosis and chronic liver disease has been well established. However, the role of intestinal microbiota in HCC development remains incompletely understood. Here, we hypothesized that Nlrp6 mediated intestinal dysbiosis may impact hepatic inflammation and HCC development.

Method: Hepatocyte-specific NEMO/IKKγ knockout mice ($NEMO^{\Delta hepa}$) were used as a model of experimental steatohepatitis. Disease progression in $NEMO^{\Delta hepa}$ mice was monitored in different hygienic/microbiota environments of our animal facility. Additionally, $Nemo^{\Delta hepa}$ mice were crossed with Nlrp6 knockout ($Nlrp6^{-/-}$) animals. Here the impact of intestinal dysbiosis on innate and adaptive immune response during progression of steatohepatitis towards HCC was studied. Finally, microbiota modulation was performed using treatment with broad-spectrum antibiotics (AB).

Results: $NEMO^{\Delta hepa}$ mice displayed striking differences in disease activity depending on the microbiota environment as evidenced by significantly elevated liver functions tests (LFTs) and tumor burden in the less restrictive area of our animal facility. In line, intestinal dysbiosis in $NEMO^{\Delta hepa}/Nlrp6^{-/-}$ mice was associated with more pronounced steatohepatitis encompassing elevated LFTs, leukocyte infiltration and apoptotic cell death, ultimately leading to aberrant hepatocyte proliferation and increased tumor burden in 52 weeks old $NEMO^{\Delta hepa}/Nlrp6^{-/-}$ mice. Interestingly, $NEMO^{\Delta hepa}/Nlrp6^{-/-}$ mice displayed an impaired gut barrier function assessed by intestinal tight junction and mucus expression, which was followed by a more pronounced innate immune response and infiltration of monocyte derived macrophages (MoMFs) in 52 weeks old $NEMO^{\Delta hepa}/Nlrp6^{-/-}$ compared to $NEMO^{\Delta hepa}$ mice. Interestingly, CD8+ cytotoxic T-cells were already suppressed at an early 13 weeks timepoint in livers of $NEMO^{\Delta hepa}/Nlrp6^{-/-}$ compared to $NEMO^{\Delta hepa}$ mice, indicating that Nlrp6-mediated intestinal dysbiosis may negatively affect antitumor immunity. Strikingly, depletion of the intestinal microbiota by administration of broad-spectrum antibiotics suppressed inflammatory cell infiltration and ameliorated steatohepatitis by promoting a restorative $Ly6C^{low}$ phenotype of hepatic macrophages.

Conclusion: Nlrp6-mediated intestinal dysbiosis promotes steatohepatitis progression and HCC development by shaping the hepatic inflammatory microenvironment. Microbiota modulation holds therapeutic potential for preventing liver disease progression.

PS-054

Serum bile acids alteration is associated with the presence of NAFLD in twins, and dose-dependent changes with increase in fibrosis stage in patients with biopsy-proven NAFLD

C. Caussy[1,2], C. Hsu[1], S. Seema[1], B. Shirin[1], K. James[1], C. Faulkner[1], R. Bettencourt[1], M. Valasek[3], L. Richards[1], B. David[1,4], R. Loomba[1,4,5]. [1]*University of California, NAFLD Research Center, San Diego;* [2]*University Lyon 1, Hospices Civils de Lyon;* [3]*University of California, Pathology, San Diego;* [4]*University of California, Medicine, Gastroenterology, San Diego;* [5]*University of California, Division of Epidemiology, Department of Family and Preventive Medicine, San Diego*
Email: ccaussy@ucsd.edu

Background and Aims: Bile acids (BA) alteration has been reported in patients with NAFLD. Data characterizing alteration in BA in the entire spectrum of NAFLD are limited. We aimed to assess serum BA level in twins with and without NAFLD, and then examine its association with stage of fibrosis and presence of NASH in patients with biopsy-proven NAFLD.

Method: This is a cross-sectional analysis of 2 prospective cohorts: a Twin and Family cohort of 156 participants assessed using MRI-PDFF, and a biopsy-proven NAFLD cohort of 156 participants using NASH CRN Histologic Scoring System. The serum level of 22 BA using LC/MS was assessed by Metabolon Inc. Differences between BA were assessed using Welch t test and Kruskal-Wallis test.

Results: In the Twin and Family cohort (mean age 46.3 yrs, 73.1% women), 23% of the subjects had NAFLD (MRI-PDFF ≥ 5%). The mean levels of 3 primary BAs and 1 secondary BA was significantly higher in NAFLD versus non-NAFLD controls including glycocholate (GCA), taurocholate (TCA), taurochenodeoxycholate (TCDCA), and ursodeoxycholate (UDCA) with fold-changes of 2.36, p = 0.046; 5.25, p = 0.02; 4.08, p = 0.03; 1.34, p = 0.002 respectively. The mean level of 2 secondary BAs were significantly lower in NAFLD versus non-NAFLD controls including glycohyocholate (GHCA) and 3b-Hydroxy-5-cholenoic acid (3beta-OH-delta 5) with fold-changes of 0.62, p = 0.004 and 0.7, p = 0.002 respectively.

In the biopsy-proven NAFLD cohort (mean age 49.8 yrs, 58.3% women), the distribution of stage 0, 1, 2, 3 and 4 fibrosis was 42.3%, 32.7%, 10.3%, 8.3%, and 6.4%, respectively; 13.0% of individuals had NAFL, 11.7% had borderline NASH and 75.3% had definite NASH. No significant differences in BA profile were seen between NAFL versus NASH. The level of primary BAs GCA, TCA, TCDA,

glycochenodeoxycholate (GCDCA) and tauro-beta-muricholate (TβMCA) was higher in fibrosis stage ≥2, ≥3 and ≥4 Figure 1. In addition, TCA and TβMCA levels increased across all stages of fibrosis (p = 0.004, and 0.001, respectively). The level of secondary BAs was higher in fibrosis stage ≥2 for Glycolithocholate (GLCA), GLCA sulfate, and taurideoxycholate (TDCA); in fibrosis stage ≥3 and ≥4 for GHCA and glycoursodeoxycholate (GUDCA); and in fibrosis stage ≥4 for tauroursodeoxycholate (TUDCA) Figure.

		Fold-change in fibrosis stage			
		F1-4 vs 0	F2-4 vs 0-1	F3-4 vs 0-2	F4 vs 0-3
Primary	Cholate (CA)	0.91	1.03	0.91	0.23*
	Glycocholate (GCA)	1.58	2.99**	3.83***	5.1**
	Glycochenodeoxycholate (GCDCA)	1.62	2.86*	4.07***	6.1**
	Taurochenodeoxycholate (TCDCA)	4.3	8.62**	11.22**	20.07**
	Taurocholate (TCA)	2.74*	5.73***	7.27**	12.17**
	Tauro-beta-muricholate (TβMCA)	4.57*	9.15***	8.13**	3.67*
Secondary	Glycolithocholate (GLCA)	1.95	2.91*	4.00	5.82
	Glycolithocholate sulfate(GLCAS)	1.31	1.66*	1.95	1.73
	Taurodeoxycholate (TDCA)	1.94	3.66*	3.09	3.61
	Glycohyocholate (GHCA)	1.7	3.4	5.48*	9.62*
	Glycoursodeoxycholate (GUDCA)	0.91	1.53	1.65*	2.41*
	Tauroursodeoxycholate (TUDCA)	2.17	4.69	4.04	8.33*

Figure 1: Serum BAs differences across fibrosis stage in biopsy-proven NAFLD.

Conclusion: Serum bile acid profile alterations are seen across the entire spectrum of NAFLD. Serum bile acid profiles did not differ significantly between NAFL versus NASH but were significantly perturbed in higher stages of fibrosis and especially in cirrhosis.
Fold change of BAs level across the dichotomized stage of fibrosis, *p < 0.05, ** p < 0.01, ***p < 0.001.

PS-055
Down-regulation of hepatic MBOAT7 by hyperinsulinemia favors steatosis development

M. Meroni[1,2], P. Dongiovanni[3], M. Longo[1], R. Rametta[4], S. Badiali[5], S. Fargion[1,2], S. Romeo[6], S. Gatti[7], L. Valenti[1,2]. *[1]University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; [2]Fondazione IRCCS Cà Granda, Internal Medicine, Milan, Italy; [3]Fondazione IRCCS Cà Granda, Milano; University of Milan, Italy, Internal Medicine, Milano, Italy; [4]Fondazione IRCCS Cà Granda, University of Milan, Italy, Internal Medicine, Italy; [5]Fondazione IRCCS Cà Granda, Surgery, Milan, Italy; [6]University of Gothenburg, Department of Molecular and Clinical Medicine, Sweden; [7]Fondazione IRCCS Cà Granda, Center for Surgical Research, Milan, Italy*
Email: luca.valenti@unimi.it

Background and Aims: We have recently shown that the rs641738 C > T variant in Membrane bound O-acyltransferase domain-containing 7 gene (MBOAT7), involved in phosphatidylinositol acyl-chain remodeling, increases the risk of developing nonalcoholic fatty liver disease (NAFLD), inflammation and fibrosis due to lower protein expression. Aim of this study was to evaluate the regulation of hepatic MBOAT7 and the impact on hepatic fat accumulation.
Methods: We examined hepatic MBOAT7 in 119 obese patients and in experimental models. We silenced hepatic MBOAT7 by i.v. administration of antisense oligonucleotides modified by morpholinos (MPO) for 4 consecutive days in C57Bl/6 male mice (n = 5) and in HepG2 cell lines, using the Crispr/Cas9 technology.
Results: In obese patients, hepatic mRNA levels of MBOAT7 progressively decreased from normal liver to simple steatosis and NASH (p < 0.05). At multivariate analysis, type 2 diabetes (p < 0.05), necroinflammation (p < 0.01) and MBOAT7 genotype (p < 0.01) were independently associated with MBOAT7 downregulation (Table 1). The mRNA and protein levels of MBOAT7 were reduced in experimental models of NAFLD, such as the methionine-choline deficient diet, but more so in genetically obese *ob/ob* mice and in insulin resistant mice with Insulin receptor haploinsufficiency, characterized by development of hyperinsulinemia (p < 0.05). Furthermore, in wild-type male mice MBOAT7 was downregulated by refeeding or by i.p. injections of insulin concomitantly with the rise of insulin levels and activation of hepatic insulin signaling through PI3K and AKT. Insulin (300 nM) downregulated MBOAT7 in primary mouse hepatocytes in a InsR/PI3Kinase/FoxO1 dependent manner. Finally, MPO induced a 45% silencing of hepatic MBOAT7 comparable to that associated with the genetic risk variant, resulting in a 80% increase in hepatic triglyceride content (p < 0.05 *vs* scramble) and in the development of microvesicular steatosis, related to enhanced expression of fatty acids transporters. Consistently, MBOAT7 knock-out cell lines developed spontaneously steatosis (p < 0.05).

Table 1:

	Estimate SE	*P* value
Age, years	−0.00±0.01	0.98
Sex, F	−0.07±0.09	0.43
BMI, Kg/m^2	+0.00±0.01	0.87
T2DM, yes	−0.16±0.08	0.04*
Steatosis	−0.02±0.07	0.84
Necroinflammation	−0.31±0.11	0.005*
PNPLA3, I148M alleles	−0.04±0.09	0.66
MBOAT7, T alleles	−0.25±0.08	0.004*

Conclusion: These data suggest that hyperinsulinemia causes down-regulation of hepatic MBOAT7, which both genetic and experimental data indicate is causally implicated in steatosis development. Further studies are needed to investigate the mechanisms linking reduced phosphatidyl-inositol desaturation by MBOAT7 with the development of steatosis and hepatic inflammation.

PS-056
NLRP3 inflammasome activation in hepatocytes results in pyroptotic cell death, release of NLRP3 particles and liver fibrosis

S. Schuster[1], F.A. Guerra[2], C.D. Johnson[1], C.J. Calvente[1], D. Povero[1], A. Eguchi[3], M.D. Mcgeough[1], H.M. Hoffman[1], P. Pelegrin[4], A. Feldstein[1]. *[1]University of California San Diego, Department of Pediatrics, San Diego, United States; [2]University of Valencia, Department of Pharmacology, Valencia, Spain; [3]Mie University, Department of Gastroenterology and Hepatology, Mie, Japan; [4]Hospital Universitario Virgen de la Arrixaca, Departamento de Cirugía, Murcia, Spain*
Email: suschuster@ucsd.edu

Background and Aims: Pyroptosis is a form of programmed cell death initiated by inflammasomes and characterized by Caspase-1 activation and pore formation in the cell membrane. Global NLRP3 inflammasome activation is sufficient to induce liver inflammation and fibrosis. Here, we tested the hypothesis that hepatocytes undergo pyroptosis upon NLRP3 inflammasome activation with subsequent release of NLRP3 particles that amplify and perpetuate inflammasome-driven fibrogenesis.
Method: In order to test the direct effects of persistent NLRP3 activation, we generated a hepatocyte-specific *Nlrp3* mutant mice strain (L351P *Nlrp3*^{KI}CreA) with constitutively activated NLRP3. Pyroptosis was assessed *ex vivo* in primary hepatocytes isolated from *Nlrp3*^{KI}CreA mice using FAM-FLICA Caspase-1/Propidium iodide (PI) assay. Liver fibrosis development and hepatic stellate cell (HSC) activation was studied in *Nlrp3*^{KI}CreA mice using Sirius red and alpha-SMA staining and qPCR analysis. HepG2 cells were incubated with LPS + Nigericin (Nig) or Palmitic acid (PA). AC-YVAD-AOM was used as an irreversible inhibitor of Caspase-1. LX2 cells were stimulated with ASC-YFP specks released from transfected HepG2 cells treated with LPS + Nig/PA or NLRP3-YFP speck particles isolated from a stable NLRP3 (p.D303N)-YFP hyperactive mutant HEK cell line to study endocytosis capability. NLRP3 particle uptake was analysed by confocal microscopy and immunoblot analysis.

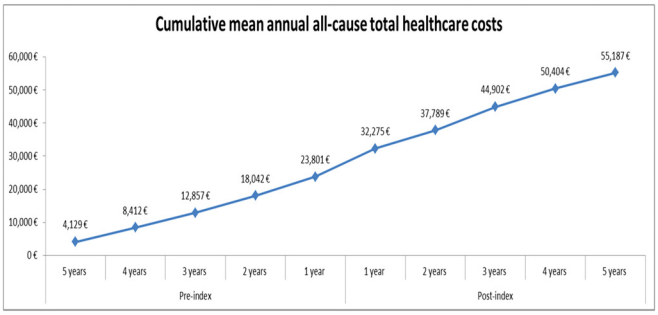
Results: Primary hepatocytes isolated from *Nlrp3*^{KI}CreA showed marked increase in pyroptotic cell death and Caspase-1 activation compared to WT control (5-fold, $p < 0.001$). Further, *Nlrp3*^{KI}CreA mice showed increased activation of HSCs (*Timp1:* 3.4-fold, *Fibronectin1:* 1.8-fold, $p < 0.05$) and liver fibrosis as assessed by morphometric quantitation of Sirius red and alpha-SMA staining (1.9-and 1.5-fold, $p < 0.05$). HepG2 cells incubated with LPS + Nig and LPS + PA showed increased Caspase-1 activation and pyroptosis as well as Caspase-1-dependent increased cell membrane permeability. Immunoblot analysis of HepG2 supernatant demonstrated the release of NLRP3 inflammasome components (NLRP3, ASC, pro-Caspase-1, pro-IL-1beta) including the activated form of Caspase-1 and mature form of IL-1beta. Further, our results revealed that LX2 cells are able to engulf ASC-YFP and NLRP3-YFP particles released from transfected HepG2 cells after pyroptosis induction or isolated from NLRP3 (p. D303N) mutant HEK cells, respectively.
Conclusion: Inflammasome activation in hepatocytes induces Caspase1-dependent pyroptosis and the release of NLRP3 inflammasome particles that are efficiently engulfed by HSC. Mice with hepatocyte-specific NLRP3 overactivation showed HSC activation and liver fibrosis demonstrating a novel crosstalk between hepatocytes and HSC. This represents a novel mechanism to propagate liver injury and liver fibrosis development.

Public health: General

PS-057
Substantial comorbidities and rising economic burden in real-world non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH) patients with compensated cirrhosis (CC): A large German claims database study

A. Canbay[1], D. Meise[2], J.S. Haas[2]. [1]*Department of Gastroenterology, Hepatology and Infectiology, University of Magdeburg Medical School, Magdeburg, Germany;* [2]*Xcenda GmbH, Hannover, Germany*
Email: ali.canbay@med.ovgu.de

Background and Aims: NAFLD/NASH is a common cause of CC in Western countries and CC is associated with increased morbidity and mortality. However, Germany-specific data is lacking. This study examined the comorbidities, mortality and health care costs among German NALFD/NASH patients once they develop CC.
Method: Patients aged ≥18 years with a NAFLD/NASH diagnosis (ICD-10-GM) between 2011 and 2016 were identified retrospectively from the InGef research claims database with about 4 million insurees. They were followed from first NAFLD/NASH diagnosis and flagged as CC patients at the first occurrence of a CC diagnosis, which identified the index date. Patients were excluded if they had <1 year of continuous enrolment (CE) pre-index and post-index, and if they presented with hepatitis, Wilson's disease, Gaucher disease, LAL-D, alcoholism incl. alcoholic liver disease, HIV, primary biliary cholangitis, primary sclerosing cholangitis or hemochromatosis. Further, progression to decompensation, hepatocellular carcinoma and liver transplant in the post-index period was not allowed. All-cause mortality was investigated within 1 year of post-index period. Mean annual costs were also examined for patient subsets with 1–5 years of CE pre-index and post-index.
Results: The study population included 555 NAFLD/NASH patients with CC having 1 year of CE pre-index and post-index. Mean age was 66.1 years and 57.3% were males. In the post-index period, 7.6% of the patients deceased. The most common comorbidities were hypertension, diabetes, and dyslipidemia with annual pre-index prevalence rates of 76.6%, 53%, and 49.2%, respectively. 555 NAFLD/NASH patients with CC cumulated €4,702,927 in 1-year post-index time period. The annual all-cause healthcare costs averaged €5,759 in the pre-index period and €8,474 in the post-index period (+47%) ($p < 0.001$). The cost driver was the inpatient setting representing 41.3% in the pre-index and 57.1% in the post-index period. Cumulative mean annual all-cause healthcare costs increased 132% over a 5-year period, from €23,801 (1-year pre-index) to €55,187 (5-year post-index).



Conclusion: German NAFLD/NASH patients with CC have a high comorbidity burden. Healthcare costs are the highest in the first year following CC diagnosis with inpatient costs as the primary driver. Cumulative mean annual all-cause costs increased 132% over a 5-year period. Novel treatment options are needed to improve patient outcomes.

PS-058
Early versus delayed hepatitis C treatment provides increased health benefits at lower costs: A pan-genotypic cost effectiveness analysis set in Scotland

B. Pinsky[1], D. Mitchell[2], Y. Sanchez[1], S. Johnson[2], S. Sammy[3]. [1]*Abbvie Inc, HEOR, North Chicago, United States;* [2]*Medicus Economics LLC, Boston, United States;* [3]*UCLA, David Geffen School of Medicine, Los Angeles, United States*
Email: brett.pinsky@abbvie.com

Background and Aims: As hepatitis C virus-(HCV) infected patients who achieve sustained virologic response from advanced liver disease states continue to face an excess risk of liver-related and extrahepatic complications, treatment in early disease states is believed to increase health benefits and reduce downstream medical costs. This study considers both liver-related and extrahepatic complications to assess the cost-effectiveness of treating HCV patients across all genotypes at different fibrosis stages in Scotland.
Method: A health state transition model of the natural history of HCV was developed to forecast liver-related and economic outcomes over a lifetime horizon. The model population and mITT efficacy rates were based on clinical trials of glecaprevir (identified by AbbVie and Enanta) and pibrentasvir. Genotype and fibrosis distribution were identified from UK patient tracker data. Costs in UK pounds were based on systematic literature review. Comparative analyses were conducted for treatment in different fibrosis stages of liver disease: mild (F0–F1); moderate (F2–F3), and compensated cirrhosis (F4/CC). Health outcomes included lifetime risks of liver decompensation (DCC), hepatocellular carcinoma (HCC), liver transplantation (LT), and liver-related death (LrD). Other outcomes included lifetime costs post-treatment and quality-adjusted life years (QALYs), both discounted at a 3.5% rate.
Results: Lower rates of DCC, HCC, LT, and LrD were predicted in HCV patients when treatment was initiated in mild vs. CC disease (DCC: 4.0% vs. 11.6%; HCC: 1.8% vs. 35.2%; LT: 0.4% vs. 2.6%; LrD: 3.8% vs. 41.1%). While only considering the liver-related complications, early vs delayed treatment resulted in lower lifetime costs (mild: £30,719; moderate: £33,055; CC: £59,137) and greater lifetime QALYs (mild: 16.20; moderate: 13.86; CC: 10.05). When extrahepatic manifestations (EHMs) are considered, lifetime costs increased (mild: £33,297; moderate: £35,402; CC: £61,204).

Table: (abstract: PS-058)

	Decompensated cirrhosis	Liver cancer	Liver transplant	Liver-related mortality	Lifetime costs (including EHMs)	Lifetime QALYs
Genotypes 1-6						
Mild (F0-F1)	4.0%	1.8%	0.4%	3.8%	£33,297	16.20
Moderate (F2-F3)	8.9%	4.0%	1.0%	9.1%	£35,402	13.86
CC (F4)	11.6%	35.2%	2.6%	41.1%	£61,204	10.05

Conclusion: Delay of HCV treatment for higher fibrosis stages resulted in increased lifetime risks of liver-related morbidity and mortality, greater lifetime costs, and lower QALYs regardless of genotype. The magnitude of this impact increases when costs associated with EHMs of HCV are considered. Treatment at earlier fibrosis stages is a cost-effective and dominant strategy (more QALYs gained at a lower cost) compared to treatment at later stages.

PS-059

Outbreak of acute hepatitis A involving young men in Lombardy Region, Italy: risk factors, clinical and virological characteristics

M. Iavarone[1], M. Viganò[2], C. Orcese[3], M. Coen[4], C. Oggioni[5], A. Spinetti[6], A. Soria[7], C. Galli[8], C. Tagliacarne[8], L. Scaramella[1], M. Merli[3], R. Rossotti[3], G.A. Gubertini[4], S. Merli[4], A. Piscitelli[5], V. Castelli[9], A. Comelli[10], D. Cereda[11], M. Gramegna[11], M. Puoti[3], A. Gori[12], M.G. Rumi[2], F. Castelli[13], P. Lampertico[1], L. Romanò[8].
[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milano, Italy; [2]Ospedale San Giuseppe, Università degli Studi di Milano, Division of Hepatology, Milano, Italy; [3]ASST Grande Ospedale Metropolitano Niguarda, Infectious Diseases Department, Milano, Italy; [4]ASST Fatebenefratelli – Sacco, First Division of Infectious Diseases, Milano, Italy; [5]ASST Santi Paolo e Carlo, Quality and Risk Management, Milano, Italy; [6]University of Brescia and ASST Spedali Civili Brescia, University Department of Infections and Tropical Diseases, Brescia, Italy; [7]San Gerardo Hospital University of Milano-Bicocca, Clinic of Infectious Diseases, Monza, Italy; [8]Università degli Studi di Milano, Dipartimento di Scienze Biomediche per la Salute, Milano, Italy; [9]San Gerardo Hospital University of Milano-Bicocca Monza, Clinic of Infectious Diseases, Monza, Italy; [10]University of Brescia and ASST Spedali Civili, University Department of Infections and Tropical Diseases, Brescia, Italy; [11]Regione Lombardia, Direzione Generale Salute, Milano, Italy; [12]San Gerardo Hospital University of Milano-Bicocca, Clinic of Infectious Diseases, Monza, Italy; [13]University of Brescia and ASST Spedali Civili Brescia, University Department of Infections and Tropical Diseases, Brescia, Italy
Email: pietro.lampertico@unimi.it

Background and Aims: Hepatitis A virus (HAV) is transmitted mainly via the faecal-oral route and/or contaminated aliments. In last decades, several outbreaks of HAV in men who have sex with men (MSM) classified HAV as a sexually transmitted disease (STD). We aimed to analyse an ongoing HAV outbreak among a large group of young MSM adults from 7 hospitals in Lombardy region in Italy with respect to patients' characteristics and viral phylogenetic analysis.
Methods: We prospectively analysed 244 cases of acute HAV between January and May 2017 recording for all patients' demographics data, risk factors, presenting symptoms, sexual orientation, co-morbidities and further STD infections. The phylogenetic correlation of the current circulating viruses among them and other HAV strains was assessed by sequencing of the VP1/2A region.
Results: Most patients were male (230, 94%) with median age 33 years (range 18–76). One hundred and thirty-three (55%) were MSM, 17% had a chronic liver disease, 19% were HIV positive, 5% were active drug users, 63% referred a possible sexual contact in last 3 months and 18% with a HAV positive partner. One hundred and eighty-one (74%) required hospitalization (median stay 7 days, range 2–44). The median ALT and bilirubin peak levels were 2,368 (47–8,914)IU/ml and 6.6 (0.4–18)mg/dl, respectively. No liver transplant was needed. Molecular phylogenetic analyses revealed that 93% (197/211) patients were infected by HAV genotype IA and 7% (14/197) by genotype IB. Moreover, all genotype IA cases belong to one of the three separate cluster recently reported in a multi-country European outbreak: 59% (117/197) of cases were infected with UK-strain, 40% (79/197) with Netherlands-strain and 1% (1/197) with Germany-strain. Interestingly, the cases infected with Netherlands strain were prevalent at the beginning of the outbreak (January 100%), while the UK-strain increased in the last months (May 68%, June 70%).
Conclusions: Ongoing HAV in Lombardy primarily affects young MSM and is phylogenetically linked to current HAV outbreaks described in other European countries. Due to the high admission rate, these outbreaks may impact the admission pattern of referral Liver and Infectious Units. Control measures, i.e. vaccinations programs tailored to the MSM community, must be taken to control further spreading.

PS-060

Food insecurity increases the risk of advanced fibrosis in diabetics with nonalcoholic fatty liver disease

R. Rosenblatt[1], A. Buckholz[2], G. Ghosh[2], A. Jesudian[1], C. Lucero[1], R. Schwartz[1], B. Fortune[1], S. Kumar[1]. *[1]New York Presbyterian Hospital – Weill Cornell Medicine, Division of Gastroenterology and Hepatology, New York, United States; [2]New York Presbyterian Hospital – Weill Cornell Medicine, Department of Medicine, New York, United States*
Email: RussellRosenblatt@gmail.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a leading cause of liver disease in developed nations. Outcomes in NAFLD are directly related to the stage of fibrosis, with an increased risk of overall and liver-related mortality with increasing stage. Diabetes, obesity, and age are well-established risk factors of advanced fibrosis in NAFLD, while there has been less investigation into the impact of economic factors. Patients with food insecurity have been found to have increased risk of both obesity and diabetes, related to lack of choice of food. This study aims to investigate the impact of food insecurity on advanced fibrosis in diabetics with NAFLD a nationally-representative survey.
Method: The National Health and Nutrition Examination Survey (NHANES), a nationally-representative survey, from 2005 to 2014 was

used. Using a validated algorithm, adult patients with diabetes were included. Patients were excluded if they had viral hepatitis, excessive alcohol consumption, were pregnant, or had transaminase elevation >500 IU/l. Advanced fibrosis was diagnosed based on the presence of an ALT > 40 and either an elevated NAFLD fibrosis score, FIB-4 score, or AST to platelet ratio index. The degree of food security was evaluated based on a validated survey included in the NHANES survey. Multivariate logistic regression was performed to evaluate for the presence of advanced fibrosis, and factors were included into the model if they independently increased the risk of advanced fibrosis.
Results: A total of 14,169,411 weighted participants were included in the sample. Most (77.0%) patients had full food security (FFS) while 6.2% had very low food security. Patients with very low food security (VLFS) were younger and more likely to be black and Hispanic. Those with VLFS also had a higher mean body mass index and mean hemoglobin A1c but had no significant differences in transaminase levels. When controlling for age, gender, race, insulin dependence, hemoglobin A1c, body mass index, and duration of diabetes, patients with VLFS had a significantly higher odds of advanced fibrosis (OR 3.34, 95% CI 1.29–8.62, p = 0.01).

Table: Risk of advanced fibrosis by food security level

Food security	OR (95% CI)	p-value
Fully food secure	REF	
Mild food insecurity	1.95 (0.91–4.20)	0.131
Low food security	1.22 (0.49–3.02)	0.75
Very low food security	3.34 (1.29–8.62)	0.01

*Controlling for age, gender, race, body mass index, diabetes duration, insulin dependence, and hemoglobin a1c.

Conclusion: In our study using a nationally-representative survey, VLFS more than tripled a diabetic patient's risk of having advanced fibrosis when controlling for other factors that can independently increase the risk of advanced fibrosis. This study highlights the importance of accounting for economic factors when evaluating patients with NAFLD.

PS-061

Cost-effectiveness analysis of hepatocellular carcinoma screening in hepatitis C cirrhosis after sustained viral response

H.F. Zangneh[1], W.W. Wong[2], B. Sander[3], C.C. Bell[4], K. Mumtaz[5], M. Kowgier[6], A. Van der Meer[6], S.P. Cleary[7], H. Janssen[8], K.K. Chan[9], J. Feld[1]. *[1]University of Toronto, Toronto General Hospital, Toronto Centre for Liver Disease, Toronto, Canada; [2]University of Toronto, School of Pharmacy, Toronto, Canada; [3]University of Toronto, Institute of Health Policy, Management and Evaluation, Canada; [4]University of Toronto, Department of Medicine, Toronto, Canada; [5]Ohio State University, Wexner Medical Center, United States; [6]Erasmus MC University Medical Center, Rotterdam, Netherlands; [7]University of Toronto, Department of Surgery, Toronto, Canada; [8]University Health Network, Toronto, Canada; [9]University of Toronto, Sunnybrook Odette Cancer Centre, Toronto, Canada*
Email: hooman.f.zangneh@mail.utoronto.ca

Background and Aims: Hepatitis C virus-related cirrhosis is strongly associated with hepatocellular carcinoma (HCC) development. After sustained virological response (SVR), the HCC risk in cirrhosis is reduced but not eliminated. Recent developments in direct antiviral agents (DAA) have increased SVR rates even in cirrhosis. HCC screening in cirrhotic patients is cost-effective before treatment; it is unknown whether it remains so after SVR.
Method: We made a Markov model to evaluate the cost-effectiveness of biannual or annual ultrasound (US) screening versus no screening in 50-year-old cirrhotic patients post-SVR. Parameter values were taken from the literature and expert opinion if unavailable. Primary outcomes are quality-adjusted life-year (QALY), cost and incremental cost-effectiveness ratio (ICER). Costs & QALYs were discounted at 5%/year.
Results: With 0.5% constant annual HCC incidence in F3 or F4 patients, biannual & annual screening provide extra 0.164 QALYs (ICER $84242/QALY) and 0.148 QALYs (ICER $53756/QALY), respectively. More recent data show the annual HCC incidence in patients with HCV-related cirrhosis post DAA-induced SVR to be as high as 1.82% which makes biannual HCC screening likely to be cost-effective (ICER $40803/QALY). Incidence has also been reported based on pre-treatment AST to platelet ratio index (APRI). With APRI < 2, the annual HCC incidence is 0.093% meaning that biannual US screening is dominated (ICER -$1024982/QALY). With APRI > 2, even without documented cirrhosis, the annual HCC incidence is 0.892% leading to an ICER of $55916/QALY for biannual screening. Some data suggest that HCC incidence increases, even after SVR, as patients age. With age-stratified HCC incidence, biannual & annual screening offered 0.466 QALYs (ICER $44170/QALY) and 0.396 QALYs (ICER $31549/QALY), respectively. Sensitivity analyses identified HCC incidence and transition rate to symptomatic disease in unscreened population as main drivers of the model.
Conclusion: For biannual US screening to be cost-effective in the post-SVR population, the constant annual HCC incidence must be above 1.1%, lower than the previous 1.5% threshold. With F3 fibrosis or pre-treatment APRI < 2, screening is very unlikely to be cost-effective, challenging current clinical practice guidelines. For cirrhotic patients, biannual or annual US screening is likely cost-effective post-SVR, mainly if HCC risk increases with age. Further data will hopefully allow for improved risk stratification to guide optimal screening strategies.

PS-062

Prevalence and explanatory factors for liver function testing and abnormality in a population-based study of children and young people

W. Li[1], K. Homer[2], K. Boomla[2], J. Robson[2], S. Hull[2], W. Alazawi[1]. *[1]The Blizard Institute, Queen Mary University of London, London, United Kingdom; [2]Centre of Primary Care and Public Health, Queen Mary University of London, London, United Kingdom*
Email: wenhao.li@doctors.org.uk

Background and Aims: Abnormal liver biochemistry is associated with increased liver- and all-cause mortality. Most studies have focussed on older adults and not children and young people (CYP) in whom obesity rates (among other liver risk factors) are rising. We determined the prevalence and explanatory factors of liver biochemistry testing and abnormal results in primary care records for CYP in an ethnically and socially diverse population.
Method: This was a retrospective study using routinely collected primary care electronic healthcare records in 150 contiguous practices in four boroughs in East London, UK. We extracted social and demographic data for all CYP aged 10–25 years who had had liver biochemistry requested between 2015–2017. Alanine transferase (ALT) was used to represent liver biochemistry requests and results. Abnormal ALT was defined as >40 U/l for both sexes. Body mass index (BMI) category thresholds were adjusted for ethnicity.
Results: In 257,746 CYP in East London, 14.1% had ALT measured within the study period. 7% of all ALT tests were abnormal. Valid BMI was captured in 84,574 individuals and the proportion of CYP classed as overweight or obese was 36%.
On multivariate analysis, factors independently associated with ALT testing included South Asian ethnicity (adjusted OR 1.76, p = 0.001, in 18–25 age group) and overweight/obese BMI categories (adjusted OR 1.15, p = 0.0001, in 18–25 age group). ALT testing was strongly associated with patients with known liver disease or those taking medication associated with liver abnormalities, albeit these were small numbers.
The same risk factors were independently associated with an abnormal high ALT result; in particular, South Asian ethnicity (adjusted OR 1.59, p = 0.001) and overweight/obese BMI (adjusted

OR 2.94, p = 0.0001). Individuals who had had an alcohol assessment completed, irrespective of the result, were protected against abnormal ALT (adjusted OR 0.77, p = 0.001).
Conclusion: In the largest population-based study of liver function testing in CYP to date, we show that a significant proportion of CYP have ALT requested and have elevated results. We have not studied abnormalities in AST or GGT, nor applied the Prati thresholds to ALT. Our data may indicate that brief alcohol-related interventions are protective. Apart from patients with prior knowledge or suspicion of liver disease, raised BMI category and ethnicity are significant factors in CYP for abnormal liver test results.

PS-063
Cases of transfusion-transmitted hepatitis E Virus infections at a tertiary referral center

D. Westhölter[1], H. Jens[2], J. Hartl[1], D. Ulrike[2], P. Sven[2], A. Francis[3], R. Meike[4], A.W. Lohse[1], M. Lutgehetmann[5], S. Pischke[1]. *[1]I. Medical Clinic and Polyclinic, University Medical Center Hamburg-Eppendorf, University Medical Center Hamburg-Eppendorf; [2]Institute of Transfusion Medicine, University Medical Center Hamburg-Eppendorf; [3]II. Medical Clinic, University Medical Center Hamburg-Eppendorf, University Medical Center Hamburg-Eppendorf; [4]University Heart Center, University Medical Center Hamburg-Eppendorf, University Medical Center Hamburg-Eppendorf; [5]Institute of Medical Microbiology, University Medical Center Hamburg-Eppendorf, University Medical Center Hamburg-Eppendorf*
Email: d.westhoelter@uke.de

Background and Aims: Hepatitis E is a major threat for immunosuppressed patients, as chronic HEV infection with possibly life-threatening complications might occur. The relevance of blood borne hepatitis E virus (HEV) infections for these patients has been discussed controversially within the last months and still requires further investigations.
Methods: All immunosuppressed patients at our center with an HEV infection between 2011 and 2017 were retrospectively studied (n = 37). All blood products given to chronically HEV infected patients were retrospectively analyzed for the presence of HEV RNA by in-house realtime PCR (LLoD 12 IU/ml).
Results: 11 immunosuppressed patients (11/37, 30%) developed chronic HEV infection. In 4/11 (36%) we were able to identify an HEV positive blood donation as source of HEV transmission. Interestingly two of the chronic HEV infected patients, who were infected by blood-borne transmission, were heart transplant recipients. Both had been treated with a combination of plasmapheresis and rituximab for humoral rejection. As these cases attracted our attention to this proceeding, we tested the remaining 3 heart transplant recipients who were treated according to the same protocol at our center within the last 5 years but none of them had acquired persistent HEV infection.
Conclusions: Blood products are a relevant source of HEV-infection for immunosuppressed individuals and in our series they are responsible for 36% of chronic HEV infections. Thus, we recommend screening of all blood products given to transplant or immunosuppressed recipients for HEV-RNA.

PS-064
Analysis of the influence of alcohol abstinence on the risk of developing hepatocellular carcinoma (HCC) in patients with alcoholic liver cirrhosis (ALC)

A. Castano-Garcia, C. Álvarez-Navascués, A. Gomez, M. Varela, M. Fraile, V. Cadahía-Rodrigo, M. Torner, M.L.G. Dieguez, M. Rodríguez. *Hospital Universitario Central de Asturias, Liver Unit. Gastroenterology and Hepatology Department, Oviedo, Spain*
Email: castaogarcia@gmail.com

Background and Aims: Cure of HCV infection and inhibition of HBV replication reduce the risk of developing HCC in patients with HCV and HBV liver cirrhosis. Abstinence is the only treatment of ALC but its effect on the risk of HCC is unknown. To investigate if abstinence reduces HCC risk in a series of patients with ALC.
Method: 602 patients with ALC, Child A/B, included in a HCC surveillance program and prospectively followed every six months were analyzed. 83% were male, mean age 55 ± 8 years, 83% have had previous cirrhosis complications and 79% had varices Abstinence was defined as null alcohol consumption from inclusion. HCC and ALC diagnosis was based on universally accepted criteria. Abstinence during follow up and 13 clinical-biological variables at inclusion were recorded. Usual statistical methods were used.
Results: During a mean follow-up of 77 ± 59 months, 298 patients (49%) remained abstinent and 93 (15,4%) developed HCC, with a mean annual incidence (MAI) of 2.4% and cumulative probability of 23% and 45% at 10 and 20 years. There were no differences in the probability of developing HCC between abstinent (MAI: 2.42%) and non-abstinent patients (MAI: 2.39%) (p = 0.88). In the univariate analysis, variables associated with HCC development were: male sex (p = 0.007), age > 55 years (p = 0.001), platelet count (PTC) <145 × 10^3/mm^3 (p = 0.003), BMI 25–30 (p = 0.002) and AST > 45 UI/l (p = 0.019). Variables associated with risk of HCC in the multivariate analysis were male sex (OR: 2.52; IC95%:1.26–5.05; p = 0.009), age > 55 years (OR: 2.15; IC95%:1.39–3.35; p = 0.001) and PTC < 145 × 103/mm3 (OR:1.94; IC95%:1.11–3.40; p = 0.019). After adjustment with these variables, abstinence was not related with the risk of developing HCC (OR: 0.96; IC95%:0.61–1.49; p = 0.86). In the subgroup of abstinent patients, development of HCC was independently associated with age > 55 (p = 0.038), PTC < 145 × 103/mm3 (p = 0.022) and previous cirrhosis complications (p = 0.048). In non-abstinent patients HCC risk was independently associated with male sex (p = 0.032), age > 55 (p = 0.005) and PTC < 145 × 103/mm3 (p = 0.025).
Conclusion: Alcohol abstinence in patients with Child A/B ALC is not associated with a reduction in the risk of developing HCC. Factors associated with HCC in ALC are sex, age and higher degree of liver dysfunction, and are similar in abstinent and non-abstinent patients. These results show the need of early diagnosis of the illness and of development of effective drugs for HCC prevention.

EASL JOURNAL OF HEPATOLOGY

Friday, 13 April 2018

General session II and award ceremony I

GS-007

First real-world data on safety and effectiveness of glecaprevir/pibrentasvir for the treatment of patients with chronic hepatitis C virus infection: Data from the German Hepatitis C-Registry

T. Berg[1], U. Naumann[4], A. Stoehr[5], C. Sick[6], G. Teuber[7], W. Schiffelholz[8], S. Mauss[9], J. Hettinger[3], H. Kleine[3], A. Pangerl[3], C. Niederau[2]. *[1]Clinic of Gastroenterology and Rheumatology, University Hospital Leipzig, Leipzig, Germany; [2]Katholisches Klinikum Oberhausen, St. Josef-Hospital, Klinik für Innere Medizin, Akademisches Lehrkrankenhaus der Universität Duisburg-Essen, Oberhausen, Germany; [3]AbbVie Inc., North Chicago, Illinois, U.S.A; [4]Praxiszentrum Kaiserdamm, Berlin, Germany; [5]IFI Studien und Projekte GmbH, Hamburg, Germany; [6]Praxisonkologie Bremen, Bremen, Germany; [7]Practice PD Dr. med. G. Teuber, Frankfurt am Main, Germany; [8]Gastroenterologische Schwerpunktpraxis, Augsburg, Germany; [9]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany*
Email: thomas.berg@medizin.uni-leipzig.de

Background and Aims: The direct-acting antivirals glecaprevir (an NS3/4A inhibitor discovered by AbbVie and Enanta) coformulated with pibrentasvir (an NS5 inhibitor) are approved to treat chronic hepatitis C virus (HCV) genotype 1–6 infection. Clinical trials demonstrated an overall cure rate of 98% with glecaprevir/pibrentasvir (G/P), but real-world data on this regimen are limited. Here we report real-world effectiveness and safety of G/P within the German Hepatitis C-Registry (DHC-R).

Method: The DHC-R is an ongoing, non-interventional, multicenter, prospective registry study. Data were collected between July 28, 2017 and February 9, 2018 from 104 sites in Germany. Adult patients with HCV genotype 1–6 infection were eligible. The analysis included patients treated with G/P according to the local label for 8, 12 or 16 weeks, with or without compensated cirrhosis, who were either HCV treatment-naïve or treatment-experienced. The primary endpoint is SVR12, assessed in patients who received at least one dose of study drug. Safety and tolerability were assessed.

Results: To date, 866 patients have enrolled; 638 patients who received the regimen according to the label are included in the analysis. The majority of patients were treatment-naïve and without cirrhosis, and thus treated for 8 weeks; Table 1 shows patient baseline demographics. Of the patients with viral load data at the end of treatment, 97% (263/271) had viral suppression. In the modified intention-to-treat population which excludes non-virologic failures, 100% (49/49) achieved SVR12. Four patients discontinued treatment; two of these discontinuations were due to an adverse event (AE) or serious AE. Four serious AEs have occurred; there have been no grade 3 or higher ALT elevations.

Conclusion: In this first real-world data analysis with the G/P regimen, G/P treatment yielded favorable effectiveness and safety results consistent with clinical trial data. Updated data including SVR4 and SVR12 results will be presented.

Acknowledgements: Medical writing support was provided by Zoë Hunter, PhD, of AbbVie and funded by AbbVie.

Table 1: Patient Demographics and Disposition

Characteristic	G/P N=638
Male, n (%)	431 (68)
White race, n (%)	602 (94)
Age, median years (range)	47 (18–86)
HCV GT1a, n (%)	218 (34)
HCV GT1b, n (%)	111 (17)
HCV GT3, n (%)	226 (35)
Baseline HCV RNA, median IU/mL (Q1–Q3)	1,455,000 (2,490,000–4,334,000)
Treatment-naive, n (%)	577 (90)
Treatment-experienced (pegIFN±RBV±SOF), n (%)	61 (10)
No cirrhosis, n (%)	593 (93)
With compensated cirrhosis, n (%)	45 (7)
On drug substitution therapy, n (%)	168 (26)
Treatment duration, 8/12/16 weeks, n (%)	589 (92)/45 (7)/4 (1)

GS-008

Sustained efficacy of adjuvant immunotherapy with cytokine-induced killer cells for hepatocellular carcinoma: an extended 5-year follow-up

J.-H. Lee[1], J.H. Lee[2], Y.-S. Lim[3], J.E. Yeon[4], T.-J. Song[5], S. Yu[1], K.M. Kim[3], Y.J. Kim[1], J.W. Lee[6], J.-H. Yoon[1]. *[1]Seoul National University College of Medicine, Department of Internal Medicine and Liver Research Institute; [2]Sungkyunkwan University School of Medicine, Department of Medicine, Samsung Medical Center; [3]University of Ulsan College of Medicine, Department of Gastroenterology, Asan Medical Center; [4]Korea University Guro Hospital, The liver cancer; [5]Korea University Ansan Hospital, Department of Surgery; [6]Korea University, Department of Statistics*
Email: yoonjh@snu.ac.kr

Background and Aims: A previous randomized controlled trial demonstrated that adjuvant immunotherapy with cytokine-induced killer (CIK) cells prolonged both recurrence-free and overall survivals of patients with hepatocellular carcinoma (HCC) receiving curative treatment. We aimed to investigated whether the efficacy of CIK cell immunotherapy might be sustained after cessation of repeated transfer of CIK cells.

Method: We performed a follow-up study of our multicenter, randomized trial reported in 2015. We included 226 patients: 114 patients in the immunotherapy group (injection of 6.4×10^9 CIK cells, 16 times during 60 weeks) and 112 patients in the control group (no treatment) after potentially curative treatments for HCC. Among them, 162 patients (89 of the immunotherapy group and 73 of controls) underwent extended follow-up until 60 months after randomization of the last patient. The primary endpoint was recurrence-free survival (RFS); secondary endpoints included overall survival.

Results: The median follow-up duration was 68.5 (interquartile range, 45.0–82.2) months. During follow-up, the immunotherapy group maintained a significantly lower risk of recurrence or death (hazard ratio [HR] with immunotherapy was 0.67; 95% confidence interval [CI], 0.48–0.94; p = 0.009 by one-sided log-rank test). The 5-year RFS rate was 44.8% in the immunotherapy group and 33.1% in the control group. HRs were also lower in the immunotherapy

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than control group for all-cause death (0.33; 95% CI, 0.15–0.76; p = 0.006).
Conclusion: In patients who underwent curative treatment for HCC, significant gain in recurrence-free and overall survival by adjuvant CIK cell immunotherapy was maintained for over 5 years. ClinicalTrials.gov number: NCT01890291.

GS-009
MGL-3196, a selective thyroid hormone receptor-beta agonist significantly decreases hepatic fat in NASH patients at 12 weeks, the primary endpoint in a 36 week serial liver biopsy study
S. Harrison[1], S. Moussa[2], M. Bashir[3], N. Alkhouri[4], J. Frias[5], S. Baum[6], B. Tetri[7], M. Bansal[8], R. Taub[9]. *[1]Oxford University; [2]University of Arizona for Medical Sciences; [3]Duke University Medical Center; [4]University Texas, San Antonio; [5]University of California San Diego, Endocrinology, San Diego, United States; [6]Florida Atlantic University; [7]St Louis University School of Medicine; [8]Icahn School of Medicine at Mount Sinai; [9]Madrigal Pharmaceuticals*
Email: rebeccataub@yahoo.com

Background and Aims: MGL-3196 is a liver-directed, orally active, highly selective THR-β agonist currently in Phase 2 for treatment of non-alcoholic steatohepatitis (NASH). In Phase 1 studies, 3196 demonstrated rapid reductions in lipids, LDL cholesterol (30%), triglycerides (40–60%), and lipoprotein(a) (Lp(a))(40%). This ongoing Phase 2 study evaluated the primary endpoint, relative reduction in (magnetic resonance imaging – proton density fat fraction) MRI-PDFF, biomarkers and safety in 116 NASH patients at 12 weeks.
Method: MGL-3196-05 (NCT02912260) is a 36 week multicenter, randomized, double-blind, placebo-controlled study in adults with biopsy-confirmed NASH (NAS ≥ 4, F1-F3) and hepatic fat fraction ≥10%, assessed by (MRI-PDFF). Randomized 2:1, MGL-3196 to placebo, patients receive MGL-3196 80mg, or placebo oral, once daily, for 36 weeks. Blinded increase or decrease in dose based on exposure was possible. The primary endpoint, relative reduction in MRI-PDFF, was assessed at 12 weeks, patients continued on treatment blinded, and, at 36 weeks, secondary endpoints were assessed by second liver biopsy and third MRI-PDFF, with ongoing safety and biomarker assessments at 12 and 36 weeks.
Results: Baseline characteristics (mean or %): age, 50.3 years; women, 50.4%; type 2 diabetes, 38.4%; BMI, 35 kg/m^2; Hispanic, 47.2%; mean hepatic fat fraction (FF), 20.2%; NAS 4.9 (44% F2-3). Baseline characteristics were similar among groups. The primary endpoint was met (p < 0.0001, LS mean), with 78 MGL-3196 treated patients demonstrating −36.3% relative and −7.6% absolute change from baseline (CFB) MRI-PDFF: −9.6%, −1.6%, respectively, in 38 placebo patients (median). Forty-seven/78 (60.3%) MGL-3196 treated (6/47 ≥ 5% weight loss) compared with 7/38 (18.4%) placebo treated (5/7 with ≥5% weight loss) demonstrated ≥30% reduction in MRI-PDFF (p < 0.0001). In MGL-3196 treated patients, lipids decreased, LDL-C −12.9, triglycerides −30.1 and Lp(a)−37.5 (% CFB relative to placebo) p < 0.0001; ALT, AST decreased 16.1%,16.2% relative to mean baseline (51.0, 35.7U/l) p < 0.01. Study drug was well-tolerated, AEs were generally mild (85%) or moderate (15%); 3 SAEs occurred and were considered unrelated (study remains blinded). Additional dose/exposure, biomarkers (safety, lipid, inflammatory, fibrosis, multiparametric MRI (subset)) still under analyses will be presented.
Conclusion: MGL-3196 QD for 12 weeks, compared with placebo, significantly decreased hepatic fat in patients with NASH relative to placebo. These combined results suggest that MGL-3196 has beneficial effects in NASH. Histopathologic assessment at 36 weeks will allow for comparison to baseline histology as well as multiple biomarkers (serologic and imaging).

GS-011
Results of a randomised controlled trial of budesonide add-on therapy in patients with primary biliary cholangitis and an incomplete response to ursodeoxycholic acid
G. Hirschfield[1], L. Kupcinskas[2], P. Ott[3], U. Beuers[4], A.M. Bergquist[5], M. Färkkilä[6], M.P. Manns[7], A. Pares[8], U. Spengler[9], R. Greinwald[10], M. Proels[10], R. Poupon[11]. *[1]NIHR Biomedical Research Centre, Centre for Liver Research, University of Birmingham; [2]Lithuanian University of Health Sciences; [3]Aarhus University, Department of Clinical Medicine; [4]Academic Medical Center, University of Amsterdam; [5]Hepatology, Karolinska University Hospital; [6]Clinic of Gastroenterology, Helsinki University Hospital; [7]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [8]Liver Unit, University of Barcelona; [9]Department of Internal Medicine I, University of Bonn; [10]Research and Development, Falk Pharma; [11]Centre de Recherche Saint-Antoine*
Email: g.hirschfield@bham.ac.uk

Background and Aims: To evaluate the impact of adding budesonide (9 mg/day Budenofalk®) to patients with PBC and inadequate response to UDCA.
Method: Patients were randomised (2:1) to a placebo-controlled, double-blind, multi-centre, clinical trial of 36-months treatment of budesonide, with UDCA (12–16 mg/kg bw/d) maintained. We enrolled patients with histologically confirmed PBC and inflammatory activity according to the Ishak-score, failure to achieve sAP levels < 1.5x upper limit of normal after at least 6 months of UDCA therapy, and high risk of disease progression. The primary efficacy endpoint was the rate of patients with improvement of liver histology with respect to inflammation (an improvement by at least 3 points in the Ishak sum score or no inflammatory activity) and no progression of fibrosis (Ludwig staging), compared to baseline at the individual last patient visit within the study. The study was terminated early due to insufficient recruitment resulting in lack of power.
Results: 90 patients were screened. 62 patients were randomised and 43 patients had paired biopsies available. Baseline data were comparable between treatment groups (mean age 54 years, 97% females, BMI 26.1, mean ALP 341 U/L, mean ALT 72 U/L, mean disease duration of 7.8 years). Mean treatment duration was 25.3 months and 29 patients completed 3 years of treatment. The primary histologic end-point, in an ITT analysis comparing patients with paired biopsies only, was not met (Table 1). The surrogate "serum levels of sAP ≤1.67 ULN and ≥15% decrease and normal total bilirubin" was met by 17/40 (42.5%) and 5/22 (22.7%) patients in BUD and PBO, respectively (P = 0.099). Mean ALP was reduced from 327 U/L to 233 U/L, and mean ALT from 70 U/L to 58 U/L in the BUD group. This compared with no treatment effect in the PBO group: mean ALP changed from 367 to 358 U/L, mean ALT from 76 to 76 U/L. 35% of BUD and 9.1% of PBO treated patients had normalisation of sAP (P = 0.023). Pruritus reported as adverse events occurred in 6/40 (15%) in BUD and 7/22 (31.8%) in PBO. Serious adverse events occurred in 17 patients (10 in the BUD- and 7 in the PBO group). Adverse events were reported in a similar number of patients across groups. Adverse drug reactions were reported for 24 patients (60%) in the BUD- and 8 patients (36%) in the PBO-group.

Table 1: Number/proportion of patients with response (%) (Last observation carried forward)

	BUD (N = 40)	PBO (N = 22)	P values (one-sided)
Improvement of liver histology, paired biopsies only, n/N (%)	11/26 (42.5)	5/17 (29.4)	0.225*
Normalisation of sAP, N (%)	14 (35.0)	2 (9.1)	0.023**

*Cochran–Mantel–Haenszel test.
**Fisher's Exact Test.

Conclusion: Up to 36 months of budesonide add-on therapy to UDCA did not associate with significant improvements in histology in high-

risk patients with PBC. However, clinically meaningful improvements in biochemical markers of disease activity were apparent.

GS-012

Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients with HCV Genotype 5 or 6 Infection: The ENDURANCE-5,6 Study

T. Asselah[1], T. Tran[2], K. Alves[3], T. Nguyen[4], F. Wong[5], A. Mahomed[6], S.G. Lim[7], S. Lee[8], A. Abergel[9], J. Sasadeusz[10], P. Krishnan[3], Z. Zhang[3], A. Pocalla[11], R. Trinh[11], E. Gane[12]. *[1]University Paris Diderot, Hepatology Department, Beaujon Hospital, Clichy, France; [2]Cedars Sinai Medical Center, Los Angeles, United States; [3]AbbVie, Inc., North Chicago, United States; [4]Research and Education, Inc., San Diego, United States; [5]Toronto General Hospital, University of Toronto, Toronto, Canada; [6]University of Witwatersrand, Charlotte Maxeke Johannesburg Academic Hospital, Department of Gastroenterology and Hepatology, Johannesburg, South Africa; [7]National University Health System, Division of Gastroenterology and Hepatology, Singapore; [8]University of Calgary, Canada; [9]CHU Estaing, France; [10]Royal Melbourne Hospital, Melbourne, Australia; [11]AbbVie, Inc., North Chicago; [12]Auckland Clinical Studies, Auckland, New Zealand*
Email: tarik.asselah@aphp.fr

Background and Aims: The pangenotypic direct-acting antivirals (DAAs) glecaprevir (developed by AbbVie and Enanta) coformulated with pibrentasvir (G/P) are approved to treat chronic HCV genotype (GT)1–6 infection. In Phase 2 and 3 studies, G/P achieved high SVR12 rates with no virologic failures in 80 patients with GT5 or 6 infection, leading to an 8-week and 12-week label indication in HCV GT1–6 patients without or with compensated cirrhosis, respectively. To increase the body of data for these genotypes, ENDURANCE-5,6 evaluates patients from countries where GT5 and GT6 are endemic, such as South Africa (GT5), Myanmar and Vietnam (GT6). This study evaluates the efficacy and safety of G/P in patients with chronic HCV GT5 or GT6 infection, with an expanded analysis of GT6 subtype diversity, for which there has been limited clinical trial data for all-oral, DAA-based therapies.

Method: ENDURANCE-5,6 is an ongoing phase 3b, non-randomized, open-label, multicenter study conducted in adults with chronic HCV GT 5 or 6 infection with or without compensated cirrhosis who are HCV treatment-naïve or experienced with interferon (IFN) or pegIFN with or without ribavirin (RBV) or sofosbuvir and RBV with or without pegIFN. G/P (300 mg/120 mg) was orally dosed once-daily for 8 or 12 weeks in patients without or with compensated cirrhosis, respectively. The primary efficacy endpoint was SVR12. Secondary endpoints were on-treatment virologic failure or relapse. Adverse events and clinical laboratory abnormalities were monitored in all patients.

Results: Seventy patients have enrolled to date, 61 and 9 in the 8- and 12-week treatment arms, respectively; 66 have completed treatment. Baseline demographics are shown in Table 1. The SVR4 among patients with available data is 61/62 (98%). One HCV GT6c-l-infected patient with compensated cirrhosis experienced virologic breakthrough at treatment week 12, and one HCV GT5a-infected patient without compensated cirrhosis who achieved SVR4 relapsed at post-treatment week 12. To date, three patients (4%) have experienced treatment-emergent serious adverse events, none of which were related to G/P or led to discontinuation; no Grade 3 alanine aminotransferase elevations have occurred.

Table 1. Baseline Demographics and Disease Characteristics

Characteristic	8-week G/P No Cirrhosis N=61	12-week G/P Cirrhosis N=9
Female, n (%)	36 (59)	4 (44)
Asian, n (%)	38 (62)	5 (56)
Age, median years (range)	57 (24–79)	65 (32–75)
Genotype 5, n (%)	20 (33)	3 (33)
Genotype 6, n (%)	41 (67)	6 (67)
GT6a/6b	19 (31)	1 (11)
GT6c-l	22 (36)	5 (56)
HCV treatment-naive, n (%)	55 (90)	8 (89)
Baseline HCV RNA, median log_{10} IU/mL (range)	6.85 (4.6–7.5)	6.29 (4.9–7.2)

Conclusion: In this ongoing dedicated study, HCV genotype 5- and 6-infected patients without and with compensated cirrhosis treated with G/P for 8 and 12 weeks, respectively, achieved high rates of SVR4. Complete SVR4 data and available SVR12 data will be presented.

Alcoholic liver disease

PS-065

Alcohol relapse after liver transplantation: impact of a novel risk assessment scoring system

N. Zakeri, D. Chatzidis, L. De Luca, N. Lazaridis, J. Ryan, R. Westbrook, D. Patch, E. Tsochatzis, L. Shepherd. *Sheila Sherlock Liver Unit, UCL Institute for Liver and Digestive Health, Royal Free Hospital, London*
Email: nekisa.zakeri@nhs.net

Background and Aims: Relapse to harmful alcohol intake following liver transplantation (LT) for alcohol-related chronic liver disease (ALD) is reported in 10–33% of patients, however no consistent predictive factors have been shown. We evaluated the predictive ability of demographic, psychosocial and addiction-related variables to determine relapse risk, both in isolation and in conjunction as a novel risk assessment scoring system; we assessed the impact of relapse on post-LT survival.

Method: Consecutive patients (n = 187) with a history of alcohol excess who underwent LT in a tertiary centre (2004–2013) were included. Demographic variables, alcohol history, substance misuse, psychiatric comorbidities and family alcohol dependence were recorded. The Relative Risk Factors for Relapse (RRFR) score consists of abstinence history, dependence diagnosis, acceptance of diagnosis, willingness to engage in treatment, social network, drug misuse, and replacement activities, and has a numerical scale of 0–27, higher values indicating greater relapse risk. Relapse outcomes, 1-year, 3-year and 5-year survival after LT were evaluated.

Results: Patients were predominantly male (87%), mean age 54 ± 7 years, mean MELD score 15.7 ± 5.8. Mean follow-up was 6.7 ± 3.2 years. 21% remained abstinent, with a high rate of slips (66%) and few lapses (4%). Relapse to harmful alcohol intake occurred in 8% of patients (15/187). In univariate analysis, age at LT ($p = 0.002$), units of alcohol per week ($p = 0.007$), past alcohol treatment ($p = 0.05$) and total RRFR score ($p = 0.03$), were associated with relapse. Multivariate logistic regression revealed younger age at LT as the only independent predictor of relapse (48 ± 7 vs. 54 ± 7 years, $p = 0.015$). 1-year, 3-year and 5-year survival after LT was 92%, 90% and 84% respectively, compared to European Liver Transplant Registry survival rates of 84%, 78% and 73%. Relapse did not have a significant effect on survival.

Conclusion: The low rate of relapse to harmful alcohol intake and high survival rate in our cohort compares favourably to published literature. Younger recipient age was the only independent predictor for relapse identified. Comprehensive pre-assessment incorporating addiction and psychosocial assessment within the RRFR score might have contributed to better patient selection and improved outcomes. Further study is required to validate criteria for relapse risk stratification to assist LT selection in patients with previous alcohol excess.

PS-066

Alcohol disrupts a meta-organismal endocrine axis in murine models and patients with AH

J. Mark Brown[1], R.N. Helsley[1], S. Marshall[1], A. Kim[2], L. Nagy[2]. *[1]Cleveland Clinic, Cellular and Molecular Medicine; [2]Cleveland Clinic, Pathobiology*
Email: len2@po.cwru.edu

Background and Aims: Alcoholic liver disease (ALD) comprises a spectrum of disorders and pathologic changes. Alcoholic hepatitis

(AH) is the most severe form of ALD and can develop at any time in the progression of disease. There is mounting evidence that intestinal microbes represent a key transmissible factor promoting inflammatory diseases such as AH. However, the mechanisms by which gut microbiota synergize with excessive alcohol intake to promote AH are largely unknown. The role of specific microbial metabolites to progression of AH is an important, but understudied, area of investigation. One such microbial metabolite, trimethylamine (TMA), is generated by gut microbes and subsequently metabolized by flavin-containing monooxygenase 3 (FMO3) in the liver to produce trimethylamine-N-oxide (TMAO). TMA activates pro-inflammatory signalling via its G protein coupled receptor Taar5. Here we have investigated whether this meta-organismal endocrine axis promotes ethanol-induced liver injury in mice and is associated with severity of AH in patients.

Method: Female C57BL/6 mice exposed to the chronic Lieber-DeCarli (25 day) liquid diet feeding paradigm or pair-fed control diets or challenged with TMA or saline. Serum and clinical data from a sub-set of 119 patients enrolled in the Defeat Alcoholic Hepatitis (DASH) consortium were analysed. AH patient and control liver samples were obtained from the Clinical Resources in Alcoholic Hepatitis at Johns Hopkins.

Results: Chronic ethanol feeding to mice increased TMA concentration in serum to ~2.5 μM. Serum concentrations of TMA in patients with AH ranged from 1.5–2 μM. Illumina microarray analysis revealed that TMA challenge to mice reorganized expression of both pro-inflammatory and cell death pathways, including changes in expression of a multiple pattern recognition receptor pathways and pro-inflammatory cytokine pathways. Expression of FMO3 protein was decreased in liver of AH patients compared to controls. When AH patients were divided by tertile based on TMAO, there was a significant negative association with MELD. Importantly, survival probability was also associated with TMAO tertile, with the lowest tertile for TMAO predicting a poorer survival probability (40.9%) compared to the high tertile for TMAO (64.8%). Challenge of PBMCs with TMA exacerbated LPS-stimulated cytokine expression in patients with AH, but not controls.

Conclusion: Collectively, data from both murine models of ethanol-induced liver injury and patients with AH suggest that the TMA-FMO3-TMAO axis is dysregulated in AH. Lower hepatic expression of FMO3 in AH was associated with a shift in the TMA/TMAO ratios, likely favoring enhanced inflammatory signaling via TMA. These studies suggest that modulation of microbial synthesis of TMA and/or interruption the pro-inflammatory signalling of TMA on immune cells may be novel therapeutic interventions in AH.

PS-067
Ductular reaction cells display an inflammatory profile and recruit neutrophils in alcoholic hepatitis.

B. Aguilar-Bravo[1], D. Rodrigo-Torres[1], M. Coll[2,3], L. Revilla[1], D. Blaya[1], L. Perea[1], J. Vallverdú[1], I. Graupera[4], E. Pose[1,4], L. Dubuquoy[5], C. Armengol[6], A.L. Nigro[7], P. Stärkel[8], P. Mathurin[5], J. Caballería[4], J. Lozano[1,3], R. Bataller[9], P. Ginès[4], P. Sancho-Bru[10]. *[1]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, Hospital Clinic, Barcelona, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [4]Hospital clinic, Liver Unit, Barcelona, Spain; [5]Hôpital Huriez, Lille Service des Maladies de l'Appareil Digestif, Lille, France; [6]Health Sciences Institute Germans Trias i Pujol (IGTP), Campus Can Ruti, Childhood Liver Oncology group (c-LOG), Badalona, Spain; [7]IRCCS-ISMETT (Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione), Department of Laboratory Medicine and Advanced Biotechnologies, Palermo, Italy; [8]Cliniques Universitaires Saint-Luc, Department of Hepato-Gastroenterology, Bruselas, Belgium; [9]Pittsburgh Liver Research Center, University of Pittsburgh Medical Center, Pittsburgh, United States; [10]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, Liver cell plasticity and tissue repair, Barcelona, Spain*
Email: aguilar@clinic.cat

Background and Aims: Alcoholic hepatitis (AH) is characterized by the expansion of ductular reaction (DR), which consists of a heterogeneous population of cells comprising reactive biliary cells and more immature facultative liver progenitor cells (LPCs). The aim of this study was to identify the transcriptomic profile of DR cells and to generate an *in vitro* model to study DR.

Methods: KRT7$^+$, KRT7$^-$ and total liver fractions were laser microdissected from liver biopsies (n = 6) of patients with AH, and the whole transcriptome was sequenced. The gene expression profile was evaluated in AH patients: in liver tissue (n = 40) by qPCR and in serum samples (n = 15) by ELISA. Human LPC organoids were generated from cirrhotic patients (n = 4) and analyzed by microarray, immunofluorescence and qPCR. Organoid-neutrophil crosstalk was assessed by incubating neutrophils with organoids conditioned medium.

Results: Transcriptomic analysis showed that DR presents a pro-inflammatory profile with expression of CXC and CCL chemokines. Gene expression of KRT7 positively correlated with the expression of CXCL1, CXCL3, CXCL5, CXCL6 and CXCL8 cytokines in AH liver tissue. Moreover, serum levels of LPC marker TROP2 correlated with circulating CXCL5 levels. Histologically, DR was associated with neutrophil infiltration at the periportal area, as demonstrated in KRT7-MPO immunofluorescence. To recreate an in vitro model of DR we generated liver organoids from cirrhotic patients, which expressed KRT7 and EpCAM as assessed by immunofluorescence. Transcriptomic analysis of organoids showed high enrichment in genes of the DR transcriptome. Organoid expression of LPC markers and inflammatory cytokines was confirmed by qPCR. Liver organoids produced CXCL5 (11.5 ± 5.6 ng/ml) in culture and stimulation with TNFα, further induced the expression of CXCL1, CXCL2, CXCL5, CXCL6, CCL20 and CCL28 as assessed by qPCR. Moreover, organoid conditioned medium enhanced neutrophils inflammatory profile.

Conclusion: DR in AH patients has a pro-inflammatory profile and is associated with neutrophils infiltration, suggesting the contribution of DR cells in neutrophil recruitment and liver inflammatory response. Human LPC organoids derived from cirrhotic patients mimicked the DR gene expression profile and enhanced neutrophils inflammatory profile, indicating their utility as a model to study DR. These results suggest that targeting LPCs may represent a novel strategy to modulate hepatic inflammatory response.

PS-068
Bile acids and intestinal dysbiosis in alcoholic hepatitis

D. Ciocan[1], C.S. Voican[2,3], L. Wrzosek[3], C. Hugot[3], D. Rainteau[4], L. Humbert[4], A.-M.C. Doulcier[3], G. Perlemuter[2,3]. *[1]INSERM, U 996, Clamart, France; [2]APHP, Hepatogastroenterology and Nutrition, Hôpital Antoine-Béclère, Clamart, France; [3]INSERM, U 996, Clamart, France; [4]INSERM, U1057, Paris, France*
Email: ciocanelro@yahoo.com

Background and Aims: Intestinal microbiota (IM) plays an important role in bile acids (BA) homeostasis, impacts the gut barrier and promotes inflammation. We aimed to study the structure of the IM and its functions in BA homeostasis in alcoholic patients according to the severity of ALD.

Method: In this prospective study, we included 4 groups of active alcoholic patients (N = 109): two non-cirrhotic: without (noAC_noAH, n = 61) or with alcoholic hepatitis (noAC_AH, n = 14) and two cirrhotic: without (AC_noAH, n = 17) or with severe alcoholic hepatitis (AC_sAH, n = 17). Plasma and fecal BA profiles, as well as IM composition were assessed.

Results: Patients with AC_sAH had an increase in total BA, primary BA, conjugated BA and total ursodeoxycholic acid in plasma. In feces,

there was a decrease in total BA and secondary BA. AC_sAH patients had a specific IM: at the phyla level, there was an increase in Actinobacteria and a decrease in Bacteroidetes; while at genus level there was 7 taxa increased and 4 decreased. Moreover, in AC_sAHc patients, as compared to AC_noAH patients, there was an increase in 4 and a decrease in 11 metabolic pathways involving upregulation of glutathion and nucleotid metabolism and downregulation of biotin metabolism.
Conclusion: Patients with AC_sAH have a specific BA pool with a shift towards more hydrophobic and toxic species that could be responsible for the specific IM associated with AC_sAH. Conversely, the IM will also change the BA pool by transforming primary BAs to secondary BAs leading to a vicious cycle between IM and BA modifications. These changes in IM structure and functions could play a role in AC_sAH initiation and progression, through BA effects on liver metabolism.

PS-069
Chronic plus binge alcohol consumption leads to Il-6 mediated inflammatory response in a new mouse model of acute-on-chronic liver injury
E. Karatayli[1], R. Hall[1], S.N. Weber[1], S. Dooley[2], F. Lammert[1]. [1]*Saarland University Medical Center, Department of Medicine II, Homburg, Germany;* [2]*Medical Faculty Mannheim, Heidelberg University, Section Molecular Hepatology, Department of Medicine II, Mannheim, Germany*
Email: Ersin.Karatayli@uks.eu

Background and Aims: Altered host response to injury in the setting of a chronically damaged liver plays a critical role in the development of acute-on-chronic liver injury, usually in the presence of an underlying precipitant. Here, we aim to combine a mouse model with pre-existing chronic liver injury (*Abcb4*$^{-/-}$) with the recently standardized ethanol feeding model (NIAAA model, *Nat Protoc* 2013) to dissect alcohol-related inflammatory responses in this novel preclinical model.
Method: Ten and 15 week-old wild type (WT) C57BL/6J and *Abcb4*$^{-/-}$ knock-out (KO) mice were either fed control (WT/Cont and KO/Cont groups) or liquid ethanol diet (5% v/v), followed by an acute ethanol binge (5 mg/kg; WT/EtOH and KO/EtOH groups). Liver-specific steady-state mRNA levels (relative to GAPDH) of IL-6, HGF, CRP and COL3A1 were evaluated using the $2^{-\Delta\Delta Ct}$ method. ELISA was performed for IL-6 and HGF in plasma. Hepatic collagen contents (hydroxyproline), plasma EtOH concentrations as well as ALT, AST and AP activities were measured. Data were analysed by ANOVA with Bonferroni post-hoc tests.
Results: Hepatic hydoxyproline and *Col3a1* expression were significantly higher in *Abcb4*$^{-/-}$ mice compared with controls and further increased by ethanol challenge. The older mice in the KO/EtOH group displayed 2-, 3- and 4-fold higher IL-6 expression vs. 15 week-old KO/Cont (all $p < 0.01$), 15 week-old WT/EtOH ($p < 0.001$) and WT/Cont groups ($p < 0.001$), respectively. This elevation was more prominent for IL-6 plasma concentrations, which reached a 10-fold increase ($p < 0.0001$) compared to age-matched controls, whereas HGF did not differ. Hepatic CRP levels were significantly ($p = 0.001$) elevated in 15 week-old *Abcb4*$^{-/-}$ mice challenged with ethanol. Male mice in this group exhibited 1.7 ($p = 0.01$) and 2.1 ($p < 0.001$)-fold higher IL-6 and CRP levels than females, respectively. Lipid droplets (LD) in liver were observed in 80% of mice challenged with ethanol, regardless of genotype. In these mice, hepatic *Pnpla3* mRNA levels were significantly ($p < 0.001$) repressed, and of note, the mean LD size was inversely correlated ($p < 0.01$) with hepatic *Pnpla3* levels.
Conclusion: We propose a novel promising set-up to model alcohol-related acute-on-chronic liver injury. We speculate that the acute inflammatory IL6-driven response might promote the transition from the stable chronic state to progressive liver damage in *Abcb4*$^{-/-}$ mice, further increasing the known and gender-specific HCC risk in this model. Repression of *Pnpla3* expression resulted in a notable expansion in LD size, indicating lipid remodelling in this model.

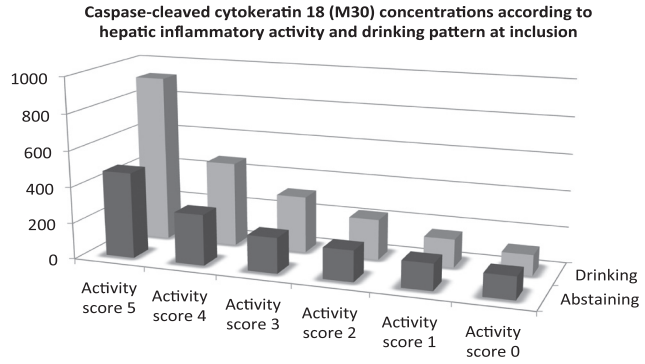
PS-070
Collagen proportionate area is an independent predictor of short and long-term survival in patients with alcoholic hepatitis
M.G. Misas[1], A. Koutsoumarakis[1], A. Hall[2], C. Covelli[1], E. Buzzetti[1], L.I. Prat[1], D. Roccarina[1], T.V. Luong[1], M. Pinzani[1], E. Tsochatzis[1]. [1]*UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, United Kingdom;* [2]*Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust and UCL Institute for Liver and Digestive Health, University College of London, London, United Kingdom*
Email: martaguemi@gmail.com

Background and Aims: Quantitative fibrosis assessment with the measurement of collagen proportionate area (CPA) predicts clinical outcomes in patients with chronic hepatitis C and non-alcoholic fatty liver disease and, in addition, is able to sub-classify cirrhosis. We tested the ability of CPA to quantify fibrosis and predict clinical outcome in patients with alcoholic hepatitis (AH).
Method: We retrospectively included a cohort of 141 patients, with biopsy-proven AH, irrespective of fibrosis stage. All patients with concomitant primary causes of liver disease were excluded. Clinical details and laboratory data were collected at biopsy time. Follow-up data were collected at the time of the last clinical follow-up or death. Liver related mortality was considered as primary outcome. For CPA analysis, we captured images of liver biopsy sections stained with picro-Sirius red and used digital image analysis to measure areas of collagen deposition. CPA was calculated as a proportion of the area of the whole parenchyma and expressed as a percentage.
Results: 83 patients (58.9%) were male with a mean age of 46 years. Mean alcohol intake prior to the episode of AH was 173.94 g/day; 47 (33.3%) patients were abstinent after the biopsy with a median abstinence period of 19 (276) months. 106 (75.2%) patients were cirrhotic at the time of the biopsy whereas 99 (70.8%) of the patients had a Maddrey score ≥32. 67 (67.7%) patients were treated with corticosteroids and 11 (11.1%) with pentoxyfilline. 63.6% of the patients treated with corticosteroids were responders based on a Lille score of <0.45. CPA significantly correlated with fibrosis stage across the whole spectrum of fibrosis. 67 patients (47.5%) died during a median follow-up of 65.48 (IQR 311.7) months. 30-days and 1-year mortality were 5% and 23.4% respectively. CPA was an independent predictor of 30-days mortality (OR 0.496, $p = 0.05$) along with the Lille score (OR 15.467, $p = 0.013$). Independent predictors of mortality at last follow up were CPA (OR 1.22, $p = 0.015$), abstinence (OR 0.315, $p < 0.001$) and ABIC Score (OR 1.323, $p = 0.002$).
Conclusion: CPA is a short and long term independent predictor of death in patients with AH and should be further explored as a prognostic index in such patients.

PS-071
Caspase-cleaved cytokeratin-18 (M30) and ActiTest predict hepatic inflammation in asymptomatic patients with alcoholic liver disease
K.H. Thorhauge[1], M. Thiele[1], B.S. Madsen[1], J.F. Hansen[2], S. Detlefsen[3], S. Antonsen[4], L.M. Rasmussen[5], A. Krag[1]. [1]*Odense University Hospital, Department of Gastroenterology and Hepatology, Odense;* [2]*Odense University Hospital, Department of Infectious Diseases;* [3]*Odense University Hospital, Department of Pathology;* [4]*Odense University Hospital Svendborg, Department of Clinical Biochemistry;* [5]*Odense University Hospital, Department of Clinical Biochemistry and Pharmacology*
Email: katrine.thorhauge@gmail.com

Background and Aims: Alcoholic cirrhosis is the cause of 500.000 deaths annually. The end-stage disease is preceded by years of subclinical progressive fibrogenesis driven by hepatic inflammation. Consequently, we need biomarkers to detect and monitor alcoholic hepatic inflammatory activity. M30 is a cytokeratin-18 based novel biomarker of hepatocyte apoptosis with high accuracy for diagnosing severe alcoholic hepatitis. It is not known whether M30 can detect subclinical liver inflammation or how it performs in comparison with

AST:ALT ratio and ActiTest; another patented inflammation marker. We therefore aimed to investigate the correlation of M30, ActiTest and AST:ALT ratio with histological inflammatory activity in asymptomatic alcoholic liver disease patients.
Method: Biopsy-controlled, single-center, prospective study in outpatients with an ongoing or prior excessive alcohol intake. Same-day liver biopsy and analysis of M30 Apoptosense® (VLV bio, Sweden), ActiTest (Biopredictive, France) and routine liver blood tests. Scoring of biopsies using the NAFLD Activity Score by a single liver pathologist. We graded hepatic inflammation using the sum of ballooning (0–2) and lobular inflammation (0–3).
Results: We included 267 patients from 2013–2016. Mean age 54 ± 11, 73% males, 52% not drinking at inclusion (average 10 weeks abstinence), 23% with severe fibrosis or cirrhosis, 48% with steatosis. The distribution of inflammatory activity (0–5) was 67/62/61/37/25/15. M30, ActiTest and whether patients where actively drinking at inclusion independently and significantly predicted increasing grade of hepatic inflammation, while AST:ALT ratio did not (Figure). M30 diagnosed presence of severe hepatic inflammation (score 4–5) with excellent accuracy (M30 AUROC 0.90, 0.85–0.94), significantly better than ActiTest and AST:ALT ratio (AUROC 0.77 and 0.74; $P < 0.001$). M30 was 122 ± 73 U/L in patients without inflammatory activity, and increased exponentially for every point increase in inflammation for a concentration of 773 ± 910 U/L in patients with ballooning = 2 and lobular inflammation = 3. ActiTest was 11.5 ± 11% in patients without inflammation, versus 36 ± 17% in patients with the highest activity score.



Conclusion: M30 and ActiTest are promising biomarkers for grading subclinical, alcoholic hepatic inflammation. M30 detect severe hepatic inflammation with excellent accuracy and increase exponentially for every grade of hepatic inflammatory activity.

PS-072
Impact of baclofen treatment in 212 alcohol-dependant patients of the french "OBADE-ANGH" series
C. Barrault[1], J.-F. Cadranel[2], C. Locher[3], T. Thévenot[4], F. Skinasi[5], D. Labarriere[6], B. Valerie[7], Y. Le Bricquir[8], V. Quentin[9], A. Garioud[10], C. Costentin[11], C. Jouan[12], H. Hagege[13], C. Jung[12]. *[1]CH Intercommunal de Créteil, gastroenterology and hepatology unit, CRETEIL, France; [2]CH Creil, gastroenterology and hematology unit, CREIL, France; [3]CH de Meaux, gastroenterology and hepatology unit, Meaux, France; [4]CHU Besançon, hepatology unit, Besançon; [5]CH Delafontaine, gastroenterology and hepatology unit, Saint Denis, France; [6]CHR Orléans, gastroenterology and hepatology unit; [7]CHU Jean Verdier, hepatology unit; [8]CH de Béziers, gastroenterology and hepatology unit; [9]CH de Saint Brieuc, gastroenterology and hepatology unit; [10]CH Creil, gastroenterology and hepatology unit; [11]CHU Henri Mondor, hepatology unit; [12]CH Intercommunal de Créteil, clinical research centre; [13]CH Intercommunal de Créteil, gastroenterology and hepatology unit*
Email: camille.barrault@chicreteil.fr

Background and Aims: Alcohol misuse is responsible for 50,000 deaths per year in France and the first cause of advanced liver disease in Europe. Baclofen has a temporary recommendation for use in the indications of (1) reduction of consumption and (2) maintenance of abstinence. Its renal elimination makes its use possible even in case of decompensated cirrhosis but few data are available. The aim of OBADE series was to evaluate: (1) the way of prescribing baclofen for alcohol misuse in gastroenterology units of ANGH (non-academic hospital) and: (2) evolution at 12 months of the reported alcohol consumption (DCA) and tolerability of treatment, especially in cases of cirrhosis. Clinical trial number is: NCT02835365.
Method: Consecutive out or inpatients of 10 gastroenterology units treated with baclofen for alcohol dependence after March 2012 (authorization for use on a case-by-case basis) were included and the data were collected prospectively or retrospectively. Psycho-social care was usually offered. We present 9 months results.
Results: Between February 2015 and December 2016, 212 patients (male 79,7%) aged 50.7 ± 10 years were included. Of these, 56 (31%) had alcoholic liver disease and 72 (38%) had cirrhosis. In the cirrhosis group, 13.5% of patients had severe acute alcoholic hepatitis (sAAHs) and 24% had ascites. We observed a history of sAAH in 22% of cases, gastrointestinal bleeding by portal hypertension in 13%, ascites in 37%, and hepatic encephalopathy in 13.5%. A metabolic syndrome was associated in 41% of cases. Three patients were transplanted from the liver. Active smoking was associated in 63% of cases and 3% of patients received opioïd substitution therapy. Baclofen was prescribed either by the addictologist (58%) or by the hepatologist (35%): in 43% of cases the patients had not received any other addictolytic drug. At M9, the median dose of baclofen was 75 mg/d (max = 260 mg/d) and DAC was significantly lower than at baseline: 30 (± 20) g/d versus 111 (± 95) g/d ($p < 0.0001$), 70% of patients had a DAC ≤ 30 g/d while 44% were completely abstinent. The evolution of DAC was the same in cirrhotic patients. In contrast, adverse effects (overall 17%) were less frequent in cirrhotic patients (5.5% vs 25.5%, $p = 0.02$) while the dose of baclofen was not different (65.5 mg vs 88 mg/day, $p = 0.09$). No discontinuation of treatment (n = 5) was related to an adverse event and no death was reported during follow-up.
Conclusion: Preliminary results from this multicentre national study suggest that baclofen treatment, integrated with medico-psycho-social care, is associated with a significant decrease in alcohol intake at 9 months, even in patient with severe ALD. The tolerance of baclofen was very good even in patients with decompensated cirrhosis. Updated results with longer follow up (M12) will be presented in April 2018.

Cirrhosis: ACLF and critical illness

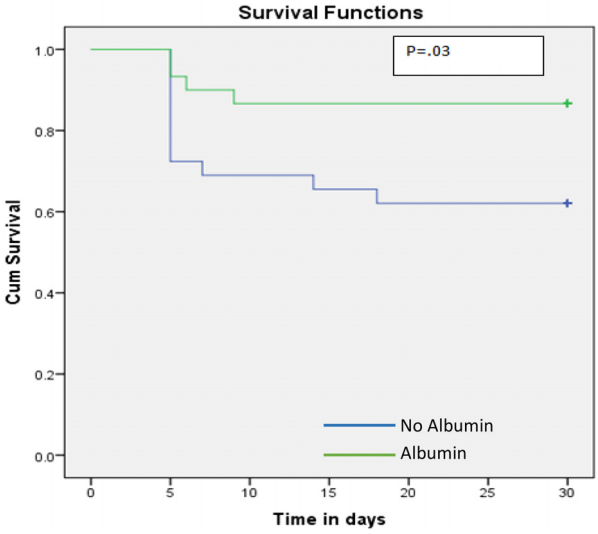
PS-073
Albumin decreases the incidence of paracentesis induced circulatory dysfunction with less than 5 litres of ascitic tap in acute on chronic liver failure (ACLF) patients: Randomized controlled trial (NCT02467348)
V. Arora[1], R. Maiwall[1], S.S. Thomas[2], V. Rajan[1], R. Ali[1], G. Kumar[3], P. Jain[3], S.K. Sarin[4]. *[1]Institute of Liver and Biliary Sciences, Hepatology, Delhi, India; [2]Institute of Liver and Biliary Sciences, Clinical Biochemistry, Delhi, India; [3]Institute of Liver and Biliary Sciences, Clinical Research and bio statistics, Delhi, India; [4]Institute of Liver and Biliary Sciences, Department of Hepatology, Vasant kunj, India*
Email: vinod_ucms@yahoo.com

Background and Aims: PICD is diagnosed by increase in plasma renin activity (PRA) (>50% from baseline or >4 ng/ml/hour) on day 6 post large volume paracentesis (>5 L). It is associated with hepatic encephalopathy (HE), hyponatremia and high mortality. Patients with ACLF have high portal pressure, cardiac output and lower systemic vascular resistance (SVR) compared to decompensated

cirrhosis. There is lack of data on the incidence, diagnosis and management of PICD in ACLF. We hypothesized an increased predisposition to circulatory dysfunction even with modest volume paracentesis (<5 L) in ACLF patients and aimed to determine the need for albumin infusion.

Method: 59 ACLF patients, undergoing paracentesis of <5 L were randomized to receive albumin (8 g/L of ascitic fluid, Gr A, n = 30) or no albumin (Gr. B, n = 29). Heart rate (HR), systolic BP (SBP), diastolic BP (DBP) were monitored for 6 days. PRA and NTpro-BNP were analysed at baseline, day 3 and 6. Hyponatremia was defined as Na < 130 Meq/l or > 5 Meq ↓, AKI as ICA-AKI criteria & HE ≥ grade 2.

Results: Baseline characteristics were comparable in two groups, including mean volume of tap (4.21 ± .15 vs 4.26 ± .24 L, p = .35), baseline PRA(19.59 ± 7.4 vs 22.52 ± 9.1 ng/ml, p = .18), HVPG (19.1 ± 4.6 vs 19.3 ± 5.7 mmHg, p = .18) & SVR 1357 ± 511 vs 1375 ± 419 dyn-sec/cm^5/m^2, p = .83). PICD was more frequent in Gr B than A (62% vs. 26%; p = 0.002). ↑ incidence of HE (24% vs 6.7%, p = .06), hyponatremia (62% vs 30%, p = .05), AKI (36% vs 11%, p = .001) and ↓ in DBP (4.37 ± 6.3% vs 9.61 ± 8.4%, p = .009) was more in Gr B than A. ↑ in PRA at day 3 correlated (p < .001, r2 = 0.8) with day 7, indicating reliability of PRA ↑ at day 3. Increase in NTproBNP was noted from baseline to day6 in Gr B (p = .009). Predictors of PICD on day6 on univariate analysis were: baseline HVPG (OR1.19,95% CI1.02–1.39, p = .02), PRA at day3 (OR1.08,95% CI = 1.02–1.15, p = .007) and non-albumin infusion (OR6.11,95%CI = 1.97–18.89, p = .002). On multivariate analysis, only non-albumin infusion (OR11.66, 95% CI 2.43–55.83, p = .002) was significant. Patients who developed PICD had higher mortality (80% vs 20%, p = .001). Gr B had a higher mortality than Gr. A patients (73% vs 26%, p = 0.03).



Conclusion: Even <5 L of ascitic tap without albumin resulted in PICD in 62% ACLF patients with increased incidence of complications &mortality. Albumin reduces the incidence of PICD and mortality to 1/3rd and is recommended as a plasma expander for even modest volume tap in ACLF patients.

PS-074

Secondary prophylaxis of hepatic encephalopathy in cirrhosis: A double blind randomized controlled trial of L-ornithine L-aspartate versus placebo

S. Varakanahalli, B. Sharma, S. Sachdeva, A. Dahale, S. Srivastava. *G B Pant Institute of Postgraduate Medical Education and Research, Gastroenterology, NEW DELHI, India*
Email: shivakumarvarakanahalli@gmail.com

Background and Aims: Hepatic encephalopathy (HE) is associated with a poor prognosis. L-ornithine L-aspartate (LOLA) has been useful in treatment of acute hepatic encephalopathy. There is no study on the prevention of recurrence of HE with LOLA.

Method: We conducted a double blind randomized controlled trial at a tertiary centre outpatient clinic. Consecutive cirrhotic patients who had recovered from HE within past 12 months were randomized to receive LOLA (6 grams thrice daily) or similar amount of placebo for 6 months. Randomization was done by computer generated random numbers to different codes by an independent observer who was unaware of patient characteristics. Patient received boxes of drugs according to their codes by the independent observer. Patients were assessed by number connection tests or figure connection tests, digit symbol test, serial dotting test, line tracing test, critical flicker frequency test, arterial ammonia and sickness impact profile scores at inclusion and at 3 months and 6 months follow up. Primary end-point was development of overt HE.

Results: Of 306 patients, 150 patients were enrolled. On intention to treat analysis, HE recurred in 11/75 (14.6%) and in 23/75 (30.6%) patients receiving LOLA and placebo respectively (p = 0.02) and hazard ratio (0.389) [95% CI = 0.174–0.870]. By Kaplan-Meier analysis, the time for first breakthrough episode of HE from the time of randomization to 6 months was (170.88) days (CI = 165.0–176.73) in LOLA group and (157.78) days (CI = 148.5–167.0) in placebo group with hazard ratio (0.43) and (p = 0.018). Mortality was similar in both groups (6.8% *vs.* 13.8%) (p = 0.18). At 6 months follow up, there was significant change in the psychometric hepatic encephalopathy scores (2.53 ± 2.18 *vs.* –0.01 ± 1.92, p < 0.001), arterial ammonia levels (–23.58 ± 14.8 *vs.* 1.41 ± 13.34 µmol/L, p < 0.001), critical flicker frequency (5.85 ± 4.82 vs 0.58 ± 4.53, p < 0.001) and sickness impact profile scores (–7.89 ± 5.52 *vs.* –0.95 ± 4.25, p < 0.001) in patients treated with LOLA compared to placebo. On multivariate analysis, only Model for end stage liver disease (MELD) score predicted the recurrence of overt HE with odds ratio (2.21) [CI 1.526–3.204] (p < 0.001).

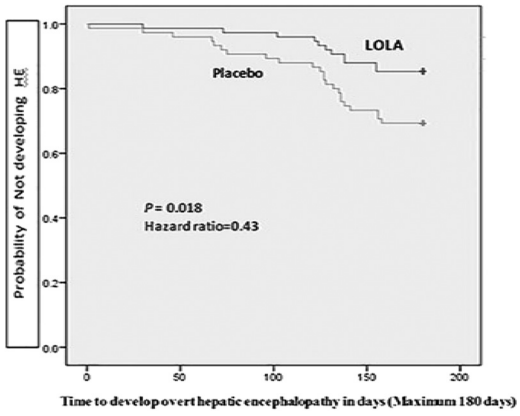


Figure: Kaplan –Meier analysis for recurrence of hepatic encephalopathy between LOLA group and placebo group.

Conclusion: LOLA is effective in the secondary prophylaxis of hepatic encephalopathy and is associated with significant improvement in psychometric hepatic encephalopathy scores, ammonia levels, critical flicker frequency scores and health related quality of life.

PS-075

Mucosal invariant T (MAIT) cells are depleted from blood in advanced cirrhosis and accumulate in the peritoneal cavity during bacterial peritonitis

O. Akinhanmi[1], S. Stengel[1], N. Köse[1], A. Stallmach[1], M. Bauer[2], T. Bruns[1]. [1]*Jena University Hospital, Dpt. of Internal Medicine IV, Jena, Germany;* [2]*Jena University Hospital, Dpt. of Anesthesiology and Intensive Care, Jena, Germany*
Email: oluwatomi.akinhanmi@med.uni-jena.de

Background and Aims: Mucosal invariant T (MAIT) cells are a subset of fast-acting unconventional T cells, which play essential roles in

mucosal immunity against pathogens. Patients hospitalized for advanced cirrhosis have a poor short-term prognosis especially when they encounter bacterial infections, such a spontaneous bacterial peritonitis (SBP) as a result of impaired immune responses. Aim of this study was to investigate the phenotype, function, and clinical relevance of MAIT cells in the peritoneal cavity during complications of cirrhosis.

Method: Peripheral blood and ascitic fluid from patients with decompensated cirrhosis and healthy controls were analyzed using flow cytometry. Vα7.2+ CD161+ CD3+ MAIT cells were quantified and markers of activation (CD69), tissue homing (Integrin αE, CCR7), immune exhaustion (PD-1), chemokine receptors, transcription factors, and intracellular cytokines were assessed.

Results: In contrast to other unconventional T cells, circulating MAIT cells were significantly lower in patients with decompensated cirrhosis (median 0.7% of T cells) compared to controls (median 4.3%; $p < 0.0001$) without significant correlation with classical liver disease scores. In the absence of SBP, the proportion of MAIT cells among T cells was higher in the peritoneal cavity than in blood (1.0% vs. 0.6%; $p = 0.02$), and peritoneal MAIT cells had a tissue homing phenotype (CD103+ CCR7-). Peripheral blood and peritoneal MAIT cells were predominantly CD8-positive and expressed more often CD69 than conventional T cells (13.9% vs. 0.4%; $p = 0.001$, 12.5% vs. 1.7%; $p = 0.01$ respectively) but did not differ in their expression of PD-1. During SBP, peritoneal MAIT cell frequency (1.2% vs. 2.7%; $p = 0.02$) and MAIT cell ascites-blood-ratio (1.4 vs. 5.2; $p = 0.007$) was increased at the day of diagnosis but normalized after 2 days of antibiotic treatment (5.2 vs. 2.0; $p = 0.06$). As compared to conventional T cells, ascitic fluid MAIT cells showed high expression of CCR6 and CXCR3 and were potent producers of IL-17 and TNF after PMA/ionomycin stimulation.

Conclusion: Recruitment and local activation of IL-17 producing CCR6+ CXCR3+ MAIT are observed in the early phases of SBP thus regulating the antimicrobial inflammatory response.

PS-076

Long-term administration of human albumin reduces hospitalization and improves survival in patients with cirrhosis and refractory ascites

M. DI Pascoli[1], S. Fasolato[1], S. Piano[2], M. Bolognesi[1], P. Angeli[3].
[1]University and General Hospital of Padova, Unit of Internal Medicine and Hepatology, Padova, Italy; [2]University of Padova, University and General Hospital of Padova, Padova, Italy; [3]of Internal Medicine and Hepatology, University and General Hospital of Padova, Padova, Italy
Email: m.dipascoli@tin.it

Background and Aims: In liver cirrhosis, ascites becomes refractory when it is not possible to resolve it through standard medical of care (SOC) with low sodium diet and diuretic medications. The clinical benefit of human albumin long-term administration for the treatment of ascites is debated, and for refractory ascites no data are available. In this study, in patients with cirrhosis and refractory ascites, we assessed the effect of long-term albumin administration on hospitalization and mortality.

Method: Seventy patients with cirrhosis and refractory ascites were prospectively and consecutively followed at the Unit of Internal Medicine and Hepatology, University and General Hospital of Padova, Italy, from January 2012 to June 2016. Forty-five patients were non-randomly assigned to receive long-term administration of human albumin at the doses of 20 grams twice per week, in association with hydro-saline restriction and the maximal daily tolerated doses of diuretics, and compared to 25 patients followed according to the SOC. When large-volume paracentesis was performed, all patients received also albumin at the dose of 6–8 grams per liter of ascites removed. Patients were followed up to the end of the study, liver transplantation, or death.

Results: There were no differences in clinical and lab data between the two groups at the time of inclusion in the study. The period free of hospitalization was significantly longer in patients treated with long-term administration of albumin: 0% of patients in the SOC group and 33% of patients treated with albumin were still free of inpatient admissions 24 months after inclusion ($p = 0.008$). Analysing separately the causes of inpatient admission, patients treated with albumin showed a reduction in the incidence of overt hepatic encephalopathy, ascites, spontaneous bacterial peritonitis (SBP) and non-SBP infections. In addition, a non-significant trend toward a reduced probability of hepatorenal syndrome was observed. The cumulative incidence of 24-months mortality was significantly lower in patients treated with albumin than in the group of patients treated with SOC (41,6% versus 65,5%; $p = 0.032$). Long-term administration of albumin was a predictor of survival both on univariate and on multivariate analysis (including age and MELD as other parameters).

Conclusion: In patients with cirrhosis and refractory ascites, long-term treatment with albumin reduces the probability of inpatient hospitalizations and improves survival.

PS-077

Continuous infusion of beta-lactam antibiotics in cirrhotic patients with bloodstream infection: results from a prospective multicentre observational study

M. Bartoletti[1], M. Giannella[1], R. Lewis[1], S. Tedeschi[1], G. Verucchi[1], P. Caraceni[2], M.T. Cerenzia[3], E.M. Seminari[4], T. Bruns[5], M. Merli[6], P. Burra[7], A.E. Maraolo[8], C. Schramm[9], N. Cobos-Tigueros[10], M. Paul[11], J. Rodríguez-Baño[12], M. Bernardi[2], P. Viale[1]. *[1]S. Orsola-Malpighi Hospital, Infectious Diseases Unit – Department of Medical and Surgical Sciences, Bologna, Italy; [2]University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; [3]Città della Salute e della Scienza, SSCVD Insufficienza epatica e Trapianto d'organo, Torino, Italy; [4]IRCCS Policlinico San Matteo, Infectious Diseases; [5]Jena University Hospital, Dpt. of Internal Medicine IV, Jena; [6]Az Osp Policlinico Umberto I – University of Rome, Gastroenterologia, Roma, Italy; [7]Padova University Hospital, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; [8]University of Naples Federico II, Department of Clinical Medicine and Surgery, Section of Infectious Diseases, Naples; [9]University Hospital Cologne, Department of Gastroenterology and Hepatology, Cologne, Germany; [10]Hospital Clínic, IDIBAPS, University of Barcelona, Barcelon; [11]Rambam Health Care Center, Division of Infectious Disease; [12]Instituto de Biomedicina de Sevilla (IBiS), Hospitales Universitarios Virgen Macarena y Virgen del Rocío/CSIC/Universidad de Sevilla, Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Sevilla, Spain*
Email: michele.bartoletti4@unibo.it

Background and Aims: Infection is a major cause of morbidity and mortality among patients with liver cirrhosis. Beta-lactams are time-dependent antibiotics frequently used to treat cirrhotic patients with infection. Previous studies on non-cirrhotic patients with infection suggest that continuous infusion (CI) of beta-lactams are associated with improved outcome. The aim of this study was to compare the 30-day mortality rate of patients receiving continuous versus intermittent administration (IA) of piperacillin-tazobactam (TZP) or carbapenems (CARs) in cirrhotic patients with BSI.

Method: This is a sub-study of the "bloodstream infection in cirrhotic patients (BICHROME) study", an observational, prospective multicentre study conducted from September 2014 to December 2015 in 17 European centres, enrolling patients with liver cirrhosis and BSI. Of the 312 patients enrolled in the core study we selected those receiving: (i) adequate empirical treatment and (ii) TZP or CAR as empiric or definitive treatment. Survival after 30 days of patients receiving CI or IA of antibiotics were compared by Kaplan-Meier curves. Efficacy of CI of TZP and CARs was assessed in a Cox regression model of 30-day mortality.

Results: During the study period 190 patients received both adequate empiric and definitive treatment. Of these, 123 received TZP or CARs as empiric or definitive treatment and were therefore analyzed. Mean age was 61 (±12) years and 83 (67%) of patients were male. The main

causes of liver cirrhosis were viral in 43 (36%), alcoholic in 32 (26%) and cryptogenic in 20 (16%) cases. Comparing patients receiving CI [38 patients (31%)] with patients treated with IA [85 patients (69%)] of TZP or CARs no differences were found in demographics and cirrhosis characteristics. Patients treated with CI of TZP or CARs were more likely to have hospital acquired infections (68% *vs.* 43%, p = 0.01), intra-abdominal infections (34% *vs.* 16%, p = 0.03) and infection caused by a multidrug-resistant Gram-negative pathogen (32% *vs.* 16%, p = 0.05). At the end of follow-up 31 patients died (25%). Mortality was significantly lower among patients receiving CI of antibiotics (Figure). In a Cox regression model including severity and source of infection, receipt of empiric CI of TZP or CARs was independently associated with a significative lower mortality [HR 0.34 (95% CI 0.11–0.93), p = 0.036]

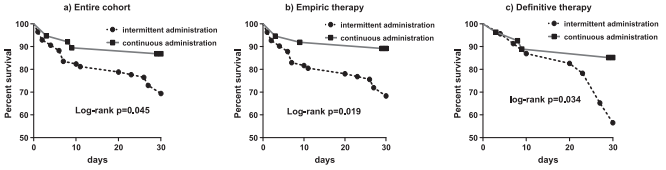


Figure: Kaplan-Meier curves indicate that patients receiving continuous versus intermittent administration of piperacillin-tazobactam or carbapenems, had a significative lower mortality rate (a). Comparable results were obtained performing separate analysis for patients receiving empiric treatment (b) or definitive treatment (c) with piperacillin-tazobactam or carbapenems.

Conclusion: In cirrhotic patients with BSI, administration of CI of beta-lactam antibiotics such as TZP or CARs is associated with improved outcome

PS-078

Therapeutic plasma-exchange improves systemic inflammation and survival in patients with acute on chronic liver failure

R. Maiwall[1], A. Choudhury[1], Z. Duan[2], Y. Chen[2], J. Hu[3], H.L. Ghazinyan[4], Q. Ning[5], K. Ma[5], G.H. Lee[6], S.G. Lim[6], S. Shah[7], C. Kalal[7], A.K. Dokmeci[8], G. Kumar[1], P. Jain[1], I. Paulson[1], S.K. Sarin[1], A. Choudhury[9]. *[1]ILBS, Hepatology, Delhi, India; [2]Beijing You'an Hospital, Hepatology, Beijing, China; [3]302 Millitary Hospital, Beijing, China; [4]Nork Clinical Hospital of Infectious Disease, Yerevan, Armenia; [5]Tongji Hospital, Tongji Medical College; [6]Yong Loo Lin School of Medicine, National University of Singapore, Singapore; [7]Global Hospital, Mumbai, India; [8]Ankara University School of Medicine; [9]ACLF APASL Research consortium, AARC Working party*
Email: rakhi_2011@yahoo.co.in

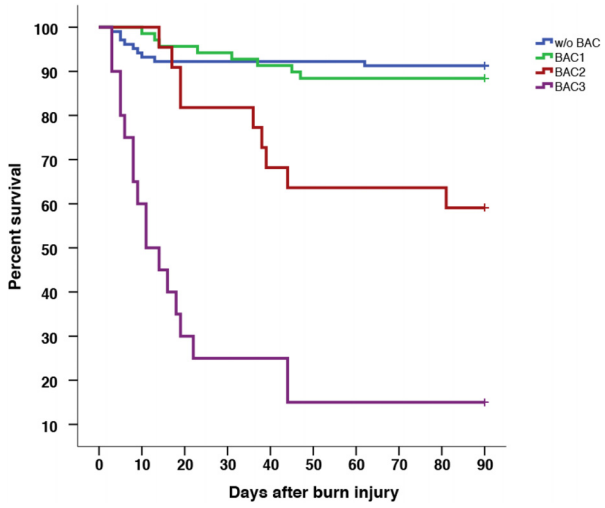
Background and Aims: Systemic Inflammation (SIRS) and infection form the pathogenetic hallmark of organ dyfunction in patients with Acute on Chronic Liver Failure (ACLF). Plasma-exchange (PE) has been shown to improve survival in patients with acute liver failure by combating SIRS, but there is paucity of data in patients with ACLF. We evaluated the role of artificial liver support systems (ALS), plasma-exchange (PE) and liver dialysis (FPSA) as compared to standard medical treatment(SMT) in improving SIRS, development of multi-organ failure(MOF) and survival (SMT) in a large multicentric-multinational cohort of ACLF patients. We also compared the efficacy of PE as compared to FPSA.
Method: Prospectively collected data from AARC data base was analysed. Matching by propensity risk score (PRS) was done to avoid selection bias. Competing risk Cox regression analysis was done to identify event specific death.
Results: ACLF patients (n = 1866,aged 44.3 ± 12.3 yrs, 93% males, 65% alcoholics) received either ALS (n = 162);[PE (n = 131), FPSA (n = 31)] or continued with SMT(n = 1704). Patients treated with ALS had a significantly lower MELD (p = 0.03) and CTP scores (p = 0.04) which was no more evident in the PRS-matched cohort (p > 0.05) (n = 208, [ALS-119;PE-94,LD-25)], SMT-89). Bacterial infections were noted in 363(19%), SIRS in 728(39%), which resolved in 511 (27%). ALS was associated with significantly(p < 0.05) higher resolution of SIRS [OR (1.56,1.03–2.34) (1.5,1.03–2.34)], lower persistence [OR(4.6,1.2–18.4) (1.09, 1.01–1.2)], development of new-onset SIRS [OR(4.38,1.1–17.5) (1.2,1.04–1.29)] and MOF [(HR(6.5,4.8–8.7)(7.1,4.5–11.1)] in pre-match and PRS-matched cohorts respectively. At 1-month, 656 (35%) died of which 233(35.5%) died of MOF, remaining due to sepsis and other causes. On multivariate Competing risk Cox-regression analysis, in both the pre-match and PRS-matched cohorts, treatment with ALS [(HR 0.11, 0.04–0.27), (HR-0.02, 0.002–0.15) and MELD score [(HR 1.1, 1.08–1.2), (HR 1.09,1.04–1.15) respectively were significant predictors of liver failure related death. Further, on subgroup analysis PE was associated with a significant survival benefit as compared to FPSA in pre-match (HR 3.4, 1.4–8.1) and PRS-matched (HR 3.9, 1.3–12.3) cohorts.
Conclusion: ALS in patients with ACLF improves systemic inflammation, lowers development of MOF and results in improved survival. Plasma-exchange has a significant survival benefit over FPSA and should be the therapy of choice in these patients.

PS-079

The relationship between burn-associated cholangiopathy and outcome of critically ill burn adults

C. de Tymowski[1], F. Depret[1], S. Soussi[1], M. Chaussard[2], N. Moreno[2], P. Sogni[3], M. Legrand[1], V. Mallet[3]. *[1]GH St-Louis-Lariboisière, Department of Anesthesiology and Critical Care and Burn Unit, Paris, France; [2]GH St-Louis-Lariboisière, Biochemistry laboratory, Paris, France; [3]Hopital Cochin, Hepatology, Paris, France*
Email: vincent.mallet@aphp.fr

Background and Aims: Burn-associated cholangiopathy (BAC) is reported among burn patients. There is a gap of knowledge on BAC-associated factors and outcomes.
Method: We conducted a retrospective, single-center, cohort study among consecutive and non-selected adult patients (n = 735) admitted in our Burn Unit (BU) between June 2012 and December 2015. Biological measures were retrieved from the biological database of our institution and merged in the patient's characteristics dataset. We selected patients with at least one of the following criteria: total body surface area burn (TBSA) ≥ 20%; full thickness BSA ≥ 10%; smoke inhalation; organ dysfunction, including the need for vasopressors and the need for mechanical ventilation, during the first 48. Patients with a length of stay BU ≤ 48 hours or with abnormal liver function tests prior to BU admission were excluded.
BAC was defined by cholestasis (ALP ≥ 1.5 times the upper limit of normal (ULN) and GGT ≥ 3 times the ULN) or by hyperbilirubinemia (total bilirubin ≥ 34.2 µmol/l) and was categorized in 3 groups: BAC1, cholestasis without any episode of hyperbilirubinemia during BU stay; BAC2: cholestasis and at least one episode of hyperbilirubinemia during BU stay; BAC3: hyperbilirubinemia without any episode cholestasis during BU stay. Acute kidney injury (AKI) was defined with the Kidney Disease Improving Global Outcomes (KDIGO) criteria. All episodes of infections were prospectively collected. The primary endpoint was 90-day mortality.
Results: Among 214 selected patients (median [IQR] age 48 [32–61], 68% male, TBSA 27 [18–45]), 111 (52%) had BAC during BU stay, including 69 (62%) patients with BAC1, 22 (20%) with BAC2 and 20 (18%) with BAC3. BAC was associated with severity at admission and complications during BU stay, including increased risk of bacteremia [adjusted OR = 3.27 95%IC (1.38–7.71); p = 0.007]. BAC2 and BAC3 patients had higher AST/ALT ratio, more nosocomial infections and septic shocks, more AKI, and higher 90-day mortality rate. A one-class increase in BAC injury was associated with 90-day mortality (adjusted hazard ratio [95% CI] 1.66 (1.07–2.58); p = 0.024; see Figure). BAC2 and BAC3 patients had the worst outcome (higher mortality): 85% of BAC3 patients died with a median survival of 11 [6–22] days, while 12% and 41% of BAC1 and BAC2 patients died, respectively.



Conclusion: BAC is independently associated with sepsis and outcome of severely burned patients.

PS-080

Adherence to EASL antibiotic treatment recommendations improves the outcomes of patients with cirrhosis and bacterial infections. Results from the ICA Global Study

S. Piano[1], V. Singh[2], P. Caraceni[3], R. Maiwall[4], C. Alessandria[5], J. Fernandez[6], E. Soares[7], D.J. Kim[8], S.E. Kim[9], M. Marino[10], J. Vorobioff[11], R. de Cassia Ribeiro Barea[12], M. Merli[13], L. Elkrief[14], V.M.V. Blasco[15], A. Krag[16], S. Singh[17], L.A. Lesmana[18], C. Toledo[19], S. Marciano[20], V. Xavier[21], F. Wong[22], N. Intagliata[23], L. Rabinowich[24], L.A. Colombato[25], S.G. Kim[26], A. Gerbes[27], F. Durand[28], J.P. Roblero[29], K. Bhamidimarri[30], T.D. Boyer[31], M. Maevskaya[32], E.L. Fassio[33], H.S. Kim[34], J.-S. Hwang[35], A. Gadano[20], S.K. Sarin[36], P. Angeli[37].
[1]University of Padova, University and General Hospital of Padova, Padova, Italy; [2]Postgraduate Institute of Medical Education and Research, Chandigarh, India; [3]University of Bologna, Bologna, Italy; [4]Institute of Liver and Biliary Sciences (ILBS), New Delhi, India; [5]University Hospital of Turin, Turin; [6]Hospital Clinic of Barcelona, Liver Unit, Barcelona, Spain; [7]Gastrocenter-Unicamp, Campinas, Brazil; [8]Hallym University College of Medicine, Chuncheon, Korea, Rep. of South; [9]Hallym University Sacred Heart Hospital, Seoul, Korea, Rep. of South; [10]Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina; [11]Universidad Nacional de Rosario, Rosario, Argentina; [12]Faculty of Medicine of Bahia, Campo Grande, Brazil; [13]Sapienza University of Rome, Rome, Italy; [14]University Hospital of Geneva, Geneva, Switzerland; [15]Hospital Vall d'Hebron, Liver Unit, Barcelona, Spain; [16]Odense University Hospital, Odense, Denmark; [17]Shri Ramachandra Bhanj Medical College, Orissa, India; [18]Digestive Disease and Oncology Centre (DDOC)-Medistra Hospital, Jakarta, Indonesia; [19]Hospital Valdivia, Universidad Australe de Chile, Valdivia, Chile; [20]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina; [21]Ghent University Hospital, Ghent, Belgium; [22]University of Toronto, Toronto, Canada; [23]University of Virginia, Charlottesville, United States; [24]Tel-Aviv Medical Center, Tel-Aviv, Israel; [25]Hospital Británico de Buenos Aires, Buenos Aires, Argentina; [26]Soonchunhyang University – Bucheon Hospital, Bucheon, Korea, Rep. of South; [27]University of Munich, Munich, Germany; [28]Hospital Beaujon, Clichy, France; [29]Universidad de Chile, Santiago, Chile; [30]University of Miami Miller School of Medicine, Miami, United States; [31]University of Arizona, Tucson, United States; [32]First Moscow State Medical University, Moscow, Russian Federation; [33]Hospital Nacional Alejandro Posadas, Buenos Aires, Argentina; [34]Hallym University College of Medicine, Kangdong, Korea, Rep. of South; [35]Keimyung University Dongsan Medical Center, Daegu, Korea, Rep. of South; [36]Institute of Liver and Biliary Sciences, Department of Hepatology, Vasant kunj, India; [37]University of Padova, Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine – DIMED, Padova, Italy
Email: pangeli@unipd.it

Background and Aims: Bacterial infections are a common cause of decompensation in patients with cirrhosis. On 2014 EASL recommendations for antibiotic treatment in patients with cirrhosis and bacterial infections were published. The effects of the adherence to these recommendations have never been investigated so far. The aim of this study was to assess the clinical impact of the adherence to EASL recommendations in patients with cirrhosis and bacterial infections.
Method: In the International Club of Ascites (ICA) "Global Study", 1,302 patients with cirrhosis and bacterial infection were included. Demographic, clinical, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. Patients were followed up until death, liver transplantation or discharge. The empirical antibiotic treatment was considered adherent to EASL recommendations if at least one of the antibiotic/combination recommended was administered.
Results: The antibiotic treatment was adherent to EASL recommendations in 61% of patients, while was broader in 14% and weaker in 25%. Northern American centers prescribed more frequently broader antibiotics (31% vs 13%; $p < 0.001$) while Northern European and Asian centers administered more frequently weaker ones (30 vs 21%; $p < 0.001$). Adherence to recommendations was poorer in pneumonia (27 vs 71%; $p < 0.001$) and nosocomial infections (54 vs 64% $p = 0.002$). In patients with positive cultures (57%), the administration of antibiotics weaker than those suggested by EASL recommendations resulted in lower antimicrobial susceptibility (50 vs 75%; $p < 0.001$). Importantly, bacteria isolated in Asian centers had a lower antimicrobial susceptibility to antibiotics suggested by EASL recommendations (58 vs 80%; $p < 0.001$), mainly due to a high prevalence of multi drug resistant bacteria (51 vs 28%; $p < 0.001$). The administration of antibiotics weaker than EASL recommendations was associated with a higher need to escalate treatment (50 vs 32%; $p < 0.001$). In addition, after adjusting for confounders (age, ACLF, quick SOFA and MELD-Na score), the administration of a weaker antibiotic regimen was associated with a higher risk to develop new organ failures (OR = 1.50; $p = 0.010$), septic shock (OR = 1.51; $p = 0.044$) and a higher in-hospital mortality (OR = 1.47; $p = 0.034$).
Conclusion: The adherence to EASL recommendations was associated with better outcomes in patients with cirrhosis and bacterial infections and should be promoted. However, different empirical antibiotic strategies should be developed in certain countries due to the high prevalence of MDR bacteria.

Experimental hepatology

PS-081

Hepatocyte-specific deletion of RuvBL1 leads to chronic liver damage and regeneration, enhancing HCC development

M. Materozzi[1,2], F. Zanieri[3], E. Ceni[3], S. Polvani[3], M. Tarocchi[3], O. Bereshchenko[4], A. Galli[3], T. Mello[3]. *[1]University of Siena, Dept. of Medicine, Surgery and Neuroscience; [2]University of Siena, Doctorate Course in Genetics, Oncology and Clinical Medicine; [3]University of Florence, Dept. of Experimental and Clinical Biomedical Sciences "Mario Serio", Firenze, Italy; [4]University of Perugia, Dept. of Medicine, Perugia, Italy*
Email: tommaso.mello@unifi.it

Background and Aims: The AAA+ ATPase RuvBL1 is overexpressed in several human cancers, including hepatocellular carcinoma (HCC), in

which high RuvBL1 expression correlates with a poor prognosis. A growing body of data from *in vitro* models supports the concept that increased RuvBL1 expression occurs in cancer to promote its growth and progression, making it an attractive target for anti-cancer therapies. However, whether RuvBL1 participates in the oncogenic transformation *in vivo* remains open to speculation. To address this question, we realized a hepatocyte-conditional RuvBL1 knock-out mouse model and evaluated the HCC onset and progression after DEN injection.

Method: Hepatocyte-conditional RuvBL1 knock-out mice were generated by crossing RuvBL1-floxed with Albumin-Cre mice. HCC was induced in male mice by single i.p DEN injection (5 mg/kg) at 14 days of age. Mice were sacrificed at 3, 6, 9 and12 months to monitor HCC onset and progression. By crossing RuvBL1 cKO mice with $B6^{mT/mG}$ mice we obtained a progeny in which mature (Alb^{+}, $RuvBL1^{-/-}$, $EGFP^{+}$) and non-mature (Alb^{-}, $RuvBL1^{wt/wt}$, $mTRed^{+}$) hepatocytes could be traced *in vivo* at single-cell resolution.

Results: Contrary to our expectation, DEN-induced cancerogenesis was strikingly increased in $RuvBL1^{hep-/-}$ *vs* Floxed mice. We found that RuvBL1 deletion in cKO mice resulted in hepatocellular damage, apoptosis and compensatory proliferation, suggesting a possible tumor-promoting mechanism. The liver damage induced by RuvBL1 deletion peaked around 2 weeks of age, corresponding to minimal RuvBL1 expression. Starting at 3 weeks of age, massive proliferation of non-mature hepatocytes and partial recovery of RuvBL1 protein levels were observed. Further characterization revealed that non-mature hepatocytes origin from $CK19^{+}CD133^{+}HNF4^{+}$ cells. We could establish that cycles of RuvBL1 deletion, hepatocytes loss and compensatory proliferation keep on occurring during the lifetime of cKO mice (followed up to 1 year).

Conclusion: This is the first report highlighting the essential role of RuvBL1 for hepatocyte survival and the impact of its loss on liver carcinogenesis. The increased HCC incidence does not reflect a tumor-suppressor role of RuvBL1, rather, it is the outcome of a chronic regenerative process from staminal precursors. This model may prove useful to investigate the mechanism underlying liver regeneration in the context of chronic hepatic damage.

PS-082

Beta-catenin-dependent erythropoiesis in adult mice deficient in hepatic ARID1A chromatin remodeler

R. Riou[1], M. Ladli[2], A. Gougelet[2], G. Cécile[2], Z. Wang[3], F. Verdier[2], S. Colnot[2]. [1]*Institut Cochin, Paris;* [2]*Institut Cochin;* [3]*University of Michigan, Department of Cardiac Surgery Cardiovascular Research Center*
Email: cecile.godard@inserm.fr

Background and Aims: One third of Hepatocellular Carcinomas (HCC) depend on activating mutations in *CTNNB1* gene encoding β-catenin. ARID1A, a SWI/SNF component, is the chromatin modifier the most frequently mutated in more than 13% of HCCs, initially found preferentially in *CTNNB1*-mutated ones. *ARI1DA* would rather be tumor suppressive, as its mutations are mainly inactivating. We hypothesized that HCC emergence and/or progression could be linked to the loss of ARID1A in a β-catenin-dependent context.
Our aim was to determine whether the loss of ARID1A increase the tumorigenic potential of β-catenin aberrant signaling in the liver.

Method: We took advantage of a transgenic murine model in which APC, the major brake of β-catenin signaling, is lost, leading within 9 months to HCC emergence. We thus engineered new transgenic models using Cre-loxP strategy, allowing hepato-specific and tamoxifen-inducible inactivation of *Apc* (leading to hepatic gain-of-function of β-catenin) and/or *Arid1a* (Apc/$Arid1a^{ko-hep}$ mice) in single hepatocytes.

Results: Seven months after tamoxifen injection, we unexpectedly observed in Apc/$Arid1a^{ko-hep}$ mice intrahepatic macroscopic amounts of red blood cells, associated with *de novo* transcription of hepatic erythropoietin (EPO). This leads to EPO secretion in the blood, to a dramatically increased hematocrit and to mouse letality. We found that this *de novo* transcription of *Epo* is cell-autonomous, occurring in mouse as well as in human primary cultures of hepatocytes only after both activation of Wnt/β-catenin pathway (obtained through *Apc* loss or through Wnt/Spondin co-stimulation) and loss of ARID1A. As a consequence of EPO systemic increase, Apc/$Arid1a^{ko-hep}$ mice became splenomegalic, with a dramatic increase of erythroid progenitor cells showing the establishment of a stress erythropoiesis.
At the molecular level, we showed by ChIP experiment an important change of histone marks at the hepatic erythropoietin enhancer in Apc/$Arid1a^{ko}$ hepatocytes compared to control ones. These marks consist in an increase of H3K27Ac and decrease of H3K27Me3, both being classically associated with increased enhancer activities. These activating histone changes are correlated with an increased binding of TCF4, a β-catenin cofactor, on *Epo* enhancer. These data altogether show that chromatin remodeling induced by ARID1A loss unmask new targets of β-catenin, such as *Epo*.

Conclusion: In liver physiology, chromatin remodeling through ARID1A is a powerful epigenetic brake, which could contribute to the shift from an embryonic liver that produces EPO to an adult liver status with no Epo transcription. Moreover, ARID1A inhibition and β-catenin signalling are new actors of the Epo transcriptional machinery, and could be used for genetic engineering of Epo for therapeutic purposes.

PS-083

Protection from Gao-Binge induced liver injury in Mif–/– Mice is associated with decreased ER stress

K. Poulsen[1,2], M. Mcmullen[1,2], M. Sheehan[3], L. Leng[4], R. Bucala[4], L. Nagy[1,2]. [1]*Cleveland Clinic, Department of Pathobiology, Cleveland, United States;* [2]*Northeast Ohio Alcohol Center, Cleveland, United States;* [3]*Cleveland Clinic, Lerner College of Medicine, Cleveland, United States;* [4]*Yale University School of Medicine, Department of Internal Medicine, New Haven, United States*
Email: poulsenk79@gmail.com

Background and Aims: Alcoholic liver disease (ALD) is a major cause of preventable morbidity and mortality worldwide. Alcoholic Hepatitis (AH) is a severe, episodic form of ALD with a high patient mortality rate. Recently, our work has provided strong evidence that the pluripotent chemokine/cytokine macrophage migration inhibitory factor (MIF) is implicated in murine models of ethanol-induced liver injury, as well as in AH patients. Utilizing the Gao-Binge model of murine steatohepatitis (mAH), here we tested the hypothesis that MIF would contribute to ethanol-induced liver injury through enhanced liver inflammation and neutrophil accumulation.

Method: Eight to ten week-old female wild-type and *Mif*–/– C57BL/6J mice were fed a 5% v/v (27% total kcal) ethanol-containing diet or pair-fed control diet for 10 days. On Day 11, mice were gavaged with 5 g/kg ethanol. MIF098 (40 mg/kg) was administered via i.p. injection at −18 h and −1 h to ethanol binge.

Results: A timecourse revealed the peak of liver injury and inflammation occurred 6 hours after ethanol binge as assessed by increased plasma ALT/AST activity. Plasma MIF levels, chemokines KC and MIP2 mRNA expression, as well as neutrophil marker Ly6G mRNA were increased at this time in wild-type mice. As expected, marked accumulation of neutrophils was detected in the livers of ethanol-fed wild-type mice. *Mif*–/– mice and wild-type mice treated with a small pharmacological inhibitor of MIF (MIF098) were protected from increased ALT/AST. Surprisingly, chemokine mRNA expression was unaffected by MIF deletion or inhibition. Despite the protection from liver injury in *Mif*–/– or MIF098-treated mice, neutrophils still accumulated in the liver, consistent with the sustained increases in chemokine expression. Bone marrow-derived neutrophils from WT and *Mif*–/– mice responded similarly to LPS challenge, as assessed by MPO release, suggesting MIF deletion or inhibition did not alter neutrophil oxidative burst. Therefore, we next asked if MIF directly injured hepatocytes in this model. Endoplasmic reticulum (ER) stress was detected in livers of mice 6 hours after binge as indicated by

increased eIF2α phosphorylation, CHOP and Grp78 mRNA expression, and CHOP protein expression. eIF2α activation and increased CHOP protein expression was prevented in *Mif*–/– mice and in wild-type mice treated with MIF098. Furthermore, liver tissue obtained from AH patient liver explants and healthy controls revealed that MIF expression and ER stress were robustly induced in AH patients.
Conclusion: Our results are consistent with MIF contributing to murine AH via induction of hepatocyte ER stress and the pathophysiological role of MIF is independent of hepatic neutrophil accumulation. Pharmacological intervention of MIF could therefore be a therapeutically-relevant target to improve outcomes in AH patients.

PS-084
Sigma 1 receptor: a potential actor in Hepato-Cellular Adenomas
L. Villemain[1], S. Prigent[1], S. Thietry[1], L. Pelletier[2], J. Zucman-Rossi[2], C. Laurent[1]. [1]*INSERM/Université Paris Sud;* [2]*INSERM/ Université Paris Descartes*
Email: laure.villemain@u-psud.fr

Background and Aims: SigR1 is an ubiquitous small protein of 223 amino acid, located in the ER, more precisely in the MAMs (Mitochondria Associated Membranes). This protein is highly expressed in the central nervous system (CNS) and the liver. SigR1 is also overexpressed in several types of cancer, especially in hormone dependent tumors such as breast and prostate cancer. In the CNS it has been shown that SigR1 is involved in neurodegenerative diseases such as Parkinson's disease, Huntington's disease and ALS (Amiotrophic Lateral Sclerosis). Although it is highly expressed in the liver, its function in this organ is totally unknown. We have been thus looking for a role of this protein in the liver.
Results: To identify a possible role of Sig1R in the liver, we looked for variations in the level of expression of this protein in different physiopathological situations, particularly in liver tumors. We found that SigR1 is overexpressed in only one type of liver tumors: HepatoCellular Adenomas (HCAs) mutated for HNF1A (H-HCA). H-HCAs are benign liver tumors that display a marked steatosis, they are mostly found in women taking oral contraceptives containing estrogens. We then investigated the effect of estrogen on the expression of the SigR1 in vivo and in three different cell lines (Huh7, HepG2 and IHH). Western blots measurements of Sig1R show that injection of 17βestradiol (10 mg/kg) induce a significant increase of the expression of Sig1R in mice liver ($n = 14$, $p < 0.05$). Similarly, incubation of Huh7, HepG2 and IHH in the presence of 17βestradiol (10 nM) induced an increase of the level of Sig1R. *In silico* analysis showed a putative ER binding site on the promoter region of Sig1R. Luciferase expression under the SigR1 promoter was highly decreased when this site was mutated. Finally, CHIP experiment showed a direct interaction between ERα and the promoter of SigR1. Otherwise, HepG2 cells overexpressing Sig1R showed a significant increase of the proliferation rate and an accumulation of lipid droplets. Moreover, the more SigR1 was overexpressed, the faster the cells grew. These findings resume the HCAs phenotype.
Conclusions: Taken together, our results suggest that Sig1R could be involved in the development of HCAs. SigR1 could be a therapeutic target, as many ligands of this protein are already used for brain diseases.

PS-085
CCAAT- Enhancer-binding protein homologous protein promotes liver ischemia and reperfusion injury by inhibiting beclin-1-mediated autophagy in hepatocytes
H. Zhou[1], Z. Rao[2], Y. Xia[1], J. Rao[1], X. Wang[1], L. Lu[1]. [1]*The First Affiliated Hospital of Nanjing Medical University, Liver Transplantation Center, Nanjing, China;* [2]*The First Affiliated Hospital of Nanjing Medical University, Dept. of Anesthesiology, Nanjing, China*
Email: doc2012zhm@163.com

Background and Aims: Critical role of endoplasmic reticulum (ER) stress has been found in ischemia and reperfusion (IR) injury models. However, the role of CCAAT-Enhancer-Binding Protein Homologous Protein (CHOP) signaling in liver IR injury still remains unclear. The aim of this study is to determine the role and its underlying mechanism of CHOP signaling in liver IR injury.
Method: Wild-type (WT) and CHOP KO mice were subjected to a murine liver partial warm ischemia model. Liver injury and hepatocellular apoptosis was compared between groups. Autophagy and its regulatory signaling pathways were analyzed both in the liver tissues and the primary hepatocytes. CHOP and autophagy signaling pathways were also studied in human liver tissues post ischemia.
Results: CHOP KO significantly decreased liver IR injury, as evidenced by lower sALT levels and better preserved liver architectures. Liver IR induced marked hepatocellular cell apoptosis, as indicated by HE/TUNEL staining and western blot analysis of cleaved-Caspase-3, BCL-2 and BCL-XL. CHOP KO mice demonstrated much less hepatocellular apoptosis but enhanced autophagy. Primary hepatocytes were isolated and subjected to an in vitro hypoxia/reoxygenation (H/R) model. CHOP KO in hepatocytes resulted in reduced cell death, as measured by LDH and CCK8 assay. Autophagy was enhanced in CHOP KO hepatocytes as evaluated by LC3B staining and the electron microscope examination. Beclin-1 activation was significantly increased in CHOP KO hepatocytes post H/R. Functionally, Beclin-1 siRNA or autophagy specific inhibitor (3-MA) effectively blocked autophagy in hepatocytes and abrogated the protective role of CHOP KO both in liver IR and hepatocyte H/R models. Finally, human liver tissues were collected in patients undergoing liver partial resection with hepatic portal blockade. CHOP and Beclin-1 activation was analyzed by Western blot. Indeed, CHOP activation was increased by liver ischemia. On the contrary, Beclin-1 activation was decreased post ischemia.
Conclusion: Our results indicated that CHOP activation promoted liver IR injury by inhibiting Beclin-1-mediated autophagy in hepatocytes. Strategies targeting CHOP or autophagy signaling may provide therapeutic effects against liver IR injury in patients.

PS-086
Faecalibacterium improves pathogenesis of nonalcoholic steatohepatitis via controlling Treg induced gut-permeability
T. Kessoku, K. Imajo, Y. Honda, Y. Ogawa, W. Tomeno, M. Yoneda, T. Kato, T. Higurashi, S. Saito, A. Nakajima. *Yokohama City University Graduate School of Medicine*
Email: nakajima-tky@umin.ac.jp

Background and Aims: Up to 25% of non-alcoholic fatty liver disease (NAFLD) patients develop a progressive inflammatory liver disease termed non-alcoholic steatohepatitis (NASH) that may progress towards cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. In recent years, several lines of evidence suggest that the gut microbiome plays important roles for the pathogenesis of NASH. We demonstrated *faecalibacterium* (*FB*) was significantly decreased with exacerbated liver fibrosis in human study. The aim of our study was to assess if *FB* improves NASH pathogenesis in mice and mechanism between *FB* and improving NASH-pathogenesis.
Method: Eight-week-old male C57BL/6J mice were randomly distributed into 3 groups of 10 animals each: a basal diet group (B), a high-fat high-fructose high-cholesterol diet (HFCD) group (H), HFCD plus administrated FB group (F). *FB* was daily administrated per os in F group. After 20 weeks of dietary treatment, the mice were euthanized and relevant tissues were prepared for subsequent analysis.
Results: *FB* abundance was significantly decreased in H group compared with B, and increased in F group compared with H group. Histological findings revealed that hepatic triglyceride contents and number of neutrophil elastase positive cells, fibrotic area were significantly decreased in F group compared with those in H group. The serum endotoxin, AST, ALT T-cho, Cho-VLDL levels, and HOMA-R were significantly decreased in F group in comparison to H

group. In OGTT test, blood glucose level in 90 min and 120 min were ameliorated in F group compared with H group. Gene expression levels of TNF-a, collagen1a1, PPRAα, CPT1a1, MTP, IRS1, IRS2, PEPCK, and G6P in the liver were significantly ameliorated in group F compared with H group. Also, in gut-permeability analysis, significant increase in gut permeability was observed in H group in comparison to that in group B, whereas the increased gut permeability was abrogated in F group in comparison to that in group H. In colon mucosa, gene expression levels of TNF-a, OCLN, CLDN4, 8, 15 were improved in F group in comparison to those in H group. Gene expression levels of FOXP3 and TGF-β were significantly increased in F group compared with those in H group. In flowcytometry, significantly increased in CD4 + CD25 + FOXP3+ cells in lamina propria lymphocyte was observed in F group compared with H group. Administration of anti-FR4 antibody on B group leads Treg depletion, resulted in the increasing intestinal permeability in B group.

Conclusion: Our study indicated that *FB*-administration improves NASH pathogenesis via ameliorating gut-permeability by inducing Treg in colon. Our results suggest that *FB* could be a candidate agent for the treatment of NASH through the improving leaky-gut.

PS-087

What drives development of HCC in non-cirrhotic NAFLD?

A. Mahdi[1,2], M. Zaki[3,4], J. Lunec[3], Q. Anstee[1], D. Tiniakos[1], R. Shukla[3], F. Oakley[1], S. Cockell[5], H.L. Reeves[1,6]. *[1]Newcastle University Medical School, Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom; [2]College of Medicine, Al-Nahrain University, Department of pathology and forensic medicine, Baghdad, Iraq; [3]Newcastle University Medical School, Northern Institute for Cancer Research, Newcastle upon Tyne, United Kingdom; [4]Minia University, Faculty of Pharmacy, Biochemistry Department, Minia, Egypt; [5]Newcastle University Medical School, Bioinformatics Support Unit, Newcastle upon Tyne, United Kingdom; [6]The Newcastle upon Tyne NHS Foundation Trust, Department of Medicine, Newcastle upon Tyne, United Kingdom*
Email: h.l.reeves@ncl.ac.uk

Background and Aims: Although the relative risk of hepatocellular carcinoma (HCC) arising in patients with NAFLD is much lower in the absence of cirrhosis, given the prevalence of NAFLD, cases are rising significantly. The mechanisms involved are poorly understood and hamper the development of surveillance tools or preventive strategies.

Method: We fed 120 C3H/HeH mice, which develop obesity and impaired glucose tolerance with age, the American lifestyle (ALIOS) or control diet – for 12, 24 or 48 weeks, some supplemented with the antioxidant bucillamine(10 mg/kg/day). NAFLD/tumours, DNA damage and proliferation were assessed by a liver histopathologist, γ-H2AX and Ki-67 immunohistochemistry. RNA-Seq was performed in 50 liver tissues.

Results: Fasting blood glucose (mean 12.8 mmol/l) was not different between dietary groups at 48 weeks, but the ALIOS diet exacerbated increases in body and liver weight. The mice developed steatosis, ballooning, lobular inflammation and fibrosis. 27 of 47 mice (control 7/23; ALIOS 20/24) developed liver tumours – 2 were adenomas and 25 were HCC. Features highly significantly associated with tumour development (Table) included liver weight, steatosis grade and presence of lipogranulomas. Ki-67 elevation indicated a proliferative process contributing to liver weight and was also associated with tumour development, as were lobular inflammation, γ-H2AX positive nuclei and fibrosis. In mice fed control or ALIOS diet supplemented with bucillamine, NASH was absent, γ-H2AX reduced >10 fold and fibrosis markedly suppressed. Despite this, the numbers of HCC (control 5/11; ALIOS 9/11) and size were unchanged. Notably, bucillamine had little impact on liver weight, steatosis, lipogranulomas or Ki-67 positive nuclei. Unsupervised clustering of non-tumour tissues RNA-Seq data created two groups with 248 differentially expressed genes. Tumour development was highly enriched in the second cluster, in association with genes in the macrophage enriched metabolic network (MEMN) (72/248, 29%, q-value = 3.16E-53; Gene set enrichment analysis (GSEA)). Ingenuity pathway analysis (IPA) highlighted upregulated cell survival (p = 5.19E-11, Z-score = 5.308) and angiogenesis (p = 2.23E-12, Z-score = 2.452) gene expression.

Tumour development at 48 weeks	No Bucillamine n=47					Bucillamine (NO reduction in tumours)	
	Chi^2			Spearman			
	no	yes	p value	correlat'n	p value	impact	p value
Body weight				**0.381**	**0.008**	**unchanged**	0.629
Liver weight				**0.686**	**<0.001**	**unchanged**	0.995
Liver Histopathology							
Steatosis grade (0/1/2/3)	4/7/8/1	0/4/20/3	**0.01**	**0.429**	**0.003**	slight ↓	0.012
Hepatocellular ballooning score (0/1/2)	5/12/3	4/20/3	0.579	0.058	0.699	absent	<0.001
Mallory Denk bodies (None/present)	14/6	13/13	0.172	0.305	0.1039	absent	<0.001
Lipogranuloma (None/present)	15/5	9/17	**0.007**	**0.481**	**0.001**	**unchanged**	0.388
Lobular Inflammation score (0/1/2)	9/10/1	4/18/5	0.06	**0.421**	**0.003**	↓↓	0.029
Portal Inflammation score (0/1/2)	18/1/1	21/5/1	0.507	0.276	0.060	unchanged	0.539
Pigmented Kupffer cells (None/present)	13/7	11/15	0.127	0.280	0.060	↓↓	0.007
Perisinusoidal fibrosis score(0/1)	6/14	1/26	**0.012**	0.361	**0.013**	↓↓	<0.001
Fibrosis stage (0/1/2/3)	6/8/6	1/14/11/1	0.064	0.355	**0.014**	↓	<0.001
NAS score (sum)				0.465	0.001	↓↓↓	<0.001
SAF score (sum)				0.467	0.001	↓↓↓	<0.001
H2AX positive nuclei (47 cases studied)				**0.353**	**0.016**	absent	<0.001
Ki-67 positive nuclei (24 cases studied)				**0.506**	**0.012**	**unchanged**	0.983

Conclusion: In this murine model of obesity related NAFLD and HCC, bucillamine treatment led to a clear amelioration of steatohepatitis but did not affect tumour burden. Therefore, NASH and DNA damage played a limited role in tumour development whilst liver weight, associated with steatosis grade, lipogranulomas and a proliferative state were key. IPA and GSEA analyses of non-tumour tissues supported a role for macrophages recruited to fat damaged hepatocytes (lipogranulomas) as promoting hepatocarcinogenesis in an obesity associated liver environment of enhanced hepatocyte proliferation.

PS-088

Hepatocyte-specific overexpression of FoxM1 transcription factor leads to spontaneous liver inflammation, fibrosis, and tumorigenesis in mice

T. Kurahashi, Y. Yoshida, S. Ogura, M. Egawa, K. Furuta, Y. Kamada, S. Kiso, T. Kodama, H. Hikita, R. Sakamori, T. Tatsumi, T. Takehara.
Osaka university, Gastroenterology and Hepatology, Suita, Japan
Email: takehara@gh.med.osaka-u.ac.jp

Background and Aims: Forkhead Box M1 (FoxM1) is a cell cycle-specific transcription factor that is overexpressed in a variety of cancers. Previously, we demonstrated that increased expression of FoxM1 is associated with a poor prognosis of patients with HCC. Although the role of FoxM1 in hepatocellular carcinoma (HCC) is well documented, its role in non-tumor hepatocytes remains unclear. To investigate this issue, we developed a new transgenic mouse model.

Method: We generated hepatocyte-specific FoxM1 conditional transgenic mice (TetO7-FoxM1/Rosa26-LSL-rtTA/Albumin-Cre: designated TG mice) using the Cre-loxP and Tet-on systems. TG and control mice (TetO7-FoxM1/Rosa26-LSL-rtTA: designated WT mice) with doxycycline (DOX) were treated to induce FoxM1 expression. Primary hepatocytes isolated from TG and WT mice were used.

Results: After treatment of DOX from the time of birth, TG mice showed increased levels of serum ALT [75.2 U/L in TG (n = 8) vs. 15.9 U/L in WT (n = 8), p < 0.05], and an increase in the number of TUNEL positive hepatocytes (p < 0.05) at 8 weeks of age. In addition, TG mice with 3 days-treatment of DOX showed increased levels of serum ALT (p < 0.01), increased gene expression of Ccl2 (p < 0.01) and infiltration of F4/80 positive macrophages in the livers of TG mice. This liver inflammation in TG mice was partially cancelled by depleting macrophages (p < 0.01). TG mice also showed an increased Siriusred-stained fibrotic area [5.6% in TG (n = 8) vs. 0.9% in WT (n = 8), p < 0.01] at 13 weeks of age, and spontaneous tumorigenesis [100% in TG (n = 10) vs. 0% in WT (n = 10), p < 0.01] at 48 weeks of age. Primary cultured hepatocytes from TG mice showed an increase in Ccl2 gene expression after induction of FoxM1. Consistently, chromatin immunoprecipitation analysis and luciferase gene reporter assay showed that FoxM1 was associated with a consensus binding site within murine Ccl2 promoter.

Conclusion: Overexpression of FoxM1 in hepatocytes causes spontaneous development of liver inflammation, fibrosis and tumorigenesis. Our data also suggest that FoxM1 might regulate inflammation-related hepatocarcinogenesis through the induction of chemokine expression.

HCV: Striving towards elimination

PS-089

Decentralized care is effective in the management of patients with hepatitis C in a public health care setting: The Punjab model

R.K. Dhiman[1], G. Grover[2], M. Premkumar[3], S. Rathi[1], M. Chopra[3], R. Kaur[3], S. Satsangi[3], S. Taneja[1], A. Duseja[4]. [1]*PGIMER, Hepatology, Chandigarh, India;* [2]*Program Officer, Department of Health and Family Welfare, Chandigarh, India;* [3]*PGIMER, Hepatolog, Chandigarh;* [4]*PGIMER, Chandigarh, India*
Email: rkpsdhiman@hotmail.com

Background and Aims: The prevalence of hepatitis C virus infection infection in Punjab, India is 3.29%, with an estimated burden of around 650,000 viremic chronic hepatitis C (CHC) patients. The Mukh Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) was launched in June 2016 to provide free treatment to all CHC patients aiming to eliminate HCV from Punjab. We assessed the feasibility of decentralized care and efficacy and safety of 12 or 24 weeks of sofosbuvir (SOF) + ledipasvir (LDV) or SOF + daclatasvir (DCV) ± ribavirin (RBV) in the treatment of CHC patients in a public health care setting.
Methods: ***Decentralized care:*** All patients were evaluated and treated at 3 Government Medical Colleges (Amritsar, Faridkot and Patiala, India) and 22 District Hospitals; they were followed up to 12-weeks post-treatment to look for sustained viral response (SVR-12). ***Health care worker capacity building:*** Around 90 medical specialists were trained in a 4-hr predefined course, followed by online continued medical education sessions by regular PGIMER-INASL-Punjab Government Extension for Community Healthcare Outcomes (ECHO) Clinic conducted fortnightly. 50 pharmacists, 2 from each of the 25 centres, dispensed medicine as per specialist prescription. ***Data Management:*** 25 trained data entry operators and Clinton Health Access Initiative (CHAI) managed epidemiological data on CHC hotspots, high-risk groups, local service providers, etc. ***Monitoring:*** Medical Alerts were used for compliance monitoring. ***Study design:*** A cost-effective algorithm was developed using SOF-based regimens to treat all patients (Figure). The diagnosis of cirrhosis was based on clinical evidence or on liver stiffness measurement (LSM) ≥12.5 kPa on fibroscan.

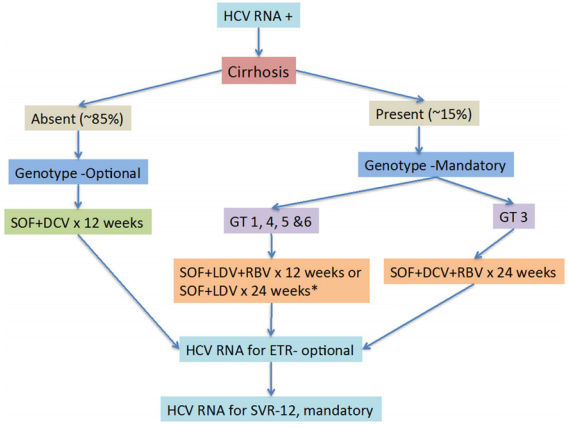


Figure: Algorithm for the treatment of chronic hepatitis C. *Ribavirin intolerant patients.

Results: We enrolled 29,371 patients (61.7% male; mean age 42 years) in 1 year, of which 19646 have completed treatment with SVR-12 of 92.5%. The program has attained maximum outreach to more vulnerable subgroups as 81.17% of these patients are from a rural background. The predominant genotype (G) was G3 (71.1%), with 14.3% cirrhotics. Cure rates in cirrhotics (93.1%) and non-cirrhotics (92.4%), and G3 (92.6%) vs non-G3 (93.1%) were comparable. Thus direct antiviral agent (DAA) based mass treatment of CHC has resulted in high cure rates irrespective of genotype, and presence of cirrhosis. On multivariate analysis only high liver stiffness measurement was a predictor of non-response. There were no major adverse events.
Conclusion: We have validated the efficacy and safety of generic all oral DAA regimens in a decentralized algorithm based public health model in Punjab, India with high cure rates regardless of genotype/presence of cirrhosis.

PS-090

Direct-acting antiviral treatment in sub-Saharan Africa: A prospective trial of Ledipasvir/Sofosbuvir for chronic Hepatitis C infection in Rwanda (the *SHARED* study)

N. Gupta[1], J. Kabahizi[2], C. Muvunyi[3], A. Mbituyumuremyi[4], J. Van Nuil[5], F. Shumbusho[3], F. Ntaganda[2], M.J. Damascene[4], C. Mukabatsinda[6], E. Musabeyezu[6], C. Ntirenganya[6], S. Nsanzimana[4], P. Grant[7]. [1]*Brigham & Women's Hospital, Division of Global Health Equity, Boston, United States;* [2]*Rwanda Military Hospital, Kigali, Rwanda;* [3]*University of Rwanda, Kigali, Rwanda;* [4]*Rwanda Biomedical Center, Kigali, Rwanda;* [5]*Partners In Health, Rwinkwavu, Rwanda;* [6]*University of Rwanda, Rwanda;* [7]*Stanford University, United States*
Email: ngupta@pih.org

Background and Aims: Direct-acting antivirals (DAAs) have not been prospectively studied or well-utilized in sub-Saharan Africa (SSA). We report preliminary results from a prospective study of ledipasvir/sofosbuvir (LDV/SOF) in Rwanda for adults with chronic hepatitis C virus (HCV) genotype (GT) 1 and GT4 infection.
Method: The "*Simplifying Hepatitis C Antiviral Therapy in Rwanda for Elsewhere in the Developing World*" (SHARED) study is a prospective trial in Rwanda evaluating the safety and efficacy of LDV/SOF (90 mg/400 mg once daily) for 12 weeks in 300 adults with HCV GT1 and/or GT4. Exclusion criteria include decompensated cirrhosis, HBV co-infection, uncontrolled HIV infection, and hepatocellular carcinoma. Sustained virologic response 12 weeks after completion of therapy (SVR12) is the primary efficacy outcome. HCV viral load and GT are determined using the Abbott testing platform.
Results: Among the 300 enrolled participants, median age is 64 (IQR 55, 72) and 63% are women. 30 (10.0%) participants are co-infected with HIV. Baseline median HCV viral load is 6.0 log10 IU/ml [IQR 5.6, 6.4]. 249 (80.3%) are reported to have GT4 only, 4 (1.3%) with GT1 only, and 47 (15.7%) with "mixed" GT1/4. Of the 164 patients who have completed study follow-up as of 30 October, 2017, 142 (86.7%) participants achieved SVR12. 16 of the 22 treatment failures were relapses after viral load <30 IU/ml at end of treatment. Risk factors for not achieving SVR12 included baseline HCV RNA >6.0 log10 (HR = 2.3; p = 0.036) and "mixed" GT1/4 (HR = 4.7; p < 0.001). Among the 11 participants reported with "mixed" GT1/4 with treatment failure, all except one were relapses. There have been no drug-related adverse events resulting in treatment discontinuation or study termination. Adherence by pill count and self-report was >98%.
Conclusion: Preliminary results suggest that LDV/SOF is a safe and effective treatment for HCV in Rwanda with a predominance of GT4. Given the association of "mixed" 1/4 GT with failure to achieve SVR12, sequencing of all viral isolates is underway to better understand the genetic heterogeneity and circulating resistance mutations of HCV GT4 infection in this region. Complete SVR12, safety data, and results of a reduced laboratory monitoring protocol for this group will be soon available. Overall, this study supports introduction and scale-up of treatment programs for HCV infection in Rwanda and similar low-income settings in SSA.

PS-091

HCV testing and linkage to care: Expanding access to HCV care through electronic health engagement

Z. Alam, D. Cook, H. Bui, L. Kausar, I. Alam. *Austin Hepatitis Center, Austin, United States*
Email: ztariq@linkagetocare.com

Background and Aims: There is an emerging epidemic of people who inject drugs (PWID), contract the hepatitis C virus (HCV), and fail to seek treatment for this curable illness. At least 75% of new HCV infections in the United States result from injection drug use. Since PWID are at an increased risk for contracting HCV, the Center for Disease Control (CDC) recommends HCV testing in this population. Therefore, we must increase education, screening, and linkage to care by working with methadone clinics, Sober Living Homes, and drug rehabilitation centers. One challenge in testing PWID is linkage to care and treatment following a positive test. Our aim is to link individuals that are HCV RNA positive to care, and utilize our electronic patient database management system (PDMS) with our Substance Abuse Treatment Center partners to fulfill the linkage portion.
Method: Longitudinal prospective cohort study with HCV screening at the above centers and utilization of a HIPPA compliant PDMS (www.linkagetocare.com). A centrally located Linkage to Care Specialist (LTCS) is notified immediately when an individual's information is entered in the system by the treatment center or self-referred. The LTCS educates the individual and proceeds to link them to care.
Results: January 2017 – October 2017, 1038 patients have gone through LTC; 503 HCV RNA positive patients referred (39% self-referred and 61% referred from 27 facilities in 19 states; 88% Texas); 57% were uninsured; 52% were between the ages of 21–40; 51% males. 398 (80%) patients were contacted by LTCS; 249 (70%) referred to a medical provider; 28% patients awaiting lab results; 2% lost contact. Patients were contacted by a LTCS within 48 hours after referral and twice before scheduling their first clinic appointment. 116 (47%) patients made it to their first appointment; 69 (60%) initiated HCV therapy; 40% were completing evaluation; 11 (16%) have finished HCV therapy; 92% were seen in office vs. 8% through telemedicine. Additionally, 47% of patients were from sober living homes, 47% from addiction treatment facilities and 6% from medical clinics.
Conclusion: Linkage to care is the missing link in treatment of chronic HCV. Our study accentuates a promising role for PWID patient engagement in electronic portals and LTCS as a tool in linking patients to the HCV care cascade. Hence, continued efforts are needed to increase and improve HCV patient electronic health engagement.

PS-092

Collocation of Buprenorphine with HCV treatment to improve adherence and reduce harm in PWID with HCV: Preliminary data from the ANCHOR study

E. Rosenthal[1], K. Hill[2], L. Nussdorf[2], P. Mathur[1], C. Gross[1], R. Silk[1], E. Akoth[1], D. Sternberg[3], N. Sidique[2], C. Chaudhury[4], B. Emmanuel[1], H. Masur[2], S. Kottilil[1], S. Kattakuzhy[1]. *[1]University of Maryland School of Medicine, Division of Clinical Care and Research, Institute of Human Virology, Baltimore, United States; [2]National Institutes of Health, Critical Care Medicine Department, Clinical Center, Bethesda, United States; [3]HIPS, Org; [4]National Institutes of Health, NIAID*
Email: nadeera.sidique@nih.gov

Background and Aims: People who inject drugs (PWID) have a significantly increased risk for acquisition of HCV and are progenitors of transmission. Studies of PWID have demonstrated decreased HCV acquisition with buprenorphine (bup) and improved HIV outcomes in patients who receive bup collocated with HIV care. Offering bup as part of HCV treatment may facilitate improvement in HCV treatment outcomes and reduce harms associated with injection drug use (IDU).
Method: ANCHOR study is a single center study embedded in an urban harm reduction center, evaluating treatment of HCV in PWID with chronic HCV, opioid use disorder (OUD), and IDU within 3 months of screening. Participants are treated with sofosbuvir/velpatasvir (SOF/VEL) and offered uptake of bup for OUD.
Results: 130 patients were screened and 71 enrolled and started SOF/VEL. Participants are predominantly male (76%), median 57 years old, black race (97%) and inject opioids once or more per day (65%). 47 (66%) patients were not on opioid agonist therapy (OAT) at screening, all of whom reported interest in bup. To date, 33 (70%) have started bup and 27 (82%) are retained on bup.
65 patients have reached week 4, 58 (89%) attended week 4 visit, and of those 55 (95%) had HCV VL < 200IU/ml at week 4. 62 (95%) patients received the second bottle of SOF/VEL. Patients on baseline OAT and those who started bup while on study were more likely to attend the week 4 visit than those not on any OAT (91% and 100% vs 55%; $p = 0.03$ and 0.0005). Patients retained on bup at week 8 were more likely to receive the third bottle of medication compared to participants not on any OAT (100% vs 82%; $p = 0.003$).
Patients who started bup during HCV treatment had a significant decline in drug use behaviors associated with HIV transmission risk (Darke HIV-Risk Taking Behaviour Scale) from day 0 to week 4 ($p = 0.004$) and day 0 to week 12 ($p = 0.0009$). No significant change was found in patients on baseline OAT or no OAT.
Data for 125 enrolled patients will be available at the time of EASL.
Conclusion: Preliminary results of the ANCHOR study support that PWID with HCV can be successfully initiated on bup during the course of HCV treatment, and that this intervention improves adherence and decreases drug use risks compared to those not on OAT. Collocating buprenorphine with HCV therapy may provide a critical opportunity to not only cure HCV, but simultaneously prevent reinfection and treat opioid use disorder in high-risk, marginalized PWID.

PS-093

HepFree: Screening migrant patients for viral hepatitis in primary care. A 90,000 patient randomised controlled trial indicates benefits are most obvious in older patients

S. Flanagan[1], V.J. Appleby[1], J. Gaviria[1], J. Kunkel[1], V. Madurasinghe[1], S. Eldridge[1], S. Moreea[2], K. Agarwal[3], E. Barnes[4], C. Griffiths[1], M. Pitt[5], A. Salmon[5], G. Foster[1]. *[1]Queen Mary University London, Blizard Institute, London, United Kingdom; [2]Bradford Institute for Health Research; [3]Kings College London; [4]University of Oxford, Nuffield Dept of Medicine, Oxford, United Kingdom; [5]University of Exeter, Medical School, Exeter, United Kingdom*
Email: stuart.flanagan@nhs.net

Background and Aims: Viral hepatitis prevalence is around 0.5% in the UK, but higher in migrant populations. No studies have identified strategies for testing and treating Hepatitis B (HBV) and Hepatitis C (HCV) in migrants in primary care. HepFree is a large, national screening trial involving 92,000 patients in control and intervention primary care practices. We report on characteristics and outcomes of patients attending for primary care viral hepatitis screening.
Methods: HepFree was a cluster randomised trial involving 58 primary care practices (8 control/50 interventional) in 3 areas of high density migrants (Bradford, East and South London) between 2013–2017. 59,390 eligible patients (aged over 18 and from a high-risk migrant population as per WHO prevalence by country) who had never tested for HBV/HCV were invited by letter for screening at intervention practices who were paid per patient tested. In control practices where local protocols applied, screening rates were measured in the 32,722 eligible adults.
Results: In intervention practices, of 59,390 invited patients, 11,611 (19.4%) tested for both HBsAg and HCV Ab, compared with 555/32,722 (1.7%) in control practices ($p = 0.011$). In intervention practices, 57.5% of tested patients were female. 32% of eligible patients from the Indian sub-continent (Bangladeshi, Indian or

Pakistani) were tested. 8.6% of eligible Black Afro-Caribbean patients were tested. 15% of patients aged 18–39 years were screened compared to 29% in patients older than 40 years. In control practices, testing rates were similar in the different ages (0.9% in patients aged <40 years, 1% in aged > 40 years). 115 patients (0.90%) tested HBsAg positive. 80 (69.5%) were male, 67 (58.2%) were East Asian, 26 (22.6%) Afro-Caribbean. 5 (4.35%) were eAg positive and 2 others (1.74%) delta positive. 6.1% had severe fibrosis or cirrhosis on ultrasound or transient elastography, mean age (MA) 46 years (range 18–83). 103 (0.81%) tested HCV Ab positive, of whom 38/103 (36.9%) were viraemic. 34 (89.5%) were SouthEast Asian, and 15.8% had severe fibrosis or cirrhosis, MA50 years (range 35–82). There were no cases of co-infection with HBV/HCV or HIV and no hepatocellular carcinoma. In 8 control practices, of 32,722 eligible patients 17/555 (3.1%) tested positive. Both testing and positivity rates were low in young (<40) indicating that screening in this group by GP invitation may not be cost-effective.

Conclusion: In this 92,000 patient study where doctors were encouraged and paid to test migrants almost 20% of eligible patients were tested. High rates of infection (1.7%) were found. Young patients are unlikely to present for testing and, if so, are unlikely to be positive. The converse is seen in older patients. These data indicate that screening in primary care should be targeted at older patients and alternative strategies applied for younger people where rates of infection are lower.

PS-094

Risk of liver fibrosis progression in patients with undiagnosed hepatitis C virus infection

D.E.M. Arraez[1], Y.N. Bujalance[2], F. Diaz-Flores[2], J.A.G. Dopico[2], E. Quintero[1], M. Hernandez-Guerra[1]. *[1]Hospital Universitario de Canarias, Gastroenterology and Hepatology Unit, Spain; [2]Hospital Universitario de Canarias, Central Laboratory Department, Spain*
Email: dalia_648@hotmail.com

Background and Aims: Hepatitis C virus (HCV) infected patients remain undiagnosed and untreated, and at risk for developing complications. Particularly, the characteristics and risk of fibrosis progression of HCV antibody-positive patients without RNA testing are unknown.

Method: We identified patients with a positive HCV antibody test performed during 2005–2007, and were classified based on whether RNA was performed during follow-up until Jan/2017 and RNA result. Clinical and laboratory variables were collected. Fibrosis stages were estimated by APRI score. We used chi-square test, Student´s t test, ANOVA and McNemar for statistical analysis.

Results: 38,246 HCV tests were performed during the studied period, of which 791 (2.01%) patients tested positive. At the end of the follow-up (median 128.6 months, range 109.8–145.9), in 49.43% (n = 391) of the subjects RNA was not tested, 13.02% (n = 103) had undetectable RNA and 37.55% (n = 297) had RNA > 15 UI. Patients who had not data for APRI calculation were excluded (n = 280). Patients without RNA testing (n = 122) compared with RNA undetectable (n = 92), were more frequently men (70% vs 47%; p = 0.001), alcohol users (53% vs 38%; p = 0.048), with lack of social support (50% vs 29%; p = 0.003) and showed higher percentage of basal significant fibrosis (≥F2) (26% vs 11%; p = 0.005). No differences were found in other evaluated variables that could have influenced in the evolution of liver fibrosis. During a median of 95.5 months (range 6.8–153.5) of follow-up, patients without RNA testing showed a significant increase in liver fibrosis (baseline median 1.1, range 0.5–6.2 vs final 1.7, range 0.5–9.3) compared with patients with undetectable RNA (baseline median 1.0, range 0.6–3.0 vs final 0.6, range 0.6–4.6), (p = 0.043). In addition, patients without RNA testing had a higher significant increase in the percentage of patients with ≥ F2 (p = 0.035) and cirrhosis (p = 0.022) at the end of the follow-up. The relative risk for ≥ F2 and cirrhosis in patients without RNA testing was 3.03 (95% CI: 1.54–5.98) and 4.31 (95% CI: 1.42–13.10), respectively.

Conclusion: In our cohort, patients with HCV antibody positivity without RNA testing are more likely to be socially excluded people. Given the increased risk of advanced fibrosis and progression to cirrhosis of these patients, urge support measures and strategies to linkage to care these difficult to treat patients.

PS-095

Marked reduction in the prevalence of hepatitis C viremia among people who inject drugs during 2nd year of the Treatment as Prevention (TraP HepC) program in Iceland

T. Tyrfingsson[1], V. Runarsdottir[1], I. Hansdottir[1,2], O.M. Bergmann[3], E.S. Björnsson[3,4], B. Johannsson[5], B. Sigurdardottir[5], R.H. Fridriksdottir[3], A. Löve[4,6], T.J. Löve[4,7], G. Sigmundsdottir[8], U.B. Hernandez[9], M. Heimisdottir[4,10], M. Gottfredsson[4,5,7], S. Olafsson[3,4]. *[1]SAA National Center for Addiction Medicine, Reykjavik, Iceland; [2]University of Iceland, Faculty of Psychology, School of Health Sciences, Reykjavik, Iceland; [3]Landspitali University Hospital, Department of Gastroenterology and Hepatology, Reykjavik, Iceland; [4]University of Iceland, Faculty of Medicine, School of Health Sciences, Reykjavik, Iceland; [5]Landspitali University Hospital, Department of Infectious Diseases, Reykjavik, Iceland; [6]Landspitali University Hospital, Department of Virology, Reykjavik, Iceland; [7]Landspitali University Hospital, Department of Science, Reykjavik, Iceland; [8]Directorate of Health, Chief Epidemiologist, Reykavik, Iceland; [9]Landspitali University Hospital, Department of science, Reykjavik, Iceland; [10]Landspitali University Hospital, Department of Finance, Reykjavik, Iceland*
Email: sigurdol@landspitali.is

Background and Aims: Iceland, with a population of 340,000, has a hepatitis C virus (HCV) seroprevalence of 0.3% and an estimated total of 800–1000 infected patients. Vogur Hospital, the countrýs largest addiction treatment center, is a key sentinel site where >90% of people who inject drugs (PWIDs), who account for the vast majority of infections, eventually seek treatment for their addiction. All admitted patients at this hospital with history of injection drug use (IDU) are screened for HCV. Therefore, Vogur provides an opportunity to monitor early trends in HCV prevalence in this important population. A nationwide treatment program was initiated in January 2016, aiming for elimination of chronic HCV infection as a public health threat.

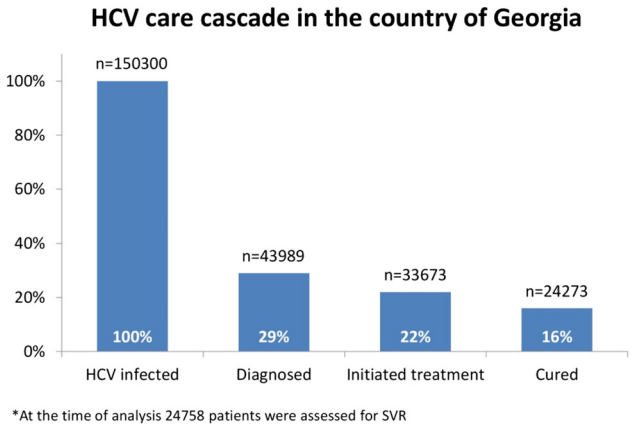
Method: Starting in 01/2016 with the TraP HepC program, all patients with HCV are offered direct acting antiviral agents (DAA) treatment on a nationwide basis. The goal is to initiate treatment for every patient within 36 months (end-2018), aiming for elimination of domestic transmission of HCV. People with history of recent IDU, patients with advanced liver disease and prisoners are prioritized. Relapses and reinfections are promptly treated. We compared the prevalence of HCV viremia among PWID admitted to Vogur Hospital during the first six months of 2015 (pre-intervention), 2016 (first 5 months of intervention) and 2017 (after 11–17 months of nationwide intervention).

Results: During the first fifteen months of the program 554 individuals were evaluated with respect to HCV treatment, 56–70% of the estimated total patient population. DAAs were initiated for 518 patients, 362 SOF/LDV-based, 155 SOF/VEL-based, and one received another regimen. The mean age was 42 years (range 18–81), 68% were males (350). Recent (within 6 months) IDU was reported by 169 (37%). Overall, of those who initiated treatment, 473 (91.3%) completed treatment, whereas 45 (8.6%) discontinued during the first 15 months of the program. HCV RNA at >12 *weeks post treatment was negative in 96% of those who completed therapy and in 51% among those who discontinued. Patients reporting recent IDU were less likely to achieve cure, 87% vs 95%, p = 0.003. The prevalence of HCV viremia among PWID admitted for addiction treatment in the first six months of 2015, i.e. prior to TraP HepC was 42%, and 40% in the first half of 2016; however in early 2017 the prevalence had dropped by 64% compared to 2015, to 15%. The prevalence odds ratio

in 2017 compared to 2015 was 0.244 (95% confidence interval 0.155–0.386), p < 0.001.
Conclusion: A major scale-up in treatment for HCV across all patient groups has been successfully initiated in Iceland. DAA treatment in the setting of recent IDU, although challenging, was generally successful. This treatment effort was associated with a significant reduction in prevalence among PWID. This key population should be a focus of treatment scale-up to curtail spread of HCV.

PS-096
Hepatitis C care cascade in the country of Georgia after 2 years of starting national hepatitis C elimination program
T. Tsertsvadze[1,2], A. Gamkrelidze[3], N. Chkhartishvili[1], L. Gvinjilia[4], A. Abutidze[1], L. Sharvadze[2,5], M. Butsashvili[6], D. Metreveli[7], M. Ezugbaia[1], T. Kuchuloria[8], S. Shadaker[9], M. Nasrullah[10], B. Skaggs[11], V. Kvaratskhelia[12], S. Zeuzem[13], N. Afdhal[14], S. Arora[15], K. Thornton[15], F. Averhoff[16]. *[1]Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia; [2]Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia; [3]National Center for Disease Control and Public Health, Tbilisi, Georgia; [4]CDC Foundation, Tbilisi, Georgia; [5]Hepatology clinic HEPA, Tbilisi, Georgia; [6]Health Research Union, Tbilisi, Georgia; [7]Medical Center Mrcheveli, Tbilisi, Georgia; [8]CDC South Caucasus Office, Tbilisi, Georgia; [9]CDC Foundation, Tbilisi, Georgia; [10]Centers for Disease Control and Prevention, Division of Viral Hepatitis National Center for HIV, Hepatitis, STD & TB Prevention, Atlanta, Georgia; [11]CDC South Caucasus Office, Tbilisi, Georgia; [12]Ministry of Labour, Health and Social Affairs of Georgia, Tbilisi, Georgia; [13]Goethe University Hospital, Frankfurt a.M., Germany; [14]Beth Israel Deaconess Medical Center Liver Center, Boston, United States; [15]University of New Mexico, Albuquerque, United States; [16]Centers for Disease Control and Prevention, Division of Viral Hepatitis National Center for HIV, Hepatitis, STD & TB Prevention, Atlanta, United States*
Email: tengizt@gol.ge

Background and Aims: In April 2015, in collaboration with U.S. CDC and commitment from Gilead Sciences to donate direct acting antivirals (DAAs), Georgia embarked on the world's first hepatitis C elimination program. The country set forth 90-95-95 targets to be achieved by 2020: (a) diagnose 90% of HCV-infected persons, (b) treat 95% of those diagnosed, and (c) cure 95% of those treated. We aimed to assess progress towards 90-95-95 targets after 2 years since the beginning of the elimination program.
Method: Four stages of hepatitis C care cascade were defined: (1) HCV infected, (2) diagnosed, (3) initiated treatment and (4) cured. The proportions of persons engaged in stages of care were quantified from the total estimated number of HCV-infected individuals. Population-based survey in 2015 estimated that around 150,000 adult people are infected with HCV in Georgia. Data on diagnosed, treated and cured patients were extracted from the national hepatitis C elimination program treatment databases for the period from April 28, 2015 through April 30, 2017. Sustained virologic response (SVR) i.e., cure were calculated using both per-protocol and modified intent-to-treat (mITT) analysis. Per-protocol approach included only those with complete SVR data, while in mITT analysis persons discontinuing treatment were also included. Persons who died or had no SVR test > 24 weeks after completing treatment were excluded from analysis.
Results: Among estimated 150000 adults living with chronic hepatitis C in Georgia, 43,989 (29.3%) were diagnosed and registered within the elimination program. 33,673 (22.4%) initiated treatment with DAA, and 24,273 (16.2%) achieved SVR (Figure). A total of 24,758 persons with complete SVR data and 601 persons who discontinued treatment, were included in treatment efficacy analysis (total 25,359 persons). Total SVR rate was 98.0% (24,273/24,758) in per-protocol analysis and 95.7% (24,273/25,359) in mITT analysis. SVR rate was 79.5% among persons receiving sofosbuvir (SOF)-based regimen, 98.5% among persons treated with ledipasvir/sofosbuvir (LDV/SOF), as initial regimen and 93.8% among persons re-treated with LDV/SOF after failure of initial SOF-based regimen.



Conclusion: Georgian hepatitis C treatment model ensures high cure rates already exceeding 2020 target with LDV/SOF and without newer generation DAAs. Scaling-up testing and diagnosis, along with effective linkage to treatment services are needed to achieve the goal of elimination.

Liver regeneration and tissue engineering

PS-097
Spatial sorting of hepatocytes reveals broad zonation of liver proteome
S. Ben-Moshe, K. Bahar Halpern, S. Itzkovitz. *Weizmann institute of science*
Email: shalev.itzkovitz@weizmann.ac.il

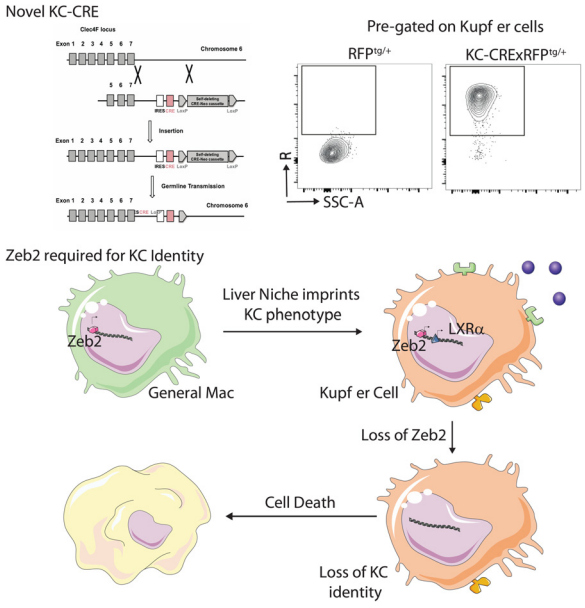
Background and Aims: The numerous metabolic and non-metabolic functions of the mammalian liver are carried out by hepatocytes in a region specific manner, depending on their position along the porto-central axis. Blood flow from the portal node to the central vein and Wnt signals secreted from the central vein create gradients of oxygen, nutrients, morphogens and hormones. These gradients impose different microenvironments, resulting in heterogeneity in gene expression. Cells positioned in different distances from the portal node and central vein are specialized for different metabolic functions. This phenomenon is termed liver zonation. Using spatially resolved single cell transcriptomics we have recently shown that around half of the liver genes are zonated, with expression level gradients peaking either in the portal layer, the central layer or even in the mid-lobule layers.
Method: Using these data, we identified two surface markers with discordant expression patterns. This allows for sorting of hepatocytes from different lobule layers using their combined levels. This spatial sorting of bulk populations enabled us to investigate the extent of zonation at the protein level, which is not yet attainable for single cells. LC-MS/MS on eight sorted different lobule layers revealed proteins zonation patterns.
Results: Zonation patterns were in general in accordance with those of the corresponding RNA. Interestingly, however, for some genes, proteins were found to be zonated, while their transcripts were not. Prominent metabolic pathways with clear protein but not RNA zonation are oxidative phosphorylation, glucose metabolism, lipid biosynthesis and proteasomal proteins.
Conclusion: This finding indicates that both transcriptional and translational regulatory mechanisms act together to establish zonation.

PS-098

Novel tools for dissecting the functions of Kupffer cells in homeostasis and disease reveal a role for the transcription factors Zeb2 and LXRa in maintaining Kupffer cell identity

C. Scott[1,2], W. T'jonck[1], D. Sichien[1], B. Johnny[1], L. Martens[1], H. Todorov[1], R. Cannoodt[1], P. De Baetselier[3], G. Berx[1], A. Beschin[3], Y. Saeys[1], M. Guilliams[3]. *[1]VIB-UGent, Center for Inflammation Research, Belgium; [2]University of Glasgow, Institute of Infection, Inflammation and Immunity, United Kingdom; [3]VIB-VUB, Center for Inflammation Research, Belgium*
Email: charlotte.scott@irc.vib-ugent.be

Background and Aims: Kupffer cells (KCs) are the most abundant macrophage (mf) population in the body. Despite this, their study remains in its infancy due to the lack of KC-specific tools. We aimed to generate new tools to specifically and unequivocally study KCs to determine their roles in homeostasis and disease, as well as investigate how these cells develop and are maintained in the liver environment.
Method: As heterogeneity has become a defining feature of different tissue mf populations, we compared the gene expression profiles of KCs with those of other mfs. This analysis identified the C-type lectin, Clec4F, to be a KC-restricted gene. Based on this, we constructed KC-DTR knock-in mice and KC-CRE mice enabling KCs to be specifically targeted for depletion or genetic manipulation. While investigating heterogeneity of tissue mfs, we also identified the conserved features of the mf lineage, including the transcription factor (TF) Zeb2, which is highly expressed by all mfs. Thus, we also sought to investigate the role of this TF in KC biology through crossing the new KC-CRE mouse to Zeb2$^{fl/fl}$ mice and examining the KC populations by flow cytometry and RNA sequencing (both bulk and single cell).
Results: KC-CRExROSA-RFP mice confirmed that the KC-CRE mice were working efficiently targeting ~95% of KCs in the liver with minimal off-target effects. Using KC-CRE mice alongside CD11c-CRE mice to target additional mf populations, we have shown that removal of Zeb2 from mfs, including KCs, results in loss of their tissue-specific identity and subsequently their death. Examination of the mechanisms involved revealed that loss of Zeb2 results in tissue-specific alterations in the transcriptional programs of the different mfs by altering expression of tissue-specific TFs. In KCs, loss of Zeb2 resulted in reduced expression of the TF LXRα. Confirming a role for LXRα, KC-CRExLXRα$^{fl/fl}$ mice revealed that LXRα expression is crucial for maintaining the KC population in the liver, with its loss, similarly to Zeb2, leading to KC death.



Conclusion: Taken together, we show here that using our novel tools we can now specifically target KCs for depletion and genetic manipulation and have identified the TF Zeb2, through the induction of LXRα, to be a crucial factor driving KC survival by maintaining KC identity.

PS-099

NAA25 and Tropomyosin regulate liver metabolic zonation, hepatocyte polarity and ploidy

L. Neri[1], V. Dominguez[2], J. Elurbide[1], M. Lasa[3], M. Ariz[4], A. Perez-Iturralde[1], B. Carte[1], L. Nicolas[5], E. Vicente[6], C.O. de Solorzano[4], A. Muñoz-Barrutia[5], B. Pintado[2], R. Aldabe[1]. *[1]CIMA, Gene therapy and regulation of gene expression, Pamplona, Spain; [2]CNB-CSIC, Transgenesis Unit, Madrid, Spain; [3]CIMA, Oncohematology, Pamplona; [4]CIMA, Imaging Platform, Pamplona; [5]Instituto de Investigación Sanitaria Gregorio Marañón, Biomedical Engineering Division, Madrid, Spain; [6]CIMA, Gene therapy and regulation of gene expression, Pamplona*
Email: raldabe@unav.es

Background and Aims: More than 15% of cellular proteins are acetylated in their first residue by the enzyme NatB. This enzymatic complex is composed by two subunits, the catalytic subunit NAA20 and the accessory subunit NAA25. Both subunits are overexpressed in human and mouse hepatocellular carcinoma (HCC) samples and downregulation of NatB subunits expression reduces cell proliferation, motility and tumorogenicity. Therefore this enzyme is a potential new target to fight HCC. We have genetically inactivated NatB accesory subunit, NAA25, in mice livers to identify the biological functions regulated by this enzyme in a healthy liver.
Method: To generate the conditional knock-out mouse we have used one ES clone provided by the German Gene Trap Consortium and to inactivate *mNAA25* in mice livers we crossed the obtained mice with B6.Cg-Tg(Alb-cre)21Mgn/J transgenic mice that express the recombinase CRE under the control of albumin promoter (mNAA25$^{\Delta hep/\Delta hep}$). Generated mice were bled and sacrificed at different time points to evaluate mice phenotype.
Results: mNAA25$^{\Delta hep/\Delta hep}$ are viable for more than 18 months without any macroscopic defect in their livers. However a biochemical analysis of 10–12 weeks old mice sera shows an increase of ammonia, ALP, bilirubin and bile salts concentration, reduced urea concentration without any other effect on other biochemical parameters like ALT, AST cholesterol, triglycerides, lactate and glucose. Once we analyzed liver sections we observed a defect of liver histology presenting mNAA25$^{\Delta hep/\Delta hep}$ mice bigger hepatocytes with bigger nuclei, a reduced number of binucleated cells and an increase of polyploidy hepatocytes. Inactivation of *mNAA25* in mouse hepatocytes activates β-catenin activity promoting an altered metabolic zonation. Consequently there is a decrease of arginase-1 positive hepatocytes and a proportional increase of Glutamine Synthetase positive hepatocytes, explaining the increase of ammonia observed in mice sera. Moreover, observed cholestasis in mNAA25$^{\Delta hep/\Delta hep}$ mice correlates with a defect in bile canaliculi structure and a defective transport of canalicular membrane proteins. It has been described that many of the cellular defects observed when NatB enzyme expression is inhibited are associated with defects of the actin cytoskeleton as one of NatB targets, tropomyosin, presents reduced its biological activity when it is not acetylated by NatB. Interestingly when we overexpressed tropomyosin 2.1 in mNAA25$^{\Delta hep/\Delta hep}$ livers we normalize several of the phenotypic defects observed in mNAA25$^{\Delta hep/\Delta hep}$ mice like: hepatocytes ploidy and hyperammonemia.
Conclusion: NAA25 and tropomyosin 2.1 are implicated in maintaining liver metabolic zonation, hepatocyte polarity and ploidy.

PS-100

A novel differentiation system to produce hepatocytes for disease modelling and drug screening

R. Tomaz, B. Wesley, K. Zacharis, D. Ortmann, L. Vallier. *Wellcome Trust – MRC Cambridge Stem Cell Institute, Department of Surgery, Cambridge, United Kingdom*
Email: rt466@cam.ac.uk

Background and Aims: Human pluripotent stem cells (hPSCs) have emerged has a promising tool for modelling diseases "in a dish", given their ability to differentiate into any tissue. Their growth capacity offers an unlimited supply of relevant cell types that can be used in drug screening. Differentiation conditions for hepatocyte-like cells (HLCs) have been successfully established. However, current methods mimic different steps of embryonic development and are limited by the lack of knowledge of signaling pathways operating in critical steps of differentiation/maturation, ultimately producing fetal-like cells. Forced expression of transcription factors (Forward Programming) has recently emerged as a robust and alternative route for conversion of hPSCs into somatic cell types, circumventing the need to mimic development. The aim of this study was to apply the forward programming system to the generation of hepatocytes *in vitro*.
Method: hPSCs were genetically engineered with an optimized inducible overexpression (OPTi-OX) platform. Cells were double targeted with the components of the Tet-ON system: a constitutively expressed transactivator responsive to doxycycline (dox) and an inducible promoter regulated by the transactivator driving the expression of the transgenes. The transgenes tested were a combination of four known hepatocyte-specific transcription factors: HNF4a, HNF1a, HNF6 and FOXA3.
Results: The four factors were robustly overexpressed in hPSCs upon treatment with 1 ug/ml of dox. Morphology changes between dox-treated and non-treated became apparent after 5 days in culture. After 15 days, dox-treated hPSCs expressing the four factors acquired a cobblestone morphology, binucleation, displayed CYP3A4 metabolic activity, and expressed hepatocyte markers such as Albumin, AFP and α1-Antitrypsin. Removal of one transcription factors was not detrimental for these functions, except for HNF4a, which was essential for the acquisition of the hepatocyte-like phenotype.
Conclusion: These results represent a first step towards the development of novel and faster methods for production of hepatocytes *in vitro*. In addition, this system can be further adapted in order to include additional transcription factors, with the potential to induce the acquisition of mature adult-like hepatocyte phenotype. Finally, these findings could be transferred to other cell types generated from hPSCs and thus provide a universal approach for generating mature cell types.

PS-101

3D bio-printing ofhuman hepatic tissue using human liver extracellular matrix as tissue-specificbioink

L. Frenguelli[1], Z. Zhang[2], L. Chikh[3], W. Al-Akkad[1], K. Rombouts[1], E. Gatenholm[3], M. Pinzani[1], H. Martinez[3], G. Mazza[4]. *[1]UCL, Institute for Liver and Digestive Health, London, United Kingdom; [2]University College London, Institute for Liver and Digestive Health, London, United Kingdom; [3]Cellink AB, Gothenburg, Sweden; [4]Institute for Liver and digestive he, London, United Kingdom*
Email: l.frenguelli@ucl.ac.uk

Background and Aims: Progress in 3D cell printing-based liver tissue engineering has been hampered by the lack of a biologically relevant bioink that mimics the 3D and biochemical structure of the liver. Decellularized extracellular matrix (ECM) represents an ideal source of bioink because it retains the structural and biochemical features of the native liver ECM. The aim of this study was to evaluate the bioprintability of human liver ECM under physiological conditions, to assess the in vitro biocompatibility with human hepatic cells and to model liver fibrosis *in vitro*.
Method: Decellularized human livers were lyophilized and solubilized using a protease-free protocol employing 0.5 M acetic acid. The solubilized ECM was mixed with cellulose-based bioink (CELLINK® Bioink) as support for bioprinting. Human hepatic cell lines (Hepg2 and LX2) were gently mixed with ECM bioink or CELLINK bioink (employed as control) using a CELLMIXER® directly into a cartridge before bioprinting. Tissue printing was performed in a BIO X 3D printer under physiological conditions (low extrusion pressure at 10 kPa and room temperature). Bioprinted tissues were maintained in 3D culture up to 14 days and exposed to TGFβ1 for 6 days in order to promote an *in vitro* fibrogenic process. The resultant bioprinted liver tissue was analysed by histology, viability assay and gene and protein expression.
Results: The printability of human liver ECM bioink was confirmed by line extrusion and spiral tests showing the precise deposition of the material with the desired spatial and temporal control. The combination of human liver ECM bioink with liver cell types resulted in an increased cell survival, engraftment and proliferation compared to cellulose-only bioink ($p < 0.001$). Pro-fibrogenic genes and proteins including αSMA ($p < 0.001$) and pro-COL1 ($p < 0.001$) were up-regulated in ECM liver bioink bioprinted LX2 cells after 6 days of TGFβ1 exposure. ECM bioink bioprinted Hepg2 cells showed spontaneous formation of spheroids after 14 days in culture with up-regulation of albumin gene expression and protein secretion after 14 days compared to 7 days ($p < 0.001$). The evaluation of both *in vitro* and *in vivo* biocompatibility with human primary hepatic cells is currently ongoing.
Conclusion: This is the first report describing the bioprinting of human hepatic tissue using human liver ECM as bioink. This is a key advance in the development of cell-instructive bioinks for the study of liver disease and for the development of 3D hepatic tissue for transplantation.

PS-102

Development of self-renewing 3D organoid culture from human fetal biliary tree stem cells (hBTSCs) as a potential system for regenerative medicine and disease modelling

S. Safarikia[1], V. Cardinale[2], G. Carpino[3], D. Costantini[4], S. DI Matteo[4], L. Nevi[4], D. Bosco[5], E. Gaudio[6], D. Alvaro[4]. *[1]Sapienza University of Rome, Department of Medicine and Medical Specialties, Rome, Italy; [2]Sapienza University of Rome, Department of Medico-Surgical Sciences and Biotechnologies, Rome, Italy; [3]University of Rome "Foro Italico", Department of Movement, Human and Health Sciences, Division of Health Sciences, Rome, Italy; [4]Sapienza University of Rome, Department of Medicine and Medical Specialties, Rome; [5]Sapienza University of Rome, Department of Experimental Medicine, Rome, Italy; [6]Sapienza University of Rome, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Rome, Italy*
Email: samira.safarikia@uniroma1.it

Background and Aims: 3D organoids represent an advanced culture technology in the field of stem cells and regenerative medicine, recapitulating embryonic development and the physiology of the tissue of origin. Adult or fetal biliary tree represent ideal cell sources of stem/progenitor cells to be used for the regenerative medicine of liver and pancreas. The aim of our study was to generate 3D organoid cultures of hBTSCs suitable for regenerative medicine of liver and pancreas and for *in vitro* disease modeling.
Method: The fetal biliary tree (n = 6, obtained from elective pregnancy termination) was digested, mechanically and enzymatically, to isolate *EpCAM/LGR5*-enriched hBTSCs. Cells were then embedded in Matrigel and cultured in an expansion organoid medium containing soluble factors typical of the stem cell niche including EGF, FGF, Noggin, R-Spondin1; these factors represent LGR5 ligands and Wnt agonists and favor the expansion of stem cells and maintenance of stemness. Culture medium was also supplemented with Forskolin, a cAMP activator, and with a TGFβR inhibitor, A83-01, to induce cell proliferation and arrest of differentiation. We analyzed

colony formation efficiency, organoid size and morphology, cell proliferation and, finally, gene expression by RT-qPCR.
Results: An average of 85 ± 7 million (n = 6) *EpCAM/LGR5* enriched fetal hBTSCs were obtained. The cells isolated from fetal biliary tree showed a high tendency to generate organoids with high colony formation efficiency (>90%). After 5 days in culture, the organoids were microscopically detected as spherical structures and after 7 days, they reached a macroscopically visible size. Cell proliferation in organoids was significantly higher compared to 2D conditions ($p < 0.05$). Fetal biliary tree organoids were composed of single layered cuboidal epithelium and inner cell masses. RT-qPCR analysis indicated that organoids expressed multipotency stem cell markers (SOX2, NANOG, OCT4), endodermal stem/progenitor cell markers (LGR5, EpCAM, PDX1, SOX17), hepatic, pancreatic and ductal markers (ALB, CYPA3, INS, CFTR, CK19) and stem/progenitor surface genes (NCAM, CD133, CD44), recapitulating major processes of self-organization during embryonic development. Specifically, organoids expressed a higher level of LGR5 compared to 2D cultures ($p < 0.05$). we have demonstrated expand organoids stably *in vitro* for at least two months when they remained phenotypically stable and suitable for regenerative medicine programs.
Conclusion: We have demonstrated that organoids expand clonogenically stable *in vitro* for at least two months, maintaining a stable phenotype of multipotent stem cells. This system has potential applications in regenerative medicine of liver and pancreas and in disease modeling.

PS-103
Development and characterization of a novel microtissue-based 3D human liver fibrosis model for anti-fibrotic drug discovery
R. Kostadinova, A. Neelakandhan, M. Kijanska, N. Zapiorkowska, S. Steiert, P. Guye, S. Messner. *InSphero AG, Schlieren, Switzerland*
Email: simon.messner@insphero.com

Background and Aims: Liver fibrosis is the excessive accumulation of extracellular matrix proteins such as collagen, which can lead to cirrhosis, liver failure and transplantation. Anti-fibrotic therapies aim at inhibiting the accumulation of fibrotic cells and preventing the deposition of extracellular matrix proteins. Although some therapeutics are effective in experimental animal models of liver fibrosis, there are currently no effective treatments against liver fibrosis on the market. The most frequently used model for *in vitro* liver fibrosis consist of simple mono-layer cultures of hepatic stellate cells (HSC), ignoring the role of hepatocyte injury or animal models of liver fibrosis, which are not predictive enough for the effect of the anti-fibrotic drugs in human. Our aim was to developand characterize of a physiological relevant 3D Human Liver Fibrosis Model, amenable for anti-fibrotic drug screening.
Method: An *in vitro* human liver model was engineered to incorporate all the relevant human liver cells such as hepatocytes, HSCs, Kupffer cells (KCs) and liver sinusoidal endothelial cells (LECs), all from primary origin. The resulting 3D InSight™ Human Liver Fibrosis model has been characterized under basal and induced liver fibrosis conditions on a morphological and phenotypic level by immuno-staining techniques and gene-expression analysis.
Results: Using the cell type specific markers and immunohistochemistry we demonstrated the presence of various cell types such as hepatocytes, HSC, KCs and LECs during the cultivation and treatment period. TGF-β1-treatment for 7 days of the 3D model activated the HSCs as detected by up to 6-fold increased expression of α-smooth muscle actin (α-SMA). The treatment of the tissues with TGF-β1 promoted the mRNA and protein expression of extracellular matrix gene expression such as collagen type I, III and IV and the pro-fibrotic markers such as platelet-derived growth factor beta (PDGF-β) and **lysyl** oxidase (Lox). Inhibition of fibrosis induction with anti-fibrotic drugs, such as ALK5-inhibitors or FXR-agonist obeticholic acid, effectively blocked fibrosis development.
Conclusion: We demonstrated that TGF-β1 treatment induces liver fibrosis in vitro and that this model system allows studying efficacy of anti-fibrotic drugs. The 3D Human Liver Fibrosis model is thus a novel, biologically relevant *in vitro* model of liver fibrosis, suitable for high-throughput efficacy screening of anti-fibrotic drugs.

PS-104
Hepatic differentiationof human induced pluripotent stem cells (iPSC) using 3D human liverextracellular matrix hydrogel
L. Frenguelli[1], R. Tomaz[2], W. Al-Akkad[1], M. Najimi[3], E. Sokal[3], M. Pinzani[1], L. Vallier[4], G. Mazza[5]. *[1]UCL, Institute for Liver and Digestive Health, London, United Kingdom; [2]Wellcome Trust-Medical Research Council Stem Cell Institute, Anne McLaren Laboratory and Department of Surgery, Cambridge University, Cambridge, United Kingdom; [3]Université Catholique de Louvain, 3Laboratory of Pediatric Hepatology & Cell Therapy, Institute of Experimental and Clinical Research, Louvain-la-Neuve, Belgium; [4]Wellcome Trust – MRC Cambridge Stem Cell Institute, Department of Surgery, Cambridge, United Kingdom; [5]Institute for Liver and digestive he, London, United Kingdom*
Email: l.frenguelli@ucl.ac.uk

Background and Aims: The development of patient-specific induced pluripotent stem cells (iPSCs) holds great promise for the realization of personalized regenerative medicine and *in vitro* disease models. A common limitation of hepatic lineages derived from iPSCs is a blunted phenotype compared with primary hepatocytes. Decellularized scaffolds composed by natural liver extracellular matrix (ECM) have recently been shown to maintain the phenotype of primary cells and to promote cell survival, proliferation and differentiation of stem cells.
The aim of this study was to evaluate the differentiation of human iPSC at different stage of differentiation towards hepatocyte-like cells by employing 3D human liver ECM hydrogel.
Method: Decellularized human livers were lyophilized and solubilized using a protease-free protocol employing 0.5 M acetic acid and sonication. The gelification of human ECM solution was induced by adding gellying polymers. Human iPSC were differentiated towards hepatocytes-like cells and reseeded into ECM hydrogel at 12 days (hepatoblast stage), 23 days (immature stage) and 30 days (mature stage) post-differentiation. 3D cell cultures were maintained *in vitro* up to 30 days for the hapatoblast and immature stage and 37 days for the mature stage. Primary human hepatocytes were used as control. 3D cultures were analysed by histology, immunofluorescence, viability assays, gene and protein expression.
Results: Human liver ECM hydrogel were successfully repopulated with human iPSC at all stages of differentiation as well as with primary hepatocytes. Viability was confirmed at the end of 3D *in vitro* differentiation. The metabolic activity of primary human hepatocytes cultured in 3D ECM hydrogels was improved at 7 days compared to 2D culture ($p < 0.01$). Immunofluorescence analysis confirmed expression of hepatic differentiation markers including A1AT and albumin. The highest level of differentiation was achieved when hepatoblast cells (12 days post-differentiation) were differentiated in vitro up to 30 days compared to shorter 3D differentiation time with both immature and mature stage. Further gene and protein expression analyses are ongoing.
Conclusion: This study demonstrated that hepatocyte-like cells derived via iPSC technology mature on 3D extracellular matrix ECM hydrogel. The differentiation can be improved if iPSC are cultured for longer period in 3D ECM hydrogel from the hepatoblast stage. This is a key advance in the development of personalised 3D technologies for the study of liver disease and for the understating of liver development.

NAFLD: Clinical and therapy

PS-105

Proof of concept study of an apoptosis-signal regulating kinase (ASK1) inhibitor (selonsertib) in combination with an acetyl-CoA carboxylase inhibitor (GS-0976) or a farnesoid X receptor agonist (GS-9674) in NASH

E. Lawitz[1], R. Herring, Jr.[2], Z.H. Younes[3], E. Gane[3], P. Ruane[4], R.A. Schall[5], C. Jia[5], R. Xu[5], B. Mccolgan[5], S. Djedjos[5], M. Subramanian[5], J.G. Mchutchison[5], R. Myers[5], M. Middleton[6], K. Li[7], M. Hellerstein[7], P. Kwo[8], M. Noureddin[9], S. Harrison[10]. *[1]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, United States; [2]Quality Medical Research, Nashville, United States; [3]Auckland Clinical Studies, Auckland, Auckland, New Zealand; [4]Ruane Clinical Research Group, Los Angeles, United States; [5]Gilead Sciences, Foster City, United States; [6]University of California at San Diego, San Diego, United States; [7]University of California Berkeley, Berkeley, United States; [8]Stanford University School of Medicine, Palo Alto, United States; [9]Cedars-Sinai Medical Center, Los Angeles, United States; [10]Pinnacle Clinical Research, San Antonio, United States*
Email: bryan.mccolgan@gilead.com

Background and Aims: Pre-clinical data suggest that combinations of an ASK1 inhibitor with an ACC inhibitor or FXR agonist are more effective than monotherapy. In this study we evaluated the safety and efficacy of these combinations in subjects with NASH.
Method: 70 subjects with NASH diagnosed by a hepatic proton density fat fraction (PDFF) ≥10% and liver stiffness ≥2.88 kPa by MRE, or biopsy consistent with NASH and stage 2–3 fibrosis were enrolled. Successive cohorts received monotherapy with SEL 18 mg, GS-0976 20 mg, or GS-9674 30 mg (n = 10/cohort), or combination therapy with SEL + GS-0976 (18/20 mg) or SEL + GS-9674 (18/30 mg) (n = 20/cohort) orally QD for 12 weeks. Centrally-read PDFF and MRE, and serum fibrosis markers were measured at baseline (BL), W4 and W12. Deuterated water was administered to measure fractional synthesis of lipids (*de novo* lipogenesis) and fibrosis-related markers (data are pending).
Results: Over 12 weeks, all regimens were safe and well-tolerated. Similar rates of AEs were observed between cohorts (Table). No subject discontinued treatment prematurely. Compared with BL, GS-0976 resulted in significant improvements in PDFF (p = 0.006) and TIMP-1 (p = 0.049), and non-significant reductions in ALT and PIII-NP (Table). GS-9674 monotherapy reduced PDFF (p = 0.010), GGT (p = 0.039), and ALT. The combination of SEL + GS-0976 led to significant reductions in PDFF (p < 0.001), ALT (p = 0.019), and PIII-NP (p = 0.057), whereas SEL + GS-9674 reduced GGT (p = 0.030).
Conclusion: In this proof of concept study in patients with NASH, 12-week treatment with the combinations of SEL + GS-0976 or SEL + GS-9674 was safe and led to improvements in hepatic steatosis, liver biochemistry, and fibrosis markers. Responses were similar with monotherapies. Studies of longer duration with histological assessment are required to better characterize the efficacy of combination versus monotherapies in NASH.

PS-106

Non-alcoholic fatty liver disease and relative risk of incident steatohepatitis, cirrhosis and hepatocellular carcinoma events in four European primary care databases

M. Alexander[1], K. Loomis[2], N. Dhalwani[3], J. van der Lei[4], T. Duarte-Salles[5], D. Prieto-Alhambra[5], D. Ansell[6], A. Pasqua[7], F. Lapi[7], P. Rijnbeek[4], M. Mosseveld[4], D. Waterworth[8], N. Sattar[9], W. Alazawi[10], S. Kendrick[11]. *[1]Real World Data, GlaxoSmithKline, Uxbridge, United Kingdom; [2]Worldwide Research and Development, Pfizer, Groton, United States; [3]Diabetes Research Centre, University of Leicester, Leicester; [4]Dept. of Medical Informatics, Erasmus Medical Centre, Rotterdam, Netherlands; [5]Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, Barcelona, Spain; [6]Quintile IMS, IQVIA, London, United Kingdom; [7]Health Search, Italian College of General Practitioners and Primary Care, Firenze, Italy; [8]Genetics and Target Sciences, GlaxoSmithKline, United States; [9]BHF Glasgow, University of Glasgow, Glasgow, United Kingdom; [10]The Blizard Institute, University of London, London, United Kingdom; [11]Medicines Research Centre, GlaxoSmithKline, Stevenage, United Kingdom*
Email: myriam.n.alexander@gsk.com

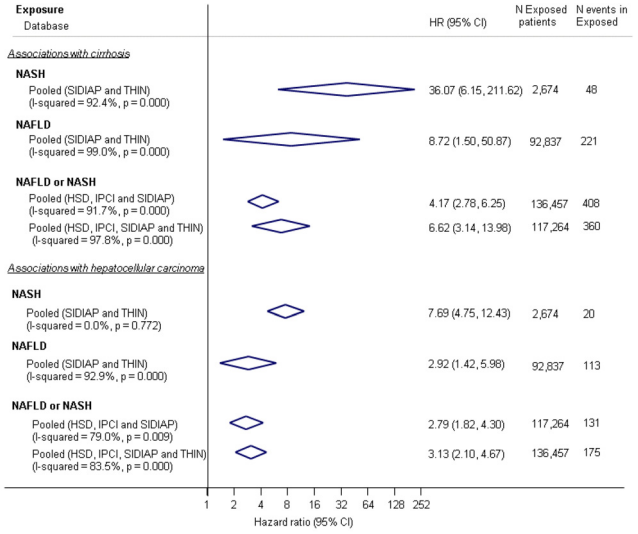
Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a condition with no clinical symptoms that progresses in some patients to steatohepatitis (NASH), cirrhosis and hepatocellular carcinoma. Here, we identified NAFLD or NASH patients from 18 million patients' records; and estimated their risk of liver disease compared to individually matched patients.
Method: Primary care data were extracted from the UK, the Netherlands, Italy and Spain. Adult patients with a NAFLD or NASH diagnosis and without past liver disease or alcohol abuse were enrolled and followed up for incident cirrhosis and hepatocellular carcinoma events. Within a database, each NAFLD patient was matched to up to 100 "non-NAFLD" patients by practice site, gender, age ±5years, and visit recorded within±6 months. Hazard ratios were estimated using Cox models adjusted for age and smoking status, and stratified by matching. Estimates were pooled across studies by random effects meta-analyses.
Results: There were 136,457 recorded NAFLD/NASH patients enrolled in our study (2,674 NASH patients only available in Spain and UK) who experienced 408 recorded cirrhosis and 175 recorded hepatocellular carcinoma events (Figure 1). At baseline, NAFLD patients had elevated transaminases levels, and were more likely to have diabetes, hypertension and obesity than matched non-NAFLD. Follow-up varied from 2–5 years in the databases. Associations were significant with non-alcoholic cirrhosis and hepatocellular carcinoma; and were 2-3x higher in NASH only patients compared to NAFLD only or NAFLD/NASH. HRs were marginally reduced when adjusting in addition for body mass index. Associations were heterogeneous

Table: (abstract: PS-105): Safety and Relative (%) Changes in Imaging, Liver Biochemistry, and Serum Fibrosis Markers at W12[†]

	SEL 18 mg (n = 10)	GS-0976 20 mg (n = 10)	GS-9674 30 mg (n = 10)	SEL + GS-0976 18/20 mg (n = 20)	SEL + GS-9674 18/30 mg (n = 20)
MRI-PDFF	7.1 (−16.3, 28.9)	−42.7* (−52.3, −19.4)	−15.6* (−17.3, −12.7)	−32.0* (−45.3, −2.6)	−9.4 (−25.0, 18.7)
≥30% reduction in MRI-PDFF	10% (1)	70% (7)	0	50% (10)	15% (3)
MRE	−8.6 (−15.6, 13.6)	−8.9 (−15.1, −6.3)	−8.3 (−14.7, 6.7)	−4.5 (−17.7, 9.3)	−5.2 (−15.3, 13.8)
ALT	−1.2 (−24.0, 11.4)	−33.5 (−39.8, −17.9)	−29.7 (−44.6, 12.1)	−27.2* (−42.8, −10.4)	−3.0 (−25.4, 8.8)
GGT	−4.4 (−17.3, 6.5)	−1.6 (−19.5, 11.5)	−19.3* (−42.5, −8.2)	10.1 (−21.5, 19.2)	−14.7* (−34.8, 0.3)
TIMP-1	2.6 (−4.0, 16.7)	−11.6* (−17.1, 1.8)	6.6* (−0.8, 8.6)	−1.9 (−11.3, 11.3)	8.1 (−4.4, 27.8)
PIII-NP	−8.7 (−20.3, 15.4)	−11.9 (−29.1, 22.2)	8.8 (2.3, 29.5)	−11.4 (−25.4, −2.9)	19.6 (−14.7, 42.6)
Grade 2 or higher AE	40% (4)	40% (4)	40% (4)	25% (5)	15% (3)

[†]All data are median (IQR) relative (%) changes from BL, or % (n).
*p < 0.05 vs. BL.

across databases: higher in the UK for incident cirrhosis; and higher in the UK and the Netherlands for hepatocellular carcinoma.



N: Number of; HR: Hazard ratio; CI: Confidence interval; THIN: The Health Improvement Network (UK); HSD: Health Search Database (Italy); SIDIAP: The Information System for Research in Primary Care (Spain); IPCI: The Integrated Primary Care Information (Netherlands). NAFLD and NASH were distinguishable in THIN and SIDIAP.

Figure: Association of NAFLD and NASH with incident liver outcomes.

Conclusion: A recorded NAFLD diagnosis is indicative of an increased risk of adverse liver outcomes; and the excess risk is graded according to severity with higher excesses in patients diagnosed as NASH. HR estimates concorded with previous studies. Heterogeneity across databases probably reflect medical practice, with the disease probably being diagnosed at a more advanced stage in the UK.

PS-107

Rare ceruloplasmin variants are associated with hyperferritinemia and increased hepatic iron in NAFLD patients: results from a NGS study

E. Corradini[1], I. Bernardis[2], P. Dongiovanni[3], E. Buzzetti[4], A. Caleffi[1], L. Artuso[2], S. Pelusi[3], E. Tenedini[2], E. Tagliafico[2], R. Rametta[3], A.L. Fracanzani[3], S. Fargion[3], A. Pietrangelo[4], L. Valenti[3]. *[1]University of Modena and Reggio Emilia, Division of Internal Medicine 2 and Center for Hemochromatosis, Modena, Italy; [2]University of Modena and Reggio Emilia, Center for Genome Research, Department of Medical and Surgical Sciences, Modena; [3]University of Milano, Fondazione IRCCS Ca' Granda Ospedale Policlinico di Milano, Department of Pathophysiology and Transplantation and Internal Medicine and Metabolic Diseases., Milan, Italy; [4]University Hospital Policlinico of Modena and University of Modena and Reggio Emilia, Division of Internal Medicine 2 and Center for Hemochromatosis, Modena, Italy*
Email: elena.corradini75@unimore.it

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a multifactorial disease resulting from the interaction of genetic and environmental factors.
Hyperferritinemia has been associated with altered hepatic iron metabolism, increased hepatic iron stores and worse hepatic and cardiometabolic outcomes in patients with NAFLD and metabolic syndrome.
Our aim was to evaluate the prevalence of genetic variants of iron-related genes and their association with HyperFt and increased hepatic iron stores in NAFLD patients.
Method: From a published cohort of 347 subjects with histological NAFLD and available serum iron parameters, hepatic iron staining and genetic characterization, 23 cases with hyperferritinemia and positive iron staining (HyperFt) and 25 controls with lowest ferritin and negative iron staining (NormoFt) were selected.
Patients with beta-thalassemia trait, increased transferrin saturation, anemia, inflammation, and, within HyperFt group, carriers of HFE genotype at risk of iron overload or ferroportin mutations were excluded.
A custom AmpliSeq™ NGS panel of 33 genes associated with iron homeostasis was designed and tested. Literature and in silico predictions were used for prioritization of possibly pathogenic mutations.
Results: The two groups did not significantly differ in components of metabolic syndrome and severity of liver disease.
Potential pathogenic variants were found in 54% of HyperFT patients and in 4% of NormoFT patients ($p = 0.0001$), and ceruloplasmin (CP) resulted to be the most mutated gene, with the identification of 4 different variants harbored in heterozygosis by 6 HyperFt patients ($p < 0.01$) (Figure 1).

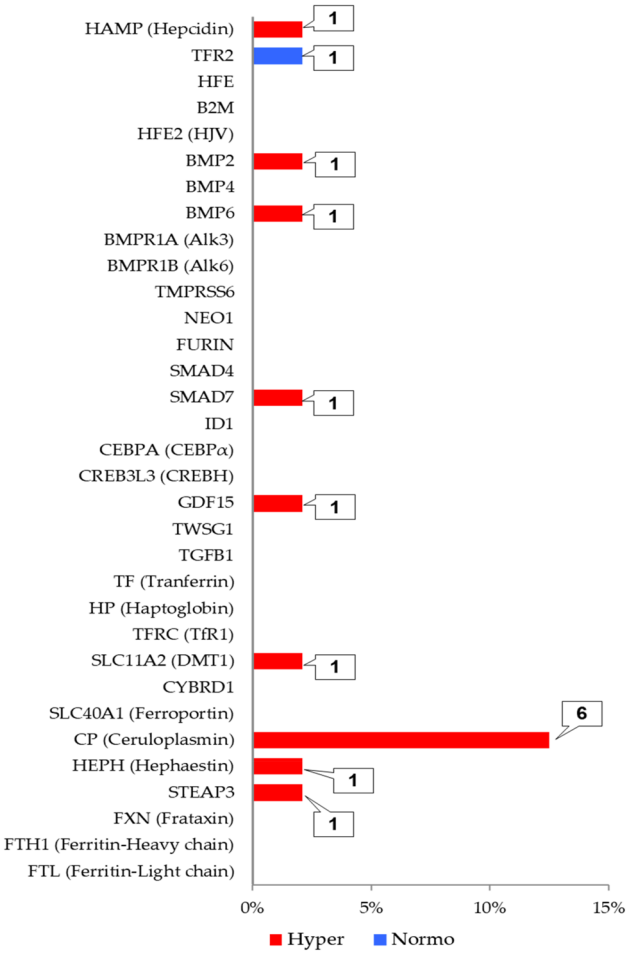


Figure 1: Number of patients carrying iron-genes pathogenic mutations in HyperFt and NormoFt group.

When polymorphisms possibly affecting iron metabolism such as TF c.829G > A or CP c.1652C > T were included in the analysis, 78% of HyperFt versus 38% of NormoFt patients resulted to have such variants ($p = 0.0016$). TMPRSS6 A736V distribution was not significantly different between IperFt and NormoFt patients.
When patients were checked for polymorphisms previously associated to advanced liver fibrosis or severe iron overload in HFE-hemochromatosis, such as PCSK7 rs2369918G > C and GNPAT rs11558492 (D519G), no significant difference in the distribution was found between the two groups.

Conclusion: Variants in non-HFE iron genes, particularly ceruloplasmin, seem associated with hyperferritinemia and increased hepatic iron stores in Italian NAFLD patients. Future studies are necessary to confirm these findings in larger cohorts and to evaluate their clinical relevance.

PS-108

The effect of intragastric balloon therapy on the intestinal microbiome in obese patients with non-alcoholic fatty liver disease, and correlations with anthropometric indices, nutritional factors, and serum immunological markers

VI Nguyen[1,2], P. Cordero[2], J. Li[2], C. Katar[2], C. Blumenthal[3], V. Male[4], A. Cuff[4], A. Wijeyesekera[5], J. Mcdonald[5], A. Perdones-Montero[5], E. Holmes[5], J. George[1], J.A. Oben[2]. *[1]Storr Liver Unit, Westmead Hospital and Westmead Millennium Institute, Sydney, Australia; [2]Institute for Liver and Digestive Health, University College London, London, United Kingdom; [3]Department of Nutrition and Dietetics, Westmead Hospital, Sydney, Australia; [4]Institute of Immunity and Transplantation, University College London, London, United Kingdom; [5]Division of Computational and Systems Medicine, Department of Surgery and Cancer, London, United Kingdom*
Email: vi.nguyen@nhs.net

Background and Aims: The prevalence of non-alcoholic fatty liver disease (NAFLD) closely parallels the obesity epidemic, and the rates of both are rising rapidly. There is growing interest in the role of the gut microbiota both in disease pathogenesis, and as potential novel therapies. The primary aim was to determine any changes in the intestinal microbiota in obese patients with NAFLD following assisted weight loss with an intragastric balloon (IGB). Secondary aims included: assessment of metabonomics and peripheral markers of inflammation, and examination for any correlations with gut microbial changes.
Method: Obese patients with NAFLD were prospectively recruited for IGB treatment. Clinical, anthropometric and nutrient data, serum biochemistry and inflammatory markers, and faecal samples for gut microbiota composition were collected at baseline, and at the end of IGB therapy (6 months).
Results: Thirty-four patients were recruited. The majority were female (70%) with an average age of 47 years. Mean baseline weight was 110.5 kg (BMI 39.4 kg/m^2), with median HOMA-IR 4.37 (1.65–4.51). Paired follow-up results were available for 28 patients: 15 successfully achieved ≥ 9.5% baseline weight loss (Group 1), while the remaining 13 patients (Group 2) did not. Significant improvements in several anthropometric and metabolic indices were observed in Group 1 (mean weight loss −17 kg, waist circumference reduction 15 cm, HOMA-IR reduction 3.05, $p < 0.01$ for all), but not in Group 2 (mean weight change −2.1 kg, HOMA-IR reduction of 1.17, $p = 0.1$). Those in Group 1 reported an average reduction in carbohydrate intake after the intervention (CHO intake in % Kilojuoles 54.5 to 49.1, $p = 0.04$), while consumption of sugar was increased in Group 2 (total sugars 77.8 g to 137.3 g, $p = 0.02$). There were no significant changes in inflammatory cytokines, but a few peripheral blood lymphocyte alterations were noted (significant increase in CD4 T-cells, and decline in NK cells in Group 1). No clinically significant changes in any gut microbial taxonomic units were observed following IGB therapy in both groups, nor were there any significant modifications in metabonomic outputs. A negative correlation with saturated fat intake and low level bacteria was observed (*Dorea*; $r = 0.28$, $p = 0.03$, and *Butyricoccus;* $r = 0.26$, $p = 0.04$).
Conclusion: In this cohort, no clinically significant alterations in the gut microflora or associated metabonomics was observed following IGB therapy, despite significant improvements in several metabolic, hepatic and immunological indices in those who achieved a substantial amount of weight loss.

PS-109

Usage of antiplatelet agents is inversely associated with liver fibrosis in patients with cardiovascular disease

K. Schwarzkopf[1], J. Bojunga[1], S. Rueschenbaum[1], Y. Martinez[1], M.M. Muecke[1], F. Seeger[2], F. Schoelzel[1], S. Zeuzem[3], M. Friedrich-Rust[1], C. Lange[1]. *[1]Department of Internal Medicine 1, J.W. Goethe-University Hospital, Frankfurt, Germany; [2]St. Elisabeth Hospital Ravensburg, Department of Cardiology, Ravensburg, Germany; [3]University of Frankfurt, Department of Medicine, Frankfurt, Germany*
Email: katharina.schwarzkopf@kgu.de

Background and Aims: In animal models platelets participate in the development of liver fibrosis, but little is known about the benefit of antiplatelet agents in preventing liver fibrosis in humans. We therefore aimed to explore the relationship between usage of antiplatelet agents and liver fibrosis in a prospective cohort study of patients at high risk of liver fibrosis and cardiovascular events.
Method: Consecutive patients undergoing elective coronary angiography at the University Hospital Frankfurt were prospectively included in the present study. Associations between usage of antiplatelet agents (acetyl salicylic acid, P2Y12 receptor antagonists) and liver fibrosis were assessed in regression models. Furthermore, the relationship between PDGF-β serum concentration, platelets, liver fibrosis and usage of antiplatelet agents was characterized.
Results: Out of 505 included patients, 337 (67%) received antiplatelet agents and 134 (27%) had liver fibrosis defined as a FibroScan® transient elastography value ≥7.9 kPa. Usage of antiplatelet agents was inversely associated with the presence of liver fibrosis in uni- and multivariate analyses (multivariate OR = 0.67, 95% CI = 0.0.51–0.89; $p = 0.006$). Usage of antiplatelet agents was inversely associated with FibroTest values as well (beta = –0.38, SD beta = 0.15, $p = 0.02$). Furthermore, there was a significant correlation between platelet counts and PDGF-β serum concentration (rho = 0.33, $p < 0.0001$), but PDGF-β serum levels were not affected by antiplatelet agents.

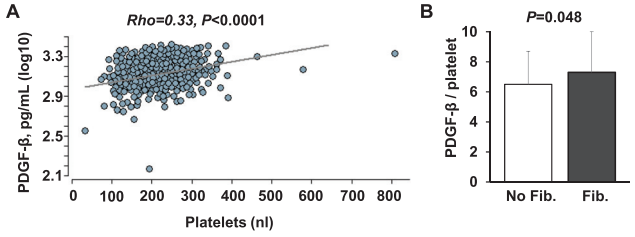


Figure: Relationship between PDGF-β serum concentration and platelet counts. (A) PDGF-β serum concentrations correlate with platelet counts, suggesting that platelets are a source of PDGF-β in humans. (B) The ratio of PDGF-β serum concentration divided through platelet count is higher in patients with liver fibrosis compared to patients without liver fibrosis. Fib., fibrosis.

Conclusion: There is a protective association between the usage of antiplatelet agents and occurrence of liver fibrosis. A randomized controlled trial is needed to explore the potential of antiplatelet agents as anti-fibrotic therapy in patients at risk for liver fibrosis progression.

PS-110

Steroidal and non-steroidal FXR agonists elicit clinically-relevant lipoprotein profiles in mice with chimeric humanized livers

R. Papazyan[1], K. Rigbolt[2], R. Lind[2], M. Feigh[2], J. Liu[3], B. Dong[3], E. Plummer[1], R.D. Lewis II[1], M. Roth[1], M. Young. *[1]Intercept Pharmaceuticals, Inc., San Diego, United States; [2]Gubra; [3]VA Palo Alto Health Care System, Palo Alto, United States*
Email: romeo.papazyan@interceptpharma.com

Background and Aims: Farnesoid X receptor (FXR) agonists are categorized into two major classes, steroidal or non-steroidal, that differ in their pharmacokinetic and possibly therapeutic properties.

Clinical and preclinical data comparing non-steroidal compounds with the first-in-class steroidal compound obeticholic acid (OCA) are lacking. Further complicating these issues, preclinical rodent models do not adequately reproduce the clinical response to FXR activation, particularly in cholesterol metabolism and the elevated circulating low-density lipoprotein cholesterol (LDL-c) associated with OCA or chenodeoxycholic acid administration in humans. It was previously shown that mice with chimeric humanized liver reproduce the human effects of OCA on circulating cholesterol. To compare the actions of steroidal and non-steroidal FXR agonists on cholesterol metabolism, chimeric mice were treated with OCA or two non-steroidal FXR agonists, INT-2228 and INT-2231, in this study.

Method: The effects of OCA (10 mg/kg/day) were evaluated in PXB chimeric mice (>80% human hepatocytes; PXB mice, PhoenixBio) as well as SCID mice (PXB background) as non-chimeric controls. In a second cohort, chimeric mice were administered vehicle (1% CMC), 10 mg/kg/day of OCA, 0.3 mg/kg/day of INT-2228, or 30 mg/kg BID of INT-2231 for 14 days. Genome-wide gene expression levels in the liver were assessed by RNA-sequencing and key genes were validated by quantitative PCR. Western blot analysis was performed for metabolic proteins associated with hepatic cholesterol metabolism. Serum lipoprotein fractions were analyzed by HPLC.

Results: Gene expression profiling in chimeric mice treated with OCA, INT-2228, or INT-2231 showed similar effects on hepatic FXR target genes, including downregulation of CYP7A1 and upregulation of NR0B2, SLC51B, and ABCB11. Furthermore, pathway analysis revealed significant downregulation of hepatic cholesterol genes (e.g. LDLR, HMGCR, HMGCS1, and MVK) across all agonist-treated groups. Consistent with the transcriptional response, protein levels of cleaved (activated) sterol regulatory element-binding protein 2 and LDLR were reduced in chimeric mice, but not in control mice. Importantly, both classes of compounds elicited similar increases (66–89%) in circulating LDL-c levels ($p < 0.001$ vs vehicle).

Conclusion: Similar to the effects of OCA, non-steroidal FXR agonists directly activate hepatic FXR and increase circulating levels of LDL-c. We conclude that changes in cholesterol metabolism and elevated LDL–c are a class effect of FXR activation.

PS-111
Preclinical and first-in human development of SGM-1019, a first-in-class novel small molecule modulator of inflammasome activity for the treatment of nonalcoholic steatohepatitis (NASH)

K. Dabbagh, G. Steven Dodson, L. Yamamoto, B. Baeza-Raja, A.W. Goodyear. *Second Genome, Inc, South San Francisco*
Email: karim@secondgenome.com

Background and Aims: Preclinical studies suggest that inflammasome activation in response to diverse stimuli drives liver inflammation and fibrosis in models of NASH. These stimuli include cellular damage in the liver and bacterial products that originate from the gastro-intestinal tract that appear to be increased in the context of western diets associated with chronic liver diseases. The study aimed to confirm that inflammasome activity in rodent NASH models and efficacy of inflammasome inhibition to reduce inflammation and fibrosis in the liver. We also sought to demonstrate the safety and pharmacological activity of SGM-1019, a novel small molecule inhibitor of inflammasome activation, in a non-human primate (NHP) model of liver inflammation and fibrosis, and in healthy human volunteers enrolled in a phase I clinical study.

Methods: Inflammasome activity in animals fed a high fat diet (HFD) was evaluated by measuring IL-1β levels from *ex vivo* stimulated whole blood and in *ex vivo* liver culture supernatants. The effect of inflammasome blockade on the development of liver inflammation and fibrosis was evaluated in the streptozotocin (STZ)-HFD-induced steatosis model of NASH following 10 weeks of treatment. The efficacy of SGM-1019 was evaluated in a 6-week carbon tetrachloride (CCl_4) exposure model of liver fibrosis in NHP. We also evaluated the pharmacokinetics, safety and pharmacodynamic effects of SGM-1019 on inflammasome activation in a phase I single and multiple ascending dose trial in healthy human volunteers.

Results: HFD fed rodents displayed enhanced whole blood IL-1β responses to LPS/ATP stimulation *in vitro* (581 pg/ml chow, 2685 pg/ml HFD, $p < 0.0001$). Cultured liver slices from these animals also displayed increased IL-1β secretion (6.58 pg/ml chow, 73.6 pg/ml HFD, $p < 0.001$) that was inhibited by inflammasome blockers (34.6 pg/mg IB-1 $p < 0.01$; 33.1 pg/ml IB-2 $p < 0.05$). 10-week treatment of diabetic mice on a HFD (STZ-HFD) treated with an inhibitor of inflammasome activation reduced liver histological fibrosis scores by 44% (2 vs 1.125, $p = 0.01$). Furthermore, in a 6-week NHP CCl_4 model, bi-daily SGM-1019 treatment for 4 weeks improved total histology scores ($p < 0.01$) driven primarily by improvements in fibrosis, hepatocyte degeneration and inflammation. Finally, SGM-1019 was safe and well tolerated in healthy human volunteers dosed for 2 weeks at all doses evaluated. Pharmacodynamic evaluation demonstrated that at the doses tested, SGM-1019 significantly inhibited inflammasome activation over the dosing period as measured by IL-1β release from *ex vivo* stimulated whole blood.

Conclusion: These studies demonstrate that the inflammasome plays a critical role in the pathogenesis of liver fibrosis and NASH, and that inhibition of inflammasome activation with SGM-1019 is a novel and potentially safe and effective way of treating patients with chronic liver diseases.

PS-112
Web-based counseling for NAFLD. Final results

A. Mazzotti, M.T. Caletti, L. Brodosi, L. Montesi, G.M. Reggiani. *Unit of Metabolic Diseases & Clinical Dietetics – S. Orsola-Malpighi Hospital, Dpt. Medical & Surgical Sciences, "Alma Mater" University, Bologna, Italy*
Email: giulio.marchesini@unibo.it

Background and Aims: Lifestyle changes are mandatory in NAFLD, but difficult to implement in busy Liver Units. We tested the feasibility and effectiveness of a web-based educational intervention aimed at lifestyle changes in NAFLD.

Method: According to our protocol, following diagnosis and motivational interviewing, NAFLD cases are invited to enter a multidisciplinary, 5-wk group-based lifestyle modification program, aimed at healthy diet and habitual physical activity, carried out by physicians, dieticians, psychologists. From 2010 to 2015, 716 subjects were observed (age 52 ± SD13) and 438 completed the program in 3 months (group cohort-GC). We developed a web-based intervention, accessed via userid and password, for individuals who could not enter GC because of logistics, job- or time-constraints (web cohort-WC, n = 278). Also the web intervention includes 5 modules, with interactive games, off-line contact with the Center, and questionnaires to investigate motivation, competence and learning. During follow-up, all subjects were only treated for comorbidities, with no specific therapy for liver disease. Surrogate markers of NAFLD severity were tested at 6-12-24-mo follow-up. Primary outcome was 10% weight loss; secondary outcomes were changes in BMI, ALT, surrogate markers (Fatty liver index-FLI, Fib-4, NAFLD Fibrosis score-NFS). WC results were tested for non-inferiority; comparison vs. GC was made by repeated-measures ANOVA.

Results: WC and GC had similar BMI (33 kg/m^2), with a higher prevalence of males (67% vs. 45%), younger age and higher education in WC. Attrition was higher in WC (OR, 2.46, 95%CI 1.68–3.61), associated with female gender, normal ALT at entry and no-diabetes. BMI decreased in both groups by nearly 2 points; the 10% weight loss target was attained in 14% (WC: 12% vs. 15% in GC, p = NS); another 20–28% attained a 5% loss. All liver enzymes decreased significantly, irrespective of treatment, but ALT normalized more frequently in WC (27% at 12-and 24-mo vs. 13% and 17% in GC). The web treatment increased the rate of ALT normalization at 6 months (OR. 2.34; 95%CI, 1.27–4.30), and 12 months (OR, 2.22; 1.33–3.73), not at 24 months (OR, 1.62; 0.94–2.78; p = 0.080), after adjustment for gender, education level, employment status, age, BMI at baseline and

presence of T2DM. FLI decreased significantly in both groups, more markedly in WC (p = 0.034); Fib-4 and NFS decreased, but only Fib-4 changes were significant in both groups.
Conclusion: The study demonstrates the feasibility, long-term effectiveness and non-inferiority of a web-program, similar to an intense group-based lifestyle counselling, in achieving 10% weight loss in subjects on active follow-up. This threshold was previously associated with improvement in fibrosis in studies where the effects of lifestyle changes were measured at NAFLD histology.
*Funded by contract n.241762 FP7-HEALTH 2009–13

Viral hepatitis: Basic science

PS-113
Characterization of host and viral proteins involved in the chromatinization of the hepatitis B virus minichromosome
M. Locatelli[1,2], J. Fresquet[1], S. Maadadi[1], J.P. Quivy[3], B. Testoni[1,2], F. Zoulim[1,2,4,5]. *[1]INSERM U1052, CNRS UMR-5286, Cancer Research Center of Lyon (CRCL), Lyon, France; [2]Université Claude-Bernard (UCBL), University of Lyon, Lyon, France; [3]Institut Curie, PSL Research University, CNRS, UMR 3664, Paris, France; [4]Laboratoire d'excellence (LabEx), DEVweCAN, Lyon, France; [5]Hospices Civils de Lyon (HCL), Lyon, France*
Email: fabien.zoulim@inserm.fr

Background and Aims: The key obstacle to cure chronic HBV infection is the persistence of the covalently closed circular DNA (cccDNA) in the liver. Upon entry into hepatocytes, the partially double stranded viral DNA (relaxed circular (rc)DNA) is released into the nucleus, where it is repaired and wrapped by histones to form an episomal chromatinized structure. To elucidate the still poorly understood mechanisms leading to cccDNA formation and chromatinization, we investigated the involvement of host factors belonging to nucleosome assembly pathways in the early establishment of cccDNA pool in infected cells.
Method: cccDNA appearance was studied by qPCR and Southern Blotting (SB) at early time points (i.e. between 30 minutes and 72 hours) post-infection in HepG2-NTCP cells and primary human hepatocytes (PHH) infected with wild type or HBx-deficient viruses. qPCR quantification of viral RNAs and DNA after siRNA was used to evaluate the impact of the knock-down of specific cellular proteins involved in chromatin remodeling on HBV replication.
Results: Knock-down of ATRX, ASF, BLM and CAF-1p60 before virus inoculation did not show any effect on viral replication or cccDNA appearance. In contrast, silencing of DAXX, CAF-1 p150 and HIRA decreased viral replication and, in the case of HIRA, led to a significant impairment of cccDNA accumulation, both in qPCR and SB. rcDNA levels remained unaffected, indicating either a possible incomplete or delayed rcDNA to cccDNA transition. Chromatin Immunoprecipitation analysis showed that HIRA was bound to cccDNA already at 2 h post-infection and that its recruitment was concomitant with the deposition of histone H3.3 and the binding of HBV capsid protein (HBc), independently from HBx protein expression (using an HBx-defective virus). By co-immunoprecipitation and Proximity Ligation assay experiments, we showed that HIRA was able to interact with HBc in infected hepatocytes and in an HepaRG cell line expressing HBc in an inducible manner.
Conclusion: Our results suggest that chromatinization of incoming viral DNA is a very early event, requiring the nucleosome assembly pathways and, particularly, the histone chaperone HIRA, representing a first step toward the identification of new therapeutic targets to impair cccDNA establishment.

PS-114
Exhaustion of virus-specific and total B cellpopulations by HBV infection
L. Salimzadeh[1], N. Le Bert[2], U.S. Gill[3], P. Kennedy[4], D. Samuel[5], N. Novikov[5], C. Frey[6], S. Fletcher[6], A. Bertoletti[2,7]. *[1]Singapore Institute for Clinical Sciences, A*STAR, Singapore, Singapore; [2]Duke-NUS Medical School, Emerging Infectious Diseases, Singapore, Singapore; [3]Blizard Institute & Barts and the London School of Medicine & Dentistry, QMUL, Hepatology Unit, Centre for Immunobiology, London, United Kingdom; [4]Blizard Institute & Barts and the London School of Medicine & Dentistry QMUL, Hepatology Unit, Centre for Immunobiology, London, United Kingdom; [5]Gilead Sciences, Department of Biology Core Support, Foster City, United States; [6]Gilead Sciences, Department of Immunology/Inflammation, Foster City, United States; [7]Singapore Immunology Network (SIgN), A*STAR, Singapore, Singapore*
Email: a0133558@u.nus.edu

Background and Aims: Despite the importance of HBV serology in disease classification, B cell biology has been poorly characterized in chronic hepatitis B (CHB) patients. Vast quantities (50–300 μg/ml) of subviral particles containing envelope component (HBsAg) are secreted during HBV infection, yet the host immune system does not mount an effective humoral response. Here we determined the impact of CHB on global and HBV-specific B cells.
Method: Total and HBsAg-specific B cells (identified by double staining with recombinant HBsAg labelled with DyLight-550 or -650) were analyzed by flow cytometry. Peripheral blood samples were obtained from HBV vaccinated subjects (n = 17), patients with resolved (anti-HBs+; n = 17), acute (longitudinal, n = 7) and chronic (different categories, n = 95) HBV infection. HBsAg, HBV-DNA and transaminase levels were quantified in all patients. Immune gene expression and capacity of antibody production of sorted memory B cell subtypes from healthy and CHB patients were analyzed by NanoString, ELISA and ELISPOT. Sorted HBsAg-specific B cells from healthy vaccinated subjects and CHB patients were studied for their ability to differentiate into antibody producing B cells.
Results: Only HBsAg-binding but not double-negative B cells from vaccinated subjects were able to produce anti-HBs after differentiation into plasma cells. In addition, HBsAg-specific plasmablasts were transiently detected following HBV booster vaccination, both demonstrating that the staining protocol identifies bona-fide anti-HBs specific B cells. Surprisingly, their frequency was comparable in CHB patients and vaccinated individuals. Global B cell analysis revealed an enrichment of atypical memory B cells (exhaustion properties, inability to produce IgG) in CHB patients, which was further augmented among HBsAg-binding cells. Transcriptional profiling found suppression of signalling pathways e.g. NF-κB and overall increased expression of genes associated with reduced functionality in CHB patients. Importantly, sorted HBsAg-binding B cells from CHB patients were unable to produce anti-HBs, despite >80% displaying a classical memory phenotype. Addition of recombinant HBsAg or serum of CHB patients to B cells from vaccinated healthy donors inhibited their ability to produce anti-HBs or limited its detection.
Conclusion: General and HBsAg-specific B cell analysis demonstrated their exhausted phenotype and reduced functionality in CHB patients. These features might contribute to anti-HBs seronegativity and persistence of HBV infection.

PS-115

Rescuing hepatitis-B-specific T cell responses by modulating cholesterol metabolism

N. Schmidt[1], L.J. Pallett[2], A. Schurich[1], K. Suveizdyte[1], O.E. Amin[1], F. Froghi[3], B.R. Davidson[3], R. Gillmore[4], T. Meyer[4,5], W. Rosenberg[3], M. Maini[1]. [1]*UCL, Infection & Immunity, London, United Kingdom;* [2]*Division of Infection & Immunity, London, United Kingdom;* [3]*UCL, Institute of Liver and Digestive Health, London, United Kingdom;* [4]*Royal Free Hospital, Oncology, London, United Kingdom;* [5]*UCL, Cancer Institute, London, United Kingdom*
Email: m.maini@ucl.ac.uk

Background and Aims: Immunotherapeutic approaches to boost HBV-specific T cells with antiviral potential require a multipronged approach to optimise these highly defective responses. A recent study demonstrated *in vitro* and *in vivo* enhancement of anti-tumour CD8 T cell efficacy by inhibition of acyl-coenzyme A:cholesterol acyltransferases (ACAT) to promote plasma membrane/lipid raft cholesterol accumulation, resulting in improved T cell receptor (TCR) clustering/signalling (*Yang et al, Nature* 2016). Since HBV-specific CD8 T cells have also been proposed to have changes in their lipid raft composition impairing MHC/peptide binding (*Reignat et al, JEM* 2002), our study aim was to investigate their potential for rescue by modulation of cholesterol metabolism.
Methods: HBV-specific T cells in PBMC were expanded from patients with chronic HBV (CHB) +/− ACAT inhibitor Avasimibe +/− PD-1 blockade. Intrahepatic lymphocytes (IHL) and tumour infiltrating lymphocytes (TIL) were stimulated with HBV peptides or anti-CD3/CD28 +/− Avasimibe.
Results Avasimibe improved effector function of HBV-specific CD8 T cells in more than 50% of patient PBMC (n = 21), with striking enhancements in some cases (maximum increase from 0.29% to 9.09% $IFNy^+CD8$, 0.33% to 4.39% TNF^+CD8 T cells). Similar effects were seen for HBV-specific CD4 T cells, with increased activation markers on responding CD4/CD8 T cells. Importantly, Avasimibe addition just 24 hours before restimulation increased binding of HLA-A2/HBV dextramers, and effector function, without changes in T cell proliferation (Ki-67, cell trace dye dilution). CD36, a high affinity transporter for long chain fatty acids, and Carnitine palmitoyltransferase 1 alpha (CPT1a), the rate limiting enzyme for mitochondrial beta-oxidation of long chain fatty acids, were both significantly increased after ACAT inhibition. Combining Avasimibe with PD-1 blockade showed a non-redundant and/or synergistic effect in PBMC from selected patients. Preliminary data indicate that the effector function of IHL and PBMC and TIL from some patients with hepatocellular carcinoma (HCC) can also be rescued.
Conclusion: We show that ACAT inhibitors, capable of re-programming cholesterol metabolism to enhance immune synapse formation, can rescue immediate effector function in HBV-specific T cells from patients with CHB or HCC. Synergism with PD-1 blockade suggests this may be a promising adjunctive approach for functional cure.

PS-116

Hepatitis E virus triggers mitochondrial fusion to promote viral replication

Y. Wang[1], W. Wang[2], S. Wang[1], M. Peppelenbosch[2], J. Zhao[1], Q. Pan[2]. [1]*302 hospital, Department of Pathology and Hepatology, Beijing, China;* [2]*Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: yijinwang927015@163.com

Background and Aims: Although hepatitis E virus (HEV) infection is generally self-limiting, severe complications and chronic hepatitis have been reported in special populations. Mitochondrial dysfunctions in hepatitis patients have been reported in many clinical studies. Liver cells contain abundant copies of mitochondria, and mitochondrial morphological dynamics, including the processes of fusion and fission, play important roles in physiology and pathogenesis. This study aims to understand mitochondrial morphological alteration in response to HEV infection and its implication in HEV replication.
Method: Liver biopsies of 17 patients with positive anti-HEV immunoglobulin (Ig) M and 5 control patients with hepatic hemangioma were reviewed for mitochondrial morphology by confocal immunofluorescent imaging. Human liver Huh-7 cells were used to model HEV infection *in vitro* and mitochondrial dynamics were observed by electron microscope and confocal immunofluorescent imaging. Lentiviral mediated RNAi was applied to silence genes that regulate mitochondrial dynamics. Viral replication was analyzed by quantitative real-time polymerase chain in reaction (qPCR).
Results: Immunofluorescent staining of liver biopsies showed that 11 out of 17 (65%) HEV infected patients presented aggregated and fused mitochondria; whereas mitochondria in all 5 uninfected control patients displayed uniform and spotty distribution. Ultrastructural analysis of HEV-infected Huh7 cells by transmission electron microscopy displayed elongated mitochondria (mitochondrial fusion) with obscure cristae. In contrast, mitochondria in uninfected cells displayed short and rod-like mitochondria with clear cristae. Consistently, confocal observation of HEV-infected cells by immunofluorescence substantiated tubular mitochondria, in contrast to dispersive and fragmented mitochondria in uninfected cells. Optic Atrophy 1 (OPA1) and mitofusion 1 (Mfn1) are the well-known positive regulators of mitochondrial fusion. In OPA1 and Mfn1 silencing cells, both the uninfected and HEV-infected cells presented fragmented mitochondria because of the impairment of the fusion machinery. Importantly, silencing of OPA1 or Mfn1 resulted in significant decrease of HEV RNA, suggesting that HEV-induced mitochondrial fusion facilitates viral infection. Further, exogenous mitochondrial dynamic regulator, ginsenoside Rg3 (G-Rg3), which had been reported to abrogate hepatitis C induced mitochondrial fission, was used to treat stable HEV infected cells. Importantly, G-Rg3 was able to promote HEV replication significantly.
Conclusion: HEV infection results in mitochondrial fusion which facilitates viral replication. Targeting mitochondrial dynamics represents a viable option for antiviral drug development against HEV.

PS-117

A microRNA screen uncovers O-Linked N-Acetylglucosamine transferase as a host factor involved in hepatitis C virus morphogenesis

S. Bandiera[1], S. Pernot[2], K. Herzog[2], C. Fauvelle[2], A. Weiss[3], S. Durand[2], W. Raffelsberger[3], L. Brino[3], T. Baumert[2], M. Zeisel[2]. [1]*Inserm U1110, Strasbourg;* [2]*Inserm U1110, Strasbourg, France;* [3]*IGBMC, Illkirch CEDEX, France*
Email: katharina.herzog@etu.unistra.fr

Background and Aims: Infection of human hepatocytes by the hepatitis C virus (HCV) is a multistep process involving both viral and host factors. Among the host factors involved in the HCV replication cycle there are microRNAs (miRNAs), a class of small non-coding RNAs that post-transcriptionally regulate gene expression in virtually every biological process. Given that miRNAs were indicated to regulate between 30% and 75% of all human genes but their role in HCV infection has never been systematically explored, we sought to exploit miRNAs as a tool for loss-of-function studies of HCV-host interactions and investigate novel factors modulating HCV infection.
Method: To systematically uncover human miRNAs affecting the HCV replication cycle, we performed a two-step functional high-throughput miRNA mimic screen in Huh7.5.1 cells infected with

recombinant cell culture-derived HCV (genotype 2a). miRNA targeting was studied using a combination of computational and functional approaches.
Results: We identified 186 miRNAs that affect HCV entry/replication, and 309 miRNAs that affect viral assembly/release. Since HCV assembly and release are currently the least well-characterized steps of the viral replication cycle, we focused on miRNA hits that modulated late steps of the HCV replication cycle. We uncovered miR-501-3p and miR-619-3p as novel modulators of HCV assembly/infectivity. Furthermore, we discovered that these miRNAs control O-linked N-acetylglucosamine transferase (OGT) protein expression in Huh7.5.1 cells. Finally, by performing functional investigation using RNA interference, we showed that OGT contributes to regulate HCV morphogenesis in liver cells.
Conclusion: In conclusion, by identifying OGT as a novel host factor regulating HCV morphogenesis, our study advanced our current understanding of the HCV-host interactions. Given that OGT was previously shown to contribute to altered metabolism in liver cancer, our results may also unravel a role of OGT as a driver for HCV-induced liver disease and hepatocarcinogenesis.

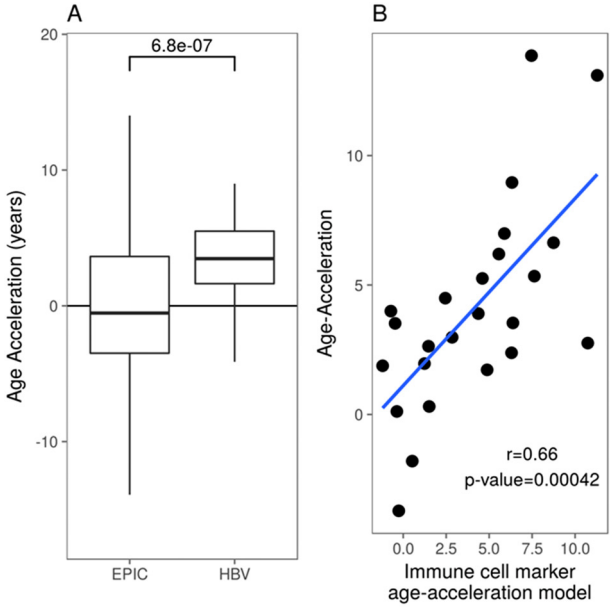
PS-118
The capacity of persistent HCV infection to regulate alloreactive T cells responses is reversed following viral eradication
E. Merritt[1], K. Childs[1], I. Carey[2], K. Agarwal[2], A. Sanchez-Fueyo[1], M. Martinez-Llordella[1]. [1]*King's College London, Liver Science Department, MRC Transplant Centre, London, United Kingdom;* [2]*King's College Hospital, Liver Science Department, London, United Kingdom*
Email: marc.martinez-llordella@kcl.ac.uk

Background and Aims: Selected liver transplant recipients can discontinue immunosuppression and maintain allograft tolerance despite persistent hepatitis C virus (HCV) infection. This phenomenon is associated with increased HCV-induced CD8+ T cell exhaustion, suggesting that HCV infection might exert beneficial effects by restraining anti-donor responses instead of increasing alloreactivity by heterologous immunity. The current availability of directly-acting anti-viral (DAA) agents offers a unique setting to study the effect of viral heterologous immunity on alloreactive T cell responses. Here we aim to investigate whether HCV-specific immunity influences anti-donor reactivity and contributes to the formation of a pro-tolerogenic microenvironment in liver allograft recipients.
Method: We have developed an in vitro assay to investigate to what extent HCV-specific T-cells cross-react with HLA antigens. T cell lines from HCV-infected non-transplanted (n = 12) and liver transplant recipients (n = 16) were derived from FACS sorted HCV-dextramer positive (HCV+) and negative (HCV-) CD8 T cells. HCV- and HCV+ T cell lines were stimulated with K562 cell lines expressing either syngeneic, 3rd party or donor HLA molecules. Alloreactivity was further investigated in HCV-infected liver transplant recipients (n = 10) before and 6 months after DAA treatment employing T cell lines and PBMCs. In addition, we assessed the relationships between the immunophenotype of circulating T cells (activation, exhaustion and regulation markers), the magnitude of endogenous type I interferon responses (serum CXCL10), and the breadth of donor-specific immune responses.
Results: We have revealed the cross-reactivity of HCV-specific CD8 T cells with allogeneic HLA molecules. In liver transplanted recipients, we detected an enrichment of donor HLA-reactive cells among the HCV+ clones compared to 3rd party HLAs (21% and 13% respectively). The increased expression of the exhaustion markers CTLA4 and PD1 in CD8 T cells and serum levels of CXCL10 significantly correlated with a reduction in donor-specific alloreactivity ($p = 0.024$ and $p = 0.035$, respectively). HCV clearance resulted in a reduction in the CD8 T cell exhaustion phenotype ($p = 0.037$). Moreover, the extent of anti-donor HLA alloreactivity increased 6 months after successful DAA treatment ($p = 0.024$). The use of PD1/CTLA4 co-blockade augmented donor-specific responses, but exclusively before viral clearance, indicating that T cell exhaustion induced by HCV infection regulates T cell alloreactivity.
Conclusion: We have documented for the first time the effects of HCV-induced heterologous immunity on allogeneic T cell responses. These findings have practical implications for the management of HCV infection following liver transplantation, and contribute to our understanding on the immunological effects of HCV eradication employing DAA.

PS-119
DNA methylation and immune cell markers demonstrate evidence of accelerated aging in patients with chronic HBV infection, with improvement during treatment
Y. Gindin[1], A. Gaggar[1], S. Kottilil[2], Z. Jiang[1], J.G. Mchutchison[1], M. Subramanian[1], H. Janssen[3], A. Lok[4], C. Ferrari[5]. [1]*Gilead Sciences Inc.;* [2]*University of Maryland School of Medicine, Institute of Human Virology;* [3]*University Health Network, Toronto, Canada;* [4]*University of Michigan Health System, Division of Gastroenterology and Hepatology, United States;* [5]*University of Parma, Unit of Infectious Diseases and Hepatology, Laboratory of Viral Immunopathology, Azienda Ospedaliero-Universitaria di Parma, and Department of Medicine and Surgery, Italy*
Email: yevgeniy.gindin@gilead.com

Background and Aims: DNA methylation (DNAm) levels are a measure of human biologic age and a set of 353 genomic markers in whole blood has been shown to be associated with accelerated aging and overall mortality in several disease states. Here, we evaluated blood DNAm and a novel immune marker model to assess biological age acceleration in patients with chronic HBV infection (CHB) and explored the effects of viral suppression on immune-imputed model of age acceleration.
Method: DNA methylation was assessed using the Infinium HumanMethylation450K BeadChip from patients with CHB virally suppressed on an oral antiviral (n = 54) and publicly available age-matched healthy control samples (n = 288). Age acceleration was calculated in CHB patients as the difference between an individual's DNAm age and one calculated from a linear model derived using the healthy control samples. Separately, peripheral blood immunophenotyping data were collected serially over 48 weeks for HBV patients who were initiated on TDF therapy (n = 195). A novel model to infer age acceleration from blood marker data was built using a regularized regression method (elastic net) from an independent dataset and validated in this study. The elastic net model identified a set of 16 immune markers, along with their coefficients, as optimal predictors of age acceleration.
Results: Age acceleration is significantly higher (median = 3.5 years; $p = 6.8 \times 10^{-7}$) in virally-suppressed patients with CHB compared to that of an independent set of normal controls (Figure 1A). For these 54 CHB subjects, age acceleration inferred from peripheral blood immunophenotyping is concordant with DNAm-based measure ($r = 0.66$, $p = 4.2 \times 10^{-4}$) (Figure 1B). Using immunophenotyping-inferred age acceleration from CHB subjects not on treatment (n = 195), age acceleration showed a significant decrease ($p = 0.0062$) after initiating antiviral therapy, with a 0.5 year median reduction in age < acceleration by Week 48 (Figure 1C). The decrease in age acceleration with antiviral therapy is associated with the decrease in relative abundance of activated T-cell subsets ($p < 0.001$).

Conclusion: Patients with CHB exhibit age acceleration, even after viral suppression. Cellular activation markers accurately predict age acceleration and could be causally related to the age acceleration process. A reduction in age acceleration as derived from immuno-phenotyping suggests potential benefit of antiviral therapy and warrants further investigation.



PS-120

Hepatitis C virus leaves epigenetic signature post cure by direct-acting antivirals that is linked to distinct mutation signature

M. Gal-Tanamy[1], S. Perez[2], A. Lavi-Itzkovitz[2], A. Kaspi[3], A. Davidovich[2], A. Tobar[4], A. Livoff[5], A. Nimer[6], E. Solomonov[7], A. El-Osta[3], G. Yaari[8], S.M. Stemmer[9], I. Haviv[1], M. Gal-Tanamy[1]. *[1]Bar-Ilan University, Faculty of Medicine, Israel; [2]Bar-Ilan University, Faculty of Medicine, Safet; [3]Monash University, Department of Diabetes, Australia; [4]Rabin Medical Center, Institute of Pathology, Israel; [5]Barzilay Medical Center, Department of Pathology, Israel; [6]Western Galilee Medical Center, Faculty of Medicine, Israel; [7]Ziv Medical Center, Department of Surgery, Israel; [8]Bar-Ilan University, Faculty of Engineering, Israel; [9]Rabin Medical Center, Davidoff Center, Israel*
Email: mgtanamy@gmail.com

Background and Aims: Hepatitis C virus (HCV) is a leading cause of hepatocellular carcinoma (HCC). While direct acting antivirals (DAAs) therapy for HCV efficiently eradicate the infection, epidemiological studies show that sustained virological response (SVR) following anti-HCV treatment does not eliminate the risk for HCC.
We hypothesize that HCV infection promotes epigenetic alternations that induce host gene expression program that is involved in cellular networks that are essential to HCV life cycle and are implicated in oncogenesis. Moreover, HCV leaves an "epigenetic signature" on the host chromatin that is not fully recovered following virus eradication after treatment with DAAs and can be reverted by epigenetic modifier drugs.
Method: The patterns of gene expression and genome-wide histone modifications for active and repressed chromatin were evaluated in HCV-infected hepatocytes before treatment and following one month of viral eradication by treatment with DAAs. To explore the link between genome wide chromatin organization and genomic signature we studied mutational signature by detecting low-frequency passenger mutations in 64 HCC samples from three etiology groups – HBV, HCV, or other.
Results: We demonstrated that HCV infection induces epigenetic changes that reprogram host gene expression and persist as "epigenetic signature" following virus eradication. Treatment of HCV-cured cells with inhibitors for different epigenetic modifiers reverted the epigenetic signature and the HCV-induced oncogenic phenotypes of cell invasion that remain persistent following DAAs treatment. Moreover, we found enrichment of C to T mutations in HCC liver biopsies on HCV etiology, compared to other HCC etiologies that may reflect the known signature of APOBEC that we observed to be upregulated in HCV infected and cured cells, and the down regulation of the base excision repair pathway that is responsible for its repair.
Conclusion: These results demonstrate that HCV-induced epigenetic missregulation that is essential for the HCV life cycle that persists following its eradication. This HCV "hit and run" scenario may explain why some chronic HCV infected patients do proceed to develop HCC after HCV eradication. Our discoveries provide a new insight into the outcomes of HCV infection and HCC development, also following SVR, and establish a novel mechanistic link between virus etiology and cancer genome.

EASL JOURNAL OF HEPATOLOGY

Saturday, 14 April 2018

General session III and award ceremony II

GS-013

Real-life effectiveness and safety of Glecaprevir/Pibrentasvir among 723 Italian patients with chronic hepatitis C: The Navigator-II study

R. D'Ambrosio[1], L. Pasulo[2], M. Puoti[3], M. Schiavini[4], P. Viganò[5], M. Vinci[6], B. Menzaghi[7], M.G. Zuin[8], A. Soria[9], A. Spinetti[10], A. Aghemo[11], M.G. Rumi[12], C. Uberti-Foppa[13], A. Pan[14], O. Spinelli[15], A. D'arminio Monforte[8], A. Capretti[8], A. Colli[16], A. Colombo[17], G. Spinzi[18], R. Centenaro[19], E. Buscarini[20], R. Soffredini[1], M. Borghi[1], M. Colpani[2], S. Lazzaroni[21], F. Maggiolo[22], A. Gori[9], P. Del Poggio[23], A. Giorgini[8], L. Morini[5], M.G. Pigozzi[10], C. Dibenedetto[8], O. Giglio[17], C.F. Magni[4], F. Noventa[24], P. Lampertico[1], S. Fagiuoli[2]. [1]*CRC "A. M. e A. Migliavacca" Center for Liver Disease Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Division of Gastroenterology and Hepatology, Milan, Italy;* [2]*ASST Papa Giovanni XXIII, Gastroenterology, Bergamo, Italy;* [3]*ASST Grande Ospedale Metropolitano Niguarda, Infectious Diseases , Milan, Italy;* [4]*ASST Sacco, Infectious Diseases, Milan, Italy;* [5]*ASST Ovest Milanese, Infectious Diseases, Legnano, Italy;* [6]*ASST Grande Ospedale Metropolitano Niguarda, Hepatology, Milan, Italy;* [7]*ASST Valle Olona - Busto Arsizio Hospital, Infectious Diseases, Busto Arsizio, Italy;* [8]*San Carlo Hospital, Rete HCV, Milan, Italy;* [9]*San Gerardo Hospital, Infectious Diseases, Monza, Italy;* [10]*ASST Brescia, Rete HCV, Brescia, Italy;* [11]*Humanitas Research Hospital and Humanitas University, Internal Medicine and Hepatology, Rozzano, Italy;* [12]*San Giuseppe Hospital, Hepatology, Milan, Italy;* [13]*San Raffaele Hospital, Infectious Diseases, Milan, Italy;* [14]*ASST Cremona, Infectious Diseases, Cremona, Italy;* [15]*ASST Lariana;* [16]*ASST Lecco, Lecco, Italy;* [17]*ASST Lariana, Lariana, Italy;* [18]*Valduce Hospital, Como, Italy;* [19]*ASST Melegnano Martesana, Vizzolo Predabissi, Italy;* [20]*ASST Crema, Gastroenterology, Crema, Italy;* [21]*ASST Papa Giovanni XXIII, Gastroenterology, Piario, Italy;* [22]*ASST Papa Giovanni XXIII, Infectious Diseases, Italy;* [23]*ASST Papa Giovanni XXIII, Gastroenterology, Zingonia, Italy;* [24]*Quovadis no profit association, Italy*
Email: roberta.dambrosio@policlinico.mi.it

Background and Aims: The efficacy and safety of Glecaprevir/Pibrentasvir (G/P) among Hepatitis C Virus (HCV) infected patients have been only investigated in clinical trials, no real-life data are available yet. The aim of the study was to investigate the effectiveness and safety of G/P in an Italian real-life setting.
Method: All HCV Italians consecutively treated with G/P within the Lombardy web-based Navigator-II Network were analysed. G/P was administered according to drug label (12 or 16 weeks). Fibrosis was determined histologically or non-invasively, through liver stiffness measurement (LSM). Sustained Virological Response 4 (SVR4) was defined as undetectable HCV-RNA 4 weeks after the end of treatment (EOT).
Results: Between October 2017 and January 2018, 723 patients (49% males) were treated with G/P. Their age was 58 (21-89) years, BMI 23.9 (15.8-39.7) Kg/m^2 and LSM 6.1 (2.5-43.0) kPa. Fibrosis was F0 in 17%, F1 in 45%, F2 in 22%, F3 in 9% and F4 in 7%. 16% of them were IFN-experienced. HCV-RNA was 1,102,600 (21-38,300,000) IU/ml, and HCV genotype 1 in 50% (35% HCV – 1b), 2 in 28%, 3 in 9% and 4 in 12%. HBV or HIV coinfection were reported in 0.3% and 6%, respectively. eGFR was 90.2 (47.0-272.5) ml/min (30% CKD1, 42% CKD2, 8% CKD3, 1% CKD4, 1% CKD5), PLT 209 (46-812) x 10^3/mm^3, ALT 50 (8-568) U/l, albumin 4.3 (2.7-5.9) g/dl, bilirubin 0.66 (0.14-4.50) mg/dl. Planned treatment duration was 8 weeks in 89%. HCV-RNA was undetected in 71% and 98% of the patients at week 4 and EOT, respectively. EOT responses were independent on fibrosis (F4 vs. non-F4: 100% *vs.* 97%, p=1.0), PLT (< 150 *vs.* ≥150 x 10^3/mm^3: 100% *vs.* 97%, p=0.64), HCV-RNA (<800,000 *vs.* ≥800,000 IU/ml: 99% *vs.* 97%, p=0.64), CKD stage (1 *vs.* 2 *vs.* 3 *vs.* 4: 95% *vs.* 97% *vs.* 100% *vs.* 100%, p=0.98), HIV (yes *vs.* no: 97% *vs.* 100%, p=1.0), age (<75 *vs.* ≥75: 97% *vs.* 100%, p=1.0), treatment duration (8 *vs.* 12/16-weeks: 97% *vs.* 100%, p=1.0) or center capability (<30 *vs.* >30 patients: 97% *vs.* 97%, p=1.0). The lowest EOT rates were observed in HCV-1 patients (HCV-1 *vs.* others: 96% *vs.* 99%, p=0.003). In the subset of patients with available off-treatment responses, the SVR4 rates were 100%. No treatment-related adverse events were reported, only one patient had to prematurely discontinue G/P.
Conclusion: In a large real-life Italian cohort of HCV patients, the virological responses and the safety profile to G/P were excellent. Full SVR results will be reported at ILC 2018.

GS-014

NGM282 improves fibrosis and NASH-related histology in 12 weeks in patients with biopsy-confirmed NASH, which is preceded by significant decreases in hepatic steatosis, liver transaminases and fibrosis markers at 6 weeks

S. Harrison[1], S. Rossi[2], M. Bashir[3], C. Guy[4], R. Banerjee[5], M. Jaros[6], S. Owers[1], B. Baxter[2], L. Ling[2], A. Depaoli[2]. [1]*Pinnacle Clinical Research, Research Department, San Antonio, United States;* [2]*NGM Bio, Clinical Research, San Francisco, United States;* [3]*Duke University, Department of Radiology, Durham, United States;* [4]*Duke University, Department of Pathology, Durham, United States;* [5]*Perspectum Diagnostics, Oxford, United Kingdom;* [6]*Summit Analytical, Denver, United States*
Email: srossi@ngmbio.com

Background and Aims: NGM282 is a non-tumorigenic analogue of human FGF19 demonstrating rapid and significant reductions in hepatic steatosis, liver transaminases and fibrosis markers after 12w of treatment with 3 and 6mg compared to placebo. The translation of these acute non-invasive changes to improvements in histology was evaluated with the addition of a 12w biopsy. MRI-PDFF, liver transaminases, Pro-C3 and multi-parametric imaging with Liver*Multi*Scan™ (LMS) were assessed at baseline, 6w and 12w to assess earlier treatment responses.
Method: Twenty-two subjects were enrolled and received NGM282 3mg daily for 12w. Key inclusion criteria included biopsy-proven NASH within 3m of screening, NAS ≥ 4 (at least 1pt in each component), stage 1–3 fibrosis and absolute liver fat content (LFC) by MRI-PDFF ≥ 8%. The primary endpoint was a reduction in absolute LFC ≥ 5%. Interim efficacy and safety were assessed on 16 subjects completing 12w of treatment. Liver biopsies were performed at screening and 12w, which were then blinded and read by an independent hepatopathologist using the NASH CRN criteria.
Results: Baseline absolute LFC (17%), ALT (84 IU) and liver inflammation-fibrosis (LIF) score by LMS (2.76) were consistent with NASH activity on biopsy. Absolute LFC changed by –9.5% and –10.9% at

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6w and 12w, respectively, with 100% meeting the primary endpoint. The decrease in relative LFC was 66% at 12w, with 100% achieving a clinically-meaningful ≥30% decrease. ALT significantly decreased by 38 IU at 2w and 53 IU by 12w. Importantly, fibrosis improved by ≥1 stage in 8 (50%) subjects, with 3 subjects improving by two stages (all Stage 3 to 1). NAS was decreased by ≥2 points (including at least 1 point of inflammation or ballooning) in 10 (63%) subjects, with 8 (50%) meeting the regulatory agency-endorsed histologic endpoints used in current Phase 3 studies. Steatosis was completely resolved in 8 (50%) subjects with all others decreasing to Stage 1 steatosis. Pro-C3 levels were significantly decreased by 6w and remained suppressed through 12w, with the greatest magnitude observed in subjects with fibrosis changes. LIF score decreased by −0.68 at 12w, consistent with the profound changes in MRI-PDFF, biomarkers and histology. LDL increased by a similar magnitude to previous studies but was mitigated within 2–4w by a statin. The most common adverse events were mild loose/frequent stools and injection site reactions.
Conclusion: Treatment of NASH with NGM282 for 12w results in unprecedented improvements in liver histology, and is preceded by significant improvements in liver transaminases, Pro-C3 and imaging by 6w. These data warrant further evaluation of NGM282 in late stage trials.

GS-015

Primary spontaneous bacterial peritonitis prophylaxis is associated with greater ICU admission and 30-day mortality compared to secondary spontaneous bacterial peritonitis prophylaxis

J.S. Bajaj[1], P. Tandon[2], J. O'leary[3], F. Wong[4], S. Biggins[5], G. Garcia-Tsao[6], P. Kamath[7], B. Maliakkal[8], M. Fallon[9], P.J. Thuluvath[10], J. Lai[11], R. Subramanian[12], H.E. Vargas[13], L. Thacker[14], R. Reddy[15]. *[1]Virginia Commonwealth University and McGuire VAMC, Gastroenterology, Hepatology and Nutrition, Richmond, United States; [2]University of Alberta, Edmonton, Canada; [3]Baylor University Medical Center, Dallas, United States; [4]University of Toronto, Medicine, Toronto, Canada; [5]University of Washington, Seattle, United States; [6]Yale University, New Haven, United States; [7]Mayo Clinic, Rochester, United States; [8]University of Tennessee, Memphis, United States; [9]University of Arizona, Phoenix, United States; [10]Mercy Medical Center & University of Maryland School of Medicine, Baltimore, United States; [11]University of California, Division of Gastroenterology, San Francisco, United States; [12]Emory University, Atlanta, United States; [13]Mayo Clinic, Scottsdale, United States; [14]Virginia Commonwealth University, Richmond, United States; [15]University of Pennsylvania, Philadelphia, United States*
Email: jasmohan.bajaj@vcuhealth.org

Background and Aims: Spontaneous bacterial peritonitis (SBP) is a major cause of death in cirrhosis and, while secondary prophylaxis (2°) is recommended to prevent recurrence, the value of long-term primary prophylaxis (1°) is uncertain, particularly given the possibility of generating antibiotic-resistant bacteria. We aimed to compare the outcomes in patients with cirrhosis on 1° *vs.* those on 2° prophylaxis for SBP in a large inpatient cohort.
Method: NACSELD (North American Consortium for Study of End-Stage Liver Disease) consists of inpatients with cirrhosis admitted non-electively in 14 centers. Cirrhosis details, reasons for admission and medications along with inpatient and 30-day course are recorded prospectively. We compared the outcomes (ICU admission, ACLF development as per NACSELD diagnostic criteria, 30-day mortality) between groups on 1° *vs.* 2° prophylaxis with propensity matching based on MELD score and serum albumin.
Results: 2731 cirrhotic pts were included of which 2239 were not on SBP prophylaxis, 305 were on 1° and 187 were on 2° SBP prophylaxis. After MELD and albumin matching 154 patients remained in each SBP prophylaxis group (Table). A significantly higher number of patients on 2° prophylaxis had previous admission, were admitted with infection, especially SBP and had admission hepatic encephalopathy and refractory ascites. Patients on 1° prophylaxis patients were more likely to have SIRS on admission and their rate of ICU admission and 30-day mortality was higher than in the 2° prophylaxis group. ACLF, nosocomial, fungal and second infections were similar between groups.
Conclusion: Despite being on primary or secondary SBP prophylaxis, a significant number of patients developed SBP. Unexpectedly, patients on 1° had poorer outcomes than those on 2° prophylaxis when propensity matched for MELD score and serum albumin. The value of SBP prophylaxis (both primary and secondary) in current times requires re-evaluation.

Mean ± SD and numbers (%)	Primary prophylaxis (n = 154)	Secondary prophylaxis (n = 154)	p-value
Age (years)	56.71 (10.39)	56.17 (9.92)	0.70
Gender (Male)	92 (60%)	107 (69%)	0.10
Diabetes	45 (30%)	47 (31%)	0.90
Admitted with infection	**37 (24%)**	**52 (40%)**	**0.005**
SBP on/during admission	**15 (10%)**	**31 (20%)**	**0.01**
Second Infection	14 (9%)	14 (9%)	1.0
Nosocomial Infection	16 (10%)	25 (16%)	0.13
Fungal Infection	10 (7%)	7 (5%)	0.59
Hospitalized in last 6 months	**91 (65%)**	**129 (90%)**	**<0.0001**
Admission PPI	98 (69%)	106 (74%)	0.36
Admission NSBB	60 (39%)	69 (46%)	0.18
Admission HE therapy	**106 (69%)**	**132 (86%)**	**0.001**
Admission Albumin	2.88 (0.71)	2.95 (0.62)	0.21
Admission Child-Pugh score	10.19 (1.99)	10.33 (1.98)	0.14
Admission MELD score	22.69 (7.54)	22.29 (7.19)	0.48
Admission SIRS (n, %)	**51 (33%)**	**35 (23%)**	**0.02**
Length of hospital stay	14.39 (17.40)	16.82 (19.74)	0.20
ACLF	23 (15%)	18 (12%)	0.42
ICU admission	**47 (31%)**	**32 (21%)**	**0.05**
30 day mortality	**29 (19%)**	**14 (9%)**	**0.01**

GS-016

A phase 1/2, randomized, placebo controlled and open label extension studies of Givosiran and investigational RNA interference therapeutic, in patients with acute intermittent porphyria

E. Sardh[1], M. Balwani[2], P. Harper[3], P. Stein[4], D. Rees[4], J. Bloomer[5], D.M. Bissell[6], C. Parket[7], J. Phillips[8], H. Bonkovsky[9], R. Desnick[10], N. Al-Tawil[11], S. Rock[12], C. Penz[12], A. Chan[12], W. Querbes[12], A. Simon[12], K. Anderson[13]. *[1]Karolinska University Hospital, Centre of Inherited Metabolic Diseases CMMS; [2]Icahn School of Medicine at Mount Sinai; [3]Karolinska University Hospital, Karolinska Institute, Porphyria Centre Sweden; [4]King's College Hospital; [5]University of Alabama; [6]University of California; [7]University of Utah, Department of Internal Medicine, Salt Lake City, United States; [8]University of Utah; [9]Wake Forest University, School of Medicine, Winston-Salem, United States; [10]Mount Sinai, Icahn School of Medicine, Department of Genetics and Genomic Sciences, New York, United States; [11]Karolinska Trial Alliance Phase 1 Unit; [12]Alnylam; [13]University of Texas Medical Branch*
Email: srock@alnylam.com

Background and Aims: Acute hepatic porphyrias (AHP) are a family of rare genetic diseases due to mutations in the enzymes responsible for heme synthesis. Central to the pathophysiology of all AHP is the induction of aminolevulinic acid synthase 1 (ALAS1), the rate limiting step in heme synthesis, which can lead to accumulation of the neurotoxic heme intermediates aminolevulinic acid (ALA) and porphobilinogen (PBG) that are causal for acute neurovisceral attacks and chronic symptoms. Givosiran is an investigational RNA interference (RNAi) therapeutic targeting liver ALAS1 to reduce ALA and PBG accumulation in AHP patients and ameliorate disease manifestations.
Methods: A phase 1, multinational, randomized, placebo-controlled, study was conducted in 3 parts; Part A single ascending dose, Part B multiple ascending dose and Part C multiple dose study to evaluate

the safety, tolerability, pharmacokinetics, and pharmacodynamics of subcutaneously administered givosiran in AIP patients. Part C also had exploratory analyses of clinical activity, including the impact of givosiran on porphyria attacks and heme treatment (ClinicalTrials.gov Identifier: NCT02452372). Patients completing Phase 1 were eligible to enrol in the open label extension study (NCT0294983).
Results: As of May 2017, givosiran was generally well tolerated in Part C (Cohorts 1–3), with no serious adverse events or clinically significant laboratory abnormalities related to study drug. Circulating ALAS1 mRNA levels had a mean (SEM) maximal reduction of 70% ± 3% relative to baseline, with concomitant ALA and PBG reductions of 77% and 76% compared to baseline, respectively, at the 2.5 mg/kg monthly dose. Patients treated with givosiran had a 73% mean decrease in the annualized attack rate (requiring hospitalization, urgent care, or hemin) compared to placebo, and a 73% mean decrease in the annualized number of hemin doses in the treatment versus run-in period. As of May 2017, the safety profile in patients in the OLE (n = 8) was consistent with that observed in Part C, as was the maintenance of clinical activity seen in the Phase 1.
Conclusions: Givosiran was generally well-tolerated and resulted in rapid, dose-dependent, and durable lowering of neurotoxic intermediates ALA and PBG. Importantly, this ALA and PBG lowering was associated with marked reductions in both the annualized attack rate and annualized hemin use. Complete Phase 1 study data will be presented along with interim study data from the Phase 1/2 OLE study.

GS-017

Reduction in the incidence of hepatitis C-related decompensated cirrhosis associated with national scale-up of direct-acting antiviral therapies targeting patients with advanced liver fibrosis

S. Hutchinson[1], H. Valerio[1], J. Dillon[2], R. Fox[3], H. Innes[1], A. Weir[4], S. Barclay[5], S. Mcdonald[1], N. Kennedy[6], A. Fraser[7], A. Stanley[5], P. Bramley[8], P. Hayes[9], D. Goldberg[4]. [1]*Glasgow Caledonian University, School of Health and Life Sciences, Glasgow, United Kingdom;* [2]*University of Dundee, Department of Molecular and Clinical Medicine, Dundee, United Kingdom;* [3]*Brownlee Centre for Infectious Diseases, Glasgow, United Kingdom;* [4]*Health Protection Scotland, Glasgow, United Kingdom;* [5]*Glasgow Royal Infirmary, Glasgow, United Kingdom;* [6]*Monklands Hospital, Airdrie, United Kingdom;* [7]*NHS Grampian, Aberdeen, United Kingdom;* [8]*Stirling Royal Infirmary, Stirling, United Kingdom;* [9]*Royal Infirmary of Edinburgh, Liver Unit, Edinburgh, United Kingdom*
Email: sharon.hutchinson2@nhs.net

Background and Aims: Direct-acting antivirals (DAAs) for chronic hepatitis C virus (HCV) have been shown to be highly effective in terminating active infection. Evidence of the impact of DAAs in averting severe liver morbidity at the population level is however lacking. Scotland, like most other countries, prioritized DAAs (following first licensing in May 2014) to patients with advanced liver fibrosis, but also set an ambitious target to reduce the incidence of HCV-related decompensated cirrhosis (DC) by 75% by 2020. Unlike most other countries, Scotland has national surveillance of HCV treatment and disease; thus, we aimed to examine the early impact of DAAs on HCV-related DC at the population level.
Method: Data on the number and characteristics of persons initiated on HCV therapy in Scotland up to March 2017 were obtained from the Scottish HCV Clinical database. Record-linkage of Scotland's HCV Diagnosis database to the national inpatient hospital database generated data on the numbers of persons with a chronic HCV diagnosis that had presented and been admitted to hospital for the first time with DC (defined as ascites, hepatic encephalopathy, hepatorenal syndrome or bleeding varices) during 2000–2016.
Results: In the three years since the introduction of DAAs (April-14 to March-17), 4,800 people were initiated on HCV therapy in Scotland, involving: 54% with genotype 1 and 38% genotype 3; 24% with F2/3 fibrosis stage, 27% compensated and 5% decompensated cirrhosis; 83% treated with DAAs; and 94% with a sustained viral response (SVR) (based on 3240 with available data to date). The number initiated on therapy was 1.6-fold and 2.8-fold higher in this period (April-14 to March-17), compared to the preceding three years, for all patients and those with compensated cirrhosis, respectively. Between 2013 and 2016, we observed a 29% reduction in first-time presentations for DC among all persons previously diagnosed with chronic HCV (Fig 1); a larger reduction (39%) was observed among those with chronic HCV at the time of DC admission. However, first-time admissions for DC doubled from 10 in 2013 to 20 in 2016 among persons who had attained SVR prior to DC presentation.

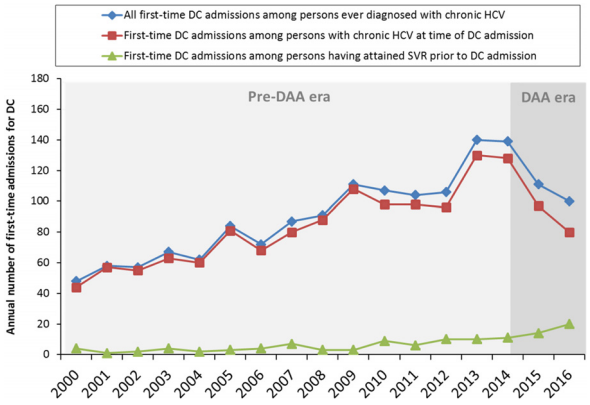


Figure 1: Annual number of first-time hospital admissions for decompensated cirrhosis (DC) in Scotland during 2000–16, among persons previously diagnosed with chronic HCV infection.

Conclusion: These data provide the first country-level evidence of the immediate impact that DAAs can have in averting HCV-related DC. Greater emphasis needs to be placed however on addressing comorbidities that pose a continued risk of liver disease progression among those attaining SVR.

GS-018

Long-term follow-up of patients with chronic HCV infection and compensated or decompensated cirrhosis following treatment with sofosbuvir-based regimens

A. Mangia[1], E. Lawitz[2], E. Gane[3], B. Conway[4], P. Ruane[5], A. Abergel[6], B. Mcnabb[7], A. Osinusi[8], F. Chen[8], H. Dvory-Sobol[8], D. Brainard[8], M. Subramanian[8], B. Leggett[9,10], José L. C. Panero[11,12], K. Agarwal[13], Z.H. Younes[14], A. Muir[15]. [1]*Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo, Italy;* [2]*Texas Liver Institute, The University of Texas Health San Antonio, San Antonio, United States;* [3]*New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand;* [4]*Vancouver Infectious Diseases Centre, Vancouver, Canada;* [5]*Ruane Medical & Liver Health Institute, Los Angeles, United States;* [6]*Service d'Hépato-gastroentérologie, CHU Estaing Clermont-Ferrand, Clermont-Ferrand, France;* [7]*Gilead Sciences, Inc.;* [8]*Gilead Sciences, Inc., Foster City, United States;* [9]*School of Medicine, University of Queensland, Brisbane, Australia;* [10]*Royal Brisbane and Women's Hospital, Brisbane, Australia;* [11]*Liver Unit, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid, Spain;* [12]*CIBERehd;* [13]*Kings College Hospital NHS Trust Foundation, London, United Kingdom;* [14]*GastroOne, Germantown, United States;* [15]*Duke University School of Medicine, Durham, United States*
Email: brian.mcnabb@gilead.com

Background and Aims: Based on early registry and cohort study results, patients with cirrhosis who achieve SVR with DAA therapy experience improvements in hepatocellular carcinoma risk, liver-related morbidity, and mortality. However, follow-up time for these studies is generally short. This analysis from the Gilead Cirrhosis Registry evaluates long-term outcomes in patients with cirrhosis who achieved SVR following treatment with a sofosbuvir-(SOF) based regimen.
Methods: Patients with cirrhosis who achieved SVR after receiving a SOF-based regimen were eligible to be enrolled within 60 weeks of

completing a treatment study or transfer from another SVR registry study, or within 2 years of achieving SVR following treatment in clinical practice. Enrolled patients return for visits every 24 weeks for up to 5 years for laboratory, clinical, and radiographic assessments of durability of SVR and clinical aspects of liver disease (HCC, CTP score, MELD score, signs of liver decompensation, liver fibrosis, transplantation, and death). Here we report select parameters. All parameters will be presented at conference proceedings.

Results: As of 5 OCT 2017, 1564 patients have been enrolled in the cirrhosis registry. Mean age (range) is 59 (26–86) years, 68% are male, and 84% and 15% of patients had pretreatment CTP scores A and B + C, respectively. Median (range) of registry follow-up time was 53 (<1–144) weeks. Overall, there were 55 observed events of HCC, in 3,922 person-years (PYs) of follow-up since the start of DAA treatment (34 cases in 3,292 PYs of follow-up for CTP A patients and 21 in 601 PYs of follow-up for CTP B + C patients). Overall, there have been 20 liver transplantations and 5 liver-related deaths. CTP class changes from pretreatment throughout the registry study are presented in the Table. Overall, patients with pretreatment CTP A cirrhosis maintained CTP A status (99% at registry week 96) while patients with pretreatment CTP B or C cirrhosis showed improvement (67% of CTP B and 86% of CTP C patients had CTP A cirrhosis at registry week 96). There were 3 virologic failures (1 reinfection and 2 without baseline samples to distinguish reinfection from relapse by sequencing).

Pretreatment CTP Class, n (%)	Registry Baseline			Registry Week 48			Registry Week 96		
	CTP A	CTP B	CTP C	CTP A	CTP B	CTP C	CTP A	CTP B	CTP C
CTP A, n = 1318	1211/1250 (97)	37/1250 (3)	2/1250 (<1)	768/793 (97)	24/793 (3)	1/793 (<1)	256/260 (99)	4/260 (2)	0/260
CTP B, n = 201	127/187 (68)	60/187 (32)	0/187	95/151 (63)	55/151 (36)	1/151 (<1)	32/48 (67)	16/48 (33)	0/48
CTP C, n = 26	10/21 (48)	11/21 (52)	0/21	13/19 (68)	6/19 (32)	0/19	6/7 (86)	0/7	1/7 (14)

Conclusion: In this ongoing registry of patients with cirrhosis who achieved SVR after treatment with a SOF-based regimen, HCC was uncommon and occurred more often in patients with decompensated cirrhosis. The majority of patients maintained or improved their CTP category relative to pretreatment through up to week 96.

Acute liver failure and liver transplantation

PS-121
Prognosis of ALF of unknown cause: results of the French multicentre prospective HASIPRO study

A. Coilly[1,2,3,4], S. Dharancy[5], C. Duvoux[6], V.D. Martino[7], Jérôme Dumortier[8], S. Radenne[9], L. Alric[10], C. Besch[11], C. Francoz[12], J. Perarnaud[13], M. Rudler[14], N. Carbonell[15], C. Silvain[16], V. Leroy[17], A.V. Pichard[18], G. Lassailly[19], F. Artru[5], T. Antonini[20], H. Agostini[21], C. Piedvache[21], J.-C. Duclos-Vallée[1], P. Ichai[20], D. Samuel[20]. *[1]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, France; [2]Univ Paris-Sud, UMR-S 1193, Villejuif F-94800, France; [3]Inserm, Unité 1193, Villejuif F-94800, France; [4]Hepatinov, Villejuif F-94800, France; [5]CHRU de Lille, Service d'Hépatologie, Hôpital Huriez, CHRU Lille, 59037 Lille; [6]AP-HP Hôpital Mondor, Service d'Hépatologie, Créteil F-94000, France; [7]Service d'Hépatologie, CHRU Jean Minjoz et Université de Franche-Comté, Besançon, France; [8]Department of Digestive Diseases, Hospices Civils de Lyon, Edouard Herriot Hospital, France; [9]Hôpital de la Croix Rousse, Service de transplantation hépatique, Lyon F-69300, France; [10]Internal medecine-Digestive department UMR 152 IRD Toulouse 3 University France; [11]Hepato-Bilio-Pancreatic Surgery and Liver Transplantation Center, Université de Strasbourg, France; [12]AP-HP Hôpital Beaujon, Service d'Hépatologie, Clichy F-92110, France; [13]Service Hépato-gastro-entérologie, CHU Tours, France; [14]AP-HP Hôpital Pitié-Salpétrière, Service d'Hépatologie, Paris F-75013, France; [15]AP-HP Hôpital Saint-Antoine, Service d'Hépatologie, Paris F-75012, France; [16]Service Hépato-gastro-entérologie, CHU Poitiers, France; [17]CHU de Grenoble, Clinique universitaire d'hépatogastroentérologie, Grenoble F-38000, France; [18]AP-HP Hôpital Cochin, Service d'Hépatologie, Paris F-75014, France; [19]HRU de Lille, Service d'Hépatologie, Hôpital Huriez, CHRU Lille, 59037 Lille; [20]AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif F-94800, France; [21]AP-HP, Hôpital Bicêtre, Unité de recherche clinique Paris-Sud, Kremlin-Bicêtre, France*
Email: audreycoilly@gmail.com

Background and aims: Acute liver failure (ALF) of unknown cause represents between 10% to 50% of ALF, worldwide. Their prognosis is poorer compared to those when a cause is identified. To date, no study has specifically focused on the prognosis of these patients. The main objective was to determine the factors associated with liver transplantation (LT)-free survival at 3 months.

Method: This prospective multicentre HASIPRO study included patients from 26 French centres between Jun 13 and Dec 16. The inclusion criteria were (1) severe ALF defined by an INR >1.5, (2) no obvious cause at admission, especially viral hepatitis A and B and drug exposure that could be involved. The quantitative variables are presented in median ± IQR.

Results: This study included 70 patients (median age: 44 y.o, 66% of female gender). At baseline, 26% of patients had grade ≥1 hepatic encephalopathy. The main biological characteristics were: ALT 1324 [426–3105] IU/L, total bilirubin 203 [74–336] μmol/L, INR 2.7 [1.9–4.2] and MELD score 27 [21–35]. Fifty-six (80%) patients were hospitalized in ICU, requiring in 40%, 28% and 13% mechanical ventilation, vasopressor agents and extra-renal dialysis, respectively. Overall and LT-free survivals were 86% and 45%, respectively (Figure 1). Of the 30 transplant patients, 46% fulfilled the KCH and/or Clichy-Villejuif criteria for LT. The sensibility, specificity, positive, negative predictive values were 43, 96, 93, 56% and 4, 93, 50, 32% for KCH and Clichy-Villejuif criteria, respectively.

One cause could be determined in 55 (76%) patients after 3 months of follow-up, mainly 16 (23%) autoimmune hepatitis, 7 (10%) DILI, 5 (7%) viral hepatitis (including 3 HEV).

In multivariate analysis, baseline criteria significantly associated with LT-free survival at 3 months were:

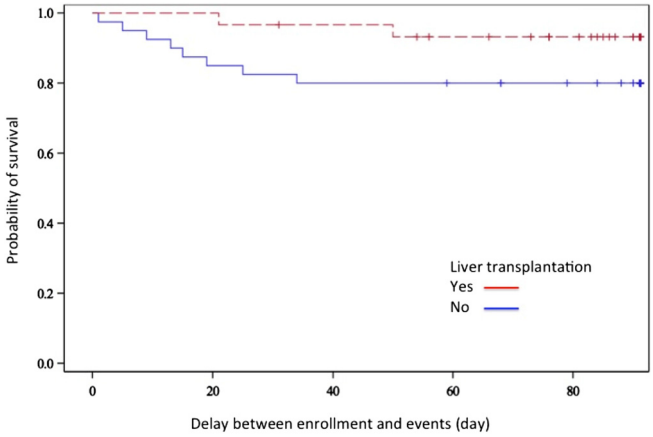


Figure 1: Three-months survival among 70 patients with ALF of unknown cause.

Conclusion: Severe ALF of unknown cause represents a proper nosological entity grouping miscellaneous causes. The prognosis is poor and LT-free survival rate is of 45% at 3 months. The usual transplantation criteria for fulminant hepatitis are not fulfilled in more than half of the patients. Therefore, it is mandatory to establish

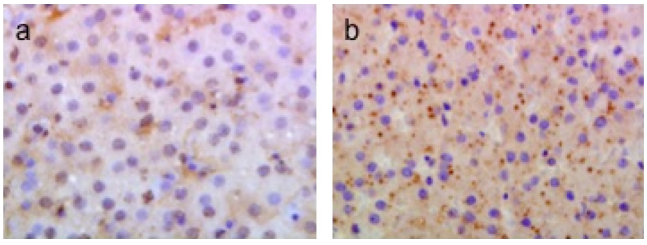
new and dynamic criteria for this population that will be presented at the meeting.

PS-122

Platelet aggregation contributing to reperfusion injury can be prevented by normothermic ex vivo liver perfusion prior to liver transplantation

D. Kollmann[1], I. Linares[1], S. Ganesh[1], R. Rosales[1], Mátyás Hamar[1], P. Urbanellis[1], A. Wiebe[1], P. Yip[2], O. Adeyi[3], M. Selzner[1], N. Selzner[1].
[1]Toronto General Hospital, Department of Surgery, Toronto Organ Preservation Laboratory, Toronto, Canada; [2]Toronto General Hospital, Laboratory Medicine Program and Department of Laboratory Medicine and Pathobiology, Toronto, Canada; [3]Toronto General Hospital, Laboratory Medicine and Pathobiology, Toronto, Canada
Email: Dagmar.kollmann@meduniwien.ac.at

Background and Aims: Normothermic ex vivo liver perfusion (NEVLP) is a rapidly evolving method of graft preservation used as an alternative to static cold storage (SCS). The role of platelets in hepatic sinusoidal endothelial cell (SEC) injury after ischemia and reperfusion has been reported mainly in SCS settings. In this study, the impact of NEVLP vs SCS on platelet aggregation and platelet-mediated SEC injury has been investigated.
Method: Pig liver transplantation (PLT) was performed with donor livers either subjected to 8hrs of SCS (SCS-group) or to NEVLP (NEVLP-group) prior to transplantation (n = 5/group). Liver biopsies were obtained 3hrs post-PLT and stained for H&E, CD31 and CD61. Platelet aggregation was scored as clumps per 5 20x HPF units (Figure 1). CD31 was scored on a scale of 1–4 (none to minimal loss of staining = 1 – diffuse loss of staining = 4). Liver enzymes, platelet counts, Platelet-factor-4 (PF-4), TGF-β and Hyaluronic Acid (HA) levels as well as other parameters (Prothrombin Time, INR, Hemoglobin) were measured during a 3-day survival period.
Results: All pigs survived for 3 days. The NEVLP-group showed significantly less ischemic injury with lower AST on postoperative day (POD)1 (581 vs. 1675 U/l, p = 0.003) & POD2 (190 vs. 1198 U/l, p = 0.005). Platelet count recovery was faster in the NEVLP- vs. SCS-group (% of baseline) at 12hrs after PLT (67% vs. 31%; p = 0.019) & at 24hrs (72% vs. 21%; p = 0.007). Intrahepatic sequestration of platelets was higher in the SCS group, with significantly more aggregation in liver sinusoids: SCS mean # clumps/5 HPF = 70 ± 46 vs. NEVLP = 4 ± 1.6, p = 0.039. Platelet aggregation correlated with SEC injury: mean SCS CD31 score = 3.6 ± 1 vs. NEVLP = 1.9 ± 0.2; p = 0.018. Consistently, HA levels were significantly higher in the SCS- vs. NEVLP-group (HA levels POD1: 1196 ± 438 vs. 193 ± 65 µg/ml, p = 0.005). Also, PF-4 levels increased in SCS, but not in NEVLP at 24hrs (SCS vs. NEVLP: 204 ng/ml vs. 104 ng/ml, p = 0.006). Both groups expressed increased TGF-ß but the increase was higher in the SCS-group and remained significantly higher at POD3 (7.4 vs. 5.3 ng/µl, p = 0.026).



Conclusion: This study demonstrates intrahepatic platelet aggregation as a contributor to and a measure of SEC injury. Platelet aggregation after reperfusion was prevented by normothermic perfusion of the grafts prior to transplantation. Therefore, NEVLP prior to transplantation allows a faster recovery of the platelet count after transplantation and might protect the liver from platelet induced SEC injury.

PS-123

The main determinant of circulating exosomal miRNA profile across a spectrum of patients with liver injury is the degree of liver failure

S. Mastoridis, V. Patel, C. Woodhouse, M. Martinez-Llordella, A. Sanchez-Fueyo. *King's College London, Institute of Liver Studies, London*
Email: sotiris.mastoridis@googlemail.com

Background and Aims: Exosomes are nanosized vesicles released by most liver cell-subsets, and are recognised to be important mediators of intercellular communication. Exosomes can alter the liver's microenvironment and exert systemic effects by transferring to other cells miRNAs contained within their protective phospholipid bilayer membrane. While liver injury is known to be associated with drastic changes in the circulating exosome and miRNA repertoires, the extent to which this is a disease-specific phenomenon and/or a response to liver cell death, liver failure, or systemic inflammation is unclear. A thorough understanding of this process is required to clarify the role of exosomes/miRNA in the pathogenesis of liver failure syndromes and their potential utility as diagnostic and prognostic biomarkers.
Method: Plasma was collected from healthy controls (HC; n = 20) and patients with acute-on-chronic liver failure (ACLF; n = 19), stable cirrhosis (SC; n = 18), decompensated cirrhosis (DC; n = 19), acute liver failure (ALF; n = 20), and non-liver sepsis (SEP; n = 10). Exosomes were isolated by size-exclusion chromatography (SEC) and their presence validated by electron microscopy, Western blot, and nanoparticle tracking analysis. miRNA was extracted from exosome isolates and a comprehensive miRnome analysis using 800 probes was performed by the Nanostring™ nCounter platform. Statistical analyses were performed using SPSS and the Limma (v3.10.2) package for R statistical environment.

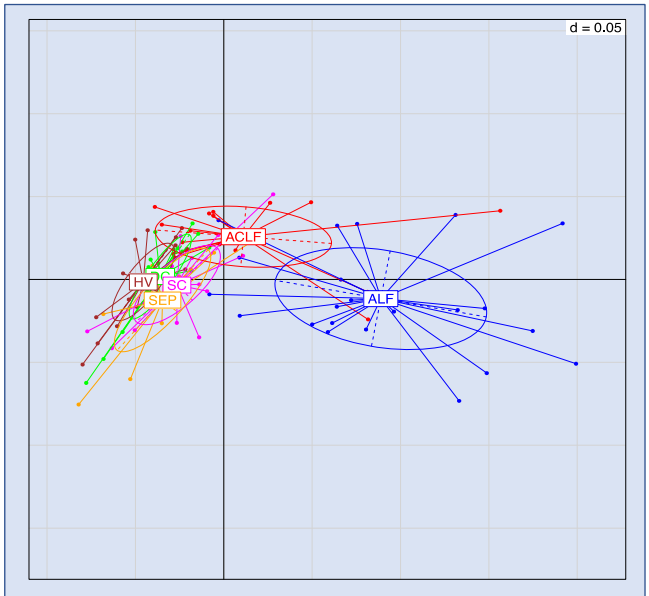


Figure 1: Principal Component Analysis (PCA) of exosomal miRNA expression profiles among six groups of study.

Results: Significantly differentially expressed exosomal miRNA were identified between all patient groups and the healthy controls. An unsupervised principal component analysis (Figure 1) revealed that the ALF and ACLF groups diverged the most from the control group. A correlation analysis showed that MELD score and other markers reflecting the degree of liver failure (e.g. Bilirubin, INR, Child-Pugh score) influenced the largest number of exosomal miRNA species, with much weaker effects exerted by broader sepsis/organ-failure

scores such as SOFA. Highly differentially expressed miRNA in LF patients' exosomes included those known to be highly expressed by liver tissue (e.g. miR-122–5p).
Conclusion: Liver damage is associated with distinct circulating exosomal miRNA profiles. This mainly correlates with the degree of liver dysfunction and not with the aetiology of liver injury, presence of sepsis or systemic inflammatory responses. Our data are the first to study exosomes and their content across a wide-spectrum of liver diseases and underlying aetiologies. Strong correlation of these miRNA with MELD-score points indirectly to their prognostic potential. Further analyses of our cohorts' clinical outcomes-data are in progress in order to clarify these associations and their functional downstream consequences.

PS-124

Early and late liver-related mortality following drug induced liver injury from amoxicillin-clavulanate

H. Tillmann[1,2], C.M. Hunt[3,4], M. Austen[5], J. Williams[5], A. Suzuki[3,4,6].
[1]Greenville VA Health Care Center, Greenville, NC, United States; [2]East Carolina University, Medicine, Division Gastroenterology, Hepatology and Nutrition, Greenville, NC, United States; [3]Duke University, Gastroenterology, Durham, NC, United States; [4]Durham VA Medical Center, HSR&D, Durham, NC, United States; [5]Central Arkansas Veterans Healthcare System, HSR&D, Little Rock, AR, United States; [6]Durham VA Medical Center, Gastroenterology, Durham, NC, United States
Email: tillmannh14@ecu.edu

Background and Aims: Amoxicillin/clavulanate (AMX/CLA) is one of the most common drugs resulting in drug induced liver injury (DILI) associated with a 17–39% hospitalization rate and 3–5% mortality rate. In the Veterans Health Administration (VHA) 2004–2014, 847,749 first AMX/CLA exposures were associated with a 0.14% DILI incidence in patients without baseline liver disease. We further assessed liver-related mortality in this population related to injury pattern and age.

	Early mortality <6 months	Late mortality (6–24 months)
Mortality by injury pattern		
Hepatocellular, not severe	2/248 (0.8%, CI 0.2–2.8%)	0/39
Severe hepatocellular [ALT > 5xULN & bili > 2xULN]	**23/62 (37.1%, CI 26.1%–49.6%)**	0/39
Mixed	4/125 (3.2%, CI 1.3–7.9%)	1/121 (0.8%, CI 0.2–4%)
Cholestatic	26/683 (3.8%, CI 2.6–5.5%)	**11/657 (1.6%, CI 0.9–2.9%)**
Controls	290/807781 (0.036%, CI 0.032–0.04%)	824/807,471 (0.1%, CI 0.09–0.11%)
Mortality by age in years		
18–45	1/121 (0.82%, CI 0.19–4.4%)	1/120 (0.83%, CI: 0.02–4.5%)
46–55	1/152 (0.66%, CI 0.16–3.5%)	3/151 (1.96%; CI: 0.7–5.6%)
56–65	17/391 (4.35%, CI 2.6–6.9%)	3/374 (0.8%; CI: 0.03%-2.3%)
66–75	16/246 (6.5%, CI 4.0–10.3%)	4/230 (1.7%; CI: 0.7–4.4%)
Age ≥76	20/225 (8.9%, CI 5.8–13.3%)	2/205 (1%; CI: 0.3–3.5%)

Method: AMX/CLA DILI was defined by ALT > 5x upper limits normal (ULN) or ALP >2xULN during the high-risk period (AMX/CLA initiation to 30 days following its discontinuation or the first 90 days after AMX/CLA initiation, whichever shorter), after excluding other causes of acute liver injury with ICD-9 codes and serology. Serious hepatocellular AMX/CLA DILI was defined by ALT > 5xULN and bilirubin > 2xULN. Liver related mortality was defined as death associated with bilirubin > 2 ULN and INR > 1.5, with early death (<6 months) and late death (6 months to 2 years of DILI). Liver-related mortality was examined by DILI phenotype and age in AMX/CLA DILI cases and AMX/CLA-treated controls without DILI.
Results: Early liver-related death occurred in 55/1135 (4.85%) DILI cases vs. 290/807,781 (0.04%) controls ($p < 0.001$). Importantly, the hepatocellular injury was significantly associated with early mortality only if being severe defined by Bilirubin > 2 ULN (see Table). An additional 13/1080 (1.2%) DILI cases and 824/807,471 (0.1%) controls ($p < 0.001$) exhibited late liver-related mortality; cholestatic DILI comprised nearly all late DILI deaths (see Table). Furthermore, age over 55 was associated with early mortality (53/862 (6.1%) / vs. 2/273 (0.7%), $p < 0.001$) yet not late liver-related mortality.
Conclusion: Nearly 5% of AMX/CLA DILI patients suffered early liver-related mortality, with highest percentage in Hy's law cases, and lowest in hepatocellular cases without significant bilirubin elevation. Death disproportionally affected the older population. Cholestatic liver injury was associated with late-liver related mortality.

Funding is VA "HSRD pilot grant (HX001865-01A1)".

PS-125

Orthotopic liver transplantation of xenogeneic livers repopulated with autologous hepatocytes: proof of normal function and consistent survival

Stéphanie Lacotte[1], G. Oldani[2], A. Peloso[2], L.A. Orci[2], V. Delaune[2], S. Vijgen[2], L. Rubbia-Brandt[2], C. Toso[2]. *[1]Centre Médical Universitaire, Genève, Switzerland; [2]University Hospital of Geneva, Genève, Switzerland*
Email: oldani@gmail.com

Background and Aims: Generation of transplantable patient-like organs in animals may solve the problem of organ shortage and potentially extend the indications for liver transplantation. However, the efficacy of this approach is yet to be demonstrated even in preclinical studies involving small animals. We challenged this idea by transplanting mouse-rat chimeric livers into baby rats, in orthotopic position. Grafts and animals survival was assessed along with liver synthetic function.
Method: Chimeric livers were created by transplanting Lewis rat hepatocytes into FRG® mice (C57Bl/6 Fah-/-/Rag2-/-/Il2rg-/-). The organs obtained were transplanted into 3-week old female Lewis rats (45 ± 3 g) without or with immunosuppression (IS) (Tacrolimus 0.6 mg/kg/day, during 56 or 112 days). The intensity of rejection was assessed by weekly graft biopsies and peripheral blood immune cells activation. Rat and mouse albumin production was measured once a week. Wild type C57Bl/6 mice were used as control donors.
Results: All non-immunosuppressed recipients experienced acute rejection and died between day 8 and 11 after transplantation.
Under calcineurin inhibitor monotherapy all chimeric liver recipients survived in good health, having normal development and weight gain. Banff score was 2–3, rejection being mostly driven by cholangiocytes. Rat albumin production was within physiologic ranges. Chimeric livers grew on average 670% (from 1.3 ± 0.2 g to 8.7 ± 1.4 g), in line with syngeneic rat controls.
By contrast, pure xenogeneic controls showed impaired growth and died before or shortly after the immunosuppression was stopped, in the 56-day IS group ($p = 0.0014$). In the 112-day IS group they all died while still on Tacrolimus ($p = 0.0013$). Banff score was never inferior to 6, rejection involving all epithelia.
Four months after implantation into rats, chimeric livers were partially repopulated by rat cholangiocytes and portal endothelial cells.
Conclusion: This is the first report showing robust survival of orthotopically transplanted chimeric livers. Moreover, the transplanted organs sustained and were able to follow normal animal growth and development after transplantation.

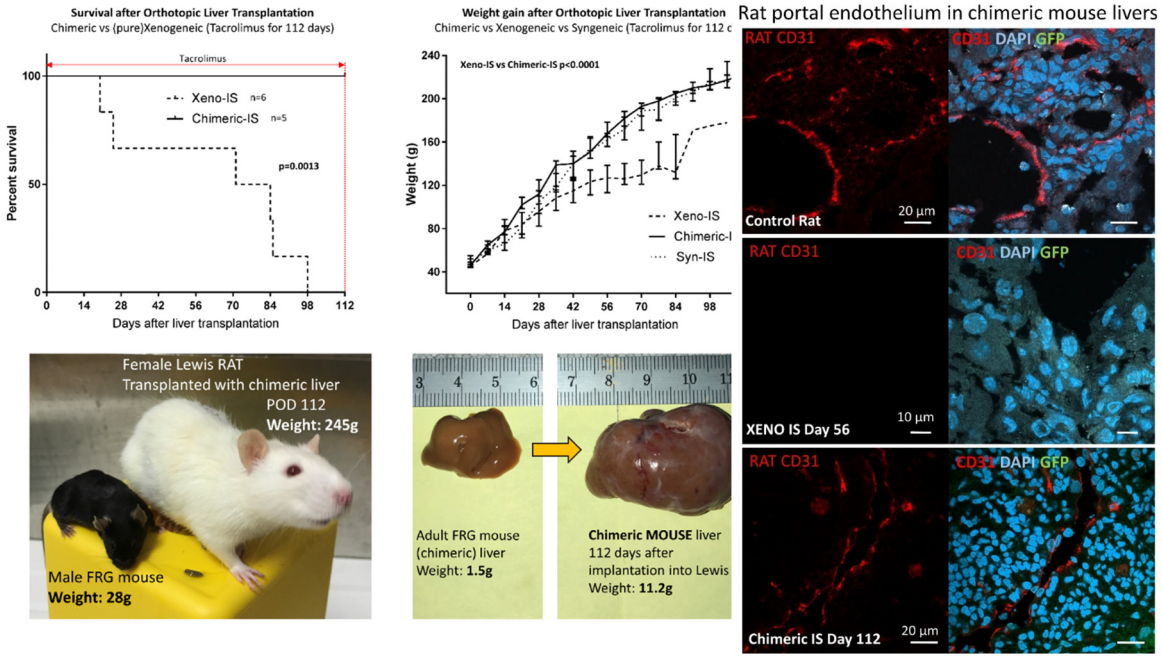


Figure: (abstract: PS-125)

PS-126

Following clinical liver transplantation, the majority of circulating cells exhibiting donor MHC are "cross-dressed" not "passenger" leukocytes

S. Mastoridis, A. Sanchez-Fueyo, M. Martinez-Llordella. *King's College London, Department of Liver Studies, London*
Email: sotiris.mastoridis@googlemail.com

Background and Aims: The dogma that following solid organ transplantation (SOT) allospecific immune responses are the consequence of graft-derived antigen presenting cells (APCs), or "passenger leukocytes", presenting donor MHC to naïve T cells has been recently challenged. Rather, mounting data from animal models of SOT highlight the salience of the semi-direct pathway of allorecognition, whereby T cell alloreactivity is triggered by recipient APCs that present intact donor MHC on their surfaces. These "cross-dressed" APCs acquire donor MHC either by direct cell contact and trogocytosis, or via allograft-derived extracellular vesicles (EVs). Our aim is to ascertain the presence of cross-dressed cells in the context of clinical liver transplantation and to establish whether this correlates with the presence of donor-derived EVs.

Methods: Peripheral blood mononuclear cells (PBMC) and platelet-poor plasma were collected from liver transplant recipients (n = 5) pre-transplant, and at post-transplant days 1, 4, 10, and 90. Donor splenocytes were collected at the time of graft harvest. HLA genotyping enabled the selection of appropriate donor-/recipient-specific HLA monoclonal antibody pairs. Advanced imaging flow cytometry with Amnis' ImageStream was used to perform phenotypic analyses of PBMC and EVs according to previously described methods. Statistical analyses were performed with GraphPad Prism 7.0.

Results: The percentage of PBMCs displaying donor MHC peaked at day 1 post-transplantation, and declined until undetectable at 90 days. In all cases, the majority of cells expressing donor MHC also expressed recipient MHC (cross-dressed). CD14+, CD16+ and CD11c+ cells accounted for the majority of cross-dressed cells, while proportions of these subsets expressing only donor-MHC (passenger leukocytes) were significantly lower ($p < 0.01$). EVs expressing donor HLA peaked at day 1 following transplantation (0.24–9.05% of total small EVs). Donor EVs formed a higher percentage of total EVs in those recipients exhibiting greatest proportions of cross-dressing at day 1 ($p < 0.001$).

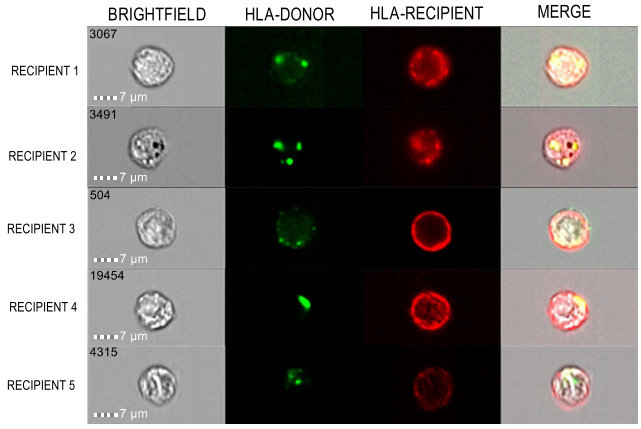


Figure 1: Recipient CD14+ cells acquire donor HLA. FACS staining performed at day 1 post-liver transplantation, with representative ImageStream™ images from 5 different transplant recipients shown.

Conclusion: This work represents the first investigation, to our knowledge, of cross-dressing in peripheral leukocytes following liver transplantation. It corroborates findings from experimental models showing cross-dressing to occur in the setting of SOT, with the predominance of "cross-dressed" over "passenger" leukocytes suggesting that in the clinical context too, these cells may play an important role. Our data suggest that the kinetics of EV release in the early post-operative period are associated with the appearance of cross-dressed cells. The functional properties of cross-dressed recipient APCs in clinical liver transplantation constitutes the basis of ongoing work.

PS-127

Intestinal microbiota modulates susceptibility to acetaminophen induced acute liver injury

C. Elfers[1], K.M. Schneider[1], A. Mohs[1], L. Lijun[1], E.J. Galvez[2], T. Strowig[2], I. Bergheim[3], E. Latz[4], C. Trautwein[1]. [1]*University Hospital RWTH Aachen, Department of Medicine III, Aachen, Germany;* [2]*Helmholtz Centre for Infection Research, Braunschweig, Germany;* [3]*University of*

Vienna, Department of Nutritional Sciences, Vienna, Austria; [4]University of Bonn, Institute of Innate Immunity, Bonn, Germany
Email: kmschneider@ukaachen.de

Background and Aims: Acetaminophen (APAP) poisoning represents the leading cause of acute liver failure (ALF) in western countries. Whereas the link between intestinal dysbiosis and chronic liver disease is well established, insight into the role of gut-liver crosstalk for drug induced liver injury (DILI) remains scarce. Here, we hypothesized that intestinal microbiota may affect the outcome of APAP induced liver failure.
Method: Male 6–8 week old wildtype (WT) and *Nlrp6*$^{-/-}$ mice were injected with a sublethal dose of APAP to induce DILI. 12 hours after injection, a comprehensive analysis of liver injury was performed based on liver functions tests (LFTs), histology, flow cytometry immunophenotyping (FACS) and 16S rRNA-based microbiota profiling. Moreover, microbiota of WT and *Nlrp6*$^{-/-}$ mice was modulated by fecal microbiota transfer (FMT).
Results: APAP administration induced significantly increased liver injury in *Nlrp6*$^{-/-}$ mice compared to WT controls as evidenced by LFTs and histological assessment, which revealed necrosis as the predominant form of cell death. Enhanced DILI in *Nlrp6*$^{-/-}$ mice was associated with markedly increased infiltration of Ly6C^{hi} monocyte derived macrophages (MoMFs) as demonstrated by FACS analysis. Interestingly, microbiota of *Nlrp6*$^{-/-}$ mice was less diverse and did not undergo a major change upon DILI. In contrast, acute liver injury in WT mice prompted a massive change in microbiota composition and a reduction of microbial diversity. These changes were associated with an expansion of colonic mucus layers in WT mice. This potentially protective response did not appear in *Nlrp6*$^{-/-}$ mice, which presented significantly increased serum endotoxin levels after APAP administration. Strikingly, WT mice gavaged with microbiota from *Nlrp6*$^{-/-}$ mice displayed significantly increased liver injury upon APAP treatment and resembled the inflammatory phenotype of *Nlrp6*$^{-/-}$ mice. Specifically, FMT skewed MoMF polarization in WT mice toward a Ly6C^{hi} inflammatory phenotype suggesting a critical function of MoMF as sensors of gut-derived signals orchestrating the inflammatory response.
Conclusion: Our data suggest an important, yet unknown function of intestinal microbiota and gut-liver crosstalk during acute liver injury. Intestinal dysbiosis – as seen in *Nlrp6*$^{-/-}$ mice and transferrable to healthy WT controls via FMT - aggravated liver injury upon APAP administration by promoting pro-inflammatory Ly6C^{hi} macrophage polarization.

Autoimmune and cholestasis 2

PS-128
Statins are associated with reduced mortality and morbidity in primary sclerosing cholangitis (PSC)

K. Stokkeland[1,2], J. Höijer[3], M. Bottai[3], K. Söderberg Löfdal[4,5], A.M. Bergquist[1,6]. *[1]Karolinska Institutet, Department of Medicine Huddinge, Unit of Gastroenterology and Rheumatology, Stockholm, Sweden; [2]Visby Hospital, Department of Medicine, Visby, Sweden; [3]Karolinska Institutet, Unit of Biostatistics, IMM, Stockholm, Sweden; [4]Karolinska Institutet, Division of Clinical Pharmacology, Department of Laboratory Medicine, Stockholm, Sweden; [5]Karolinska University Hospital, Department of Clinical Pharmacology, Stockholm, Sweden; [6]Karolinska University Hospital, Unit of Hepatology, Center of Digestive Diseases, Stockholm, Sweden*
Email: knut.stokkeland@gotland.se

Background and Aims: There is increasing evidence that statins is beneficial in chronic liver and cholestatic liver disease. The aim was to study the impact of exposure of different drugs including statins on death, liver transplantation, liver cancer and variceal bleeding in patients with primary sclerosing cholangitis.
Method: We performed a register-based cohort study of patients with a diagnosis of PSC between 2005 and 2016 in Sweden (n = 2 914). PSC was defined using the combination of the ICD-10 codes for cholangitis (K830) and either ulcerative colitis, UC (K51), or Crohn's disease, CD (K50). Data from the Patient Register, the Prescribed Drug Register, the Death Certificate Register were used. Use of drugs with possible positive effects on liver disease and its progression were studied. Outcomes were, death, liver transplantation (LT), liver cancer and bleeding esophageal varices.
Results: Mean age (IQR) at PSC diagnosis was 41.4 (25.6–56.1) years. The total follow up time were 11 769 years and 3.4% was transplanted and 19.9% died during the study period. There were 58% of the patients who had UC, 13% had CD and 29% had been diagnosed with both CD and UC during the study. Frequency of drug use were: UDCA 60.2%, 5-ASA 74.4%, azathioprine/mercaptopurins 33.7%, antibiotics 91%, antimycotics 12.1%, metronidazole 34.2%, corticosteroids 69.3% and statins 13.9%. Hazard ratios (CI: 95%) for all-cause mortality and the combined endpoints death or LT and death or LT, liver cancer or variceal bleeding are shown in Table 1.

Table 1: Hazard ratios (CI:95%) for death, liver transplantation or variceal bleeding with use of different drugs in 2914 patients with PSC

	All-cause mortality (N = 2 914)	Death or LT (N = 2 794)	Death, LT, liver cancer or variceal bleeding (N = 2 740)
UDCA	1.04 (0.87–1.25)	1.34 (1.12–1.62)	1.45 (1.24–2.80)
5-ASA	0.91 (0.77–1.09)	0.90 (0.74–1.09)	0.97 (0.80–1.18)
Azathioprine	0.66 (0.52–0.84)	0.65 (0.50–0.83)	0.72 (0.56–0.93)
Antibiotics	1.70 (1.27–2.29)	2.27 (1.70–3.05)	1.99 (1.52–2.61)
Antimycotics	2.78 (2.24–3.44)	3.13 (2.48–3.94)	2.43 (1.88–3.13)
Metronidazole	1.27 (1.06–1.53)	1.20 (0.99–1.47)	1.31 (1.07–1.59)
Corticosteroids	1.94 (1.60–2.34)	2.14 (1.75–2.60)	1.68 (1.39–2.04)
Statins	0.68 (0.54–0.88)	0.50 (0.28–0.66)	0.54 (0.41–0.71)

Conclusion: Statins and azathioprine use were associated with decreased risks of death, liver transplantation and variceal bleeding in patients with PSC. UDCA was not associated with a reduced mortality.

PS-129
Usefulness of serum metabolic profiling in the search of novel diagnostic biomarkers for primary sclerosing cholangitis, intrahepatic cholangiocarcinoma and hepatocellular carcinoma

Jesús Banales[1,2], M. Iñarrairaegui[2,3], A. Arbelaiz[4], P. Milkiewicz[5], J. Muntané[2,6], A. Lacasta[1], L. Muñoz-Bellvis[7], L.M. Gonzalez[7], E. Arretxe[8], C. Alonso[8], L. Bujanda[2,9], J. Marin[2,10], B. Sangro[2,3], R. Macias[2,10]. *[1]Biodonostia Research Institute, Department of Liver and Gastrointestinal Diseases, San Sebastian, Spain; [2]National Institute for the Study of Liver and Gastrointestinal Diseases (CIBERehd, Instituto de Salud Carlos III), Madrid, Spain; [3]Clínica Universidad de Navarra, IDISNA, Liver Unit, Pamplona, Spain; [4]Biodonostia Research Institute, Donostia University Hospital, University of the Basque Country (UPV/EHU), Spain; [5]Medical University of Warsaw, Liver and Internal Medicine Unit; [6]"Virgen del Rocío" University Hospital/IBiS/CSIC/ University of Sevilla, General Surgery, Sevilla, Spain; [7]University Hospital of Salamanca, IBSAL, General and Gastrointestinal Surgery, Salamanca, Spain; [8]OWL Metabolomics, Derio, Spain; [9]Donostia University Hospital, Department of Liver and Gastrointestinal Diseases; [10]University of Salamanca, IBSAL, CIBERehd, Physiology and Pharmacology, Salamanca, Spain*
Email: jjgmarin@usal.es

Background and Aims: In patients with primary sclerosing cholangitis (PSC), a condition with increased risk of developing intrahepatic cholangiocarcinoma (iCCA), the progression of the disease to a

malignant lesion often escapes detection. Moreover, in some cases, the differential diagnosis between iCCA and hepatocellular carcinoma (HCC) is difficult. Since early diagnosis of iCCA and HCC by non-invasive methods remains a challenge and the analysis of low-molecular weight metabolites, by new high-throughput techniques, provides a potential source of information to identify novel biomarkers, here we have investigated whether serum metabolomics profiles can be useful to discriminate in the diagnosis of iCCA and PSC or HCC.

Method: Chloroform/methanol and methanol extracts obtained from the serum of patients with PSC, iCCA, or HCC and healthy individuals (n = 20 in each group) were analyzed using ultra-performance liquid chromatography coupled to mass spectrometry (UHPLC-MS).

Results: Using this approach 438 metabolites were identified. Significant changes in the levels of several compounds belonging to different chemical families were found in all the comparisons. Thus, levels of 151 metabolites were altered in PSC versus controls and 49 of them (mainly phosphatidylcholines and lysophosphatidylcholines) were significantly different compared to iCCA. A diagnostic model was built through linear discriminant analyses. An algorithm consisting of PC(34:3) + histidine accurately permitted to differentiate PSC and iCCA. The proposed model yielded an area under the receiver operating characteristic curve (AUROC) of 0.990, 100% sensitivity, 70% specificity and 85% accuracy. Concentrations of 148 metabolites were significantly altered in HCC versus controls, and 16 of them (amino acids, sphingomyelins, diacylglycerols and triacylglycerols), were significantly different compared to iCCA. Levels of 52 metabolites were significantly altered in iCCA versus controls and, of them, 4 amino acids permitted to discriminate iCCA from HCC. An algorithm consisting of glycine + aspartic acid permitted to differentiate both types of tumors with an AUROC of 0.885, a sensitivity of 95%, a specificity of 65%, and an accuracy of 80%.

Conclusion: Specific changes in serum metabolite concentrations useful to distinguish iCCA from PSC or HCC have been identified. Validation studies are needed to determine the actual clinical value of these biomarkers in the diagnosis of these liver diseases.

PS-130

Fra-2 transgenic mice develop a phenotype of spontaneous primary sclerosing cholangitis

F. Steinbach[1], S. Rosigkeit[1], E. Wagner[2], E. Bockamp[1], D. Schuppan[1,3].
[1]*University Medical Center Mainz, 1Institute of Translational Immunology and Research center for Immune Therapy, Mainz, Germany;* [2]*Spanish National Cancer Research Center, 2BBVA Foundation-CNIO Cancer Cell Biology Program, Madrid, Spain;* [3]*Division of Gastroenterology, Beth Israel Deaconess Medical Center, Harvard Medical School, Division of Gastroenterology and Hepatology, Boston, United States*
Email: detlef.schuppan@unimedizin-mainz.de

Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic liver disease characterized by inflammation and fibrosis of the bile ducts. We have developed a transgenic mouse that overexpresses Fra-2, an alternative component of the transcription factor AP-1 which is responsible for cell proliferation, inflammation, wound healing. Interestingly, Fra-2 drives dermal fibrosis and serves as a novel model of systemic sclerosis affecting the skin and lungs. Here, we describe a novel phenotype developing in older Fra-2 transgenic mice that display core features of PSC.

Method: Fra-2 mice were bred from heterozygous males and wildtype females as described (Eferl et al., 2008). Newborn heterozygous Fra-2 and control mice were maintained for up to 16 weeks. Mice were sacrificed at age 11 and 16 weeks. Liver histology was scored on H&E stained sections, and liver collagen determined via hydroxyproline (HYP) quantification and Sirius Red morphometry. Immune cell infiltration and the expression of the fibrosis promoting cholangiocyte integrin αvβ6 were examined by immunohistochemistry (IHC).

Results: At 11 and especially 16 weeks of age, mice had developed stage 3–4 fibrosis with prominent periportal ductular proliferations surrounded by a rim of connective tissue. Sirius red stained collagen was upregulated 5fold in Fra-2 transgenic vs wildtype control mice which corresponded with biochemical collagen deposition as determined by HYP content. Fibrosis in Fra-2 transgenic mice was characterized by a prominent immune cell infiltration surrounding actively proliferating ductular structures. Ductular structures strongly expressed the integrin αvβ6, an activator of TGFβ1, as observed in human PSC.

Conclusion: Fra-2 is a master transcription factor of fibrogenic gene expression. Apart from skin and lung fibrosis, its overexpression induces rapidly progressive biliary fibrosis resembling PSC. Apart from these mice serving as a valuable preclinical model to evaluate therapies for PSC, Fra-2 itself appears to be an important molecular target for antifibrotic therapies in PSC.

PS-131

A novel model of acute and specific biliary cell injury reveals a crucial role of circulating monocytes in promoting ductular reaction and cholestasis

A. Guillot[1], D. Feng[1], S.-J. Kim[1], L. Guerri[2], S. Dai[3], F. Liu[3], X. Qin[3], D. Goldman[2], B. Gao[1]. [1]*NIH / NIAAA, Laboratory of Liver Diseases, Rockville, United States;* [2]*NIH / NIAAA, Laboratory of Neurogenetics, Rockville;* [3]*Temple University School of Medicine, Department of Neuroscience, United States*
Email: adrien.guillot@nih.gov

Background and Aims: Kupffer cells represent the liver resident macrophage population. Following tissue injury and together with infiltrating monocytes, they are thought to play critical roles in controlling the inflammatory environment and favoring tissue repair. Ductular reactions, which consist of immune infiltrates, fibrogenesis and cholangiocytes proliferation in liver portal areas, are observed in chronic liver diseases; however, the mechanisms underlying cholangiocyte injury and regeneration remain obscure due to the lack of a model with specific cholangiocyte injury. Thus, our studies aim to provide a conditional and cell specific model, leading to acute biliary cell death and allowing for the study of subsequent immune response and bile duct regeneration.

Method: For this purpose, we generated transgenic mice expressing a tamoxifen inducible Cre recombinase inducing human CD59 (hCD59) protein expression in Sox9-positive cells. Injected intermedilysin (ILY) toxin specifically binds to hCD59 to lyse the targeted cells with no off-target effects. Cre-negative hCD59-floxed littermates were used as negative controls. Mice expressing GFP under the CX3CR1 promoter were used to trace infiltrating monocytes. Kupffer cells and recruited monocytes were also identified by immunohistochemistry by using anti-Clec4f and anti-Iba-1 antibodies. Liver injury was shown by TUNEL staining, serum analysis, and bile acid quantitation. Biliary cell proliferation was evaluated by BrdU incorporation in pan-cytokeratin positive cells. Macrophages were depleted by injecting clodronate-loaded liposome prior to ILY injection.

Results: Following tamoxifen injection, we observed that hCD59 expression was restricted to bile duct cells. ILY injection led to a specific biliary epithelial cell death in this transgenic line. Subsequently, bile duct injury was associated with intense inflammatory cell recruitment around portal areas, mostly GFP-positive and Clec4f-negative infiltrated monocytes, while Kupffer cells did not accumulate in damaged portal areas. Lastly in our model, macrophage depletion reduced biliary cell regeneration as well as portal fibrogenesis, and intrahepatic bile acid accumulation although biliary cell injury was identical.

Conclusion: The hCD59-Sox9Cre mice represent an innovative, cell specific, and conditional model to study acute biliary cell injury and subsequent bile duct regeneration and repopulation. By using this model, we demonstrated that recruited monocytes play an important role in promoting ductular reaction, as well as cholestasis.

PS-132

Characterization of miR deregulation in cholangiocarcinoma (CCA): Consequences in tumor heterogeneity and drug resistance

P. Munoz-Garrido[1,2], L. Satriano[1], D. Høgdall[1,3], J. Banales[4], A. Ghazal[1], C.O. Rourke[4], J. Andersen[1], J. Marquardt[5]. [1]*Biotech Research & Innovation Center (BRIC), Health Science Faculty, University of Copenhagen, Copenhagen N, Denmark;* [2]* *Sheilla Sherlock Fellow;* [3]*Herlev and Gentofte Hospital, Copenhagen University Hospital, Department of Oncology, Herlev, Denmark;* [4]*Biodonostia Research Institute, Department of Liver Diseases, San Sebastian, Spain,* [5]*Biotech Research & Innovation Center (BRIC), Health Science Faculty, University of Copenhagen, Copenhagen, Denmark;* [6]*Johannes Gutenberg University, Department of Medicine I, Lichtenberg Research Group, Mainz, Germany*
Email: jesper.andersen@bric.ku.dk

Background and Aims: A characteristic hallmark of cholangiocarcinoma (CCA) is its genomic heterogeneity, which inevitably manifests in therapeutic resistance. The molecular mechanisms driving tumorigenesis, and the basis for why CCA malignancies demonstrate resistance remains unclear. We elucidate the deregulated miR landscape in a CCA patient cohort characterizing the miR involvement in disease onset and role in eliciting drug resistance.
Method: Illumina small RNAseq (miRseq) was performed at high coverage (avg. 30M reads) in 212 fresh frozen samples. Also, for *in vitro* modeling, 18 CCA and normal cell lines were analyzed. Patient-matched gene expression and mutational profiles of all CCA samples were generated. Integration of deregulated miR and aberrant gene expression was performed. High throughput screening (HTS) of >2,700 miR mimics was analyzed in primary normal human cholangiocyte (NHC) and patient-derived CCA cells evaluating their role in regulating proliferation and morphology. Gemcitabine resistant CCA cell lines were established to elucidate the role of miRs in drug refractory disease.
Results: To distinguish deregulated miR expression in CCA, samples were divided into intrahepatic (iCCA, n = 99), perihilar (pCCA, n = 10) and distal disease (dCCA, n = 18), including matched adjacent tissues (n = 63) and normal controls (n = 23). Determination of deregulated miRs was performed by a well-established miR workflow (miRDeep2/DEseq2). Data was processed with cutoffs of Padj. < 0.01 and IFC > 2. We have defined a total of 29 significant miRs (19 up and 10 down) in tumor samples compared to matched adjacent tissues (AUC = 0.99). Correlation of aberrantly expressed miRs and *best fit* model system was evaluated to manipulate select miRs and by HTS. Gene expression and mutational profiles of CCAs and adjacent normal tissue were analyzed and integrated with miRs. In the miR mimics library screen siAKT (decreased proliferation) and taurocholic acid (increased proliferation) were used as controls. Morphological changes were analyzed by fluorescent phalloidin membrane staining. Screening of NHC cells revealed 50 miRs that significantly increased the normal proliferation rate, of which mir-26b is a positive control known to be elevated in CCA. Additionally, 35 miRs significantly inhibited cellular proliferation and will be evaluated further as putative targets in CCA.
Conclusion: The results obtained in this study provide new biological and molecular knowledge on CCA heterogeneity and lead to improve the current understanding of the pathobiology of miR-driven chemoresistance. Further analyses focused on identifying novel drug targets will bring miR biology forward as a therapeutic aim in CCA.

PS-133

Novel role of amphiregulin in bile acids metabolism and protection from cholestatic liver injury

E. Santamaria[1], C. Rodriguez-Ortigosa[1], I. Uriarte[1], M.U. Latasa[1], R. Urtasun[1], B. Sangro[2], P. Milkiewicz[3,4], M. Milkiewicz[5], M. Monte[6], J. Marin[6], M.G. Fernandez-Barrena[7], Matías Avila[1], C. Berasain[7]. [1]*CIMA-University of Navarra. CIBERehd, IdiSNA, Hepatology, Pamplona, Spain;* [2]*Clinica Universidad de Navarra and CIBERehd, Liver Unit, Pamplona, Spain;* [3]*Medical University of Warsaw, Liver and Internal Medicine Unit, Warsaw, Poland;* [4]*Pomeranian Medical University, Translational Medicine Group, Szczecin, Poland;* [5]*Pomeranian Medical University, Department of Medical Biology, Szczecin, Poland;* [6]*University of Salamanca, IBSAL, CIBERehd, Dept. Physiology and Pharmacology, Salamanca, Spain;* [7]*CIMA-University of Navarra. CIBERehd, IdiSNA., Hepatology*
Email: maavila@unav.es

Background and Aims: Many acute and chronic liver diseases are accompanied by cholestasis. Intrahepatic accumulation of bile acids (BAs) may cause hepatocytes and cholangiocytes death. Upon liver injury, a potent protective and regenerative response is mounted to restore the architecture and function of the organ. However, when this reparative reaction chronifies liver fibrosis and tumorigenesis may ensue. A better understanding of this reaction is required to devise hepatoprotective strategies, as well as antifibrogenic and antineoplastic therapies. The epidermal growth factor receptor (EGFR) signaling system is essential for regeneration after most types of experimental liver injury, including cholestatic injury. EGFR can be activated by a wide family of growth factors, among which amphiregulin (AR) was identified as a key mediator of liver regeneration. Here we have studied the role of AR during cholestatic liver injury and the mutual regulation of AR expression and BA synthesis.
Method: We used two models of cholestatic liver injury: bile duct ligation (BDL) and oral alpha-naphtyl-isothiocyanate (ANIT) administration in wild type (AR-WT) and AR knockout (AR-KO) mice. AR expression was examined in: (i) livers from patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC); (ii) mice and cultured liver cells treated with BAs; and (iii) farnesoid X receptor knockout mice (FXR-KO) after BDL. The cytoprotective capacity of AR was evaluated in vitro and in vivo.
Results: AR mRNA and protein were up-regulated in the liver of PBC and PSC patients (hepatocytes and cholangiocytes). Oral BA administration to mice induces ileal and hepatic AR expression, and cholestyramine feeding reduces postprandial ileal and liver AR upregulation. AR-KO mice display higher Cyp7a1 expression and intrahepatic BA concentrations than AR-WT mice. Liver AR expression was markedly enhanced in BDL and ANIT groups of AR-WT mice. Liver damage was markedly exacerbated in AR-KOs. BAs induced AR expression in cultured liver cells partially through FXR. Consistently, after BDL FXR-KO mice show reduced liver AR expression than FXR-WT. AR treatment protected from BDL-induced liver injury and from BAs toxicity in cultured liver cells.
Conclusion: AR participates in BA homeostasis under physiological conditions. Liver AR expression is activated during cholestasis partially through FXR. AR plays an important role in protecting the liver from BA induced toxicity.

PS-134

International experience of vedolizumab in primary sclerosis cholangitis and inflammatory bowel disease

K. Williamson[1], E. Lytvyak[2], A.E. Kremer[3], M. de Krijger[4], P. Trivedi[5], D. Estes[6], L. Yu[7], D. Pratt[8], A. de Vries[9], K.K. Yimam[10], L. Daretti[11], C.H. Liu[12], C. Bowlus[12], M. Vetter[3], H.-U. Marschall[13], A. Montano-Loza[14], R.W.G. Chapman[15], M. Marzioni[11], S. Keshav[15], C. Ponsioen[16], G. Hirschfield[5], C. Levy[17] and on belalf of PSC Study Group. [1]*University of Oxford, Translational Gastroenterology Unit, Oxford, United Kingdom;* [2]*University of Alberta, Division of Gastroenterology, Edmonton, Canada;* [3]*Friedrich-Alexander-University, Department of Medicine, Erlangen, Germany;* [4]*Academic Medical Center, Department of Gastroenterology and Hepatology, Amsterdam, Netherlands;* [5]*University of Birmingham, Centre for Liver Research and NIHR Biomedical Research Centre, Birmingham, United Kingdom;* [6]*University of Miami, Division of Hepatology, Miami, United States;* [7]*University of Washington Medical Center, Liver Care & Transplantation Services, Seattle, United States;* [8]*Massachusetts General Hospital,*

Autoimmune and Cholestatic Liver Center, Boston, United States; [9]Erasmus Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [10]California Pacific Medical Center, Department of Gastroenterology and Hepatology, San Francisco, United States; [11]Ospedali Riuniti University Hospital, Clinic of Gastroenterology and Hepatology, Ancona, Italy; [12]University of California Davis, Division of Gastroenterology and Hepatology, Davis, United States; [13]Sahlgrenska Academy, University of Gothenburg, Department of Molecular and Clinical Medicine, Gothenburg, Sweden; [14]University of Alberta, Division of Gastroenterology and Hepatology, Edmonton, Canada; [15]University of Oxford, Translational Gastroenterology Unit, Nuffield Department of Medicine, Oxford, United Kingdom; [16]Academic Medical Center, Amsterdam, Department of Gastroenterology and Hepatology, Amsterdam, Netherlands; [17]University of Miami, Division of Hepatology, Miami, United Kingdom
Email: katewilly@hotmail.com

Background and Aims: Vedolizumab (VDZ) appears to be an attractive option for treating Primary Sclerosing Cholangitis (PSC) as it targets gut-homing lymphocytes which have been linked with the pathophysiology of PSC. VDZ has been proven to be beneficial in inflammatory bowel disease (IBD) but there is little data on the effect of VDZ in PSC/IBD.
Method: A retrospective audit was carried out by the International PSC Study Group of patients with PSC who had received VDZ for their IBD. General demographics and variables pertaining to liver enzymes and IBD response were obtained, comparing baseline with day 42, and last follow-up. Patients receiving VDZ post-liver transplant were not included. Paired T-tests were used for comparisons pre- and post-VDZ, and, unless otherwise stated, data stated as means with 95%CI.
Results: 60 patients with PSC/IBD received VDZ from 11 centres in North America and Europe. 37 (61.7%) were male, with mean age at PSC diagnosis 30y (range 13–86) and mean age at IBD diagnosis 25y (range 9–62). 54 (90.0%) patients had classical PSC, 4 (6.7%) had small-duct PSC, and 2 (3.3%) had PSC-AIH overlap; 15 (25.0%) had cirrhosis. 40 (66.7%) had UC, 15 (25.0%) had Crohn's disease, 4 (6.7%) had IBD-unspecified, and 1 had unknown IBD subtype. 35 patients (58.3%) were on concomitant ursodeoxycholic acid. 33 (55.0%) had previously had anti-TNF therapy, 21 (35.5%) were anti-TNF naïve, and 6 had unknown anti-TNF status.
The median duration of VDZ was 363 days (range 14–2609). VDZ was ceased in 28 patients (46.7%) during the study period, mostly for lack of efficacy (21, 75%), with 3 stopping for adverse reactions, 3 for other reasons (compliance, insurance), 1 unknown.
The mean ALP at baseline was 2.38xULN (1.82–2.94) vs. 2.59xULN at Day 42 (1.93–3.24, p = 0.32), and at last follow-up (whilst still on VDZ) was 2.76xULN (2.09–3.44, p = 0.06 vs. baseline). When comparing with ALP at baseline, the proportion of patients who had any drop in ALP was 43.9% at day 42 (mean drop −20.2%, −4.0 to −26.31) and 50.9% at last follow-up (mean drop −22.6%, −15.1 to −30.2), whilst only 5.3% dropped ALP by at least 40% at day 42 (8.8% at last follow up).
There was a rise in mean ALT at baseline vs. last follow-up: 61.6IU/L (49.1–74.1) vs. 79.8IU/L (61.9–97.6, p = 0.0078), and a similar rise in AST: 56.9IU/L (43.4–70.4) vs. 71.9IU/L (54.6–89.1, p = 0.055).
44 patients had data available for endoscopic IBD response. 25 (56.8%) improved, compared with 19 (43.2%) who had unchanged or worsened endoscopic appearance. Of those who had an IBD response, 60.0% had an ALP drop from baseline to last follow up compared with only 42.1% in IBD non-responders, but this was not statistically significant (p = 0.36).
Conclusion: Whilst VDZ appears moderately effective for IBD in PSC/IBD, there was no effect on ALP response, (though a trend towards ALP rise), and there was a small rise in ALT. These observations may be due to the natural course of the underlying PSC.

Cirrhosis: Portal hypertension, and complication

PS-135

A spleen stiffness measurement-based model for recognition of high risk varices: Baveno VI criteria and beyond

F. Ravaioli[1], A. Colecchia[1,2], G. Marasco[1], A. Colli[3], E. Dajti[1], A. DI Biase[4], M. L. B. Reggiani[1], A. Berzigotti[5], M. Pinzani[6], D. Festi[1]. *[1]University of Bologna, Department of Medical and Surgical Sciences (DIMEC), Bologna, Italy; [2]Azienda Ospedaliera Universitaria Integrata, Verona, UOC. Gastroenterologia, Verona, Italy; [3]General Hospital, Lecco, Italy, Department of Internal Medicine, Lecco, Italy; [4]University of Modena, Department of Pediatrics, Modena, Italy; [5]University of Bern, Switzerland, Hepatology, Inselspital, University Clinic of Visceral Surgery and Medicine (UVCM), Bern, Switzerland; [6]University College London, London, Great Britain., Department of Hepatology, Royal Free Hospital NHS Trust; Institute for Liver and Digestive Health, London, Italy*
Email: antonio.colecchia@aovr.veneto.it

Background and Aims: Recently, Baveno VI guidelines suggested that esophagogastroduodenoscopy (EGD) can be avoided in patients with cACLD who have a liver stiffness measurement (LSM) <20 kPa and platelet count >150,000/mm^3. We aimed to assess the performance of spleen stiffness measurement (SSM) in ruling out patients with high risk varices (HRV); we also aimed to validate Baveno VI criteria in a large population and assess how the sequential use of Baveno VI criteria and SSM could safely avoid the need for endoscopy.
Method: We retrospectively analysed 498 cACLD patients who had undergone LSM/SSM by transient elastography (TE), platelet count and EGDs from 2012 to 2016 referred to our tertiary centre. We performed multivariate analysis and split validation to define the role of SSM in predicting HRV. The derivation dataset consisted of 54 randomly selected cases and 129 randomly selected controls from the original datasets of 100 cases and 398 controls; consequently, the validation dataset includes 46 cases and 123 controls.
Results: At the multivariate analysis, SSM (OR = 1.108; 95%CI = 1.072–1.145), LSM (OR = 1.068; 95%CI = 1.042–1.096), platelet count (OR = 0.985; 95%CI = 0.979–0.993) and Child-Pugh B (OR = 3.066; 95%CI = 1.654–5.692) were independent predictors of HRV. With the aim of identifying, by SSM ROC curves, the most accurate SSM cut-off to rule out patients with HRV [corresponding to a low probability (<5%) of HRV presence], a cut-off ≤ 46 kPa was chosen. The performance of SSM (≤46 kPa) in ruling out HRV showed a sensitivity of 97.8%, a specificity of 44.9%, NPV of 98.9% and an LR- of 0.05. Applying the newly identified SSM cut-off (≤46 kPa) or Baveno VI criteria, 36.7% and 21.7% of patients in the validation cohort could have avoided EGD, with HRV being missed in 1% in both cases. The combination of SSM with Baveno VI criteria would have made it possible to avoid an additional 22.5% of EGDs if compared with Baveno VI criteria alone, thus reaching a final value of 44.2% of avoided EGD, with <5% missed HRV.
Conclusion: Our study indicates that SSM is not only an independent predictor of the presence of HRV but is also an accurate and non-invasive test for ruling out HRV and that combining it with Baveno VI criteria in a simple sequential algorithm makes it possible to safely avoid a significant larger proportion of unnecessary endoscopies.

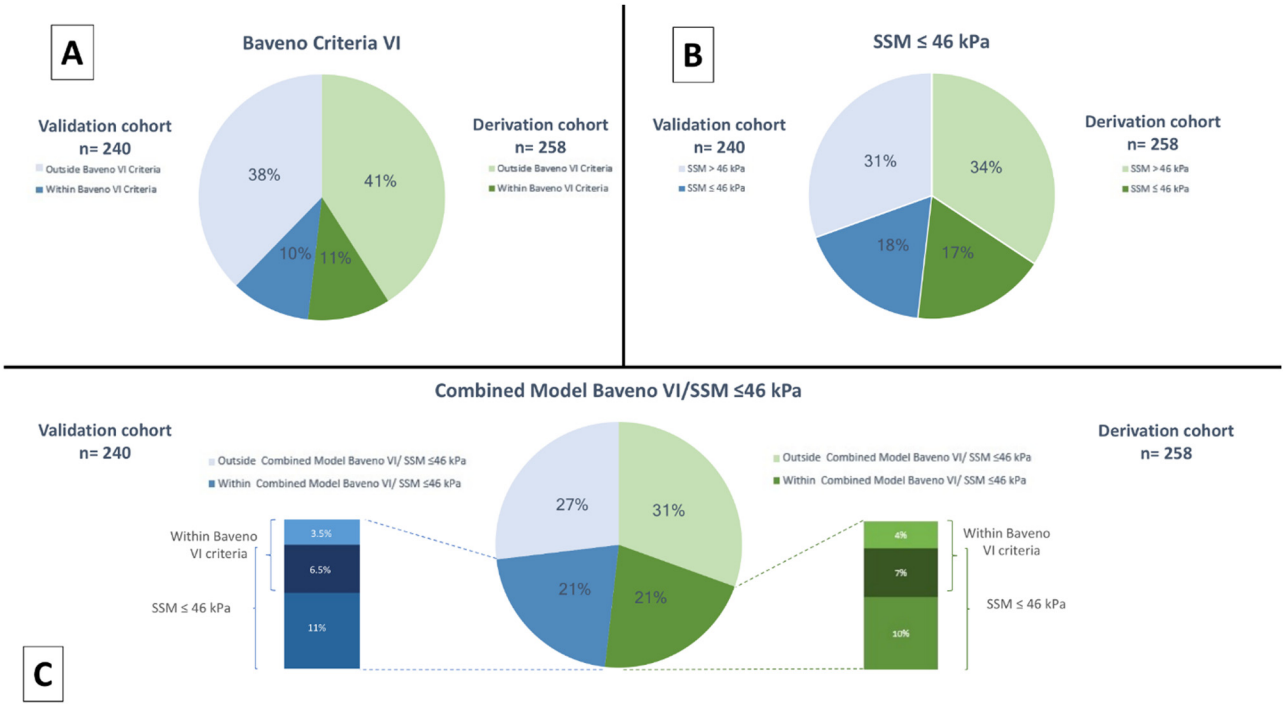


Figure: (abstract: PS-135): Rate of spared endoscopies by each of the considered non-invasive models. All percentages (%) are referred to the entire population (n = 498), represented as the combination of the derivation and validation cohort. In the new combined model Baveno VI/SSM ≤ 46 kPa, the rate of the spared endoscopies is reported also in the column graphs as the sum of the patients that fulfill only the Baveno VI Criteria (SSM > 46 kPa), patients with SSM ≤ 46 kPa (and outside Baveno VI Criteria) and patients that would have avoided endoscopy according to both models (in overlapping area).

PS-136

Non-invasive measurement of HVPG using graph analysis of dynamic contrast-enhanced ultrasound: the CLEVER study

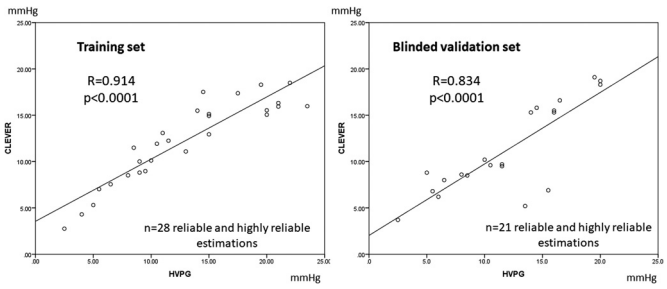
A. Berzigotti[1,2], F. Piscaglia[3], I. Amat-Roldan[4], R. Gilabert[5], B. Procopet[2], H. Stefanescu[3], I. Bilbao[4], V. Sansone[3], G. Allegretti[4,6,7], S. Lens[8], G. P. J. Carlos[2], J. Bosch[2] and Clever Study Investigators[4,7,8].
[1]Inselspital, Hepatology; [2]Liver Unit, Hospital Clinic, IDIBAPS and CIBERehd, Hepatic Hemodynamic Laboratory, Barcelona, Spain; [3]University of Bologna, DIMEC, Bologna, Italy; [4]Ymaging, SL, Barcelona, Spain; [5]Hospital Clinic, IDIBAPS, Radiology, Barcelona, Spain; [6]IDIBAPS, Barcelona; [7]University of Bologna, Bologna, Italy; [8]Liver Unit, Hospital Clinic, IDIBAPS and CIBERehd, Barcelona, Spain
Email: annalisa.berzigotti@insel.ch

Background and Aims: Hepatic venous pressure gradient (HVPG) is the standard-of-care method to assess portal pressure in patients with chronic liver disease (CLD). HVPG has a strong independent prognostic value, but it is invasive, which limits its routine use. Non-invasive methods providing an accurate estimate of HVPG are an unmet need in hepatology. Preliminary data suggested that graph analysis of dynamic contrast enhanced ultrasonography (DCE-US) of the liver allows calculating the degree of derangement of the hepatic microcirculation and mirrors the severity of portal hypertension (Amat-Roldan et al. Radiology 2015). The EC-funded prospective CLEVER study (FP7-IAPP-GA-2013-612273-CLEVER) aimed at developing a novel automatized software based on DCE-US able to improve prognostication in cirrhosis. Here we report the applicability and diagnostic accuracy of the CLEVER software to assess portal hypertension as compared to HVPG in a large population of patients with CLD studied in one of the participating centers.

Method: The present results were obtained in a subgroup of 152 patients with CLD undergoing clinically indicated HVPG measurement who had DCE-US for CLEVER assessment on the same day. 90 secs after starting a continuous infusion of 4.8 ml of SonoVue (Bracco, Switzerland) lasting 3 min, one or more videoclips of the right hepatic lobe parenchyma were recorded, including microbubble disruption and reperfusion (20 seconds clips; Acuson Sequoia). The CLEVER software estimates the HVPG by offline graph model analysis of the vascular connectomes on the microbubbles reperfusion images. 83 patients (training set) were used to develop 5 equipment-calibrated models for HVPG estimation. The computer algorithm automatically selects the best HVPG prediction model, and provides a grading of reliability of the HVPG estimation ("poorly reliable", "reliable" or "highly reliable"). 69 patients were used as blinded validation set.

Results: The CLEVER software was able to provide portal pressure estimations from CEUS videos in 85/152 patients (56%). Applicability increased when >2 videoclips were acquired: 51% with one acquisition, 56% with 2, 81% with 3, and 100% with 4.

Reliability and correlation with HVPG. In the training set 28/50 patients (range of HVPG 2.5–26 mmHg) had reliable or highly reliable CLEVER results. In them, the correlation between HVPG and the CLEVER estimation was excellent: R = 0.914, p < 0.0001. In the validation set 21/35 patients had reliable or highly reliable results. The correlation between HVPG and CLEVER output was R = 0.834, p < 0.0001 (Figure).



Conclusion: We developed and validated the DCE-US based CLEVER software which allows an accurate non-invasive estimation of portal pressure in patients with CLD. Multiple acquisitions during the same contrast infusion are required to increase the applicability of the method.

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Effect of B-blockers on the systemic hemodynamics of decompensated cirrhosis and survival

E. Alvarado[1,2], B. Cuyas[1], M.García Guix[1], A. Ardevol[1], R. Montañés[1], M. Poca[1,2], M. Concepciòn[1], S. Bazaga[1], G. Iborra[1], C. Aracil[3], X. Torras[1,2], C. Guarner[1,2], C. Villanueva[1,2]. *[1]Hospital de la Santa Creu i Sant Pau, Gastroenterology and Hepatology department, Barcelona, Spain; [2]Centro de Investigación Biomédica en Red en el Área temática de Enfermedades Hepáticas, Spain; [3]Hospital Universitari Arnau de Vilanova, Gastroenterology and Hepatology department, Spain*
Email: ealvaradot@santpau.cat

Background and Aims: Whether β-blockers can be harmful in cirrhosis is currently debatable. Different circulatory changes occur in advanced cirrhosis, including an intensification of hyperdynamic circulation. Because maintenance of blood pressure and cardiac output is essential in advanced cirrhosis, the effect of β-blockers on such hemodynamic parameters can be detrimental. The aim of this study was to evaluate whether the effect of β-blockers on the systemic hemodynamic of advanced cirrhosis may influence survival.
Method: From January 2005 to January 2016 patients with cirrhosis and ascites who had high-risk esophageal varices without previous bleeding, referred for primary prophylaxis, were consecutively included in the study. A hepatic and systemic hemodynamic assessment was performed at baseline and again 1–3 months later, under treatment with non-selective β-blockers (NSBB), either propranolol or carvedilol.
Results: Among 403 patients with varices referred, 190 with ascites were included. The mean Child-Pugh score was 8 (IQR, 7–9), mean MELD was 13 (IQR, 10–15) and age was 61 years (IQR, 53–68). During a follow-up of 36 months (IQR, 16–62), 27 patients (14%) had variceal bleeding, 31 (16%) hepatorenal syndrome, 38 (20%) SBP, 31 (15) developed a HCC, 18 (9%) had OLT and 73 (38%) died. As compared with patients surviving, those who died were older (64 ± 10 *vs.* 59 ± 9 y, p = 0.001), had lower baseline albumin (30 ± 4 *vs.* 32 ± 5 G/L, p = 0.007) and worse Child-Pugh (8.1 ± 1.5 *vs.* 7.1 ± 1.5, p = 0.01). Baseline hemodynamic parameters were similar between both groups, except for a higher HVPG in those who died (20.6 ± 4 *vs.* 18.9 ± 4, p = 0.03). However, at the control 1–3 months of treatment with NSBB patients who died had a higher decrease of cardiac output (CO) from baseline (19 ± 13 *vs.* 14 ± 17%, p = 0.05) with a lower final value (5.7 ± 1.5 *vs.* 6.6 ± 1.5 L/min, p = 0.01) and had lower mean arterial pressure (MAP: 76 ± 9 vs 85 ± 15 mmHg, p = 0.01) than survivors. By Cox regression analysis, age, baseline Child-Pugh and HVPG and CO at 1–3 months were independent predictors of dead. The probability of death was higher in patients with a CO < 5 L/min at 1–3 months of treatment with NSBB than in those with CO ≥ 5 L/min (death risk of 19% *vs.* 5% at 1 year and 42% *vs.* 15% at 3 years, p < 0.001 by log-rank).
Conclusion: Among patients with decompensated cirrhotic treated with NSBB, those who died have lower CO and MAP under treatment with NSBB than those surviving (in addition to worse liver function and higher HVPG at baseline). CO had an independent prognostic value and the risk of death was higher in patients with CO < 5 L/min. Our results suggest that monitoring CO under treatment with NSBB can be helpful to improve outcomes.

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The global prevalence of Wilson disease from next-generation sequencing data

S. Brackley[1], J. Gao[1], J. Mann[2]. *[1]University of Cambridge, School of Clinical Medicine, Cambridge, United Kingdom; [2]University of Cambridge, Department of Paediatrics, Cambridge, United Kingdom*
Email: smb202@cam.ac.uk

Background and Aims: Wilson Disease (WD) is an autosomal recessive disorder of copper metabolism, caused by mutations in the ATP7B gene. Its prevalence is widely quoted as 1 in 30,000, but this figure predates the discovery of the gene responsible and recent estimates have been much higher. We aimed to: (1) meta-analyse previous prevalence estimates for WD, and (2) estimate the prevalence of WD across ethnicities from population sequencing data, using a validated method.
Method: MEDLINE and EMBASE were systematically searched for articles related to Wilson disease. Previous prevalence estimates were meta-analysed using an inverse variance model with a double arcsin transformation.
ClinVar and the University of Alberta WD database were used to identify disease-causing mutations in ATP7B. Coding sequence nucleotide changes for each variant were identified and converted to human genome coordinates (hg38) using the Mutalyzer program (https://mutalyzer.nl/). Variants were then filtered for those previously defined as "disease variants" and, for missense mutations, "deleterious" or "damaging" on SIFT and Polyphen-2 respectively. The Ensembl Variant Effect Predictor (https://ensembl.org/Tools/VEP) was used to annotate variants with allele frequencies from gnomAD and 1000G data sets. A pooled global prevalence estimate was generated using the Hardy-Weinberg equation. In addition, we estimated the prevalence for 8 separate ethnicities.
Results: 1,003 abstracts were screened and 12 studies were included, reporting population prevalences ranging from 0.4 to 135 per 100,000. Meta-analysis of previous data gave an estimate of 5.54 per 100,000 (95% CI 5.45–5.63).
787 unique variants in ATP7B were identified. 569 were classified as disease-causing variants, of which 539 were categorised as pathogenic after excluding missense mutations likely to be tolerant by SIFT/Polyphen-2 analysis. 155 mutations had been identified in gnomAD. Based on these allele frequencies, the overall prevalence of WD was 13.90 per 100,000 (95% CI 12.63–15.31). East Asian ethnicity had the highest estimated prevalence (37.56 per 100,000 (95% CI 28.23–50.09)) compared to only 1.75 per 100,000 (95% CI 1.00–3.00) in the African-American population.

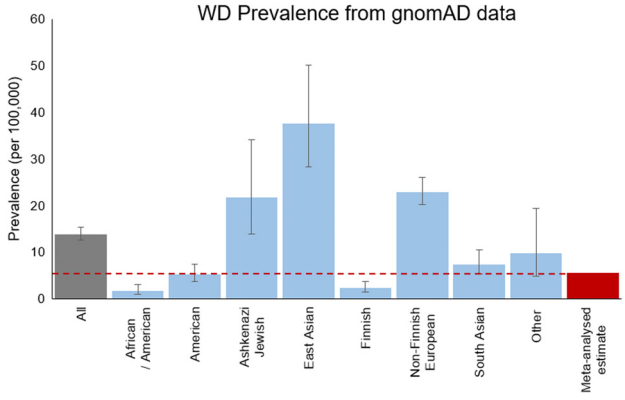

Figure: Estimated prevalence of WD by ethnicity as calculated from gnomAD allele frequency data (blue, error bars indicate 95% CI) compared to meta-analysis of current literature (red).

Conclusion: These data provide the first global prevalence estimate of Wilson disease in addition to an unbiased description of the multi-ethnic risk. This has implication for genetic counselling and clinical suspicion of the disorder across ethnicities.

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Contemporary practice patterns and outcomes after transjugular intrahepatic portosystemic shunt placement: A multicenter U.S. experience of 1146 patients

J. Boike[1], J. Ge[2], M. German[3], N. Jest[4], G. Morelli[4], E. Spengler[3], A. Said[3], A. Lee[5], A. Hristov[5], K.P. Kolli[6,7], J. Lai[8], A. Desai[9], S. Junna[10], B. Pokhrel[11], T. Couri[12], S. Paul[13], C. Frenette[14], N. Christian-Miller[14], M. Laurito[15], E. Verna[16], U. Rahim[17], A. Goel[17], A. Das[18], S. Pine[1], D. Gregory[1], L. Vanwagner[1]. *[1]Northwestern University Feinberg School of Medicine, Gastroenterology & Hepatology, Chicago, United States; [2]University of California San Francisco, Medicine, San Francisco; [3]University of Wisconsin Hospital, Department of Internal Medicine, Division of Gastroenterology, Madison, United States; [4]University of Florida, Division of Gastroenterology, Hepatology and Nutrition , Gainesville, United States; [5]University of Wisconsin Hospital, Internal Medicine, Madison, United States; [6]University of California San Francisco, Radiology, San Francisco, United States; [7]University of California San Francisco, Department of Radiology and Biomedical Imaging, San Francisco, United States; [8]University of California San Francisco, Medicine, Division of Gastroenterology, San Francisco, United States; [9]University of Arizona, Thomas D. Boyer Liver Institute, Division of Gastroenterology and Hepatology, Tucson; [10]University of Arizona, Department of Internal Medicine, Tucson, United States; [11]University of Arizona, Division of Gastroenterology and Hepatology, Tucson, United States; [12]University of Chicago, Medicine, Chicago, United States; [13]University of Chicago, Division of Gastroenterology and Hepatology, Chicago, United States; [14]Scripps Clinic, Scripps Center for organ Transplantation, La Jolla, United States; [15]Columbia University, Department of Liver Transplant and Clinical Research Center, New York, United States; [16]Columbia University, Department of Gastroenterology, New York, United States; [17]Stanford University Medical Center, Division of Gastroenterology and Hepatology, Palo Alto, United States; [18]Northwestern University Feinberg School of Medicine, Chicago, United States*
Email: justinboike@gmail.com

Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for complications of portal hypertension but is associated with risk of hepatic decompensation. Prior data have demonstrated 30-day survival ranging between 46%–88% but these studies have been limited to single center experience and included non-contemporary experience. We aimed to assess contemporary practice patterns and outcomes following TIPS placement among a multi-center sample of patients with cirrhosis in the United States.

Methods: This was a multi-center retrospective cohort study of all patients with cirrhosis who underwent TIPS placement from 2010 through 2015 with outcomes through 2016 across nine tertiary academic medical centers. Kaplan-Meier estimates with log rank test were used to estimate overall and transplant-free survival across quartiles of model of end-stage liver disease (MELD) score. Patients were censored at date of death, transplantation, or last follow-up.

Results: TIPS recipients (n = 1146) were mean age of 57 (standard deviation 9.9) years old, 61% male, 92% Caucasian and 84% non-Hispanic. Mean MELD score was 16 (SD 6.6) and median 15 (range 6.4–58.5); 34% of recipients had alcohol-induced cirrhosis, 30% Hepatitis C, 20% non-alcoholic fatty liver disease, and 16% other. Indications for TIPS were ascites (40%), variceal hemorrhage (31%), combination of ascites and variceal bleeding history (10%), hepato-hydrothorax (6%), treatment of portal vein thrombosis (5%), and other (7%). Covered stents were used in 89%, revision was required in 31% and liver transplantation subsequently performed in 21% of patients. Transplant-free survival at 30, 90, and 365 days was 81%, 70%, 54% with a mean survival of 2.7 years. Increasing MELD quartiles above the median was inversely associated with 30 and 90-day survival (Figure 1a, p = 0.003). After 90 days, the probability of survival was significantly improved for those with MELD scores less than 19 compared to those in highest MELD quartile (Figure 1b, p < 0.0001).

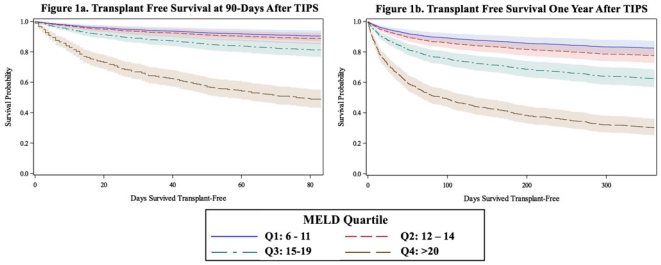

Figure: Kaplan-Meier curves with 95% confidence intervals of transplant-free survival for MELD quartiles at 90-days after TIPS (1a) and one year after TIPS (1b).

Conclusion: In a large U.S. multicenter cohort of TIPS recipients, 30-day and 90-day survival is excellent in recipients with MELD less than 19. These findings provide the liver community with important information to assist in the management of portal hypertensive complications in patients with cirrhosis and challenge the historical MELD cutoff of 15 for undergoing TIPS.

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Early-TIPS improves survival in cirrhotic patients with high-risk varical bleeding: Results of a China multicenter observational study

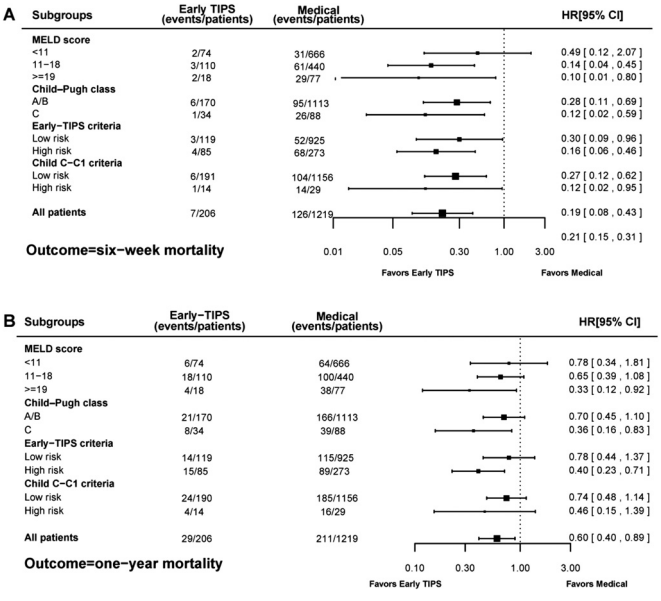
Y. LV[1], L. Zuo[1], X. Zhu[2], J. Zhao[3], H. Xue[4], Z. Jiang[5], Y. Zhuge[6], C. Zhang[7], J. Sun[8], P. Ding[9], W. Ren[10], Y. Li[11], K. Zhang[12], W. Zhang[13], C. He[1], J. Zhong[2], Q. Peng[14], F. MA[4], J. Luo[5], M. Zhang[6], G. Wang[7], M. Sun[11], J. Dong[15], W. Guo[1], W. Bai[1], K. Li[1], J. Tie[1], H. Chen[1], Q. Wang[1], H. Liu[1], J. Niu[1], Z. Wang[1], B. Luo[1], X. Li[1], Y. Zhu[1], Z. Yin[1], D. Fan[16], G. Han[1]. *[1]National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Department of Liver Diseases and Digestive Interventional Radiology, Xi'an, China; [2]The First Affiliated Hospital of Nanchang University, Department of Gastroenterology and Hepatology, Nanchang, China; [3]The Southern Medical University, Department of Interventional Radiology, Guangzhou,, China; [4]First Affiliated Hospital of Xi'an Jiaotong University, Department of Gastroenterology, Xi'an, China; [5]The Third Affiliated Hospital, Sun Yat-sen University, Department of Radiology, Guangzhou, China; [6]Affiliated Drum Tower Hospital of Nanjing University Medical School, Department of Gastroenterology, Nanjing, China; [7]Shandong Provincial Hospital affiliated to Shandong University, Department of Gastroenterology, Jinan; [8]The First Affiliated Hospital, School of Medicine, Zhejiang University, Department of Hepatobiliary and Pancreatic Interventional Center, Hangzhou, China; [9]The First Affiliated Hospital of Zhengzhou University,, Department of Vascular and Endovascular Surgery, Zhengzhou, China; [10]The First Affiliated Hospital of Xinjiang Medical University, Department of Interventional Radiology, Urumqi, China; [11]The Second Affiliated Hospital of Kunming University, Department of Interventional Radiology, Kunming, China; [12]Henan Provincial People's Hospital, Interventional Therapy Center, Zhengzhou, China; [13]The First Affiliated Hospital of Zhengzhou University, Department of Radiology, Zhengzhou, China; [14]The Southern Medical University, Department of Interventional Radiology, Guangzhou, China; [15]Henan Provincial People's Hospital, Interventional Therapy Center, Henan, China; [16]National Clinical Research Center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, State Key Laboratory of Cancer Biology, Xi'an, China*
Email: hangh@fmmu.edu.cn

Background and Aims: Early TIPS has been shown to improve survival in high-risk patients (Child B + active bleeding at endoscopy or Child C10–13, early-TIPS criteria) with cirrhosis and acute variceal bleeding (AVB).However, it has been suggested that early-TIPS criteria may overestimate the risk in a significant proportion of patients and

the survival benefit conferred by early TIPS in such patients has been questioned. Alternative criteria have been proposed to refine the criteria to identify candidates for early-TIPS, such as model for end-stage liver disease (MELD) score ≥19 (MELD19 criteria) and Child-Pugh class C with plasma level of creatinine ≥1 mg/dl (ChildC–C1 criteria). The present study aimed to evaluate the role of early TIPS in a large cohort of patients with AVB to validate these systems of risk analysis

Method: A total 1425 cirrhotic patients (90% Child A/B) with AVB who received standard treatment (medical group, n = 1219), or early TIPS (placed within 72 hours from admission, n = 206) and had no exclusion criteria (HCC beyond Milan, age >75, creatinine ≥3 mg/dl, complete PVT or Child >13) were retrospectively included from 12 academic hospitals in China from 2010 to 2016. Fine and Gray competing risk analysis were used to compare the outcomes between early-TIPS group and medical group after adjusting for important baseline characteristics or by using propensity score.

Results: Among 1425 patients with AVB, the 6-week and 1-year mortality were 3.4% and 14.1% in early-TIPS group versus 14.1% and 17.3% in medical group, respectively. Among 95 (7%) patients classified as high risk by the MELD19 criteria, early-TIPS group had a lower risk of mortality in both at 6 weeks (11.1% *vs.* 37.7%, adjust HR = 0.10; 95% CI: 0.01–0.80) and 1 year (22.2% *vs.* 49.4%, adjust HR = 0.33; 95% CI: 0.12–0.92). Similar results were observed among the 358 (25%) patients classified as high risk by the early TIPS criteria (4.7% *vs.* 24.9% at 6-week and 17.6% *vs.* 32.6% at one year, p < 0.001). Among the 43 (3%) patients classified as high risk by the ChildC–C1 criteria, early-TIPS group had a lower risk of 6-week mortality (7.1% *vs.* 48.3%, adjust HR = 0.12; 95% CI: 0.02–0.95) but similar risk of 1-year mortality (28.6% *vs.* 55.2%, adjust HR = 0.46; 95% CI: 0.15–1.39) compared to medical group.



Conclusion: Early-TIPS improves both short and long term survival in high risk variceal bleeder identified by MELD19 criteria and early-TIPS criteria but only short-term survival per ChildC-C1 criteria.

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Resistance training improves muscle size and muscle strength in liver cirrhosis – a randomized controlled trial

L. Aamann[1], G. Dam[1], M. Borre[1], A. Drljevic-Nielsen[2], K. Overgaard[3], H. Andersen[4], H. Vilstrup[1], N.K. Aagaard[1]. *[1]Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; [2]Aarhus University Hospital, Department of Radiology, Aarhus, Denmark; [3]Aarhus University, Department of Public Health - Sport Science, Aarhus, Denmark; [4]Aarhus University Hospital, Department of Neurology, Aarhus, Denmark*
Email: luise.aamann@gmail.com

Background and Aims: Sarcopenia in liver cirrhosis leads to diminished muscle strength and quality of life (QoL) and increases mortality. Resistance training and adequate protein intake reduce muscle wasting and improve physical performance in other chronic diseases. We evaluated the effect of resistance training on muscle size and strength, physical performance and QoL in cirrhotic patients on a standard high protein diet.

Method: Thirty-nine patients (exercise n = 20, control = 19) with Child Pugh A/B cirrhosis were allocated to resistance training in groups of five or a control group. A dietitian guided all patients. If recorded daily protein consumption was less than 1.2 of protein/kg/day, supplements were provided.

The exercise group conducted supervised resistance training one hour three times weekly for 12 weeks. Muscle cross sectional area (CSA) was measured by magnetic resonance imaging of m. quadriceps (scan at 60% of femur length) and muscle strength by isokinetic knee extension peak torque at velocity of 90 degrees/sec. The short form questionnaire (SF-36) and 6-minute walk test (6MWT) tested QoL and performance. Outcomes were assessed at baseline and follow-up by blinded investigators.

Results: Thirty-five patients completed the study (exercise n = 19, control = 15). Protein intake including supplements was equal in both groups.

In the exercise group, CSA of m. quadriceps increased by 616 mm^2 (5,847 mm^2 to 6,462 mm^2; ±398SD; p < 0.001), compared to 92 mm^2 (5,585 mm^2 to 5,677 mm^2; ±453SD; p = 0.45) in controls. At study end, the exercise group had a higher gain in CSA of 524 mm^2 (95% CI 222–826) compared to controls (p < 0.001).

Correspondingly, the peak torque increased in the exercise group by 15 Nm (119–134 Nm; ±16SD; p < 0.001) versus controls, who increased by 4 Nm (106–110 Nm; ±14SD; p = 0.30). Thus, the exercise group had a strength gain 11 Nm (95% CI: 0–22) greater compared to controls (p = 0.05).

The exercise group improved the mental component score (SF-36) by 4.1 (49.9–54.0; ±6.2SD; p = 0.01) and 6MWT by 32 m (509–541 m; ±42SD, p = 0.005), though not significantly different from controls, who also improved but to a lesser degree.

Conclusion: Resistance training improved muscle size and muscle strength in patients with liver cirrhosis compared to controls. Physical performance and mental component score (SF-36) improved within the exercise group. The results regarding resistance training are novel and readily applicable in the rehabilitation of patients with liver cirrhosis.

Clinical developments in metabolic and rare disease

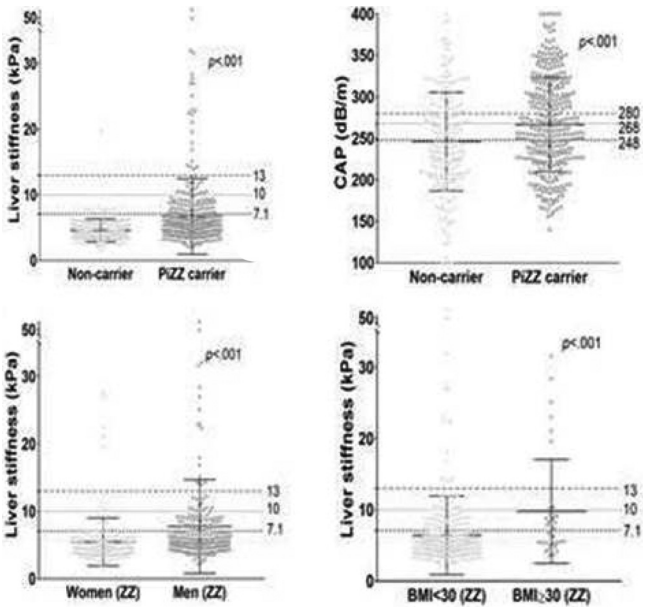
PS-142

Liver fibrosis and metabolic alterations in adults with homozygous alpha1-antitrypsin deficiency (PiZZ genotype)

K. Hamesch[1,2], V. Woditsch[1], M. Mandorfer[3], L.S. Moeller[4], Vítor Pereira[5], M.P. Delgado[6], M.C. Reichert[7], C.V. Heimes[8], J. Voss[8], I. Spivak[8], N. Gueldiken[8], A. Arslanow[7,9], B. Schaefer[10], H. Zoller[10], E. Aigner[11], T. Reiberger[3], W. Martin[12], B. Siegmund[12], Y. Eray[13], B. Danilo[14,15], J. Stolk[16], W. Gleiber[17], V. Knipel[18], W. Windisch[18], R. Bals[7], A.R. Koczulla[19], M. Miravitlles[20], S. Janciauskiene[21], J. Genesca[6], F. Lammert[7], M. Trauner[3], A. Krag[4], C. Trautwein[8], P. Strnad[2,8]. *[1]University Hospital RWTH Aachen, Medical Clinic III, Aachen, Germany; [2]Coordinating Center for Alpha1-Antitrypsin Deficiency-Related Liver Disease of the European Reference Network (ERN) "Rare Liver" and the European Association for the Study of the Liver (EASL) Registry Group "Alpha1-Liver", Germany; [3]Medical University Vienna, Clinic for Gastroenterology und Hepatology, Austria; [4]Odense University Hospital, Department of Gastroenterology and Hepatology, Denmark; [5]Centro Hospitalar do Funchal, Centro Hospitalar do Funchal, Madeira, Portugal; [6]Vall d'Hebron Hospital, Clinic for Gastroenterology und Hepatology, Barcelona, Spain; [7]Saarland University Medical Center, Department of Internal Medicine II, Germany; [8]University Hospital Aachen, Medical Clinic III, Aachen, Germany; [9]University Hospital Mainz, Department of Gastroenterology, Germany; [10]Medical University Innsbruck, Medical University Innsbruck, Austria; [11]Salzburg University Hospital, Salzburg University Hospital, Austria; [12]Charité Berlin, Center for Internal Medicine, Germany; [13]Medical Care Centre, Dr Stein and Colleagues, Medical Care Centre, Dr Stein and Colleagues, Germany; [14]University Hopsital Aachen, Department of Psychiatry, Psychotherapy and Psychosomatics, Aachen, Germany; [15]Jülich-Aachen Research Alliance, JARA-BRAIN, Germany; [16]Leiden University Medical Center, Clinic for Pulmonology, Belgium; [17]University Hospital Frankfurt, Clinic for Pulmonology, Germany; [18]Clinic Cologne-Merheim, Clinic for Pulmonology, Germany; [19]Marburg University Hospital, Clinic for Pulmonology, Germany; [20]Vall d'Hebron Hospital, Clinic for Pulmonology, Barcelona, Spain; [21]Medical University Hannover, German Center for Lung Research (DZL), Germany*
Email: vwoditsch@ukaachen.de

Background and Aims: Alpha1-antitrypsin deficiency (AATD) is among the most common genetic disorders but the liver phenotypes in adults remain poorly characterized. Therefore, we conducted a case-control study comparing adult carriers of the classical homozygous Z mutation ('PiZZ" genotype) with non-carriers.

Method: In cooperation with patient organizations and specialized respiratory physicians, we recruited 403 adults with the PiZZ genotype from Germany, Austria, Denmark, Portugal, Spain, Belgium, and the Netherlands (mean age 54 years, 45% female, mean BMI 24.8 kg/m^2) as well as 234 non-carriers without AAT mutation. Participants underwent a thorough clinical and laboratory workup to exclude hepatic comorbidity and to assess pulmonary symptoms. FibroScan determined liver fibrosis via liver stiffness measurement (LSM) and liver steatosis via controlled attenuation parameter (CAP). Data were adjusted for age, sex, BMI, diabetes mellitus and alcohol consumption.



Results: Serum liver enzymes (ALT, AST, GGT, and ALP) were mostly within the normal range, but significantly higher in PiZZ carriers compared to non-carriers. Significant liver fibrosis (LSM ≥ 7.1 kPa) was observed in 24% of PiZZ subjects (95/403), whereas advanced liver fibrosis (LSM ≥ 10.0 kPa) was present in 13.2% PiZZ carriers (53/403) and in 1.3% of non-carriers (OR = 18.9 [4.4–80.3]). Severe liver steatosis (CAP ≥ 280 dB/m) was detected in 39% of PiZZ patients (157/403) vs. 31% of non-carriers (OR = 2.1 [1.4–3.3]). Likewise, PiZ-overexpressing mice developed hepatic steatosis. Lower serum triglyceride, VLDL, and LDL cholesterol levels detected in PiZZ patients indicated impaired hepatic lipid secretion. The observed metabolic alterations and increased liver fibrosis/steatosis were also detected, when only patients without AAT augmentation therapy were considered. Moreover, the presence of liver fibrosis or steatosis was not associated with the severity of lung disease (COPD assessment test or need for long-term oxygen therapy). Several demographic and laboratory parameters discriminated between PiZZ carriers with and without significant liver fibrosis. Using a machine-learning algorithm, a score consisting of gender, BMI, GGT and platelet count predicted the presence of significant liver fibrosis with 85% accuracy (AUROC 0.77). As only 45% of PiZZ adults receive regular assessment of liver enzymes, this score might help to determine which patients deserve further hepatologic workup.

Conclusion: This study defines the liver phenotype of adult PiZZ carriers and uncovers associated metabolic alterations. Together with the identified predictors, these findings facilitate the hepatologic assessment and counseling of PiZZ patients.

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EXPLORE: A prospective, multinational natural history study of patients with acute hepatic porphyria with recurrent attacks

L. Gouya[1], J. Bloomer[2], M. Balwani[3], D.M. Bissell[4], D. Rees[5], U. Stölzel[6], J. Phillips[7], R.K. Kauppinen[8], J.L. Langendonk[9], R. Desnick[3], J.C. Deybach[1], H. Bonkovsky[10], C. Parket[7], H. Naik[3], M. Badminton[11], P. Stein[5], E. Minder[12], J. Windyga[13], P. Martasek[14], M.D. Cappellini[15], P. Ventura[16], E. Sardh[17], P. Harper[18], S. Sandberg[19], A. Aarsand[19], F. Alegre[20], A. Ivanova[21], S. Rock[22], A. Chan[22], W. Querbes[22], C. Penz[22], A. Simon[22], K. Anderson[23]. *[1]Centre Francais des Porphyries, Centre de Référence Maladies Rares Porphyries, Colombes, France; [2]University of Alabama; [3]Icahn School of Medicine at Mount Sinai; [4]University of California; [5]King's College Hospital; [6]Klinikum Chemnitz; [7]University of Utah; [8]University Hospital of Helsinki; [9]Erasmus Medical Center; [10]Wake*

Forest University; [11]University Hospital of Wales; [12]Stadtspital Triemli; [13]Instytut Hematologii i Transfuzjologii; [14]Univerzita Karlova v Praze; [15]University of Milan; [16]Università degli Studi di Modena e Reggio Emilia; [17]Karolinska University Hospital, Karolinska Institute; [18]Karolinska University Hospital; [19]Norwegian Porphyria Centre (NAPOS); [20]Clinica Universidad de Navarra; [21]St. Ivan Rilski University Hospital; [22]Alnylam; [23]University of Texas Medical Branch
Email: srock@alnylam.com

Background and Aims: Acute Hepatic Porphyrias are rare, often misdiagnosed genetic diseases caused by a mutation in aminolevulinic acid synthase 1 enzyme responsible for heme synthesis. This results in the accumulation of neurotoxic heme intermediates, aminolevulinic acid and porphobilinogen that can cause life-threatening attacks and chronic, debilitating symptoms due to injury to the nervous system. The most debilitating and frequent symptom during attacks is severe neurovisceral pain, most often in the abdomen, back, or limbs. Other common attack manifestations include nausea, fatigue, hypertension, tachycardia, motor weakness, and hyponatremia. Patients experiencing attacks often require urgent medical care. Chronic symptoms, most commonly pain, nausea, and fatigue, also occur in most patients and often contribute to a high disease burden and poor quality of life. We will be presenting updated ≥12-month data.
Method: EXPLORE is a prospective, international, observational study characterizing the natural history and clinical management of patients with hepatic porphyrias with recurrent attacks (≥3 attacks/year) or who receive prophylactic treatment to prevent attacks. Patient medical history, physical examination and porphyrin biomarkers, along with questionnaires on porphyria activity were collected.
Results: 112 patients enrolled from 13 countries and were followed for 12 months. Mean patient age is 39 years, with 89% female, and 93% with AIP, 4% variegate porphyria, and 3% hereditary coproporphyria. Patients reported 9.3 attacks in the 12 months prior to the study, with pain being the most common symptom, occurring in 99% of attacks. Mean attack duration was 7 days. Chronic symptoms were reported by 65% of patients, with pain being the most frequent symptom. On study annualized attack rate was 4.9 attacks/person, of which 77% required treatment at a healthcare visit or with hemin. For those patients on hemin prophylactically, attacks occurred with a mean attack rate per person-year of 4.0. Mean ALA and PBG levels at screening (during non-attack) were markedly increased to 8 times and 20 times the upper limit of normal, respectively.
Conclusion: EXPLORE, the first international natural history study in patients with hepatic porphyria and recurrent attacks, demonstrates that patients suffer from attacks and chronic symptoms. Given morbidity and mortality, there remains an unmet need for novel therapies to prevent attacks and treat chronic symptoms.

PS-144
Effect of sebelipase alfa on liver parameters over 96 weeks in a diverse population of children and adults with lysosomal acid lipase deficiency

B. Burton[1], A.C. Sanchez[2], M. Kostyleva[3], K. Allen[4], F. Abel[5]. *[1]Ann and Robert H. Lurie Children's Hospital, Chicago, United States; [2]Hospital Infantil de México Federico Gómez, Mexico City, Mexico; [3]Russian Children's Clinical Hospital, Moscow, Russian Federation; [4]Alexion Pharmaceuticals, Inc., New Haven, United States; [5]Alexion Pharmaceuticals, Inc., Zurich, Switzerland*
Email: bburton@luriechildrens.org

Background and Aims: Lysosomal acid lipase deficiency (LAL-D) is a rare, progressive disease characterized by accumulation of cholesteryl esters and triglycerides in the liver that leads to dyslipidemia, hepatomegaly, and liver cell damage. Sebelipase alfa (SA) is a recombinant human LAL indicated for the treatment of LAL-D.

Characteristic	Baseline	Week 96	% Change from baseline
ALT, U/L	63.5	34.0	−44.4
ALT >1.5xULN, n (%)	18/31 (58)	5/27 (19)	
AST, U/L	65.5	42.0	−38.4
AST >1.5xULN, n (%)	15/31 (48)	2/27 (7)	
UK-MELD score	46.5	45.5	−0.6
Fibrosis, n (%)*	20/30 (67)	12/17 (71)	
Cirrhosis, n (%)*	8/30 (27)	4/17 (24)	
Liver volume, MN	1.4	1.2	−17.6
Liver fat content, %	8.1	6.5	−14.9
Spleen volume, MN	2.6	2.2	−16.5

n = 31, unless otherwise noted; results are medians. MN = multiples of normal. *Fibrosis = Ishak score of 1–4; cirrhosis = Ishak score of 5–6.

Method: In this multicenter, open-label study, eligible patients >8 months of age were given SA 1 mg/kg by IV infusion every other week for up to 96 weeks. Dose escalation to 3 mg/kg every other week and subsequently to 3 mg/kg weekly was allowed for patients who met protocol-defined criteria; dose reductions for tolerability were permitted to 0.35 mg/kg every other week. Reported here are effects on liver parameters at 96 weeks of SA exposure.
Results: A total of 31 patients were enrolled; median age was 12 y (range 3–55 y). Two patients (6%) had a prior liver transplant. No inferential statistical analyses were conducted as part of this study. Clinical characteristics at Baseline and Week 96 are provided in the table. Marked reductions in ALT and AST were observed. Liver fibrosis improved or did not progress in 7 of 13 patients (54%) with pairwise samples at Baseline and Week 96 and with Baseline Ishak stage of 0–5. Three patients had a ≥1-point reduction in Ishak stage, including 2 patients who had a ≥2-point reduction. One of 3 patients with Baseline stage of 6 and a pairwise sample at Week 96 improved to stage 2. SA was generally well tolerated. Most adverse events (AEs) were mild to moderate in severity. Three patients (10%) experienced infusion-associated reactions that were at most mild (n = 2) or moderate (n = 1) in severity. There were no discontinuations due to AEs. Two patients (6%) were positive for anti-drug antibodies on 1 occasion each; neither developed neutralizing antibodies.
Conclusion: Long-term treatment with SA was well tolerated and resulted in sustained improvements in markers of liver injury in this diverse population of patients with LAL-D.

PS-145
Autologous cell/gene therapy approach of hemophilia B using patient specific induced Pluripotent Stem Cells

E. Luce[1,2,3], C. Steichen[1], M. Antonietta[1], S. Goulinet[1], T. Lambert[4], A. Weber[1], T.H. Nguyen[5], O. Christophe[6], A. Dubart-Kupperschmitt[1]. *[1]INSERM, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France; [2]Université Paris-Sud, 94800 Villejuif, France; [3]Département Hospitalo-Universitaire Hépatinov, Hôpital Paul Brousse, Villejuif, F-94800, France; [4]Centre de Référence pour le Traitement des Hémophiles, Hôpital de Bicêtre, F-94276, France; [5]INSERM Unité Mixte de Recherche (UMR_S) 1064, CHU Hôtel Dieu, Nantes, F-44093, France; [6]INSERM Unité Mixte de Recherche (UMR_S) 1176, Hôpital de Bicêtre, Kremlin-Bicêtre, F-94276, France*
Email: anne.dubart@inserm.fr

Background and Aims: Hemophilia B (HB) is a genetic disorder due to an impaired activity of clotting factor IX (FIX), synthesized by hepatocytes. Current treatment based on regular intravenous injections of FIX is very restrictive, costly and only palliative. Gene therapy trials show promising results but their long-term efficacy is still unknown. It is therefore important to explore other therapeutic strategies. This project thus aims to bring a proof of concept for autologous cell/gene therapy of inherited liver diseases by transplanting hepatocytes differentiated from genetically corrected patient-specific induced pluripotent stem cells (iPSCs).

Method: We reprogrammed skin fibroblasts from a severe hemophilia B patient (FIX activity <1%) into iPSCs. Using the CRISPR/Cas9 technology, we then targeted the genomic insertion of a cassette including the hepatic specific apolipoprotein AII (*APOAII)* promoter driving the expression of a *F9* mini-gene. Non-corrected and corrected iPSCs were differentiated into hepatocytes in 2D cultures and in 3D spheroids to study the expression of *F9* mRNA.
Results: HB patient-specific fibroblasts were reprogrammed and one iPSC clone was deeply characterized for self-renewal and pluripotency. Karyotype of the iPSCs was normal and DNA sequencing confirmed the presence of the patient's mutation. CRISPR/Cas9 technology allowed accurate monoallelic correction at the targeted *AAVS1* safe harbor locus. The corrected or non-corrected iPSCs were differentiated into hepatocytes. Due to the promoter used, the *F9* mRNA expressed by the therapeutic cassette is detected earlier during differentiation compared to endogenous *F9* mRNA detected later in the non-corrected clone. Q-RT-PCR confirmed a higher expression of *F9* mRNA in the corrected clone in both 2D and 3D conditions.
Conclusion: We reprogrammed skin fibroblasts from a severe HB patient. HB-iPSCs were genetically corrected by targeted insertion of a therapeutic cassette using CRISPR/Cas9 technology. Corrected and non-corrected iPSCs were differentiated into hepatocytes in both 2D and 3D culture conditions. We detect the *F9* mRNA from the therapeutic cassette at early stages of differentiation compared to the endogenous one. Quantitative RT-PCR confirmed the higher level of FIX mRNA in corrected cells. The therapeutic efficacy, namely the FIX activity, of the correction approach is currently assessed *in vitro*, and *in vivo*, by transplanting corrected iPSC-derived HLCs into a HB mouse model.

PS-146
Low density lipoprotein receptor-deficient hepatocytes differentiated from induced pluripotent stem cells allow familial Hypercholesterolemia modelling, CRISPR/Cas-mediated genetic correction, and productive hepatitis C virus infection

Jérôme Caron[1,2,3], Véronique Pène[4], L. Tolosa[5], M. Villaret[4], E. Luce[6], Angélique Fourrier[7], S. Sami[8], E. Bruckert[8], María José Gómez-Lechón[5,9], T.H. Nguyen[7], A.R. Rosenberg[2], A. Weber[2], A. Dubart-Kupperschmitt[6].
[1]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, France; [2]UMR_S1193, Université Paris-Sud, Hôpital Paul Brousse, Villejuif, F-94807, France; [3]DHU Hepatinov, Hôpital Paul Brousse, Villejuif, F-94807, France; [4]Université Paris Descartes, EA4474 "Hepatitis C Virology", Paris, France; [5]Unidad de Hepatología Experimental, Instituto de Investigación Sanitaria La Fe, Valencia, Spain; [6]INSERM, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France; [7]INSERM UMR1064, Nantes, France; [8]Service d'Endocrinologie Métabolisme, Hôpital Pitié-Salpêtrière Paris, F-75651, France; [9]CIBERehd, FIS, Barcelona, Spain
Email: anne.dubart@inserm.fr

Background and Aims: Familial Hypercholesterolemia type IIa (FH) is a liver genetic disorder caused by mutations in the Low Density Lipoprotein receptor (LDLR) and resulting in premature cardiovascular diseases. Hepatocytes are the only cells able to metabolize cholesterol into bile acids and are therefore the target for FH cell/gene therapy approaches but access to patient cells is restricted. Here, we investigated whether hepatocytes differentiated from induced pluripotent stem cells (iPSCs) from an FH-homozygous patient (FH-iHeps) could model the disease pathophysiology and be corrected by CRISPR/Cas9-mediated targeted recombination, and whether FH-iHeps and corrected iHeps (corr-FH-iHeps) were permissive to hepatitis C virus (HCV) infection.
Method: Using a non-integrative approach, we generated iPSCs from an LDLR-deficient (homozygous null mutation) FH-patient (FH-iPSCs). They were differentiated using a protocol recapitulating liver embryogenesis. For genetic correction, we constructed CRISPR/Cas9 and homologous recombination template plasmids targeting the *AAVS1* safe harbor genomic site and harbored the LDLR cDNA controlled by *apolipoprotein A2* promoter. Upon HCV inoculation, viral replication and production were quantified.
Results: FH-iHeps showed functional hallmarks of human hepatocytes and recapitulated the pathophysiology of FH characterized by an absence of LDLR expression and function. Genetically corrected FH-iPSCs showed monoallelic targeted integration, maintained pluripotency and a normal karyotype. Using the same protocol as for their uncorrected counterparts, we have differentiated them into functional iHeps (corr-FH-iHeps) where LDLR expression and function were restored and inducible by treatment with pravastatin, a lipid-lowering drug. Finally, we have inoculated both FH-iHeps and corr-FH-iHeps with cell-culture derived HCV particles and have demonstrated that they were as permissive to viral infection as primary human hepatocytes. Interestingly, virus production in FH-iHeps was significantly lower than in corr-FH-iHeps, indicating an indirect role of the LDLR in the viral morphogenesis steps rather than a direct one in the entry steps as previously suggested.
Conclusion: Our system provides a useful model for reassessing the controversial role of the LDLR in the HCV life cycle. It could also be used as a platform to screen drugs for treating dyslipidemia and it represents a novel approach to genetically correct metabolic diseases.

PS-147
ARO-AAT, a subcutaneous RNAi-based therapeutic for alpha-1 antitrypsin-related liver disease, demonstrates liver exposure-response and efficacy in preclinical studies

C. Wooddell[1], K. Blomenkamp[2], H. Chen[1], J. Griffin[1], R. Zhu[1], Q. Chu[1], H. Hamilton[1], J. Hegge[1], D. Christianson[3], Z. Li[1], J. Teckman[2], B. Given[3].
[1]Arrowhead Pharmaceuticals, Arrowhead Madison, Madison, United States; [2]Saint Louis University, Pediatrics, St. Louis, United States; [3]Arrowhead Pharmaceuticals, Arrowhead Pasadena, Pasadena, United States
Email: cwooddell@arrowheadpharma.com

Background and Aims: Alpha-1 antitrypsin (AAT) deficiency is an autosomal co-dominant genetic disorder. AAT is an abundant serum protein primarily synthesized in liver. The PiZ mutation results in mis-folded protein (Z-AAT) that accumulates as polymers in hepatocytes and can lead to fibrosis, cirrhosis and HCC. Preventing, slowing or reversing liver accumulation of mutant protein could alter the course of AATD-related liver disease (AATDLD). Aside from liver transplant, there are no treatment options for aggressive AATDLD. We previously described an intravenous RNA interference (RNAi)-based therapeutic that demonstrated proof of concept efficacy in the PiZ mouse model expressing human Z-AAT and deep knockdown (KD) in healthy volunteers and patients (Wooddell et al, AASLD 2016, Turner *et al*, EASL 2016). Here we describe a subcutaneous RNAi therapeutic with liver selectivity, ARO-AAT, dose-dependent liver exposure and AAT KD that results in decreased Z-AAT protein in PiZ mouse liver. We hypothesize that the pharmacokinetics and selectivity of ARO-AAT will allow low doses to progress into the clinic with deep and durable target KD.
Methods: Pharmacokinetics were evaluated in rats and NHP. Biodistribution was evaluated in rats. Serum AAT reduction was evaluated in NHP and PiZ mice. ARO-AAT liver exposure and efficacy of AAT mRNA and protein reduction were evaluated in PiZ mice (1, 2, 4 and 8 mg/kg). Efficacy of ARO-AAT for reduction of Z-AAT protein production and accumulation was evaluated in PiZ mice.
Results: ARO-AAT in rats demonstrated high tissue distribution with highest exposure in liver through day 16. Peak levels were measured at day 4. Kidney contained the 2nd highest levels, which were 8.7-fold less than in liver. Liver AAT mRNA reduction was observed in PiZ mice across all doses tested (1, 2, 4, and 8 mg/kg) and days measured (days 8, 15, 22, 29 and 43). PiZ mice given 8 injections (4 mg/kg), dosed every other week, had undetectable monomeric Z-AAT protein and significantly reduced polymer accumulation in liver compared to

untreated mice. Mean serum AAT KD of 89–91% persisted at least 7 weeks following a second dose of 3 mg/kg in NHP.

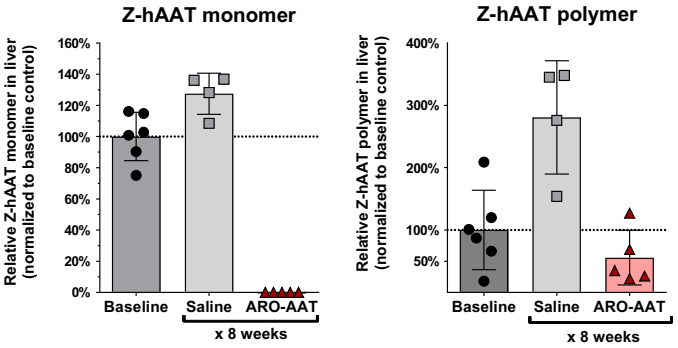


Figure: ARO-AAT reduces liver Z-AAT monomer and polymer content in PiZ mouse liver.

Conclusion: ARO-AAT, a new therapeutic candidate, selectivity targets the liver and reduces liver Z-AAT protein following multi-dose treatment. This subcutaneous RNAi therapeutic holds promise for treatment of patients with AATDLD.

PS-148

Gene therapy optimization for Wilson's disease

O. Murillo-Sauca[1], D. Moreno[1], C. Gazquez[1], M. Barberia[1], I. Cenzano[1], S.M. Solchaga[1], Iñigo Navarro[2], J.M. Prieto[3], R. Hernandez[1], G. González-Aseguinolaza[1,4]. *[1]Center for Applied Medical Research (CIMA)-University of Navarra, Gene Therapy, Pamplona, Spain; [2]University of Navarra, Chemistry and Edaphology, Pamplona, Spain; [3]Center for Applied Medical Research (CIMA)-University of Navarra, Pamplona, Spain; [4]Vivet Therapeutics, Paris, France*
Email: omurillo@unav.es

Background and Aims: Recently, we have demonstrated that an adeno-associated vector serotype 8 carrying the human ATP7B cDNA provides long-term correction of copper metabolism in Wilson's disease (WD) young male mice. However, the size of this vector genome (5.1 Kb) surpasses the optimal size of a packaged AAV genome representing a major drawback for its clinical application. Furthermore, the efficacy of this vector in female mice and in animals with advanced disease (12 weeks) is notably lower than in young male mice. In this work, our main objective was to develop an optimized version of the gene therapy vector for clinical use.
Method: To generate a smaller version of ATP7B, the first four metal binding sites (MBS) from the amino terminal region of the protein were deleted Δ57–486-ATP7B. An AAV vector expressing a mini ATP7B transporter under the control of a liver specific promoter was produced. Additionally, a recently developed synthetic AAV vector, AAV-Anc80, was used to limit the potential impact of preexisting immunity and to improve liver transduction. WD mice at different stages of the disease were treated and copper-related parameters, liver damage and additional parameters altered in WD disease were evaluated.
Results: The AAV vector expressing the mini-AP7B transporter showed a superior therapeutic efficacy in animals of both genders and in animals with advanced disease than the vector expressing the full-length protein. Moreover, we found that WD gene therapy, in addition to restore copper homeostasis and prevent liver damage, also significantly improved a number of additional parameters including cholestasis and haematological alterations observed in WD patients.
Conclusion: Our data demonstrate that gene therapy using an optimized gene therapy vector provides long-term correction of copper metabolism and additional pathological aspects associated with copper accumulation in WD animals independently of the gender and stage of the disease.

Clinical impact of HCV cure

PS-149

Disease outcomes after DAA-induced SVR: data from the resist-HCV cohort

V. Calvaruso[1], S. Petta[1], I. Cacciola[2], G. Cabibbo[1], C. Fabio[3], M.A. DI Rosolini[4], A. Davì[4], M.R. Cannavò[5], M. Russello[6], M.Di Stefano[7], G. Scifo[8], F. DI Lorenzo[9], P. Tullio[10], L.N. Larocca[11], A. Montineri[12], G. Fuduli[13], A. DI Giacomo[14], M. Cannizzaro[15], S. Madonia[15], A. Licata[16], G. Malizia[17], G. Alaimo[18], G. Bertino[19], B. Cacopardo[20], C. Iacobello[21], A. Averna[22], L. Guarneri[23], I. Scalisi[24], G. Mazzola[25], L. Mondello[26], P. Vincenzo[27], G. Squadrito[28], C. Camma[29], G. Raimondo[28], A. Craxi[29], V. DI Marco[29]. *[1]University of Palermo, Gastroenterology and Hepatology Unit, DIBIMIS, Palermo, Italy; [2]University of Messina, Internal Medicine and Hepatology Unit; [3]Ospedale Buccheri La Ferla, Palermo; [4]Ospedale di Modica, Modica; [5]Ospedale Nuovo Garibaldi, Catania; [6]Ospedale Nuovo Garibaldi Nesima, Catania; [7]Ospedale di Siracusa, Malattie Infettive, Siracusa; [8]Ospedale di Siracusa, Malattie Infettive; [9]Ospedale Civico "Di Cristina-Benfratelli", Palermo; [10]ARNAS, "Civico-Benfratelli" Hospital , Palermo; [11]Ospedale Ferrarotto, Malattie Infettive, Catania; [12]A.O.U. Policlinico-Vittorio Emanuele, U.O. of Infectious Diseases and Hepatology; [13]Ospedale di Comiso, Comiso; [14]Ospedale di Comiso; [15]Villa Sofia-Cervello Hospital, Internal Medicine, Palermo; [16]University of Palermo, Internal Medicine, Palermo; [17]Villa Sofia-Cervello Hospital, Gastroenterology Unit, Palermo; [18]Ospedale di Agrigento, Internal Medicine, Agrigento; [19]University of Catania, Internal Medicine, Catania; [20]Ospedale Nuovo Garibaldi Nesima, Malattie Infettive, Catania; [21]Ospedale Cannizzaro, Malattie Infettive, Catania; [22]Ospedale di Caltanissetta, malattie Infettive, Caltanissetta; [23]Po Nuovo Umberto I, Malattie Infettive, Enna; [24]Ospedale di Mazara del Vallo, Internal Medicine, Mazara del Vallo; [25]University of Palermo, Department of Sciences for Health Promotion "G. D'Alessandro", Palermo; [26]Ospedale Papardo , Malattie Infettive, Messina; [27]Ospedale sant'antonio trapani, Malattie Infettive, Trapani; [28]University of Messina, Internal Medicin and Hepatology Unit, Messina; [29]University of Palermo, Gastroenterology & Hepatology, Di.Bi.M.I.S., Palermo*
Email: vincenza.calvaruso@unipa.it

Background and Aims: Large scale, real life data on the long term course of liver disease after HCV clearance obtained with DAAs are still scanty, and the separate effects on hepatic and non-hepatic causes of death still unclear.
Methods: We evaluated 4,147 patients (mean age 65.7 ± 11.5 years, 57.6% males) included in the prospective RESIST-HCV cohort who started DAAs treatment in 22 Centres between March 2015 and April 2017. All patients were follow after SVR to register liver-related and unrelated outcomes. The primary endpoint was the evaluation of survival since starting DAAs. Cox regression analysis was used to assess the predictors of liver-related and unrelated death.
Results: Patients were observed for a median of 50 weeks (range 1–199), 934 (22.5%) had diagnosis of chronic hepatitis (F3 in >90%), 2851 (68.7%) had Child A cirrhosis and 362 (8.7%) had Child B cirrhosis. Overall, 3,766 patients (90.8%) achieved SVR while 381 patients (9.2%) were HCV-RNA positive at the last control. Fifty-five patients (1.3%) died during the observation: 25 of them died for liver related causes and 30 for unrelated causes (16: cardiovascular disease, 6: sepsis, 8: other). The lack of SVR was associated with an increased incidence of overall mortality in comparison to patients with SVR, (hazard ratio [HR] 28.9; 95%confidence interval [CI], 16.5–50.8; $p < 0.001$) and death from liver-related and unrelated causes (HR: 18.5, 95%CI:8.2–41.3; $p < 0.001$ and HR, 45.5; 95%CI: 19.3–107.4; $p < 0.001$ respectively). By multivariate Cox regression analysis lack of SVR (HR: 14.9, 95%CI: 6.3–35.1; $p < 0.001$) and Child B cirrhosis (HR:29.4, 95% CI:3.8–223.9; $p < 0.001$) were independently related with liver

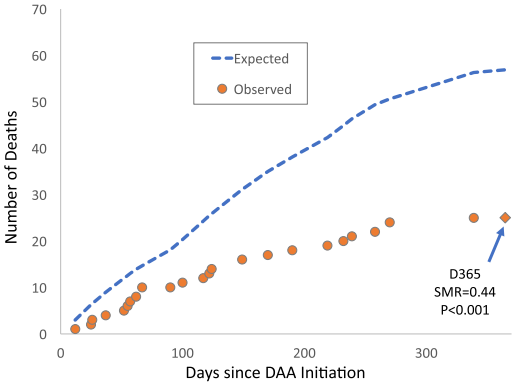
mortality. Independent predictors of liver-unrelated mortality were no SVR (HR: 41.77, 95%CI: 17.30–100.87; p < 0.001), Child B cirrhosis (HR: 3.00,95% CI:1.36–6.22; p = 0.006), BMI (HR:0.89, 95%CI:0.81–0.98, p = 0.023) and diabetes (HR: 2.38, 95%CI:1.13–5.00, p = 0.022)
Conclusions: In this real world setting using a variety of DAA regimens SVR reduced overall mortality and risk of liver-related and unrelated deaths at all stages of disease, nut mostly in Child A cirrhosis. The effect on cardiovascular deaths, which is evident also in the pre-cirrhotic stages deserves further follow up and investigation.

PS-150
Long-term impact of HCV eradication after all-oral therapy in patients with clinical significant portal hypertension
S. Lens[1], E. Alvarado[2], Z. Mariño[1], J. Martinez[3], M.-C. Londoño[1], E. Llop[4], J.I. Fortea[5], L. Ibañez[6], R. Bañares[6], A. Puente[5], A. Albillos[3], José L. C. Panero[4], X. Torras[2], A. Baiges[1], V. Hernandez-Gea[1], J. Bosch[7], C. Villanueva[2], X. Forns[1], J.-C. Garcia-Pagan[1]. *[1]Hospital Clinic, IDIBAPS, CIBERehd, University of Barcelona, Liver Unit, Spain; [2]Hospital Santa Creu i Sant Pau. CIBERehd., Gastroenterology Department, Spain; [3]Hospital Ramon y Cajal. Universidad de Alcalá. Madrid. CIBEREHD., Gastroenterology and Hepatology Department, Spain; [4]Hospital Universitario Puerta de Hierro, Majadahonda, CIBERehd., Liver Unit, Madrid, Spain; [5]Marqués de Valdecilla University Hospital.IDIVAL. Santander. CIBERehd., Digestive Diseases Department, Spain; [6]Hospital Gregorio Marañón. Madrid. CIBERehd., Liver Unit, Spain; [7]Switzerland*
Email: slens@clinic.ub.es

Background and Aims: Previous data from our group showed that clinical significant portal hypertension (CSPH, HVPG > 10 mmHg) persists 24 weeks after sustained virological response (SVR) in up to 78% of patients with HCV-related cirrhosis treated with all-oral antivirals. These patients remain at risk of decompensation. However, long-term hemodynamic data is not available in this population.
Method: Multicenter prospective study of patients with HCV-related cirrhosis and CSPH achieving SVR after all-oral antiviral therapy. Patients with CSPH 24 weeks after therapy underwent a new hemodynamic assessment 96 weeks after end of treatment (SVR24 and SVR96, respectively).
Results: 226 cirrhotic patients with CSPH at baseline (BL) were included, 176 remained with CSPH at SVR24 (Lens et al. Gastroent 2017); 56 of them have SVR96 data. Most patients (77%) were CTP-A; 48 (86%) had esophageal varices (EV; 39% large) and 19 (34%) previous liver decompensation (LD). BL-HVPG was 17.3 ± 4.3 mmHg. Overall, HVPG decreased overtime –2 ± 3.2 mmHg at SVR24 and –4.3 ± 3.6 mmHg at SVR96 (both, p < 0.01). A clinically relevant decrease (>20%) was observed in 18 (32%) patients at SVR24 and in 35 (62%) at SVR96. Nevertheless, 43 (76%) patients at SVR96 still had CSPH. Cumulative CSPH persistence was 76% at SVR24 and 59% at SVR96. Interestingly, HVPG increased between SVR24-SVR96 in 10% of patients (any risk factor??). Among the 43 patients with LSM at all time points (BL-LSM 31–16 kPa), LSM decreased overtime –5.7–12 at SVR24 and –8.6–13 kPa at SVR96 (both p < 0.01). Importantly, six out of 10 patients with LSM <13.6 kPa at SVR96 still had CSPH. All previously LD patients remained compensated except 3 patients. De novo LD occurred in 2 patients. In addition, EV developed in 1 patient and increased in size in 4 patients, all patients had CSPH.
Conclusion: SVR to all-oral antiviral regimens is associated with a progressive reduction in portal pressure in patients with CSPH at baseline. However, CSPH may persist in up to 59% of patients even in the long-term, indicating persistent risk of decompensation and EV development/progression. In addition, currently available LSM cut-offs are not reliable to rule out CSPH after SVR.

PS-151
Survival benefits of direct-acting antiviral therapy in patients with decompensated hepatitis C cirrhosis
W.R. Kim[1], A. Osinusi[2], A. Mannalithara[1], R.A. Schall[2], D. Brainard[3]. *[1]Stanford University, Division of Gastroenterology and Hepatology, Stanford, United States; [2]Gilead Sciences, Foster City, [3]Gilead Sciences, Gilead Sciences, Foster City, United States*
Email: wrkim@stanford.edu

Background and Aims: Current direct-acting antiviral (DAA) therapy for hepatitis C virus (HCV) infection leads to sustained virological response (SVR) in the vast majority of patients, even in those with decompensated cirrhosis. SVR in patients with decompensated cirrhosis has been associated with improvement in liver function; however, the extent to which DAA impacts on mortality remains to be determined. We analyse mortality in patients who participated in clinical trials evaluating sofosbuvir-based regimens in patients with decompensated HCV cirrhosis (GS-US-334-0125, SOLAR and ASTRAL studies), in comparison with mortality predicted by a survival model derived in untreated HCV patients.
Method: Observed incidence of death was obtained from GS-US-334-0125 study, the pre-transplant cohorts of the SOLAR-1 and -2 studies, and the ASTRAL-4 study. In determining expected mortality without DAA therapy in the study participants, a previously validated prediction model was applied to estimate survival probability of each individual patient up to one year. The model, consisting of age, MELD-Na, sodium, albumin, and hepatic encephalopathy (HE), had been derived in patients with hepatic decompensation awaiting liver transplantation in the pre-DAA era. We computed the standardized mortality ratio (SMR), with which the observed and expected numbers of deaths were compared from the start of DAA therapy.
Results: There was a total of 492 patients, whose median age was 58 years, MELD 12, sodium 137 mEq/l and albumin 2.9 g/dl. Ascites and HE were common (79% and 63%, respectively). Altogether, 411/479 (86%) patients achieved SVR12. During the follow up, there were 25 deaths within one year of DAA therapy start, including 15 in the SOLAR and 10 in the ASTRAL data; no deaths occurred in GS-US-334-0125. The number of observed deaths in the clinical trials closely followed the expected/predicted numbers early in the treatment course (Figure). Starting at 100 days after initiation of DAA, however, the observed number of deaths was statistically significantly smaller than expected (SMR = 0.54, 95% confidence interval [CI] = 0.30–0.98). All subsequent deaths occurred at a lower frequency than expected. The last (25th) death during the study period occurred on day 339, when the SMR had decreased to 0.44 (95% CI = 0.30–0.65), which remained unchanged at the end of the analysis (day 365).



Conclusion: DAA therapy in patients with decompensated HCV cirrhosis leads to significantly decreased mortality, which may be apparent as early as 100 days after the initiation of therapy with the risk of mortality decreasing to 44% of the expected by the end of the first year.

PS-152

IFN-free DAA treatment of cirrhotic HCV patients with or without history of HCC: a multicenter prospective trial in Italy

A. Sangiovanni[1], E. Alimenti[1], M. Barone[2], L.S. Belli[3], E. Biganzoli[4], G. Borgia[5], M. Brunacci[6], M. Brunetto[7], R. D'ambrosio[8], S. Fargion[9], R. Filomia[10], M. Gambato[11], R. Gattai[12], E.G. Giannini[6], S. Maimone[10], L. Marzi[13], F. Oliveri[7], G. Pellegatta[14], G. Raimondo[15], M.G. Rumi[16], F.P. Russo[11], I. Serio[17], N. Terreni[18], L. Valenti[19], E. Villa[13], P. Lampertico[20]. *[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Italy; [2]University of Bari, Gastroenterology Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), Italy; [3]ASST Grande Ospedale Metropolitano Niguarda, UOC Epatologia e Gastroenterologia, Italy; [4]IRCCS Istituto Nazionale Tumori, Unit of Medical Statistics, biometry and bioinformatics, Milano, Italy; [5]University of Naples 'Federico II, Department of Clinical Medicine and Surgery, Section of Infectious Diseases, Napoli, Italy; [6]University of Genoa, Gastroenterology Unit, Department of Internal Medicine, Genova, Italy; [7]University Hospital of Pisa, Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Pisa, Italy; [8]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milano, Italy; [9]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Internal Medicine and Metabolic Diseases, Milano, Italy; [10]University Hospital of Messina, Division of Clinical and Molecular Hepatology, Messina, Italy; [11]Padua University Hospital, Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology; [12]University Hospital of Pisa, Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses; [13]Azienda Ospedaliero-Universitaria Policlinico di Modena, Gastroenterology Unit; [14]University of Genoa, Gastroenterology Unit, Department of Internal Medicine; [15]University Hospital of Messina, Division of Clinical and Molecular Hepatology; [16]Ospedale San Giuseppe, University of Milan, Division of Hepatology; [17]University of Bologna, Department of Medical and Surgical Sciences; [18]Valduce Hospital, Division of Gastroenterology, Como, Italy; [19]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Internal Medicine and Metabolic Diseases; [20]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milano, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: Whether sustained virologic response (SVR) to Interferon (IFN) free direct antiviral agents (DAAs) therapy is associated with an increased risk of developing HCC is a matter of debate. Aim of this study was to evaluate whether the incidence of de novo or recurrent HCC increases after starting DAA treatment and which variables are associated with HCC development.

Method: In a multicenter prospective cohort enrolled between Jun. 2014 and Sept 2017, 1,030 consecutive HCV cirrhotic patients with no history of HCC (Group 1): 603 (59%) males, median age 66 years (22–85), and 122 consecutive patients with radiological CR to HCC treatment (Group 2): 83 (68%) males, median age 73 years (48–86) were enrolled and treated with IFN-free DAA. SVR was obtained in 955 (97%) in group 1, pending SVR in 42 cases, and in 112 (95%) in group 2, pending 6 cases. Time from last imaging and last HCC treatment, age, gender, Child, AFP, HCV GT, presence of undefined/non-malignant liver nodules, duration of DAA therapy, were considered. Hazard rate analysis on time was performed to assess instant HCC incidence and recurrence, comparing values across the entire follow-up with flexible non-parametric smoothing techniques and parametric survival. Multivariable Cox regression analysis was performed to assess the association of variables with HCC development and recurrence.

Results: In SVR patients, during a median follow-up of 62 wks (range 1–174) de novo HCC occurred in group 1 in 36 patients (10/93 with undefined/non-malignant nodules), corresponding to an annual incidence of 3.8%, and during a median follow up of 48 wks (range 1–116) HCC recurred in 33 in group 2, corresponding to an annual incidence of 32.7%. Looking to smoothed estimation, an underlying non monotonic trend was observed in both groups with a peak of HCC instant incidence at 47 wks in group 1 and at 30 weeks in group 2. By multivariable Cox regression models, the presence of undefined/non-malignant hepatic nodules (HR = 3.5 CI 1.7–7.3, p = 0.001, with a time dependent relation, and Child-Pugh (HR = 1.6, 95%CI 1.2–2.1, p < 0.001) were associated with de novo HCC incidence in group 1, while overall no variables showed evidence of association with HCC recurrence.

Conclusion: IFN-free DAA treatment of HCV cirrhotic patients allows, in SVR population, a progressive decrease of de novo and recurrent HCC incidence after a non significant increased number of HCC observed at 30 weeks after stating DAA in patients with history of previous HCC and at 47 weeks after starting DAA in patients without history of HCC. Presence of undefined/non-malignant liver nodules and Child-Pugh class are independently associated with de-novo HCC development, being the presence of undefined/non-malignant hepatic nodules associated with the increased number of HCC at 47 weeks.

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HCC recurrence under all-oral DAAs-based antiviral therapy in HCV-infected patients: data from Navigatore web platform

M. Gambato[1], F.P. Russo[1], S. Piovesan[2], A. Romano[3], A. Zanetto[1], G. Anastassopoulos[2], F. Capra[4], V. Paon[4], I. Franceschet[5], A. Carlotto[6], S. Storato[7], M. De Bona[8], P. Rovere[9], C. Manuppelli[10], M.T. Giordani[11], L. Lomonaco[12], P. Angeli[3], A. Alberti[2], P. Burra[1]. *[1]Multivisceral Transplant Unit and Gastroenterology, Padova University Hospital; [2]Department of Molecular Medicine, University of Padova; [3]Unit of Hepatic Emergencies and Liver Transplantation, University of Padova, Department of Surgery; [4]Internal Medicine, University of Verona, Italy; [5]Gastroenterology, Mestre Hospital (VE), Italy; [6]Department of Infectious Diseases, Schio (VI), Italy; [7]Negrar Hospital, Verona, Italy; [8]Gastroenterology of Feltre Hospital (BL), Italy; [9]Department of Infectious Diseases, Legnago Hospital (VR), Italy; [10]Department of General Medicine, San Martino Hospital (BL), Italy; [11]Department of Infectious Diseases, Vicenza Hospital, Italy; [12]Gastroenterology, Bussolengo Hospital (VR), Italy*
Email: martina.gambato@gmail.com

Background and Aims: Nowadays, using high effective and safe all-oral direct acting antivirals (DAAs), most cirrhotic patients can be cured. Unexpectedly, some studies reported high early hepatocellular carcinoma (HCC) recurrence rate after curative treatment (up to 30%), in HCC patients receiving antiviral therapy (AT). However, conflicting data still exists in this setting. We aimed to analyze HCC recurrence rate in a cohort of HCV-infected patients with prior HCC who underwent AT after achieving complete radiologic response.

Methods: HCV-infected patients with prior HCC who underwent AT between 01–2015 and 04–2017, included in the Navigatore web-based platform in Italy (>2000 participants), were considered for the study (n = 132). Clinical, virological and HCC-related features before starting AT and during the follow-up were registered. Patients treated with AT after LT (n = 23) or during the waiting list for LT (active HCC, n = 8) were excluded.

Results: One-hundred and one HCV-HCC patients who received AT after complete radiologic response were included (67% male, median age 68 years). Most of them (79%) were Child-Pugh (CTP) class A and median MELD was 9. They received different DAA regimens: 44% SOF/LDV, 22% SOF/RBV, 18% 3D, 11% SOF + DCV, 5% SOF + SMV, according to HCV genotype (65% G1) and clinical features. SVR12 was 91%. Baseline BCLC stage at HCC treatment was BCLC 0 in 37% and A in 63% with a median AFP of 11 ng/mL; 68% received resection/ablation and 32% TACE before starting AT. After a median follow-up of 22 months (IQR 15–27) since start DAA, the rate of HCC recurrence was

32.6% (33/101). The median time between the last radiological evaluation (no-active HCC) and AT was 2.5 months (IQR 1–5), with no difference between patients with HCC recurrence (H-R) compared to those without HCC recurrence (no H-R). Comparing the 2 groups (H-R vs no H-R) no difference was detected in term of CTP, MELD, APRI score, liver stiffness and BMI. The pattern of recurrence was: intrahepatic lesion (single nodule in 16/33, multifocal in 16/33) and extra-hepatic lesions in 1 patient who died. Nearly half of patients (16/33) received loco-regional treatment, 39% (13/33) resection, ablation or LT, 2/33 best supportive care and 2/33 are awaiting HCC treatment.

Conclusion: In this preliminary analysis, the rate of HCC recurrence in patients treated with DAAs was nearly 30%. Since the time between HCC eradication and DAAs starting was short, the real impact of DAAs on HCC natural course is still unclear. Full data analysis is still ongoing and will be presented at ILC2018.

PS-154

SVR is the strongest predictor of occurrence and recurrence of hepatocellular carcinoma in HCV cirrhotic patients after treatment with DAAs: a prospective multi-centric Italian study

A. Lleo[1], A. Aglitti[2], A. Ciancio[3], V. Di Marco[4], A. Aghemo[1], P. Lampertico[5], M. Brunetto[6], M.G. Zuin[7], P. Andreone[8], E. Villa[9], G. Troshina[3], V. Calvaruso[4], E. Degasperi[5], B. Coco[6], A. Giorgini[7], F. Conti[8], A. DI Leo[10], L. Marzi[9], V. Boccaccio[1], S. Bollani[11], P. Maisonneuve[12], M.G. Rendina[10], M. Persico[2], S. Bruno[1].

[1]Humanitas University, Department of Biomedical Sciences, Div. Internal Medicine and Hepatology, Rozzano, MI; [2]University of Salerno, Internal Medicine and Hepatology Unit; [3]University of Torino, Gastroenterology; [4]University of Palermo, Gastroenterology; [5]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Gastroenterology and Hepatology; [6]University Hospital of Pisa, Hepatology; [7]San Paolo Hospital, Internal Medicine and Hepatology; [8]University of Bologna, Scienze Mediche e Chirurgiche; [9]University of Modena, Hepatology; [10]University of Bari, Gastroenterology and Digestive Endoscopy; [11]Ospedale Fatebenefratelli e Oftalmico, Internal Medicine; [12]European Institute of Oncology, Division of Epidemiology and Biostatistics

Email: ana.lleo@humanitas.it

Background and Aims: Patients with hepatitis C virus (HCV) related cirrhosis have an expected high rate of progression to liver decompensation and hepatocellular carcinoma (HCC); dramatic improvement in viral eradication rates has been reached with direct antiviral agents (DAAs). Nevertheless, the real benefit of viral eradication after DAAs on disease progression, including HCC development, are still limited and controversial. We aim to prospectively assess the risk of HCC occurrence and early recurrence in a large prospective cohort of DAA-treated HCV-cirrhotic patients.

Methods: We analysed data prospectively collected from HCV-infected cirrhotic patients consecutively treated with DAA from January to December 2015 in 10 tertiary liver centers in Italy. Patients with either compensated or decompensated cirrhosis and/or previous HCC were enrolled.

Results: 1,927 patients were included; 161 patients had a previous history of HCC. Most patients were in Child Pugh class A (88% without history of HCC and 85% of patients with previously treated HCC), and the mean MELD score was 8 in both groups. 1,832 patients (95%) achieved SVR. No difference in SVR rates was observed regardless the history of HCC. Of the 161 patients with past HCC, 38 developed tumor recurrence during the follow-up (incidence person-year 24.8%). Patients with SVR had a significantly lower rate of HCC recurrence. Cox regression analysis highlighted SVR (HR 8.43; 95%CI: 2.85–24.9; p = 0.0001) and alfafetoprotein (HR 6.50; 95%CI: 1.91–22.1; p = 0.002) as independent predictors of HCC recurrence. Both SVR and alfafetoprotein were confirmed as solid predictors of recurrence at the multivariate analysis. 50/1,766 patients (2.8%) without a previous HCC history developed HCC during the follow-up (cumulative incidence p-year, 2.4%). Patients with SVR had a significantly lower rate of HCC recurrence at all time points. SVR was confirmed as the strongest predictor of HCC incidence from the univariate (HR 6.31; 95%CI: 3.07–13.0; p < 0.0001) and multivariate analysis (HR 5.02; 95%CI: 2.34–10.8; p < 0.0001).

Conclusions: This large real-life study highlights that SVR is associated with a significant decrease of recurrent or de novo HCC in cirrhotic patients treated with DAA. Longer follow up is underway to confirm these findings.

PS-155

Risk of total non-hepatic cancer following treatment for HCV infection with direct-acting antiviral agents

A. Chokkalingam[1], A. Singer[1], L. Telep[1], A. Osinusi[2], D. Brainard[3].

[1]Gilead Sciences, Epidemiology, Foster City, United States; [2]Gilead Sciences, Clinical Research, Foster City, United States; [3]Gilead Sciences, Gilead Sciences, Foster City, United States

Email: anand.chokkalingam@gilead.com

Background and Aims: Hepatitis C virus (HCV) infection has been associated with extrahepatic co-morbidities. Prior to the introduction of direct-acting antiviral (DAA) agents, HCV therapy involved interferon (IFN), which has been reported to have anti-tumour effects, but has substantial side effects and has low sustained virologic response (SVR) rates. In contrast, DAAs are well-tolerated and have SVR rates >90%. To characterize the long-term effects of DAA-based therapy, we examined the risk of total non-hepatic cancer associated with DAA treatment, vs IFN treatment in the pre-DAA era.

Methods: Among 367,156 adults with chronic HCV infection enrolled between January 2006 and March 2017 in a U.S. administrative claims database, we identified 22,894 who were exposed to DAAs (follow-up through March 2017), and 10,989 who were exposed to IFN prior to May 2011 (introduction of boceprevir, follow-up through November 2013). All patients had ≥12 months of prior enrolment and no evidence of prior cancer at baseline. Absolute rates per 100 person-years (PY) of cancer events (identified by diagnostic claims, excluding liver cancer) were calculated, along with exact 95% Poisson confidence intervals (CIs). Hazard ratios (HRs) estimating cancer risk associated with DAA vs pre-DAA IFN were estimated using Cox proportional hazards methods, after adjustment for covariates and incorporation of weighting based on treatment propensity scores.

Results: Following DAA exposure and IFN exposure, median follow-up was 0.94 PY (Q1, Q3: 0.48 PY, 1.69 PY) and 2.59 PY (Q1, Q3: 1.12 PY, 4.15 PY), respectively. The absolute rate of total non-hepatic cancer following DAA exposure was slightly higher than that following IFN exposure: 6.07 per 100 PY (95%CI: 5.78–6.38) vs 5.52 per 100 PY (95% CI: 5.26–5.79). However, after adjustment for covariates including age, gender, and baseline comorbidities and medication use, as well as propensity score weighting, DAA exposure was associated with a significantly reduced risk relative to IFN exposure (HR: 0.86, 95%CI: 0.80–0.93). Further analyses, including analyses by major cancer site, are planned.

Conclusions: In this study, we found DAA exposure was associated with a lower risk of total non-hepatic cancer, relative to IFN. Given the well-described differences in SVR rates between DAA and IFN-based regimens, we hypothesize that the reduced risk of non-hepatic cancer associated with DAA therapy may reflect the long-term impact of successful HCV treatment at a population level.

HBV and HDV: Current and emerging treatments

PS-156

Safety and efficacy at 1 year after switching from Tenofovir Disoproxil Fumurate to Tenofovir Alafenamide in chronic HBV patients with risk factors for TDF use

E. Gane[1], W.-K. Seto[2], H. Janssen[3], F.A. Caruntu[4], H.J. Kim[5], D. Abdurakhmanov[6], S. Nishiguchi[7], H. Andrzej[8], H. Bae[9], S. Mo[10], V. Suri[10], A. Gaggar[10], J.F. Flaherty[10], J.-H. Kao[11], M. Brunetto[12], M.B. Ferret[13]. *[1]Auckland Clinical Studies, Auckland, New Zealand; [2]Queen Mary Hospital, Hong Kong, Hong Kong; [3]Toronto General Hospital, Toronto, ON, Canada; [4]Infectious Diseases, National Institute for Infectious Diseases Matei Bals, Bucharest, Romania; [5]Chung-Ang Hospital, Seoul, Korea; [6]Sechenov First Moscow State Medical University, Moscow, Russia; [7]Hyogo College of Medicine Hospital, Hyogo, Japan; [8]SP ZOZ Wojewodzki Szpital Zakazny w Warszawie, Warsaw, Poland; [9]Asian Pacific Liver Center, Los Angeles, California, United States; [10]Gilead Sciences, Inc., Foster City, CA, USA; [11]National Taiwan University, Taipei, Taiwan; [12]UO Epatologia, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; [13]Hospital Universitari Vall d'Hebron, Barcelona, Spain*
Email: vithika.suri@gilead.com

Background and Aims: In Phase 3 studies in chronic hepatitis B (CHB) patients**,** tenofovir alafenamide (TAF), a new tenofovir (TFV) prodrug, has shown noninferior efficacy to tenofovir disoproxil fumarate (TDF) at Weeks 48 and 96, with superior bone and renal safety. TAF is a preferred treatment in the 2017 EASL HBV Guidelines, especially in patients with risk factors for TDF-associated renal and bone effects. We assessed the 1 year safety and efficacy in CHB patients with TDF risk factors (RF) who were switched from TDF to TAF.

Method: In 2 identically-designed studies, HBeAg-positive and -negative patients were randomized 2:1 to TAF 25 mg or TDF 300 mg QD and treated in a double-blind fashion for 96 weeks, after which patients received open-label (OL) TAF. Renal (serum creatinine [sCr], eGFR by Cockcroft-Gault [$eGFR_{CG}$] and urine biomarkers of tubular function) and bone (serial DXA scans at hip/spine and serum bone biomarkers) safety parameters, antiviral efficacy (HBV DNA < 29 IU/ml), and ALT normalization were assessed in the subset of switched patients having baseline RF for TDF: Age > 60 yr, osteoporosis of hip/spine, ≥Stage 2 chronic kidney disease (CKD), albuminurina (UACR > 30mg/g), hypophosphatemia (PO_4 <2.5 mg/dl), or comorbidities associated with CKD (e.g. HTN, DM, obesity).

Results: Of 1,298 patients randomized and treated, 540 switched to OL TAF at Week 96 (TAF→TAF in 360; TDF→TAF in 180), of whom 284 (53%) had ≥1 TDF RF; 123 (23%) patients had ≥2 RF. Baseline demographics were similar between groups. Renal and bone safety results at Week 144 are summarized in the table. At Week 144, TDF patients switched to TAF showed improvements in renal (sCr, $eGFR_{CG}$) parameters with a higher percentage of patients showing improvement vs worsening of CKD stage. Improvements in hip and spine BMD were seen at 1 year following switch. Patients continuing TAF showed similar small changes in renal/bone parameters. Antiviral efficacy was maintained in both groups and TDF patients switching to TAF at Week 96 had increased rates of ALT normalization at Week 144.

Table: Renal and bone safety results at Week 144 in CHB patients with TDF risk factors switched from TDF to TAF at Week 96

Change from Open-label (Week 96) baseline:	TDF→TAF (n = 101)	p value[a]
Renal parameters		
Serum creatinine, mean (SD) change (mg/dl)	−0.018 (0.064)	0.008
$eGFR_{CG}$, median (Q1, Q3) change (ml/min)	+3.0 (−1.8, 7.8)	<0.001
≥1 stage improvement in CKD stage from Week 96 (OL baseline) to Week 144, n/N (%)	9/51 (18)	ND[b]
≥1 stage worsening in CKD stage from Week 96 (OL baseline) to Week 144, n/N (%)	4/95 (4)	ND
Bone parameters		
Hip BMD, mean (SD) % change	+0.97 (2.88)	0.002
Spine BMD, mean (SD) % change	+2.18 (3.36)	<0.001

[a]p values from T test; [b]ND is testing not done.

Conclusion: CHB patients with risk factors for TDF toxicity who are switched from TDF to TAF have improved bone and renal safety and normalization of ALT levels whilst efficacy was maintained in this subgroup at one year.

PS-157

Continuing Besifovir Dipivoxil Maleate versus switching from Tenofovir Disoproxil Fumarate for treatment of chronic hepatitis B: 96 weeks results of phase 3 trial

S.H. Ahn[1], W. Kim[2], H.J. Yim[3], J.M. Yang[4], J.Y. Jang[5], Y.O. Kweon[6], Y.K. Cho[7], Y.J. Kim[8], G.Y. Hong[9], D.J. Kim[10], S.H. Um[3], J.H. Sohn[11], J.-W. Lee[12], S.J. Park[13], B.S. Lee[14], J.H. Kim[15], H.S. Kim[16], S.K. Yoon[17], M.Y. Kim[18], K.S. Lee[1], Y.-S. Lim[19], W.S. Lee[20], K.-H. Han[1]. *[1]Yonsei University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [2]Seoul National University College of Medicine, Seoul Metropolitan Government Boramae Medical Center, Department of Internal Medicine, Seoul, Korea, Rep. of South; [3]Korea University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [4]Catholic University Medical College St. Vincent's Hospital, Department of Internal Medicine, Suwon, Korea, Rep. of South; [5]College of Medicine, Soonchunhyang University, Department of Internal Medicine, Seoul, Korea, Rep. of South; [6]Kyungpook National University College of Medicine, Department of Internal Medicine, Daegu, Korea, Rep. of South; [7]Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [8]Seoul National University College of Medicine, Department of Internal Medicine and Liver Research Institute, Seoul, Korea, Rep. of South; [9]Kwangju Christian Hospital, Department of Internal Medicine, Gwangju, Korea, Rep. of South; [10]Hallym University College of Medicine, Department of Internal Medicine, Chuncheon, Korea, Rep. of South; [11]Hanyang University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [12]Inha University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [13]Paik Hospital, Inje University, Department of Internal Medicine, Pusan, Korea, Rep. of South; [14]Chungnam National University School of Medicine, Department of Gastroenterology and Hepatology, Daegeon, Korea, Rep. of South; [15]Department of Internal Medicine, Gacheon University College of Medicine, Incheon, Korea, Rep. of South; [16]Soonchunhyang University College of Medicine, Department of Internal Medicine, Cheonan, Korea, Rep. of South; [17]Catholic University of Korea, Department of Internal Medicine, Seoul, Korea, Rep. of South; [18]Yonsei University Wonju College of Medicine, Department of Internal Medicine, Wonju, Korea, Rep. of South; [19]Asan Medical Center, University of Ulsan College of Medicine, Department of Gastoenterology, Seoul, Korea, Rep. of South; [20]Chonnam University Medical School, Department of Internal Medicine, Gwangju, Korea, Rep. of South*
Email: gihankhys@yuhs.ac

Background and Aims: Besifovir dipivoxil maleate (BSV) is an acyclic nucleotide phosphonate with a potent antiviral activity against hepatitis B virus (HBV). In the former phase 3 study, an antiviral efficacy of BSV for forty-eight week was shown to be comparable to

tenofovir disoproxil fumarate (TDF) in treatment-naïve chronic hepatitis B (CHB) patients. We evaluated long-term efficacy and safety of BSV in chronic hepatitis B patients who were positive or negative for hepatitis B e antigen (HBeAg+ or HBeAg-) in the extended follow up of a phase 3 study.

Method: After 48 weeks of double-blind comparison of BSV to TDF, eligible patients who had agreed with the extended study continued to participate in the open-label BSV study. The presented data were collected for 96 weeks. We evaluated virological, serological, and biochemical responses for efficacy analysis, and bone mineral density (BMD) and renal outcomes for safety analysis for both BSV group (BSV-BSV) and the group switched from TDF (TDF-BSV). The primary endpoint was the proportion with HBV DNA <400 copies/ml (response rate).

Results: Among 197 patients who received randomized treatments, 170 (87%) patients entered the open-label phase, and 161 (82%) completed 96 weeks of the study. The response rate of those who have taken BSV over 96 weeks is 87.21% while 85.71% of patients who switched the treatment from TDF were respondent. HBeAg seroconversion and ALT normalization were shown in 11.54% and 73.26% of patients in the BSV-BSV group, respectively. There were no drug resistant mutations to BSV and no adverse events related to bone mineral density or renal function. The safety profile was similar for the two groups.

Conclusion: BSV maintained efficacy in both suppression of HBV DNA and ALT normalization over 96 weeks without any evidence of resistance to BSV. Also, BSV is safe, well tolerated, and effective for those who have switched to BSV from TDF.

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Increased incidence of HBsAg seroclearance in HBeAg negative chronic hepatitis B patients discontinued Nuc therapy comparing to natural course–a propensity score matched study

W.-J. Jeng[1,3,5], H.-I. Yang[2,6], Y.-C. Chen[1,3,5], J. Liu[2,4], R.-N. Chien[1,3,5], I.-S. Sheen[1,5], C.-J. Chen[2], Y.-F. Liaw[3,5]. *[1]Department of Gastroenterology and Hepatology, Chang Gung Memorial Hospital, Linkou; [2]Genomic Research Center, Academia Sinica; [3]College of Medicine, Chang Gung University; [4]Stanford University School od Medicine and Lucile Packard Children's Hospital; [5]Liver research Unit, Chang Gung Memorial Hospital, Linkou; [6]Institute of Clinical Medicine, National Yang Ming University*

Email: liveryfl@gmail.com

Background and Aims: Hepatitis B s antigen (HBsAg) loss is a rare event during nucleos(t)ide analogue (Nuc) therapy but may increase in HBeAg negative chronic hepatitis B patients with sustained remission during off Nuc follow-up. It is unknown whether the incidence during and off Nuc is the effect of therapy or just an event of the natural course of chronic hepatitis B.

Aim: To test whether the incidence of HBsAg seroclearance in HBeAg negative CHB patients with finite Nuc therapy is higher than that of subjects in REVEAL natural history cohort.

Method: A total of 762 HBeAg negative CHB patients received finite Nuc therapy from Chang Gung Memorial Hospital were compared to 2,772 HBeAg negative REVEAL-CHB cohort patients whose baseline HBV DNA and HBsAg quantification data were available. Propensity score matching (PSM) on age, gender, cirrhosis, baseline ALT, HBV DNA and HBsAg (qHBsAg) levels were applied. The Incidence of HBsAg seroclearance was calculated. Cox regression model was used for investigating predictors of HBsAg seroclearance after adjustment for PSM-variables.

Results: Before adjustment, the Nuc-treated cohort showed older age, greater proportion of male, liver cirrhosis and genotype B, higher ALT, HBV DNA and qHBsAg levels and shorter follow-up duration. After 1:1 propensity score matching, there were 262 patients each in Nuc-treated and REVEAL cohort. The incidence rate of HBsAg seroclearance in Nuc-treated cohort was 105.637 x 10^4 person-year while it was 82.790 x 10^4 person-year in REVEAL cohort. Kaplan-Meier analysis showed higher cumulative HBsAg seroclearance rate in patients with finite Nuc-therapy (p = 0.001). The difference became more apparent after 6 years of follow-up since the entry of treatment (treatment duration: mean: 3.1 years). Multivariate Cox regression analysis showed that lower qHBsAg at entry (>=1000 vs. <1000, adjusted HR: 0.167(0.072–0.388), p < 0.0001) and patients with finite Nuc treatment (vs. REVEAL, adjusted HR: 3.41 (1.634–7.116), p = 0.0011) were two independent predictors for HBsAg seroclearance.

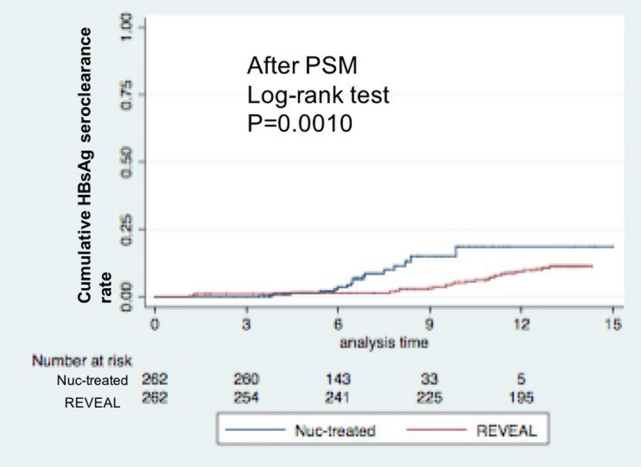


Figure: Cumulative HBsAg seroclearance rate of Nuc-treated cohort and REVEAL cohort after propensity score matching of age, gender, cirrhosis, baseline HBV DNA, qHBsAg and ALT.

Conclusion: The findings (1) patients with finite Nuc therapy had significantly higher incidence of HBsAg seroclearance than that during the natural course of CHB; (2) finite Nuc therapy was an independent factor for HBsAg seroclearance; indicate that HBsAg seroclearance in patients with finite Nuc therapy reflects the effect of therapy rather than just a natural event of HBeAg-negative CHB.

PS-159

Rates and predictors of HBsAg loss after discontinuation of effective long-term Entecavir or Tenofovir therapy in non-cirrhotic HBeAg-negative chronic hepatitis B patients: Results from the DARING-B prospective Greek study

M. Papatheodoridis[1], E. Rigopoulou[2], E. Hadziyannis[3], Z. Kalliopi[2], V. Xourafas[1], A. Lyberopoulou[2], N. Gatselis[2], I. Vlachogiannakos[1], S. Manolakopoulos[1], G. Dalekos[2], G. Papatheodoridis[1]. *[1]Medical School of National and Kapodistrian University of Athens, Laikon General Hospital, Department of Gastroenterology, Athens, Greece; [2]Thessaly University Medical School, Department of Medicine and Research Laboratory of Internal Medicine, Larissa, Greece; [3] Medical School of National and Kapodistrian University of Athens, Hippokrateion General Hospital, 2nd Department of Internal Medicine, Athens, Greece*

Email: gepapath@med.uoa.gr

Background and Aims: According to the recent European guidelines, cessation of nucleoside analogues (NAs) may be attempted in selected non-cirrhotic Chronic Hepatitis B patients (CHBe-) patients who have remained in long-term remission under NAs and will remain under close monitoring. Although virological relapses are common, they may be transient and lead to long-term remission and even HBsAg loss, the ideal endpoint of HBV therapy. This prospective study carefully assessed the rates and predictors of off-NAs HBsAg loss in non-cirrhotic CHBe- patients with long-term virological remission under entecavir (ETV) or tenofovir (TDF).

Method: 60 patients (M/F:39/21, age:59 ± 11 years) with CHBe- and no cirrhosis before therapy (Ishak-stage ≤ 4 and/or elastographic stiffness <10 kPa), who had received ETV/TDF for ≥4 years and had undetectable HBVDNA for ≥3 years consented to participate. None had coinfection, HCC or liver transplantation. All agreed to remain

under close follow-up (monthly for first 3 months and every 2/3 months thereafter in case of detectable/undetectable HBVDNA). Serum ALT, HBV DNA, HBsAg and interferon-inducible protein 10 (IP10) levels were determined at each visit after stopping ETV/TDF.
Results: Mean patient follow up has been 19 ± 9 months. No patient died or developed jaundice or decompensation. The cumulative rates of virological relapse defined as HBV DNA > 2000 IU/ml were 63%, 67% and 70% at 6, 12, and 18 months and of HBsAg loss were 5%, 10%, 20% and 30% at 0, 6, 12, and 18 months after NAs cessation. The probability of subsequent HBsAg loss was not affected by age, sex, liver fibrosis severity, pretreatment ALT or HBV DNA levels, but it was significantly higher in patients with lower HBsAg serum levels at NAs cessation [HR per 100IU/l: 1.35 (95%CI: 1.09–1.69), p = 0.008] or at month 1 [HR per 100IU/l:1.28 (1.05–1.56), p = 0.016], higher ALT at month 1 [HR per 10IU/l: 1.12 (1.01–1.26), p = 0.033] and higher IP10 at month 1 [HR per 10IU/l: 1.09 (1.01–1.19), p = 0.021].
Conclusion: Our prospective study shows that discontinuation of effective long-term (≥4-year) ETV/TDF therapy in non-cirrhotic CHBe- patients can lead to increasing HBsAg loss rates exceeding 20% after the first year of follow-up. Higher probability of subsequent HBsAg loss is associated with lower serum HBsAg levels at treatment cessation and at month 1 but also with higher ALT and IP10 levels at month 1 after ETV/TDF cessation suggesting that untreated early post-treatment flares may lead to immune control and functional cure.

PS-160
Effects of SB9200 (Inarigivir) therapy on immune responses in patients with chronic hepatitis B
R. Walsh[1], R. Hammond[1], K. Jackson[1], R. Edwards[1], C. Macfarlane[2], R. Iyer[2], M.-F. Yuen[3], H. Chan[4], N. Afdhal[2], S. Locarnini[1]. *[1]Victorian Infectious Diseases Reference Laboratory, Australia; [2]Spring Bank Pharmaceuticals, United States; [3]University of Hong Kong, Hong Kong; [4]The Chinese University of Hong Kong, Hong Kong*
Email: renae.walsh@mh.org.au

Background and Aims: Inarigivir (SB9200) is a small molecule dinucleotide orally active HBV antiviral with both direct acting and immune modulatory activity, stimulating the host innate antiviral response. It binds to the cytosolic pattern recognition receptor retinoic-acid-inducible gene (RIG-I) to enhance RIG-I binding to the 5'-epsilon region of the HBV pregenomic RNA. The ACHIEVE trial is a double-blind placebo (PL) controlled study of ascending doses of Inarigivir PO daily monotherapy or PL for 12 weeks, followed by a switch to 300 mg Tenofovir daily for a further 12 weeks. We report here the comparative effects of low dose Inarigivir monotherapy on the anti-HBs antibody (Ab) response (HBsAg epitope profile, and complexed Ab) on thirty-eight naive non-cirrhotic HBV patients randomised 4:1 to twelve weeks of 25 mg or 50 mg Inarigivir or placebo.
Method and Results: Inarigivir therapy resulted in significant decline in HBV DNA, HBV RNA and HBcrAg levels in the majority of treated patients with modest decline in HBsAg. Inarigivir therapy cohorts (25 mg and 50 mg doses) were further analysed for effects on immune responses, applying bioassays for developing Ab response markers predictive of HBsAg clearance including development of HBsAg clearance profile (CP) and complexed HBsAg/anti-HBs. A decline in HBV DNA together with the development of a HBsAg CP during the 12 weeks of Inarigivir therapy was observed in 1/16 (6%) subjects who received 25 mg of drug, and this response increased to 4/13 (31%) of subjects receiving 50mg of drug. This relationship was not observed in any PL subjects (n = 8) during the 12 weeks treatment period. The detection of anti-HBs Ab complexed with HBsAg, indicative of an underlying or emerging immune response, was enhanced from 2/16 (12%) in the 25 mg treatment cohort, to 6/13 (46%) in the 50mg Inarigivir therapy cohort during the 12 weeks of treatment. Furthermore, the development of complexed anti-HBs was enhanced in 6/13 (46%) of patients in the 50mg treatment cohort compared to the PL arm with only 1/4 (25%) subjects developing complexed anti-HBs.
Conclusion: Serum biomarkers indicative of Ab response were found to display a strong trend during 12 weeks of Inarigivir therapy compared to PL. Predictive markers of anti-HBs response were enhanced in the 50mg versus 25mg Inarigivir therapy cohorts, revealing a dose response relationship of nascent immune recovery due to low dose Inarigivir therapy, suggesting higher doses should be further studied.

PS-161
Subanalysis of the LOWR HDV-2 study reveals high response rates to Lonafarnib in patients with low viral loads
C. Yurdaydin[1,2], C. Kalkan[2], F. Karakaya[2], A. Caliskan[2], S. Karatayli[2], O. Keskin[2], R. Idilman[2], M. Bozdayı[2], C. Koh[3], T. Heller[3], J. Glenn[4]. *[1]Gastroenterology, Turkey; [2]Division of Gastroenterology, University of Ankara Medical School, Turkey; [3]Liver Diseases Branch, NIDDK; [4]Division of Gastroenterology and Hepatology and Department of Microbiology and Immunology, Stanford University School of Medicine*
Email: cihan.yurdaydin@medicine.ankara.edu.tr

Background and Aims: The LOWR HDV-2 study explored multiple combinations of LNF and RTV, with or without PEG-IFNα, for 12 to 48 weeks, in patients chronically infected with HDV. Antiviral responses were observed in all treatment groups. Here we sought to analyze response rates as a function of baseline viral loads (BVL) among patients completing 24 weeks of the various LNF-based regimens.
Method: 33 patients completed 24 weeks of the following LNF-based regimens:
Group 1 (n = 14): LNF 50 mg BID + RTV 100 mg BID. This included 2 re-treatment patients, who had previously been treated with a short oral course of LNF based therapy (LNF 200 mg BID or LNF 300 mg BID for 12 weeks), and achieved HDV RNA negativity for 6 months, followed by a return of HDV RNA to low BVL < 4 log; Group 2 (n = 6): LNF 25 mg BID + RTV 100 mg BID; Group 3 (n = 4): LNF 50 mg BID + RTV 100 mg BID + PEG-IFNα 180 micrograms QW; Group 4 (n = 5): LNF 25 mg BID + RTV 100 mg BID + PEG-IFNα 180 micrograms QW; Group 5 (n = 4): LNF 50 mg BID + RTV 100 mg BID + addition of PEG-IFNα 180micrograms QW for weeks 12–24. 12 of 33 (36%) patients had low BVL, defined as <4 logIU/ml and 21 of 33 (64%) patients had BVL > 4 logIU/ml. HDV RNA was measured by validated RoboGene® HDV RNA Quantification (LOQ: 14IU/ml; LOD 8IU/ml). Responders were defined as patients achieving >2 log drop in HDV RNA (or BLOQ for patients with BVL < 2 log) at the end of 24 weeks.
Results: 21 of 33 (64%) patients across all treatment groups were responders at 24 weeks. For patients with BVL > 4 log, response rate was 12 of 21 (57%). Response rate at 24 weeks for patients with low BVL < 4 log was higher, 9 of 12 (75%), described below:
7 of 7 (100%) patients treated with all oral LNF 50 mg BID + RTV 100 mg BID (Group 1) were BLOQ (n = 2) or PCR-negative (n = 5) at 24 weeks, including the 2 re-treatment patients. 1 of 1 patients from Group 4 and 1 of 1 patients from Group 5 became BLOQ at 24 weeks. 0 of 3 (0%) patients from Group 2 were BLOQ at 24 weeks. Group 3 had no patients with low BVL
Conclusion: 6-month LNF-based regimens achieved virologic responses in a majority of patients. All oral LNF 50 mg BID + RTV 100 mg BID appears to be particularly attractive for patients with low BVL, as 100% of patients were responders. These results also suggest that prolonged control of HDV may be achieved in appropriate patients by 6-month pulse therapy with all oral LNF 50 mg BID + RTV 100 mg BID, in both LNF naïve and experienced patients.

PS-162

Strong intrahepatic decline of hepatitis D virus RNA and antigen after 24 weeks of treatment with Myrcludex B in combinationwith Tenofovir in chronic HBV/HDV infected patients: Interim results from a multicenter, open-label phase 2b clinical trial

L. Allweiss[1], C. Dettmer[1], T. Volz[1], K. Giersch[1], A. Alexandrov[2], H. Wedemeyer[3,4], S. Urban[4,5], J.-H. Bockmann[1,4], M. Luetgehmann[4,6], M. Dandri[1,4]. *[1]University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany; [2]MYR GmbH, Bad Homburg, Germany; [3]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [4]German Center for Infection Research (DZIF), Hannover, Heidelberg and Hamburg-Lübeck-Borstel Partner Sites; [5]University Hospital Heidelberg, Department of Infectious Diseases, Molecular Virology; [6]University Medical Center Hamburg-Eppendorf, Department of Medical Microbiology, Virology and Hygiene, Hamburg, Germany*
Email: lenaallweiss@hotmail.com

Background and Aims: Besides interferon alpha there is no approved treatment for patients chronically infected with hepatitis delta virus (HDV). Myrcludex B (MyrB) is a first-in-class entry inhibitor which blocks the HBV/HDV receptor sodium taurocholate co-transporter NTCP. Interim results of this phase 2b clinical trial on chronically HBV/HDV co-infected individuals receiving MyrB daily in combination with TDF demonstrated a dose-dependent HDV RNA decline in serum, which was accompanied by ALT reduction and normalization in some patients *(Wedemeyer et al., Hepatology 2017, DOI: 10.1002/hep.29500)*. Here we investigated the efficacy of MyrB treatment in reducing HDV intrahepatically using paired liver biopsies obtained at baseline (BL) and week 24.
Method: 120 HBeAg-negative patients with chronic Hepatitis D were randomized in 4 treatment arms. TDF treatment (245mg/day) started at least 12w prior to MyrB. MyrB was administered s.c. once daily at 2 (A), 5 (B) or 10 (C) mg for 24w. Patients in arm D received TDF alone. BL biopsies were available for 31 patients, paired liver biopsies for 22 patients. Virological parameters were assessed by qPCR and immunohistochemistry. Expression of inflammatory genes was determined by qPCR.
Results: At w24, intrahepatic HDV RNA declined in all MyrB arms with median reductions from BL by 0.78 log in A (n = 7), 1.07 log in B (n = 5) and by 1.34 log in C (n = 7). TDF treatment (D) showed modest HDV RNA reductions (0.30 logIU/ml, n = 3). Median HBV infection levels at BL (n = 31) were 0.23 HBV DNA copies/cell, 0.03 cccDNA copies/cell, 2.5 total HBV RNA/GAPDH; among paired biopsies, the strongest median reduction of HBV RNA (0.4 log) and total HBV DNA (0.6log) was determined in group C. Of note, immunohistochemistry revealed a substantial and dose-dependent decrease of HDAg+ cells. Accordingly, transcriptional levels of inflammatory chemokines decreased (e.g. CXCL10 median 0.45 Δlog 10) and such reduction was more pronounced in patients with intrahepatic HDV RNA decline of $\geq$1 log10.
Conclusion: Intrahepatic levels of HDV RNA and of HDAg+ cells strongly declined after 24 weeks of MyrB treatment in a dose-dependent manner. The concomitant ALT reduction and decrease of inflammatory cytokines suggests that the drop of HDV infection can diminish liver inflammation. Because of the strong decline of intrahepatic HDV infection levels induced by blocking HDV entry and turnover, HDV clearance might be achievable upon prolonged treatment durations.

Inflammation and fibrosis

PS-163

The I148M PNPLA3 impairs LXR signaling and cholesterol metabolism in human hepatic stellate cells

F. Bruschi[1], T. Claudel[1], M. Tardelli[1], A. Caligiuri[2], P. Starlinger[3], F. Marra[2], M. Trauner[1]. *[1]Medical University of Vienna, Division of Gastroenterology and Hepatology, Internal Medicine III, Vienna, Austria; [2]Medical University of Florence, Clinical Pathophysiology Department, Florence, Austria; [3]Medical University of Vienna, Department of Surgery, Vienna, Austria*
Email: francesca.bruschi@meduniwien.ac.at

Background and Aims: The I148M variant of the human PNPLA3 gene is strongly associated with hepatic steatosis and its progression toward severity of liver diseases, such as cirrhosis and cancer. Hepatic stellate cells (HSC) are key drivers of liver fibrosis and carriers of I148M PNPLA3 display higher pro-fibrogenic and pro-inflammatory profile compared to wild type (WT) PNPLA3 expressing HSC. Deranged cholesterol homeostasis and its accumulation promote liver fibrosis, but the impact of the I148M variant on cholesterol metabolism in HSCs has not yet been explored.
Method: Primary human HSC were isolated and sorted in two groups, according to the different PNPLA3 genotype (WT = wild type, I148M = variant). Moreover, we generated stably overexpressing WT and I148M PNPLA3 LX-2 cells. Total and free cholesterol were quantified by ELISA, expression and activity of cholesterol related genes was investigated via q-PCR, western blot and luciferase assays. LXR localization and tissue expression was evaluated using immunofluorescence staining in healthy and NASH liver specimen.
Results: Total (TC) and free cholesterol (FC) were significantly increased in HSC carrying the I148M PNPLA3, compared to WT carriers ($p < 0.01$). In line with increased cholesterol content, HSC expressing the PNPLA3 variant have lower expression of the cellular cholesterol sensor SREBP-2 and, subsequently, of its downstream key targets, such as LDL receptor (LDLr), for exogenous cholesterol uptake and HMG-CoA reductase, the limiting enzyme for cholesterol synthesis, at both protein and mRNA levels ($p < 0.01$). Liver staining showed that LXRα expression decreased in NASH patients, compared to healthy livers ($p < 0.05$), while LXRα was induced during primary human HSC activation, whereas the β isoform was high in quiescence state. LXR target genes, such as ABCA1, SREBP-1c, FAS and ACC1 were decreased in I148M HSC ($p < 0.01$), when conversely the synthetic LXR agonist T0901317 increased ABCA1 and reduced collagen1α1 expression. Moreover, luciferase assays using the LXR-RE and LXR constructs, showed that LXR activity was reduced in I148M HSC, but can be rescued by the T0901317.
Conclusion: We hereby report that HSC carrying the I148M PNPLA3 accumulate cholesterol, which does not derive from increased endogenous synthesis or uptake, but from diminished export via LXR activity. We propose that impaired LXR signaling is a consequence of reduced PPARγ activity, thus contributing to reinforce HSC activation and promoting fibrosis development.

PS-164

Induced pluripotent stem cell derived liver model for the study of PNPLA3-induced non-alcoholic fatty liver disease

S. Tilson[1,2,3], C.M. Morell[2], A.-S. Lenaerts[2], T.J. Liang[3], L. Vallier[1,2]. *[1]Wellcome Trust Sanger Insitute, Cellular Genetics, Hinxton, United Kingdom; [2]Wellcome Trust-Medical Research Council Stem Cell Institute, Surgery, Cambridge, United Kingdom; [3]National Institute of Diabetes and Digestive and Kidney Disease, Liver Disease Branch, Bethesda, United States*
Email: lv225@cam.ac.uk

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) represents a growing public health burden. NAFLD is defined by

accumulation of fat within the liver which ranges in severity from simple steatosis through non-alcoholic steatohepatitis (NASH). Until recently, NAFLD has been considered a largely metabolic disease; however, recent studies have suggested that genetic factors could also majorly influence disease onset and evolution. Accordingly, genome wide association studies (GWAS) have identified the I148M variant in the gene coding for Patatin-like phospholipase domain-containing protein 3 (PNPLA3) which is strongly associated with NAFLD without underlying metabolic disease. However, very little is known about the mechanisms by which it influences disease development and progression. In order to elucidate these mechanisms, we have developed an *in vitro*, 3D co-culture liver model which takes advantage of the unique properties of human induced pluripotent stem cells (hiPSCs) and the CRISPR/CAS9 gene editing technology.
Method: We used CRISPR/CAS9 to generate hiPSC lines with either a complete knock-out of the PNPLA3 gene or with the I148M variant knocked-in. These genetically edited cells were then differentiated into hepatocytes and macrophages to model the metabolic and inflammatory aspects of the disease respectively. These cells were then cultured together in a three-dimensional matrix and treated with free fatty acids to model NAFLD *in vitro*.
Results: Both the knock-out and knock-in clones showed similar differentiation efficiency toward hepatocytes as wild-type cells thereby suggesting that the PNPLA3 mutations do not affect differentiation capacity of the hiPSC cells. Our results showed that several hepatic cell types can be grown together in the 3D system and establish significant cellular interactions. Furthermore, these cells showed enhanced maturity, functionality, and cell survival. Following treatment with free fatty acids, hepatocytes demonstrated significant lipid droplet accumulation and macrophages showed differential expression of inflammatory genes, in both wild type and genetically edited cells. Mutations in PNPLA3 altered the pattern of response to lipid induced stress indicating that PNPLA3 may affect lipid metabolism in our system.
Conclusion: Once fully established and characterized, these hiPSC lines will provide the first opportunity to fully analyse the role of PNPLA3 in the development and progression of NAFLD *in vitro*.

PS-165
Interfering with local fibrotic platelet activation significantly inhibits fibrosis in multiple animal models: suggestions of the importance of the platelet-wound healing axis for fibrosis

K. Stuart[1], H. Kabra[1], S. Jalgaonkar[1], T. Skurnac[1], A. Woolley[1], N. Snead[1], N. Bachtell[2], D. Leeming[3], M. Karsdal[3], J. Paderi[1]. *[1]Symic Bio, Research, Emeryville, United States; [2]Symic Bio, Medical, Emeryville, United States; [3]Nordic Bioscience, Biomarkers and Research, Herlev, Denmark*
Email: kstuart@symicbio.com

Background and Aims: Platelets are the largest source of TGF-beta and PDGF, both very pro-fibrogenic factors; consequently, the fibrosis-platelet activation axis has been suggested to play a key role in fibrosis progression. SBR-294 is a novel molecule designed to inhibit platelet activation on collagen within the fibrotic liver. It is composed of collagen-binding peptides grafted to a synthetic glycosaminoglycan (GAG). The peptides serve to disrupt collagen-mediated platelet activation while the GAG itself has potent anti-fibrotic properties. We tested the hypothesis that these dual mechanisms would demonstrate a reduction in fibrosis progression in two models of liver fibrosis.
Method: In vitro, SBR-294 was investigated for its ability to inhibit platelet-collagen activation as well as hepatic stellate cell activation and proliferation. In vivo, two separate models of liver fibrosis were investigated to establish the effects of SBR-294 with differing disease insults. In the carbon tetrachloride (CCl4) model, liver fibrosis was induced in mice by repeated intraperitoneal administration of CCl4 twice weekly over a 4-week period, with concurrent dosing of SBR-294. Liver fibrosis was assessed through liver biochemical and histological markers, as well as serum levels of pro-C3. In the STAM™ model, fibrosis was induced by a single subcutaneous injection of streptozotocin after birth and feeding of a high fat diet beginning at 4 weeks of age. SBR-294 was administered between weeks 5 and week 9, at which point livers were collected for histological and biochemical analysis.
Results: In vitro data demonstrates that SBR-294 dose dependently inhibited platelet binding to collagen surfaces with an IC50 of approximately 20 nM. In addition, SBR-294 inhibited hepatic stellate cell proliferation and activation in a dose-dependent manner. SBR-294 reduced the progression of liver fibrosis in two in vivo models of liver disease. In the CCL4 study, SBR-294 treatment significantly decreased collagen in the liver, as measured by hydroxyproline content and Sirius Red staining ($p < 0.01$). Additionally, mRNA levels of both types I and III collagen were significantly reduced ($p < 0.05$), and serum pro-C3 levels were decreased in mice treated with SBR-294. In the STAM model, SBR-294 reduced Sirius Red staining, as well as liver triglycerides ($p < 0.05$). In both studies SBR-294 had no deleterious effects to the liver, indicating a positive safety profile.
Conclusion: We have demonstrated the ability of SBR-294 blocks platelets binding and subsequent activation in vitro that resulted in reduced fibrosis in two distinct animal models in vivo. The results are important for the platelet-wound healing fibrosis axis.

PS-166
Anti-inflammatory and anti-fibrogenic effects of monoacylglycerol lipase inhibitors in the liver involve macrophage autophagy

D. Chokr[1,2], A. Habib[1,3], J. Wan[1], P. Hegde[1], P. Letteron[1], N. Pilard[1], A. Mansouri[1], A. Brouillet[4], E. Weiss[1], R. Moreau[1], M. Trauner[5], S. Lotersztajn[1]. *[1]INSERM-UMR1149, Centre de Recherche sur l'Inflammation, Paris, France; [2]Lebanese University, Laboratory of Cancer Biology and Molecular Immunology, Faculty of Sciences I, Hadath, Lebanon; [3]American University of Beirut, Biochemistry and Molecular Genetics, Beirut, Lebanon; [4]INSERM U 955, Eq 18, Hopital Henri Mondor, Creteil, France; [5]Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Medicine III, Vienna, Austria*
Email: ah31@aub.edu.lb

Background and Aims: Monoacylglycerol lipase (MAGL) is the rate-limiting enzyme in the degradation of monoacylglycerols. In addition to its role in lipid catabolism, MAGL is also a component of the endocannabinoid system as it degrades 2-arachidonoyl glycerol, an endogenous ligand for the cannabinoid receptors CB1 and CB2, into arachidonic acid. Recent studies have identified inhibition of MAGL as an interesting anti-inflammatory strategy in several experimental models of chronic inflammatory diseases. In the present study, we investigated the consequences of MAGL inhibition on inflammation and fibrosis during chronic liver injury, and the mechanisms involved.
Method: C57BL/6 mice and mice with global invalidation of MAGL ($MAGL^{-/-}$), or myeloid-specific deletion of either MAGL ($MAGL^{Mye-/-}$) or ATG5 ($Atg5^{Mye-/-}$), were used. Fibrosis was induced by repeated injections of carbon tetrachloride (CCl_4) or bile duct ligation. *In vitro* studies were performed on peritoneal or bone-marrow derived macrophages, and Kupffer cells.
Results: $MAGL^{-/-}$ or C57BL/6 mice exposed to the MAGL inhibitor MJN110 developed less fibrosis upon chronic administration of CCl_4 or following bile duct ligation, respectively, as reflected by decreased sirius red staining, reduced fibrogenic cell accumulation and low levels of fibrogenic genes, as well as decreased expresssion of inflammatory genes in the liver. Moreover, CCl_4-exposed $MAGL^{Mye-/-}$ mice showed a similar anti-inflammatory and anti-fibrogenic phenotype. In keeping, LPS-stimulated peritoneal, bone marrow-derived macrophages or Kupffer cells exposed to MJN110 or isolated from $MAGL^{Mye-/-}$ mice displayed reduced expression of inflammatory mediators. Since macrophage autophagy protects against inflammation and fibrosis in the liver (*Lodder et al, Autophagy, 2015; Denaes et al, Sci Rep., 2016*), we investigated

whether macrophage autophagy mediates the anti-inflammatory effects of MAGL inhibitors. MJN110 enhanced LC3 II lipidation and autophagic flux in isolated macrophages. Moreover, whereas the MAGL inhibitor MJN110 decreased the production of inflammatory mediators in LPS-stimulated macrophages from WT mice, this anti-inflammatory effect was lost in $Atg5^{Mye-/-}$ macrophages.
Conclusion: Overall, these data unravel MAGL as a novel immuno-metabolic target and demonstrate that MAGL inhibitors may be considered as interesting as anti-fibrogenic compounds.

PS-167
IL-33 regulates immune-mediated hepatitis by induction of Areg+ ILC2, M2 macrophages and ST2+ Tregs
A. Ochel, G. Tiegs, K. Neumann. *Experimental Immunology and Hepatology, Center for Experimental Medicine, Hamburg, Germany*
Email: a.ochel@uke.de

Background and Aims: Immune-mediated liver injury such as autoimmune hepatitis is characterized by T cell-mediated necroinflammation. The alarmin interleukin (IL) -33 is rapidly released from necrotic hepatocytes and induces activation of immune cells, such as type 2 innate lymphoid cells (ILC2) and regulatory T cells (Tregs), by binding to ST2. IL-33 dampens immune-mediated liver injury in a yet unknown mechanism. The epidermal growth factor like molecule amphiregulin (Areg) mediates tissue regeneration and enhances suppressive function of Tregs. Moreover, Areg is expressed by activated ILC2. This prompted us to investigate whether ILC2-derived Areg regulates immune-mediated hepatitis in an IL-33 dependent manner.
Method: Wildtype mice and $ST2^{-/-}$ mice were treated with IL-33 on 3 consecutive days. Subsequently, immune-mediated hepatitis was induced by Concanavalin A (ConA). Immune cells were analyzed 24 h later by flow cytometry. Transcriptional profiles were analyzed by quantitative RT-PCR.
Results: IL-33 pre-treatment protected wildtype mice from ConA-hepatitis as shown by significantly reduced serum ALT values. This correlated with increased frequencies of hepatic ILC2, eosinophiles, macrophages and Tregs, respectively. ILC2 from both IL-33/ConA- as well as IL-33-treated mice expressed the activation markers CD25, KLRG1 and Areg. Despite expression of CD25, ILC2 from ConA-treated mice failed to express KLRG1 and Areg. Eosinophils were un-activated in response to IL-33, demonstrated by downregulation of CD25, CD69, and CD62L. Macrophages were increased in response to either IL-33/ConA, IL-33 or ConA-treatment. Yet, macrophages were $Ly6c^{lo}$ $CD11c^{-}$ upon IL-33/ConA or IL-33-treatment and expressed the M2 markers *Arg-1*, *Ym-1* and *Areg*, suggesting an anti-inflammatory phenotype. In contrast, ConA-treatment alone induced pro-inflammatory $Ly6c^{hi}$ $CD11c^{+}$ macrophages. Wildtype Tregs showed increased ST2 expression in response to all treatment regimens. However, significantly increased frequencies of $ST2^{+}$ Tregs were only observed in the IL-33/ConA group. Interestingly, even higher frequencies of Tregs were found in $ST2^{-/-}$ mice, but these mice developed a more severe hepatitis than wildtype animals, suggesting that $ST2^{+}$ Tregs are crucial regulators of immune-mediated hepatitis.
Conclusion: IL-33 mediated protection from hepatitis might be due to activation of $Areg^{+}$ ILC2, polarization of M2 macrophages and activation of $ST2^{+}$ Tregs.

PS-168
TGR5-mediated signalling in the regulation of biliary epithlium permeability
K. Nicolas[1], M. Gregory[1], U.-B. Jose[1], S. Hayat[1], D. Isabelle[1], T. Zahra[1], G. Julien[1], C. Ullmer[2], E. Klaus[3], T. Tordjmann[1]. *[1]INSERM, U1174, Orsay, France; [2]Roche Innovation Center, Basel; [3]Muenster University, Institute of Medical Biochemistry, Muenster, Germany*
Email: thierry.tordjmann@u-psud.fr

Background and Aims: Bile acids (BA) are signaling molecules that bind to the nuclear receptor FXR (Farnesoid-X-Receptor) or to the membrane receptor TGR5 (Takeda G-protein coupled Receptor 5). When challenged with BA overload models (partial hepatectomy, Bile Duct Ligation (BDL)), TGR5-KO mice exhibit massive hepatic peribiliary necrosis as compared with WT mice, suggesting that an alteration of biliary epithelial permeability may occur in the absence of TGR5. In a separate study, we confirmed that TGR5, highly expressed in cholangiocytes, regulates paracellular permeability in the biliary epithelium through an impact on expression and phosphorylation of the tight junction protein JAM-A. However, TGR5-related signaling pathways involved in this context were completely unknown.
Method: A specific TGR5 agonist (RO5527239 (Roche)) and a specific EGF Receptor (EGFR) inhibitor (AG1478 *in vitro*, Erlotinib *in vivo*) were used in mice and in cultured cells (NRC, MDCK transfected or not with TGR5-GFP or JAM-A non phosphorylatable S285A mutant (Tet-Off = TO). PKC, c-Src kinase, MAPK pathway (Erk1 /2), JAM-A expression and phosphorylation were studied by western blot (WB) and immunofluorescence. Functional studies were performed on cells cultured on inserts for Trans Epithelial Resistance (TER) measurements. BDL were performed on JAM-A-KO mice treated or not with RO5527239, and liver injury was analyzed (plasma ALT and liver sections H&E staining).
Results: *In vivo* and *in vitro*, TGR5 agonist treatment induced an increase in JAM-A expression and phosphorylation and this effect was significantly dependent on EGFR transactivation. Importantly, EGFR inhibition also strongly reduced the TGR5-dependent increase in TER. Moreover, the impact of TGR5 on TER critically required JAM-A phosphorylation, as shown by the abolition of TGR5-induced TER increase in JAM-A S285A mutant MDCK-TO. This was in line with *in vivo* observations, as TGR5 agonist treatment significantly protected WT but not JAM-A-KO mice from BDL-induced liver injury. Our WB data suggest that TGR5-dependent JAM-A phosphorylation depends on PKCs, MAPK and c-Src.
Conclusion: Our *in vitro* and *in vivo* studies help to clarify the mechanisms by which the BA receptor TGR5 reinforces the sealing of biliary epithelium, by controlling expression and phosphorylation of the tight junction protein JAM-A, at least in part through EGFR-dependent processes.

PS-169
Ductular reaction cells promote angiogenesis via SLIT2/ROBO1 pathway in chronic liver disease
M. Coll[1,2], E. Garcia-Pras[1,2], B. Aguilar-Bravo[1], J. Gallego[1,2], D. Blaya[1], J. Vallverdú[1], L. Perea[1], I. Graupera[3], E. Pose[3], J. Lozano[2], R. Bataller[4], P. Ginès[3], J.-G. Geng[5], M. Fernandez[1,2], P. Sancho-Bru[6]. *[1]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [2]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [3]Liver Unit, Hospital Clinic Barcelona; [4]Division of Gastroenterology, Hepatology and Nutrition, Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [5]Department of Biologic and Materials Sciences, University of Michigan School of Dentistry, Ann Arbor, Michigan, United States; [6]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain., Liver cell plasticity and tissue repair Group, Spain*
Email: mdcoll@clinic.ub.es

Background and Aims: Ductular reaction (DR) expands in response to massive liver damage and loss of replicative capacity of hepatocytes in alcoholic liver diseases (ALD) and it is a key feature of alcoholic hepatitis (AH). DR consists of a heterogeneous population comprising liver progenitor cells (LPCs). Biological functions of DR and LPCs in chronic liver damage are not well understood. The secretory protein Slit2 and its receptor Robo1 are known to regulate cell growth, migration and vascularization. The aim of this study was to investigate the potential role of DR in regulating angiogenesis in chronic liver diseases and whether this repair process is mediated by slit2-Robo1 signaling.

Method: Gene expression of Slit2, Robo1 and progenitor markers was assessed by qPCR in liver biopsies of AH (n = 30) and healthy (n = 6) individuals. Correlation of markers of LPC and angiogenesis and SLIT2 and ROBO1 was assessed in transcriptomic data from patients with AH (n = 29) and chronic ALD (n = 12). Gene and protein expression of Slit2 was assessed in a mouse model of LPC expansion (DDC diet). Angiogenesis was examined in $Robo1^{+/-}Robo2^{+/-}$ mice fed with DDC by quantifying area occupied by $CD31^{+}$ cells and by analyzing von willebrand factor expression. LPCs- induced vasculogenesis was evaluated by incubating conditioned medium from LPC organoids generated from cirrhotic livers with human endothelial cells (HUVECs).
Results: Liver expression of SLIT2 and ROBO1 was significantly higher in patients with AH compared with healthy controls. The transcriptomic analysis of ALD progression revealed that markers of angiogenesis strongly correlated with DR expansion. In addition, LPC markers showed a strong positive correlation with the expression of SLIT2 and ROBO1. The association of DR with SLIT2 and Robo1 was confirmed by qPCR in patients with AH. Moreover, SLIT2 was found highly expressed at protein and gene expression level in DR cells isolated from DDC treated mice. $ROBO1/2^{-/+}$ mice treated with DDC diet displayed a reduced intrahepatic neovascular density at the periportal area whereas no impact on expansion of DR was observed. Conditioned medium of cirrhotic LPC organoids induced tube formation of endothelial cells.
Conclusion: DR is associated with angiogenesis markers and with SLIT2/ROBO1 expression in ALD progression. Moreover, SLIT2/ROBO1 pathway mediates angiogenesis in experimental model of chronic liver injury and DR induces vasculogenesis in vitro. These results suggest, that DR contribute to liver tissue repair by promoting angiogenesis through SLIT2/Robo1 signaling pathway.

Liver tumours: Experimental

PS-170
Therapeutic targeting of LGR5 tumor initiating cells in liver cancer

W. Cao, M. Li, J. Liu, B. Ma, W. Wang, M. Peppelenbosch, Q. Pan.
Erasmus University Medical Center, Gastroenterology and Hepatology
Email: q.pan@erasmusmc.nl

Background and Aims: Tumor initiating cells/cancer stem cells are thought to be responsible for the failure of treatment and tumor recurrence. Thus, the concept that therapeutic targeting these cells has attracted great interest. Leucine-rich repeat-containing G-protein coupled receptor 5 (Lgr5) is a recently identified stem cell marker. Here we investigate the role of LGR5-expressing cells in liver cancer, and the potential of therapeutic targeting.
Method: A LGR5-promotor driven diphtheria toxin (DT) receptor knock-in mouse model with a GFP reporter was used. Carbon tetrachloride (CCl_4) was used to induce chronic liver injury and diethylnitrosamine (DEN) was used to induce primary liver tumor in mice. Tumor organoids were cultured from primary liver tumors and DT was used to specifically ablate LGR5 expressing cells. Sorafenib and chemotherapeutic agent (5-FU) were combined with DT to treat liver tumors.
Results: In DEN-induced hepatic tumors, the percentage of LGR5 cells is significantly higher as compared to tumor adjacent tissue (n = 28, $p < 0.05$, 3-fold higher), and this even more apparent when compared to tissue of CCl_4-induced chronic injury (n = 28, $p < 0.001$, 52-fold higher). Tumor organoids generated by *ex vivo* culturing of primary mouse liver tumor contain a LGR5-expressing cell population. Subcutaneous transplantation of these tumor organoids into immunodeficient NOG mice results in solid tumors, which retain a LGR5 positive compartment. Isolation and transplantation of single $LGR5^{+}$ cells from mouse tumor into NOG mice formed tumor again. Thus, these cells have tumor initiating/cancer stem cell-like properties. Interestingly, the treatment of Sorafenib and 5-FU enriched the LGR5-expressing cells in liver tumor organoids. More importantly, the depletion of LGR5 tumor initiating cells by DT administration effectively delayed the tumor formation *in vivo* and the combination therapy of Sorafenib & DT or 5-FU & DT remarkably reduced the growth of tumor organoids.
Conclusion: LGR5 marks tumor initiating cells in liver cancer, which can be specifically targeted to inhibit tumor growth. Thus, innovative therapeutic approaches shall be further explored to effectively targeting these cells for combating liver cancer.

PS-171
Endoplasmic reticulum stress in hepatic stellate cells contributes to the progression of hepatocellular carcinoma

F. Heindryckx[1], N. Pavlovic[1], Pär Gerwins[1,2]. [1]*Uppsala University, Medical Cell Biology, Uppsala, Sweden;* [2]*Akademiska sjukhuset, Radiology, Uppsala, Sweden*
Email: fempie@gmail.com

Background and Aims: One of the key players in the progression of cirrhosis to hepatocellular carcinoma (HCC) is the hepatic stellate cell, which is activated during liver damage. Activated stellate cells create a favourable tumour environment and produce growth factors and cytokines that enhance tumour cell proliferation and migration. We have recently shown that inhibiting the endoplasmic reticulum (ER) stress-induced IRE1a signalling pathway blocks stellate cell activation *in vitro* and reduces liver fibrosis *in vivo*. We now wanted to identify the role of ER-stress in the cross-talk between stellate cells and cancer cells in HCC.
Method: HCC was induced in mice by weekly injections with diethylnitrosamine. Mice were treated with an IRE1a inhibitor 4u8C or control, samples were taken after 25 weeks. Tumour burden and collagen deposition was quantified on H&E and Sirius red staining, respectively. The HCC-cell lines (HepG2 and Huh7) and stellate cell line (LX2) were co-cultured using transwell assays and RNA was isolated after 48 hours. Tumour spheroids were formed by culturing HepG2 and LX2 cells on ultra-low-attachment plates on which viability was measured by resazurin. Non-directional and directional migration (chemotaxis) was assessed on fluorescently labelled cells using scratch wound assays and 2D CellDirectors, respectively. ER-stress was inhibited *in vitro* with 100 uM 4u8C.
Results: Treatment with 4u8C significantly decreased the number of tumours in vivo, compared to untreated controls. Sirius red staining showed a significant decrease in collagen deposition after treatment with 4u8C, compared to controls. Co-culturing experiments confirmed that tumour cells (HepG2 and Huh7) secrete factors that significantly increase mRNA expression of ER-stress markers (CHOP, spliced XBP1 and BiP) in LX2 cells. Co-culturing also led to significantly increased mRNA expression of stellate cell activation markers (aSMA and collagen) compared to mono-cultures. This was significantly decreased when 4u8C was added to the co-cultures. Tumour spheroid growth was significantly reduced in co-cultures after treatment with 4u8C. Co-culturing HepG2 and LX2 cells significantly increased migration on a scratch wound compared to mono-cultures. Treatment with 4u8C significantly decreased non-directional and directional migration towards a gradient of chemo-attractant in stellate cell - tumour cell co-cultures in 2D CellDirectors.
Conclusion: Our results suggest that ER-stress is an important mediator in the communication between stellate cells and cancer cells. Tumour cells secrete factors that induce ER-stress in stellate cells, which contributes to their activation. Blocking the IRE1a ER-stress pathway reduces stellate cell activation, tumour cell proliferation and migration. Components of the ER stress pathway may therefore be therapeutically relevant for HCC-patients.

PS-172

Genetic inactivation of Nrf2 prevents clonal expansion of carcinogen-initiated cells in a nutritional model of rat hepatocarcinogenesis

C. Orrú[1], M. Szydlowska[1], K. Taguchi[2], A. Perra[1], G.M. Ledda[1], M. Yamamoto[2], A. Columbano[1]. [1]*University of Cagliari, Biomedical Sciences, Cagliari, Italy;* [2]*Tohoku University, Medical Biochemistry, Sendai, Japan*
Email: claudiaorr16@gmail.com

Background and Aims: Dysregulation of the Keap1-Nrf2 pathway has been observed in experimental and human tumors, suggesting its possible role in cancer development. Here we assessed whether Nrf2 activation occurs at early steps of rat hepatocarcinogenesis, therefore being critical for the onset of hepatocellular carcinoma (HCC).
Method: Wild type (WT) and *Nrf2* knockout (KO) rats were treated with a single injection of diethylnitrosamine (DENA) followed by choline-devoid methionine-deficient (CMD) diet. This experimental model causes massive fatty liver and steatohepatitis with fibrosis, and allows to identify early stages of hepatocarcinogenesis. RNA was isolated from laser-microdissected preneoplastic nodules. qRT-PCR and Sanger analyses were performed to evaluate the expression of Nrf2-target genes and *Nrf2* mutations. Preneoplastic lesions were identified by immunohistochemistry for the placental form of glutathione S-transferase (GSTP), glucose-6-phosphate dehydrogenase (G6PD) and gamma-glutamyl-transpeptidase (GGT).
Results: We found that activation of Nrf2 takes place already in early preneoplastic lesions, revealed by the preneoplastic marker GSTP. *Nrf2* missense mutations, known to disrupt the Keap1-Nrf2 binding region, were present in 44% of GSTP-positive foci. To directly investigate whether Nrf2 is critical for initiation and/or clonal expansion of DENA-induced DNA-damaged hepatocytes, we used *Nrf2* KO rats. While *Nrf2* genetic inactivation did not alter DENA-induced initiation, it led to increased liver injury and chronic compensatory hepatocyte regeneration in rats given DENA and fed CMD diet. However, in spite of such a permissive environment, the liver of *Nrf2* KO rats did not display any preneoplastic lesion unlike that of WT animals.
Conclusion: These results demonstrate that, in a model of hepatocarcinogenesis resembling human non-alcoholic fatty liver disease (NAFLD): (i) Nrf2 is activated at early steps of the tumorigenic process; (ii) Nrf2 is mandatory for the clonal expansion of initiated cells and is therefore critical in HCC onset and progression.

PS-173

Primary liver cancers display divergent epimutator phenotypes in localized and metastatic disease

C.O. Rourke[1], S. Haefliger[2], J. Haegele[2], K. Burmeister[2], M. Matter[2], J. Andersen[1]. [1]*University of Copenhagen, Biotech Research & Innovation Centre, Copenhagen, Denmark;* [2]*University Hospital of Basel, Institute of Pathology, Basel, Switzerland*
Email: colm.rourke@bric.ku.dk

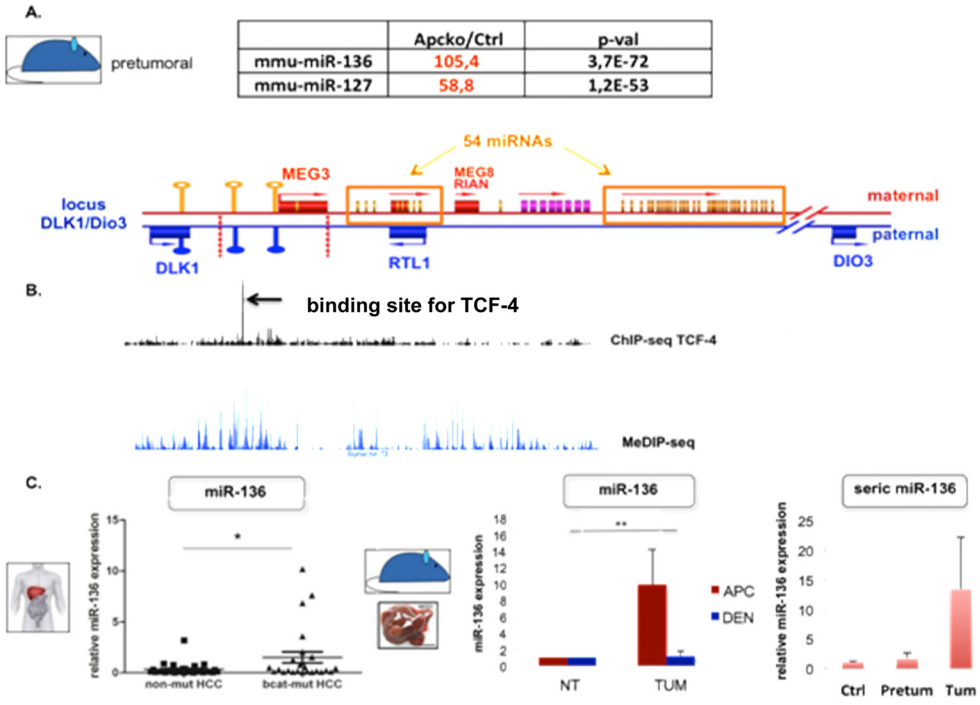
Background and Aims: Treatment with curative intent is compromised in a majority of primary liver cancer (PLC) patients due to advanced and metastatic disease at diagnosis. Genetic variants that drive progression remain elusive. Epigenetic alterations ("epimutations") comprise alternative genomic perturbation mechanisms which, given their dynamic nature, may facilitate rapid tumour diversification both in disease onset and progression. In this study, we deconstruct the epimutational landscapes of PLCs in primary and metastatic patient cohorts.
Method: We have integrated large-scale epigenomic data sets generated with Infinium Human Methylation 450 k BeadChips and stratified PLCs as intrahepatic cholangiocarcinoma (iCCA; n = 186), hepatocellular carcinoma (HCC; n = 366), combined hepatocellular cholangiocarcinoma (CHC; n = 13). Importantly, rapid autopsy samples for primary and metastatic iCCA (n = 24) and HCC (n = 38) underwent histopathological evaluation (histology, FISH) and 450 k methylation profiling. Differentially Methylated Regions (DMRs), Copy Number Alterations (CNAs) and network interaction hotspots were analysed.
Results: Extensive epigenome remodelling was detected in PLCs. Remarkably, HCC was uncovered as a disease predominantly hypomethylated ($p < 0.0001$) and iCCA a grossly hypermethylating disorder ($p < 0.0001$). Similar to histopathology, CHC displayed epigenomic features of both iCCA and HCC. Pan-cancer analysis of 6073 tumours (12 cancer types) confirmed iCCA and HCC as polarized extremes of epimutational processes in cancer. Divergent interactome hotspots of aberrant methylation were revealed, including *CASP8* promoter hypermethylation (iCCA), *CDKN1A* promoter hypermethylation (HCC) and *FGFR2* promoter hypomethylation in CHC. Progression of primary to metastatic PLC correlated with morphological changes (differentiation, grade, cytology) in 35% patients. Prominently, a disease stage-specific shift in epimutation modes was defined, with increasing proportions of hypermethylation in metastatic HCC and vice versa in metastatic iCCA. Intra-patient tracking of tumour evolution revealed that epimutations are highly clonal and display branched evolutionary patterns. Metastasis DMRs targeted cytoskeletal networks, such as *ELN* (HCC) and *MMP9* (iCCA).
Conclusion: PLCs are epimutationally polarized in primary and metastatic stages of disease, suggesting fundamental differences in their pathogenesis. Further studies will functionally trace genetic alterations and edit epimutations to assess their therapeutic potential.

PS-174

Upregulation of the imprinted DLK1/DIO3 locus in response to beta-catenin activation: a promising target for HCC treatment

Angélique Gougelet[1,2,3], D. Anais[1,2,3], G. Cécile[1,2,3], B. Terris[1,2,3], C. Perret[1,2,3], S. Colnot[1,2,3]. [1]*Institut Cochin-INSERM U1016, Paris, France;* [2]*CNRS UMR8104, Paris;* [3]*Université Paris-Descartes-Sorbonne Paris Cité, Paris, France*
Email: angelique.gougelet@inserm.fr

Background and Aims: We showed that miR-34a inhibition halves tumour progression, exclusively for HCC with β-catenin (β-cat) mutation, which concerns a third of HCC patients. We now attempt to determine if the targeting of a panel of miRNAs could be of therapeutic benefit.
Method: This project is realized on transgenic mice exhibiting an overactivation of β-cat signalling following the deletion of its inhibitor *Apc* (Apc^{KO}). This Cre-lox-based model is liver-specific and inducible by tamoxifen injection. Depending on the dose, mice either wholly exhibit hepatocytes with β-cat overactivation or develop tumours, with a genetic program similar to those of human HCC.
Results: In precancerous Apc^{KO} hepatocytes and, to a lesser extent, in tumors, β-cat activation upregulated the imprinted DLK1/DIO3 locus, including the 54 miRNAs, the long non-coding RNA MEG3, and the coding RNA DLK1, either expressed from the maternal or the paternal strand, meaning that parental imprinting is altered after β-cat activation. Using deep-sequencing approaches in Apc^{KO} hepatocytes, we showed that β-cat directly binds upstream of the locus and promotes its hypermethylation in intragenic regions, presuming a direct regulation by β-cat and DNA methylation. Kinetic sorting of Apc^{KO} hepatocytes from the tumoral model revealed that its hypermethylation and its overexpression are observable at day six after β-cat activation. Additionally, in coculture experiments, we observed that non-parenchymal cells also participate to the DLK1/DIO3 locus expression in hepatocytes, through mechanisms, which remain to be elucidated. Importantly, exposure of Apc^{KO} hepatocytes to demethylating agent reduced the locus expression and cell proliferation, similarly to β-cat or MEG3 silencing. In future, we will explore how genome editing of the β-cat binding site upstream of the



A: miRNA-seq results **B:** ChIP-seq anti-TCF-4 and MeDIP-seq in APC^{KO} hepatocytes. **C:** measurement of miR-136 by qPCR NT : non-tumoral tissue non-tumoral, TUM : tumors, DEN : tumors obtained by diethylnitrosamine (independent on β-catenin), mut : β-catenin mutation, pretum : pretumoral

Figure: (abstract: PS-174)

locus affects the fate of Apc^{KO} hepatocytes and tumorigenesis. Preliminary experiments suggested that CRISPR/Cas9 editing of this site impaired the locus expression in Apc^{KO} hepatocytes, as expected. **Conclusion:** This project supports that the β-cat-dependent upregulation of the DLK1/DIO3 locus in early stages could be implicated in hepatocyte transformation towards a precancerous state. A control of the locus expression in hepatocytes should improve HCC treatment. Since miR-136, a miRNA produced from the locus, was also detectable in the serum in case of HCC, in mouse and human, its detection might also be useful for HCC diagnosis.

PS-175

Axin1 deficiency in human and mouse hepatocytes induces hepatocellular carcinoma in the absence of beta-catenin activation

A. Shirley[1], C. Coulouarn[2], R. Bruno[1], S. Mathilde[1], P. Bossard[1], S. Romain[1], J. Calderaro[3], J. Zucman-Rossi[3], J. Pierre-Alexandre[1], C. Perret[1], Hélène Gilgenkrantz[1,4]. [1]*Cochin, INSERM U 1016, Development Reproduction and Cancer, Paris, France;* [2]*Université Rennes 1, Nutrition Metabolims and Cancer, Rennes, France;* [3]*INSERM UMR 1162, Functional Genomics of Solid Tumors, Paris, France;* [4]*Centre de Recherche sur l'Inflammation, Faculté de médecine Bichat, Paris, France*
Email: helene.gilgenkrantz@inserm.fr

Background and Aims: The Wnt/beta-catenin pathway is the most frequently deregulated pathway in hepatocellular carcinoma (HCC). Inactivating mutations of the gene encoding AXIN1, a known negative regulator of the Wnt/β-catenin signaling pathway, are observed in about 10% of HCCs. Whole-genome studies usually place HCC with *AXIN1* mutations and *CTNNB1* mutations in the group of tumors with Wnt/β-catenin activated program. However, it has been shown that HCCs with activating *CTNNB1* mutations form a group of HCCs, with a different histology, prognosis and genomic signature compared to those with inactivating biallelic *AXIN1* mutations. We aimed at understanding the relationship between *CTNNB1* mutations, *AXIN1* mutations and the activation level of the Wnt/β-catenin program.
Method: We evaluated two independent human HCC datasets for the expression of a 23-β-catenin target genes program. We modeled *Axin1* loss of function tumorigenesis in two engineered mouse models and performed gene expression profiling.
Results: Based on gene expression, we defined three levels of β-catenin program activation: strong, weak or no activation. While more than 80% *CTNNB1*-mutated tumors were found in the strong or in the weak activation program, most of the *AXIN1*-mutated tumors (>70%) were found in the subgroup with no activation. We validated this result by demonstrating that mice with a hepatocyte specific *Axin1* deletion developed HCC in the absence of β-catenin induction. We defined a 329-gene signature common in human and mouse *AXIN1* mutated HCC that is highly enriched in Notch and YAP oncogenic signatures.
Conclusion: *AXIN1*-mutated HCCs occur independently of the Wnt/β-catenin pathway and involve Notch and YAP pathways. These pathways constitute potential interesting targets for the treatment of HCC due to *AXIN1* mutations.

PS-176

Cytokine-induced killer cells recruit myeloid derived suppressor cells in HCC, which can be targeted by a PDE5 inhibitor

S.J. Yu[1,2], C. Ma[1], B. Heinrich[1], Z. Brown[1], M. Sandhu[1], Q. Zhang[1], Q. Fu[1], D. Agdashian[1], F. Korangy[1], T. Greten[1]. [1]*National Institutes of Health, Gastrointestinal Malignancy Section, Thoracic and Gastrointestinal Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, United States;* [2]*Seoul National University College of Medicine,*

Department of Internal Medicine and Liver Research Institute, Seoul, Korea, Rep. of South
Email: tim.greten@nih.gov

Background and Aims: Cytokine induced killer (CIK) cell-based immunotherapy has been shown to be effective as adjuvant single agent therapy in patients with early stage hepatocellular carcinoma (HCC). However, its efficacy is lacking in advanced HCC. Increased myeloid-derived suppressor cells (MDSCs), a tumor-promoting immune subset which correlates with tumor progression, have been found in HCC patients.
Method: LDH cytotoxicity assay was performed to explore whether MDSCs can suppress CIK cell lytic function against HCC cells *in vitro*. We used tadalafil, a FDA approved PDE5 inhibitor, to test whether it could suppress MDSCs. To test whether tadalafil enhance CIK antitumor effects *in vivo*, we established three different tumor models using two different HCC murine cell lines (RIL-175 and BNL), subcutaneous and orthotropic tumor models, using two different mouse strains (C57BL/6 and BALB/c).
Results: Here, we describe an accumulation of tumor infiltrating MDSCs upon CIK cell infusion *in vivo*. We show that MDSCs efficiently suppress the cytotoxicity of CIK cells against HCC tumor *cells in vitro*. CIK anti-tumor effects can be enhanced by tadalafil. Mechanistically, tadalafil suppressed MDSCs function by blocking both ARG1 and iNOS. *In vivo* studies confirmed that tadalafil augments the efficacy of CIK cell-based immunotherapy for HCC in subcutaneous and orthotropic murine HCC models. In three different tumor models using two different HCC murine cell lines, subcutaneous and orthotropic tumor models, using two different mouse strains, a consistent increase of MDSC levels after CIK cell single therapy was observed in tumor tissues. Tadalafil treatment prevented MDSC accumulation in the tumor microenvironment upon CIK cell therapy and increased its efficacy. Finally, tadalafil also suppressed the function of human $CD14^{+}HLA\text{-}DR^{-/low}$ MDSCs and enhanced human CIK function against HCC cell lines *in vitro*.
Conclusion: Our results suggest that targeting MDSCs is an efficient strategy to enhance the antitumor efficacy of CIK cells for the treatment of patients with HCC.

NAFLD: Diagnostics and non-invasive assessment

PS-177

Noninvasvie prediction of oesophageal varics by liver stiffness measurement and platelet values in patients with liver cirrhosis due to nonalcoholic fatty liver disease: A multicenter cross-sectional study

S. Petta[1], G. Sebastiani[2], E. Bugianesi[3], M. Viganò[4], W. Sun V. Wong[5], A. Berzigotti[6], A.L. Fracanzani[7], Q. Anstee[8], F. Marra[9], M. Barbara[1], V. Calvaruso[1], C. Camma[1], V. Di Marco[1], R. Lombardi[10], M.G. Rumi[4], A. Craxi[11], V. De Ledinghen[11]. *[1]Sezione di Gastroenterologia e Epatologia, Di.Bi.M.I.S, Università di Palermo, Italia , Sezione di Gastroenterologia e Epatologia, Di.Bi.M.I.S, Università di Palermo, Italia , Palermo, Italy; [2]Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal QC, Canada, Division of Gastroenterology and Hepatology, McGill University Health Centre, Montreal QC, Canada, Toronto, Canada; [3]Division of Gastroenterology, Department of Medical Sciences, University of Torino, Torino, Italy, Division of Gastroenterology, Department of Medical Sciences, University of Torino, Torino, Italy, Torino, Italy; [4]Hepatology Unit, Ospedale San Giuseppe, University of Milan, Milan, Italy; [5]Affiliation of Vincent Wong: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, Affiliation of Vincent Wong: Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, Hong Kong, Hong Kong; [6]Swiss Liver Center, Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Switzerland, Swiss Liver Center, Hepatology, University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Switzerland, Bern, Switzerland; [7]Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Italy; [8]Institute of Cellular Medicine, Newcastle-upon-Tyne, United Kingdom; [9]Dipartimento di Medicina Sperimentale e Clinica, University of Florence, Italy; Research Center DENOTHE, University of Florence, Italy, Dipartimento di Medicina Sperimentale e Clinica, University of Florence, Italy; Research Center DENOTHE, University of Florence, Italy, Firenze, Italy; [10]Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Milano, Italy; [11]Centre d'Investigation de la Fibrose Hépatique, Hôpital Haut-Lévêque, Bordeaux University Hospital, Pessac, France, Centre d'Investigation de la Fibrose Hépatique, Hôpital Haut-Lévêque, Bordeaux University Hospital, Pessac, France, Bordeaux, France*
Email: petsa@inwind.it

Background and Aims: Baveno VI and extended Baveno VI criteria, based on the combination of liver stiffness(LS) with platelet(PLT) values, have been proposed to avoid unnecessary oesophagogastroduodenoscopy(OGD) screening for large oesophageal varices(OV) needing treatment (OVNT). However, this approach has not been validated in patients with NASH cirrosis. In this study, we aimed to validate these criteria for OVNT in this group, also considering potential differences in LS values with the M and XL probes. We also investigated whether these criteria could be useful for avoiding OGD in patients at low risk of any grade EV.
Method: We evaluated in 10 centers 791 patients with NAFLD related compensated cirrhosis who had OGD within 6 month of reliable LSM. LSM was obtained by FibroScan machine by using M and/or XL probe. Baveno VI(LS <20 and PLT > 150,000) and extended Baveno VI(LSM <25 and PLT > 110,000) criteria were tested.
Results: Any grade OV were found in 31.2% of the population, while OVNT in 11.5%. Three-hundred thirty-eight patients had LSM by M probe only, 138 patients by XL probe only, and 314 by both M and XL probes. In the subgroup of 314 patients with both M and XL probes (training set) Baveno VI and Baveno VI extended criteria spared 33.3% and 58% of OGD, respectively, missing 0.9% and 3.8% of large OV, respectively (Table 1). In this subgroup we identified as the best thresholds for rule-out large OV, PLT > 110,000 and LSM < 30 KPa for M probe, and PLT > 110,000 and LSM < 25 KPa for XL probe. The use of these thresholds allowed sparing 68.5% and 65% of OGD, respectively, by missing 4.2% and 4.9% of large OV, respectively. These results were validated in the 338 patients with LSM by only M probe, and in the 138 with LSM by only XL probe. In the first group PLT > 110,000 and LSM < 30 KPa was confirmed better than Baveno and Baveno VI (61.8% VS. 33.4% vs 54.1% spared endoscopy, and 4.8% vs. 4.4% vs 4.4% of missed large OV). Similar good results were obtained in the second group –138 patients with LSM by only XL probe- for PLT > 110,000 and LSM < 25 KPa (46.4% of spared endoscopy, and 1.6% of missed large OV). When looking at any grade OV as the main outcome, the best identified thresholds in the training set of 314 patients with LSM by both M and X probes, were PLT > 180,000 and LSM < 25 KPa for M probe (33.4% spared OGD and 9.5% missed any grade OV in training set; 31.4% and 13.2%, respectively, in validation set), and PLT > 180,000 and LSM < 20 KPa for XL probe (33.4% spared OGD and 10.5% missed any grade OV in training set; 23.2% and 9.4%, respectively, in validation set). Sensitivity analysis considering separately all the centers overall confirmed the reported results.
Conclusion: The combination of PLT and LSM values – stratified according to FibroScan probe- could help to identify patients with

compensated NAFLD-related cirrhosis at low risk of any grade OV and of large OV, in whom OGD screening can be safely sparred.

PS-178

Prediction of fibrosis improvement in patients with advanced fibrosis due to NASH using a machine learning approach: Unravelling the placebo response

A. Sanyal[1], T. Nguyen[2], L. Wang[2], Y. Xiao[2], C. Jia[2], R. Xu[2], S. Djedjos[2], M. Subramanian[2], R. Myers[2], V. Ratziu[3], N. Afdhal[4], J. Bosch[5], S. Harrison[6], Z. Goodman[7]. *[1]Virginia Commonwealth University, Richmond, VA, USA; [2]Gilead Sciences, Inc., Foster City, CA, USA; [3]Hôpital Pitié-Salpêtrière, Paris, France; [4]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA, USA; [5]Inselspital, Bern University, Switzerland, and IDIBAPS, University of Barcelona, Spain; [6]Pinnacle Clinical Research, San Antonio, TX, USA; [7]Inova Fairfax Hospital, Falls Church, VA, USA*
Email: asanyal@mcvh-vcu.edu

Background: Fibrosis improvement (FI) is an important endpoint in clinical trials of therapies for NASH. Our aim was to identify predictors of FI using machine learning in patients with advanced fibrosis due to NASH who received the ineffective therapy simtuzumab (SIM).
Methods: A machine learning algorithm (GUIDE v26.4) was applied to data from two Phase 2b trials of SIM in adults with NASH and advanced fibrosis (NASH CRN F3-F4) to develop predictive models for ≥1-stage FI at Week 48 (W48). The trials were stopped due to lack of efficacy so treatment groups were combined for this analysis. We used clinical, histologic, and serum fibrosis marker data to construct models including only baseline (BL) data or BL plus longitudinal data through W48. A variable importance score (VIS) assessed the aggregated variable contribution across the intermediate nodes of a GUIDE tree. Variables with VIS ≥0.7 in ≥75% of 100 bootstrapped GUIDE trees were considered to be associated with FI. The predictive performance of the models (AUROCs and misclassification error rates) was calculated using 100 bootstrapped GUIDE trees with 10-fold cross validation.
Results: 410/477 randomized subjects (86%) with complete clinical and histologic data were included. 48 subjects (12%) had FI at W48 (F3, 18%; F4, 6.5%). Predictive models including only noninvasive BL data performed well and similarly to full models including histological data (AUROCs 0.79–0.82; Table). Addition of longitudinal data only slightly improved model performance. Variables associated with FI in the full BL model (in >90% of bootstrap trees) included lower NASH CRN and Ishak fibrosis stage and hepatic α-smooth muscle actin expression. Noninvasive variables identified in both models included lower BL AST, ELF, hyaluronic acid, APRI, FIB-4, FibroTest (≥95% of bootstrap trees), α2-macroglobulin, NAFLD fibrosis score, TIMP-1, PIII-NP, and serum LOXL2 (75–95% of trees). The optimal GUIDE tree categorized subjects according to BL AST ≤ vs. >30 U/l (AUROC 0.70; 95%CI 0.63–0.77) independent of fibrosis stage. FI was identified in 27% (30/110) of subjects with BL AST ≤ 30 U/l vs only 6% (18/300) of those with AST >30 U/l. Similar findings were observed with models restricted to subjects with bridging (F3) fibrosis.

Table: Model Performance for FI at W48

Model	Model Parameters	AUROC (95% CI)	Error Rate (95% CI)
Baseline	Full	0.79 (0.67, 0.86)	0.27 (0.15, 0.52)
	Noninvasive	0.79 (0.70, 0.85)	0.27 (0.17, 0.47)
Longitudinal	Full	0.82 (0.72, 0.89)	0.25 (0.16, 0.39)
	Noninvasive	0.81 (0.73, 0.89)	0.26 (0.14, 0.41)

Conclusion: Machine learning models suggest that spontaneous FI over 48 weeks in subjects with advanced fibrosis due to NASH is greatest in those with lower disease severity at BL. These data suggest that the placebo response in clinical trials can be minimized via refinement of patient selection using noninvasive markers.

PS-179

Hepamet Score: a new non-invasive method for NAFLD-related fibrosis screening in clinical practice

J. Ampuero[1], Rocío Aller[2], Rocío Gallego-Durán[1], Jesús Banales[3], J. Crespo[4], E. Vilar-Gomez[5], S. Petta[6], C. Garcia-Monzon[7], N. Mora-Cuadrado[2], M. Castellanos-Fernandez[5], A. Craxi[6], María Jesús Pareja[8], Raúl Jiménez-Agüero[3], J. Caballería[9], María T. A. Loste[4], D. Escudero-García[10], J. Gómez-Camarero[11], José L.C. Panero[12], D.A. De Luis Román[2], L.G. Fabian[5], V. Di Marco[6], Águeda Gónzalez-Rodriguez[7], M. Latorre[13], A. Albillos[14], Víctor Aguilar-Urbano[15], J. Salmerón[16], José L. Olcoz-Goñi[17], P. Aspichueta[18], Álvaro Santos-Laso[3], O. Lo Iacono[19], P. Iruzubieta[4], I. Graupera[9], M. García-Torres[10], E. Badia-Aranda[11], J.A. Guerra[12], Rubén Francés[20], H. Pastor[1], E. Del Pozo-Maroto[7], M. Diago[13], R. Martin-Mateos[14], S. Benlloch[21], C. Fernández-Rodríguez[22], F.J.G.-S. Rey[23], P. Estevez[24], R.J. Andrade[25], J. Turnés[26], M.R. Gomez[1]. *[1]Hospital Universitario Virgen del Rocio, Sevilla. Instituto de Biomedicina de Sevilla. CiberEHD, Spain; [2]Hospital Clínico Universitario de Valladolid. Centro de Investigación de Endocrinología y Nutrición. Universidad de Valladolid, Spain; [3]Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute – Donostia University Hospital –, University of the Basque country (UPV/EHU), Ikerbasque, CIBERehd, San Sebastián, Spain; [4]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [5]Instituto Nacional de Gastroenterología, La Habana, Cuba; [6]Dipartimento Biomedico di Medicina Interna e Specialistica, Università di Palermo, Palermo, Italy; [7]Liver Research Unit Hospital Universitario Santa Cristina Instituto de Investigación Sanitaria Princesa Madrid, Spain; [8]Hospital Universitario Juan Ramón Jiménez, Huelva, Spain, Spain; [9]Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBPAS). Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD). Barcelona, Spain; [10]Hospital Clínico de Valencia, Spain; [11]Hospital Universitario de Burgos, Spain; [12]Hospital Universitario Puerta de Hierro, Madrid, Spain; [13] Hospital General Universitario de Valencia, Spain; [14]Hospital Universitario Ramón y Cajal, Madrid, Spain; [15]Agencia Sanitaria Costa del Sol, Marbella, Spain, Spain; [16]Hospital Universitario San Cecilio, Granada, Spain, Spain; [17]Hospital Universitario de León, Spain, Spain; [18]Biocruces Research Institute, Barakaldo. Department of Physiology, Faculty of Medicine and Nursing, University of Basque country UPV/EHU, Leioa, Department of Physiology, Faculty of Medicine and Nursing; [19]Hospital Univeristario Tajo, Aranjuez, Spain, Spain; [20]CIBERehd-Hospital General Universitario de Alicante. Universidad Miguel Hernández, Spain, Spain; [21]Hospital Universitari i Politecnic La Fe, Valencia. CIBERehd, Spain, Spain; [22]Hospital Universitario Fundación de Alcorcón, Universidad Rey Juan Carlos, Spain, Spain; [23]Hospital Universitario La Paz, CIBERehd, Madrid, Spain; [24]Complejo Hospitalario Universitario de Vigo, Spain, Spain; [25]Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain, Spain; [26]Complejo Hospitalario de Pontevedra, Spain, Spain*
Email: javi.ampuero@gmail.com

Background and Aims: To develop a non-invasive tool to predict fibrosis stage in NAFLD patients.
Method: International study including biopsy-proven NAFLD patients from Spain (n = 768), USA (n = 281) and Italy (n = 288). Fibrosis was staged according to Kleiner score. Hepamet score was developed in the Spanish cohort and validated in the two external subsets. Hepamet score was compared with NAFLD fibrosis score (NFS) and FIB4 predicting ≥F2, ≥F3 and F4. Diagnostic accuracy was assessed according to AUROC, sensitivity, specificity, positive and negative predictive values, correct classification and grey zone.
Results: In the estimation cohort (adjusted by ALT, BMI and triglycerides), age [45–64 yo OR 2.71 (95%CI 1.06–6.91) & age ≥65 yo OR 5.62 (95%CI 2.07–15.27)], female [OR 2.28 (95%CI 1.26–4.13)], T2DM [OR 2.19 (95%CI 1.25–3.85)], HOMA ≥ 4 [OR 7.35 (95%CI 2.61–

20.69)], albumin ≤ 4g/dl [OR 2.56 (95%CI 1.18–5.55)], platelets ≤ 150.000 [OR 10.1 (95%CI 4.11–24.78)] and AST [35–69 UI/ml OR 2.40 (95%CI 1.34–4.28) & AST ≥ 70 UI/ml OR 7.68 (95%CI 3.33–17.71)] were related to advanced fibrosis. Diagnostic accuracy is shown in Table. Validation in USA and Italy subsets: (a) ≥F2: 0.80 (95%CI 0.74–0.86), 0.76 (95%CI 0.70–0.81); (b) ≥F3 0.86 (95%CI 0.80–0.91), 0.83 (95%CI 0.77–0.88); (c) cirrhosis 0.92 (95%CI 0.87–0.97), 0.82 (95%CI 0.75–0.89).

Conclusion: Hepamet Score is a non-invasive tool to determine fibrosis in NAFLD patients. Hepamet score is superior to available methods (FIB4 and NFS), improving diagnostic accuracy and correct classification, as well as narrowing grey zone. It could be useful as fibrosis screening method in patients at risk of suffering NAFLD-related fibrosis.

	AUROC	Cut-off	Se	Sp	PPV	NPV	Grey zone	Correct classification
Fibrosis (F2)								
FIB4	0.75(95% CI	1.30	57%	79%	44%	87%	23.30%	65.75%
	0.70–0.79)	2.67	20%	98%	76%	81%		
NFS	0.72(95% CI	−1.455	64%	61%	31%	86%	32.90%	53%
	0.67–0.76)	0.675	26%	92%	48%	82%		
Hepamet	0.78(95% CI	12	58%	84%	51%	88%	11.30%	74.7%
Score	0.74–0.82)	24	41%	94%	66%	85%		
Fibrosis (F3)								
FIB4	0.78(95% CI	1.30	68%	76%	29%	94%	23.30%	70.80%
	0.72–0.84)	2.67	33%	98%	67%	91%		
NFS	0.77(95% CI	−1.455	76%	59%	21%	95%	32.90%	56.40%
	0.72–0.82)	0.675	35%	91%	35%	91%		
Hepamet	0.86(95% CI	12	80%	83%	39%	97%	11.30%	79.2%
Score	0.82–0.90)	24	55%	92%	49%	94%		
		24	74%	88%	16%	99%		
Cirrhosis (F4)								
FIB4	0.88(95% CI	1.30	91%	73%	9%	100%	23.30%	72.10%
	0.80–0.96)	2.67	57%	96%	28%	99%		
NFS	0.84(95% CI	−1.455	86%	56%	6%	99%	32.90%	56.30%
	0.75–0.92)	0.675	55%	89%	13%	98%		
Hepamet	0.92(95% CI	12	96%	77%	11%	100%	11.30%	77%
Score	0.88–0.97)							

PS-180

Performance of controlled attenuation parameter (CAP) to assess steatosis in a large prospective multicentre UK study of patients with non-alcoholic fatty liver disease (NAFLD)

P. Eddowes[1], M. Allison[2], E. Tsochatzis[3], Q. Anstee[4], D. Sheridan[5], I.N. Guha[6], J. Cobbold[7], V. Paradis[8], P. Bedossa[8], P. Newsome[9]. *[1]NIHR Birmingham Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom; [2]Liver Unit, Cambridge Biomedical Research Centre, Addenbrookes Hospital, Cambridge, United Kingdom; [3]UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom; [4]Institute of Cellular Medicine, Newcastle-upon-Tyne, United Kingdom; [5]Institute of Translational and Stratified Medicine, Plymouth University, Plymouth, United Kingdom; [6]NIHR Nottingham Biomedical Research Centre, NHS Trust and University of Nottingham, Nottingham, United Kingdom; [7]Department of Gastroenterology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, United Kingdom; [8]Department of Pathology, Physiology and Imaging, Beaujon Hospital Paris Diderot University, Clichy, France; [9]NIHR Birmingham Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom*
Email: p.n.newsome@bham.ac.uk

Background and Aims: The objective of this prospective study was to evaluate the diagnostic performance of CAP by FibroScan using either the M or XL probe, selected using the machine-embedded automated probe selection tool, in a cohort of patients with NAFLD versus steatosis at liver biopsy.

Method: According to the sample size calculation, 450 patients were enrolled to undergo FibroScan examination within 2 weeks of a clinically indicated liver biopsy (LB) for suspected NAFLD. Recruitment took place (Mar 2014–Jan 2017) at seven UK centres. LB were scored by two expert pathologists in a blinded manner with consensus using the NASH CRN system. NASH was diagnosed using the FLIP algorithm.

Diagnostic performance was assessed using area under the receiver operating curve (AUC). Cut-offs are computed for the Youden index and a sensitivity and a specificity of 90%.

Results: Among the 408 patients who completed the study, 381 had a valid FibroScan examination with CAP and a LB interpretable according to pathologist. 45% were female, with a median age 54 [IQR 18] years and BMI 33.8 [9.3] kg/m². Steatosis distribution was: S0: 12%, S1: 23%, S2: 28%, S3: 36%. 64% had NASH. The performance of CAP in distinguishing categories of steatosis is shown in the figure below.

	S ≥ S1	S ≥ S2	S = S3
CAP	AUC = **0.87** [0.82–0.92]	AUC = **0.77** [0.71–0.82]	AUC = **0.70** [0.65–0.75]
	$Cutoff_{Youden}$ = **302** dB/m	$Cutoff_{Youden}$ = **331** dB/m	$Cutoff_{Youden}$ = **337** dB/m
	Se = 0.80/Sp = 0.83	Se = 0.70/Sp = 0.76	Se = 0.72/Sp = 0.63
	PPV = 0.97/NPV = 0.37	PPV = 0.84/NPV = 0.58	PPV = 0.52/NPV = 0.80
	$Cutoff_{Se=0.90}$ = **274** dB/m	$Cutoff_{Se=0.90}$ = **292** dB/m	$Cutoff_{Se=0.90}$ = **302** dB/m
	Se = 0.90/Sp = 0.60	Se = 0.90/Sp = 0.45	Se = 0.90/Sp = 0.38
	PPV = 0.94/NPV = 0.47	PPV = 0.75/NPV = 0.71	PPV = 0.45/NPV = 0.87
	$Cutoff_{Sp=0.90}$ = **325** dB/m	$Cutoff_{Sp=0.90}$ = **370** dB/m	$Cutoff_{Sp=0.90}$ = **398** dB/m
	Se = 0.66/Sp = 0.89	Se = 0.34/Sp = 0.90	Se = 0.14/Sp = 0.90
	PPV = 0.98/NPV = 0.27	PPV = 0.86/NPV = 0.43	PPV = 0.45/NPV = 0.65

AUC: area under the receiver operating curve; Se: sensitivity; Sp: specificity; PPV: positive predictive value.
NPV: negative predictive value.

Conclusion: CAP had good performance to distinguish steatosis (S ≥ 1) but showed modest performance for the detection of higher grades of steatosis.

PS-181

Identification of serum protein biomarkers for non-invasive discrimination between NASH and simple steatosis using SOMAscan

M. Lai[1], H. Otu[2], L. Ngo[1], S. Dillon[1], X. Gu[1], N. Afdhal[1], T. Libermann[1].
[1]Beth Israel Deaconess Medical Center, Medicine, Boston, United States; [2]University of Nebraska – Lincoln, Lincoln, United States
Email: tliberma@bidmc.harvard.edu

Background and Aims: The gold standard for diagnosing NASH is liver biopsy. There is currently no high accuracy non-invasive test to discriminate between NASH and simple steatosis. We applied the SOMAscan proteomics platform that enables measurement of 1,310 proteins, including very low abundant proteins, to discover potential serum protein biomarkers for differentiating between NASH and simple steatosis and NASH with and without advanced fibrosis.

Method: Using SOMAscan (SomaLogic; Boulder, CO), quantitative serum protein profiles were generated from 20 subjects with simple steatosis, 20 subjects with NASH without advanced fibrosis (F0-2 fibrosis), and 20 subjects with NASH with advanced fibrosis (F3-4 fibrosis). To develop high accuracy predictors with the lowest number of proteins for discriminating NASH from simple steatosis and NASH with from NASH without advanced fibrosis discriminatory analysis was performed using 10,000 sub-sampled datasets. Each dataset contained a 4-fold split (i.e., 75%) of the original sample size. Counting the number of times a protein was identified with an adj. $p < 0.01$ in a "split" ranked these proteins according to their frequencies. Prediction accuracy, sensitivity and specificity of every combination of the top 10 proteins was determined to identify the highest accuracy predictors.

Results: A Leave-One-Out-Cross-Validation prediction accuracy of 91.7% was achieved for differentiating between NASH and simple steatosis using a 45-protein signature (adj. $p < 0.01$). A 43-protein predictor (adj. $p < 0.01$) that discriminated between NASH with advanced fibrosis and NASH without advanced fibrosis achieved 95%

prediction accuracy. Prediction analysis using combinations of the top 10 proteins identified a 5-protein signature (THBS2, BCL2A1, COLEC11, N6AMT1, GDF15) that distinguished between NASH and simple steatosis with an average 4-fold cross validation accuracy of 91.6% (93.9%sensitivity; 87% specificity) and AUROC of 0.9275. A 6-protein panel (SELE, IGFBP7, IGFBP5, NAGK, DCN, IL1R2) discriminated between NASH with advanced fibrosis and NASH without advanced fibrosis with an average 4-fold cross validation accuracy of 98.1% (96.2% sensitivity; 100% specificity) and AUROC of 1.

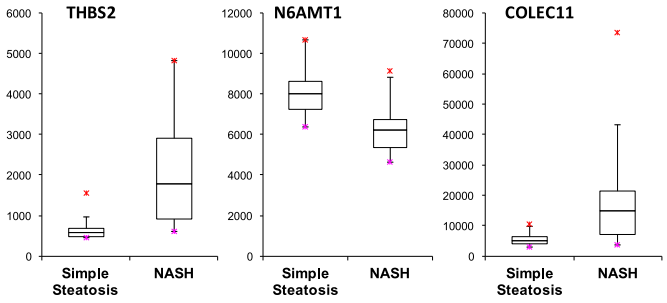


Figure: Box and Whisker Plots for 3 serum proteins that discriminate between NASH and simple steatosis.

Conclusion: This study demonstrates the feasibility of SOMAscan to discover high accuracy serum protein biomarkers linked to NASH and fibrosis. We aim to independently validate the diagnostic accuracy of these predictors in larger scale, prospective studies.

PS-182

The development of the diabetes liver fibrosis score: A new prediction model to detect advanced fibrosis in diabetics with nonalcoholic fatty liver disease

A. Singh[1], R. Lopez[1], A. Vigni[2], E. Lawitz[2], F. Poordad[2], A. Scott[2], T. Okubote[2], M. Scott[2], M. Mansouri[2], N. Alkhouri[3]. [1]*Cleveland Clinic, Gastroenterology and Hepatology, Cleveland, United States;* [2]*Texas Liver Institute, Gastroenterology and Hepatology, San Antonio, United States;* [3]*Texas Liver Institute, Texas Liver Institute, San Antonio, United States*
Email: singha4@ccf.org

Background and Aims: Patients with type 2 diabetes (T2DM) and nonalcoholic fatty liver disease (NAFLD) are at increased risk of having advanced fibrosis (AF). Recent data suggest that commonly used fibrosis scores such as the NAFLD fibrosis score (NFS) and FIB4 scores may have low sensitivity and negative predictive value when used specifically in a diabetic population. The aim of this study was to develop a simple noninvasive fibrosis score of AF in diabetics and compare its performance to other fibrosis scores.

Method: Using ICD-9 codes, patients with T2DM who had a liver biopsy for suspected NAFLD were identified. Patients with secondary causes of hepatic steatosis were excluded. Only patients with available clinical and laboratory data within 24-month period of liver biopsies were used for the analysis. Biopsies were assessed by a liver pathologist and the stage of fibrosis was determined (F0–F4) with AF being F3–4. A univariable analysis was performed to assess factors associated with advanced fibrosis. A predictive model was developed using logistic regression analysis. Discrimination and calibration for model performance were used for internal model validation. Receiver Operating Characteristics (ROC) analysis was performed to assess the value of the newly created score as well as known noninvasive fibrosis scores. Decision curve analysis (DCA) was performed to assess the net benefit of the predictive model.

Results: Out of 1,318 patients with T2DM and liver biopsies, 592 met inclusion criteria and 201 had AF. Mean age (years) at biopsy was 55.9 ± 11.2, 56% were females, 91% were overweight or obese. The new predictive model called the Diabetes Liver Fibrosis Score (DLFS) included the following variables: age, hypertension, chronic kidney disease, the use of statins, platelet count, and AST. The score has values ranging from 0 to 100. The AUROC for this model was 0.79 (95% CI: 0.75, 0.83) and internal validation of the model using bootstrap resampling showed an AUROC of 0.779. A score of 68.9 or higher maximizes specificity and PPV (98% and 86%, respectively). On the other hand, a score of 14.5 or lower maximizes sensitivity and NPV (95% and 92%, respectively). DLFS was significantly better than AST/ALT ($p < 0.001$), APRI ($p = 0.002$) and NFS ($p < 0.001$) at differentiating subjects with and without AF. There was no difference in AUCs when compared to FIB-4 score ($p = 0.13$) but decision curve analysis showed that our model provides more net benefit over a larger range of threshold probabilities (Figure).

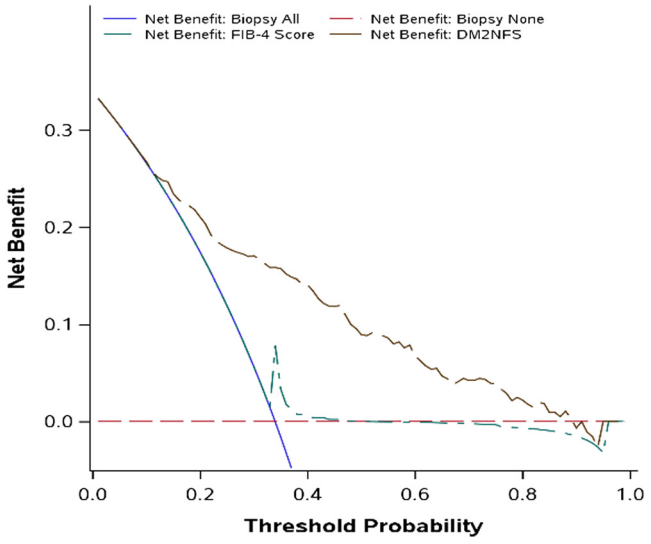


Figure: Decision curve analysis (DCA) showing the net benefit of DLSF in comparison to FIB4 score.

Conclusion: We developed a new diabetes-specific noninvasive fibrosis score that outperformed currently used fibrosis scores and may help in identifying diabetics at significant risk for liver-related morbidity.

PS-183

Long term prognostic value of the FibroTest in patients with non-alcoholic-fatty-liver disease (NAFLD), compared to chronic hepatitis C (CHC), B (CHB), and alcoholic liver disease (ALD)

M. Munteanu[1], J. Moussalli[2], M. Rudler[2], P. Lebray[2], H. Perazzo[2], J. Massard[2], R. Pais[2], F. Charlotte[2], V. Thibault[2], L. Olivier[2], L. Hannoun[2], M.A. Valantin[3], Y. Ngo[1], F. Drane[1], F.I. Bismut[3], O. Deckmyn[1], C. Housset[4], D. Thabut[4], V. Ratziu[5], T. Poynard[2]. [1]*BioPredictive, Research, Paris, France;* [2]*APHP, Hepatology, Paris, France;* [3]*APHP, MIT, Paris, France;* [4]*INSERM, UMR938, Paris, France;* [5]*UPMC, Heptology, France*
Email: tpoynard@teaser.fr

Background and Aims: Although the FibroTest (FT) has been validated as a biomarker for the diagnosis of the stages of fibrosis in NAFLD with results similar to those in CHC, CHB and ALD, it has not yet been confirmed for the prediction of liver related death (Lrd), possibly due to the lower incidence of Lrd and the higher non-liver-related causes of mortality (APT 2014). The primary aim was to assess the long-term prognostic value of FT for Lrd in NAFLD.

Method: All patients (pts) in the prospective FibroFrance-NCT01927133 cohort who underwent a FT between 1997 and 2012 were pre-included. Mortality status was obtained from the physician, the hospital or the national register. The cause of death was classified as Lrd, "cardiovascular" (CVrd) and "other". Survival analyses (events defined as death or transplantation) were based on univariate (KaplanMeier, Logrank, AUROC) and multivariate (Cox-Risk-Ratio (CRR)) analyses, taking into account age, gender and response to antiviral treatment as covariates. The independent prognostic value of each FT component was assessed for each liver disease. The main endpoint was the performance of the FT (AUROC/CRR), for Lrd, compared to results observed in CHC, the most validated population.
Results: A total of 7,012 pts were included; 1,070, 3,420, 2,027 and 495 with NAFLD, CHC, CHB, and ALD, respectively. At baseline, NAFLD pts were older than those with CHC (median;95%CI), 57(56-58) vs 48 (47–49) years old; (p = 0.0001), similar for male prevalence 57% vs 59%;(p = 0.30), and had a lower severity of fibrosis presumed by FT (mean FT;95%CI and % cirrhosis (F4) (0.24;0.22–0.25;6.8% F4) vs (0.45;0.43–0.46; 21.7% F4); (p = 0.0001). Mean follow-up was 7 years. Survival at 15 years without Lrd (SwLrd) in patients with NAFLD was 94% (91–97; 38 Lrd) and 91% (89–92; 223 Lrd; p = 0.007) in CHC. The prognostic value (AUROC/CRR) of FT for SwLRD in patients with NAFLD was highly significant (p = 0.0001) .92(0.87–0.95)/1638(342–7839) and not different from CHC. 89(0.87–0.91)/2657(993–6586). Staging of NAFLD into 7 categories using FT predicted decreasing 5-year SwLrd in F4.3 vs F4.2 and F4.1 (Figure) as validated previously in CHC and CHB (J Hepatol 2014). The prognostic value of FT in NAFLD. 56(0.51–0.60)/3.9(2.4–6.4) for overall survival (OS) (n death = 249), was significant (p = 0.0001) but lower than that observed in CHC (n = 489)0.76(0.73–0.78)/32(22–46), as expected because of the lower incidence of Lrd in NAFLD vs CHC. FT was also significant (p = 0.0001) for the prediction of CVrd .62(0.53–0.70)/vs. 58(0.51–0.65) in CHC, driven by a decrease in Apo1 and older age. Using CHB/ALD instead of CHC reported the same results.

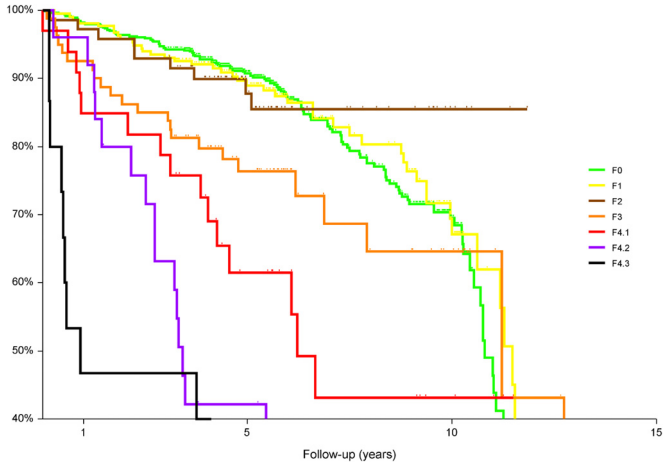


Figure: Survival according to 7 stages of fibrosis presumed by the FibroTest in 1,070 NAFLD patients.

Conclusion: The FibroTest has a high predictive value for survival without liver disease or transplantation in patients with NAFLD, similar to that observed in patients with CHC, CHB, and ALD.

Late breaker: Orals

LBO-001

A multicenter, randomized, double-blind, PLB-controlled trial of Galectin-3 inhibitor (GR-MD-02) in patients with NASH cirrhosis and portal hypertension

N. Chalasani[1], G. Garcia-Tsao[2], Z. Goodman[3], E. Lawitz[4], M. Abdelmalek[5], M. Rinella[6], M. Ryan[7], M. Noureddin[8], C. Jue[9], M. Pyko[1], A. Allgood[10], H. Shlevin[10], R. Horton[10], E. Zomer[10], P. Traber[10], R. Loomba[11], B. Tetri[12], A. Sanyal[13], S. Harrison[14]. *[1]Indiana University School of Medicine; [2]Yale University School of Medicine; [3]Inova Fairfax Hospital; [4]The Texas Liver Institute; [5]Duke University Medical Center; [6]Northwestern University – Feinberg School of Medicine; [7]Digestive and Liver Disease Specialists; [8]Cedars Sinai Medical Center; [9]Digestive Health Specialists; [10]Galectin Therapeutics; [11]University of California San Diego Medical Center; [12]Saint Louis University; [13]Virginia Commonwealth University; [14]Pinnacle Clinical Research*
Email: nchalasa@iu.edu

Background and Aims: Galectin-3 protein is implicated in the pathogenesis of NASH and toxin-induced fibrosis in animal models, both of which were improved by GR-MD-02, a novel gal-3 inhibitor. To test the safety and efficacy of GR-MD-02 in patients with NASH cirrhosis and PH.
Method: Phase 2B study randomized adults with NASH cirrhosis and portal hypertension (PH) to receive either placebo (PLB), or GR-MD-02 at 2 mg/kg (GR2), or GR-MD-02 at 8 mg/kg (GR8) in 26 biweekly intravenous infusions over 52 weeks. Eligibility criteria were HVPG ≥ 6 mmHg, no or small varices, NASH cirrhosis by biopsy, and no complications from cirrhosis. Primary endpoint was change in HVPG (Δ HVPG) at the end of treatment (EOT), compared to baseline (BL); secondary endpoints were changes in liver histology and the development of complications. Subgroup analyses were conducted in (a) no esophageal varices at BL and (b) mild PH (HVPG between ≥6 and <10 mmHg) at BL.
Results: 162 patients were randomized to receive PLB (n = 54), GR2 (n = 54), or GR8 (n-54). BL demographic, clinical, and laboratory characteristics were similar among the 3 groups. Baseline HVPG (mmHg) was 11.6 ± 4 in PLB, 12.3 ± 4.3 in GR2, and 12.7 ± 4.2 GR8 groups. 81 patients had no esophageal varices at BL (33 PLB, 25 GR2, and 23 in GR8) and 53 had mild PH (20 PLB, 17 GR2, and 16 in GR8). The total patient population had no statistically significant difference in Δ HVPG between PLB and GR (Δ PLB = 0.3 mmHg, Δ GR2 = −0.37 mmHg, Δ GR8 = −0.42 mmHg). There was no effect on fibrosis or NAFLD Activity Score, but there was a statistically significant improvement in hepatocyte ballooning with GR2 (p = 0.03) and a trend with GR8 (p = 0.09) versus PLB.
In patients without varices, there was a significant difference in ΔHVPG between PLB and GR2 (PLB = 0.8 mmHg, GR-2 = −1.08 mmHG, p < 0.01 vs PLB) but not with GR8 (−0.42 mmHg), p = 0.36 vs PLB). Also, significantly fewer patients receiving active treatment developed new varices at E0T (PLB 6, GR2 = 0 (p = 0.02) and GR8 = 1 (p = 0.12) and for combined treatment groups versus PLB (p = 0.01). In mild PH, there was a significant difference in ΔHVPG between PLB and both treated groups (PLB = 1.7 mmHg, GR2 = −0.2, p = 0.055 vs PLB, GR8 = −0.2, p = 0.036 vs PLB). Responder analysis, defined as the percent who had both ↓HVPG ≥ 2 mmHg and ≥ 20% ↓HVPG was significantly higher in GR2 (13% PLB vs. 43% in GR-2, p = 0.01) but not GR8 (18%, p = ns). GR2 and GR8 were well tolerated with similar proportion of AEs and SAEs; more patients discontinued GR8 with AE (n = 5), 0 in PLB or GR2.
Conclusion: GR-MD-02 did not improve HVPG or liver fibrosis in the entire study population, but significantly improved hepatocyte ballooning. Significant and clinically relevant beneficial effects of GR2 were evident in NASH cirrhosis without varices, or those with

mild PH. Significantly fewer GR2 patients developed new varices at EOT. These data warrant further investigating GR-MD-02 in patients with NASH cirrhosis without varices.

LBO-002

NGM282, an engineered analogue of FGF19, significantly improves markers of bile acid synthesis, hepatic injury and fibrosis in PSC patients: Results of a phase 2, multicenter, randomized, double-blind, placebo-controlled trial

G. Hirschfield[1], O. Chazouillères[2], J. Ph Drenth[3], D. Thorburn[4], S. Harrison[5], C. Landis[6], M.J. Mayo[7], A. Muir[8], J.F. Trotter[9], M. Karsdal[10], M. Jaros[11], L. Ling[12], K.H. Kim[12], S. Rossi[12], R.M. Somaratne[12], A. Depaoli[12], U. Beuers[13]. *[1]University of Birmingham, Birmingham, United Kingdom; [2]Assistance Publique Hopitaux de Paris, Hepatology and Gastroenterology, Paris, France; [3]Radboud University, Nijmegen, Netherlands; [4]Royal Free Hospital, London, United Kingdom; [5]Pinnacle Clinical Research, Live Oak, United States; [6]University of Washington, Medicine, Seattle, United States; [7]University Texas Southwestern Medical Center, Medicine, Dallas, United States; [8]Duke University Medical Center, Medicine, Durham, United States; [9]Texas Digestive Disease Consultants, Clinical Research, Southlake, United States; [10]Nordic Biosciences, Herlev, Denmark; [11]Summit Analytical, Chicago, United States; [12]NGM Bio, Clinical Development, S. San Francisco, United States; [13]AMC, University of Amsterdam, Amsterdam, Netherlands*
Email: srossi@ngmbio.com

Background and Aims: PSC is an inflammatory, cholestatic and progressively fibrotic liver disease devoid of effective medical interventions. NGM282, an engineered, non-tumorigenic FGF19 analogue, is an experimental agent in development for chronic liver diseases that potently regulates CYP7A1-mediated bile acid (BA) homeostasis. We evaluated the biologic activity and safety of NGM282 in patients with PSC.

Method: Sixty-two patients, with diagnosed PSC by EASL criteria and an elevated ALP >1.5 x ULN at Baseline (BL), were randomized to NGM282 1mg, 3mg or placebo as a daily SC injection for 12W. Treatment was stratified by current UDCA treatment at BL. Enrollment criteria allowed for PSC patients with stable dominant strictures, small duct disease, features of autoimmune hepatitis and compensated cirrhosis. The primary endpoint was change in ALP from BL to W12, with secondary endpoints of safety as well as surrogate biomarkers of BA synthesis, hepatic injury and liver fibrosis.

Results: Potent target engagement was seen in NGM282-treated subjects *vs.* placebo, with significant reductions in C4 and serum BA (Table 1). At W12, ALP was not significantly reduced from BL in either UDCA-treated or -untreated subjects. However, ALT and AST significantly improved with both doses as early as W1 and sustained through W12 with the 3mg dose. Moreover, total Enhanced Liver Fibrosis [ELF] Score, PIIINP and TIMP-1 also decreased, with the greatest effect in those stratified to higher risk disease (ELF >9.8 at BL, n = 26). Decreases in PRO-C3 were significant across both treatment arms. There was no difference in PSC-related clinical events between NGM282 *vs.* placebo study arms. No drug-induced pruritus was observed in either NGM282 study arm. There was no evidence of neutralizing anti-drug antibodies detected during or after NGM282 treatment. The most common adverse events in NGM282-treated subjects were diarrhea, frequent stools and injection site reactions, the majority of which were mild and resolved while on treatment.

Conclusion: NGM282 potently inhibited BA synthesis, decreased markers of hepatic inflammation and significantly improved markers of fibroblastic response and matrix formation in PSC patients, consistent with effects seen in NASH patients. The significant improvements in PRO-C3, ELF and serum transaminases support longer trials of NGM282 in PSC, with a focus on liver fibrosis as a meaningful surrogate endpoint of efficacy.

Table 1: Mean Change from BL to W12 of Key Biomarkers

	Placebo (n = 20)	NGM282 1 mg (n = 21)	NGM282 3 mg (n = 21)
C4 (ng/ml)	0.4	−7.9#	−14.7*
Total Serum BA minus UDCA (umol/l)	−4.03	−12.6#	−16.8#
ALP (U/l)	5	26	−3
ALT (U/l)	−4	−3	−40#
AST (U/l)	−5	−8	−23#
ELF Score	0.06	−0.33#	−0.31
Pts w/ELF ≥9.8 at Baseline	0	−0.53*	−0.58#
PRO-C3 (ng/ml)	3.4	−6.3*	−10#

#p < 0.01;*p < 0.05.

LBO-003

RO7049389, a core protein allosteric modulator, demonstrates robust anti-HBV activity in chronic hepatitis B patients and is safe and well tolerated

E. Gane[1], A. Liu[2], M-F. Yuen[3], C. Schwabe[1], Q. Bo[2], S. Das[4], L. Gao[2], X. Zhou[2], Y. Wang[2], E. Coakley[5], Y. Jin[2]. *[1]Auckland Clinical Studies, Auckland, New Zealand; [2]Roche Innovation Center Shanghai, Shanghai, China; [3]Unversity of Hong Kong, Medicine, Hong Kong, China; [4]Roche Products Limited, Shire Park, United Kingdom; [5]Roche Innovation Centre New York, New York, United States*
Email: sudip.das@roche.com

Background and Aims: RO7049389 is a small molecule, Class I HBV core protein allosteric modulator (CpAM). It induces formation of abnormal hepatitis B virus (HBV) core aggregates resulting in defective capsid assembly thereby suppressing HBV replication. In the AAV-HBV mouse model, robust HBV DNA declines (≈3.0 $\log_{10}$ copies/ml) were observed over 56 days of dosing.

Method: The ongoing Phase I study investigates the safety, tolerability, pharmacokinetics (PK), and anti-HBV activity of RO7049389. Study Part 1 evaluates the safety and PK of single ascending doses (SAD) of RO7049389/placebo (5 dosing cohorts from 150–2000 mg) and multiple ascending doses (MAD) (5 dosing cohorts from 200–800 mg BID x 14 days) in healthy volunteers (HVs). Study Part 2 also interrogates the anti-HBV effects of RO7049389 in untreated chronic HBV (CHB) patients (4 planned cohorts BID x 28 days).

Results: 75 HVs have been dosed in this study. Across the dosing range, RO7049389 was rapidly absorbed and eliminated from plasma. A trend of greater than dose-proportional increases in exposure from 150 to 1000 mg, and approximately dose-proportional increases from 1000 to 2000 mg were observed in SAD cohorts. Accumulation of RO7049389 in MAD cohorts was minimal or none.

A blinded safety evaluation demonstrated that RO7049389/placebo in HVs was well tolerated in the SAD and MAD cohorts. In Part 1, a total of 55 adverse events (AEs) were reported in 36/75 HVs. In Part 2, a total of 14 AEs were reported in 3/7 patients. All AEs were reported as being mild in intensity with only five being considered as related to RO7049389, these were: nausea, abdominal discomfort, rash and 2 cases of headache. No serious AEs or AEs leading to drug discontinuation were reported and no clinically significant changes in ECG parameters, vital signs, or laboratory safety test results were observed.

Six CHB patients completed 28 days dosing period of RO7049389 at a dose of 200mg BID. Robust and continued HBV DNA declines from pre-dosing levels were observed, with median (maximal) decline being 2.7 (3.4) $\log_{10}$ IU/ml and below the limits of detection in 3/6 patients. No on-treatment virologic rebound was observed.

Conclusion: The RO7049389 appears to be safe, generally well tolerated and demonstrates robust anti-HBV activity over 28 days of dosing in patients with CHB.

LBO-004

Safety, pharmakokinetics and antiviral activity of novel capsid assembly modulator (CAM) JNJ-56136379 (JNJ-6379) in treatment-naive chronic hepatitis B (CHB) patients without cirrhosis

F. Zoulim[1,2], J.Z. Yogaratnam[3], J.J. Vandenbossche[4], O. Lenz[4], W. Talloen[4], C. Vistuer[4], I. Moscalu[5], A. Streinu-Cercel[6], S. Bourgeois[7], M. Buti[8], J. Crespo[9], J.M. Pascasio[10], C. Sarrazin[11], T. Vanwolleghem[12,13], L. Blatt[3], J. Fry[3]. *[1]Croix Rousse Hospital, Hospices Civils de Lyon, Department of Hepatology, Lyon, France; [2]INSERM U1052-Cancer Research Institute of Lyon, Lyon, France; [3]Alios Biopharma (a Janssen Pharmaceutical Company of Johnson & Johnson), South San Francisco, United States; [4]Janssen Pharmaceuticals BV, Beerse, Belgium; [5]Spitalul Clinic Republican, Chisinau, Moldova; [6]National Institute for Infectious Diseases "Prof. Dr. Matei Balş, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [7]ZNA Jan Palfijn, Clinical Pharmacology Unit, Merksem, Belgium; [8]Hospital Universitario Vall d'Hebrón, Unidad de Heptologia, Barcelona, Spain; [9]Hospital Universitario Marques de Valdecilla, Servicio Aparato Digestivo, IDIVAL, Santander, Spain; [10]Hospital Universitario Virgen del Rocio, UGC Enfermedades Digestivas, Sevilla, Spain; [11]Medizinische Klinik II, St. Josefs-Hospital, Wiesbaden, Germany; [12]Erasmus MC, University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [13]University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium*
Email: fabien.zoulim@inserm.fr

Background and Aims: JNJ-6379 is a potent and selective HBV replication inhibitor with a dual mode of action, inhibiting both early and late steps of the viral life cycle. This study aims to evaluate safety, pharmacokinetics and antiviral activity of multiple ascending doses of JNJ-6379 in CHB patients.

Method: Treatment-naïve, HBeAg-positive or -negative CHB patients, with plasma HBV DNA >2000 IU/mL, METAVIR <F3 and ALT/AST <2.5 the upper limit of normal, were enrolled into this ongoing, randomized, double-blind, placebo-controlled Phase 1b study. Patients were randomized in a 3:1 ratio to receive JNJ-6379 or placebo for 28 days with 8 weeks follow-up. To date, 3 groups have been evaluated (25 mg QD [after 100 mg loading dose], 75 mg QD and 150 mg QD). Evaluation of a fourth group (250 mg QD) is ongoing.

Results: Across all groups (n = 36), median age was 42.5 years (range: 21–58), 83% males, 78% Caucasian, 11% Asian, 6% Black/African American, 6% other/not reported. 25% of patients were HBeAg-positive.

At Day 29, substantial reductions from baseline in HBV DNA (Table) and HBV RNA were observed in all 3 treatment groups. No notable changes in HBsAg were observed.

Adverse events (AEs) or laboratory abnormalities ≥Grade 3 were infrequent (≤3 patients/dose); 64% (23/36) experienced ≥1 AE on treatment (25 mg, n = 9/12; 75 mg, n = 6/12; 150 mg, n = 8/12). There was one serious AE (right frontal lobe mass, unrelated to study drug), one discontinuation due to AEs (isolated ALT/AST flare with no bilirubin elevation, likely related to study drug), and no dose-limiting toxicities. After repeated administration, drug exposure increased in a dose-dependent manner. Apparent drug clearance was low, and similar across groups and ethnicities.

Conclusion: JNJ-6379 administered for 28 days was generally well tolerated and resulted in potent antiviral activity at all doses evaluated, and the data from this study warrants additional evaluation of the compound in phase 2a.

LBO-005

The impact of combining Selective Internal Radiation Therapy (SIRT) with Sorafenib on overall survival in patients with advanced hepatocellular carcinoma: The Soramic trial palliative cohort

J. Ricke[2], B. Sangro[3], H. Amthauer[4], I. Bargellini[5], P. Bartenstein[6], E. De Toni[7], A. Gasbarrini[8], H.-J. Klümpen[9], M. Peck-Radosavljevic[10], P. Popovic[11], O. Rosmorduc[12], E. Schott[13], M. Van Buskirk[14], P. Malfertheiner[15]. *[1]Ludwig-Maximilians University Munich, Department of Radiology, Munich, Germany; [2]Maximilians University Munich, Department of Radiology, Munich, Germany; [3]Clinica Universidad de Navarra, Liver unit, Pamplona, Spain; [4]Charite University Hospital Berlin, Department of Nuclear Medicine, Berlin, Germany; [5]University of Pisa, Department of Diagnostic and Interventional Radiology, Pisa, Italy; [6]Ludwig-Maximilians University Munich, Department of Nuclear Medicine, Munich, Germany; [7]Ludwig-Maximilians University Munich, Department of Gastroenterology, Munich, Germany; [8]Catholic University of Rome, Department of Gastroenterology, Rome, Italy; [9]Academic Medical Center, University of Amsterdam, Department of Medical Oncology, Amsterdam, Netherlands; [10]Klinikum Klagenfurt, Department of Gastroenterology Austria, Klagenfurt, Austria; [11]Ljubljana University Medical Centre, Slovenia, Department of Radiology, Ljubljana, Slovenia; [12]University Hospital St. Antoine, Department of Hepatogastroenterology, Paris, France; [13]Charite University Hospital Berlin, Department of Gastroenterology, Berlin, Germany; [14]Data Reduction LLC, Chester, United States; [15]University Hospital Magdeburg, Department of Gastroenterology, Hepatology and Infectious Diseases, Madgeburg, Germany*
Email: jens.ricke@med.uni-muenchen.de

Background and Aims: SORAMIC is an RCT comprising diagnostic, local ablation and palliative studies. Based on the result of the diagnostic study patients were assigned to either the local ablation or palliative cohort. The palliative treatment cohort (reported here) was designed to determine the efficacy and safety of combining SIRT (Selective Internal Radiation Therapy) with sorafenib in patients with advanced HCC.

Method: In the palliative treatment cohort, patients not eligible for TACE were randomised 11:10 to either SIRT with Y-90 resin microspheres plus sorafenib (target dose 400 mg bid) or sorafenib alone. The primary endpoint was overall survival (OS; Kaplan-Meier analysis) in the intention-to-treat population.

Results: In the ITT palliative treatment cohort, 214 patients were randomised to SIRT + sorafenib and 205 to sorafenib alone. Median OS was 12.1 months (95% confidence interval [CI], 10.4–14.6) in the SIRT + sorafenib arm, and 11.5 months (95% CI, 9.9–13.9) in the sorafenib arm (hazard ratio [HR], 1.018; 95% CI, 0.821–1.262; p = 0.8726). In the per-protocol group, median OS was 12.6 months (95% CI, 11.6–16.0) in the SIRT + sorafenib arm (n = 134), and 11.5 months (95% CI, 9.8–13.9) in the sorafenib arm (n = 200; HR, 0.919; 95% CI, 0.722–1.170; p = 0.4914). Subgroup analyses of the per-protocol population revealed a survival benefit of SIRT+ sorafenib for: patients ≤65y (HR 0.820); without PVT (HR 0.745); Child Pugh A vs B (HR 0.356); BCLC A & B vs C (HR 0.800). When stratified by PVT, a survival benefit was seen in: patients ≤65y (HR 0.736); without cirrhosis (HR 0.746); Child Pugh A vs B (HR 0.356); without metastases (HR 0.804). Adverse events (AEs) of Common Terminology Criteria for AE Grade ≥3 were reported in 128/176 (72.7%) patients in the SIRT + sorafenib arm and 126/193 (65.3%) patients in the sorafenib arm, respectively.

Conclusion: The addition of SIRT to sorafenib did not result in a significant improvement in Overall Survival compared to sorafenib alone. Subgroup analyses led to hypothesis generating results for patient groups with potential clinical benefit.

LBO-006

JKB-121 in patients with nonalcoholic steatohepatitis: A phase 2 double blind randomized placebo control study

A.M. Diehl[1], S. Harrison[2], S. Caldwell[3], M. Rinella[4], A. Paredes[5], C. Moylan[6], C. Guy[7], M. Bashir[8], Y. Wang, PhD[6], Dr. L. Miller[9], A. Chang, PhD[9], E. Sc Wu, PhD[9], M. Abdelmalek[9]. *[1]Duke University, Division of Gastroenterology, Durham, United States; [2]Pinnacle Research, San Antonio, United States; [3]University of Virgina Health System, Charlottesville, United States; [4]Northwestern Univrsity, Division of Gastroenterology, Chicago, United States; [5]Brooke Army Hospital, Division of Gastroenterology, San Antonio, United States; [6]Duke University, Division of Gastroenterology, Durham; [7]Duke University, Department of Pathology, Durham, United States; [8]Duke University, Center of Advanced Magnetic Resonance Development, Durham, United States; [9]TaiwanJ Pharmaceuticals Co, Ltd, Zhubei City, Taiwan*
Email: manal.abdelmalek@duke.edu

Background and Aims: NASH is a rapidly growing cause of chronic liver disease worldwide with significant medical need for effective treatments. TLR-4 is a key mediator of obesity-associated inflammation, insulin resistance and hepatic inflammation and fibrosis. JKB-121 is a weak antagonist of the TLR-4 receptor demonstrated to prevent NASH in a methionine/choline deficient diet fed rat model of NAFLD, decrease NASH and fibrosis in STAM model and inhibit hepatic stellate cell activation and collagen expression in vitro. The aim of this study was to assess the safety/tolerability and biologic activity of JKB-121 in patients with biopsy-proven NASH.
Methods: This is a multicenter, randomized (1:1:1), double-blind, placebo-controlled study in adults with biopsy-proven NASH with a NAS ≥ 4 (1 point in each component), stage 1–3 fibrosis, ≥6% liver fat content (LFC) by MRI-PDFF, and elevated liver aminotransferases (ALT > 40 U/l for women and > 60 U/l for men). Randomization was stratified by diabetes status. Patients received JKB-121 5 mg, 10 mg, or placebo twice daily for 24 weeks. The primary endpoint was reduction in LFC by MRI-PDFF and/or serum ALT at 24 weeks. Exploratory endpoints included serum biomarkers (FIB4, Fibro Test).
Results: 65 patients were randomized (median age, 51.0 years; woman, 68%; type 2 diabetes 66%; median BMI 35.2; median LFC 17.3%; median ALT 69 ± 36 U/l). Baseline characteristics, including histologic grade and stage, LFC, and biochemical parameters were comparable among groups. At week 24, median relative and absolute LFC improved in all groups with no difference in JKB-121 treatment groups compared to placebo (p > 0.05). At week 24, in JKB-121 5 mg, 10 mg vs placebo, change in ALT was -5.4 U/l, -3.8 U/l, and -15.2 U/l, p > 0.05) with biochemical remission (ALT < 40 U/l on two consecutive measures) in 28.5%, 18.2%, and 31.8%, respectively, (p > 0.05). JKB-121 did not improve BMI, glycosylated hemoglobin, HOMA-IR, total-, LDL-, HDL-cholesterol or triglycerides compared to placebo. Fib4 improved in the placebo group (p < 0.05). The most frequent drug-related adverse events (AEs) in JKB-121-treated patients were nausea (26.4% vs 22.7% in placebo), dizziness (36% vs 0%), constipation (9.1% vs 4.5%), vomiting (14.3% vs 4.5%), fatigue (9.1% vs 4.5%), and most AEs were mild. Serious AEs occurred in two patients; neither were considered drug-related. There were no deaths. Drug-related AEs leading to withdrawal in 10 mg, 5 mg vs placebo occurred in 27.3%, 9.5% vs 0%, respectively.
Conclusions: A notable improvement in LFC, ALT and FIB4 was observed in the placebo group in this 24 week NASH study. JKB-121 did not further improve the response rate in patients with NASH (F1-F3) compared to placebo. Given the multiple relevant biologic pathways of TLR-4 in pathogenesis NASH, further investigation of TLR-4 inhibition, as well as factors contributing to higher placebo response rates, is warranted.

Table 1

	Placebo (n=22)	JKB-121 5 mg (n=21)	JKB-121 10 mg (n=22)
Median relative LFC Δ (SE) from baseline to week 24 *vs placebo*	-2.30% (4.27%) *	1.10% (4.82%) *p=0.03*	-2.40% (5.15%) *p=0.17*
Median absolute LFC Δ (SE) from baseline to week 24 *vs placebo*	3.30% (3.27%)*	3.20% (2.88%)* *p=0.57*	4.40% (2.55%)* *p=0.66*
Patients with>5% relative reduction in LFC (% pts)	63%	41%	64%
20% reduction in ALT at week 24 (% patients)	91%	57%	41%
Biochemical Remission	33.3%	27.8%	30.8%
Δ in Fibro Test (SE) from baseline to week 24	-0.036 (0.06)	0.002 (0.09)	0.013 (0.12)
Δ in Fib4 (SE) from baseline to week 24	-0.38 (0.67)*	-0.09 (0.61)	0.08 (0.80)
Completed Study	21 (95.5%)	18 (85.7%)	13 (59.1%)
Drug-related adverse events	0	2 (9.5%)	6 (27.3%)
Withdrawal /Lost to follow-up	1 (4.8%)	1(4.8%)	3 (13.6%)
** p<0.05*			

LBO-007

Early assessment of safety and efficacy of tropifexor, a potent non bile-acid FXR agonist, in patients with primary biliary cholangitis: An interim analysis of an ongoing phase 2 study

C. Schramm[1], G. Hirschfield[2], A.L. Mason[3], H. Wedemeyer[4], L. Klickstein[5], S. Neelakantham[5], P. Koo[5], J. Sanni[5], M. Badman[5], D. Jones[6]. *[1]University Medical Centre Hamburg-Eppendorf, Department of Medicine and Martin Zeitz Centre for Rare Diseases, Hamburg, Germany; [2]University of Birmingham, National Institute of Health Research (NIHR) Biomedical Research Unit (BRU) and Centre for Liver Research, Birmingham, United Kingdom; [3]University of Alberta, Division of Gastroenterology and Hepatology, Edmonton, Canada; [4]Universitätsklinikum Essen, Klinik für Gastroenterologie und Hepatologie, Essen, Germany; [5]Novartis Institutes for BioMedical Research, Translational Medicine, Cambridge, United States; [6]Newcastle University, Institute of Cellular Medicine, Newcastle-upon-Tyne, United Kingdom*
Email: michael.badman@gmail.com

Background and Aims: In patients with primary biliary cholangitis (PBC), incomplete response to first-line therapy with ursodiol (UDCA) is associated with increased risk of cirrhosis and death. The bile acid FXR agonist obeticholic acid is approved as second-line therapy for PBC. Tropifexor (LJN452) is a selective and highly potent, non-bile acid FXR agonist that reduces cholestasis and hepatocellular damage in rodent models. This trial was designed to test the safety, tolerability and preliminary efficacy of tropifexor in PBC patients.
Method: This ongoing multi-part, international, double blind, placebo controlled, ascending dose Phase 2 study enrolled PBC patients with an inadequate response to UDCA (ALP ≥ 1.67xULN or Bilirubin > ULN), who were taking UDCA. Patients were randomized in cohorts (approx. 10 active to 5 placebo) to receive 30 µg, 60 µg or 90 µg of tropifexor once daily, or matching placebo, for 4 weeks. A planned interim analysis was conducted on completion of Cohort 3 (90 µg tropifexor). The pre-specified primary efficacy outcome was change in GGT from baseline to avoid the confounding effect of FXR mediated induction of ALP. Safety analyses included number of subjects to discontinue, evaluation of adverse events and laboratory markers.
Results: There were no deaths, non-fatal serious adverse events or discontinuations due to adverse events or itch. Baseline demographic and biochemical parameters were similar across groups (ALP 358, 317, 281 and 323 iU for pooled placebo, 30, 60 and 90 µg tropifexor arms). There was a brisk decrease in GGT, ALP, ALT and AST (tabulated below) with 72% reduction in GGT at 90 µg tropifexor at day 28. Biochemical markers had not yet reached their maximum changes at completion of dosing. Reductions in HDL of 33% and 26% occurred at doses of 60 µg and 90 µg tropifexor respectively and returned to baseline by end of study. There was no increase in total or LDL cholesterol at any dose of tropifexor tested.
Conclusion: Tropifexor was generally safe and well tolerated at the doses tested. The dose dependent activity on markers of cholestasis (GGT) and hepatocellular damage (ALT) indicates the potential benefit of FXR agonism by tropifexor in PBC. The absence of

discernible increase in itch raises the possibility that tropifexor may have a tolerability advantage over obeticholic acid. Tropifexor shows promise as a potential future therapy for PBC and longer term studies are warranted.

Table: Summary of mean change (%) from baseline at day 28 and repeated measures analysis for LFT parameters

%change	Placebo (n = 16)	Tropifexor 30 µg (n = 10)	Tropifexor 60 µg (n = 9)	Tropifexor 90 µg (n = 12)
GGT	−15	−26	159**	−72**
ALP	−2	−10	−26*	−15
Bilirubin	−9	−9	−1	−17
Albumin	−1	2	−3	1
ALT	0	10	−30*	−41**
AST	−5	9	−14	−26*

*p < 0.05 **p < 0.001 vs placebo by repeated measures of analysis of covariance of log-transformed ratio to baseline.

LBO-008

A phase 3b, open-label, randomized, pragmatic study of glecaprevir/pibrentasvir +/− ribavirin (RBV) for HCV genotype 1 subjects who previously failed an NS5A Inhibitor + sofosbuvir (SOF) therapy

A. Lok[1], I. Willner[2], R. Reddy[3], M. Hassan[4], F. Hinestrosa[5], M. Shiffman[6], M. Sulkowski[7], R. Brown[8], G. Morelli[9], J. Peter[9], M.W. Fried[10], M. Vainorius[10], L. Michael[10], G. Wang[9], Y. Hu[11], J. Kort[11], D.R. Nelson[9]. *[1]University of Michigan, Ann Arbor, United States; [2]Medical University of South Carolina, Charleston, United States; [3]University of Pennsylvania, Philadelphia, United States; [4]University of Minnesota, Minneapolis, United States; [5]Orlando Immunology Center, Orlando, United States; [6]Liver Institute of Virginia, Richmond, United States; [7]Johns Hopkins, Baltimore, United States; [8]Weill Cornell Medicine, New York, United States; [9]University of Florida, Gainesville, United States; [10]University of North Carolina Chapel Hill, Chapel Hill, United States; [11]AbbVie, Mettawa, United States*
Email: joy.peter@medicine.ufl.edu

Background and Aims: The fixed dose combination of once daily 300 mg glecaprevir, an HCV NS3/4A protease inhibitor (PI), and 120mg pibrentasvir (GP), an NS5A inhibitor (NS5Ai), was FDA approved for the treatment of chronic HCV infection; including genotype 1 (GT1) patients who failed a prior NS5Ai-containing regimen without prior exposure to a PI. The aimes of this study are: (1) to add further evidence in GT1 NS5Ai/SOF ±RBV failures utilizing the FDA label-consistent GP regimen given for 16 weeks and (2) to explore a shorter 12-week duration of GP in non-cirrhotic subjects and compensated cirrhotics (RBV added).

Total Started	Arm A GP 12 wks (n = 71)	Arm B GP 16 wks (n = 41)	Arm C GP + RBV 12 wks (n = 22)	Arm D GP 16 wks (n = 20)
	Non-Cirrhosis		Cirrhosis	
GT 1/1A	56(79%)	31(78%)	18(82%)	17(85%)
White	42(59%)	18(45%)	13(59%)	14(70%)
Black	27(38%)	21(53%)	8(36%)	6(30%)
Male	59(83%)	32(80%)	16(72%)	17(85%)
SAE	1(1%)	0(0%)	1(1%)	0(1%)
Response*	(n = 49)	(n = 16)	(n = 17)	(n = 11)
SVR 4	**96%**	**100%**	**82%**	**100%**
Relapse	1(2.4%)	0(0%)	0(0%)	0(0%)
Breakthrough	1(2.4%)	0(0%)	3(18%)	0(0%)

*Among those reaching time point.

Method: NS5Ai plus SOF±RBV-experienced, chronic HCV GT1 participants were randomized as follows: up to 150 non-cirrhotics (NC) in 2:1 ratio to *Arm A- GP for 12 weeks (NC-12)* and *Arm B- GP for 16 weeks* (*NC-16*) and up to 100 with compensated cirrhosis (CC) in a 1:1 ratio to *Arms C-GP + weight-based RBV BID for 12 weeks (CC-12 + R)* and *Arm D-GP for 16 weeks (CC-16).* Randomization is stratified by GT1 subtype (1b or non-1b). All baseline samples and any virologic failure samples are subject to deep sequencing for NS3 and NS5A resistance-associated substitutions. Primary endpoint is sustained virologic response 12 weeks post treatment (SVR12).
Results: To date, 196/154 subjects have been screened/dosed. The primary reason for screen failures was decompensated cirrhosis. The enrolled population is mostly male (81%), 40% Black, and majority are GT1a (83%). Of the dosed 112 NCs, 69% have reached SVR4 or 12 (SVR 4/12). In NC-12, 47/49 (96%) and in NC-16 16/16 (100%) achieved SVR4/12. Among 42 dosed CCs, 14/17 (82%) in CC-12 + R and 11/11 (100%) in CC-16 achieved SVR4/12 to date (TABLE 1). 5 treatment failures were observed: 2 in NC-12 (1 relapse, 1 breakthrough) and 3 in CC-12 + R, which were all breakthroughs, leading to suspension of the CC-12 + R arm. There have been no early treatment discontinuations to date. The most frequent adverse events (AEs) are fatigue (10%) and headache (15%). Two serious AEs, a small bowel obstruction (Arm A) and sepsis (Arm C)- have been observed.
Conclusion: Patients who failed direct acting antiviral HCV therapy represent a challenging population with few retreatment options. To date, treatment failure has occurred in 3% of NCs and 11% of CCs, all confined to the experimental 12 week regimens. Complete outcome and resistance data of this large ongoing study of GP for prior GT1 NS5Ai + SOF ±RBV failures will be presented.

EASL JOURNAL OF HEPATOLOGY

Posters Thursday, 12 April 2018

Late breaker: Posters

LBP-001

Long-term efficacy and safety of WTX101 in Wilson disease: Data from an ongoing extension of a phase 2 study (WTX101-201)

K.H. Weiss[1], F. Askari[2], P. Ferenci[3], A. Ala[4], A. Czlonkowska[5], D. Nicholl[6], J. Bronstein[7], D. Bega[8], M. Schilsky[9]. [1]*University Hospital Heidelberg, Heidelberg, Germany;* [2]*University of Michigan, Ann Arbor, United States;* [3]*Medical University of Vienna, Vienna, Austria;* [4]*The Royal Surrey County Hospital NHS Foundation Trust, Guildford, United Kingdom;* [5]*Institute of Psychiatry and Neurology, Warsaw, Poland;* [6]*Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom;* [7]*University of California Los Angeles, Los Angeles, United States;* [8]*Northwestern University, Chicago, United States;* [9]*Yale University Medical Center, New Haven, United States*
Email: KarlHeinz.Weiss@med.uni-heidelberg.de

Background and Aims: WTX101 (bis-choline tetrathiomolybdate) is a copper-protein-binding agent that reduces plasma non-ceruloplasmin bound copper (NCC) by forming tripartite complexes with albumin and increases biliary copper excretion. In a Phase 2 study in Wilson disease (WD), oral once-daily WTX101 rapidly reduced $NCC_{corrected}$ (corrected for copper in tripartite complexes), improved disability and neurological status, and stabilized liver function over 24 weeks. We present preliminary 72-week efficacy and safety data from an ongoing Phase 2 study extension, the first prospective report on long-term disease control with WTX101 in WD.
Method: All 22 patients completing the 24-week open-label, single-arm Phase 2 study opted to continue once-daily response-guided treatment with WTX101 in the extension. Key parameters reviewed to 72 weeks included hepatic status, $NCC_{corrected}$, neurological status, safety and tolerability.
Results: Mean ALT, international normalized ratio, albumin, and Model for End-Stage Liver Disease score improved or remained stable between week 24 and 72. Reversible ALT elevations requiring dose adjustments, observed in 39% of patients (at > = 30 mg/day) to week 24, were not observed in the extension. Elevated mean (SD) $NCC_{corrected}$ at baseline (3.6 [2.1] μM) was reduced and controlled at week 24 (0.9 [1.0] μM) and remained controlled at week 72 (0.5 [0.7] μM) with accompanying continuous improvements in disability and neurological status in most patients. Low platelet (56%) and neutrophil (32%) counts were common at baseline, with similar reporting throughout follow-up; low hemoglobin was infrequent. Most cytopenias were not accompanied by low NCC levels and unlikely to reflect copper deficiency. Two subjects had evidence of neutropenia accompanied by mild anemia and low NCC potentially consistent with copper deficiency at week 36 and 72, respectively; both responded rapidly to dose reduction. Overall, the number of reported adverse events (AEs) and serious AEs (SAEs) decreased by more than 50% from weeks 1–24 (175 AEs and 11 SAEs) to weeks 25–72 (71 AEs and 4 SAEs). Between week 24 and 72, 89% of AEs were mild or moderate, with 89% considered unrelated or unlikely related to therapy.
Conclusion: Once-daily treatment of WD patients with WTX101 up to 72 weeks provided long-term disease control as shown by sustained improvements in NCC, disability and neurological status and stable hepatic function, with a favorable tolerability profile.

LBP-002

Treatment efficacy and safety of seladelpar, a selective peroxisome proliferator-activated receptor delta agonist, in primary biliary cholangitis patients: 12- and 26-week analysis from an ongoing international, randomized, dose raging phase 2 study

G. Hirschfield[1], P. Boudes[2], C. Bowlus[3], N. Gitlin[4], G. Michael[5], S. Harrison[6], S.C. Gordon[7], R. Aspinall[8], Y. Doerffel[9], A.E. Kremer[10], D. Sheridan[11], B. Bacon[12], C. Berg[13], B. Borg[14], T. Hassanein[15], J. Odin[16], M. Shiffman[17], P.J. Thuluvath[18], D. Thorburn[19], D. Bernstein[20], P. Buggisch[21], L. Corless[22], C. Levy[23], M.J. Mayo[24], M.G. Swain[25], J. Vierling[26], M.-A. Wörns[27], A.(S.) Steinberg, MD, PhD[2], S. Bergheanu[28], Y.-J. Choi, PhD[2], M. Varga[2], R. Martin[2], C. Mcwherter[2], D. Jones[29]. [1]*University of Birmingham, Birmingham, United Kingdom;* [2]*CymaBay Therapeutics, Newark, United States;* [3]*University of California Davis, Sacramento, United States;* [4]*Atlanta Gastroenterology Associates, Atlanta, United States;* [5]*Digestive Healthcare of Georgia, Atlanta, United States;* [6]*Pinnacle Clinical Research, San Antonio, United States;* [7]*Henri Ford Health System, Detroit, United States;* [8]*Queen Alexandra Hospital, Portsmouth, United Kingdom;* [9]*Charité Hospital, Berlin, Germany;* [10]*Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany;* [11]*Plymouth Hospitals NHS Trust & Plymouth University, Plymouth, United Kingdom;* [12]*Saint Louis University School of Medicine, Saint Louis, United States;* [13]*Universitätsklinik Tübingen, Tübingen, Germany;* [14]*Southern Therapy and Advanced Research, Jackson, United States;* [15]*Southern California Research Center, Coronado, United States;* [16]*Icahn School of Medicine at Mount Sinai, New York, United States;* [17]*Liver Institute of Virginia, Richmond, United States;* [18]*The Institute for Digestive Health & Liver Disease at Mercy, Baltimore, United States;* [19]*Royal Free London, London, United Kingdom;* [20]*Hofstra Northwell School of Medicine, Manhasset, United States;* [21]*IFI at the Asklepiosklinik St. Georg, Hamburg, Germany;* [22]*Hull Royal Infirmary, Hull, United States;* [23]*Division of Hepatology, University of Miami, Miami, United States;* [24]*University of Texas, Southwestern Medical center, Dallas, United States;* [25]*University of Calgary, Calgary, Canada;* [26]*Advanced Liver Therapies, Baylor College of Medicine, Houston;* [27]*Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Mainz, Germany;* [28]*Saberg Clinical Research BV, The Hague, United States;* [29]*University of Newcastle, Newcastle upon Tyne, United States*
Email: pboudes@cymabay.com

Background and Aims: Seladelpar is a potent and selective PPAR-delta agonist with potential as a new therapeutic approach for patients with inflammatory liver diseases. From an ongoing open-label phase 2 study in patients with primary biliary cholangitis (PBC), we report biochemical, disease symptom, and safety data with up to 26 weeks of treatment across three doses (2 mg, 5 mg and 10 mg) of seladelpar.
Methods: Randomized, open-label study (EudraCT**:** 2016-002996-91) of patients with PBC that were either inadequately responding to ursodeoxycholic acid (UDCA, alkaline phosphatase -AP- ≥1.67x upper limit of normal) or intolerant of UDCA. Data up to 12 weeks evaluated seladelpar doses of 2, 5 and 10 mg/day. Data up to 26 weeks evaluated

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doses of 5 and 10 mg/day. After 12 weeks, patients on 5 mg could escalate to 10 mg if their AP treatment goal was not achieved. The primary efficacy outcome is the AP % change from baseline. Secondary outcomes include AP responder analyses, and changes in other liver, metabolic, and inflammatory markers. Pruritus was evaluated with a visual analogue scale (VAS, 0–100) and specific questionnaires. Safety analysis includes evaluation of adverse events (AE) and laboratory markers.

Results: As of January 2018, 71 patients were exposed to at least one dose of seladelpar, of whom 53 received 12 weeks of treatment and 42 received 26 weeks of treatment. At baseline, mean AP were 358, 333, and 262 UI/l in the 2, 5, and 10 mg groups, respectively. At 12 weeks, changes in AP were -21%, -33%, and -45% in the 2 (n = 6), 5 (n = 25), and 10 (n = 22) mg groups, respectively. At 26 weeks, 69%, 67%, and 79% of patients had an AP < 1.67 x ULN in the 5 (n = 13), 5 to 10 (n = 6), and 10 mg (n = 19) groups, respectively, and falls in AP were equal across regimens: -45%, -43%, and -43%, respectively. Overall, 29% had a normal AP at 26 weeks. At 12 weeks, median ALT changes were -9%, -28%, and -35% in the 2, 5, and 10 mg groups, respectively and decreases were maintained at 26 weeks in the 5 and 10 mg groups (≥-40%).

Seladelpar did not increase pruritus. Baseline median pruritus VAS was 10 and 36 in the 5 and 10 mg group, respectively, and patients in the 10 mg group experienced consistent decreases during follow up (-24% at week 26) suggesting anti-pruritic activity. Seladelpar was generally safe and well tolerated, with no transaminase elevation safety signal. There were 6 serious AEs and none were deemed related to seladelpar.

Conclusion: In patients with PBC, Seladelpar demonstrates potent and sustained anti-cholestatic and anti-inflammatory efficacy over 26 weeks of administration (10mg daily, or 5 mg titrated to 10 mg). Treatment efficacy is not associated with pruritus, and future studies will evaluate long term efficacy, safety as well as potential anti-pruritic properties.

LBP-003

Scheduled endoscopic dilatation of dominant strictures improves survival in patients with primary sclerosing cholangitis

C. Rupp[1,2], T. Hippchen[1], D. Gotthardt[1], A. Stiehl[1], P. Sauer[1]. [1]*Medical University Hospital (New Krehl Clinic), Internal Medicine IV, Heidelberg, Germany;* [2]*Medical University Hospital (New Krehl Clinic), Interdisciplinary Endoscopy Unit, Heidelberg, Germany*
Email: christian_rupp@med.uni-heidelberg.de

Background and Aims: Endoscopic treatment of dominant strictures in patients with Primary sclerosing Cholangitis (PSC) is recommended in those patients present with symptoms. Benefits following dilatation or stenting included improvement of clinical symptoms and of liver biochemical test results, as well as a longer transplantation-free survival compared to that predicted in survival models. The impact on actual long term survival of a scheduled endoscopic treatment independent of symptoms up to a resolution of dominant strictures has not been evaluated so far.

In this prospective trial, we compared clinical outcome and long-term survival in PSC patients with adherence to a provided scheduled endoscopic surveillance and treatment program to that in PSC patients receiving endoscopic diagnostic and therapy only on clinical demand.

Method: PSC patients that were treated at our tertiary center between 1987 and 2016 were included into the study. All patients were offered to participate in an endoscopic surveillance and treatment program with scheduled endoscopic interventions (scheduled group). Diagnostic ERC was performed annually and endoscopic treatment of identified DS was carried out in defined intervals up to a complete resolution of the stricture. Patients who refused to participate received surveillance with clinical evaluation, liver function tests and imaging methods, including liver ultrasound and magnetic resonance imaging in frequent intervals. Endoscopic intervention was performed in case of deterioration of cholestasis or signs of acute cholangitis (on demand group).

Results: The final study cohort comprises 286 PSC patients. 133 (46.5%) patients received ERC according to our proposed scheduled program. In the 153 (53.5%) remaining cases ERC was conducted on demand. Clinical and laboratory baseline characteristics did not differ between both groups. After a follow-up period of thirty years the transplantation-free survival in patients with scheduled endoscopic therapy was significantly higher compared to patients with on demand therapy (median: 17.9 vs. 15.2 years; log-rank: p = 0.008). In subgroup analysis benefit of scheduled ERC was achieved in patients with dominant stricture (17.8 vs. 11.1 years; log-rank: p < 0.001), but not in patients without dominant stricture (21.0 vs. 18.7 years; log-rank: p = 0.8). Multivariate analysis confirmed presence of inflammatory bowel disease IBD (p = 0.03), presence of DS (0.006), Mayo risk score MRS (p = 0.02) and adherence to scheduled endoscopy (p = 0.005) independently associated with transplantation-free survival.

Conclusion: Scheduled endoscopic surveillance and therapy improves transplantation-free survival in PSC patients with dominant strictures.

LBP-004

Long term outcomes of treatment with Trientine in Wilson disease: Final results from a multicentre study in patients withdrawn from d-Penicillamine therapy

K.H. Weiss[1], N. Manolaki[2], M.G. Zuin[3], C. Kruse[4], A. Dhawan[5]. [1]*University Hospital Heidelberg, Internal Medicine IV, Heidelberg, Germany;* [2]*"Aghia Sophia" Children's Hospital, 2nd Department of Pediatrics, Athens, Greece;* [3]*University of Milan, Department of Health Sciences, Milan, Italy;* [4]*Univar B.V., Medical Affairs, Rotterdam, Netherlands;* [5]*King's College Hospital London, Paediatric Liver GI Nutrition Centre, London, United Kingdom*
Email: KarlHeinz.Weiss@med.uni-heidelberg.de

Background and Aims: Trientine dihydrochloride (Trientine; UNIVAR B.V.) is a common treatment for Wilson Disease. This study aimed to assess efficacy, safety, and tolerability outcomes of Trientine chelator-based treatment after withdrawal of d-Penicillamine. ClinicalTrials.gov Identifier: NCT02426905.

Method: In a multicenter, retrospective cohort study assessments were performed for 6, 12, 24, 36 and 48 month time points and at the latest available follow-up after Trientine initiation. A total of 81 patients were enrolled into the study, with 77 (95.1%) patients included in the intention to treat (ITT) population. Primary endpoint was investigator rated outcome of hepatic and neurologic symptoms, additional efficacy analysis included copper parameter, LFTs. Safety reporting included SAE and discontinuation rate.

Results: Of the 77 patients included in the ITT population, 16 (20.8%) patients were under the age of 18 years. Reasons for discontinuation of D-Penicilamine were adverse events (58 [75.3%] patients) or lack of clinical improvement (12 [15.6%] patients).

On average, patients were treated with trientine for 73.3 (±74.76) months. The mean total dose per day during treatment was 1005.7 (±425.32) mg. Treatment with trientine improved hepatic symptoms in 49.4% of patients, with 35.1% asymptomatic, 10.4% unchanged and 5.2% worsened, whereas neurological symptoms remained unchanged in 36.4% of patients, with 46.8% asymptomatic, 14.3% improved and 2.6% worsened. Overall, the median NCC concentration showed a decrease from baseline to latest follow up (n = 35 [–0.613 ± 1.7318]).

A total of 17 (22.1%) patients experienced a serious TEAE. The majority of these TEAEs were resolved, resolved with sequelae or improved. Only two serious TEAEs were considered related to trientine and both resolved. Treatment with trientine was permanently discontinued due to a TEAE in 1 (1.3%) patient (anemia). Two (2.6%) patients discontinued trientine treatment due to inadequate hepatic response.

Figure 1; Hepatic and Neurological Outcome Over Time (ITT)

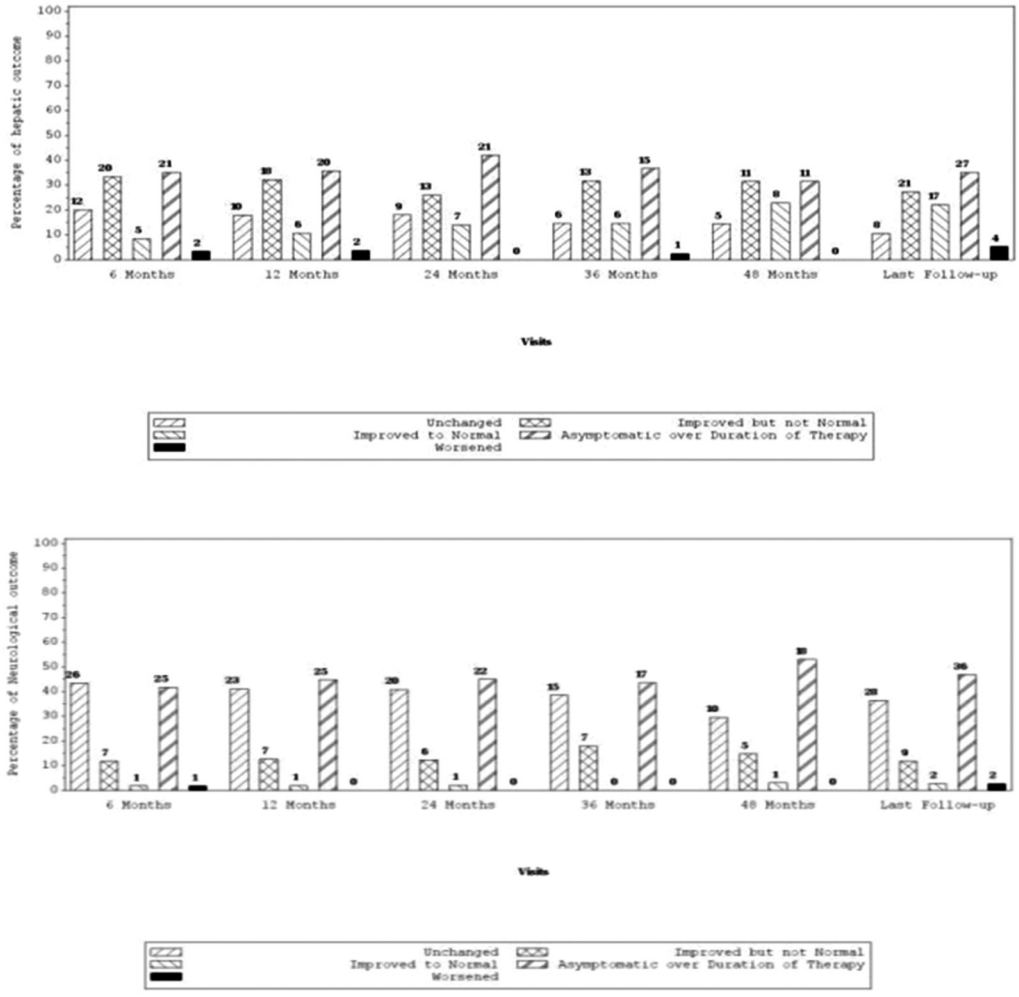


Figure: (abstract: LBP-004)

Conclusion: Anti-copper therapy with trientine was effective following withdrawal of treatment with d-Penicillamine. Trientine well tolerated and the rates of symptomatic deterioration were lower than reported in previous series. These findings supports Trientine's prominent role in Wilson Disease management.

LBP-005

Results of a placebo-controlled double blind randomised trial to investigate the efficacy of rifaximin-alpha versus placebo in improving systemic inflammation in patients with cirrhosis and chronic hepatic encephalopathy (RIFSYS Trial)

V. Patel[1], M.J.W. Mcphail[1], A. Zamalloa[1], S. Støy[1,2], G.M. Vijay[1], X. Huang[1], G. Rogers[3], J. Choo[3], L. Edwards[1], E. Gray[1], C. Woodhouse[1], S. Gencer[4], M. Coen[4], J. Wendon[1], K. Bruce[5], D. Shawcross[1]. *[1]King's College London, Liver Sciences, 1st Floor James Black Centre, School of Immunology & Microbial Sciences, Faculty of Life Sciences and Medicine, London, United Kingdom; [2]Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; [3]South Australian Health and Medical Research Institute, Microbiome Research, Adelaide, Australia; [4]Imperial College London, Biomolecular Medicine, Division of Computational and Systems Medicine, Department of Surgery and Cancer, London, United Kingdom; [5]King's College London, Institute of Pharmaceutical Science, 5th Floor Franklin-Wilkins Building, London, United Kingdom*

Email: debbie.shawcross@kcl.ac.uk

Background and Aims: Rifaximin-α is efficacious in the prevention of the recurrence of overt hepatic encephalopathy (HE) but its mechanism of action remains unclear. We postulated that rifaximin reduces gut microbiota-derived endotoxaemia and systemic inflammation which is a known driver of HE and contributes to cirrhosis associated immune dysfunction and susceptibility to developing infection.

Methods: A randomised placebo-controlled double blind study of rifaximin-α versus placebo was performed in 38 patients with cirrhosis and chronic persistent overt HE or with ≥2 episodes of overt HE in the previous 6 months; 19 in each arm. Rifaximin-α 550mg (TARGAXAN) twice daily or placebo was administered for 90-days. The primary outcome was a 50% reduction in spontaneous neutrophil oxidative burst (OB) after 30-days. Secondary outcomes included Psychometric Hepatic Encephalopathy Scale (PHES) testing, 16S rRNA faecal microbiota profiling, plasma, urine and faecal ^{1H}NMR metabolic profiling, whole blood bacterial DNA quantification, neutrophil TLR4 expression and plasma cytokine analyses. Assessments were undertaken at baseline and at 30 and 90-days.

Results: Patients were well matched with no significant difference in their median MELD [11(8–15) rifaximin vs 10(8–12) placebo], ammonia or HE grade. Participants on rifaximin but not placebo normalised their HE grade by day-30 [grade 1 to 0; p = 0.014]. Trail's A (PHES) improved significantly on rifaximin compared to placebo over 90-days; p = 0.012 and line tracing after 30-days; p = 0.023. OB did not

change. While a non-significant reduction (p = 0.09) in neutrophil TLR4 expression (surrogate marker of circulating endotoxin) after 30-days of rifaximin was observed, significant (p < 0.001) reductions in plasma TNFα occurred to day-90. Despite this there were no global changes in gut microbiota composition as assessed by alpha and beta diversity. Minor changes in circulating whole blood microbiota profiles were observed with rifaximin but no change in endogonenous metabonomic profile.

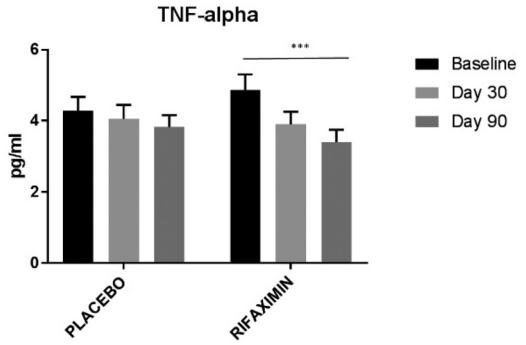


Figure: Plasma TNFα concentrations over 90 days demonstrating significant (***, p < 0.001) reductions in the group receiving rifaximin.

Conclusions: In addition to providing significant benefit in cognitive function, rifaximin led to a reduction in systemic inflammation in the absence of any change in gut microbiota composition. Quantitative metagenomic profiling of paired saliva and faecal samples is now being undertaken to interrogate this further.

LBP-006

PBI-4050, a potential anti-fibrotic drug, improves liver fibrosis in Alström Syndrome, an ultra-rare disease

S. Baig[1], T. Geberhiwot[1], L. Gagnon[2], B. Grouix[2], P. Laurin[2], L. Foulkes[3], C. Dorion[2], F. Cesari[2], O. Vaughan[3], J. Moran[2]. [1]*Queen Elizabeth Hospital, Centre for Rare Disease, Birmingham, United Kingdom;* [2]*Prometic Biosciences Inc., Laval, Canada;* [3]*Prometic Biosciences Ltd., United Kingdom*
Email: l.gagnon@prometic.com

Background and Aims: Fatty liver in Alström syndrome (AS) is observed in early childhood and is rapidly progressive compared to the common metabolic syndrome-related NASH: 50% of patients manifest severe fibrosis/cirrhosis (F3/F4) by early adulthood. PBI-4050 is an orally active drug candidate in phase 3 clinical trials for Idiopathic Pulmonary Fibrosis; it has demonstrated strong anti-fibrotic activity in numerous animal models of fibrosis in the liver, kidney, lung, heart or pancreas. PBI-4050 has been shown to significantly reduce liver fibrosis in CCl4-induced liver fibrosis, in bile duct ligation, in obese and in diabetic (*ob/ob* and *db/db*) mouse models. The aim of this study was to determine if PBI-4050 can improve liver fibrosis in AS patients.
Method: A phase 2, single-centre, single-arm, open-label study was undertaken in adult subjects with AS. The primary objective was to evaluate the safety and tolerability of 800 mg PBI-4050 administered orally once daily for up to 84 weeks, with secondary/exploratory objectives including evaluation of liver fibrosis (enzyme levels, quantitative MRI and FibroScan® analysis). An interim analysis was performed to compare the baseline and last available measurement for each patient.
Results: Twelve adult subjects (8 males, 4 females) with AS were enrolled. There were no drug-related serious adverse events, and PBI-4050 was well tolerated. The interim analysis suggests that treatment with PBI-4050 reduced liver fibrosis as measured by quantitative MRI [T1-corrected score] (p = 0.02, 95% CI -92.3, -9.8), and also correlated with the lowering of mean FibroScan® values from 10.2 to 8.6 kPa (p = 0.05, 95% -2.9, -0.3). Furthermore, the results of insulin clamp studies showed that PBI-4050 reduced mean endogenous glucose production (EGP) (1.88 to 0.89, ↓47%, p = 0.03); EGP is an indicator of hepatic insulin resistance.
Conclusion: These results demonstrate the potential of PBI-4050 to improve liver fibrosis, and support its further development as a treatment for liver fibrosis in AS.

LBP-007

Phase 1/2a trial of a bioartificial liver support system for acute liver failure patients

S. Lee[1], J.-H. Lee[2], D.-H. Lee[3], H. Park[2], Y. Kim[2], M. Park[2], E.M. Jang[3], J.G. Jung[3], J.K. Noh[3], Y. Hee-Hun[3], S.-K. Lee[4]. [1]*Samsung Medical Center, Department of Surgery, Seoul, Korea, Rep. of South;* [2]*Samsung Medical Center;* [3]*Lifeliver, Co.Ltd;* [4]*Samsung Medical Center, Department of Surgery*
Email: sukkoo.lee@samsung.com

Background and Aims: Bioartificial liver (BAL) support offers a potential means of improving survival of acute liver failure (ALF) patients by providing partial liver function until a suitable donor liver is found or the native liver undergoes regeneration. Previous studies have suggested that ALF patients treated using BAL maintain a more stable medical condition, which may positively influence outcome after liver transplant (LT). This clinical trial was conducted to evaluate the safety and efficacy of the LifeLiver BAL system in ALF patients.
Method: Patients with evidence of acute liver failure exhibiting hepatic encephalopathy grade 2 or worse who were listed for deceased donor liver transplant were eligible for enrollment. Hepatocytes were harvested from 3~4 weeks old male pigs weighing 4 to 10 kg, raised in a sterile environment. The isolate hepatocytes were cultured to form spheroids and were then mixed with 1.5% alginate solution and placed in a high content/speed immobilization apparatus and dropped into 100mM calcium solution. The Ca-alginate-immobilized hepatocyte spheroid beads were packed within the bioreactor of the BAL system. BAL treatment was continued for up to 12 hours.
Results: Six patients were given BAL treatment and were included in the safety analysis. Adverse events related to BAL treatment included coagulopathy (increased INR), pneumonia, sepsis and disease progression. One patient developed upper gastrointestinal tract bleeding and sepsis following BAL treatment and eventually died while waiting for transplant. No evidence of porcine endogenous retrovirus (PERV) were seen.
Five patients completed the study per protocol and were included in the efficacy analysis. Four patients showed apparent decrease in serum ammonia levels and MELD scores during BAL treatment. Hepatic encephalopathy either decreased or remained stable throughout the BAL treatment period in 4 patients.
Conclusion: The LifeLiver BAL support system showed safety and efficacy in ALF patients with hepatic encephalopathy. Two patients were successfully bridged to liver transplantation.

LBP-008

Addition of pegylated interferon alfa-2a to an ongoing nucleos(t)ide treatment accelerates decrease of HBs-antigen levels in patients with chronic hepatitis B: Results from the PADD-ON study

M. Sprinzl[1], A. Grambihler[1], G. Teuber[2], C. Antoni[3], S. Zeuzem[4], T. Discher[5], M. Cornberg[6], T. Berg[7], H. Loehr[8], F. Tacke[9], F. Lammert[10], E. Schott[11], C. Berg[12], E. Zizer[13], R. Heyne[14], U. Spengler[15], R. Thimme[16], A. Pathil[17], H. Klinker[18], K. Weigand[19], M. Riedl[20], J. Wosniok[20], U. Alshuth[21], J. Kittner[1], M. Schuchmann[22], P.R. Galle[1]. [1]*University Medical Center, Mainz, Medical Department I, Mainz, Germany;* [2]*Medical Practice for Internal Medicine, Frankfurt, Frankfurt, Germany;* [3]*University Mannheim, Medical Department II, Section Hepatology, Mannheim, Germany;* [4]*University Frankfurt, Medical Department I, Frankfurt, Germany;* [5]*University Giessen, Medical Department II, Giessen, Germany;* [6]*Medical University Hannover, Clinic for Gastroenterology, Hepatology and Endocrinology, Hannover,*

Germany; [7]University Clinic Leipzig, Section of Hepatology, Clinic of Gastroenterology and Hepatology, Leipzig, Germany; [8]Medical Practice for Gastroenterology, Wiesbaden, Wiesbaden, Germany; [9]University Aachen, Medical Department III, Aachen, Germany; [10]Saarland University Medical Center, Homburg, Department of Medicine II, Homburg, Germany; [11]Charite Berlin, Medical Department, Section Hepatology and Gastroenterology, Berlin, Germany; [12]University Tübingen, Medical Department I, Tübingen, Germany; [13]University Ulm, Medical Department I, Ulm, Germany; [14]Medical Practice, Checkpoint Charlie, Berlin, Berlin, Germany; [15]University Bonn, Medical Department I, Bonn, Germany; [16]University Freiburg, Medical Department II, Freiburg, Germany; [17]University Heidelberg, Medical Department IV, Heidelberg, Germany; [18]University Würzburg, Medical Department II, Würzburg, Germany; [19]University Regensburg, Medical Department I, Regensburg, Germany; [20]University Mainz, Interdisziplinäre Zentrum Klinische Studien (IZKS), Mainz, Germany; [21]Roche Pharma AG, Grenzach-Wyhlen, Medical Affairs, Grenzach-Wyhlen, Germany; [22]Klinikum Konstanz, Medical Department I, Konstanz, Germany
Email: martin.sprinzl@unimedizin-mainz.de

Background and Aims: Patients with chronic hepatitis B (cHB) regularly require long-term nucleos(t)ide analogue (NUC) treatment, because HBsAg loss is rarely achieved. Therefore we studied the addition of pegylated interferon alfa-2a (Peg-IFN) to an ongoing NUC therapy in patients with HBeAg-negative cHB, aiming to reduce serum HBs-antigen concentrations.
Patients and Methods: HBeAg-negative cHB patients (HBsAg >100 IU/ml) under effective NUC treatment for ≥1 year were randomized to receive additional Peg-IFN (180µg/week) for 48 weeks (Peg-IFN group, n = 112) or continuing NUC monotherapy (control group, n = 58) in a prospective open-label phase IIb study (EudraCT-Nr: 2011-002812-10). The modified intention-to-treat (mITT) population (n = 165), covering ≥1 post-baseline HBsAg assessment is reported. Primary response after 48 weeks of treatment was defined by reduction of ≥1log10 in serum HBsAg concentration compared to baseline. Secondary endpoints were HBsAg seroconversion and overall HBsAg concentrations. Adverse events (AEs) were assessed. Fisher's Exact test[#], T test[$], chi[2] test[§].
Results: The mITT population was predominantly male (74.6%) and Caucasian (75.2%). Liver elastrography assessment resulted in an average of 6.5 kPa and 6.9 kPa in the interferon- and control- group, respectively. HBV genotyping was available in 20.6% (n = 34/131), showing HBV genotype D (81.8%) and genotype A (9.1%) most frequently. The mean HBsAg concentration in the interferon group (6,548 ± 10,326 IU/ml) at baseline was lower than in the control group (8,427 ± 12,660 IU/ml) but differences were not statistically significant ($p > 0.05^{\$}$).
Primary response (HBsAg log drop) was achieved in 24.5% (n = 26/110) of the Peg-IFN group compared to 1.9% (n = 1/55) in the control group ($p < 0.0001^{\#}$). Six patients (5.5%) in the Peg-IFN group had a HBsAg seroconversion, whereas none occurred in the control group ($p > 0.05^{\#}$). In the Peg-IFN group HBsAg loss was observed in 15.8% (n = 16/110), whereas the control group failed HBsAg clearance ($p < 0.05^{\S}$). Most patients (94.6% in the Peg-IFN- and 58.6% in the control-group) experienced at least one AE. Only 27 (3.2%) AEs were graded as severe. No death was reported.
Conclusions: The addition of Peg-IFN to an ongoing NUC regimen accelerates HBsAg reduction in comparison to standard NUC therapy of HBeAg negative cHB patients. Further exploratory analyses to identify predictive factors in order to optimize the balance between benefit and adverse events are ongoing.

LBP-009

Long term real life follow-up of patients with chronic hepatitis C virus and decompensated cirrhosis after direct acting antivirals – what is the clinical benefit of antiviral treatment?

M. Cheung[1], D. Mutimer[2], K. Agarwal[3], A. Brown[4], M. Aldersley[5], G. Foster[6], W. Irving[7]. *[1]Blizard Institute, Barts & The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [2]Queen Elizabeth Hospital, Centre for Liver Research and NIHR biomedical Research Unit, Birmingham, United Kingdom; [3]Institute of Liver Studies, King's College Hospital, London, United Kingdom; [4]St. Mary's Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; [5]St. James's University Hospital, Leeds, United Kingdom; [6]Blizard Institute, Barts & The London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom; [7]NIHR Nottingham Digestive Diseases Biomedical Research Unit, Nottingham, United Kingdom*
Email: michelle.cheung@qmul.ac.uk

Background and Aims: Efficacy of direct acting antivirals (DAA) in treating chronic hepatitis C virus (HCV) is well established, however the long term clinical benefits of achieving sustained virological response (SVR) in patients with advanced liver disease is unclear. We describe the ongoing follow up of patients with decompensated cirrhosis treated with sofosbuvir + ledipasvir or daclatasvir +/- ribavirin on the Expanded Access Programme (EAP) in England.
Method: Out of 843 patients treated on the EAP, we included patients started between April-November 2014 who achieved SVR12, and all patients with virological failure. Only patients with a history of decompensation and/or Child B7 liver disease at treatment baseline were analysed. Patients who died or were lost to follow-up before 12 weeks post treatment end were excluded. Data was prospectively collected from treatment sites through a national biobank HCV Research UK, which included death, hepatocellular carcinoma (HCC), liver transplant, wait list status, latest available MELD scores.
Results: There were 330 SVR and 124 treatment failures, of whom 53 achieved viral clearance with retreatment. Five patients were lost to follow up prior to retreatment outcomes. Median follow up was 136 weeks (range 24–174) from treatment start. Baseline characteristics (74% male, median age 54 and MELD 12) were similar in the 383 HCV

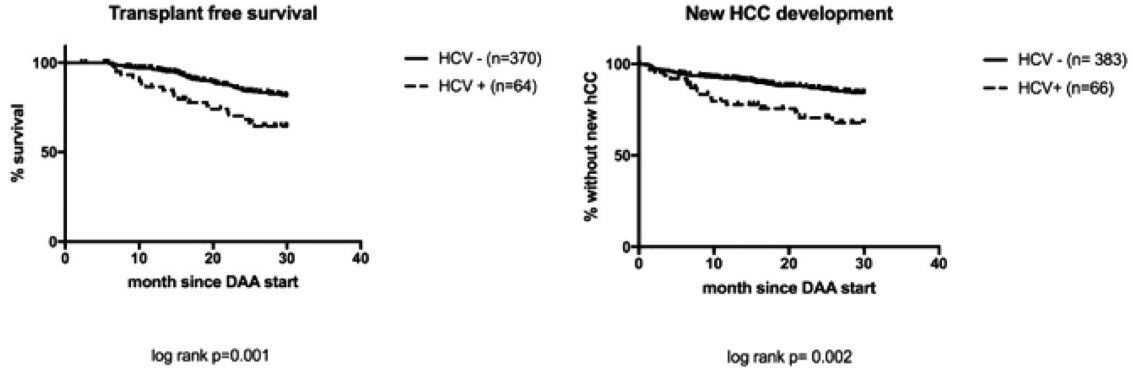


Figure: (abstract: LBP-009)

cleared patients and 66 patients who remained viraemic, apart from proportion of genotype 3 infections (43 vs 62%).
At 30 months, hazard ratios for death and new HCCs were 0.44 (95% CI 0.23–0.84) and 0.43 (0.21–0.88) respectively, between HCV clear and viraemic patients. Among 42 patients with baseline HCC only 1 recurred after DAA.
Conclusion: This large real life cohort shows sustained benefit in survival and HCC development in patients with decompensated cirrhosis following viral clearance.

LBP-010
High efficacy and safety of grazoprevir and elbasvir for 8 weeks in treatment-naive, non-severe fibrosis HCV GT1b-infected patients: Interim Results of the STREAGER Study
A. Abergel[1], C. Hezode[2], T. Asselah[3], D. Larrey[4], J. Gournay[5], V. Loustaud-Ratti[6], V.D. Martino[7], I.F. Hubert[8], D. Samuel[9], B. Chanteranne[1], M. Dodel[1], F. Faure[1], B. Pereira[1], G. Lamblin[1], C. Campos[1], L. Muti[1], M. Reymond[1], C. Teilhet[1]. *[1]Chu Estaing, Clermont-Ferrand, France; [2]Henri Mondor Hospital (AP-HP), Créteil, France; [3]Beaujon Hospital (AP-HP), Clichy, France; [4]Hospital Gui De Chauliac, Montpellier, France; [5]Nantes University Hospital Hotel-Dieu, Nantes, France; [6]Hospital Center University De Limoges Dupuytren, Limoges, France; [7]Regional University Hospital of Besançon Jean Minjoz, Besançon, France; [8]C.H.U. d'Angers, Angers, France; [9]Paul-Brousse Hospital (AP-HP), Villejuif, France*
Email: aabergel@chu-clermontferrand.fr

Background and Aims: Genotype 1b is the most common HCV genotype globally, accounting for the largest proportion of infections in Europe, Latin America, Russia, Turkey, and East Asia. Reducing treatment duration can improve adherence and reduce drug exposure. Accordingly, we evaluate the efficacy of 8 weeks of the protease inhibitor grazoprevir 100 mg/d (GZR) and NS5A inhibitor elbasvir 50 mg/d (EBR) among treatment-naïve patients, with non-severe fibrosis. Recommend adding combined as a fixed dose combination single tablet.
Method: Pooled analysis included the 82 first treatment-naïve (TN), with non-severe fibrosis (Fibroscan®<9.5 kPa and Fibrotest®<0.59), HCV GT1b-mono-infected patients without advanced kidney disease enrolled in STREAGER trial, a study which aims to include 120 patients. The primary end point was the proportion of patients with HCV RNA below the lower limit of quantification (LLOQ) 12 weeks after treatment (SVR12).

Table: Relapsers characteristics

Genotype	Age	Sex	Viral Load at screen (IU/ml)	Fibrosis (Fibroscan®)	RAS at relapse
1b	52	M	14.000.000	6.4 kPa	Y93H
1e	57	M	453.899	9.1 kPa	L28M R30Q A92T Y93H
1b	60	F	16.437.573	5.1kPa	L31M Y93H

Results: Mean age was 54 ± 13 years, 37% were male, viral load higher than 800.000 IU/ml: 51/82 (62%); ALT higher than the upper limit of normal: 35/82 (43%). Using Fibrotest® (FT), 48 had a F0-F1 fibrosis score (FT < 0.32); by Fibroscan® (FS) 73 had F0-1 fibrosis score (FS < 7.1 kPa). By end of treatment (EOT), 95% (78/82) of patients had HCV RNA < LLOQ. No adverse event grade III or IV was observed. Relapse occurred in 3 patients, including one patient with genotype 1b by Innolipa and one patient with genotype 1e by sequencing (wrongly included) (Table). After excluding the patient with genotype 1e, SVR12 was 79/81 (98%). In addition, it's important to note that another patient relapsed 24 weeks after EOT (SVR24) despite reaching SVR 12. Additional efficacy data will be available at the EASL meeting.

Conclusion: High SVR12 (79/81, 98%) was achieved in a TN non severe fibrosis GT1b-infected population in patients treated for 8 weeks by the combination grazoprevir and elbasvir.

LBP-011
A pilot study of empagliflozin for the treatment of non-alcoholic steatohepatitis in patients with type 2 diabetes mellitus
L.L. Lai[1], S. Vethakkan[1], N.R.N. Mustapha[2], S. Mahadeva[1], W.-K. Chan[1]. *[1]University of Malaya, Department of Medicine, Kuala Lumpur, Malaysia; [2]Hospital Sultanah Bahiyah, Department of Pathology, Alor Setar, Malaysia*
Email: wahkheong2003@hotmail.com

Background and Aims: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) are a novel class of drugs that lower glucose by inducing renal glycosuria. SGLT2i confers multiple metabolic benefits and improves cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM). There is limited human data on SGLT2i for the treatment of non-alcoholic steatohepatitis (NASH).
Method: In this investigator-initiated, single-arm, open-label, pilot study, empagliflozin 25mg daily was added to usual therapy of T2DM for 24 weeks in nine consecutive biopsy-proven non-cirrhotic NASH patients who had no prior exposure to SGLT2i therapy. A repeat liver biopsy was performed at the end of treatment. Histopathological examination was reported according to Non-alcoholic Steatohepatitis Clinical Research Network scoring system. The histological outcomes were compared with the placebo group of a 48-week clinical trial previously conducted at the same centre. Hepatic steatosis at baseline and follow-up were also evaluated by measurement of volumetric liver fat fraction (VLFF) using HepaFat-Scan.
Results: Median age was 55 (47–60) years old and 44% were male. All patients were obese with median body mass index of 30 (28–35) kg per m^2. The distribution of fibrosis stage at baseline was F0, 11%; F1, 67%; F3, 22%. There was significant reduction in BMI (median change, Δ = –0.7 kg per m^2, p = 0.011), waist circumference (Δ = –3 cm, p = 0.033), systolic blood pressure (Δ = –9 mmHg, p = 0.024), diastolic blood pressure (Δ = –6 mmHg, p = 0.033), fasting blood glucose (Δ = –1.7 mmol/l, p = 0.008), total cholesterol (Δ = –0.5 mmol/l, p = 0.011), gamma glutamyl transpeptidase (Δ = –19U/l, p = 0.013), VLLF (Δ = –7.8%, p = 0.017) and histological steatosis grade (Δ = –1, p = 0.014). All histological components either remained unchanged or improved, except in one patient who had worsening hepatocyte ballooning. The histological outcomes of patients who received empagliflozin, and when compared with historical placebo, are shown in Figure 1. Empagliflozin resulted in significantly greater steatosis improvement (78% vs. 26%, p = 0.025) and fibrosis improvement (33% vs. 6%, p = 0.040) compared with historical placebo.

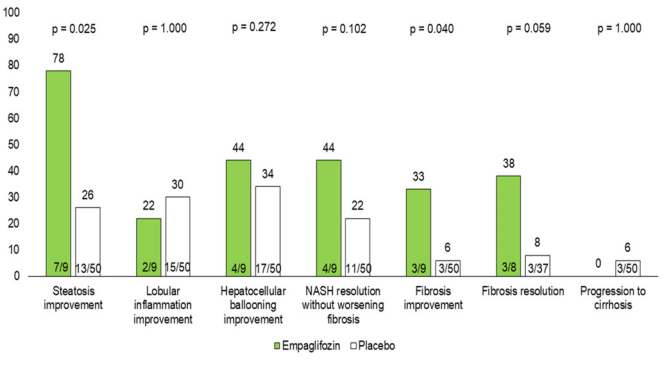


Figure 1: The histological outcomes of patients who received empagliflozin compared with placebo. Note: The placebo group is from a separate 48-week clinical trial previously conducted at the same centre.

Conclusion: This pilot study provides primary histological evidence that brief therapy with empagliflozin may be useful for the treatment of NASH. These promising preliminary findings justify the need for a

larger randomized, double-blind, placebo-controlled trial of empagliflozin in NASH for a longer duration.

LBP-012

Interim safety, tolerability pharmacokinetics, and antiviral activity of ABI-H0731, a novel core protein allosteric modulator, in healthy volunteers and non-cirrhotic viremic subjects with chronic hepatitis B

M.-F. Yuen[1,2], K. Agarwal[3], E. Gane[4,5], C. Schwabe[4], W. Cheng[6,7], W. Sievert[8], D.J. Kim[9], S.H. Ahn[10], Y.-S. Lim[11], K. Visvanathan[12], E. Ruby[13], S. Liaw[13], R. Colonno[13], U. Lopatin[13]. *[1]Queen Mary Hospital, Hong Kong; [2]The University of Hong Kong, Hong Kong; [3]King's College Hospital, London, United Kingdom; [4]Auckland Clinical Studies, Auckland, New Zealand; [5]New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; [6]Linear Clinical Research, Nedlands, Australia; [7]Royal Perth Hospital, Department of Gastroenterology & Hepatology, Perth, Australia; [8]Monash Health, Melbourne, Australia; [9]Hallym university, Korea, Rep. of South; [10]Severance Hospital, Korea, Rep. of South; [11]Asan Medical Center, University of Ulsan College of Medicine, Department of Gastroenterology, Seoul, Korea, Rep. of South; [12]St Vincents Hospital, University of Melbourne, East Melbourne, Australia; [13]Assembly Biosciences, San Francisco, United States*
Email: uri@assemblybio.com

Background and Aims: Core Protein Allosteric Modifiers (CpAMs) target the HBV core protein, a pleotropic protein involved in multiple steps of the HBV life cycle. ABI-H0731 is a potent and selective CpAM being developed to improve functional cure rates for chronic HBV (CHB) infection. Here we report the interim results on safety, tolerability, pharmacokinetic (PK) and antiviral efficacy in two ongoing studies: ABI-H0731-102 in healthy volunteers and ABI-H0731-101(B) in non-cirrhotic, viremic CHB patients.
Method: Up to 12 healthy volunteers or viremic CHB patients per cohort were randomized (10:2) and treated with 100–400 mg ABI-H0731 or placebo once daily for up to 14 days (Study 102) or up to 28 days (Study 101(B)) in double-blinded, placebo-controlled fashion. Patients were stratified by HBeAg status (7 pos:5 neg). Safety, PK and pharmacodynamic responses were monitored.
Results: Forty-nine subjects have been dosed to date in studies 102 (n = 24) and 101(B) (n = 25). Median (range) age was 38 (24–61) and 40 (26–55) years, respectively. In both studies, the majority were male (≥90%), with 13% and 76% Asian in studies 102 and 101(B), respectively. Mean baseline HBV DNA levels were 8.0 ± 1.1 $\log_{10}$ in HBeAg pos and 3.8 ± 1.5 $\log_{10}$ IU/ml in HBeAg neg patients. No serious adverse events (AEs) and no dose limiting laboratory toxicities have occurred in either study. A single G3 treatment-emergent AE leading to drug discontinuation was seen at 400 mg, otherwise all TEAEs were mild (G1) and/or unrelated to study drug. Treatment emergent laboratory abnormalities were infrequent, mild and/or deemed unrelated to study drug. Exposures increased in a dose proportional manner and were similar between CHB patients and healthy subjects. Steady state was readily achieved (<5 days) with approximately 2-fold accumulation seen in both patients and volunteers. HBV declines of 1.3 ± 0.3 and 2.2 ± 1.0 $\log_{10}$ IU/ml were seen in HBeAg pos/neg subjects (respectively) at 100 mg/day, the lowest dose tested, with greater declines observed at higher doses. HBV RNA reductions were generally proportional to reductions of plasma HBV DNA.
Conclusion: Preliminary data indicate that ABI-H0731 is generally safe and well tolerated, has a dose-proportional PK profile in patients similar to that in healthy volunteers, and once daily dosing results in potent antiviral activity. ABI-H0731 is progressing to Phase 2a proof of concept studies in 2018.

LBP-013

Comparisons the durability of 6 months and 12 months prolonged treatment duration after cessation chemotherapy in chronic hepatitis B patients with prophylaxis antiviral therapy: A open level randomized clinical trial

T.-H. Hu[1], P.-L. Tseng[1,2], M.C. Tsai[1,2], K.-C. Chang[1], Y.-H. Yen[1].
[1]Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan, Division of Hepato-Gastroenterology, Department of Internal Medicine, Taiwan; [2]Graduate Institute of Clinical Medical Sciences, Taiwan
Email: dr.hu@msa.hinet.net

Background and Aims: Prophylaxis antiviral therapy is the current recommendation for chronic hepatitis B patient receiving chemotherapy. According the American Association for the Study of Liver Diseases guideline in 2009, the treatment duration is guided by baseline HBV-DNA. However, there is no report to compare the ideal consolidation antiviral therapy duration after cessation chemotherapy. The aim of our study was to compare the relapse rate of finite 6-month and 12-month consolidation antiviral therapy in patients with HBV-DNA < 2000 IU/ml or HBV-DNA ≥ 2000 IU/ml after cessation chemotherapy.
Method: The enrolled patients were randomized into 4 groups. Patients received Tenofovir 300 mg or Entecavir 0.5 mg once daily orally one week before chemotherapy. In patients with baseline HBV DNA < 2000 IU/ml, consolidation therapy for 6 months after cessation of chemotherapy was assigned as group A and consolidation therapy for 12 months was assigned as group B. In patients with baseline HBV DNA ≥ 2000 IU/ml, consolidation therapy for 6 months was assigned as group C and consolidation therapy for 12 months was assigned as group D. Virological relapse was defined as the elevation of serum HBV DNA level > 1 log10 (IU/ml) with 3-month interval after cessation TDF or ETV treatment. Clinical relapse was defined as serum HBV DNA ≥ 2000 IU/ml and ALT > 80 IU/l after cessation antiviral therapy.
Results: A total of 61 patients were enrolled from 2013 to 2016. Fifty-six (91.8%) patients were HBeAg negative and 28 patients (45.9%) were breast cancer. Overall 1-year virological and clinical relapse was 52.1% and 23.2% respectively. There was no difference of virological and clinical relapse rate between the group A, B, C and D. Virological relapsers had higher end-treatment HBsAg levels than non-relapsers. Clinical relapsers had higher pretreatment ALT and HBV DNA than non-relapsers. In univariate analysis, end-treatment HBsAg level ≥ 500 IU/ml and pre-treatment HBV DNA ≥ 2000 IU/ml were predictors of virological relapse. Pre-treatment HBV DNA ≥ 2000 IU/ml and ALT ≥ 40 IU/ml were predictors of clinical relapse. In multi-variate analysis, end-treatment HBsAg level ≥ 500 IU/ml was the significant predictor in predicting virological relapse (adjust hazard ratio (HR): 2.77 p = 0.02). Pre-treatment ALT ≥ 40 IU/ml was the significant predictor in predicting clinical relapse (HR: 11.20; p = 0.003).
Conclusion: There is no difference in relapse rate between 6 months or 12 months prolonged antiviral therapy in patients with HBV DNA < or ≥2000 IU/ml after cessation chemotherapy. Patient with ALT ≥ 40 IU/ml and/or end-treatment HBsAg level ≥ 500 IU/ml should be close monitored after cessation NA therapy in area with limited resource or should keep antiviral therapy to the end point of HBV treatment.

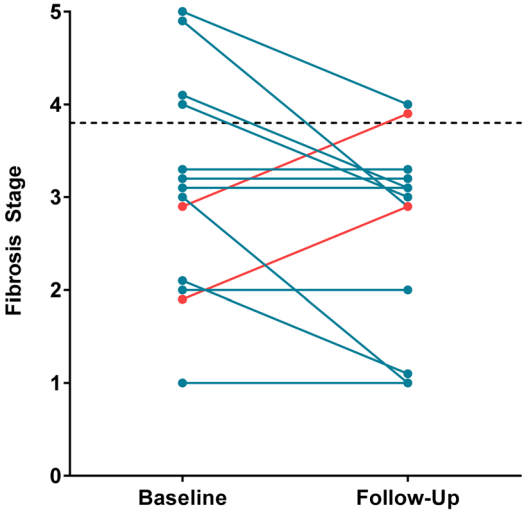
LBP-014

Long-Term Obeticholic Acid (OCA) treatment associated with reversal or stabilization of fibrosis/cirrhosis in patients with Primary Biliary Cholangitis (PBC)

C. Bowlus[1], P. Pockros[2], A.E Kremer[3], A. Pares[4], L. Forman[5], J.P. Drenth[6], S. Ryder[7], E.S. Malecha[8], R. Pencek[8], U. Iloeje[8], L. Macconell[8], D. Shapiro[8], B. Pierre[9]. *[1]University of California-Davis, Sacramento, United States; [2]Scripps Clinic, La Jolla, United States; [3]Friedrich-Alexander-University Erlangen-Nürnberg, Department of Medicine 1, Erlangen, Germany; [4]University of Barcelona, IDIBAPS, CIBERehd, Hospital Clinic, Barcelona, Spain; [5]University of Colorado, Denver, School*

of Medicine, Aurora, United States; [6]Radboud University Medical Center, Nijmegen, Netherlands; [7]National Institute for Health Research Nottingham Digestive Diseases Biomedical Research Unit (NDDBRU), Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, United Kingdom; [8]Intercept Pharmaceuticals, Inc., San Diego, United States; [9]Service d'Anatomie Pathologique, Clichy, France
Email: christopher.bowlus@ucdmc.ucdavis.edu

Background and Aims: OCA, a selective and potent FXR agonist is licensed for PBC treatment in combination with UDCA (UDCA inadequate response), or as monotherapy (UDCA intolerance). POISE, a 12-month double-blind (DB), placebo-controlled Phase 3 study with an open-label extension, demonstrated the efficacy (biochemical response) and safety of OCA in PBC patients unresponsive/intolerant to UDCA. Liver histology is optional for diagnosing PBC and is infrequently used, but remains the gold standard for assessing liver fibrosis. PBC is progressive, with UDCA non-response associated with significant fibrosis progression. In preclinical models and non-PBC clinical studies, FXR agonism with OCA has shown anti-fibrotic properties. The aim of this POISE substudy was to evaluate the effect of 3-years of OCA therapy on fibrosis progression using paired liver biopsies.
Method: Patients enrolled into POISE had the option to participate in a biopsy substudy. These patients had biopsies prior to (≤1 year from DB baseline) and after 3 years (range: 2.9–3.0 y) of OCA treatment. Biopsies were centrally read and assessed with a 6-tier staging system (F0 = no fibrosis, F1 = periportal fibrosis, F2 = bridging fibrosis with rare septa, F3 = bridging fibrosis with many septa, F4 = incomplete cirrhosis, F5 = cirrhosis).
Results: 13 patients (58 years, 12 female, 11 Caucasian, 13 on UDCA, baseline median ALP: 322 U/l and direct bilirubin: 1.5 uM) had paired biopsies adequate for analysis. At baseline, 9 patients presented with precirrhotic fibrosis [F1 (n = 1), F2 (n = 3), F3 (n = 5)]) and 4 with cirrhosis [F4 (n = 2), F5 (n = 2)]. At the last visit prior to biopsy, ALP was reduced and direct bilirubin was comparable to baseline (median changes: -99 U/l and 0.0 uM, respectively). After 3 years of OCA, the majority of patients improved (n = 6, 46%) or maintained (n = 5, 38%) histological stage, while 2 patients (15%) worsened (figure). Of the 4 patients with baseline cirrhosis, 3 (75%) improved to fibrosis without cirrhosis.



Scoring system: 0=no fibrosis, 1=periportal fibrosis, 2=bridging fibrosis with rare septa, 3=bridging fibrosis with many septa, 4=incomplete cirrhosis, 5= cirrhosis. Dashed line separates fibrotic and cirrhotic stages.

Figure: Fibrosis stage at baseline and follow-up.

Conclusion: The vast majority (85%) of these patients with incomplete response to UDCA achieved stabilization or regression of fibrosis/cirrhosis after 3 years of OCA. These data are consistent with the observed anti-fibrotic properties of FXR agonism and suggest that OCA can slow or reverse histological progression in PBC patients who have had an incomplete response to UDCA. The effect of OCA on clinical outcomes is under evaluation in the Phase 4 COBALT study (EudraCT:2014-005012-42).

LBP-015
Safety, tolerability, and pharmacokinetics of BMS-986263/ND-L02-s0201, a novel targeted lipid nanoparticle delivering HSP47 siRNA, in healthy participants: A randomised, placebo-controlled, double-blind, phase 1 study

B. Soule, G. Tirucherai, U. Kavita, S. Kundu, R. Christian. *Bristol-Myers Squibb, Bristol-Myers Squibb, Princeton, United States*
Email: benjamin.soule@bms.com

Background and Aims: BMS-986263/ND-L02-s0201 is an intravenously (IV) administered lipid nanoparticle containing a small interfering ribonucleic acid (siRNA) that inhibits production of heat shock protein 47 (HSP47, a collagen-specific chaperone). This novel formulation uses Vitamin A-moieties conjugated to the nanoparticle surface to maximize drug delivery to hepatic stellate cells. Preclinical and previous phase 1b/2 data suggest that disrupting collagen synthesis via HSP47 inhibition may reverse fibrosis and may represent a new treatment (tx) strategy for advanced liver fibrosis. This phase 1 study evaluated safety, tolerability, and pharmacokinetics (PK) of fixed dose BMS-986263 in healthy participants (ppts).
Method: IM025-001 was a three part, randomised, placebo-(PBO) controlled, double-blind, parallel-group study in healthy non-Japanese (Part A) and Japanese (JPN; Part B) adults aged 18–55 years weighing 60–90 kg; Part C is ongoing. Ppts were pretreated with antihistamines as a precaution to prevent infusion reactions, which occurred in 21% of BMS-986263–treated ppts in a phase 1a study, and received either BMS-986263 90 mg IV or PBO once weekly (QW) for 3 weeks. The primary objective was safety and tolerability of BMS-986263.
Results: Of 25 ppts, 20 received BMS-986263 (Part A, n = 12; Part B, n = 8) and 5 received PBO (Part A, n= 2; Part B, n = 3). Most ppts were men (92%), median age was 35.5 years, and 57% of Part A ppts were white. The study was completed by 22 (88%) ppts. Two non-JPN ppts (1 BMS-986263; 1 PBO) refused pre-tx antihistamines, and 1 JPN ppt (BMS-986263) withdrew consent. No deaths, discontinuations due to adverse events (AEs), or serious AEs were reported (table). PK samples for BMS-986263 plasma concentrations collected on Days 1 and 15 showed that geometric mean peak concentration, overall exposure, and total clearance of HSP47 siRNA were comparable between non-JPN and JPN ppts, with no apparent relationship between body weight and BMS-986263 exposure.

AEs, n (%)	BMS-986263 n = 20	Placebo n = 5
Ppts with		
≥1 AE	17 (85)	3 (60)
≥1 mild AE	16 (80)	3 (60)
Infusion reaction	1 (5)	0
Most common (≥15%)		
Phlebitis	7 (35)	0
Burning sensation	4 (20)	1 (20)
Headache	3 (15)	0

Conclusion: BMS-986263 90 mg IV QW for 3 weeks was generally well tolerated with no clinically meaningful differences in tolerability or PK profiles for healthy non-JPN vs JPN ppts. These results support further study of BMS-986263 in patients with advanced liver fibrosis.

LBP-016

Autologouos peripheral blood stem cell transplantation improves long term survival of patients with cirrhosis without increasing risk of hepatocellular carcinoma

G. Guo, X. Zhou, C. Guo, Z. Han, Y. Chen, Y. Han. *Xijing Hospital, the Fourth Military Medical University, Department of Gastroenterology, Xìan, China*
Email: hanying@fmmu.edu.cn

Background and Aims: Stem cell treatment may improve liver function in cirrhosis. However, the long-term effects of stem cell treatment on survival and risk of hepatocellular carcinoma (HCC) has not been established.
Method: We took advantage of a large cohort of decompensated cirrhotic patients treated with autologous peripheral blood stem cell (PBSC) transplantation (n = 282), compared with standard medical treatment (SMT, n = 286) over a 10 year period and analyzed the survival and incidence of HCC Conventional Cox proportional hazard regression was used to determine the hazard ratio (HR) for treatment modality and other prognostic factors. Propensity score (PS) matching was used to corroborate the findings.
Results: The long term survival rate was significantly higher in the PBSC group than SMT (p = 0.007 by Log Rank test). The benefit of PBSC on survival was observed in both CTP class B (p = 0.015) and class C patients (p = 0.027) and was confirmed in PS matched patients (p = 0.001). The overall incidence of HCC was comparable between the PBSC and SMT group (18.1% vs. 19.2% for the entire study population and 21.1% vs. 20.4% for matched patients, p = 0.255). PBSC was an independent prognostic factor for survival for both the entire and PS matched cohorts. Other prognostic factors include age, Child-Turcotte-Pugh (CTP) class and hyponatremia.
Conclusion: In conclusion, our data support the long term benefits and safety of PBSC transplantation.

LBP-017

Plasma mSEPT9: A novel circulating cell-free DNA-based epigenetic biomarker to diagnose hepatocellular carcinoma

A. Oussalah[1,2], S. Rischer[3], M. Bensenane[4], G. Conroy[4], P. Filhine-Tresarrieu[2], R. Debard[2], D. Forest-Tramoy[2], T. Josse[2], D. Reinicke[3], M. Garcia[2], A. Luc[5], C. Baumann[5], A. Ayav[6], V. Laurent[7], M. Hollenbach[8], C. Ripoll[3], R.-M. Guéant-Rodriguez[1,2], B. Namour[1,2], A. Zipprich[3], M. Fleischhacker[3], J.-P. Bronowicki[1,4], J.-L. Guéant[1,2].
[1]INSERM, U954, NGERE – Nutrition, Genetics, and Environmental Risk Exposure, Faculty of Medicine of Nancy, University of Lorraine, Vandoeuvre-lès-Nancy, F-54000, France; [2]Department of Molecular Medicine and Personalized Therapeutics, Department of Biochemistry, Molecular Biology, Nutrition, and Metabolism, University Hospital of Nancy, Vandoeuvre-lès-Nancy, F-54000, France; [3]First Department of Internal Medicine, Martin Luther University Halle-Wittenberg, Ernst-Grube-Str. 40, 06120 Halle (Saale), Germany; [4]Department of Hepatology and Gastroenterology, University Hospital of Nancy, Vandoeuvre-lès-Nancy, F-54000, France; [5]ESPRI-BioBase Unit, Methodological and Biostatistical Support Unit, Platform of Clinical Research Support PARC, University Hospital of Nancy, Vandoeuvre-lès-Nancy, F-54000, France; [6]Department of Digestive, Hepatobiliary and Endocrine Surgery, University Hospital of Nancy, Vandoeuvre-lès-Nancy, F-54000, France; [7]Department of Radiology, University Hospital of Nancy, Vandoeuvre-lès-Nancy, F-54000, France; [8]Division of Gastroenterology and Rheumatology, Department of Medicine, Dermatology and Neurology, University of Leipzig, Liebigstraße 20, D-04103, Leipzig, Germany
Email: abderrahim.oussalah@univ-lorraine.fr

Background and Aims: Patients with cirrhosis are at a high risk of hepatocellular carcinoma (HCC). The *SEPT9* gene is a key regulator of cell division and tumor suppressor whose hypermethylation is associated with liver carcinogenesis. The primary aim of this study was to evaluate the diagnostic accuracy of a PCR-based assay for the analysis of *SEPT9* promoter methylation in circulating cell-free DNA (m*SEPT9*) for diagnosing HCC among cirrhotic patients.
Method: We report two phase II biomarker studies that included cirrhotic patients with or without HCC from France (initial study) and Germany (replication study). All patients received clinical and biological evaluations, and liver imaging according to current recommendations. The primary outcome was defined as the presence of HCC according to guidelines from the American Association for the Study of Liver Diseases. The adjudicating physicians were blinded to patient results associated with the m*SEPT9* test.
Results: We included 289 patients with cirrhosis (initial: 186; replication: 103), among whom 98 had HCC (initial: 51; replication: 47). The m*SEPT9* test exhibited high diagnostic accuracy for HCC diagnosis, with an area under the receiver operating characteristic curve (AUROC) of 0.944 (0.900–0.970, p < 0.0001) in the initial study (replication: 0.930 [0.862–0.971, p < 0.0001]; meta-analysis: AUROC = 0.940 [0.910–0.970, p < 0.0001]). In multivariate logistic regression analysis, the number of positive m*SEPT9* triplicates was the only independent variable significantly associated with HCC diagnosis (initial: OR = 6.30, for each m*SEPT9* positive triplicate [2.92–13.61, p < 0.0001]; replication: OR = 6.07 [3.25–11.35, p < 0.0001]; meta-analysis: OR = 6.15 [2.93–9.38, p < 0.0001]). AUROC associated with the discrimination of the logistic regression models in initial and validation studies were 0.969 (0.930–0.989) and 0.942 (0.878–0.978), respectively, with a pooled AUROC of 0.962 ([0.937–0.987, p < 0.0001]).

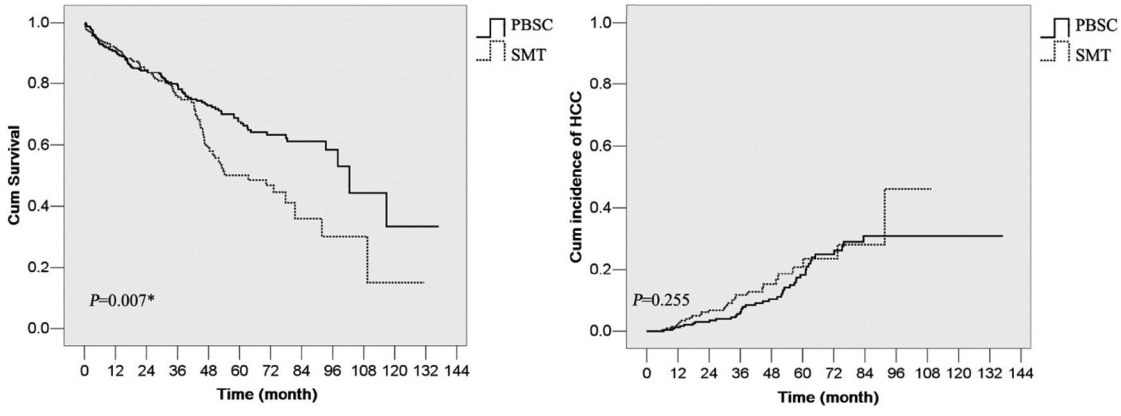


Figure 1: (abstract LBP-016)

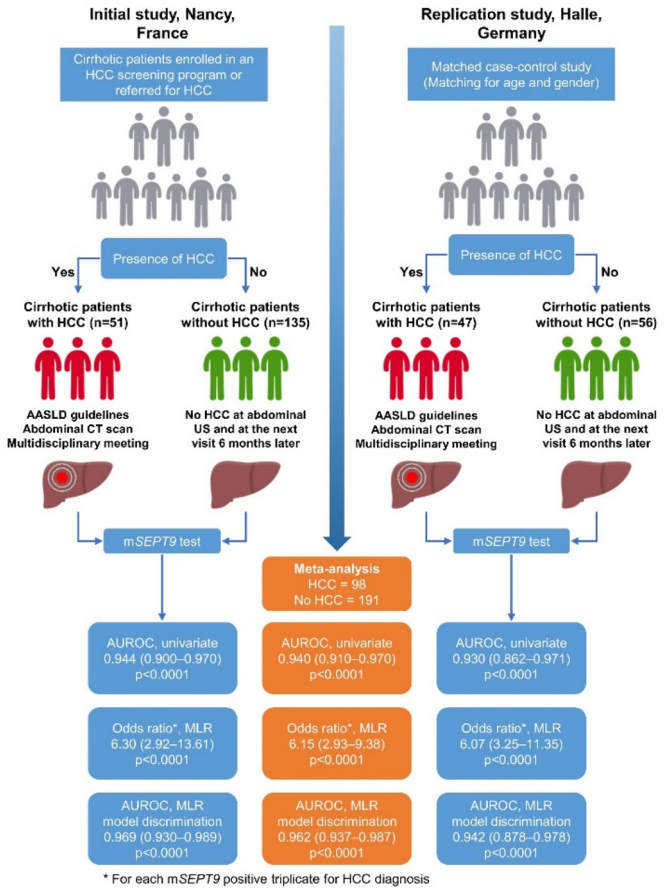


Figure 1: Study design and diagnostic accuracy measures obtained in the initial (Nancy, France) and replication (Halle, Germany) studies, and their meta-analysis for the assessment of the m*SEPT9* test to diagnose hepatocellular carcinoma.

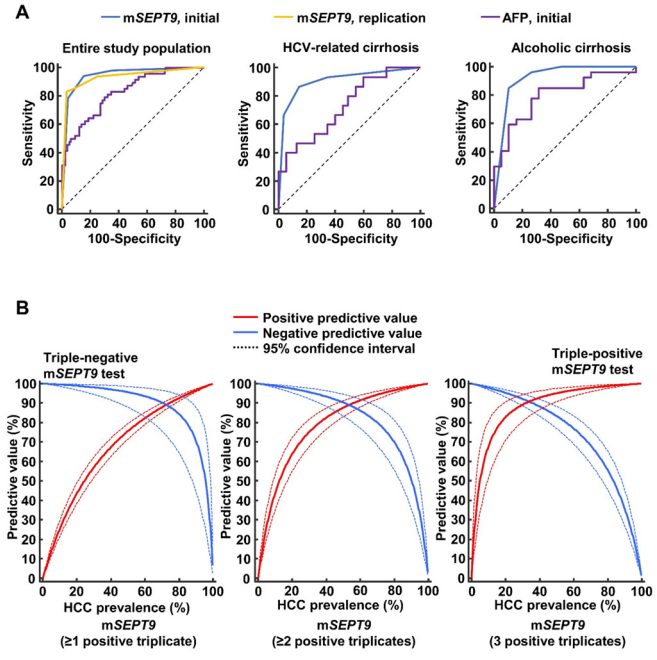


Figure 2: (A) Diagnostic accuracy of the m*SEPT9* test for hepatocellular carcinoma diagnosis in the initial and replication studies. (B) Bayesian estimation of the positive and negative predictive values of the three m*SEPT9* test thresholds for HCC diagnosis.

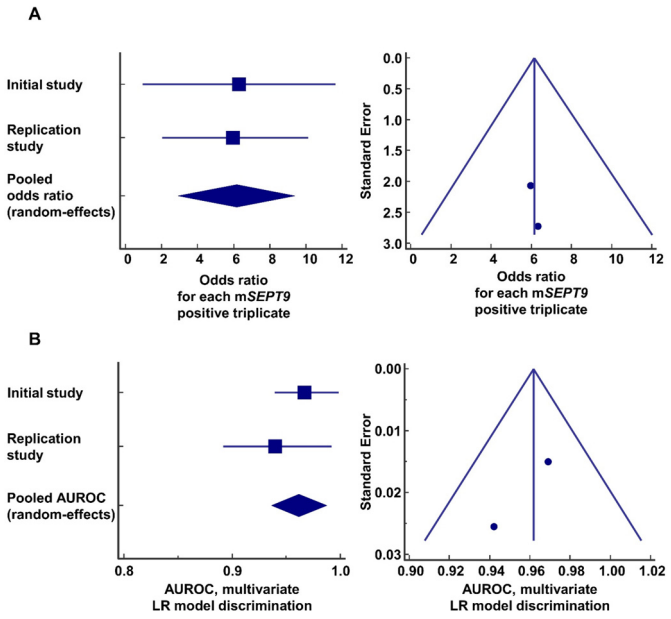


Figure 3: Meta-analysis of the ORs and AUROCs from initial and replication studies for the association between a positive m*SEPT9* triplicate and the diagnosis of hepatocellular carcinoma.

Conclusion: Among patients with cirrhosis, the m*SEPT9* test constitutes a promising circulating epigenetic biomarker for HCC diagnosis at the individual patient level.

LBP-018

A human in vitro three-dimensional bioprinted tissue system can be used to model nutritional damage and protective effects of MSDC-0602K, a novel modulator of the mitochondrial pyruvate carrier

J. Colca[1], D. Carter[2], A. Rothmeier[2], T. Murphy[2], A. Chen[2]. [1]*Cirius Therapeutics, Kalamazoo, United States;* [2]*Organovo, San Diego, United States*
Email: jcolca@ciriustx.com

Background and Aims: A major trigger for the development of NASH is overnutrition. The growing global incidence of NASH mirrors the availability of nutrients. Over-nutrition also results in insulin resistance and type-2 diabetes, which are often co-morbidities associated with NASH and which are known to drive more adverse outcomes. MSDC-0602K, a modulator of the mitochondrial pyruvate carrier (MPC), is in clinical trials as a potential treatment for NASH. Preclinical studies have shown that the mitochondrial pyruvate carrier is increased in expression in animals fed a high fat diet. Moreover, selective knockouts of each of the mitochondrial proteins that make up the carrier have shown that the MPC is a key driver of both NASH pathology and pharmacology of MSDC-0602K. Here we have evaluated whether a bioprinted human organoid system can be used to model the effects of MSDC-0602K in human tissues. Such a system might be used to strengthen the understanding of the pharmacology and provide evidence for non-invasive biomarkers that might predict clinical response.
Method: For each study, ExVive™ Human Liver Tissue (Organovo, San Diego) was fabricated by bioprinting primary human hepatocytes, hepatic stellate cells, Kupffer cells, and endothelial cells into a 3D tissue architecture. Tissues matured in vitro for 3 days and then were challenged with various concentrations of fructose and fatty acids. In some cases, the insults included pulse concentrations of lipopolysaccharide (LPS). MSDC-0602 (Cmax clinical levels) was added with the treatments after the initiation of the nutrient changes. Tissues were stained for α-smooth muscle actin for stellate cell activation

and Masson's Trichrome for content of collagen. Medium was collected for potential markers of tissue damage.
Results: The combination of fructose and fatty acids produced an increase in smooth muscle actin and collagen. Nutrient stimuli alone produced NASH-type liver pathology including steatosis, inflammation, ballooning, and fibrosis. Further damage could also be produced by adding a pulse challenge with LPS. The histological damage could be reduced by adding MSDC-0602 either in parallel with or up to one week after the challenge. Analysis of media demonstrated that the nutrient damage response included the release to the medium of mitochondrial DNA.
Conclusion: These data show that the human in vitro 3D bioprinted liver model can be adapted for demonstrating NASH-type liver pathology and the pharmacology of the novel MPC modulator can be modeled in this system. Three exposures of MSDC-0602K are currently being evaluated in a large Phase 2b clinical trial in subjects with biopsy-confirmed NASH. Samples collected for biomarkers in this trial will be evaluated for changes in parameters that are being identified by this human organoid system including evidence of protection of mitochondria.

LBP-019
13C-methacetin breath test is a highly accurate non-invasive point of care test for detecting CSPH in patients with NASH
J. Bosch[1], C. Bureau[2], N. Chalasani[3], E. Lawitz[4], M. Abdelmalek[5], M. Rinella[6], S. Harrison[7], A. Berzigotti[8], A. Sanyal[9], M. Noureddin[10], D. Rockey[11], T.I. Ber[12], Y. Ilan[13], G. Garcia-Tsao[14]. *[1]Hospital Clinic, Spain; [2]Hopital Purpan, France; [3]Indiana University School of Medicine, United States; [4]The Texas Liver Institute, United States; [5]Duke University, United States; [6]Northwestern, United States; [7]San Antonio Military Medical Center, United States; [8]Inselspital Bern, Switzerland; [9]Virginia Commonwealth University, United States; [10]Cedars Sinai Medical Center, United States; [11]Medical University of South Carolina, United States; [12]Exalenz Bioscience, Israel; [13]Hadassah, Israel; [14]Veteran Affairs Hospital, West Haven, United States*
Email: jbosch@clinic.cat

Background and Aims: Hepatic Venous Pressure Gradient (HVPG), a measurement of portal pressure, correlates with chronic liver disease severity. Clinically significant portal hypertension (CSPH), defined as HVPG ≥ 10 mmHg is associated with an increased risk of decompensation in patients with compensated cirrhosis. Esophageal varices (EV) indicate the presence of CSPH and are also predictive of decompensation. The ^{13}C-Methacetin Breath Test (MBT) using the Exalenz BreathID® System, is a non-invasive, real-time molecular correlation spectroscopy assay that quantitates hepatic cytochrome p450 1A2 metabolism of ingested non-radioactive ^{13}C-labeled methacetin by measuring the abundance of $^{13}CO_2$ in expired breath. The MBT measures a relevant liver metabolic function that has been shown to reflect the degree of overall liver impairment. Here we aimed to determine the accuracy of the MBT in the detection of CSPH.
Method: MBT was performed on 257 patients with NASH- compensated cirrhosis (i.e. no prior variceal hemorrhage, ascites or encephalopathy), pooled from two prospective studies, all of whom had HVPG measured and upper endoscopy performed in a period near the MBT.
Results: Of the 257 NASH-cirrhosis patients, 158 were female (61.5%), median age was 58.7 years, median BMI was 34.6 g/m^2, and median HVPG was 10.6 mmHg (range 1.5–27.5 mmHg). Of the total, 122 (47.5%) had CSPH and/or EV; 61 had CSPH and EV, 47 had CSPH but no EV and 14 had EV without CSPH. MBT values, adjusted by percentage dose recovered (PDR) and noise, allowed to establish a cut-off to accurately rule–in the presence of CSPH/EV. Only 15/257 (5.8%) of patients were wrongly classified as having CSPH. The MBT-based rule-in model had a sensitivity of 76.3%, specificity of 84.5%, PPV was 89.1% (82.6%-93.7%) and NPV was 68.3% with a CI 95% of 0.837–0.925 ($p < 0.0001$) and AUROC of 0.881.

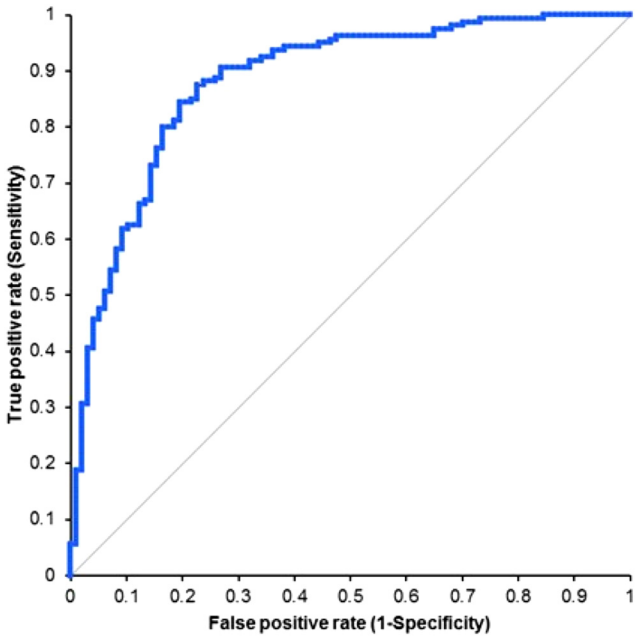
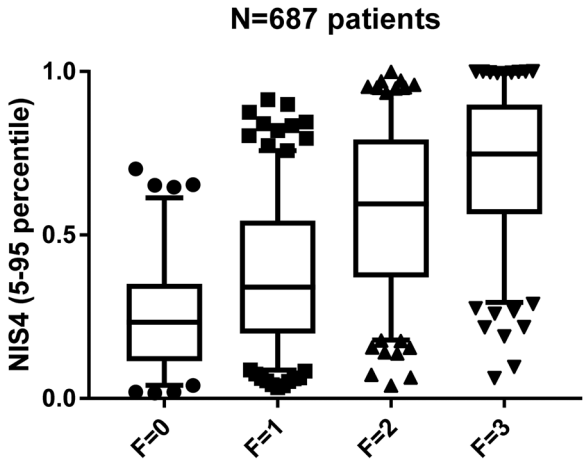


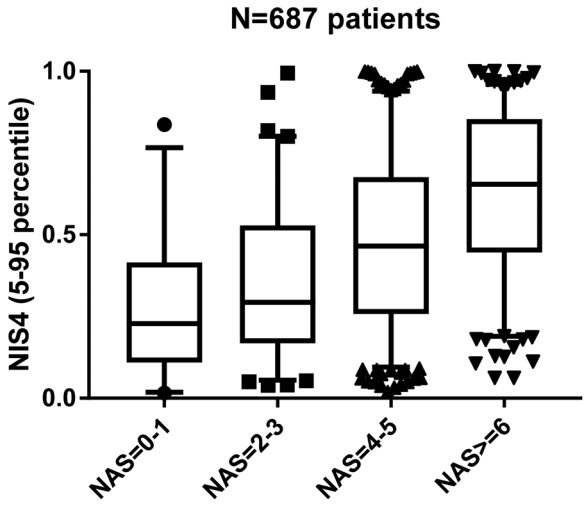
Figure 1: Shows a ROC curve for the detection of CSPH.

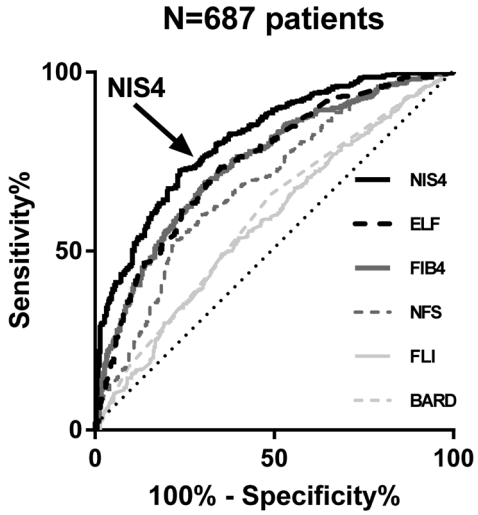
Conclusion: The MBT is highly accurate at detecting CSPH in patients with NASH- compensated cirrhosis. MBT provides a valid point-of-care tool for identifying patients at increased risk for hepatic decompensation in a non-invasive and non-operator dependent fashion.

LBP-020
Validation of NIS4 algorithm for detection of NASH at risk of cirrhosis in 467 NAFLD patients prospectively screened for inclusion in the RESOLVE-IT trial
R. Hanf[1], C. Pierre[2], M. Zouher[2], G. Cordonnier[1], J. Brozek[1], E. Praca[1], F.B. Sudrick[1], P. Bedossa[3], Q. Anstee[4], S. Francque[5], S. Harrison[6], V. Ratziu[7], S. Megnien[2], A. Roudot[2], D. Hum[8], A. Sanyal[9]. *[1]GENFIT sa, Loos, France; [2]GENFIT sa, Paris, France; [3]Department of Pathology, Hopital Beaujon, Paris, France; [4]Institute of cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, United Kingdom; [5]Antwerp University Hospital, Belgium; [6]Pinnacle Clinical Research, San Antion, United States; [7]Hopital Pitié Salpétrière, Paris, France; [8]GENFIT sa, Loos, France; [9]Virginia Commonwealth University, Richmond, United States*
Email: remy.hanf@genfit.com

Background and Aims: Using the GOLDEN trial as a training cohort, we have previously reported diagnostic performances of a non-invasive score (NIS4) using four circulating biomarkers (miR-34a, Alpha2-macroglobulin/A2M, YKL-40 and HbA1C) for calculation of the risk (0–1) of NASH progression to cirrhosis. The aim of this study was clinical validation of NIS4 in a large independent population of patients prospectively screened for inclusion in RESOLVE-IT trial.
Method: NASH patients At-Risk-of-Cirrhosis (ARC) were defined by NAS ≥ 4 and F ≥ 2 and patients Not-At-Risk-of-Cirrhosis (NARC) by NAS < 4 and/or F < 2. The training cohort (GOLDEN or G) comprised 220 patients (ARC/NARC = 95/125). The validation cohort (RESOLVE or R) comprised 467 patients (ARC/NARC = 255/212). Diagnostic performances (ARC vs NARC) in G and R were compared (AUROC, sensitivity, specificity). Merged cohort (M) with 687 patients was used for optimization of coefficients, assessment of relations with NAS and Fibrosis score (F), and comparison with existing scores.







Results: A higher rate of ARC was obtained in R vs G (55% vs 43%), but distributions of patients according to NAS or fibrosis score in ARC and NARC groups were comparable in the 2 cohorts. In R as in G, circulating levels were higher in ARC vs NARC ($p < 0.0001$) for miR-34a (2.82 ± 0.26 vs 2.54 ± 0.3 log10 copies/µL), A2M (2.61 ± 0.87 vs 2.04 ± 0.78 g/l), YKL40 (119 ± 162 vs 56 ± 41 ng/ml) and HbA1c (6.36 ± 0.97 vs 5.96 ± 0.89%). NIS4 was significantly ($p < 0.0001$) higher in ARC vs NARC patients (0.659 ± 0.015 vs 0.345 ± 0.016). NIS4 showed similar diagnostic performances in G and R cohorts for detection of ARC: AUROC = 0.81 (0.73–0.86) in G and AUROC = 0.81 (0.77–0.85) in R. Comparison of NIS4 in R vs G at optimal cutoff for G, sensitivity (68% vs 74%), specificity (77% vs 82%) total accuracy (72% vs 79%), PPV (78% vs 76%) and NPV (66% vs 81%) were only slightly to moderately affected. In M (n = 687) after optimization, AUROC reached 0.82 (0.78–0.85). At optimal cutoff for M, sensitivity and specificity were 76% and 76% respectively. In M, NIS4 gradually increased with NAS and fibrosis and was more potent than existing scores for detection ARC vs NARC (see figures).

Conclusion: This study validates NIS4 clinical performances for detection of ARC in a large population of patients prospectively screened for suspicion of progressive NASH at 133 hepatology centers in 25 countries. In this context, NIS4 outperforms existing scores, supporting its use in medical practice.

LBP-021

The percentage of patients with HCV infection in need of a liver transplant is rapidly declining while their survival after transplantation is improving: A study based on European liver transplant registry

G. Perricone[1], C. Mazzarelli[1], R. Viganò[1], C. Duvoux[2], P. Cortesi[3], R. Facchetti[3], M. Vangeli[1], V. Karam[4], R. Adam[4], M. Strazzabosco[5], L.S. Belli[6]. *[1]ASST GOM Niguarda, Hepatology and Gastroenterology Unit, Milan, Italy; [2]Henri Mondor Hospital-APHP, Liver Transplant Unit, Creteil, France; [3]University of Milan-Bicocca, Research Centre on Public Health, Monza, Italy; [4]Hôpital Paul Brousse, Centre Hépatobiliaire, Villejuif, France; [5]Yale University, Section of Digestive Diseases, New Haven, United States; [6]ASST GOM Niguarda, Hepatology and Gastroenterology Unit, Milan*

Email: giovanni.perricone@ospedaleniguarda.it

Background and Aims: Direct-acting antiviral (DAA) drugs have dramatically improved the outcome of patients with hepatitis C virus (HCV) infection. Possible changes in liver transplant (LT) indications and of patient survival after LT after the approval of DAAs were analysed.

Method: This is a cohort study based on data from the European Liver Transplant Registry (ELTR). A total of 36.382 adult LTs were performed between January 2007 and June 2017 due to HCV, hepatitis B virus (HBV), alcohol and non-alcoholic steatohepatitis (NASH). The era of LT was divided into interferon (IFN; 2007–2010), protease inhibitor (PI; 2011–2013) and second generation direct-acting antiviral (DAA; 2014- June 2017).

Results: The percentage of LTs due to HCV varied significantly over time ($p < 0.0001$), decreasing from 22.8% in IFN era to 10.6% in the DAA era, while NASH increased. Within the DAA era, the percentage of LTs due to HCV significantly decreased from 21.1% (first semester 2014) to 10.6% (first semester 2017). This decline was more evident in patients with HCV related de-compensation (HCV-DC, -68.8%) than in those with HCC associated to HCV (HCV-HCC, -34.0%). Three-year survival of LT recipients with HCV infection has improved from 65.1% in IFN era to 76.9% and is currently comparable to the survival of patients with HBV infection ($p = 0.3807$).

Conclusion: In Europe the percentage of LTs performed because of HCV infection is rapidly declining. This trend is expected to continue with the increasing access to DAA therapy. For the first time after many years, survival of HCV recipients is improving thanks to the advent of DAAs.

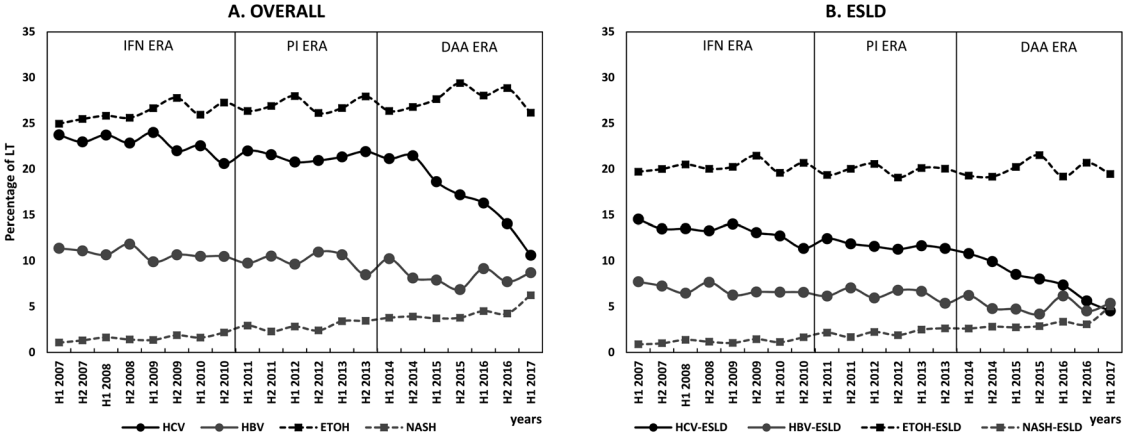


Figure: (abstract: LBP-021): Percentage of LT by etiology of liver disease and indication.X-axis is the semester of LT registration.H1 = first semester; H2 = second semester; LT = Liver transplant; HCV = Hepatitis C; HBV = Hepatitis B; ETOH = alcohol; NASH = Nonalcoholic steatohepatitis.

LBP-022

Mas-related G-protein coupled receptor type D (MrgD) antagonism produces splanchnic vasculature-specific effects, leading to a large reduction in portal pressure in cirrhotic animals

L. Gunarathne[1], A. Zulli[2], T. Qaradakhi[2], R. Smith[2], A.B. Tacey[2], P. Angus[1,3], C. Herath[1]. [1]*The University of Melbourne, Department of Medicine, Austin Health, Heidelberg, Australia;* [2]*The Victoria University, College of Health and Biomedicine, Werribee, Australia;* [3]*Austin Health, Department of Gastroenterology and Hepatology, Heidelberg, Australia*
Email: wgunarathne@student.unimelb.edu.au

Background and Aims: Portal hypertension (PHT) and bleeding from varices is the major cause of morbidity and mortality in patients with cirrhosis. Although the current pharmacological mainstay to reduce portal pressure (PP) by decreasing splanchnic inflow is non-specific beta-blockade, most patients (>60%) do not achieve an optimal response and 15% of patients are unable to tolerate these drugs. In this study, we therefore investigated the role of vasodilatory Mas-related G-protein coupled receptor type D (MrgD) in PHT and whether blockade of this receptor produces a clinically significant reduction in PP in cirrhotic animals.
Method: Liver disease was inducted in male Sprague Dawley rats by bile duct ligation (BDL) surgery or twice weekly carbon tetrachloride (CCl4) injections. Two weeks after BDL and 8 weeks after CCl4 injections, the animals received either the Mas receptor (MasR) antagonist A779 or MrgD antagonist D-Pro^7-Ang-(1-7) (D-Pro) (28 μg/kg/hr) for 2 weeks via subcutaneously implanted osmotic mini pumps. Healthy, sham-operated, BDL and CCl4 animals receiving saline infusion served as controls. After treatment the rats were cannulated to measure PP and mean arterial pressure (MAP). Coloured microsphere technique was used to calculate splanchnic vascular resistance (SVR) and hepatic vascular resistance (HVR). Mesenteric resistance vessels were obtained from a separate group of animals treated in vivo to study vasodilatory response to acetylcholine (Ach).
Results: Both A779 and D-Pro significantly ($p < 0.05$) reduced PP in both models compared to saline-infused controls; however, this reduction was larger in CCl4 rats with MrgD than MasR blockade. Whilst MasR blockade produced an off-target effect by elevating MAP ($p < 0.05$) in BDL rats, the effect of MrgD blockade confined to splanchnic vascular bed. Treatment with both drugs significantly ($p < 0.05$) increased SVR and HVR in both models compared to saline-infused disease controls. However, the increase in SVR with MrgD blockade was greater than that of MasR blockade. Mesenteric resistant vessels isolated from *in-vivo* D-Pro treated rats showed the least relaxation (45%) to Ach whereas those isolated from *in-vivo* A779 treated rats showed a maximum relaxation, similar to that of the disease controls and healthy rats (85%).
Conclusion: We have identified MrgD receptor, a new member of the renin angiotensin system, as a potential therapeutic target to design and develop drugs that can specifically block splanchnic vasodilatation to produce a clinically significant reduction in PP.

LBP-023

HCV treatment with DAA in patients listed for liver transplant does not result in an increased risk of HCC recurrence post-liver transplant

C. Mazzarelli[1,2], F. Invernizzi[3], A. Suddle[2], M.F. Donato[3], L.S. Belli[1], M.D. Cannon[2], S. Marenco[4], D. Angrisani[1], M. Iavarone[3]. [1]*ASST Ospedale Niguarda, Hepatology and Gastroenterology, Milano, Italy;* [2]*King's College Hospital NHS Foundation Trust, Institute of Liver Studies, London, United Kingdom;* [3]*IRCCS Ca' Granda Ospedale Maggiore Policlinico, Hepatology, Milano, Italy;* [4]*Hepatology and Gastroenterology, Policlinico S.Martino, Genova, Italy*
Email: chiaramazzarelli@hotmail.com

Background and Aims: Concerns about an increased risk of Hepatocellular carcinoma (HCC) recurrence in HCV cirrhotic patients treated with direct-acting antiviral treatment (DAA) has been recently raised. Few studies have explored and analyzed the long-term impact of DAA treatment in patients awaiting liver transplant (LT). Aim of this study was to assess the risk of HCC recurrence post-LT in HCC-HCV patients treated with DAA while on the waiting list.
Method: A retrospective analysis of HCV-HCC patients treated with DAA pre-trasplant from June 2014 to June 2017, in 4 different European liver transplant centers (ASST Ospedale Niguarda, Milan Italy, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy, King's College Hospital, London, UK and Ospedale S. Martino, Genova, Italy) was performed. Data was analyzed using SPSS version 22.0.
Results: 94 patients with HCC, of whom 95% were within Milan criteria for LT at imaging, received a DAA-based treatment while active on the LT wait list. The demographic and clinical characteristics are reported in the Table. 89/94 (94.7%) achieved SVR-12. After a median follow-up post-LT of 18 months (6–39), 6 (6.4%) patients experienced HCC recurrence: the number of viable nodules and microvascular invasion at explant pathology were the only variables statistically associated with tumor recurrence ($p < 0.001$ and 0.05 respectively) while BMI, diabetes mellitus and DAA treatment regimen were not associated with the risk of HCC recurrence.

Table 1: Demographic and clinical characteristics of the study cohort (n = 94)

	Overall
Median Age, y (IQR)	58 (39–71)
Male Gender, n (%)	75 (79.7)
BMI, (IQR)	25 (17–35)
Diabetes, n (%)	26 (27.7)
Cirrhosis, n (%)	
Child A (CTP score 5–6)	58 (61.7)
Child B (CTP score 7–9)	24 (25.5)
Child C (CTP score ≥10)	12 (12.7)
MELD	10 (6–32)
HCV treatment, n (%)	
SOF + RBV	27 (28.7)
SOF + NS5A inhibitor*±RBV	56 (59.6)
3D or 2 D combo	9 (9.6)
Others	2 (2.1)
Milan transplant criteria in, n (%)	91 (94.9)
Milan transplant critera out/UCSF in, n (%)	3 (5.1)
Largest nodule at listing, cm	2,5 (1–5)
AFP at transplant, ng/ml	8 (2–175)
Bridging treatment, n (%)	75 (79.8)
Time from DAA to transplant, mos	4,5 (0–48)
Time from HCC diagnosis to transplant, mos	13 (0–78)
Number of active nodules at the explant	
No nodules	23 (24.5)
1–3	57 (55.3)
4–6	10 (10.6)
>6	4 (4.3)
Moderate or not-differentiated HCC, n (%)	35 (37.6)
Vascular invasion, n (%)	21 (22.1)
Type of IS post-transplant, n (%)	
CNI (Cya or FK)	65 (69.2)
CNI + MMF or AZA	23 (24.5)
CNI + mTOR	6 (6.3)

Conclusion: In this retrospective study, the achievement of viral eradication of HCC during wait list time) was not associated with an increased risk of HCC recurrence post-LT. In our multi-centric series, we confirmed that tumor burden at explant is the only predictor of recurrence after LT, with no evidence for a negative impact of viral eradication by DAA regimens during the waiting list.

LBP-024

Increased risk of liver cancer in cirrhotic patients associated to direct acting antivirals

M. Reig[1,2], Z. Mariño[2,3], A. Darnell[4], S. Lens[2,3], V. Sapena[5,6], A. Díaz[5], E. Belmonte[4], C. Perelló[6,7], J.L.C. Panero[6,7], C.R. de Lope[8], S. Llerena[8], X. Torras[6,9], A.G. Moya[6,9], M. Sala[6,10], R. Morillas[6,10], B. Minguez[6,11], J. Llaneras[6,11], S. Coll[12], J.A. Carrión[12], M. Iñarrairaegui[6,13], B. Sangro[6,13], R. Vilana[6,14], M. Sole[5,6], C. Ayuso[6,15], J. Ríos[16], X. Forns[2,3], J. Bruix[1,2] and On Behalf of the Hcc-Ciberehd Task Force. Ciberehd[2].
[1]Hospital Clinic, BCLC group. Liver Unit.IDIBAPS, University of Barcelona, Barcelona, Spain; [2]CIBERehd, Spain; [3]Hospital Clinic, Liver Unit. IDIBAPS. University of Barcelona, Barcelona, Spain; [4]Hospital Clinic, BCLC group. Radiology Department. IDIBAPS. University of Barcelona., Barcelona, Spain; [5]Hospital Clinic, BCLC group. Pathology Department. IDIBAPS. University of Barcelona., Barcelona, Spain; [6]CIBERehd; [7] Hospital Univesitario Puerta de Hierro., Liver Unit, Madrid, Spain; [8]Hospital Universitario Marqués de Valdecilla, Department of Gastroenterology. IDIVAL., Santander, Spain; [9]Hospital Santa Creu i Sant Pau, Department of Gastroenterology, Barcelona, Spain; [10]Hospital Germans Trias i Pujol, Department of Gastroenterology. Liver Unit, Barcelona, Spain; [11]Hospital Universitari Vall d'Hebron., Liver Unit, Department of Internal Medicine. VHIR. Universitat Autonoma de Barcelona., Barcelona, Spain; [12]Hospital del Mar, Liver Section, Gastroenterology Department.IMIM. Universitat Autonoma de Barcelona, Barcelona, Spain; [13]Clinica Universidad de Navarra, Liver Unit. IDISNA, Pamplona, Spain; [14]Hospital Clinic, BCLC group. Radiology Department. IDIBAPS. University of Barcelona., Barcelona, Spain; [15]Hospital Clinic, BCLC group. Liver Unit. IDIBAPS. University of Barcelona., Barcelona, Spain; [16]Hospital Clinic, Medical Statistics core facility, IDIBAPS. Biostatistics Unit, Faculty of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain
Email: mreig1@clinic.ub.es

Background and Aims: Despite the very high efficacy of direct acting antivirals to eradicate hepatitis C virus infection, the impact on hepatocellular carcinoma development remains controversial. We analyzed the clinical and radiological outcomes of cirrhotic patients treated with interferon-free regimens, to estimate the risk of developing de novo hepatocellular carcinoma.
Method: Retrospective, multicenter study of cirrhotic patients treated with direct acting antivirals until October 2015. Clinical and radiologic characteristics before starting interferon-free regimens, at follow-up and at hepatocellular carcinoma development were collected. Hepatocellular carcinoma incidence was expressed as HCC/100 patients-year.
Results: 1,123 patients were included (60.6% males, 83.8% Child-Pugh A). 95.2% achieved sustained virological response. Seventy-two patients developed hepatocellular carcinoma after a median clinical follow-up of 19.6 months, HCC incidence: 3.73 HCC/100 patients-year (95% CI 2.96; 4.70). The median follow-up by imaging has been 12.3 months and hepatocellular carcinoma cases were detected at a median of 10.3 months after starting DAA. Baseline impaired liver function (Child-Pugh B/C vs. A), alcohol intake (vs. no) and clinically significant portal hypertension at baseline (vs. absence) were associated to higher risk. Relative risk was significantly increased in patients with non-characterized nodules at baseline [2.83 (95%CI: 1.55–5.16)] vs those without non-characterized nodules (Figure 1). Hepatocellular carcinoma risk in patients matching the HALT-C or EPIC trials profile (HCC prevention by IFN vs. placebo) was significantly increased as compared to such population (2.53 and 2.26, respectively), irrespective of the presence of non-characterized nodules.

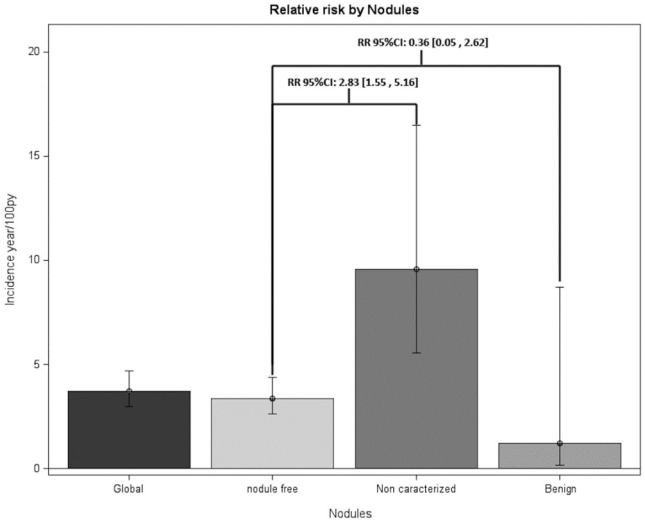


Figure 1: Incidence of HCC per HCC/100PY (95%CI) in the global cohort (black) and divided according to baseline ultrasonographic findings.

Conclusion: These data expose a time association between direct acting antivirals treatment and development of hepatocellular carcinoma. More advanced liver disease and presence of non-characterized nodules prior to therapy are associated to increased risk, but the analysis of the patients matched for EPIC and HALT should prime further research to clarify the mechanisms of cancer emergence associated to antiviral therapy.

LBP-025

Prophylaxis with CMV-hyperimmunglobulin reduces immunologic graft damage in critically ill liver transplant patients

A. Kornberg[1], U. Witt[1], K. Müller[2], M. Achernhammer[1], J. Kornberg[3], K. Thrum[4]. [1]*Technical University Munich, ´Department of Surgery, Munich, Germany;* [2]*FSU Jena;* [3]*LMU Munich, Klinikum Großhadern, Anesthesiology, Munich, Germany;* [4]*Helios Klinikum Berlin, Institute of Pathology*
Email: arnokornberg@aol.com

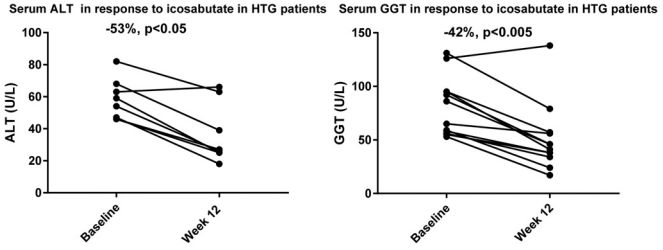
Background and Aims: Liver transplantation (LT) in critically ill cirrhotic patients is associated with high mortality due to sceptical and immunologic complications. Experimental studies suggested that hyperimmunoglobulins (Ig) exert anti-inflammatory and immunosupportive capabilities. We hypothesized, that prophylactic administration of cytomegalovirus (CMV) Ig might be beneficial in immunologically compromised liver transplant patients. This was analysed in a series of critically ill cirrhotic patients.
Method: Forty liver transplant patients with a median MELD score of 38 at LT were included. According to donor/recipient CMV status, 5000IE CMVIg (Cytotect®, Biotest, Germany) was prophylactically administered (D+ and/or R+) daily for a minimum of 7 days post-LT. Immunosuppression consisted of a triple regimen (Tac, MMF, Pred). Serological parameters of pro-inflammatory and -immunologic activation (C-reactive protein [CRP]; procalcitonin [PCT]; interleukin 6 [IL-6]) were continuously assessed. Prognostic factors of outcome were analyzed by uni- and multivariate analysis.
Results: Twenty-four patients received CMVIg (60%) Fatal risk triad (intubation + dialysis + catecholamines) was present in 7 patients of the CMVIg- (29.2%) and 7 of the non-CMVIg-group (43.7%; p = 0.343). Frequency of donor-specific antibodies at LT tended to be higher in the prophylaxis group (29.1% vs. 6.3%; p = 0.07). Rate of biopsy proven allograft rejection was significantly lower in the CMVIg-group (0% versus 37%; $p < 0.001$), despite comparable peak Tac levels (11.1 vs. 12.3 µg/l). None of CMVIg-patients (0%), but 6 and 4 non-CMVIg-recipients (37.5%; 25%; $p < 0.01$) developed CMV and EBV viremia, respectively. Posttransplant peak values of CRP (4.9 vs. 16.3 mg/dl), PCT (10.5 vs. 71.2 ng/ml) and IL-6 (91.7 vs. 333.1 pg/ml) were significantly lower in the prophylaxis group ($p < 0.001$). Sepsis-related mortality rate was significantly higher in the non-CMVIg subset (68% versus 16.6%; p = 0.001). In multivariate analysis, CMVIg prophylaxis was identified as most powerful promoter of survival and freedom of sepsis (HR = 6.0; 95%CI 2.09–17.35; p = 0.001).
Conclusion: Early post-LT prophylaxis with CMVIg reduces pro-inflammatory and immunologic graft damage in critically ill liver transplant patients without any adverse effects. To the best of our knowledge, this has not yet been described. Our data justify validation in a multicenter approach.

LBP-026

A structurally engineered fatty acid, icosabutate, displays optimised absorption, distribution and metabolism properties for targeting hepatic inflammation and normalises elevated liver enzymes in dyslipidemic patients

D.A. Fraser[1], X.-Y. Wang[2], T. Skjaeret[1], J. Kastelein[3], D. Schuppan[2,4]. [1]*NorthSeaTherapeutics, Naarden, Netherlands;* [2]*Institute of Translational Immunology, Mainz, Germany;* [3]*Academic Medical Center, Department of Vascular Medicine, Amsterdam, Netherlands;* [4]*Division of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, United States*
Email: david.fraser@northseatherapeutics.com

Background and Aims: The use of fatty acids as efficacious oral drugs targeting inflammatory/fibrotic liver disease is inherently restricted due to extensive (auto) beta-oxidation as an energy source, systemic distribution and incorporation into complex lipids. Icosabutate is structurally engineered fatty acid (SEFA) designed to overcome these inherent limitations and may offer a novel approach to treat necroinflammation and subsequent fibrosis in NASH. We tested the absorption, distribution, metabolism, excretion (ADME) and hepatic anti-inflammatory properties of icosabutate in rodents in addition to its effects upon elevated liver enzymes in patients with hypertriglyceridemia (HTG).
Method: ADME properties of icosabutate were assessed in rodents *in vivo* and human hepatocytes *in vitro*. Treatment effects [introduced from week 7–12 of a 12-week high-fat (31% of total calories) diet (HFD) in 9-week old C56BL/6J mice] of low-and high-dose icosabutate (56 mg/kg ICOSA-L and 112 mg/kg ICOSA-H orally) vs a GLP-1 agonist (Bydureon, 0.4 mg/kg weekly) on hepatic inflammatory gene expression were also assessed. The liver enzyme response to 12-weeks treatment with icosabutate 600 mg o.d. or placebo was also measured in HTG patients with elevated (>1 to $\leq$ 3 X ULN) alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT) levels in a phase 2 study (CTN 4016 13201) investigating the hypolipidemic effects of icosabutate.
Results: In contrast to unmodified long-chain fatty acids (LCFA), icosabutate was absorbed via the portal vein (>99%), with rapid hepatic accumulation, minimal systemic distribution and rapid excretion (<95% complete at 48hrs) in rats. In Huh7 cells, minimal incorporation into complex lipids resulted in a high concentration of the bioactive non-esterified fraction (>85%) versus an unmodified LCFA (<10%). HFD fed mice gained significant weight and developed hyperlipidemia and insulin resistance. Icosabutate induced potent decreases in hepatic TNF-alpha ($p < 0.005$ and <0.0001 for ICOSA-L and ICOSA-H, respectively) and IL-1beta transcripts (both $p < 0.01$). Bydureon had no significant effect on either transcript. In patients with HTG and elevated liver enzymes, treatment with icosabutate reduced median ALT by 53% from 56.5 to 26.5 U/l (n = 8, $p < 0.05$) and GGT by 42% from 75.5 to 43.5 U/l (n= 12, $p < 0.005$). Elevated liver enzymes in patients receiving placebo were unchanged [ALT 54.5 and 58 U/l at baseline and week 12 (n = 12, p = 0.98) respectively, GGT 101 U/l at both timepoints (n = 15, p = 0.55)]



Conclusion: Icosabutate overcomes the inherent ADME limitations of unmodified fatty acids as oral drugs targeting inflammatory pathways in the liver. A 600 mg/day dose normalised elevated liver enzymes in dyslipidemic patients. Icosabutate may thus offer a novel and potent therapeutic approach to inflammatory and fibrotic disorders of the liver, including NASH.

LBP-027

Rifaximin reduces the incidence of sepsis and all cause admissions whilst on the liver transplant waiting list

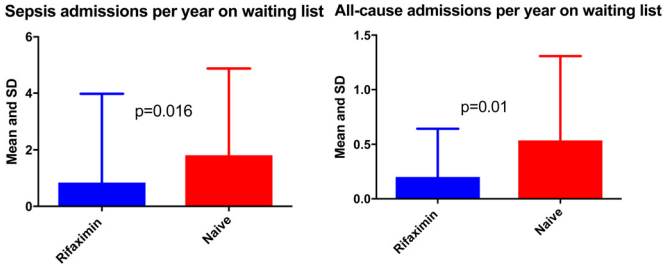
S. Salehi[1], S. Lim[1], M. Heneghan[1], V. Aluvihare[1], N. Heaton[1], V. Patel[1,2], D. Shawcross[1,3]. [1]*Institute of Liver Studies and Transplantation, King's College Hospital, London, United Kingdom;* [2]*Institute of Hepatology, Foundation for Liver Research, London, United Kingdom;* [3]*King's College London, Liver Sciences, 1st Floor James Black Centre, School of Immunology & Microbial Sciences, Faculty of Life Sciences and Medicine, London, United Kingdom*
Email: debbie.shawcross@kcl.ac.uk

Background and Aims: Rifaximin reduces the risk of recurrence of overt hepatic encephalopathy (HE). In UK clinical practice, treatment has been associated with significant reductions in hospitalisation, bed days (including critical care), emergency department attendances

and 30-day readmissions. The aim of this study was to examine the outcomes of patients listed for liver transplantation at King's College Hospital with a diagnosis of HE at listing treated with rifaximin compared to those naïve to the drug. The primary objective was to compare frequency and duration of all cause hospital admissions. Secondary objectives included incidence of sepsis and admissions related to complications of cirrhosis, admissions to critical care and mortality.

Method: The electronic patient records of patients who were listed for liver transplantation over a 2-year period [1st January 2014–31st January 2016] were retrospectively reviewed. Patients were included if they had at least two historic episodes of overt HE or were clinically encephalopathic at the time of transplant assessment.

Results: Of the 622 adult patients listed for transplantation during that time, 101 were listed with a diagnosis of HE. 66 patients were being treated with rifaximin and 35 were naïve. 82% of those on rifaximin and 71% of those on placebo were on concurrent lactulose therapy. The rifaximin-naïve group were marginally younger [49 versus 55; p = 0.006] but otherwise the groups were not statistically different in their characteristics. Alcohol was the most common aetiology and the median maximum grade of HE was 2. The baseline median MELD was 13 (IQR10-16) in the rifaximin-treated cohort and 14 (10–17.5) in the naïve. Patients treated with rifaximin had significantly reduced all-cause admissions on the waiting list (p = 0.01), episodes of sepsis including spontaneous bacterial peritonitis (p = 0.016), admissions related to ascites (p = 0.024), variceal bleeding (p = 0.024) and were less likely to warrant prioritisation (p = 0.04). Mean length of stay was reduced in the rifaximin-treated group (14.4 versus 8.7 days). Overall mortality and admissions related to HE did not differ.



Conclusion: Rifaximin prescribed for the recurrence of overt HE in patients with advanced cirrhosis listed for liver transplantation improved outcomes on the waiting list with a significant reduction in all cause hospital admissions and episodes of sepsis.

LBP-028

The kynurenine pathway in cirrhosis. Relationship with the development of acute decompensation and acute-on-chronic liver failure, clinical course and mortality

J. Clària[1,2], R. Moreau[1,3], F. Fenaille[4], A. Amoros[5], C. Junot[4], H. Gronbaek[6], M. Coenraad[7], K. Oettl[8], P. Caraceni[9], C. Alessandria[10], J. Trebicka[5,11], M. Pavesi[5], C.D. Gomez[5], A. Albillos[12], T. Gustot[13], T. Welzel[14], J. Fernandez[2,5], R.E. Stauber[8], F. Saliba[15], N. Butin[4], B. Colsch[16], C. Moreno[13], F. Durand[17], F. Nevens[18], R. Bañares[19], D. Benten[20], P. Ginès[2], A. Gerbes[21], R. Jalan[22], P. Angeli[23], M. Bernardi[9], V. Arroyo[1]. *[1]European Foundation for the study of chronic liver failure, Grifols Chair, Barcelona, Spain; [2]Hospital Clínic, Barcelona, Spain; [3]Inserm U1149, Centre de Recherche sur l'Inflammation, Paris, France; [4]CEA, iBiTec-S; [5]European Foundation for the study of chronic liver failure, Barcelona, Spain; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Leiden University Medical Center, Leiden, Netherlands; [8]Medical University of Graz, Graz, Austria; [9]Università di Bologna, Bologna, Italy; [10]San Giovanni Battista Hospital, Torino, Italy; [11]UKB University of Bonn, Bonn, Germany; [12]Hospital Ramón y Cajal, Madrid, Spain; [13]Hospital Erasme, Bruxelles, Belgium; [14]J.W. Goethe University Hospital, Frankfurt am Main, Germany; [15]Paul-Brousse Hospital (AP-HP), Villejuif, France; [16]CEA, iBiTec-S; [17]Beaujon Hospital (AP-HP), Clichy, France; [18]Hospital Gasthuisberg Leuven, Leuven, Belgium; [19]Complutense University of Madrid, Madrid, Spain; [20]University Hospital Hamburg-Eppendorf, Hamburg, Germany; [21]Ludwig-Maximilians-Universität Hospital München, München, Germany; [22]University College London, Royal Free Hospital, United Kingdom; [23]University of Padova, Padova, Italy*
Email: jclaria@clinic.ub.es

Background and Aims: Systemic inflammation (SI) is involved in the pathogenesis of acute decompensation (AD) and acute-on-chronic liver failure (ACLF) in cirrhosis. In other diseases (i.e. severe sepsis or pancreatitis) SI activates tryptophan (Trp) degradation via the kynurenine pathway (KP), giving rise to toxic metabolites that cause tissue/organ damage and immunosuppression. We aimed to characterize the poorly known KP in patients with cirrhosis.

Methods: The circulating levels of Trp, metabolic markers of KP activity (kynurenine, kynurenic acid and quinolinic acid), SI (cytokines, sCD163 and sCD206) and oxidative stress (irreversible oxidized albumin) were measured at enrolment in 40 healthy subjects, 39 patients with compensated cirrhosis (no history of AD), 342 patients hospitalized with AD (no ACLF) and 180 patients with ACLF, and repeated in 258 patients during 28-day follow-up.

Results: *First:* among the whole group of patients, KP activity at enrolment was found to be normal in compensated cirrhosis, increased in AD and further increased in ACLF, in parallel with SI and oxidative stress; it was significantly higher in ACLF with kidney failure than in ACLF without kidney failure (Figure 1, values represented in quadratic scale). *Second*: among the patients with AD at enrolment, baseline KP overactivity was significantly higher in patients who did (n = 56) than in those who did not (n = 286) develop ACLF during hospitalization, suggesting that overactivation of the KP precedes ACLF development. *Third*: among "uninfected" patients with ACLF at enrolment (n = 108), those who developed nosocomial infections (n = 61; 56.4%) showed higher baseline KP activity and immune suppression (significantly higher levels of sCD206 and IL-10) than those without nosocomial infections, suggesting a relationship between KP overactivity, immunosuppression and nosocomial infections in ACLF. *Fourth*: among patients with follow-up samples, the 28-day course of AD or ACLF (worsening, improvement, stable) closely correlated with parallel changes in KP activity. *Fifth*: higher baseline KP activity at enrolment independently predicted mortality in patients with AD and in those with ACLF.

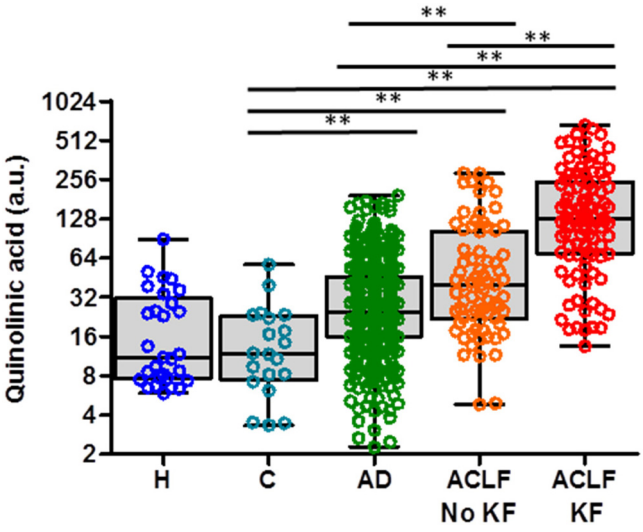


Figure: Serum levels of quinolinic acid at enrolment in healthy subjects (H) and patients with compensated cirrhosis (C), acute decompensation (AD) and acute-on-chronic liver failure (ACLF) without (No KF) and with (KF) kidney failure. Values are in arbitrary units (a.u.) corresponding to peak area/5×10^4 and represented in quadratic scale. **, p < 0.001.

Conclusions: This study shows that features of KP activation appear in patients with AD and culminate in those with ACLF. Moreover, it suggests a role for KP overactivity in the pathogenesis of AD and ACLF, clinical course and mortality.

LBP-029

Viral integration profiles in the plasma cell-free DNA from patients with HBV infection well represent tumor clone compositions during HCC development

D. Zhang[1], W. Chen[1], K. Zhang[2], P. Dong[3], U. Protzer[2], C. Zeng[3]. *[1]Beijing Institute of Genomics, Chinese Academy of Sciences, Key Laboratory of Genomic and Precision Medicine, Beijing, China; [2]Technical University of Munich/ Helmholtz Zentrum München, Institute of Virology, Munich, Germany; [3]Beijing You'an Hospital Affiliated with Capital Medical University, Department of Hepatology, Beijing, China*
Email: dakezhang@gmail.com

Background and Aims: Host genome integration of HBV sequence is considered significant in shaping the immune response to HBV antigens and the development of hepatocellular carcinoma (HCC). Detection and characterization of the integration events in plasma will provide a non-invasive approach for disease monitoring.

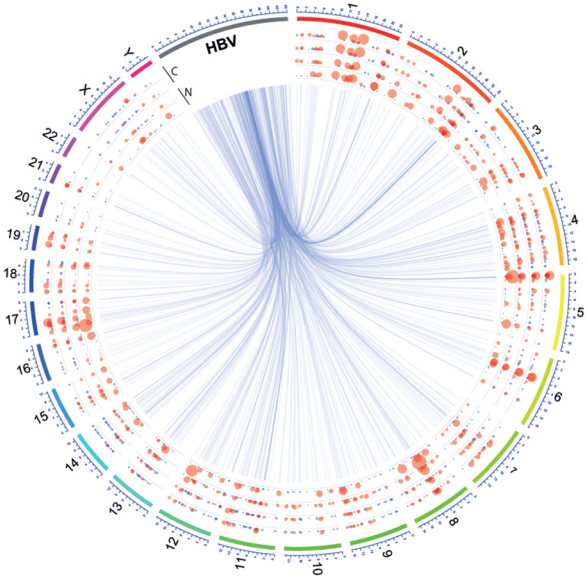


Figure 1: All integrations connecting the viral and human genomes.

Method: We developed a probe-based capture strategy to enrich integrated HBV DNA for deep sequencing analysis of viral and host genome integration sites in paired patient samples including tumour, liver tissue adjacent to tumor and plasma.

Results: In 20 paired tumour and liver tissues, integrations had been detected in all 17 HBV positive HCC but not in any of negative controls. Each patient had 2 tumor samples and 2 normal samples analyzed and in total 424 integrations were identified with an average coverage of 138. Further attempt to monitor viral integrations in plasma showed that, all HCC patients had integrations detected in cfDNA samples. Particularly, over 70% of integrations in tumour tissues were also found in paired plasma cfDNA with significant high abundance. Meanwhile, none of the 70 integration events specific to paired normal tissues was observed in plasma cfDNA. Notably, integration candidates in the plasma from chronic hepatitis B patients showed the same viral breakpoint distribution as those in tumour tissues, with hotspot around nt1600–1900, but without prominent abundance observed. Furthermore, we paired host breakpoints according to their distance in human genome and then grouped into 4 viral patterns according to junction mapping features. Particularly, the majority of Pattern I events (81.2%, 112/138) retained the complete opening reading frame for HBV surface proteins.

Conclusion: The heterogeneity of integration profiles indicated the complexity of integration occurrence in hepatocyte clonal expansion, with possibly distinct biological consequences. Monitoring changes in plasma circulating integration events may serve as a biomarker for liver immune responses, hepatocyte clonal expansion, and tumour development in chronic hepatitis B patients.

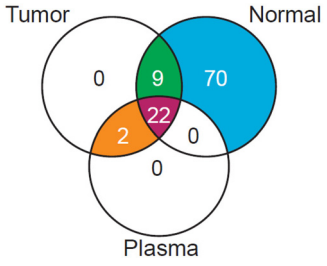


Figure 2: Detection of integration in plasma samples from HCC patients.

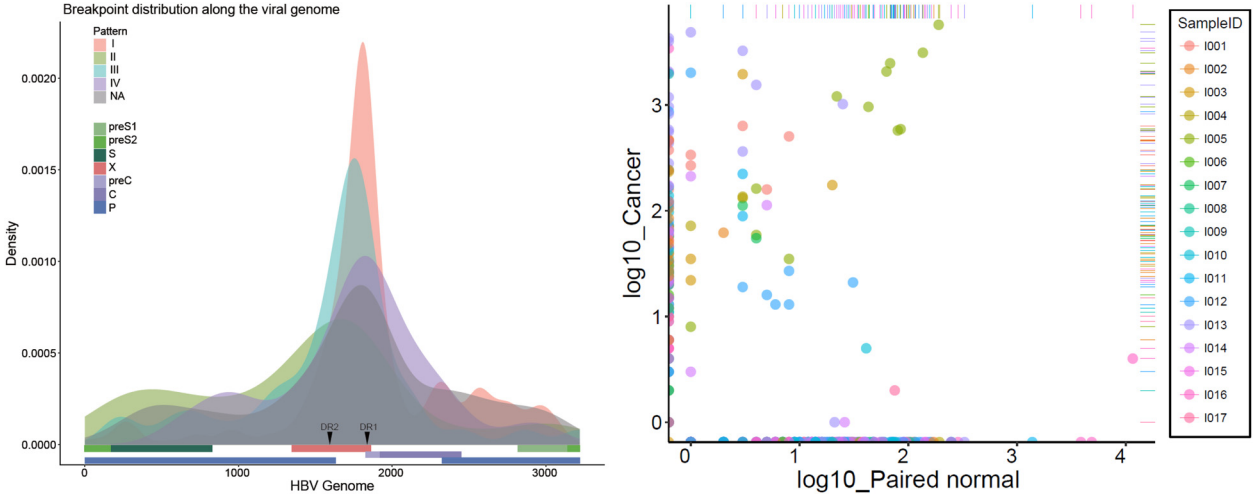


Figure 3: (abstract: LBP-029): Hotspot of breakpoints of integrations in HBV genome (left) and sequencing coverage of integration events in tumor and paired normal tissues (right).

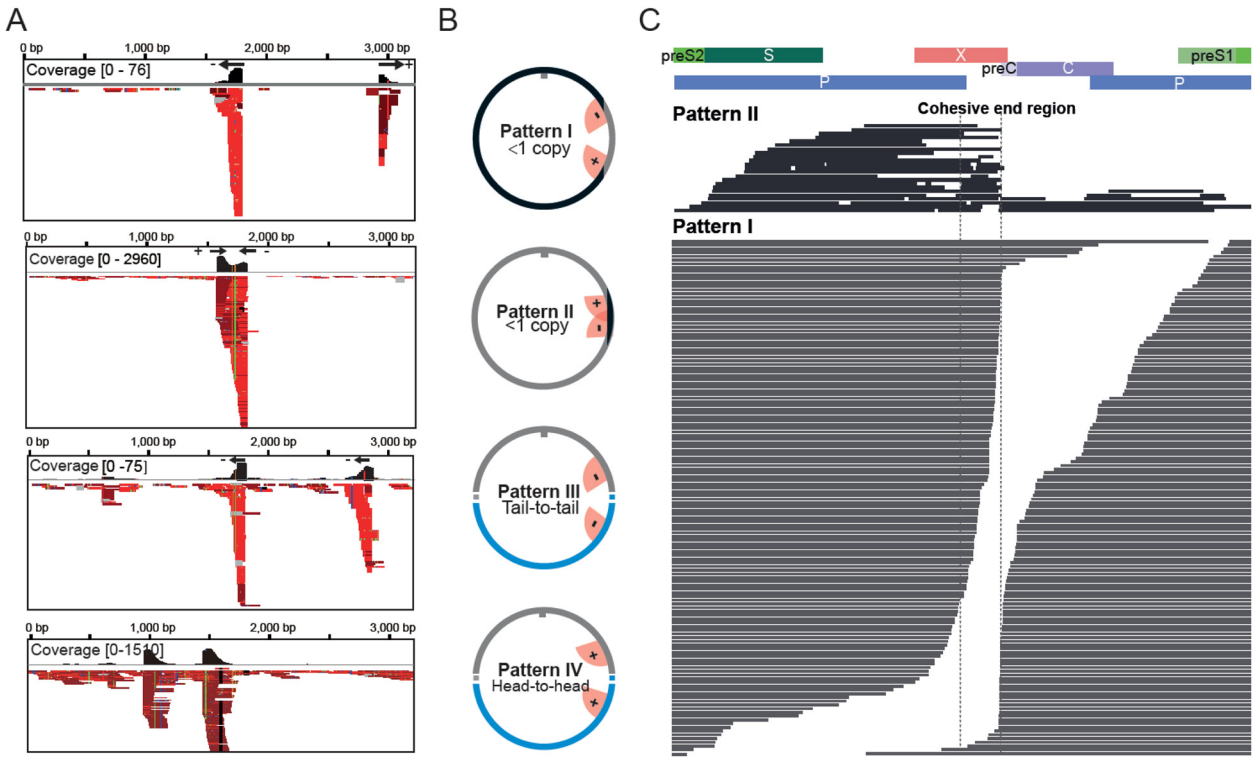


Figure 4: (abstract: LBP-029): Integration patterns according to features of junction mapping in HBV genome.

LBP-030

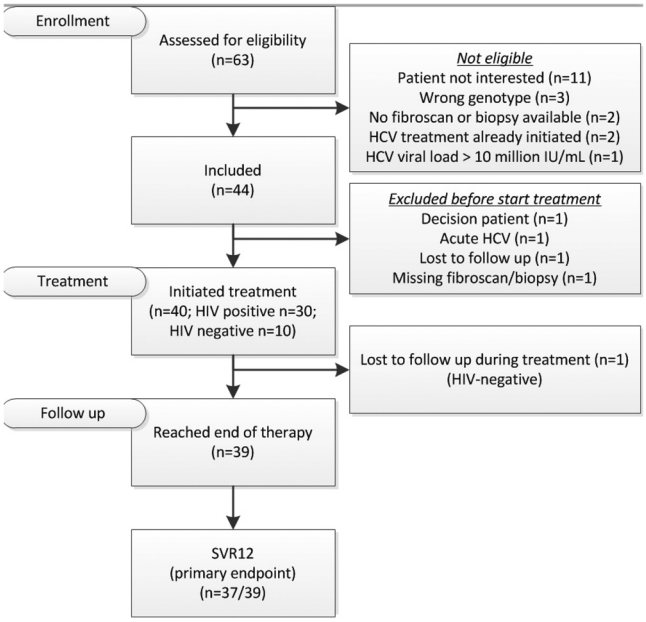
8 weeks of ledipasvir-sofosbuvir for non-cirrhotic patients with HCV genotype 4: A single-arm multicenter phase 3b study (HepNed-001)

A. Boerekamps[1], T. Vanwolleghem[2], M. van der Valk[3], E. Van den Berk Guido[4], D. Posthouwe[5], D. Anton[6], B.V. Hoek[7], S. Ramsoekh[8], M.V. Kasteren[9], J. Schinkel[10], E. Florence[11], J.E. Arends[12], B. Rijnders[1]. [1]*Erasmus MC, Department of Internal Medicine and Infectious Diseases, Rotterdam, Netherlands;* [2]*University Hospital Antwerp, Department of Gastroenterology and Hepatology, Edegem, Belgium;* [3]*Academic Medical Centre, Department of Internal Medicine and Infectious Diseases, Amsterdam, Netherlands;* [4]*OLVG location East, Department of Internal Medicine and Infectious Diseases, Amsterdam, Netherlands;* [5]*MUMC+, Department of Internal Medicine and Infectious Diseases, Maastricht, Netherlands;* [6]*Radboudumc, Department of Internal Medicine and Infectious Diseases, Nijmegen, Netherlands;* [7]*Leiden University Medical Center, Department of Gastroenterology and Hepatology, Leiden, Netherlands;* [8]*VUmc, Department of Gastroenterology and Hepatology, Amsterdam, Netherlands;* [9]*ETZ Elisabeth, Department of Internal Medicine and Infectious Diseases, Tilburg, Netherlands;* [10]*Academic Medical Centre, Department of Medical Microbiology, Section of Clinical Virology, Amsterdam-Zuidoost, Netherlands;* [11]*Institute of Tropical Medicine Antwerp, Department of Clinical Sciences, Antwerpen, Belgium;* [12]*UMC Utrecht, Department of Internal Medicine and Infectious Diseases, Utrecht, Netherlands*
Email: a.boerekamps@erasmusmc.nl

Background and Aims: Direct-acting antiviral therapy (DAA) for hepatitis C infection (HCV) is cost-effective but the budget impact can be substantial. For non-cirrhotic patients shortening treatment to 8 weeks of ledipasvir-sofosbuvir (LDP/SOF) may be a valid option, as demonstrated by high sustained virological response (SVR) rates in genotype 1. We hypothesized that 8 weeks of LDP/SOF is effective for non-cirrhotic genotype 4 patients as well.

Method: Single arm prospective multicentre clinical trial in 10 centres (clinicaltrialregister.eu 2016-000318-31). Non-cirrhotic DAA-naive chronic HCV genotype 4 infected patients received 8 weeks of LDP/SOF 90/400 mg QD. Inclusion criteria were HCV RNA <10 million IU/ml and FibroScan (FS) <12.5 kPa. The primary endpoint was the SVR 12 weeks after treatment (SVR12) in the on-treatment (OT) population. A cure of the baseline HCV virus but a diagnosis of a HCV *re*infection at SVR12 was not considered treatment failure. Secondary endpoints were SVR12 in the HIV-positive patients and in patients with HCV RNA <6 million IU/ml. With 41 evaluable patients, the study would be 90% powered for non-inferiority (d = 10%) compared with a fixed SVR12 of 95%.

Results: From 4/2016 to 6/2017, 63 patients were screened, 44 enrolled and 40 started therapy (Figure 1). Most were male (n = 34) and Caucasian (n = 32). Mean age was 51 years (±10). 21 were men who have sex with men (MSM), 5 were ex-intravenous drug users. Median time since HCV diagnosis was 4 years (IQR 4.5–7.6), HCV load was 1.1E6 IU/ml (IQR 3.4E5-3.6E6) and FS was 5.6 kPa (IQR 4.5–7.6). 30 were HIV-positive, all on cART with mean CD4 807 cells/µl and HIV viral load <50 c/ml in all but 1. One patient got lost to follow-up (HCV at week 4 < 15 IU/ml). In the OT population of 39 patients, 33 were HCV RNA negative and 6 HCV RNA positive at SVR12. In 4 of these 6 a HCV reinfection was confirmed; by genotyping in 2 patients (both genotype 1 at SVR12) and by phylogenetical analysis in 2 patients with genotype 4 at SVR12. Thus, therapy for the baseline virus was successful 37/39 or 95% of patients (exact 95% CI 83–99%). Unfortunately, the lower limit of the 95% CI of the SVR12 was <85%. Therefore, non-inferiority could not be demonstrated. In the 2 failures, HCV RNA at baseline was 9.8E5 and 8.7E6 IU/ml and no resistance-associated mutations (RAMs) were detected at SVR12. SVR12 was 28/30 for HIV-positive and 9/9 in HIV-negative patients (p = 1.0). All reinfections were observed in MSM which, given the short follow-up period, resulted in a very high reinfection incidence of 49.7/100 PYFU for this group.



Conclusion: 8 weeks of LDP/SOF was highly effective and no RAMs were detected in the 2 failures.

LBP-031

A deep-learning approach for pattern recognition allows rapid and reproducible quantification of histological NASH parameters: Integration into the QuPath platform

E. Rexhepaj[1], D. Nathalie[1], N. Benoit[1], H. Alison[1], B. Carole[1], R. Walczak[1], S. Megnien[1], D. Hum[1], B. Staels[2], J. Brozek[1]. *[1]GENFIT sa, Loos, France; [2]Institut Pasteur de Lille, Inserm UMR101, CHU Lille, Université Lille, EGID, Lille, France*
Email: elton.rexhepaj@genfit.com

Background and Aims: The histological evaluation of nonalcoholic steatohepatitis (NASH) activity index by microscopy is time-consuming and limited by inter/intra observer variability. This is mainly due to significant subjectivity in the interpretation of histological patterns. Deep-Learning (DL) technologies have been recently used to quantify the typical histological patterns of NASH in a reproducible manner. The aim of this work was to establish pattern recognition models to reproduce manual annotations of disease activity (ballooning and inflammation) scoring in NASH animal models. Finally, we illustrate how such models can be integrated in a open-source computational pathology software (QuPath) to increase user acceptance and experience.

Method: Animal models mimicking NASH were used to evaluate ballooning and inflammation. An expert evaluated the ballooning and inflammation scores for all animals included in the study. Additionally, DL models were constructed to detect ballooned hepatocytes and inflammatory cells. A first cohort (n = 33) was selected as a training set to calibrate the inflammation and ballooning grade prediction upon two independent cohorts (n = 180) were used to validate predictions.

Results: The DL algorithms showed excellent accuracy at predicting cell histological patterns related to ballooning (Accuracy = 92.1%) and inflammation (Accuracy = 91%). In the independent validation cohorts, excellent agreement was observed between the manually scored and fully-automated annotations of ballooned hepatocytes (K = 0.84, K = 0.81). Moreover, an excellent correlation was also observed between manual and WSI-based automated scoring of inflammation (Rho = 0.907).

Conclusion: Automated scoring of ballooning and inflammation showed a high correlation with manual annotations. In comparison with manual annotations, DL-based scoring systems integrated in QuPath allow an exhaustive and reproducible analysis of all cells in a biopsy. For example, they give special attention to specific regions of cells more difficult to interpret by experts. These prediction scores are now ready to be used for high-throughput activity scoring in pre-clinical studies or as companion diagnostic tools for clinical applications.

LBP-032

Safety and efficacy of ravidasvir plus sofosbuvir 12 weeks in non-cirrhotic and 24 weeks in cirrhotic patients with hepatitis C virus genotypes 1, 2, 3 and 6: The STORM-C-1 phase II/III trial

I. Andrieux-Meyer[1], S.-S. Tan[2], N. Salvadori[3], F. Simon[1], T.R. Cressey[3,4,5], H.R.H.M. Said[6], M.R.A. Hassan[7], H. Omar[8], H.P. Tee[9], W.-K. Chan[10], K.L. Goh[10], S.F.S. Omar[11], A. Kamarulzaman[11], S. Kumar[12], S. Thongsawat[13], K. Thetket[14], A. Avihingsanon[15], S. Khemnark[16], S. Thanprasertsuk[17], J.-M. Piedagnel[1], J. Brenner[18], S. Siva[1], N. Asimah[1], N. Da Silva[1], B. Pecoul[1], M. Lallemant[1], S. Murad[19]. *[1]Drugs for Neglected Diseases Initiative, Geneva, Switzerland; [2]Selayang Hospital, Department of Hepatology, Malaysia; [3]Chiang Mai University, Faculty of Associated Medical Sciences, PHPT/IRD, Chiang Mai, Thailand; [4]Harvard T.H. Chan School of Public Health, Department of Immunology & Infectious Diseases, Boston, United States; [5]University of Liverpool, Department of Molecular & Clinical Pharmacology, Liverpool, United Kingdom; [6]Hospital Ampang, Department of Medicine/ Gastroenterology, Malaysia; [7]Hospital Sultanah Bahiyah, Department of Medicine/Gastroenterology, Malaysia; [8]Hospital Selayang, Department of Hepatology, Malaysia; [9]Hospital Tengku Ampuan Afzan, Department of Medicine/Gastroenterology, Malaysia; [10]University of Malaya, Faculty of Medicine, Department of Medicine, Gastroenterology and Hepatology Unit, Malaysia; [11]University of Malaya, Faculty of Medicine, Department of Medicine, Infectious Disease Unit, Malaysia; [12]Hospital Sungai Buloh, Department of Medicine/Infectious Disease, Malaysia, [13]Chiang Mai University, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand, [14]Nakornping Hospital, Chiang Mai, Thailand, [15]Chulalongkorn University, King Chulalongkorn Memorial Hospital/ HIV-NAT, Bangkok, Thailand, [16]Bamrasnaradura Infectious Diseases Institute, Nonthaburi, Thailand, [17]Ministry of Public Health, Bangkok, Thailand, [18]DNDi, Geneva, Switzerland, [19]Ministry of Health, Kuala Lumpur, Malaysia*

Background and Aims: In low and middle income countries, affordable direct-acting antivirals for the treatment of hepatitis C virus (HCV) infection are urgently needed. The combination of ravidasvir, a pangenotypic NS5A inhibitor, and sofosbuvir has shown excellent efficacy and safety in HCV patients with genotype 4 (Esmat 2018). The STORM-C-1 trial aims to assess the safety and efficacy of sofosbuvir plus ravidasvir in Malaysia and Thailand where genotypes 1 and 3 are prevalent.

Method: STORM-C-1 is a two-stage, open label, multicentre clinical trial. HCV patients with no cirrhosis (Metavir F0-F3) or compensated cirrhosis (Metavir F4 and Child-Turcotte-Pugh class A) were eligible, regardless of HCV genotype (GT), HIV infection status or prior interferon-based treatment. Once-daily sofosbuvir (400 mg) and ravidasvir (200 mg) was given for 12 weeks if no cirrhosis and 24 weeks if compensated cirrhosis. Patients with no current injection drug use at the eligibility visit who received at least one dose of a study drug were included in the intent to treat (ITT) analysis. The primary endpoint was a sustained virologic response at 12 weeks post-treatment (SVR12). Patients with missing SVR12 outcome were considered as failures. A sample size of 300 patients ensured sufficient precision in the SVR12 rates overall and within key subgroups to proceed safely to the second stage of the study.

Results: From October 2016 to June 2017, 301 patients were enrolled and 300 were included in the ITT analysis: 230 (77%) were males; median age was 47 years; 97 had HCV GT1a, 28 GT1b, 2 GT2, 158 GT3 and 15 GT6; 81 (27%) had compensated cirrhosis; 90 (30%) were co-infected with HIV; and 99 (33%) had prior interferon-based treatment. Overall, 291/300 patients (97.0%) achieved SVR12

(95% confidence interval [CI]: 94.4% to 98.6%). In particular, 51/53 GT3 cirrhotic patients (96.2%) achieved SVR12 (95% CI: 87.0% to 99.5%). In the per protocol analysis, 288/293 patients (98.3%) achieved SVR12 (95% CI: 96.1% to 99.4%). Three patients prematurely discontinued study treatment due to adverse events. There were no deaths and no discontinuations due to serious adverse events related to study treatment.

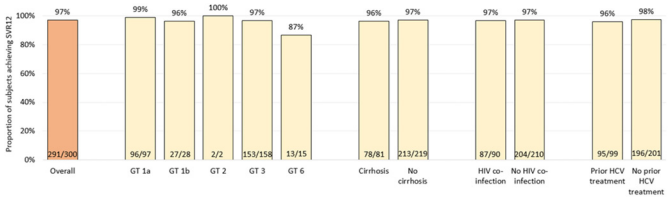


Figure: SVR12 rates overall and within key subgroups in the intent to treat analysis.

Conclusion: With 12 weeks of treatment in non-cirrhotic and 24 weeks in cirrhotic patients, sofosbuvir plus ravidasvir was highly effective, regardless of HCV GT, HIV infection and previous interferon experience. Treatment was well tolerated in all subgroups.

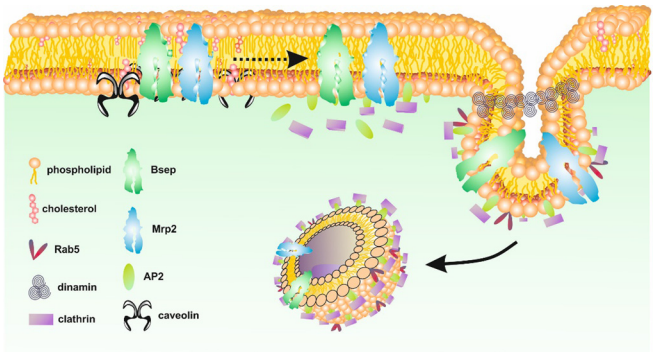
Molecular and cellular biology

THU-001

Internalization of canalicular transporters in estradiol 17ß-D-glucuronide-induced cholestasis involves shift from "raft" to "non-raft" membrane domains and clathrin-mediated endocytosis

G.S. Miszczuk, I. Barosso, R. Andermatten, M.C. Larocca, J. Marrone, R.A. Marinelli, A.C. Boaglio, E.S. Pozzi, M.G. Roma, F.A. Crocenzi.
Institute of Experimental Physiology (CONICET-UNR), Faculty of Biochemical & Pharmaceutical Sciences, Rosario, Argentina
Email: fcrocen@unr.edu.ar

Background and Aims: Impaired canalicular secretion due to exacerbated endocytosis of canalicular carriers relevant to bile formation, such as Bsep and Mrp2, is a main, common pathomechanism in both experimental and human cholestasis. Nevertheless, the mechanisms governing this process are unknown. We studied the involvement of clathrin- and caveolin-mediated endocytosis in estradiol 17β-D-glucuronide (E17G)-induced cholestasis, an experimental model which partially mimics pregnancy-induced cholestasis.
Method: E17G was administered to isolated rat hepatocyte couplets (IRHC), sandwich-cultured rat hepatocytes (SCRH), isolated and perfused rat livers (IPRL), and whole rats. Clathrin involvement in E17G-induced endocytosis of Bsep and Mrp2 was evaluated in IRHC by using either the inhibitor of clathrin-mediated endocytosis (CME), monodansylcadaverine (MDC), or a K^+ depletion protocol, whereas caveolin involvement was evaluated by using the specific inhibitors, filipin and genistein. In SCRH, CME was blocked by knockdown of the clathrin adaptor protein AP2 with specific siRNAs. Bsep/Mrp2 localization was studied in IRHC by immunofluorescence staining followed by confocal microscopy, and statistical comparison of the densitometric profiles along a line perpendicular to the canaliculus (Mann-Whitney test). Colocalization of Mrp2 with the components of CME machinery AP2, Rab5, and clathrin was evaluated in SCRH in confocal images, by using the plugins "Image calculator" and "AND". In liver tissue, distribution of Bsep and Mrp2 between caveolin-enriched, "raft" plasma membrane microdomains and clathrin-enriched, "non-raft" ones was assessed by western blot of these carriers in "raft" and "non-raft" fractions obtained by detergent treatment of highly purified plasma membranes.
Results: MDC and K^+ depletion, but not filipin or genistein, prevented E17G-induced endocytosis and the functional failure of Bsep and Mrp2 in IRHC. Immunofluorescence and confocal microscopy studies showed that, in E17G-treated IRHC, there was a significant increase in colocalization of Mrp2 with clathrin, AP2, and Rab5. Knockdown of AP2 in SCRH completely prevented E17G-induced Bsep and Mrp2 endocytosis. MDC significantly counteracted the impairment in bile flow and biliary output of Bsep and Mrp2 substrates, as well as the endocytosis of these carriers induced by E17G in IPRL. Bsep and Mrp2, which were mostly present in "raft" membrane domains in control rats, were largely redistributed to "non-raft" domains in livers from E17G-treated rats, from where they can be readily recruited for CME.



Postulated mechanism of E17G-induced endocytosis of the canalicular transporters Bsep and Mrp2. These transporters, which are normally enriched in raft microdomains, suffer a shift towards non-raft microdomains, where the components of the clathrin-dependent endocytic machinery are recruited, leading to their endocytosis.

Conclusion: Clathrin-mediated endocytosis is involved in the internalization of Bsep and Mrp2 in E17G-induced cholestasis. The shift of these transporters from "raft" to "non-raft" lipid domains could be a prerequisite for the transporters to be endocytosed under cholestatic conditions.

THU-002

Different micro-environtmental factors induce proliferation, epithelial-mesenchymal transition (EMT) and senescence of primary cultures of human biliary tree stem/progenitor cells (hBTSCs), recapitulating the pathological features typical of human cholangiopathies

D. Costantini[1], G. Carpino[2], V. Cardinale[3], D. Overi[4], L. Nevi[1], S. Di Matteo[1], S. Safarikia[1], F. Melandro[5], P.B. Berloco[5], E. Gaudio[6], D. Alvaro[1]. [1]*Sapienza University of Rome, Department of Medicine and Medical Specialties, Rome, Italy;* [2]*"Foro Italico" University of Rome, Department of Movement, Human and Health Sciences, Division of Health Sciences, Rome, Italy;* [3]*Sapienza University of Rome, Department of Medico-Surgical Sciences and Biotechnologies, Polo Pontino, Latina, Italy;* [4]*Sapienza University of Rome, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Rome, Italy;* [5]*Sapienza University of Rome, Department of General Surgery and Organ Transplantation, Rome, Italy;* [6]*Sapienza University of Rome, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Division of Human Anatomy, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Rome, Italy*
Email: daniele.costantini@uniroma1.it

Background and Aims: The activation of human biliary tree stem/progenitor cells (hBTSCs) located in peribiliary glands (PBGs) have been recently described in different cholangiopathies, including Primary Sclerosing Cholangitis (PSC) and Cholangiocarcinoma (CCA). In these pathologies, hBTSCs also display features of EMT, senescence and dysplasia. The aim of the present study was to investigate putative agents reproducing in primary cultures of hBTSCs the pathologic features observed in PBGs of human cholangiopathies.
Method: hBTSCs were isolated from donor organs (n = 6), cultured in self-renewal control conditions (Kubota's Medium, KM) and exposed (from 24 hours to 10 days) to increasing concentrations of

lipopolysaccharides (LPS), oxysterols, hydrophobic biliary salts, or high glucose. Viability (MTS assay), Population Doubling (PD), the expression (RT-qPCR) of pluripotency, transit-amplifying compartment, EMT, pNF-kB and HDAC6 genes and senescence associated secreted phenotype (SASP) by IF and ELISA were examined.
Results: Glycochenodeoxycholate (0.5 mM), LPS (200 ng/ml), oxysterols [(+)-4-Cholesten-3-one (0.14 mM), Cholesta-4,6-dien-3-one (0.14 mM), 5α-Cholestan-3-one (0.14 mM) or high concentrations of Glucose (28 mM) did not affected the viability of hBTSCs. LPS, Cholesta-4, 6-dien-3-one and Glucose induced a significant increase of cell proliferation after 10 days of exposure ($p < 0.01$). The MTS assay confirmed a high proliferation rate after chronic exposure (10 days) to LPS, oxysterols, or high glucose ($p < 0.01$). Cholesta-4, 6-dien-3-one determined a significant increase of markers of transit-amplifying compartment and EMT ($p < 0.05$) while, bacterial LPS and high Glucose determined an increased expression of PCNA and EMT genes. Senescent cells increased after 10 days of exposure to each of the investigated factor compared to controls ($p < 0.01$). LPS, Cholesta-4, 6-dien-3-one and high Glucose induced enhanced IL-6 secretion compared to controls ($p < 0.01$). In addition, conditioned cell cultures expressed high levels of pNF-kB and HDAC6 ($p < 0.01$), and traces of LC3 protein suggesting inflammation-induced autophagy.
Conclusion: We identified different micro-environmental factors capable to induce in hBTSCs proliferation, enhanced expression of pluripotency and transit-amplifying genes, EMT and senescence, recapitulating the pathologic features described in PBGs of human cholangiopathies. IL-6, the overexpression of pNF-kB and HDAC6 and activation of autophagy are involved in these pathologic changes.

THU-003
Transcriptional repressors Zeb1 and Zeb2 regulate collagen production in drug-induced hepatic stellate cell activation in mice

I. Mannaerts, L. Stradiot, N. Eysackers, L. van Grunsven.
Vrije Universiteit Brussel, BMWE-LIVR, Brussel, Belgium
Email: inge.mannaerts@vub.ac.be

Background and Aims: Upon liver injury, hepatic stellate cells become activated myofibroblast-like cells. They lose their vitamin A storing capacity and become collagen producing cells with migratory capacities. This transdifferentiation has been compared to an epithelial to mesenchymal differentiation. This is a strictly orchestrated process, in which a role for E-box repressors, including Snail family members and Zeb proteins, and a role for the miR-200 family has been established. Both the transcriptional repressors and microRNAs that regulate the epithelial to mesenchymal differentiation are transforming growth factor-β sensitive regulators. In this study we investigated the role of Zeb proteins (δef1 and Sip1) and miR-200 family members during stellate cell activation, migration and fibrosis.
Method: BalbC mice were used to isolate primary hepatic stellate cells, cells were activated by culture in fetal bovine serum containing medium. Repeated carbontetrachloride administration to mice induced liver fibrosis and liver cell types were isolated from these mice using the recently published UFACS3 flow cytometry protocol. The role of ZEB proteins was investigated by siRNA mediated silencing in vitro and in vivo. In vivo targeting of the siRNA to stellate cells was obtained by coupling vitamin A to liposome carriers. Effects of ZEB knock down were evaluated by real time polymerase chain reaction, immunohistochemistry, western blot and migration and proliferation assays.
Results: An siRNA mediated silencing of Zfhx1 repressors induced a strong up-regulation of E-cadherin and resulted in a mild decrease of stellate cell activation marker Acta2. In addition, ectopic expression of miR-200c also induced E-cadherin mRNA and protein expression and reduced stellate cell migration in a transwell migration assay. Finally, we have used vitamin-A coupled liposomes to knock down Zeb1 and Zeb 2 in vivo in a chronic fibrosis model. Selective delivery was confirmed by lowered RNA levels of Zeb1 and Zeb2 in stellate cells, but not in other non-parenchymal cells. While the silencing Zeb1 and Zeb2 was modest, a significant reduction in collagen1a1 and collagen3a1 was observed.
Conclusion: E-box repressors Zeb1 and Zeb2 are important players in the regulation of stellate cell activation in vitro and in vivo.

THU-004
Dechipering the role of Axin2/Lgr5+ pericentral hepatocytes

L. Planas-Paz, T. Sun, M. Pikiolek, V. Orsini, Y. Yang, F. Cong, J. Tchorz.
Novartis, Basel, Switzerland
Email: lara.planas_paz@novartis.com

Background and Aims: The liver has an intrinsically high capacity to regenerate both during homeostasis and in response to various distinct etiological insults. Hepatocytes throughout the liver lobule can re-enter the cell cycle to proliferate and restore liver mass. Axin2+ pericentral hepatocytes have been proposed as a novel liver stem cell population refuelling the entire hepatocyte pool during homeostasis. However, existing Axin2 lineage tracing mice suffer from a heterozygous deletion of Axin2, a known tumour suppressor. We identified Lgr5 as a marker of Axin2+ pericentral hepatocytes and, using Lgr5 lineage tracing experiments, showed that pericentral hepatocytes are not liver stem cells.

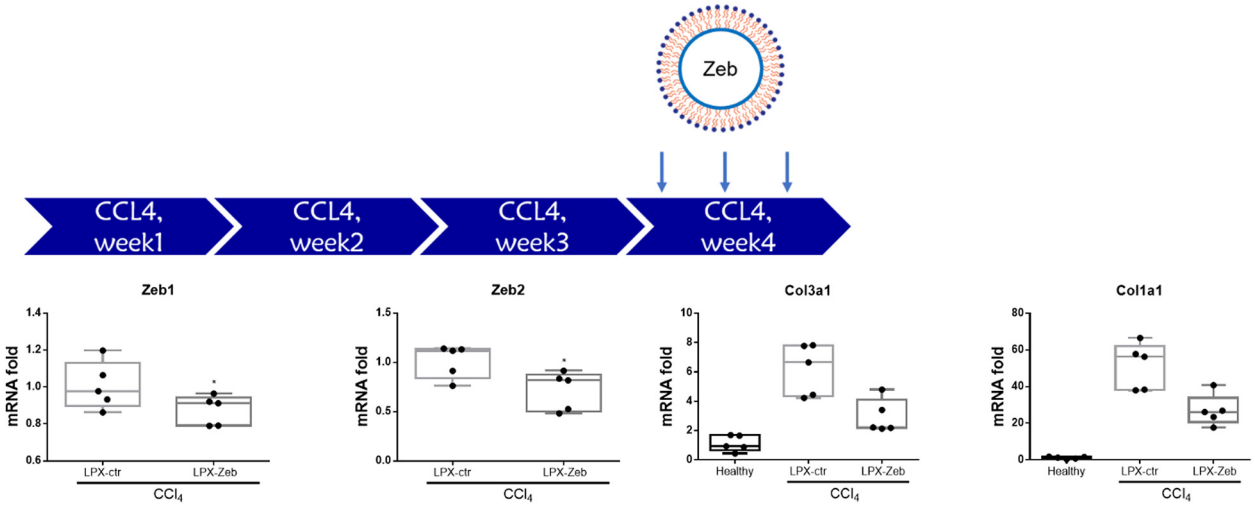


Figure: (abstract: THU_003)

Method: We generated a novel BAC-transgenic Axin2 lineage tracing model that does not suffer from heterozygous deletion of Axin2. We performed Axin2 lineage tracing in stomach, intestine and liver in homeostasis, as well as during regeneration from a diet-induced injury in the liver.
Results: Our Axin2 lineage tracing model confirmed expansion of Wnt-dependent tissue stem cells in the gut and stomach identified with previous Axin2 or Lgr5 lineage tracing. In contrast, we did not observe a significant expansion of Axin2+ hepatocytes during liver homeostasis over 10 months. Moreover, EdU labelling experiments revealed no zonal dominance during this process. While Axin2+ hepatocytes significantly expanded during DDC-induced liver regeneration, they never reached far into the parenchyma or periportal space.
Conclusion: Together, our data argue against the hypothesis that pericentral hepatocytes represent a liver stem cell niche.

THU-005
A combined laser microdissection and proteomic analysis method for identification of liver tumors signatures

E. Henriet[1], A.A. Hammoud[2], J.-W. Dupuy[3], B. Dartigues[3], Z. Ezzoukhry[2], N. Dugot-Senant[4], T. Leste-Lasserre[5], M. Nikolski[3], B.L. Bail[2,6], J.-F. Blanc[2,6], C. Balabaud[2], P. Bioulac-Sage[2,6], A.-A. Raymond[2,4,7], F. Saltel[2,7]. *[1]BaRITon INSERM 1053, Bordeaux Cedex, France; [2]BaRITOn INSERM 1053; [3]CGFB Bordeaux; [4]TBM Core US 005; [5]Institut Magendie; [6]CHU Bordeaux; [7]Equal work*
Email: anne-aurelie.raymond@inserm.fr

Background and Aims: Since several years, research efforts concentrated on the identification of genomic abnormalities in tumors offering the prospect of personalized treatments and thus a better management of patients. However, proteins expression is the downstream result of these combined genomic anomalies in tumors and is essential for a better understanding of the mechanisms of cancer initiation, tumoral progression, metastatic scattering and to identify new biomarkers and pharmacological targets.
Method: Mass spectrometry is the method of choice to identify, characterize and quantify the proteins in a complex sample. The Oncoprot platform (http://www.tbmcore.u-bordeaux.fr/oncoprot/) developed a method combining laser microdissection and mass spectrometry analysis to compare the proteomic profiles of tumors. This procedure has been optimized for the study of FFPE tissue sections even on small material obtained from biopsy.
Results: We made the proof of concept on Hepatocellular adenomas (HCA), rare benign tumors that constitute a heterogeneous entity, divided into several groups based on patho-molecular features (1) HCA with inactivating mutations of HNF1A, (2) Inflammatory HCA with diverse mutations leading to the activation of STAT3, (3) HCA with activating beta-catenin. In the case of unclassified HCA (UHCA), which were identified by default, a high risk of bleeding remained a clinical issue. The objective of this study was to explore UHCA proteome in the purpose of identifying specific biomarkers. We compared tumoral and non-tumoral proteins expression levels in HCA, H-HCA, IHCA, b-HCA, and UHCA. Using the Oncoprot's process, we searched for proteins specifically deregulated in UHCA. First, we demonstrated that proteomic profiles allow us to discriminate between known HCA subtypes by the identification of classical biomarkers of each HCA subgroup. We revealed specific upregulation of the synthesis of the arginine pathway associated with an overexpression of argininosuccinate synthase (ASS1) and arginosuccinate lyase (ASL) in UHCA. Moreover, arginine is the substrate for nitric oxide synthesis, a factor involved in vascular permeability. ASS1 immunohistochemistry identified all the UHCA, of which 64.7% presented clinical bleeding manifestations.
Conclusion: In conclusion, we demonstrated the power of mass spectrometry coupled with laser microdissection to identify tumoral signatures and robust biomarkers. We can now answer to other clinical needs to propose new biomarkers for diagnosis, prognosis and to predict the response to treatments.

THU-006
Identificiation of compounds targeting CD133-positive hepatogellular carcinoma while minimizing the damage on hepatocytes by phenotypic high-content screening

H.R. Seo[1], Y. Song[1], I. Choi[2], S.-H. Kim[1]. *[1]Institut Pasteur Korea, Cancer Biology Research Laboratory, Gyeonggi-do, Republic of South Korea; [2]Institut Pasteur Korea, Bioinformatics, Gyeonggi-do, Republic of South Korea*
Email: shr1261@ip-korea.org

Background and Aims: Cancer stem cells (CSCs) are considered the "Achilles heel" due to their strong resistance to chemotherapy and radiotherapy. Thus, the recent advancements in the use of liver cancer stem cells (LCSC) to develop efficient and organized means to an antitumor agent is quickly gaining recognition as a novel goal. In our previous study, we characterized CSCs in primary hepatocellular carcinoma (HCC) and identified CD133 as a CSC cell-surface marker. In this study, we proposed to use non-target based high throughput screening approach to specifically target AFP$^+$/CD133$^+$ HCC present in mixed populations of HCC cells with hepatocytes.
Method: To find hit compound, which specifically targets AFP+/CD133+ HCC without damaging hepatocytes, mixed cell culture system were developed. Using this system, high throughput screening was performed. The first hit compounds were validated through dose response curve analysis with fluorescence image-based phenomic screening. Secondary hits from dose response curve study were validated through drug sensitivities in liver cancer stem cell spheroids, dose response curve study in sorted cells with CD133 (CD133$^-$ and CD133$^+$ HCC cells), and analyzing the CD133 protein levels. Final hit was validated with xenograft model.

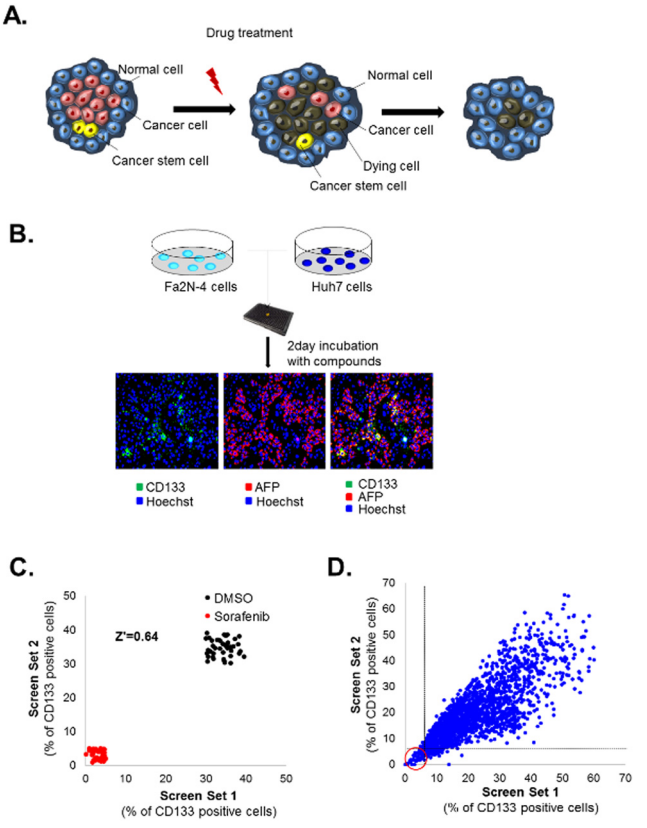


Figure 1: Hepatocellular carcinoma (HCC)-mixed culture system for liver cancer stem cells (LCSCs)-targeting drug screening.

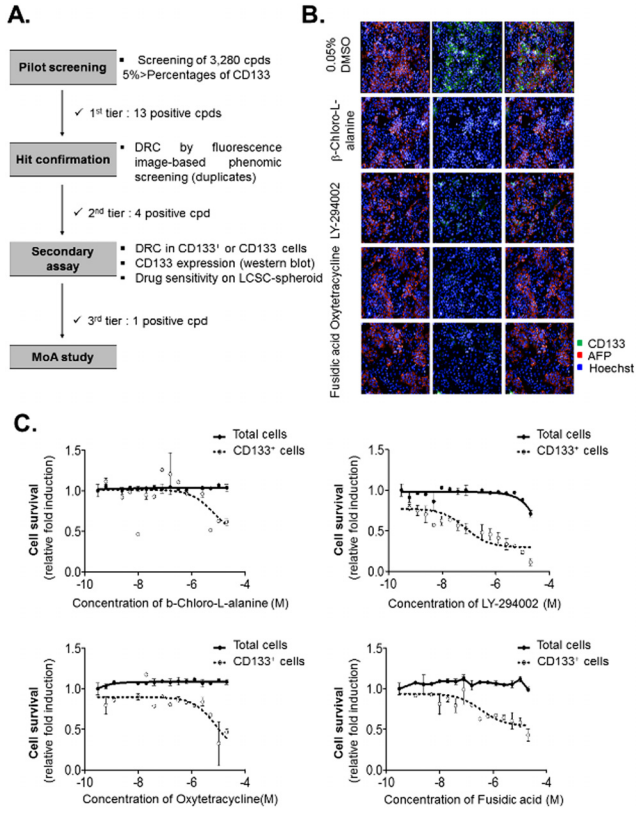


Figure 2: Four hit compounds from HCC-mixed LCSC-targeting screening.

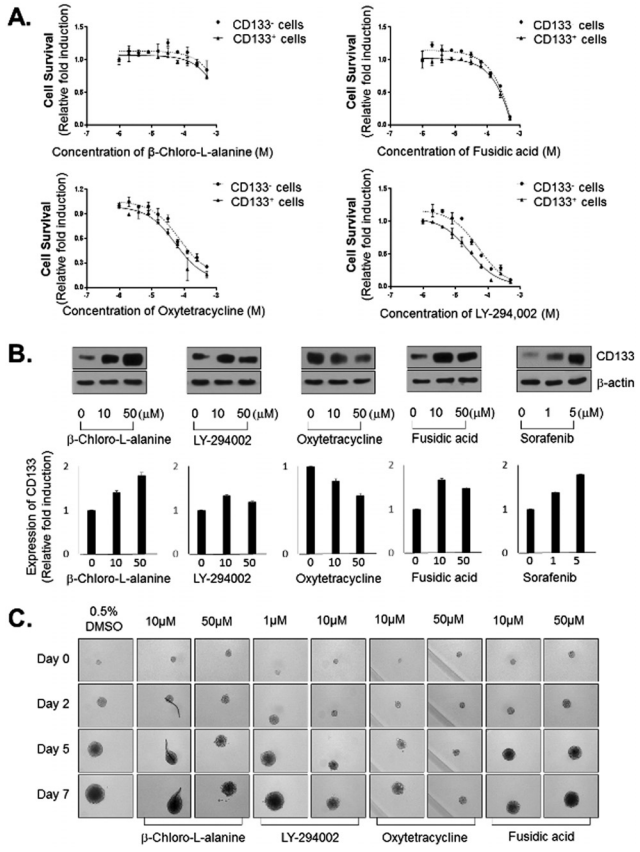


Figure 3: Suppressing LCSC properties of 4 hit compounds.

Results: To determine whether oxytetracycline targets LCSC, we examined whether oxytetracycline treatment could change the CD133 expression, spheroid forming ability as well as the levels of stem cell-related markers. Treatment of spheroid-forming LCSC with oxytetracycline effectively decreased the spheroid formation as well as the $CD133^+$ cell population. Oxytetracycline treatment suppressed expression of CD133 without changing of expression of other stem cell-related markers. Importantly, these series of phenomena by treatment of oxytetracycline occurs because of alteration of CD133 protein stability by oxytetracycline. Alterations in the malignant properties of $AFP^+/CD133^+$ HCC by oxytetracycline were also investigated by xenograft assay in nude mice. Treatment of oxytetracycline significantly attenuated tumor formation and $CD133^+$ cell population in xenograft mice.

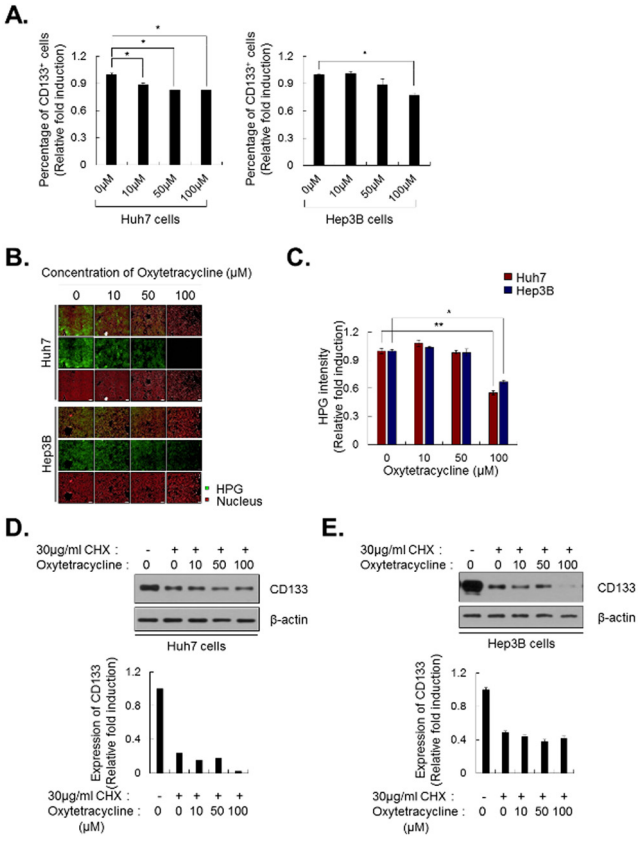


Figure 4: Decrease of CD133 levels by oxytetracycline.

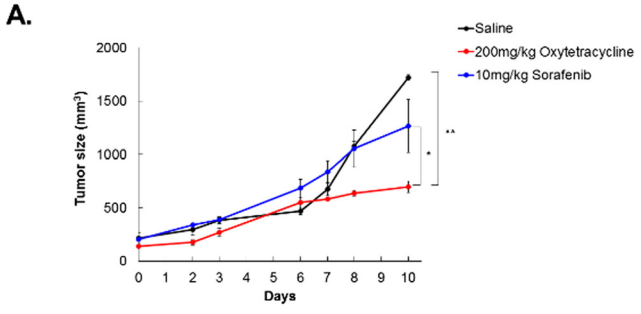


Figure 5: Decrease of tumor size and $CD133^+$ population in mouse model.

Conclusion: These results indicate that the oxytetracycline suppresses stemness and malignancies in HCC cells through destabilization of CD133 in LCSC population, providing novel therapeutic strategies targeting specifically cancer stem-like cells.

Table 1: (abstract: THU-006): List of primary hit compounds

	Name of compounds	Mechanism of action
1	5'-Amino-5'-deoxyadenosine p-toluenesulfonate salt	Adenosine analog.
2	trans-Azetidine-2,4-dicarboxylic acid	mGluR1 and mGluR5 metabotropic glutamate receptor agonist
3	Chlormethiazole hydrochloride	GABA(A) agonist; glycine receptor modulator
4	beta-Chloro-L-alanine hydrochloride	Alanine aminotransferase inhibitor
5	1,10-Diaminodecane	Inverse agonist at the polyamine recognition site of the NMDA glutamate receptors
6	LY-294,002 hydrochloride	Specific phosphatidylinositol 3-kinase (PI3K) inhibitor.
7	Pentamidine isethionate	NMDA glutamate receptor antagonist
8	PAPP	Selective 5-HT1A serotonin receptor agonist
9	Mebendazole	Glucose transport inhibitor
10	Oxytetracycline	Ribosomal protein synthesis inhibitor
11	Fusidic acid sodium salt	Protein synthesis inhibitor GTPase coupled
12	(S)-(-)-Atenolol	Adrenergic receptor antagonist
13	Tetramisole hydrochloride	Alkaline phosphatase inhibitor

THU-007

Negative allosteric modulators of metabotropic glutamate receptor subtype 5 protect against hepatic ischemia/reperfusion injury

C. Berardo[1], V. Siciliano[1], L.G. Di Pasqua[1], P. Richelmi[1], F. Nicoletti[2,3], M. Vairetti[1], A. Ferrigno[1]. *[1]University of Pavia, Internal Medicine and Therapeutics, Pavia, Italy; [2]Neuromed, Pozzilli, Italy; [3]University of Rome, La Sapienza, Physiology and Pharmacology, Roma, Italy*
Email: clarissa.berardo01@universitadipavia.it

Background and Aims: The negative allosteric modulator (NAM) of metabotropic glutamate receptor subtype 5 (mGluR5) 2-methyl-6-(phenylethynyl) pyridine (MPEP) improves viability of anoxic hepatocytes. In microglia and astrocytes, ATP production and release were reduced by MPEP. Since ATP depletion is involved in ischemic damage, aims of this study were: to understand the mechanism of MPEP-mediated ATP depletion, to compare different NAMs with regard to protection against ischemia and to assess liver functionality in an *ex vivo* model of ischemia/reperfusion (I/R) injury.
Method: Isolated hepatocytes from male Wistar rats were exposed to 90 min anoxia at 37°C, with NAMs: MPEP and 3-((2-methyl-4-thiazolyl)ethynyl)pyridine (MTEP) at 3–30 µM, Fenobam (Fen) at 1-10-50-100 µM. Hepatocytes viability was evaluated by trypan blue exclusion and LDH release. Isolated mitochondria from rat livers were treated with MPEP, MTEP, Fen at 0.3-3-30 µM. Mitochondrial respiratory control ratio, membrane potential, ROS production and F_1F_O-ATPase activity were gauged, using a respiration chamber, the rhodamine spectrofluorometric method, the H_2DCFDA assay and an enzymatic spectrophotometric kit, respectively. ATP was assessed by the luciferin/luciferase method in isolated hepatocytes, mitochondria as well as in an acellular buffer containing 10 µM ATP and MPEP, MTEP, Fen at 0.3-3-30 µM. Wildtype and mGluR5 knockout livers from Balb c mice were isolated, subjected to I/R and treated with MPEP 0.3 µM; LDH, AST and TNF-alpha release were evaluated.
Results: MPEP 30 µM, MTEP 3 µM and Fen 50 µM improved significantly the viability of anoxic hepatocytes respect to anoxic controls. ATP content was monitored before and after N_2 insufflation. MPEP significantly lowered ATP content respect to oxygenated controls; MPEP-treated cells showed a slower decline in ATP after N_2 insufflation. The same trend was observed for MTEP but not for Fen. In mitochondria, MPEP induced a dose-dependent ATP depletion, without affecting mitochondrial functionality. In an acellular solution only MPEP and MTEP reduced ATP content. The addition of MPEP during I/R significantly reduced LDH, AST and TNF-alpha release respect to ischemic controls.
Conclusion: Isolated hepatocytes were protected by MPEP, MTEP and Fen against ischemic injury. Although an MPEP-dependent ATP depletion occurred in isolated hepatocytes, mitochondria and acellular solutions, mitochondrial functionality was not affected and, in an *ex vivo* model, MPEP was able to reduce the hepatic I/R injury.

THU-008

Rapid generation of somatic liver knockouts using multiplex CRISPR/Cas9 editing

K.-D. Bissig, D. Moore, J.C. Marini, S. Elsea, B. Bissig, X. Legras, F. Pankowicz, K. Kim, C.S. Martins, M. Barzi, R. Wooton-Kee, W. Lagor. *Baylor College of Medicine, Houston, United States*
Email: bissig@bcm.edu

Background and Aims: Despite advances in gene editing technologies, generation of tissue-specific knockout mice remain time-consuming and expensive and so far, knockouts for more than three genes in parallel have not been established.
Method: Here, we describe a novel technique termed Somatic Liver Knockout (SLiK), which uses CRISPR-Cas9 genome editing in adult mice to generate full-liver knockouts for any desired gene or genes in just a few weeks.
Results: To demonstrate the utility of SLiK, we generated two distinct mouse models for genes not amenable to conventional gene knockout – argininosuccinate lyase (*Asl*) and ATP-binding cassette, sub-family B member 11 (*Abcb11*). Furthermore, we were able to use SLiK to rapidly generate mice with five genes simultaneously knocked out from the murine liver.
Conclusion: Our studies demonstrate broad applicability of SLiK ranging from disease modeling for inborn errors of metabolism to more complex pathway analysis requiring multiple knockouts in parallel.

THU-009

Common immunological and cellular pathways of human alcoholic hepatitis and murine models of alcohol consumption

A. Vogle, E. Burnett, H. Fey, C. Aloman. *Rush University Medical Center, Internal Medicine, Chicago, United States*
Email: voglealyx@gmail.com

Background and Aims: Murine models of chronic alcohol consumption often use ethanol containing isocaloric liquid diets (Lieber-DeCarli, Nanji) or ethanol-in-water (Meadows-Cook). Isocaloric diets produce steatosis and minimal inflammation, while ethanol-in-water causes only minimal histological liver damage. These models are used to investigate new treatments for alcoholic hepatitis but it is unclear whether these models have similar immunological changes and early fibrogenesis. In this study we assessed the degree of similarity of

immunological changes and fibrogenesis of each model with alcoholic hepatitis.
Method: C57BL/6 mice were alcohol-fed via Lieber-DeCarli or Nanji isocaloric liquid diet for 4 weeks or per Meadows-Cook method for 12 weeks. Liver histology was assessed by H&E and Oil Red-O staining. Transcripts for chemokines and cytokines, T-cell immune responses, endothelial adhesion molecules, and fibrogenic markers were assessed by qPCR of liver tissue. Murine data from each diet was compared to both alcoholic hepatitis and healthy subjects' human microarray data from the public domain (GSE28619).
Results: There is extensive variability of chemokines, cytokines and adhesion molecules mRNA despite minimal histological changes observed in murine models: (1) CCL2, CCL20, and CXCL10 mRNA are up-regulated in human alcoholic hepatitis and only the Nanji diet induces up-regulation in CCL2 and CCL20 while CXCL10 is down-regulated. (2) As reported, TNFα mRNA is not affected in alcoholic hepatitis patients while in the Lieber-DeCarli diet it is up-regulated. (3) E-selectin is the only common change of adhesion molecules in every murine group and alcoholic hepatitis. Surprisingly, transcriptional control of hepatic Th1 immune response is only minimally affected in alcoholic hepatitis patients, while it decreased in isocaloric diets. Similar control for Th2 is observed in isocaloric models and human disease, while decreases in Th17 are only seen in alcoholic hepatitis. Unexpectedly, in spite of almost no hepatic histological features, Meadows-Cook diet, and not isocaloric diets, mimic human alcohol-induced fibrogenesis when fibrogenic marker transcripts are measured.
Conclusion: Any investigation of new treatments of alcoholic hepatitis in the existing murine model of alcohol consumption should take into account the extensive variability of immunological and fibrogenesis mechanisms between murine models themselves and between murine models and human alcoholic hepatitis.

THU-010
Demethylation increases the expression of type 3 inositol 1, 4, 5-trisphosphate receptor in hepatocytes

R.M. Florentino[1], A. França[2], A.C.M.L. Filho[1], M.C. Fonseca[3], A.G. Oliveira[1], C.X. Lima[4], P.V.T. Vidigal[5], M. de Fátima Leite[1]. *[1]UFMG, Physiology and Biophysics, Belo Horizonte, Brazil; [2]UFMG, Molecular Medicine, Belo Horizonte, Brazil; [3]CNPEM, LNBio, Campinas, Brazil; [4]UFMG, Surgery, Belo Horizonte, Brazil; [5]UFMG, Pathological Anatomy and Forensic Medicine, Belo Horizonte, Brazil*
Email: rodrigomachado@ufmg.br

Background and Aims: Calcium regulates a wide range of activities in hepatocytes, from secretion to metabolism to proliferation. The type 1 and the type 2 inositol 1,4,5-trisphosphate receptor (InsP3R) are the only intracellular calcium channels present in hepatocytes, which lack the type 3 InsP3R (InsP3R-3) isoform under normal conditions, but show its increased expression in several models of hepatocellular diseases. Bioinformatics analysis demonstrates that the InsP3R-3 promoter region has a large number of CpG islands, likely sites of methylation that supress its expression under physiological condition. Moreover, we also observed that the levels of methylation at the InsP3R-3 promoter region are lower in patients with hepatocarcinoma than healthy controls. Thus, our aim is to investigate whether demethylation of cytosine sites at InsP3R-3 promoter region regulates its expression in hepatocytes, and whether it is involved in hepatocarcinogenesis.
Method: To induce demethylation, swiss male mice were treated, intraperitoneally, with 5′-azacitidine (5′-aza) and the $InsP_3R$-3 expression level was assessed by real-time PCR, western blotting, immunofluorescence and immunohistochemistry. Calcium signaling in hepatocytes was evaluated *in vivo,* with fluo-4/AM, after vasopressin stimulation. The proliferative capacity of the liver was assessed at 24 and 48 hours after partial hepatectomy. To determine the $InsP_3R$-3 expression level in hepatocarcinogenesis, immunohistochemistry was performed in human liver sections from pre-neoplastic and neoplastic stage.
Results: Treatment with 5′-aza increased the expression of liver $InsP_3R$-3 (control = 1.0 ± 0.1 a.u.; 5′-aza = 1.7 ± 0.2 a.u, $p < 0.05$ and $n = 5$) and its expression was shown to be concentrated at the pericentral but abscent at the periportal region. Similarly with the InsP3R-3 expression pattern, the amplitude of calcium signalling was greater in hepatocytes located at the pericentral region (control = 13.1 ± 0.9 a.u.; 5′-aza = 40.8 ± 1.7 a.u, $p < 0.05$ and $n = 5$). Livers that express InsP3R-3 showed increased proliferative capacity compared to control (control = 47.8 ± 3.1 positive cells; 5′-aza = 75.7 ± 3.5 positive cells, $p < 0.05$ and $n = 5$). Moreover, we found that $InsP_3R$-3 expression is observed not only in neoplastic but also in pre-neoplastic stages.
Conclusion: We show that methylation regulates the expression of $InsP_3R$-3 in the hepatocytes, causing an increase in liver proliferation rate.

THU-011
Correction of ATP7B restores its sub-cellular localisation in hepatocytes from Wilson's disease induced pluripotent stem cells

J. Yang[1], M.A. Esteban[2], H.-F. Tse[3]. *[1]Departmemnt of Medicine, the University of Hong Kong, Hong Kong SAR, China; [2]Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China; [3]Queen Mary Hospital, the University of Hong Kong, Hong Kong SAR, China*
Email: jyyang@hku.hk

Background and Aims: Wilson's disease (WD) is an inherited liver disorder caused by mutations in ATP7B, whose malfunction leads to copper accumulation throughout the body and results in varied clinical phenotypes including liver failure and neuropsychiatric manifestations. Induced pluripotent stem cell (iPSC) technology combined with targeted genetic modifications offer the prospect of autologous transplantation using differentiated cells derived from corrected patient-specific iPSCs, with potential application in treatments for inherent disorders. Here, we aimed to correct ATP7B genetically in a footprint-free manner with CRISPR/Cas9 and *piggyBac* or ssODNs in iPSC from a WD patient.
Method: We employed CRISPR/Cas9 and *piggyBac* or ssODNs to achieve footprint-free correction of a homozygous point mutation (R778L) of ATP7B of WD iPSCs. The resulted iPSCs were subjected to off-target analysis in the top potential sites via Sanger sequencing, detection of external sequences by PCR, as well as karyotype analysis, and test of pluripotency by immunofluorescences and teratoma assay. Then, the corrected iPSCs were differentiated into hepatocyte-like cells (iHeps) and subjected to phenotype analysis.
Results: After several rounds of screening, we obtained seamless corrected iPSCs of ATP7B from both approaches, which showed robust efficiency in targeted genome editing. The resulting iPSCs were free of external sequences, show no signs of specific cleavage in the top potential off-target sites, retained full pluripotency and normal karyotypes, and could differentiate into functional iHeps efficiently, which displayed markers of primary human hepatocytes including α1-antitrypsin and albumin, stored glycogen and lipids, and secreted albumin. Importantly, these genetically corrected iHeps had restored ATP7B normal subcellular location, displaying around 90% co-localization (versus 30% co-localization in uncorrected iHeps) with the trans-Golgi network marker p230.
Conclusion: Our results highlight the potential of using combinations of CRISRP/Cas9 and *piggyBac* or ssODNs to produce footprint-free, genetically corrected patient-specific iPSCs. Our results also provide an important proof of principle for employing CRISPR/Cas9 to obtain genetically corrected iHeps for autologous cell-based therapies for other hereditary liver disorders.

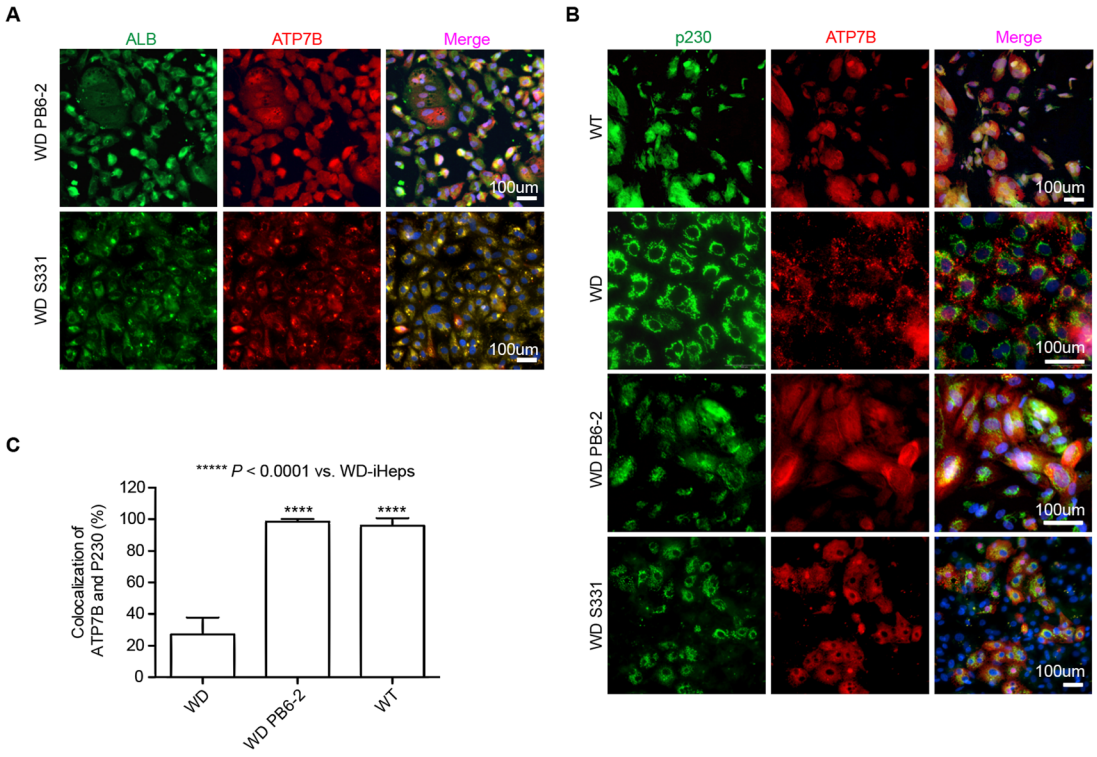


Figure: (abstract: THU_011)

THU-012

Alternative splicing regulation during the course of liver disease

H. Wang[1,2], B. Lekbaby[1], N. Fares[3], T. Attout[1], A. Schnuriger[1], A.-M.C. Doulcier[4], G. Panasyuk[5], J. Augustin[1], G. Perlemuter[4], I. Bieche[6], S. Vacher[6], J. Hall[3], P. Merle[3], D. Kremsdorf[7], I. Chemin[3], P. Soussan[1,7]. [1]*Pierre and Marie Curie University, Centre d'immunologie et de maladie infectieuse, Paris, France;* [2]*University of California San Diego, Department of Pathology, San Diego, United States;* [3]*INSERM, Centre de Recherche en Cancérologie de Lyon, Lyon, France;* [4]*INSERM, U996, Clamart, France;* [5]*INSERM, U1151, Paris, France;* [6]*Institut Curie, Institut Curie – Hôpital, Paris, France;* [7]*INSERM, U1135, Paris, France*
Email: patrick.soussan@inserm.fr

Background and Aims: Regulation of alternative splicing (AS), in which transregulatory splicing factors play a critical role, coordinates the transcriptome of eukaryotes. Impairment of AS has been recurrently associated to liver disease development. The aim of this study was to investigate the expression of splicing factors and its significance on AS regulation at different stages of the course of liver disease toward hepatocellular carcinoma (HCC).
Method: A panel of 10 splicing factors was studied by western blot in 6 liver disease mouse models including chronic inflammation, fibrosis, two models of steatosis and cancer and compared to their own littermate controls. Impact on AS regulation of 7 genes associated with liver disorder was studied by RT-qPCR. Then, splicing factors expression (PSF, SRSF6 and SRSF3) and AS regulation of *SRSF3*, *INSR* and *SLK* genes were assessed by RTqPCR in a French cohort of 179 HCC patients and correlated with clinical and biological parameters.
Results: Unique signature of splicing factors modulation (upregulation in 85% of cases) was characterized in each studied mouse model of liver disease. Surprisingly, 5/10 splicing factors were deregulated in NAFLD mouse model while only 2/10 were observed in both liver cancer models. Disruption of AS regulation of 7 selected genes, associated with liver disease, was not thoroughly concordant with the splicing factors expression signature. Quantification of 3 splicing factors and AS regulation of INSR and SLK genes, frequently modulated in liver disease mouse models, revealed their upregulations in tumor compared to non-tumor regions of HCC patients. Splitting results according to clinical and biological parameters of HCC showed that tumor recurrence was associated with AS regulation of INSR and unexpectedly, a correlation between upregulation of splicing factors expression in tumors and overall patient survival within 60-months follow-up post-surgical resection of HCC.
Conclusion: All liver injuries induced in mice differentially altered the expression of a splicing factors panel. Despite the intricate relationship between splicing factors expression and AS regulation, association with survival rate of HCC patients opens a new field on their contribution to the course of liver disease.

THU-013

Improving the efficacy of hepatocyte transplantation using alpha-1 antitrypsin as an immune modulator

C. Lee[1], A. Dhawan[2], C. Filippi[1], R. Mitry[1], V. Iansante[1], R.F. Dacosta[1], S. Lehec[1], A. Chandrashekran[1], T. Strom[3], M. Koulmanda[3], E. Fitzpatrick[2]. [1]*Dhawan Lab, Institute of Liver Studies, King's College London, London, United Kingdom;* [2]*Paediatric Liver, GI and Nutrition Centre, King's College Hospital, London;* [3]*Departments of Medicine and Surgery, The Transplant Institute, Institute, Beth Israel Deaconess Medical Center/Harvard, Medical School, Boston, United States*
Email: emer.fitzpatrick@kcl.ac.uk

Background and Aims: For patients with liver-based metabolic disorders, hepatocyte transplantation can be an effective bridge until a liver becomes available. However, long term function of transplanted hepatocytes has not been achieved. This is partly attributed to activation of innate immune response that leads to rapid clearance of hepatocytes shortly after transplantation. Alpha-1 antitrypsin (AAT) is a natural immune modulator with anti-inflammatory effects. Our aim was to determine if AAT could improve engraftment of transplanted hepatocytes and investigate its mechanism of action.
Method: ***In Vitro:*** A tubing loop model was used to analyse activation of the immune response when human hepatocytes (HH) were in contact with ABO-matched blood and 4 mg/ml AAT. Platelet and

white cell counts, complement and cytokine expression were analysed. ***In vivo:*** Primary rat hepatocytes were isolated from 250 g male Sprague Dawley rats. Female littermates underwent tail vein injection of AAT (120 mg/kg) or saline (control) prior to the intrasplenic transplantation of 2×10^7 eGFP male hepatocytes. At 24 h, 48 h and 1 wk, liver was collected for immunohistochemical analysis and DNA isolated for Y chromosome (SRY) gene expression. Hepatic mononuclear cells (HMNC's) were isolated and immune cell infiltration analysed using flow cytometry. Blood samples were used to analyse cytokine expression analysed using a Milliplex Map rat cytokine/bead panel.
Results: ***In Vitro:*** In the loop model, HH elicited a significant drop in platelet count with thrombus formation compared to controls (51×10^9 cell/L ± 15 vs 173×10^9 cell/L ± 8, $p < 0.001$, $n = 6$). Loops containing AAT and HH showed no drop in platelet count with no thrombus formation (140×10^9 cell/L ± 13, $p > 0.05$, $n = 6$). AAT treatment decreased IL-1β(1.7 vs 3.9 ng/ml), IL-6(0.4 vs 1.1 ng/ml) and IFN-γ (0.4 vs 1.3 ng/ml, $p < 0.05$, $n = 5$) and increased anti-inflammatory IL-1RA compared to non-treated loops (913 vs 719 ng/ml)($n = 5$, $p < 0.05$). ***In vivo*** There were significantly more eGFP hepatocytes in AAT treated livers compared to untreated at 24 h and 48 h (24 hrs; 4.5 ± 1.4% vs 1.0 ± 0.2%, $^{**}p < 0.01$ and 48 hrs 2.1 ± 0.5 vs 1.0 ± 0.3%, $^{*}p < 0.05$). Engraftment of male hepatocytes detected using SRY was 10-fold higher in the AAT treated group at 48 h compared to control and 4-fold higher at 1 wk ($n = 3$). AAT decreased the percentage of CD86 + ve activated macrophages compared to untreated controls at 48 hrs (10% vs 14.6%), 1-week (2.3% vs 6.9% and 1 month (2.1% vs 3.6%). AAT also decreased concentrations of pro-inflammatory cytokines in vivo; IL-1β, IL-1, IL-6 and IL-2 compared to controls 1 h post transplantation.
Conclusion: AAT improves engraftment of transplanted hepatocytes by inhibition of inflammatory cytokines and immune cell infiltration. AAT may significantly prolong cell survival and function, improving the clinical outcomes of the technique for children with liver based metabolic disease.

THU-014

Rab35 drives Hepatocellular Carcinoma development via action of Erk1/2 pathway

X. Wang, X. Xie, R. Fei, N. Wu, X. Cong, L. Wei, H. Chen. *Peking University Hepatology Institute, Peking University People's Hospital, Beijing, China*
Email: chenhongsong2999@163.com

Background and Aims: The Rab family of GTPases regulate many major biological processes in both tumorigenesis and tumor progression. Rab35, a member of Ras-related small GTPase family, has been reported to play a role in several cancer types. However, its biological functions and the underlying molecular mechanisms in hepatocellular carcinoma (HCC) remain unknown.
Method: The mRNA expression pattern of Rab35 in HCC tumor was analyzed by bioinformatics analysis of RNA Sequencing (RNA-seq) data of liver hepatocellular carcinoma (LIHC) in the Cancer Genome Atlas (TCGA) project. Its expression was further validated by QRT-PCR analysis of an independent HCC cohort and HCC cell lines. Then, Rab35 was knocked down in HCC cell lines using lentivirus mediated CRISPR/Cas9. The impact of Rab35 silence on the clonogenic growth and migration of HCC cell lines was used to determine its importance in the HCC. At last, we also examined the Erk1/2 phosphorylation level while overexpressing or knocking-down Rab35 in HCC cell lines.
Results: In this study, we found that the expression of Rab35 was elevated in HCC tissues and HCC cell lines. Strikingly, the Rab35 mRNA level is significantly correlated with the overall survival time of HCC patients in both TCGA LIHC cohort and an independent HCC cohort. Rab35 overexpression is tightly linked to high mortality in both cohorts. We further proved that overexpression of Rab35 promoted the clonogenic growth and migration of the HCC cells, while knocking down the expression of Rab35 inhibited the clonogenic growth and migration of the HCC cells. Moreover, we found that Rab35 overexpression significantly increased Erk1/2 activation monitored by p-Erk1/2 in Huh7 and MHCC-97H cell lines. In contrast, Rab35 knocking down substantially impaired Erk1/2 activation.
Conclusion: These results suggest that the Rab35 could driver Hepatocellular Carcinoma development via activation of Erk1/2 signaling pathway.

THU-015

hASCs-derived exosomes rescuing rats with acute liver failure by releasing lncRNA H19

Y. Jin, H. Li, X. Wang, C. Chen, Q. Fu. *Shanghai Public Health Clinical Center, Fudan Universitym Shanghai, China*
Email: 1182008211@qq.com

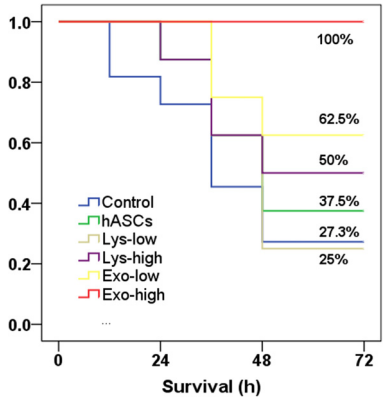
Background and Aims: It has been confirmed that the stem cells promote the regeneration of damaged tissues mainly through the "paracrine effect". As the major carrier responsible for exocytosis of the stem cells, exosome is highly likely to play an important role in stem cell therapy.
Method:

(1) Human adipose-derived stem cells (hASCs) were separated from human adipose tissues and used to prepare hASCs exosomes with modified multi-ultrafiltration concentration method of our research group.
(2) 78 rats with acute liver failure were randomly assigned to 5 groups to receive treatment with the same volume of low concentration (20 μg/rat) and high concentration (100 μg/rat) of hASCs exosomes, low concentration (20 μg/rat) and high concentration (100 μg/rat) of hASCs lysis buffer as well as hASCs (2×10^6 cells/rat) or phosphate buffer solution (PBS), respectively, through femoral vein infusion. The survival rate of rats was observed, and analyses on gene sequencing and signal pathways conducted to explore the potential mechanism of hASCs exosomes in treating the rat models with acute liver failure.
(3) 25 rats with acute liver failure rats were randomly assigned to 3 groups to receive the treatment of the same volume of hASCs exosomes (100 μg/rat), hASCs exosomes with silent H19 gene (100 μg/rat) or phosphate buffer solution (PBS), respectively, by femoral vein infusion. The survival rate of the rats was analyzed.

Results:

(1) The rat survival curves showed that rat survival rate was 100% and 62.5% respectively in the high concentration and low concentration hASCs exosome group, significantly higher than in the PBS control group (27.3%) ($P < 0.05$); According to the results of gene sequencing for rat liver tissues, hASCs exosome transplant significantly upregulated the genes associated with blood coagulation function and drug metabolism pathways, and dramatically downregulated the genes related to inflammatory responses and chemokine signaling pathways (Figure 1).
(2) Signaling pathway analysis revealed an evident upregulation in long chain non-coding RNA (lncRNA) H19 in the liver tissues of rats in hASCs exosome groups, which is likely associated with the upregulation of pathways related to blood coagulation function as well as drug metabolism. A decrease in the rat survival rate to 40% was observed in the rats with acute liver failure when treated with H19 gene silencing hASCs, with a statistical significance as compared with the hASCs exosome groups (Figure 2).

Conclusion: hASCs exosomes can accelerate the regeneration of the damaged liver cells and improve the survival rate of rats with acute liver failure probably by upregulate the pathways associated with blood coagulation function and drug metabolism as a result of lncRNA H19 release.



THU-016

A novel Akt activator SC79 prevents lethal hepatic failure induced by Fas-mediated apoptosis of hepatocytes

W. Liu, Z.-T. Jing, S.-X. Wu, Y. He, W. Chen, X.-J. Lin, X. Lin. *Fujian Medical University, Key Laboratory of Ministry of Education for Gastrointestinal Cancer, Fuzhou, China*
Email: linxu70@126.com

Background and Aims: Acute liver failure (ALF) remains a serious clinical problem for which the underlying pathogenesis remains unclear and effective therapies are lacking. Fas receptor/ligand (Fas/FasL) system, which is negatively regulated by AKT pathway, is known to play a prominent role in hepatocytic cell death. The aim of this study is to investigate the effects and mechanisms of a novel of Akt activator SC79 in regulating Fas/FasL-mediated apoptotic signaling and death in hepatocytes.
Method: HepG2 and primary mouse hepatocytes (PMHs) were treated with agonistic anti-Fas antibody CH11or Jo2 respectively, cell apoptosis were measured by TUNEL and Annexin V binding assay. Protein level or modification were detected by western blot. Mice were pretreated intraperitoneally with SC79 or DMSO before administration of Jo2 antibody, mice were sacrificed at various time points after Jo2 injection, serum ALT and AST were determined.
Results: SC79 protected hepatocytes from agonistic anti-Fas antibody CH11- or Jo2-induced apoptosis and significantly prolonged the survival of mice with a lethal dose of Jo2. Under Fas signaling stimulation, SC79 inhibited Fas aggregation, prevented recruitment of the adaptor molecule Fas-associated death domain (FADD) and procaspase-8 into the death-inducing signaling complex (DISC), but enhanced recruitment of cellular FLICE-inhibitory protein S and L ($FLIP_{L/S}$) at the DISC. Confirmedly, all the SC79-induced hepatoprotectiveand DISC interruptive effects could be reversed by the Akt inhibitorLY294002.
Conclusion: SC79 prevents hepatocytes from Fas-induced lethal hepatic apoptosis. The potent alleviation of Fas-mediated hepatotoxicity by SC79 highlights the potential of our findings for immediate therapeutic translation.

THU-017

New insights in Transforming Growth Factor Beta signalling pathway on tumor suppression and metastatic potential in primary liver cancer

S. Pereira[1], L. Rodrigues[1], D. Castven[1], F. Mahn[1], P. Galle[2], J. Marquardt[1], S. Dooley[2], N.M. Beinker[2], D. Strand[1], H. Lang[3], P. Grimminger[3].
[1]*Universitätmedizin Mainz, Department of Medicine I, Mainz, Germany;* [2]*Molecular Hepatology- Alcohol-Associated Diseases, Department of Medicine II. Medical Faculty Mannheim Heidelberg University, Mannheim, Mainz, Germany;* [3]*Universitätmedizin Mainz, Department of Surgery, Mainz, Germany*
Email: jsharon_sharon@yahoo.co.in

Background and Aims: Transforming Growth Factor Beta (TGF-beta) belongs to a superfamily of cytokines that exerts pleiotropic effects on different processes and cell types in the liver. During cancer progression while TGF-beta signaling induces tumor suppressor effects at pre-neoplastic and early tumor stages, cytostatic effects of TGF-beta are often lost in progressed stages due to (epi-) genetic disruption of several members of the (TGF-beta) signaling pathway. This progressed stage is characterized by activation of a "late TGF-beta signature" which promotes the phenotypic switch from tumor suppressor to promoter of cancer. Consequently, cancer cells display an epithelial-mesenchymal-transition (EMT) phenotype by acquiring pro-metastatic properties.
Method: Newly generated primary (HCC & CCA) and established cell lines (PLC & HuCCT-1) were exposed to TGF-β1 and TGF-β2 (1 ng/ml) for 72 hr. Next Generation Sequencing Analysis was performed to identify significant differences in gene expression patterns. Appropriate statistical and bioinformatics tools (IPA) was used to study pathways and networks to understand how they these genes interact biologically. The effect of TGF-β on tumor-initiating potential was determined by colony and sphere formation assays. Invasive and migratory properties were determined using the wound healing assay.
Results: Treatment with TGF-β1 and TGF-β2 led to a significant reduction in colony and spheroid forming ability in all investigated cell lines. Consistent with the reduced *in vitro* tumorigenicity and spherogenicity, a drastic effect of TGF-β1 on the putative tumor-initiating cell population was observed, reflected by the down-regulation of stemness markers CD133 and EpCAM. Interestingly, treatment with TGF-β1 led to a significant increase in the expression of CD44 accompanied by the activation of established epithelial-mesenchymal-transition markers (Vimentin). A significant down-regulation of E-Cadherin paralleled by upregulation in SNAIL transcription factor was seen. Consequently, enhanced migratory and invasive properties of HCC and CCA were observed evidenced by increased wound healing and invasion. In addition, pathways enriched with differentially expressed genes known to be involved in EMT (P13K, WNT/β-Catenin pathway) were identified by NGS analysis.
Conclusion: In conclusion, we here confirm the cytostatic effect of TGF-β1 and TGF-β2 by reducing the frequency of cancer cells in both HCC and iCCA. Further, TFG-β1 seems to be an important regulator in progressed PLCs. These context-dependent dichotomic effects should be considered in TGF-β based therapeutic approaches. We would further validate the obtained findings in vivo using a battery of different xenotransplantation models representing the observed in vitro findings.

THU-018

Amiodarone-induced adipose tissue endoplasmic reticulum stress and lipolysis may contribute to hepatic lipid accumulation

I. Houri, E. Hubel, R. Avraham, I. Zvibel, O. Shibolet. *Tel Aviv Sourasky Medical Center, Gastroenterology, Tel Aviv*
Email: inbalhourio@gmail.com

Background and Aims: Amiodarone is a widely used anti-arrhythmic drug. One of its common side effects is liver lipid accumulation and steatosis. We have previously shown that amiodarone induces endoplasmic reticulum (ER) stress and activates the unfolded protein response (UPR) in an acute model of liver damage. Hepatic lipid accumulation may be due to de novo triglyceride synthesis or to increased uptake of adipose-tissue-derived free fatty acids (FFA). We investigated the effects of amiodarone on hepatic lipogenesis and on adipose tissue lipolysis and secretion of FFA in a newly established chronic model of amiodarone injury.
Method: A chronic model of amiodarone-induced liver damage and lipid accumulation was implemented by daily intraperitoneal injection of amiodarone (150 mg/g BW per day) for four days.
Results: Mice treated with amiodarone had increased hepatic triglycerides (TG) and reduced serum TG compared to controls. There was increased ER stress/UPR in the livers of mice that received

amiodarone, as well as reduced hepatic lipogenesis. In addition, amiodarone significantly induced hepatic gene expression of FFA binding proteins CD36 and Fatty acid binding protein 4 (FABP4) and increased protein levels of CD36, suggesting increased uptake of FFA. Investigating the effect of amiodarone on visceral adipose tissue, we detected increased expression of ER stress markers and reduced gene expression of adipose tissue-specific markers (Leptin, Adiponectin and Fabp4), demonstrating for the first time that amiodarone can induce ER stress in adipose tissue. Adipose ER stress was shown to stimulate lipolysis, and indeed, we have found increased lipolysis following amiodarone treatment, demonstrated by increased serum FFA and increased expression of pHSL.
Conclusion: We have shown a novel mechanism involved in amiodarone-induced hepatic lipid accumulation, mediated by amiodarone induction of adipose tissue ER stress and lipolysis and followed by increased hepatic uptake of FFA.

THU-019

Effect of melatonin on the circadian clock pathway in liver fibrosis and progression to hepatocarcinoma

B.G. Fernández[1], D.I.S. Paniagua[1], I. Crespo[1], B.S. Miguel de Vega[1], D.M. Sánchez[1], F. Jorquera[2], J. González-Gállego[1], M.J.T. González[1]. *[1]CIBEREHD. Institute of Biomedicine, University of León, León, Spain; [2]Department of Gastroenterology, University Complex Hospital of León, León, Spain*
Email: bgonf@unileon.es

Background and Aims: Recent studies suggest a relationship between circadian rhythms and pathologic processes, including fibrosis and cancer. The main regulator of clock genes is the heterodimer BMAL1-CLOCK, which regulates the expression of transcriptional repressors cryptochrome (CRY) and period (PER). The nuclear receptor REV-ERB plays pivotal role in the modulation of the circadian rhythm as a negative regulator. Melatonin exhibits antifibrotic and oncostatic features, playing a protective role in a wide range of liver diseases. The aim of this study was to determinate the effect of melatonin on the circadian clock pathway disturbances in liver fibrosis and hepatocarcinoma (HC).
Method: Fibrosis was induced in C57BL/6J mice with CCl_4 twice a week for 4 or 6 wk; melatonin was given at 5 or 10 mg/kg/day i.p. beginning 2 wk after the start of CCl_4 administration. We investigated whether melatonin has its antifibrotic effect through the modulation of the REV-ERBα expression, using a REV-ERB agonist, SR9009 in human stellate cells LX2. Cells were exposed to the ligand at 10 μM during 24 h. Melatonin groups received the indole at 100 or 500 μM two hours after SR9009. HC was induced in ICR mice receiving DEN once a week for 8 wk; melatonin was given at 5 or 10 mg/kg/day i.p. beginning 4 wk after the onset of DEN administration and ending at 10, 20, 30 and 40 wk. The expression of circadian clock markers was analyzed by qRT-PCR and Western-blot.
Results: The expression of CLOCK, BMAL1, REV-ERB, PERs and CRYs were deregulated in CCl_4 animals and in DEN-treated mice since the first time-points, reaching a higher effect at 6 and 40 wk, respectively. These alterations were significantly prevented in animals receiving melatonin. REV-ERBα expression was significantly increased in CCl_4 animals, and melatonin abolished this effect. SR9009-treated LX2 cells showed an increase in the expression of clock markers CLOCK, BMAL1, PER and CRY, which were similar to those observed in cells receiving melatonin.
Conclusion: The results of this study confirm that circadian rhythms play a crucial role in fibrosis and carcinogenesis. Restoration by melatonin of the clock genes disruption reveals novel molecular pathways that may account for the protective effect of the indole.

This work was supported by AECC and CEPA Fundation, Spain.

THU-020

Unravelling the role of the Hedgehog siganlling pathway in the hepato-ovarian axis

C. Rennert[1,2], F. Eplinius[3], U. Hofmann[4], W. Schmidt-Heck[5], A. Ricken[3], R. Gebhardt[6], M. Matz-Soja[6]. *[1]Saxonian Incubator for Clinical Translation (SIKT), Leipzig University, Leipzig, Germany; [2]Department of Hepatobiliary and Transplantation Surgery, Faculty of Medicine, University Hospital Leipzig, Leipzig; [3]Institute of Anatomy, Faculty of Medicine, Leipzig University, Leipzig, Germany; [4]Dr. Margarete Fischer-Bosch Institute of Clinical Pharmacology, University of Tübingen, Stuttgart, Germany; [5]Leibniz Institute for Natural Product Research and Infection Biology, Hans Knöll Institute, Jena, Germany; [6]Rudolf-Schönheimer-Institute of Biochemistry, Faculty of Medicine, Leipzig University, Leipzig, Germany*
Email: christiane.rennert2@medizin.uni-leipzig.de

Background and Aims: The Hedgehog signalling pathway is known to be involved in embryogenesis, development, and carcinogenesis. Because of its role in cancer development and progression it has become an interesting target for anti-cancer therapy. The inhibition of Smoothened, a Hedgehog receptor, shows promising preliminary results in clinical trials. However, inhibition of Hedgehog signalling pathway may have adverse side effects in the remaining body.
Method: Our previous work in adult mice showed hepatic Hedgehog signalling to be involved in the control of the insulin-like growth factor axis and the lipid metabolism. We here investigated mice with an embryonic and hepatocyte-specific Smoothened deletion (SAC mice), and mice with a conditional, hepatocyte-specific deletion of Smoothened at 8 weeks of age (SLC mice).
Results: Deletion of Smoothened resulted in masculinization and infertility in female mice. We detected an androgenisation characterized by a 3.3-fold increase of testosterone in female SAC-KO mice at 12 weeks of age. The changes obviously resulted from a surprisingly induced steroidogenic gene expression (Star, Cyp17a1) in hepatocytes, but not in classic steroidogenic organs (ovary and adrenal gland). Along with the elevated testosterone levels the female SAC-KO mice showed signs of infertility. The animals lacked oestrus cyclicity and their reproductive organs were immature. In the ovaries, folliculogenesis was impaired and no corpora lutea were seen. These findings resemble polycystic ovarian syndrome (PCOS). They could be widely confirmed in the SLC mice. The female SLC-KO mice showed a similar induction of steroidogenic gene expression in the liver and a reduced number of corpora lutea in the ovaries after an extended period of 8 months.
Conclusion: In summary, down-regulation of hepatic Hedgehog signalling leads to an impaired hormonal balance by induction of steroidogenesis in the female liver and results in androgenisation and infertility. This indicates that the liver may crucially influence reproduction under disease conditions.

THU-021

WDHD1 is a candidate driver gene in Hepatocellular Carcinoma

J. Cai[1], K. Zhang[1], Y. Tian[2]. *[1]Peking University International Hospital, Department of Hepatobiliary Surgery, Beijing, China; [2]Peking University International Hospital, Department of Hepatobiliary Surgery, Beijing, China*
Email: caijun9527@sina.com

Background and Aims: Cell cycle checkpoint pathways are key to ensure that the genome is accurately replicated. Dysfunctions or mutations of these pathways are important in the pathogenesis of malignant tumors. WDHD1 (WD repeat and high mobility group [HMG]-box DNA-binding protein 1) is an adaptor molecule crucial for DNA replication and play a role in G1 checkpoint control. But, it has not been fully understand how WDHD1 involved in the carcinogenesis and progress of HCC. Here, we aim to study the importance of WDHD1 in the HCC.
Method: The mRNA expression pattern of WDHD1 in HCC tumor was analyzed by bioinformatics analysis of RNA Sequencing (RNA-seq)

data of liver hepatocellular carcinoma (LIHC) in the Cancer Genome Atlas (TCGA) project. It was further validated by QRT-PCR analysis of an independent HCC cohort and HCC cell lines. WDHD1 was knocked down in HCC cell lines using lentivirus-mediated shRNA. The impact of WDHD1 silence on the in vitro clonogenic growth, and on cell cycle and replication of HCC cell lines was used to determine its importance in the HCC.
Results: The mRNA level of WDHD1 was dramatically higher in HCC tumor tissues than in normal liver tissues according to both the LIHC RNAseq data and the QRT-PCR analysis of an independent HCC cohort. Strikingly, the WDHD1 mRNA level significantly correlated with the recurrent-free survival time of HCC patients in both TCGA LIHC data set and our own HCC cohort. WDHD1 overexpression is significantly linked to high mortality in both cohorts. Moreover, all six analyzed HCC cell lines cell overexpressed WDHD1. The clonogenic potential of SK-HEP-1 and Huh7 was significantly inhibited after knockdown of WDHD1 with shRNA. Notably, knockdown of WDHD1 led to an increase in the G1 arrest and decrease in BrdU incorporation. These results demonstrate an important role of WDHD1 in the G1 cell cycle control and S-phase entry of HCC cells.
Conclusion: These results suggest that the WDHD1 is a candidate driver gene in Hepatocellular Carcinoma that involved in cell cycle control.

THU-022
Investigating the effect of adrenomedullin on hepatic NF-kB activation by 2D and 3D hepatic cell cultures

S.D. Martin[1], E. Caon[2], D. Gabbia[1], G. Zigiotto[1], Z. Zhang[3], L. Frenguelli[1], W. Al-Akkad[2], S. Sarcognato[4], G. Maria[4], G. Mazza[5], M. Pinzani[2], K. Rombouts[2]. *[1]University of Padova, Department of Pharmaceutical and Pharmacological Sciences, Padova, United Kingdom; [2]University College London, Institute for Liver and Digestive Health, London, United Kingdom; [3]University College London, Institute for Liver and Digestive Health, London, United Kingdom; [4]University of Padova, Department of Medicine, Italy; [5]Institute for Liver and Digestive Health, London, United Kingdom*
Email: k.rombouts@ucl.ac.uk

Background and Aims: Adrenomedullin (ADM) is a neuropeptide exerting multiple effects through autocrine/paracrine mechanisms. ADM plays an immunomodulatory role and has anti-inflammatory activity in various diseases but its role has not been investigated in liver diseases. We assessed the hepatic ADM expression in different inflammatory liver diseases (HCV, AIH, NASH) and the mechanism(s) by which ADM affects NF-kB activation in classical 2D and a new 3D model.
Method: Immunofluorescence analysis was performed on liver tissue samples to assess ADM expression and α-SMA colocalization. HepG2 and LX2 were exposed to LPS (1 ng/mL), ADM (10–7M) for 24 hrs, ADM (10–7M) for 4 hrs followed by LPS for 24 hrs. ICC for p65 nuclear translocation and QRT-PCR was performed. Human liver 3D scaffolds were obtained by decellularization of healthy and cirrhotic livers. LX2, a hHSC cell line, or primary hHSCs were cultured on scaffolds for 10 days. Primary hHSC in healthy scaffolds were treated as above, or with LPS for 1–3 hrs, PDGF-BB (1–10 ng/mL), or TGFbeta1 (2–5 ng/mL) for 24 hrs. Human HSCs in cirrhotic scaffolds were exposed to ADM for 4 hrs. QRT-PCR was performed.
Results: Human HSCs ADM-related fluorescence intensity in NASH patients (n = 5) was less than in HCV (n = 5) and AIH (n = 5) patients, but the degree of colocalization was similar in all patients. ADM pretreatment of LX2 and HepG2 in 2D, followed by LPS exposure significantly reduced p65 nuclear translocation and increased NF-kB inhibitor IkBα gene expression. LPS treatment in HepG2 decreased ADM expression whereas exogenous ADM pretreatment counteracts this effect. ADM gene expression was decreased in TGFbeta1 and LPS-treated hHSCs cultured in 2D and was upregulated in 3D vs 2D. In contrast, TGFbeta1 and PDGF-BB-treated hHSCs in 3D showed a reduced ADM gene expression. ADM pretreatment in hHSCs in healthy scaffolds increased ADM gene expression, reduced NFKB1, but not NFKB2, and completely abrogated the effect of subsequent exposure to all stimuli. ADM gene expression was upregulated in hHSCs in cirrhotic scaffolds vs healthy scaffolds and exogenous ADM treatment favoured hHSCs deactivation in cirrhotic liver scaffolds.
Conclusion: This study shows that ADM expression changes with respect to the aetiology of liver inflammation. ADM leads to a reduction in activation of the canonical NF-kB pathway in hepatic cells in both 2D and 3D cultures. These findings suggest that the ADM system as a possible pharmacological target for the management of inflammatory liver diseases.

THU-023
DNA methylation profiling of hepatitis C virus patients treated with direct acting antivirals identifies consistent methylation changes in livers and blood

A. Vasanthakumar[1], D. Quarless[1], E. Dilmukhametova[1], M. Abunimeh[1], C. Konefal[1], S. Abel[1], K. Idler[1], G. Lauer[2], A. Kim[2], R. Chung[2], D. Cohen[1], J.W. Davis[1], E. Dumas[1], J.F. Waring[1]. *[1]AbbVie; [2]Harvard Medical School*
Email: aparna.vasanthakumar@abbvie.com

Background and Aims: Chronic Hepatitis C virus (HCV) infection can induce progressive liver fibrosis which often leads to cirrhosis and liver failure. Direct acting antiviral (DAA) treatment regimens show high sustained virological response rates in HCV-infected patients, yet their impact on long-term clinical outcomes is unknown. Numerous studies have demonstrated that epigenetic mechanisms, e.g. DNA methylation (DNAm), control molecular events underlying liver disease development and progression. We hypothesize that DNAm associates with clinical outcomes after DAA treatment, including immune changes and liver fibrogenesis. Our main objectives were to investigate whether peripheral blood (PB) DNAm functions as a surrogate for liver DNAm and to detect longitudinal DNAm changes in PB following DAA treatment.
Method: PB and liver fine needle aspirates (L-FNA) were obtained from patients receiving the 3-DAA regimen which included paritaprevir (identified by AbbVie & Enanta) [#NCT02476617]. PB was collected on day0 (D0), end of treatment (EOT/Week 12), post-treatment weeks 12 and 24 (PTW12 and PTW24). For a subset of subjects, L-FNAs were collected at D0 and PTW12. DNAm was assayed by bisulfite pyrosequencing and Illumina EPICarrays.
Results: An *IFNL3* locus is known to associate with response to interferon therapy. We previously demonstrated *IFNL3* genotype-associated differential methylation in PB, and were able to replicate the finding in the current study (Table 1). Notably, the L-FNA samples demonstrated similar differential DNAm (Table 1), which supports the hypothesis that PB is a surrogate for liver DNAm at this locus. Genome-wide DNAm data were normalized and QC-d using established protocols. Comparison of PB DNAm at D0vsEOT, D0vsPTW12, and D0vsPTW24 generated 93, 91, and 1862 differentially methylated positions (DMPs) at FDR = 10%. Several DMPs were located near promoters of genes associated with inflammation and liver disease, including *IL20RA*, which was hypermethylated, and *MPO* which was hypomethylated post-treatment. Ongoing work is examining common DMPs in liver and PB.
Conclusion: This is the first study to demonstrate that genotype-associated DNAm changes upstream of the *IFNL3* gene in PB are preserved in liver. Time-dependent regional DNAm changes were observed in promoters of genes associated with inflammatory and liver functions, which supports the significance of longitudinal DNAm data to elucidate DAA treatment related long-term clinical outcome features.
Disclosures: AbbVie funded the study and participated in the study design, research, analysis, data collection, interpretation of data, and review and approval of the abstract. AV, DQ, ED, MA, CK, SJA, KBI, DEC, JWD, EOD, and JFW are AbbVie employees and may hold AbbVie

Table 1: (abstract: THU-023)

Table 1: DNA methylation (Average% ± SD) on Day 0 at the *IFNL3* promoter

		Peripheral Blood		Liver Fine Needle Aspirates	
		Number of Subjects	DNA methylation (Average% ± SD)	Number of Subjects	DNA methylation (Average% ± SD)
rs12979860 genotype	CC	7	25.8 ± 2.7	2	27.4 ± 5.3
	CT	13	34.9 ± 5.4	9	37.93 ±4.1
	TT	3	43.85 ± 9.6	1	57.4*
p-value (ANOVA)		<0.001		<0.05	

** Since this group had n=1, the data point was excluded from statistical analyses*

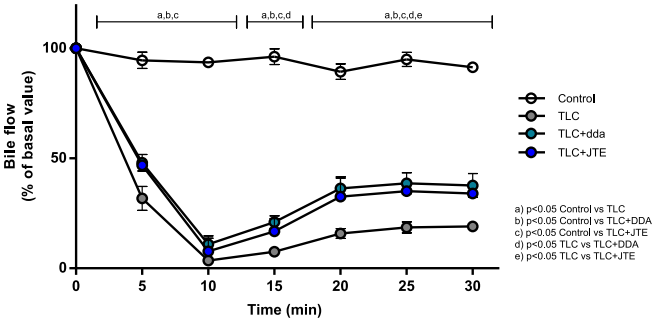
stock/options. GML, AYK, and RTC are employees of Massachusetts General Hospital and have no further relationships to disclose.

THU-025

Involvement of sphingosine-1P receptor 2 (S1PR2) in taurolithocholate-induced impairment of multidrug resistence-associated protein 2 (Mrp2) in rat

R. Andermatten, N. Ciriaci, M.V. Razori, G. Miszczuk, I. Barosso, E.S. Pozzi. *Instituto de Fisiología Experimental, CONICET-UNR, Rosario, Argentina*
Email: esanchez@fbioyf.unr.edu.ar

Background and Aims: Taurolithocholate (TLC), a cholestatic bile salt, induces internalization of Mrp2. Signaling proteins, such as PI3K/AKT, participate in this cholestasis but the initial receptor/s remain/s unknown. We focused our study in adenylyl cyclase (AC)/PKA, recently involved in estrogen-induced cholestasis, and in potential TLC receptors. S1PR2 arose as a possible initial TLC receptor since it interacts with bile salts and potentially activates AC.
Method: Isolated rat hepatocyte couplets were preincubated with the S1PR2 antagonist JTE-013 (JTE, 10 μM), AC inhibitor MDL12330 (MDL, 20 μM) or PKA inhibitor KT5720 (KT, 250 nM) and then exposed to TLC (2.5 μM). Couplets were also co-preincubated with JTE and either MDL, KT or PI3K inhibitor wortmannin (W, 100 nM). Changes in Mrp2 activity were evaluated by assessing the canalicular vacuolar accumulation (cVA) of glutathione methylfluorescein (GMF), an Mrp2 substrate. Mrp2 localization was studied by immunofluorescence, followed by confocal microscopy. PKA and AKT activation were determined by western blot using an antibody against phospho PKA substrate and phospho AKT. In isolated rat liver, cholestasis was induced by intraportal injection of TLC (4.5 μmol/liver). Inhibitors JTE or DDA (AC inhibitor) were administered 10 min before TLC. Finally, biliary flow was measured for 30 min in 5 min-periods.
Results: (% of control ± SEM; n = 3–9) Treatment with JTE, MDL, KT and W partially prevented TLC-induced impairment in Mrp2 activity: TLC (55 ± 2a), TLC + JTE (79 ± 2a,b), TLC + MDL (80 ± 9a,b), TLC + KT (74 ± 10a,b), TLC + W (77 ± 6a,b). JTE preventive effects did not improve the actions of MDL, KT or W: TLC + JTE + MDL (84 ± 6a,b), TLC + JTE + KT(76 ± 3a,b), TLC + JTE + W (79 ± 6a,b), suggesting that S1PR2, AC, PKA and PI3K share the same pathway. Activation of PKA induced by TLC decreased in presence of JTE: TLC (248 ± 15a), TLC + JTE (138 ± 33b). The same phenomenon occurs with AKT phosphorylation: TLC (584 ± 23a), TLC + JTE (161 ± 27a,b). Localization studies showed that JTE, MDL, KT and W prevented the delocalization of Mrp2 induced by TLC. TLC diminished bile flow (see figure). JTE or DDA only increased recovery after the initial drop. a: $p < 0.05$ vs control, b: $p < 0.05$ vs TLC.



Conclusion: Interaction of TLC with S1PR2 would be one of the first events in the signaling pathway that leads to Mrp2 activity impairment, followed by AC, PKA and PI3K/AKT activation. This pathway would be implied in retaining Mrp2 in an intracellular domain rather than promoting canalicular transporter desinsertion.

THU-026

The analysis of delta40p53, one of p53 splicing isoforms, in hepatocellular carcinoma cells

H. Nakao[1], A. Ota[2], T. Ohashi[3], R. Kitano[3], M. Sakamoto[3], Y. Sumida[3], Y. Nakade[3], K. Ito[3], M. Yoneda[3]. *[1]Aichi medical University, Division of Hepatology and Pancreatology, Department of Internal Medicine, Nagakute, Japan; [2]Aichi Medical University, Department of Biochemistry, Nagakute, Japan; [3]Aichi Medical University, Division of Hepatology and Pancreatology, Nagakute, Japan*
Email: hnakao@aichi-med-u.ac.jp

Background and Aims: Splicing isoforms of certain genes impact on genetic biodiversity in mammals. The tumor suppressor *TP53* gene plays an important role in the regulation of tumorigenesis in hepatocellular carcinoma (HCC). Though delta40p53α (Δ40p53) is the naturally occurring p53 isoforms that lacks N-terminal transactivation domain, yet little is known about the role of Δ40p53 in the development of HCC. The aim of this study is to clarify the role of Δ40p53 in HCC.
Method: To accomplish this study, we established $p53^{+/\Delta 40}$ HepG2 cells, which was heterozygous endogenous exon 2-deleted p53 HepG2 cell using Cre/loxP system. Also, we established $p53^{-/-}$ HepG2 cells, which endogenousTP53 were knocked out by using CRISPR-Cas9. Other cell lines used in this study were HuH-1 ($TP53^{WT}$), HepG2 ($TP53^{WT}$), Hep3B ($TP53^{-/-}$), HuH-7($TP53^{Y220C}$), and PLC/PRF/5 ($TP53^{R249S}$). For cell proliferation assay, MTT assay and Clonogenic

assay were used. Annexin V and caspase-3/7 activity assay were performed for apoptosis assay. FACS and SA-β-galactosidase assay were used for cellular senescence analysis. Transient *p53* knockdown was performed using *p53* siRNA. Quantitative RT-PCR was used for mRNA analysis and Western blot analysis was used for protein analysis.

Results: The clonogenicity and MTT assays showed that tumor cell growth was suppressed in the $p53^{+/\Delta 40}$ cells. The β-galactosidase assay revealed that the percentage of SA-β-gal-positive cells was significantly higher in $p53^{+/\Delta 40}$ clones compared to control clones. Western blot showed that protein expression of $p21^{WAF/CIP1}$, but not those of BAX and PUMA, significant increase in $p53^{+/\Delta 40}$ clones. Caspase-3/7 activity and the percentage of apoptotic cells did not significantly increase in the $p53^{+/\Delta 40}$ clones compared to control clones, suggesting that the growth suppression was not a result of increased apoptosis. The mRNA of IL-8, MDM2, $p21^{WAF/CIP1}$ and FAS were increased in $p53^{+/\Delta 40}$ clones. These results indicated that cellular senescence is accelerated in the $p53^{+/\Delta 40}$ clones. Besides, the tumor suppressor activity of Δ40p53 was shown in TP53 knockdown condition using siRNA and exogenous expression of Δ40p53. Moreover, Δ40p53 itself exerted tumor activity in TP53-deleted cells, $p53^{-/-}$.

Conclusion: Δ40p53 suppressed tumor cell proliferation and induces cellular senescence in HCC cells.

THU-027

CCNT1 mediates mTor inhibitor related antiviral effects in HCV genotype 2a

A. Frey, M. Trippler, G. Gerken, K. Herzer. *University Hospital Essen, Department of Gastroenterology and Hepatology, Essen, Germany*
Email: kerstin.herzer@uk-essen.de

Background and Aims: The mTor inhibitor Everolimus is in use for immunosuppression (IS) after liver transplantation (LT). However, its effect on HCV replication and reinfection after LT, in particular in the context of antiviral treatment, still remains to be clarified. Previously, we were able to show that mTor inhibitors reduce the viral load in HCV genotype (GT) 2a patients *in vivo* and the replication activity *in vitro*. Aim of this study is to elucidate the molecular background of the effect of mTor inhibitors on the GT2a HCV replication activity.

Method: The viral load of 20 GT2 patients with a HCV reinfection after LT was determined by qRT-PCR before and 8 weeks after addition of everolimus (EVR) to a tacrolimus (TAC) – based immunosuppression. The GT2a HCV replicon cell line (Huh7.5 JFH/SG-Feo) was treated for 48 h with the mTor inhibitors EVR and sirolimus (SRL). HCV replication activity was quantified by luciferase assay. A gene expression profile was generated using GeneChip® Human Transcriptome Array 2.0 and qRT-PCR. A Cyclin T1 (*CCNT1*) knockdown was generated by siRNA. The protein expression of *CCNT1* and *GAPDH* as loading control was analyzed by western blot.

Results: HCV viral load of GT2a patients was significantly reduced ($p \leq 0.0001$) after conversion to an EVR based immunosuppression regime. *In vitro* mTor-inhibitor application to GT2a replicon cells decreased HCV replication activity to 60% ($p \leq 0.0005$). A hierarchical cluster analysis revealed the viral replication related cell factor *CCNT1* as significantly regulated after EVR treatment. In vitro, the *CCNT1* expression increased up to 1.5-fold (EVR: $p \leq 0.005$, SRL: $p \leq 0.05$) compared to controls. A *CCNT1* knockdown (average: 60%; $p \leq 0.01$) in GT2a cells completely abolished the antiviral effect of mTor inhibitors on HCV replication activity (EVR: $p \leq 0.05$; SRL ≤ 0.05).

Conclusion: The herein presented results suggest that mTor inhibitors impair HCV replication activity via *CCNT1* upregulation. Further factors are likely to be involved in these regulatory mechanisms and are currently under further investigation.

THU-028

Cerium oxide nanoparticles protect against oxidant mediated injury and recover kinase activity of multiple pathways in human-derived hepatocellular carcinoma cells

M.P. Corominas[1], S.C. Restoy[1], G. Casals[1], D. Oró[1], J. Ribera[1], E. Casals[2], P. Casado-Izquierdo[3], G.F. Varo[1,4], P. Cutillas[3], V. Puntes[2,5,6], W. Jiménez[1,4]. *[1]Biochemistry and Molecular Genetics Service, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [2]Vall d'Hebron Insitute of Research (VHIR), Barcelona, Spain; [3]Barts Cancer Institute, Queen Mary University of London, London, United Kingdom; [4]Department of Biomedicine, University of Barcelona, Barcelona, Spain; [5]Institut Català de Nanociència i Nanotecnologia (ICN2), Bellaterra, Spain; [6]Institut Català de Recerca i Estudis Avançats (ICREA), Barcelona, Spain*
Email: mperramon@clinic.cat

Background and Aims: Cerium oxide nanoparticles (CeO_2NPs) possess powerful antioxidant properties, thus emerging as a therapeutic tool in conditions characterized by presence of reactive oxygen species (ROS), including liver disease. Here, we assessed whether CeO_2NPs are able to prevent or attenuate oxidant injury in the human hepatic cell line HepG2. The aim of the study was to elucidate whether CeO_2NPs display beneficial effects in hepatic human cells and investigate the basic mechanisms involved in this phenomenon.

Method: The effect of CeO_2NPs on cell viability and ROS scavenging in H_2O_2- or lipopolysaccaride (LPS)-treated HepG2 cells was determined using MTS technique and Dichloro-dihydro-fluorescein diacetate assay, respectively. In addition, the differential expression of proinflammatory and/or oxidative stress-related genes was analyzed by Real-time polymerase chain reaction (PCR) and an oxidative stress gene expression PCR array. Finally, a phosphoproteomic analysis was conducted in order to find out which kinase signalling pathways are modulated by CeO_2NPs.

Results: CeO_2NPs did not modify HepG2 cell viability in basal conditions but restored H_2O_2- and LPS-induced cell death. Moreover, CeO_2NPs prevented H_2O_2-induced overexpression of genes with oxidase activity, including myeloperoxidase (MPO) and Prostaglandin-Endoperoxide Synthase 1 (PTGS1). This was also observed on analyzing inducible nitric oxide synthase (iNOS). Furthermore, H_2O_2 significantly induced an increase in the intensity of phosphorylation which was partially or totally reverted following CeO_2NPs exposure in 39 of a total of 3254 identified and quantified peptides. These peptides were related to cellular proliferation, stress response, cytoskeleton signalling, and gene transcription regulation. In addition, a Kinase Substrate Enrichment Analysis revealed that CeO_2NPs acted modulating MAP/ERK, AKT, CK2A1, and PRKCA signalling pathways, reverting H_2O_2 effects

Conclusion: CeO_2NPs protect human-derived hepatocytes from exogenous and endogenous oxidative damage via reduction of ROS generation and inflammatory gene response regulating MAP/ERK, AKT, CK2A1, and PRKCA signalling pathways.

Acknowledgments: This work was supported by two grants from MINECO (SAF15-64126-R and P74844I/15/00777).

THU-029

Interaction between hepatic sinusoidalendothelial cells and monocytes modulates IL33 driven Th2 dependent liver fibrogenesis

J. Reissing, M. Inzaugarat, M. Frissen, L. Lijun, D. Kroy, M.-L. Berres, A. Wree, C. Trautwein, Z.H. Wolfgang. *Klinik für Gastroenterologie, Stoffwechselerkrankungen und Internistische Intensivmedizin, Aachen, Germany*
Email: jreissing@ukaachen.de

Background and Aims: We have previously shown that Th2-polarized CD4+ T-cells are involved in the establishment and

progression of liver fibrosis. We could demonstrate that Th2-inducing and related cytokines correlate with the stage of fibrosis. IL33 as a key driver of Th2 response also has promigratory effect. IL33 level is elevated intrahepatically as well as the systemically in late stages of fibrosis. In vitro studies corroborated that human macrophages and monocytes have the capacity to secrete IL33. Given the fact that monocyte infiltration is pivotal during liver Fibrogenesis we sought to investigate how human monocyte migrate across hepatic sinusoidal endothelial cells (HSEC) impacts on the secretion of IL33. Furthermore we studied the direct role of HSEC in IL33 biology during liver injury.

Method: CD14+ monocytes were isolated from healthy donors and either cultured with serum and liver supernatant of diseased patients or prompted to trans-well migration assay. To this end HSEC were seeded onto membranes with 3 μm pores until grown confluent. After co-incubation postmigratory monocytes were harvested and characterized by qPCR and ELISA. In order to simulate liver environment the lower compartment of this trans-well assay was supplemented with liver supernatant. Accordingly, we evaluated the contribution of HSEC to IL33 secretion upon different stimuli.

Results: Conditioned liver supernatant but not serum of patients with fibrosis led to the release of IL33 by CD14+ monocytes. Transendothelial migration across activated HSEC increased the IL33 expressed. In line postmigratory monocytes displayed less CD14 and higher CD64 surface expression indicating maturation towards a macrophage phenotype. Blocking experiments yielded that IL1β and IFNγ contained in the liver supernatant but not TLR4 ligands such as LPS lead to the induction of IL33 expression. Besides indirect mechanisms HSEC also directly contributed to raised IL33 levels. In trans-well migration assays TNFα stimulated HSECs enable exclusively Th2 polarized CD4+ T-cell, but not naïve Th0 or Th1 cells, to transmigrate.

Conclusion: IL33 expressing cell types including monocytes and HSEC form a gradient of IL33 facilitating T-cell recruitment to the liver dependent on various inflammatory stimuli present in injured tissue. In conclusion HSEC and monocyte interaction controls IL33 driven liver fibrogenesis.

THU-030

Stereochemistry enhances pharmacological properties of APOC3 antisense oligonucleotides

L. Apponi[1], N. Iwamoto[2], M. Frank-Kamenetsky[1], H. Yang[1], M. Braun[1], A. Shah[1], D. Butler[3], G. Lu[1], V. Vathipadiekal[1], S. Menon[1], K. Bowman[4], L. Pittet[5], J. Zhang[1], Z. Zhong[1], C. Vargeese[6], S. Standley[1]. *[1]Wave Life Sciences, Biology, Cambridge, United States; [2]Wave Life Sciences, Oligo Chemistry and Biochemistry Research, Cambridge, United States; [3]Wave Life Sciences, Medicinal Chemistry, Cambridge, United States; [4]Wave Life Sciences, Process Development, Cambridge, United States; [5]Wave Life Sciences, Alliance and Program Management, Cambridge, United States; [6]Wave Life Sciences, Drug Discovery, Cambridge, United States*
Email: lapponi@wavelifesci.com

Background and Aims: Apolipoprotein C-III (ApoC-III) is a protein produced by hepatocytes in the liver that regulates plasma triglycerides. Human genetic studies have established the role of ApoC-III in hypertriglyceridemia and cardiovascular disease. ApoC-III therapeutics currently in clinical trials utilize stereorandom antisense oligonucleotides (ASOs) to target APOC3 mRNA. By contrast, the aims of this preclinical study were to develop a stereopure oligonucleotide targeting APOC3 mRNA and to determine whether stereochemistry enhances pharmacological properties of APOC3 ASOs.

Method: Stereopure APOC3 ASOs were generated using Wave Life Sciences' proprietary technology that enables precise control of stereochemistry. Stereorandom and stereopure APOC3 ASOs were tested *in vitro* and *in vivo*. *In vitro* potency of APOC3 ASOs was measured using Hep3B human hepatocytes. *In vivo* activity of GalNAc-conjugated APOC3 ASOs was measured using mice harbouring the human APOC3 transgene. Mice were dosed s.c. with APOC3 ASOs, and liver APOC3 mRNA levels were measured by qPCR, and serum hApoC-III protein levels were measured by ELISA. ASO liver exposure was measured by hybridization ELISA.

Results: Stereopure and stereorandom ASOs had similar *in vitro* potencies. Both stereorandom and stereopure GalNAc-conjugated APOC3 ASOs demonstrated >90% knockdown of serum hApoC-III *in vivo* at one week after treatment in human APOC3 transgenic mice. However, treatment with stereopure ASOs extended the duration of effect by 4 weeks compared to treatment with stereorandom ASOs. A dose response study of these ASOs in human APOC3 transgenic mice demonstrated a dose-response relationship for all three ASOs. The stereopure ASO was significantly more active than the stereorandom ASOs at the 1 mg/kg dose. At this dose, stereorandom ASOs showed ~45% reduction of liver mRNA and 70% reduction of serum hApoC-III protein, while the stereopure ASO showed 75% reduction of mRNA and 90% reduction of serum hApoC-III protein. ASO liver exposure demonstrated a PK/PD correlation for stereorandom and stereopure ASOs. Furthermore, liver exposure of stereopure ASOs was up to 4.5-fold greater than stereorandom ASOs.

Conclusion: These results suggest that stereochemistry increases both the duration and the potency of APOC3 ASOs, thereby potentially enhancing the pharmacological properties of ASOs for APOC3 targeting in the clinic.

THU-031

Hypoxia strongly modulates hepcidin mRNA expression via macrophage-hepatocyte crosstalk

I. Silva[1], T. Peccerella[2], G. Millonig[1], H. Seitz[1], S. Mueller[1], V. Rausch[1]. *[1]Center for Alcohol Research and Salem Medical Center, University of Heidelberg, Heidelberg, Germany; [2]Salem Medical Center and Center for Alcohol Research and Liver Disease, University of Heidelberg, Heidelberg, Germany*
Email: ines.silva@uni-heidelberg.de

Background and Aims: Liver-secreted hepcidin is the systemic masterswitch of iron homeostasis and its dysregulation is a key event for carcinogenic iron accumulation in most of chronic liver diseases. Hepcidin is strongly upregulated by iron, inflammation, cytokines or H_2O_2 but the role of liver monocyte-derived macrophages and Kupffer cells on hepcidin regulation under (patho)physiological conditions is poorly understood. We here investigate the cellular crosstalk involved in hepatic hepcidin regulation by developing an *in vitro* co-culture model of hepatocytes and macrophages mimicking physiological cell distribution and oxygen levels.

Method: Huh7 cell and THP-1 monocytes differentiated into macrophages were directly co-cultured at a physiological (10:1) or inflamed (4:1) cellular proportion under normoxic (21% O_2) or hypoxic conditions (1 or 5% O_2) over 24 h. The incubation of Huh7 cells with macrophage conditioned medium was also investigated. Hepcidin mRNA levels were assessed by qRT-PCR, cellular hypoxia was confirmed by staining of pimonidazole adducts and increased levels of H_2O_2 were detected by Prx2 immunoblotting. Contribution of STAT3 and BMP/SMAD pathway on the transcriptional upregulation of hepcidin was analyzed by STAT3, pSTAT3, pSMAD1/5/8 and SMAD1 western blot. A cytokine array was carried out to assess the role of macrophage-secreted cytokines.

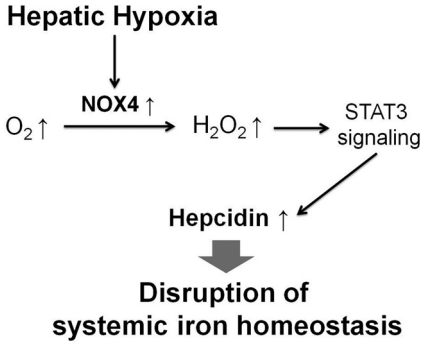
Results: We first demonstrated that the presence of macrophages leads to significantly increased hepcidin mRNA levels. This effect was even potentiated when co-cultivated cells were maintained under low O_2 levels (1% and 5% O_2) and the induction of hepcidin was more pronounced under 1% O_2 as compared to 5%O_2. Interestingly, hepcidin was also upregulated when exposed to macrophage-conditioned medium suggesting the role of a soluble and secreted factor in mediating hepatocyte hepcidin regulation. Western Blot analysis points towards the involvement of STAT3 and BMP signaling pathway, since pSTAT3 and pSMAD1/5/8 are increased in co-cultures or Huh7 cells treated with macrophage-conditioned medium. Finally,

the induction of Prx2 and IL-1β under these conditions suggests a synergistic role H_2O_2 or an H_2O_2-releasing oxidase on hepcidin regulation.
Conclusion: Our findings underscore the importance of the hepatocyte/macrophage crosstalk for hepatic hepcidin regulation that include a secreted factor (IL-1β, TGF-β) and H_2O_2 release by oxidases such as NOX2 under (patho)physiological low oxygen levels.

THU-032
Hypoxia enhances H2O2-mediated upreguation of hepcidin: potential role of oxidases in iron regulation

I. Silva, V. Rausch, T. Peccerella, G. Millonig, H. Seitz, S. Mueller. *Center for Alcohol Research and Salem Medical Center, University of Heidelberg, Heidelberg*
Email: ines.silva@uni-heidelberg.de

Background and Aims: The liver-secreted peptide hepcidin plays a major role in the regulation of iron homeostasis being also critical for the pathological liver iron accumulation in alcoholic liver disease (ALD). Iron, inflammation, cytokines or H_2O_2 are able to induce hepcidin expression, however the role of hypoxia alone and in combination with low levels of H_2O_2 is poorly understood. We here study hepcidin signaling in liver cells under hypoxia and H_2O_2 and the involvement of oxidases, such as NOX4, as potential upstream hepcidin regulators.
Method: Two hypoxic systems (hypoxia chamber and the enzymatic GOX/CAT system) were used to maintain low oxygen level (5% O_2) over 24 hours in Huh7 cells and in primary human hepatocytes, the later system also allowing the control low steady state (ss) H_2O_2 levels. The role of hypoxia on hepcidin promoter activity was assessed by transfecting the cells with Luciferase reporter hepcidin promoter constructs. Transfection of hepatoma cells with ODD-GFP constructs was carried out in order to competitively inhibit HIF1α degradation. The involvement of the liver expressed NADPH oxidase 4 (NOX4) as well as urate oxidase (UOX) was assessed by overexpressing NOX4 or UOX promoter constructs. Hepcidin and NOX4 mRNA levels were studied by qRT-PCR. Cellular hypoxia was confirmed by staining of pimonidazole adducts and H_2O_2 levels were analyzed by Prx2 western blot.



Results: We first show that hypoxia generated either by hypoxia chamber or the GOX/CAT system induced hepcidin mRNA in Huh7 cells and primary human hepatocytes over 24 h. Hypoxia-mediated induction of hepcidin was further potentiated during co-exposure of cells with low ss H_2O_2 levels predominantly at the transcriptional level via STAT3 signaling pathway. Both, Prx2 oxidation and STAT3 phosphorylation mirrored intracellular H_2O_2 and changes in hepcidin mRNA levels. Notably, NOX4 was also strongly upregulated in hepatocytes during hypoxia, suggesting a mechanistic role in mediating hepcidin upregulation. Overexpression of NOX4 increased hepcidin mRNA and this effect was even higher at low O_2 levels. Moreover, similar results were obtained after overexpression of UOX in Huh7 cells. Blockage of HIF1α degradation caused indeed specific HIF1α accumulation, however hepcidin upregulation was not detected. This clearly showed that hypoxia-mediated hepcidin regulation occurs independently of HIF1α.
Conclusion: We here show that hypoxia drastically enhances the H_2O_2-mediated induction of hepcidin via STAT3 in hepatocytes. Our data suggest that oxidases such as NOX4 play a major role in the regulation of hepcidin.

THU-033
Reduced PI3K pathway in NK cells of F4-NAFLD patients inhibited mTOR expressions and was correlated with their impaired function

J. Amer[1], A. Salhab[2], R. Safadi[1]. [1]*Hadassah Hebrew University Hospital, Jerusalem, Israel;* [2]*Hadassah Hebrew University Hospital, Jerusalem*
Email: johnnyamer@hotmail.com

Background and Aims: Stimulation of Natural Killer cells (NK, $CD56^+$) directly kill the activated hepatic stellate cells (HSCs). We investigated changes in insulin receptor on NK cells as a potential cause for their impairment in Nonalcoholic-Fatty Liver-Disease (NAFLD).
Methods: Fresh peripheral blood NK cells isolated from healthy volunteers and 72 NAFLD patients (histology documented adults lacking full criteria of metabolic-syndrome), and characterized by flow-cytometry.
Results: Histologic progression of liver injury significantly correlated with elevated pro-inflammatory serum cytokines and insulin resistance. NK cells stimulation marker (CD107a) over-expressed in low-fibrosis patients, but kept low in advanced-fibrosis (*NK impairment*). Insulin receptors expressed on 68.6 ± 8% of healthy peripheral $CD56^{dim}$ population ($CD16^+$), but significantly reduced in all NAFLD stages. Western blot analysis of NK cells form NAFLD patients with F4 fibrosis showed to have dramatically reduction in PI3K pathway. ERK/MAP kinase pathway showed also reductions in these patients. These results were correlated with inhibitions in mTOR activity ($p = 0.001$). NK stimulations with insulin (physiologic levels) reversed these effects. Compared to normal HOMA NK-cells by *in-vitro* co-culture with HSCs, high-HOMA $CD56^{dim}$ cells (with F3-F4) exhibited increased apoptosis and fail to block HSCs activation. While insulin incubation stimulated NK cell activation and killing of HSCs. Rapamycin reduced $CD56^{dim}$ expressions of insulin receptors (mimicking NAFLD insulin resistance) and prevented the insulin stimulation effect on NK cells.
Conclusion: Insulin exposure stimulates NK cells to enhance HSCs killing and prevent fibrosis progression. Insulin receptors mediate NK cell stimulation by insulin via PI3K pathway and as a consequence the mTOR pathway. Systemic Insulin-Resistance in NAFLD includes the NK cells. Therefore, insulin fails to stimulate NK cells due to low insulin receptor NK expressions and or low serum insulin levels, which leads to cirrhosis and probably cancer.

THU-034
Constructing a cell-type resolved human liver proteome atlas

L. Niu[1,2], P. Geyer[1,2], M. Mann[1,2]. [1]*University of Copenhagen, Novo Nordisk Foundation Center for Protein Research, Copenhagen, Denmark;* [2]*Max Planck Institute of Biochemistry, Proteomics and Signal Transduction, Planegg, Germany*
Email: lili.niu@cpr.ku.dk

Background and Aims: The liver lobule is composed of parenchymal cells (hepatocytes and bile duct cells) and non-parenchymal cells (liver sinusoidal endothelial cells, Kupffer cells and hepatic stellate cells). In contrast to hepatocytes, which occupy almost 80% of the liver volume, non-parenchymal cells only contribute 6.5%. Although hepatocytes perform the majority of numerous liver functions, it has been increasingly recognized that hepatocytes together with non-parenchymal cells cooperate to achieve a wide variety of vital functions in liver homeostasis. Disturbance or malfunction of any of these cells can contribute to multiple diseases, such as non-alcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma.

Modern mass spectrometry (MS)-based proteomics is a powerful tool to globally investigate the biological functions of individual cell types in mammalian organs. Characterizing nearly complete proteomes of the different liver cell types would dramatically aid in understanding their functions at the molecular level. In the past, several murine deep liver proteomes have been described, providing new insight into functions of the liver. The most comprehensive MS-based human liver proteome so far is generated by The Human Proteome Organization (HuPO)-a database called "Liverbase". However, its coverage of expressed liver proteins is still far from complete.
In this study, we aim to use MS-based proteomics to systematically characterize cell-type resolved human liver proteomes.
Method: Isolated primary cell types as well as corresponding immortalized cell lines are being analysed in great depth by next-generation proteomic technology. Human liver tissue samples from healthy and cirrhotic patients are also included in our study to compare their differences in protein expression and metabolic pathways.
Results: Our preliminary results indicate that more than 10,000 proteins can be quantified in cell types as well as in liver tissues, which should lead to the largest and most accurate reflection of the human liver to database. We plan to make this in-depth and user-friendly database will be public available, to be used as a resource by the whole community. It can also be used to perform comparative analysis to reveal cell-type-specific proteomic profiles as well as the "division of labour" and biological processes among distinct cell types. The comparison between healthy and cirrhotic liver tissue identifies differential protein expression profiles and altered metabolic pathways.
Conclusion: Upon completion, our extensive liver protein database will represent a very broad proteome map of the human liver at cell-type resolution. This MS-based liver proteome atlas will serve as a reference database for basic research as well as biomarker discovery studies in the context of liver disease.

THU-035

Metabolic rewiring and de novo lipogenesis induced by Glucokinase expression in hepatocarcinoma cell line

B. Panthu[1], G. Rautureau[2], C. Jacquemin[1], B. Elena-Herrmann[2], P. Andre[1], O. Diaz[1], V. Lotteau[1]. *[1]INSERM U 1111 – CNRS UMR5308 Université Lyon 1, ENS de Lyon, Centre de Recherche International en Infectiologie, Lyon, France; [2]Institut des Sciences Analytiques, UMR 5280 CNRS, Villeurbanne, France*
Email: vincent.lotteau@inserm.fr

Background and Aims: Human hepatocarcinoma cell lines are in vitro models for the study of lipid metabolism, hepatic steatosis and carcinogenesis. However, these cells have an unbalanced lipid metabolism that is strongly dependent on exogenous fatty acids to synthesize triglycerides and lipoproteins. This motivates the need for a physiologically relevant hepatocyte *in vitro* model allowing a deep analysis of the cellular mechanisms that regulate glycolysis, *de novo* lipogenesis and lipoprotein synthesis in normal and pathological situations.
Method: Like virtually all cancer cells, hepatocarcinoma cells express the "cancer-type" hexokinase isoenzyme HK2. Here, we restored the hepatic hexokinase isoenzyme (glucokinase, GCK) expression in the paragon hepatocarcinoma cell line Huh7 invalidated for HK2 by CRISPR-Cas9. Endo- and exo-metabolites have been analysed by a combined approach of biochemistry and high-field Nuclear Magnetic Resonance metabolomics.
Results: Metabolomic analysis highlighted that although glucose consumption remains identical in HK2-Huh7 and GCK-Huh7 cells, a profound metabolic remodelling toward *de novo* lipogenesis occurred in GCK-Huh7 cells. Accompanying *de novo* lipogenesis are an increased consumption of pyruvate by mitochondria, a truncated TCA cycle at the level of succinate dehydrogenase with a reduced mitochondrial respiration and activated pentose phosphate and glutamine pathways. This drastic metabolic remodelling sensitized GCK-Huh7 cells to both fructose-induced lipid accumulation and viral infection.
Conclusion: Restoring GCK expression in current hepatoma cells has induced a large scale metabolic remodelling with a balanced lipid metabolism mimicking *in vivo* lipogenesis. This physiologically-relevant hepatocyte model will certainly provide improved clues to control liver inflammation, NASH and tumorigenesis.

THU-036

Role of septin 9 in interferon gsignalling and the development of cholangiocarcinoma

J. Peng[1,2], D. Ouazib[1,2], Y. Ding[1,2], N. Benzoubir[1,2], D. Samuel[3], A. Gassama[1,2]. *[1]INSERM, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France; [2]Univ Paris-Sud, UMR-S 1193, Université Paris-Saclay, Villejuif; [3]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, F-94800, France, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France*
Email: yifanding903@gmail.com

Background and Aims: Hepatobiliary cancer comprises a heterogeneous group of malignancies. Our proteomic study revealed that septin 9 was found among of proteins only detected in Cholangiocarcinoma (CCA) tissue. Thus suggesting that septin 9 might contribute to the progression of CCA.
Septin 9 is a member of a conserved family of GTP-binding proteins that have roles in cytokinesis, vesicle trafficking and cell migration. Although the potential role of septin 9 in carcinogenesis has remained unspecified. We identified different partners of septin 9 including molecules of phosphoinositides signalling. These studies revealed a role of septin 9 in the regulation of interferon γ (IFNγ) signaling.
The aims of this study is to determine the function of septin 9 in CCA and its identified partners in the regulation of IFNγ signalling.
Method: We used MzChA-1 cells (Biliary adenocarcinoma cell line) and Hela cells to perform the study. Cells were transfected using the cDNA and siRNA of septin 9 and its partners. Proteins were analysed by immunoblot or immunofluorescence. Immunohistochemistry was performed on paraffin sections tissus array of CCA.
Results: Our results show the association of septin 9 with PIs specially PtdIns5P. Upon stimulation of cells with IFNγ, we observed a recruitment of septin 9 and PtdIns5P in the perinuclear area. Septin 9, regulated STAT1 phosphorylation after INFγ treatment.
IFNγ treatment induced PD-L1 (Programmed death-ligand 1) expression at membrane which expression is considered as an adaptive resistance mechanism that protects tumor cells from T cell-mediated-destruction and promotes cancer progression. Interestingly, flow cytometry analysis showed Septin 9 expression upregulated PD-L1 after IFNγ treatment. Furthermore, we showed a new role of septin 9 in endosomal trafficking which is responsible of accumulation of PDL1.
PD-L1 expression was analyzed in different type of CCA and the data were correlated with clinicopathological features, density of tumor-infiltrating lymphocytes (TILs). PDL1 expression is higher in CCA than the other liver cancers. Of interest a positive relationship was observed between PD-L1, the number of CD3 and CD8 TILs and septin 9 expression.
Conclusion: We identified a new molecular cascade that regulate endolysosomal trafficking and responsible for PDL1 disregulated in CCA. Together these findings have provided the rationale for further development of diagnosis markers and immunotherapy treatments against CCA.

THU-037

Molecular and histological characterization of the pathological events in a model of cirrhosis and hepatocarcinoma

M.P. Castro-Gil[1], J.E. Torres-Mena[1], C.D. López[1], S. Muñoz-Montero[2], R.M. Salgado-Curiel[3], E. Krötzsch[3], J.I. Pérez-Carreón[1]. *[1]National Institute of Genomic Medicine, Liver Diseases Laboratory, Mexico city, Mexico; [2]National Institute of Genomic Medicine, Computational Genomics, Mexico City, Mexico; [3]National Institute of Rehabilitation, Laboratory of Connective Tissue, Mexico City, Mexico*
Email: polesia77@gmail.com

Background and Aims: Despite the increasing knowledge in the basis of hepatocellular carcinoma (HCC) there are few studies comprising molecular and histological features in a carcinogenic development scheme. One of the constitutive properties of pre-neoplastic and neoplastic nodules in rat hepatocarcinogenesis models is the expression of the enzyme Gamma Gluatmyltranferase (GGT). On the other hand, the expression of the biliary/progenitor cell marker Keratin 19 (K19), has gained importance in the field because it is associated with a poor prognosis. In a healthy liver, both markers are only expressed in cholangiocytes and hepatic progenitor cells. Nevertheless, they can be observed in neoplastic hepatocytes. Our Aim was to determine the transcriptome profile of pre-tumoral and tumoral lesions GGT/K19 positive, and their surrounding context in collagen deposition in a rat model of hepatocarcinogenesis.
Method: Hepatocarcinogenesis was induced in Fisher 344 rats using the Schiffer's protocol that consists in weekly intraperitoneal injections of diethylnitrosamine (DEN) which causes cirrhosis at 12 weeks (pretumoral) and multifocal HCC at 18 weeks (tumoral). Normal livers of non-treated rats were used as controls. Fibrosis process (i.e. collagen deposition) and hepatic damage were evaluated through 2 histologic methods; Herovici's staining and GGT histochemistry. GGT/K19 lesions were captured using laser microdissection and RNA obtained from these samples was sequenced by NGS (RNA-Seq).
Results: Normal liver tissues presented GGT and collagen deposition only in bile ducts and blood vessels, while pretumoral tissues presented type III collagen around nodules. The amount of collagen increased in tumors as compared to the pretumoral tissues and presence of both, type I and type III collagen was observed. Type III collagen is not as stiff as type I, it is linked with recent and acute healing processes. Type I collagen is related to a mature healing state. Previous studies have revealed that lax environments are associated with progenitor characteristics. This statement may justify the presence of pretumoral and tumoral lesions GGT/K19 positive. RNA sequencing data were analyzed through a principal component analysis (PCA), showing that samples cluster in two main groups; Normal Liver and Liver Lesions. The lack of distinction between pretumoral and tumoral lesions by PCA may be the consequence of the same phenotypical selection criteria. Further gene enrichment analysis may provide differences within the tissular context that might contribute to understanding liver carcinogenesis.
Conclusion: Schiffer's protocol is a hepatocarcinogenesis model useful for the study of the progression of pretumoral lesions with progenitor characteristics. The tumorigenic state of these lesions may be influenced by extracellular characteristics such as the type of collagen deposition.

THU-038

The emerging realm of morphogens in the adult liver of mice and human – a deep insight into distribution, interaction and regulation

E. Schröder[1], C. Rennert[2], J. Böttger[1], D. Meierhofer[3], R. Gajowski[3], C. Stöpel[4], H. Stefan[4], W. von Schönfels[5], C. Schafmayer[5], M. Brosch[6], J. Hampe[6], R. Gebhardt[1], M. Matz-Soja[1]. *[1]Rudolf-Schönheimer-Institute of Biochemistry, Faculty of Medicine, Leipzig, Germany; [2]Saxonian Incubator for Clinical Translation (SIKT), Leipzig University; [3]Max Planck Institute for Molecular Genetics, Mass Spectrometry Faculty, Berlin, Germany; [4]Institute for Computer Science, Leipzig University, Leipzig, Germany; [5]Department of General Surgery and Thoracic Surgery, University Hospital Schleswig-Holstein, Kiel, Germany; [6]Medical Department 1, University Hospital Dresden, Dresden, Germany*
Email: madlen.matz@medizin.uni-leipzig.de

Background and Aims: Morphogens like Hedgehog (Hh) and Wnt/β-Catenin (Wnt) are known to govern developmental processes in embryogenesis, tissue differentiation and regeneration. More recently, the impact of those morphogens on adult cell physiology and metabolism has sparked increasing interest. Most metabolic pathways in the liver are strongly zonated, partially caused by adapting to changing contents of nutrients and oxygen within the porto-central axis. The question of how morphogens contribute to the lobular distribution of metabolic pathways, is part of an evolving field in science since the last decade. Initially, the pericentral located Wnt pathway was thought to be exclusively responsible for liver zonation of ammonia and glucose metabolism. Recently, our group demonstrated that the Hh pathway has an immense impact on lipid metabolism in the adult liver of mice and man. For a better understanding of metabolic liver zonation under morphogenic control, we aimed to demonstrate the mutual impact and zonal distribution of Hh and Wnt/β-Catenin signaling.
Method: To address this question, human material was used as well as different mouse models were bred, which allow a hepatocyte-specific modulation of these pathways in adult mice. To depict the porto-central distribution of different pathway markers, liver slices were stained by immunohistochemistry and analyzed by the modular software tool TiQuant. This tool allows an efficient quantification of biological tissues based on volume data obtained by biomedical image modalities. In addition, proteome profiling of murine liver samples was used to study the global impact of morphogens on the metabolic liver function.
Results: The immunohistological analysis indicates where central proteins of Hh and Wnt are localized and how they influence each other upon pathway modulation. Furthermore, the outcome of the proteome approach provides deep insights on how morphogens regulate the liver metabolism in detail and contribute to a better understanding of the fine tuning mechanism in metabolic zonation of the liver.
Conclusion: Our results give a deep insight for the first time into the distribution, interaction and localization of morphogenic pathways like Wnt and Hh in the adult liver of mice and humans. From the results we conclude a strong crosstalk between Wnt and Hh signaling pathways which orchestrate the metabolic zonation of the liver.

THU-039

Direct and indirect hepatoprotective mechanism of CBLB502 a TLR5 agonist

N. Melin[1], R. Fahrner[2], A. Keogh[1], M. Medova[1], Y. Zimmer[1], D. Aebersold[1], D. Candinas[1], G. Beldi[1], D. Stroka[1]. *[1]University of Bern, Department for BioMedical Research, Bern, Switzerland; [2]Uniklinikum-jena, Klinik für Allgemein-, Viszeral- und Gefäßchirurgie, Jena, Germany*
Email: nicolas.melin@dbmr.unibe.ch

Background and Aims: CBLB502 is a synthesized peptide from bacterial flagellin known to be an agonist of toll-like receptor 5 (TLR5) showing protective properties in various model. Here we investigated its potential hepatoprotective effect and mechanism of action.

Method: A mouse model of partial liver ischemia reperfusion (I/R) was used to assess the hepatoprotective effect of CBLB502 against acute liver injury and assessed by serum ALT/AST levels and tissue myeloperoxidase activity. Hepatic NF-kappaB and Stat3 signaling was evaluated by western blot and q-PCR. Serum cytokine were measured by cytokine bead array.
Results: Preliminary data show that in mice treated with 0.2 mg kg^{-1} CBLB502 I.P., there is a beneficial influence on clinical symptoms of hepatic ischemia reperfusion injury by reducing ALT/AST and myeloperoxidase activity. Direct protective mechanism, was shown by induction of NF-kappaB signaling in hepatocytes and liver as well as downstream cytoprotective genes. In parallel, TLR5 induced cytokine response was accessed showing increased in various serum cytokines and IL-22 level was the most striking (2 μg/ml). IL-22 produced by cells found in colon and MLN was shown to activate Stat3 signaling in hepatocyte thus inducing hepatoprotection through an indirect mechanism.
Conclusion: I/R injury associated with hepatic resections and liver transplantation remains a serious complication in clinical practice. Hepatic damage could potentially be diminished by prior activation of an innate immune response targeting TLR5.

THU-040

Towards understanding the mechanisms of chlorpromazine-induced hepatic toxicity using a human HepaRG-based model

J. Brzeszczynska, K. Morgan, F. Brzeszczynski, K. Samuel, P. Hayes, J. Plevris. *University of Edinburgh, Hepatology Laboratory, Edinburgh, United Kingdom*
Email: j.plevris@ed.ac.uk

Background and Aims: We have previously shown, using impedance biosensor technology, that chlorpromazine (CPZ) induces early, dose-dependent disruption of tight junctions even at sub-toxic CPZ levels (25 μM).[1] In this study we investigated the molecular mechanisms that may mediate the hepatic alterations induced by CPZ in the human HepaRG model and in particular those related to inflammation and oxidative stress.
Method: HepaRG cells were exposed to CPZ concentrations of 25, 50 and 100 μM for 24 h. Cell viability was assessed by ATP-depletion assay (CellTiter-Glo). Assessment of cytoskeleton intergrity was performed by TJ-associated/F-actin expression following CPZ challenge. A number of molecular markers were analysed using qPCR (N = 3). The fold change in expression of target genes relative to the internal control genes (TOP1, UBC and GAPDH) was calculated. QRT-PCR data were presented as the fold change in gene expression normalised to the average value of 3 common endogenous reference genes and relative to control (untreated cells).
Results: CPZ induced extensive cell death at 100 μM. At concentrations of 25 and 50 μM, cell viability by ATP-depletion assay was not significantly impaired. As previously demonstrated, cytoskeletal changes suggestive of tight junction disruption were seen. CPZ provoked a dose dependent inflammatory response [3-fold at 25 μM and 10-fold at 50 μM) for IL-6 as well as 2.7-fold at 25 μM and 8-fold at 50 μM for TNFα. This response was associated with 0.5-fold down regulation of HNF4α transcript and cytochrome 3A4 at 50 μM. mRNA expression of bile canalicular transporters ABCB11 (bile salt exporter pump), ABCB4 (phospholipids transporter) and ABCB1 (drug efflux transporter) was decreased. 50 μM of CPZ induced 20-fold increase in the expression of ABCB11 likely to represent a hepatoportective response to accumulation of toxic bile acids (BA). GGT1 a key anti-oxidative compound was up regulated. Expression of Bax (pro apoptotic gene) was increased at 50 μM, while the Bcl2 anti apoptotic gene was upregulated in 25 and 50 μM CPZ treated cells. AIF1 and p53 gene expressions were unchanged. Nrf2 was up regulated by 2.3-fold in 50 μM CPZ treated cells.
Conclusion: Our results show that an inflammatory response is induced by CPZ at 25 and 50 μM, resulting in activation of anti oxidant and anti apoptotic defence pathways Nrf2 and Bcl2 with evidence of intracellular oxidative stress perhaps caused by accumulation of bile acids with reduction of cytochrome 3A4 activity and adaptive upregulation of GGT1. In conclusion we demonstrate that CPZ appears to cause disruption of hepatic cytoskeleton through an inflammatory response and induction of intracellular oxidative stress.

Reference

1. Kozlowska *et al.* Mechanistic insight into chlorpromazine-induced hepatic tight junction disruption using a human HepaRG-based LiverBioChip Impedance biosensor. Abstract UEGW 2015.

THU-041

Uncovering the liver Notch code using high-throughput reporter imaging on micropatterns

J. Mašek[1], C. Vervuurt[1], S. Hankeova[2], U. Lendahl[2], A. Lindqvist[2], E. Andersson[1]. *[1]Karolinska Institute, Department of Sciences and Nutrition, Huddinge, Sweden; [2]Karolinska Institute, CMB, Stockholm, Sweden*
Email: jan.masek@ki.se

Background and Aims: Notch signaling is a key communication system in animals, which can, when disturbed, drive both liver disease and cancer. Mutation of either *JAGGED1* or *NOTCH2* leads to the dominant genetic multisystemic disorder Alagille syndrome (also known as arteriohepatic dysplasia) characterised by impaired biliary development (1). We have recently shown that homozygous Jag1H268Q mutation mimics Alagille syndrome in mouse, including cholestasis, bile duct paucity and heart defects (2). This mutation generates a hypomorphic ligand with impaired capability to induce Notch signaling, and hampered ability to interact with specific Notch receptors: Jag1H268Q binds Notch2, but not Notch1, and to a lesser degree Notch3. Almost all Notch receptors and ligands are expressed in developing embryonic liver (3, 4). However, the parameters dictating the output of Notch receptor-ligand interaction diversity – the "Notch code" – remains poorly understood.

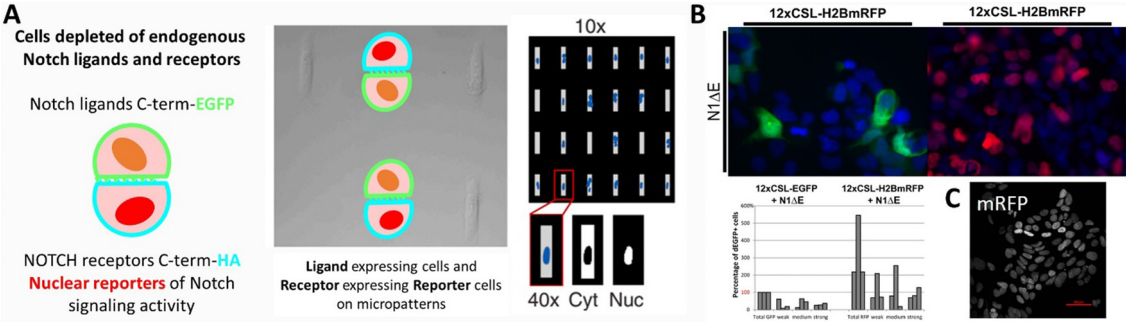


Figure: (abstract: THU-041)

Our aim is to address the combinatorial code of individual Notch ligands and receptors, in a clean system and with single-cell resolution, allowing us to predict and fine tune Notch signaling.
Method: We are generating a cell line, devoid of all endogenous Notch sinaling components, using CRISPR/Cas9 technology. Individual receptors and ligands will then be re-introduced in defined combinations, allowing us to assess their output using high-throughput microscopy on micropatterns.
Results: We have developed high-throughput reporter imaging on micropatterns that allows for quantification of Notch signaling in individual cells or doublets of cells.
Conclusion: We have achieved reproducible measurement of Notch signalling activity by stable integration of our new 12xCSL-H2B-mRFP reporter into HEK293 Flp-in cells.
High-throughput reporter imaging on micropatterns. (**A**) Schematic representation of the planned experiment. 16,000 fibronectin-coated patches per slide allow for automated, high-throughput assessment of Notch signaling strength and duration. Adapted from (5). (**B**) Comparison of signal robustness in response to Notch stimuli (constitutively active Notch1 - N1dE) between the 12xCSL-d1EGFP and newly generated 12xCSL-H2BmRFP reporters in transient transfection. Nuclear reporter signal will be easier to quantify in an automated fashion. (**C**) Different levels of endogenous Notch activation in stable12xCSL-H2BmRFP reporter line generated using HEK Flp-IN system (Thermo Fisher Scientific).

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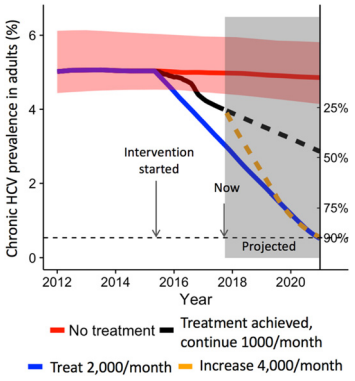
Public Health

THU-047

Interim evaluation and projected impact of the hepatitis C virus elimination program in Georgia

J. Walker[1], L. Gvinjilia[2], M. Nasrullah[3], A. Gamkrelidze[4], J. Morgan[5], P. Vickerman[1]. *[1]University of Bristol, Population Health Sciences Bristol, United Kingdom; [2]CDC Foundation, Tbilisi, Georgia; [3]CDC, Division of Viral Hepatitis, United States; [4]National Center for Disease Control and Public Health, Tbilisi, Georgia; [5]CDC, Global Disease Detection, Division of Global Health Protection, Tbilisi, Georgia*
Email: jogwalker@gmail.com

Background and Aims: Georgia has one of the highest hepatitis C virus (HCV) prevalence rates in the world, with >5% of the adult population (~150,000 people) chronically infected. In April 2015, the Georgian government, in collaboration with CDC and other partners, launched a national program to eliminate HCV through scaling up HCV treatment and prevention interventions, with the aim of achieving a 90% reduction in prevalence by 2020. We evaluate the impact of the HCV treatment program as of 30 September 2017, and assess the feasibility of achieving the elimination goal by 2020.
Method: We developed a dynamic HCV transmission model that aims to capture the current and historical epidemic dynamics of HCV in Georgia, including the main drivers of transmission. Using the 2015 national sero-survey and prior surveys conducted among people who inject drugs (PWID) from 1997–2015, the model was calibrated to data on HCV prevalence by age, gender and PWID status, and the age distribution of PWID. We use the model to project the interim impact of treatment strategies currently being undertaken as part of the ongoing Georgia HCV elimination program, while accounting for treatment failure/loss to follow up, in order to determine whether they are on track to achieving their HCV elimination target by 2020, or whether strategies need to be modified to ensure success.
Results: A treatment rate of 2,000 patients/month was required from the beginning of the national program to achieve a 90% reduction in prevalence by the end of 2020, with equal treatment rates of PWID and the general population. From April 2015 to September 2017, 39,396 patients were treated, an average of ~1,300 per month; but the treatment rate has recently declined from a peak of 4,500/month in September 2016 to 2100/month in November-December 2016, and 1000/month in August–September 2017, with a sustained virological response rate (SVR) of 98% per-protocol or 78% intent to treat. The treatments achieved have, as of September 2017, reduced adult chronic prevalence by 21% (15–29%) to 4.0% (3.3–5.2%), reduced total incidence by 19% (13–27%), and prevented 1457 (802–2563) new infections and 80 (27–140) HCV-related deaths. If the treatment rate of 1000 patients initiated per month continues, prevalence will have halved by 2020, and reduce by 90% by 2028. In order to reach a 90% reduction by 2020, with the same SVR rate, the treatment rate must be quadrupled to about 4,000 per month (Figure).



Conclusion: The Georgia HCV elimination program has accomplished an impressive scale up of treatment, which has already had an impact on prevalence and incidence, and averted deaths due to HCV. However, treatment initiation has fallen short of the target and extensive scale up is needed to achieve a 90% reduction by 2020.

THU-048

Protective effect of cannabis and coffee consumption on HCV-related mortality in French HIV-HCV co-infected patients (ANRS CO13 HEPAVIH cohort)

C. Protopopescu[1,2], M.E. Santos[3,4], P. Sogni[5], F. Marcellin[1,2], L. Esterle[6], L. Wittkop[6,7], E. Rosenthal[8,9], P. Morlat[10], P. Roux[1,2], W.N. de Araújo[4], D. Salmon-Céron[11,12], M.P. Carrieri[1,2]. *[1]Aix Marseille Univ. INSERM, IRD, SESSTIM, Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale, Marseille, France; [2]ORS PACA, Observatoire régional de la santé Provence-Alpes-Côte d'Azur, Marseille, France; [3]Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Vigilância, Prevenção e Controle das IST, do HIV/Aids e das Hepatites Virais, Brazilia, Brazil; [4]Universidade de Brasília, Faculdade de Ciências da Saúde, Programa de Pós-Graduação em Saúde Coletiva, Brazilia, Brazil; [5]Université Paris Descartes, Inserm U-1223, Unité d'Hépatologie, AP-HP, Hôpital Cochin, Paris, France; [6]Univ. Bordeaux, ISPED, Inserm, Bordeaux Population Health Research Center, team MORPH3EUS, UMR 1219, CIC-EC 1401, Bordeaux, France; [7]CHU de Bordeaux, Pole de santé publique, Service d'information médicale, Bordeaux, France; [8]Nice Sophia-Antipolis University, Nice, France; [9]Department of Internal Medicine, L'Archet Hospital, Nice, France; [10]Service de médecine interne, Hôpital Saint André, CHU de Bordeaux, Université de Bordeaux, Bordeaux, France; [11]Université Paris Descartes, Paris, France; [12]Service Maladies infectieuses et tropicales, AP-HP, Hôpital Cochin, Paris, France*
Email: fabienne.marcellin@inserm.fr

Background and Aims: Cannabis is frequently used by HIV-HCV co-infected individuals to relieve disease-related symptoms. Its use is associated with reduced risk of insulin resistance and steatosis, two conditions linked to increased mortality risk. We aimed to evaluate the impact of cannabis, coffee and other psychoactive substances (alcohol and tobacco) on HCV-related mortality, taking into account competing causes of death.
Method: ANRS CO13 HEPAVIH is a French nationwide prospective cohort of HIV-HCV co-infected patients collecting medical and psychosocial/behavioural data. We used Fine and Gray's competing-risk proportional sub-hazards model to estimate the effect of cannabis and of other psychoactive substances on HCV-related mortality, taking into account competing causes of death and adjusting for HIV/HCV clinical characteristics.

Table: Characteristics of the study population and factors independently associated with HCV-related mortality* (the ANRS CO13 HEPAVIH cohort, n = 1,028)

		%	No. of HCV deaths	aSHR	95% CI	p-value
Smoking status§	Current	71.8	59	1		
	Never/past	26.5	15	0.36	0.14–0.95	0.039
Coffee	≤1	51.3	24	1		
consumption§	2	22.1	6	0.83	0.33–2.10	0.698
(cups/day)	≥3	26.6	3	0.37	0.15–0.88	0.025
Cannabis	Never/sometimes	65.5	50	1		
consumption§	Regularly/daily	24.8	18	0.32	0.11–0.98	0.047

§measured at baseline
*The multivariate model is adjusted for gender, BMI, history of HCC/liver transplantation, previous indirect clinical signs of cirrhosis, CD4 cell count, HIV clinical stage.

Results: Over a median 5-year follow-up period, 77 deaths (including 33 HCV-related deaths) occurred among 1,028 eligible patients. In the multivariable analysis, regular/daily cannabis use, ≥3 cups of coffee/day and not smoking were independently associated with a 68%, 63%, and 64% reduction in HCV-related mortality (adjusted sub-hazard ratio (aSHR) [95%CI]: 0.32[0.11–0.98], 0.37[0.15–0.88], and 0.36[0.14–0.95]), respectively. Results were adjusted for gender, BMI and the following HCV-mortality risk factors: history of hepatocellular carcinoma (HCC)/liver transplantation, previous indirect clinical signs of cirrhosis, CD4 cell count, and HIV clinical stage. No significant association was found between alcohol consumption and HCV-mortality risk.
Conclusion: These results confirm the benefits of elevated coffee consumption and highlight the protective role of regular/daily cannabis use on HCV-mortality risk, despite the negative impact of smoking. Further research is needed to understand the causal mechanism involved.

THU-049
Treatment of Hepatitis C in dedicated homeless GP practice by a multidisciplinary team

K. Davidson[1], K. Macbeth[2], C. Scott[2], J. Budd[3], A. Bathgate[2], P. Hayes[2].
[1]*NHS Lothian, Pharmacy, Edinburgh, United Kingdom;* [2]*Royal Infirmary of Edinburgh, Hepatology;* [3]*Edinburgh Access Practice, Edinburgh*
Email: katherine.davidson@luht.scot.nhs.uk

Background and Aims: In the UK, prevalence of Hepatitis C Virus (HCV) is 50 times higher in the homeless population than the general population.[1] With availability of highly effective, well tolerated Direct Acting Antivirals (DAA), HCV is an easily curable disease as reflected in clinical trials and real world data. However, the homeless are likely to have high rate of multimorbidity, polypharmacy and less likely to engage with hospital services, where traditionally HCV treatment has been delivered from.
In Lothian, there has been an established HCV outreach service at a dedicated general practice for the homeless. This model utilizes a multidisciplinary team (MDT) of GP, support workers together with hepatology nurse practitioner from secondary care. With the advent of DAA, there was a role for a clinical pharmacist to ensure safe and effective use of medicines. HCV medicines were supplied via community pharmacy, often on a daily observed basis which allowed support and monitoring of adherence.
Method: From October "16 to November "17, DAA treatment was commenced. Treatment was led by hepatology nurse practitioner, with input from GP, practice based support workers and consultant hepatologist. The clinical pharmacist advised on Drug Drug Interactions (DDI) and liaised with community pharmacist for supply of medicines. Sustained Viral Response (SVR) was measured 12 weeks after cessation of treatment.
Results:

Total number of patients	31
Male	21 (67.7%)
Age (years)	41 (23–57)
F0–1	23 (74.2%)
F2-3	6 (19.4%)
F4	2 (6.5%)
Fibroscan® available	7 (22.6%)
Genotype 1	20 (64.5%)
Genotype 3	11 (35.5%)
Mean Viral Load (IU/ml)	1,543,345 (6809–8,870,263)
Treatment experienced	4 (12.9%)
Illicit drug use	Previous injectors: 25 Current injectors: 6
HCV treatment	Ombitasvir/Paritaprevir/ritonavir + Dasabuvir + ribavirin (RBV): 4 (12.9%) Elbasvir/Grazoprevir+/−RBV: 11 (35.5%) Ledipasvir/Sofosbuvir+/−RBV: 4 (12.9%) Sofosbuvir/Velpatasvir: 11 (35.5%) Sofosbuvir + Peg-Interferon + RBV: 1 (3.2%)
Average number of medicines per patient	3.4 (1–10)
Opioid substitution therapy (OST)	26 (83.8%)
Number medicines with DDI (n = 105)	11 (10.5%) All amber Treatment changes/Dose adjustments: 0
Dispensing frequency	Daily observed 26 (83.8%)* (*Sunday+/−evening doses unobserved)

To date, 91.7% (n = 24) patients completed >90% treatment. SVR 12 weeks has been achieved in 83% of patients (n = 12). Further data awaited.
Conclusion: This data demonstrates successful treatment of HCV can be delivered in an outreach setting convenient to patients with proactive support of MDT. Pharmacists can support treatment and adherence, particularly through linkage to supply of OST. Engaging with this cohort is key in contributing to goal of eradication of HCV and improving health outcomes in this population.

(1) Infectious diseases among homeless populations. National Institute for Health and Clinical Excellence April 2013.

THU-050
Comorbid disease burden in patients with primary liver pathologies- data from a comprehensive analysis of serial transient elastography and other liver disease evaluations at the Toronto liver centre (CASTLE-TLC)

M. Elkashab[1], H. Dallali[1], S. Kausar[1], M. Farshadi[2], M. Khurram[1], O. Muraru[1], M. Khan[3], J. Palmart[4], S. Loo[4], M. Magnes[1], K. Boctor[1].
[1]*Toronto Liver Centre, Hepatology, Toronto, Canada;* [2]*Toronto Liver Centre, Hepatology, Canada;* [3]*Gilead Sciences Canada, Research;* [4]*Advisory Physicians Research Services Inc., Biostatistics*
Email: boctork@gmail.com

Background and Aims: There is increasing interest in characterizing the burden of comorbidities in patients with liver disease of diverse

Table: (abstract: THU-050)

Table 1 Demographics / Comorbidities

	Total		NAFLD / NASH		Chronic HBV only		Chronic HCV only		Other (incl HepB/C & Other)	
N	3,610		1,722		585		580		716	
Gender, N(%) Male	2,030	56.2%	1,008	58.5%	296	50.6%	318	54.8%	407	56.8%
BMI Category, N(%)										
<25	180	5.0%	68	3.9%	39	6.7%	25	4.3%	47	6.6%
25-30	278	7.7%	188	10.9%	23	3.9%	28	4.8%	39	5.4%
> 30.0	926	25.7%	722	42.0%	39	6.6%	64	11.1%	101	14.1%
BMI / Obesity unknown	2,226	61.7%	744	43.2%	484	82.7%	463	79.8%	529	73.9%
HTN, N(%)	967	26.8%	573	33.3%	61	10.4%	137	23.6%	193	27.0%
Dyslipidemia, N(%)	962	26.6%	661	38.4%	74	12.6%	83	14.3%	143	20.0%
Diabetes, N(%)	583	16.1%	399	23.2%	32	5.5%	58	10.0%	94	13.1%
CAD, N(%)	134	3.7%	75	4.4%	4	0.7%	25	4.3%	30	4.2%
GERD, N(%)	407	11.3%	230	13.4%	50	8.5%	54	9.3%	72	10.1%
Cancer, N(%)	246	6.8%	104	6.0%	16	2.7%	30	5.2%	95	13.3%
Type of CA (those who reported) N	246		104		16		30		95	
Liver CA (incl HCC)	71	28.9%	14	13.5%	2	12.5%	3	10.0%	52	55.3%
Breast CA	52	21.1%	32	30.8%	4	25.0%	6	20.0%	10	10.6%
Thyroid CA	20	8.1%	12	11.5%	1	6.3%	2	6.7%	5	5.3%
Prostate CA	16	6.5%	8	7.7%	1	6.3%	2	6.7%	5	5.3%
Uterus CA	14	5.7%	9	8.7%	0	0.0%	2	6.7%	3	3.2%
Gastrointestinal CA	12	4.9%	6	5.8%	2	13.3%	2	6.9%	2	2.1%
Colon CA	10	4.1%	1	1.0%	0	0.0%	1	3.3%	8	8.5%

etiology. There is evidence that aging patients with chronic hepatitis B have a higher incidence of diabetes, hypertension and renal insufficiency. Similarly, clinical manifestations of late stage NAFLD and NASH have been associated with many aspects of metabolic dysfunction. This analysis, the first in an ongoing long-term retrospective analysis, aims to assess the burden of comorbidities in liver disease patients at a large urban liver clinic in Toronto, Canada.

Methods: 3,610 patient charts were retrospectively reviewed and was assigned to one of the following primary liver disease categories: chronic hepatitis B (HBV), chronic hepatitis C (HCV), NAFLD/NASH, autoimmune liver disease (AIH), alcoholic liver disease (ALD), and others. Patient age, sex, BMI, serial liver histology and serology were collected to look at the incidence of obesity (BMI > 29.9), hypertension (HTN), dyslipidemia, type II diabetes, gastroesophageal reflux disease (GERD), cardiovascular disease (CVD), thyroid disease, and various carcinomas.

Results: 3,610 patient charts reviewed: 56.2% males, 43.8% female; percent distribution of liver disease were as follows: NAFLD/NASH 47.7%, HCV only 16.1%, HBV only 16.2%, others 19.8%, with 52.9% ≥50 years of age at last visit. 58.9% of patients were reported to have only 1 liver disease; and 41.1% were reported to have 2 or more liver conditions. The most frequently reported comorbidities were HTN (26.8%), dyslipidemia (26.6%), diabetes (16.1%), thyroid disease (14.4%), and GERD (11.3%). HTN, dyslipidemia and diabetes occurred with greater frequency in the NAFLD/NASH patients compared to those with viral hepatitis (HBV and HCV). Cancer of any type was reported in 6.8% of patients (246/3610), with the following cancers found most frequently: liver/HCC (28.9%) breast (21.1%), and thyroid (8.1%). NAFLD /NASH contributed to 42.2% of overall cancer incidence, with higher number of breast and thyroid cancer reported in NAFLD/NASH patients. Further breakdown by disease etiology seen in Table.

Conclusion: The burden of comorbidities is high among a large sample of liver disease patients of diverse etiology, and is particularly pronounced in patients with NAFLD/NASH, with slightly higher percentage of certain cancers seen in NAFLD/NASH patients compared to other liver disease patients, although the incidence of cancer reported in this cohort was low. While these data are in agreement with much of the emerging data in patients with NAFLD/NASH, data collection for this study will continue with future analyses currently being planned.

*All authors have contributed equally to this study.

**Acknowledgements & Funding, made possible with financial support from Gilead Sciences Canada.

THU-051

Patient monitoring of changes in the European policy response to viral hepatitis C treatment: Hep-CORE findings from 2016 to 2017

J. Lazarus[1,2], S.R. Stumo[1], C. Gore[3], M. Harris[4], G. Hendrickx[5], M. Jauffret-Roustide[6], A. Kautz[7], M. Maticic[8], T. Reic[9], K. Safreed-Harmon[1]. *[1]University of Barcelona, Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, Barcelona, Spain; [2]University of Copenhagen, CHIP, Rigshospitalet, Copenhagen, Denmark; [3]The Hepatitis C Trust, London, United Kingdom; [4]London School of Hygiene and Tropical Medicine, London, United Kingdom; [5]University of Antwerp, Viral Hepatitis Prevention Board, Centre for the Evaluation of Vaccination, Vaccine and Infectious Diseases Institute, Antwerp, Belgium; [6]Inserm U988/CNRS UMR 8211/EHESS/Paris Descartes University, Cermes 3, France; [7]Leberhilfe Projekt gUG, Germany; [8]Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, Ljubljana, Slovenia; [9]European Liver Patients' Association, Brusells, Belgium*

Email: Jeffrey.Lazarus@isglobal.org

Background and Aims: Fifteen million people are infected with chronic viral hepatitis C in the WHO European Region, leading to 112,500 deaths per year. With the advent of direct-acting antiviral treatment regimens, eliminating hepatitis C by 2030 is feasible. The aim of this study was to examine patient group perspectives on whether European countries have national policies in place to support necessary scale-up of hepatitis C treatment.

Methods: The 2017 Hep-CORE study was carried out in 25 European countries with one patient group serving as the respondent for each country. It repeated 11 items from the 2016 survey, including questions about an approved national hepatitis C strategy, treatment in non-hospital settings and prisons, and restrictions on direct-acting antiviral access. Data were analysed descriptively and compared to 2016 findings.

Results: In 2017, an approved national hepatitis C strategy and/or action plan was reported in 12 countries (48%) (Table 1). The prior year, 11 countries (44%) reported having a strategy. In both years, respondents from five countries (20%) reported that hepatitis C

treatment was available in non-hospital settings. Treatment was reported to be available in prisons in 17 countries (68%) in 2016 and 18 countries (72%) in 2017. In 2016 and 2017 respectively, three countries (12%) and seven countries (28%) reported no restrictions on access to direct-acting antivirals (data not shown). The most frequently reported restrictions in both years were fibrosis level and current injecting drug use.

Table 1: Hepatitis C treatment policies reported by patient groups in 25 European countries, 2016–17

	Number of countries (%) 2016	2017
Written national strategy and/or action plan	11 (44%)	12 (48%)
Treatment in non-hospital settings	5 (20%)	5 (20%)
Treatment in prisons	17 (68%)	18 (72%)
Fibrosis level: restriction on access to direct-acting antivirals	18 (72%)	13 (52%)
Current injecting drug use: restriction on access to direct-acting antivirals	13 (52%)	8 (32%)

Conclusions: In 2017, patient groups reported that less than half of the 25 study countries had a hepatitis C strategy and/or action plan, despite this being an essential indicator of national readiness to address the disease. There were slight improvements in treatment policies from 2016 to 2017, most notably regarding restrictions on direct-acting antiviral access. In order to reach WHO hepatitis C elimination goals, many European Member States must still make key policy changes.

THU-052

Heterogeneity in hepatitis C virus treatment prescribing and uptake in Australia: a geospatial analysis of a year of unrestricted treatment access

N. Scott[1,2], S. Hainsworth[1], R. Sacks-Davis[1,2], A. Pedrana[1,2], J. Doyle[1,3], M. Hellard[1,2,3]. *[1]Burnet Institute, Disease Elimination, Melbourne, Australia; [2]Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; [3]The Alfred and Monash University, Department of Infectious Diseases, Melbourne, Australia*
Email: Nick.Scott@burnet.edu.au

Background and Aims: Direct-acting antiviral (DAA) treatments became available for all people living with hepatitis C virus (PLHCV) in Australia in March 2016, with an estimated 20% of PLHCV treated in the first year. However, the geographical distribution of treatment uptake and the impact of non-specialists' ability to prescribe DAAs is not clear. We assess how treatment rates, the percentage of PLHCV treated and the proportion of treatments prescribed by specialists varies by geographical area.
Method: DAA treatment initiation data from the Australian Pharmaceutical Benefits Scheme were analysed for the period 1 March 2016 to 30 June 2017 across Australia's 338 Statistical Area 3 (SA3) geographical areas. Statistical regression models were used to test for correlations between the population demographics and healthcare service coverage of geographical areas and (a) their associated treatment rates; and (b) the proportion of prescriptions written by specialists compared to non-specialists.
Results: Five percent of SA3s (18/338) had no treatment initiations. Among those that did, there were a median of 76 (IQR 35–207; range 4–3834) treatment initiations per 100,000 population, corresponding to an estimated median of 7.9% (IQR 2.9–23.6%; range 0–100%) of PLHCV treated within each area. Major cities, areas of socio-economic advantage and areas with a lower proportion of the population born overseas had higher per-capita treatment rates with 54% (24059/44382) of treatment initiations prescribed by liver/HCV specialists. Prescribing patterns varied by geographical area and by prescriber type; of the 320 areas with any treatment initiations, 163 areas (51%) had prescription written by non-specialists only. For the 157 areas with some specialist prescribers, a median 60.0% (IQR 37.5–78.2%) of prescriptions were written by specialists. As areas became more regional, had a higher proportion of indigenous Australians or a higher proportion of people born overseas, non-specialist prescribing increased.

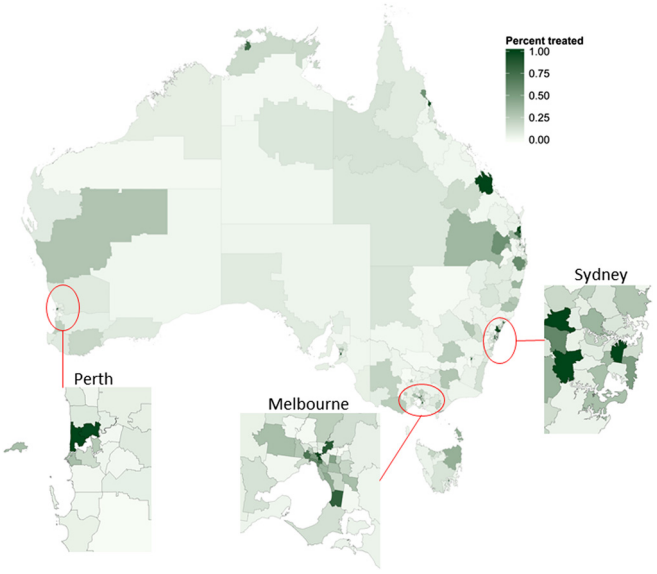


Figure: Percentage of people living with HCV who commenced DAA treatment from each of Australia's Statistical Area 3 geographical regions.
Conclusion: Despite national-level treatment uptake of 20% of PLHCV, more than half of SA3s may have treated less than 8% of PLHCV. Non-specialist prescribing appears to be significantly facilitating DAA uptake in non-metropolitan areas and among marginalised communities.

THU-053

Moderate and severe renal impairment in European CHB patients treated with TDF or ETV: a 7-year retrospective cohort study in 490 patients (on behalf of the ReCoRd investigators group)

P. Lampertico[1], J.F. Flaherty[2], M. Op Den Brouw[3], I.L. Rose[4], I. Faghmous[5], C. Phulpin[6], A. Van Troostenburg[7], H. Ramroth[5]. *[1]Fondazione IRCCS Ca Grande Ospedale Maggiore Policlinico, Unita Operativa Complessa, Milano, Italy; [2]Gilead Sciences, Clinical Research, Foster City, United States; [3]Gilead Sciences, Medical Affairs, Foster City, United States; [4]Gilead Sciences, Medical Safety Science, Foster City, United States; [5]Gilead Sciences, DSPH/Epidemiology, Uxbridge, United Kingdom; [6]Gilead Sciences, Clinical Operations, Uxbridge, United Kingdom; [7]Gilead Sciences, Exec Drug Safety, Great Abington, United Kingdom*
Email: Heribert.Ramroth@gilead.com

Background and Aims: There are limited data on the safety and efficacy of tenofovir disoproxil fumarate (TDF) and entecavir (ETV) in adult patients with moderate and severe renal impairment and dose adjustments of TDF and ETV are recommended in patients with decreasing creatinine clearance (eGFR < 50 ml/min) when the potential benefits of treatment are considered to outweigh the potential risks. We conducted a European retrospective, observational study of the safety, including renal safety, and effectiveness of TDF or ETV in chronic hepatitis B (CHB) patients with moderate or severe renal impairment.
Method: This study was conducted at 54 clinical sites in France, Germany, Italy, Spain and UK in CHB monoinfected patients 18 years and older who had experienced at least one occurrence of moderate or severe renal impairment with creatinine clearance (CrCL) (by Cockcroft Gault formula) of 20–60 mL/min, while concomitantly receiving treatment with either TDF or ETV at any time between April 2008 and December 2015. Adverse events (AEs) of special interest (AESI) included proximal tubulopathy (PRT) and/or renal tubular

dysfunction (RTD), renal AEs leading to withdrawal of treatment, renal serious AEs (SAEs), and decline in renal function if reported as a non-serious AE. An inverse probability treatment weighted (IPTW) approach was used to compare both study arms.

Results: 490 patients were enrolled in the study (67% TDF; 33% ETV) with a mean observation period of 3.3 years. Age and sex distributions were similar with 68% of patients being male. In the TDF and ETV groups, 30% and 58% of patients were treatment naïve, respectively. At the start of the observation period, 38% of TDF) and 23% of ETV patients reported clinical evidence of cirrhosis; evidence of decompensated liver disease was reported in 5% and 8% of patients, respectively; approximately 90% of patients were HBeAg negative, and renal impairment was present in 40% and 57% of TDF and ETV patients, respectively. Of patients receiving TDF, 48% had received a reduced dose at some point in the treatment course compared with 27% ETV-treated patients. AESIs were observed in 41 TDF patients (13%) compared with 11 (7%) ETV patients: Hazard ratio 1.8 (95% CI 0.9–3.6) (IPTW analyses). Only TDF were reported to have AESI of PRT or RTD (n = 11) and 26 TDF patients required treatment discontinuation. At study entry, 88% and 73% of TDF and ETV patients were virally suppressed (HBV DNA <69 IU/mL); there were no differences in the rates of virological suppression over time between both study arms.

Conclusion: In this retrospective cohort of patients with moderate to severe renal impairment only TDF patients were reported to have PRT or RTD or required treatment discontinuation. This data supports the need for newer treatments for CHB patients with renal impairment.

THU-054

The time trend of proportion and mortality rate of admissions associated with acute respiratory illness in cirrhotic patients with diverse ethnicity and socioeconomic status: an analysis on the U.S. National Inpatient Sample

B. Zou[1], Y.H. Yeo[1], D. Jeong[1], E. Sheen[1], H. Park[2], D.H. Lee[1], G. Garcia[1], M. Nguyen[1]. *[1]Stanford University Medical Centre, Division of Gastroenterology and Hepatology, Palo Alto, United States; [2]University of Florida College of Pharmacy, Pharmaceutical Outcomes & Policy, United States*

Email: mindiehn@stanford.edu

Background and Aims: Liver cirrhosis has become a major public health concern in the U.S. Cirrhotic patients might be more vulnerable to acute respiratory illness (ARI). The study aimed to explore the time trend of the prevalence and mortality rate of ARI-associated admissions in cirrhotic patients.

Method: A retrospective study was performed using the National Inpatient Sample database. We investigated the time trend of the proportion and mortality of ARI associated hospital admissions in patients with cirrhosis and compare the inpatient mortality rates for admissions with and without ARI from 2005 to 2011 in this population. We also performed subgroup analysis for the year 2011 by race and ethnicity, cause of cirrhosis and income levels.

Results: A total of 880,005 hospitalizations associated with cirrhosis were identified between 2005 and 2011. The total number of admissions associated with cirrhosis increased from 102,158 to 160,246 during 2005–2011. The proportion of ARI-related admissions witnessed an overall upward trend from 2005 (5.47%) to 2011 (7.09%). There was a decreasing trend for the mortality rates of both ARI-related and non-ARI-related admissions, but the mortality rate of ARI admissions was consistently higher than that of non-ARI (Figure). In 2011, the proportion of ARI-related admissions was significantly higher in Whites compared to Hispanics (7.48% vs. 5.36%, p < .0001). By aetiologies, the prevalence of ARI-related admissions was highest in non-alcoholic fatty liver disease (NAFLD) (8.16%) followed by hepatitis B virus (7.86%), hepatitis C virus (7.58%), other liver disease (7.41%) and alcoholic liver disease (ALD) (5.86%) (p < 0.0001). However, inpatient mortality rates for admissions associated with ARI was highest in ALD (11.94%) and lowest in NAFLD (4.62%) (p < 0.0001). Furthermore, the proportion of ARI-related hospitalizations was significantly higher in the lower quartile of the income levels (7.75% vs. 6.20%, p < 0.0001).

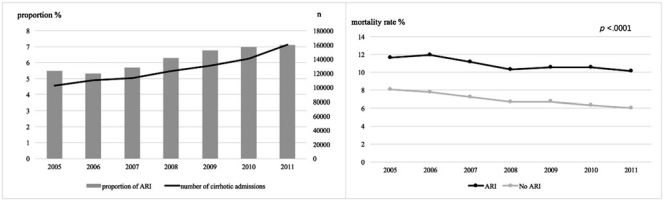


Figure: The time trend of number of admissions in patients with cirrhosis, proportion of ARI among these admissions and mortality rates for admitted cirrhotic patients with and without ARI from 2005 to 2011.

Conclusion: There was an increasing trend of proportion of ARI-related admissions between 2005 and 2011. In addition, higher mortality rates were observed in ARI-associated admissions compared to admissions without ARI. Physicians should consider preventive measures to curtail the disease burden of ARI in cirrhotic patients, especially in those with ALD, NAFLD and low-income.

THU-055

The cost-effectiveness of needle and syringe provision in preventing transmission of Hepatitis C virus in people who inject drugs

Z. Ward[1], S. Sweeney[2], L. Platt[2], L. Guinness[2], L. Maher[3], V. Hope[4], M. Hickman[1], J. Smith[5], R. Ayres[6], I. Hainey[7], T. Chamberlain[8], P. Vickerman[1]. *[1]University of Bristol; [2]London School of Hygiene & Tropical Medicine; [3]University of New South Wales, Kirby Institute; [4]Liverpool John Moores University; [5]Public Health Wales; [6]Bristol Drugs Project; [7]Cair Scotland; [8]Addaction*

Email: zoe.ward@bristol.ac.uk

Background and Aims: Over 80% of Hepatitis C virus (HCV) infections in the United Kingdom (UK) are acquired by people who inject drugs (PWID). Needle and syringe programmes (NSP) are a major component of most harm reduction strategies and a recent Cochrane systematic review has shown high coverage needle and syringe provision (HCNSP defined as obtaining more than one sterile needle and syringe per injection reported) can halve the risk of HCV acquisition amongst PWID. This study evaluated the impact and cost-effectiveness of current levels of NSPs in preventing HCV transmission in the UK and determined the cost-effectiveness of HCNSP when HCV treatment is scaled up to reach the World Health Organization (WHO) target of reducing HCV incidence by 90% by 2030.

Method: Three UK settings with different HCV antibody prevalence were described using a dynamic transmission model: Bristol (60%), Dundee (46%) and Walsall (32%). The model estimated the prevention benefits achieved by the status quo scenario (HCNSP coverage Bristol 56%, Walsall 28%, Dundee 49%) from 2016 compared to a counterfactual scenario where the effectiveness of HCNSP on HCV transmission risk was removed for 10 years. A healthcare perspective was taken with the health benefits measured in quality adjusted life years (QALY). Costs and QALY's were discounted at 3.5% over the 50-year time horizon. A willingness to pay (WTP) threshold of £20,000 per QALY was used for the incremental cost-effectiveness ratio (ICER) and a scenario analysis whereby direct acting antiviral HCV treatment numbers were increased to achieve the WHO elimination targets was carried out.

Results: Compared to removing NSP for 10 years, current HCNSP is associated with costs of £454,711 and 502 QALYs gained over 50 years in Bristol, cost savings of £972,074 and 195 QALYs in Dundee and costs of £398,592 and 192 QALYs in Walsall. The ICER was cost saving in Dundee and £906 and £2,076 per QALY in Bristol and Walsall respectively. Treatments per 1000 PWID need to be scaled up in

Bristol (from 9 to 43) and Walsall (from 2 to 18) to reach the WHO elimination targets with no treatment scale up needed in Dundee. Scaling up treatments resulted in NSP being cost saving in Bristol and remaining cost-effective in Walsall with an ICER of £9330 per QALY.
Conclusion: NSPs are highly likely to be cost-effective at the £20,000 per QALY threshold, and could be cost saving in many settings. As HCV treatment is scaled up NSPs remain cost-effective.

THU-056
Population health and economic impact of reaching the WHO 2030 targets in chronic hepatitis B diagnosis and treatment in the United States

M. Toy[1], D. Hutton[2], S. So[1]. [1]*Stanford University School of Medicine, Surgery, Palo Alto, United States;* [2]*University of Michigan School of Public Health, Health Management and Policy, Ann Arbor, United States*
Email: mtoy@stanford.edu

Background and Aims: In the U.S., an estimated 34% of the people living with chronic hepatitis B (CHB) were diagnosed and 45% were on treatment if medically indicated in 2015. The aim of this study is to assess the health and economic impact in achieving the WHO targets of 90% CHB diagnosed and 80% on treatment by 2030. We also evaluated the impact if the targets can be achieved by 2025.
Method: A Markov model was developed to simulate long-term outcomes of CHB (risks for cirrhosis, hepatocellular carcinoma (HCC), and CHB-related death) under three scenarios: current practice (34% diagnosed, 33% linked to care and 45% treated); a steady increased rate of screening, care and treatment to reach the WHO targets by 2030, and an accelerated pace to reach the targets by 2025. We used age-group and gender-specific disease progression estimates. We simulated an open cohort of foreign-born individuals including the population currently living in the U.S. as well as U.S. Census projected migration of people from high prevalence areas over a 50-year time period. We included screening costs, costs of linking patients to care, and costs of treatment to assess the investments required.
Results: Reaching the WHO target of 90% CHB diagnosed by 2030 will involve screening of 14.5 million foreign born individuals from endemic countries to diagnose 870,000 new CHB cases at the cost of $1.3 billion over a 15 year period. This effort will be cost-effective compared to current practice ($45,583 per QALY). Most of the total costs will be spent on treatment, as compared to screening and linkage to care. This approach will reduce 34% of HCC, 50% of decompensated cirrhosis, and 36% of CHB-related deaths. Annual screening costs could be substantial, peaking at $141 or $105 million, depending on the time line of 10 or 15 years. Once the peak is reached (2025 or 2030), the cost of screening will drop (Figure). Accelerating the pace of screening to achieve the WHO targets by 2025 would be even more cost-effective ($44,610 per QALY) and would result in more health gains (reduce HCC by 43%, decompensated cirrhosis by 63%, and CHB-related deaths by 47%).
Conclusion: Increasing CHB screening, care and treatment to reach the WHO targets by 2030 or at an accelerated pace by 2025 are both cost effective in the U.S. and would avert 36–47% of CHB-related deaths.

THU-057
Quantifying the impact of achieving the World Health Organization global health sector strategy goals for hepatitis C in the EURO region

S. Robbins, S. Blach, S. Brandon, C. Estes, I. Gamkrelidze, H. Nde, D. Razavi-Shearer-Spink, J. Schmelzer, H. Razavi. *Center for Disease Analysis Foundation, Polaris Observatory, Lafayette, United States*
Email: srobbins@cdafound.org

Background and Aims: The EURO region has one of the highest reported prevalence rates of Hepatitis C virus (HCV), with an estimated prevalence of 1.5%, or approximately 14 million infections in 2015. The development of direct acting anti-viral (DAA) therapy drastically shifted the current treatment paradigm for the Hepatitis C virus (HCV) from disease management to elimination. An understanding of disease burden is necessary to develop evidence-based public health strategies for elimination of HCV. We forecast the current and future disease burden of HCV in the European region and developed a strategy to achieve the World Health Organization (WHO) Global Health Sector Strategy (GHSS) Goals for Hepatitis by 2030.

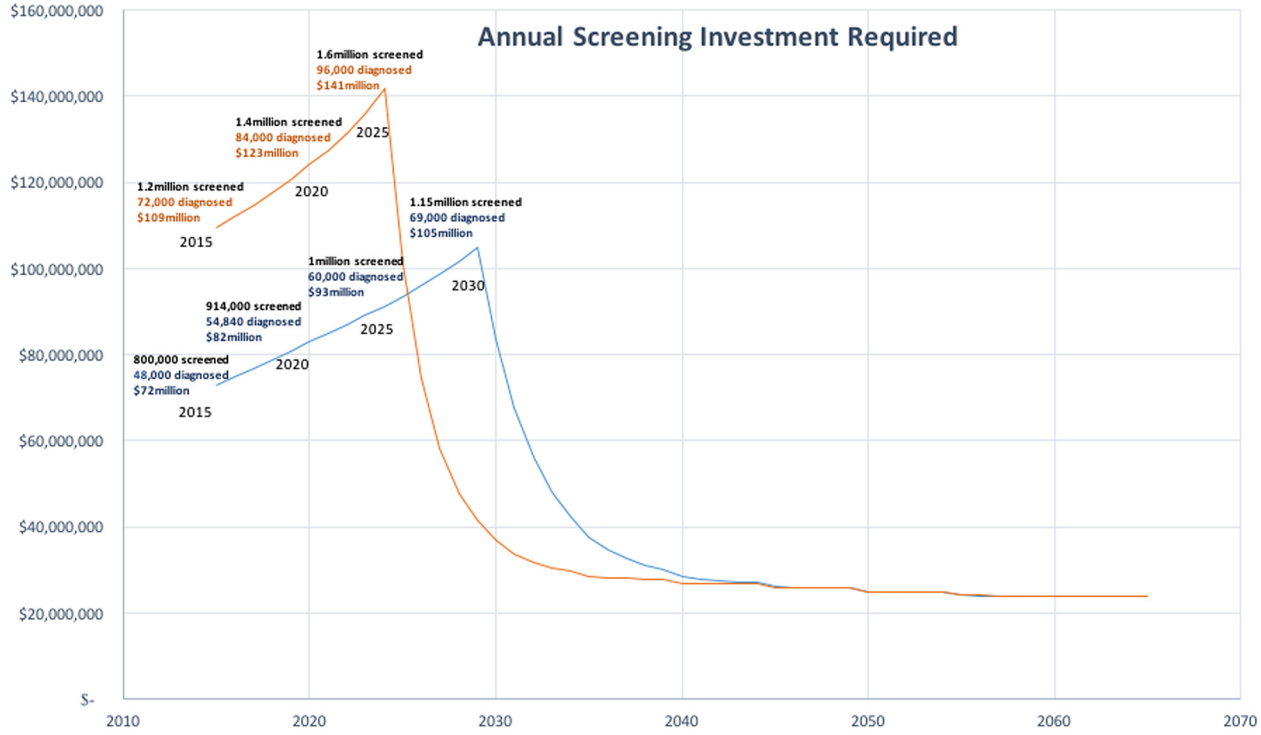


Figure: (abstract: THU_056)

Method: 53 EURO-country specific models were built and regional averages were applied to country populations when country-specific data was not available. Country estimates were then aggregated into a regional disease burden model. This disease progression model was used to quantify the size of the HCV-infected population by HCV-sequelae from 2016 through 2030.

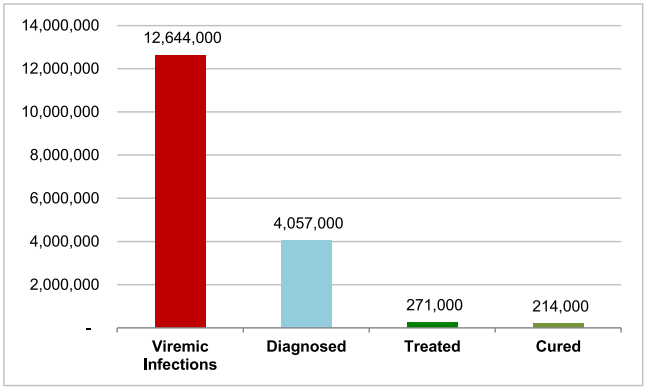


Figure 1: EURO Cascade of Care, 2016.

Results: In 2016, there were an estimated 12.6 million viremic infections in the EURO region, and 60% of all infections were found in those born between 1949 and 1989. Given the current standard of care over the next fifteen years, the total HCV-infected population in the EURO region is expected to increase by an estimated 1% by 2030. Liver related morbidity and mortality is forecasted to increase 40–45% by 2030. To achieve the GHSS goals, a significant increase in total number of patients screened and linked to care is necessary. The number of individuals diagnosed annually would need to increase to 800,000 by 2022 and the number of patients treated annually to 900,000 patients by 2025. Viremic infections are forecasted to decline by 75% by 2030; while decompensated cirrhosis cases, hepatocellular carcinoma cases, and liver related deaths will decline by 70–75% by the same year.

Conclusion: Total viremic infections are expected to increase by 1% in the EURO region over the next two decades. The WHO Goals can be achieved if drastic increases in the number of diagnosed and linked-to-care patients are met. Targeted screening strategies coupled with increased access to DAA therapy are needed to achieve these goals.

THU-058
Quantifying the impact of achieving the World Health Organization global health sector strategy goals for hepatitis C in the African Region

S. Robbins, S. Blach, S. Brandon, C. Estes, I. Gamkrelidze, H. Nde, D. Razavi-Shearer-Spink, J. Schmelzer, H. Razavi. *Center for Disease Analysis Foundation, Polaris Observatory, Lafayette, United States*
Email: srobbins@cdafound.org

Background and Aims: The development of direct acting anti-viral (DAA) therapy drastically shifted the current treatment paradigm for the Hepatitis C virus (HCV) from disease management to elimination. An understanding of disease burden is necessary in order to create evidence-based public health strategies for elimination of HCV. The AFRO region has one of the highest incidence rates of Hepatitis C worldwide. In 2015, approximately 136,000 deaths, or 10% of the total 399,000 reported deaths due to HCV that year, occurred in the AFRO region. We forecast the current and future disease burden of HCV in the African region and developed a strategy to achieve the World Health Organization (WHO) Global Health Sector Strategy (GHSS) Goals for Hepatitis by 2030.
Method: 35 AFRO-country specific models were built and regional averages were applied to country populations when country-specific data was not available. Country estimates were then aggregated into a regional disease burden model. This disease progression model was used to quantify the size of the HCV-infected population by HCV-sequelae from 2016 through 2030.
Results: In 2016, there were an estimated 11.6 million viremic infections in the AFRO region, and more than 65% of all infections were found in those born between 1953 and 1988. Relative to the current standard of care over the next fifteen years, the total HCV-infected population in the AFRO region is expected to decrease by less than 10% by 2030. Total cases of hepatocellular carcinoma (HCC) are

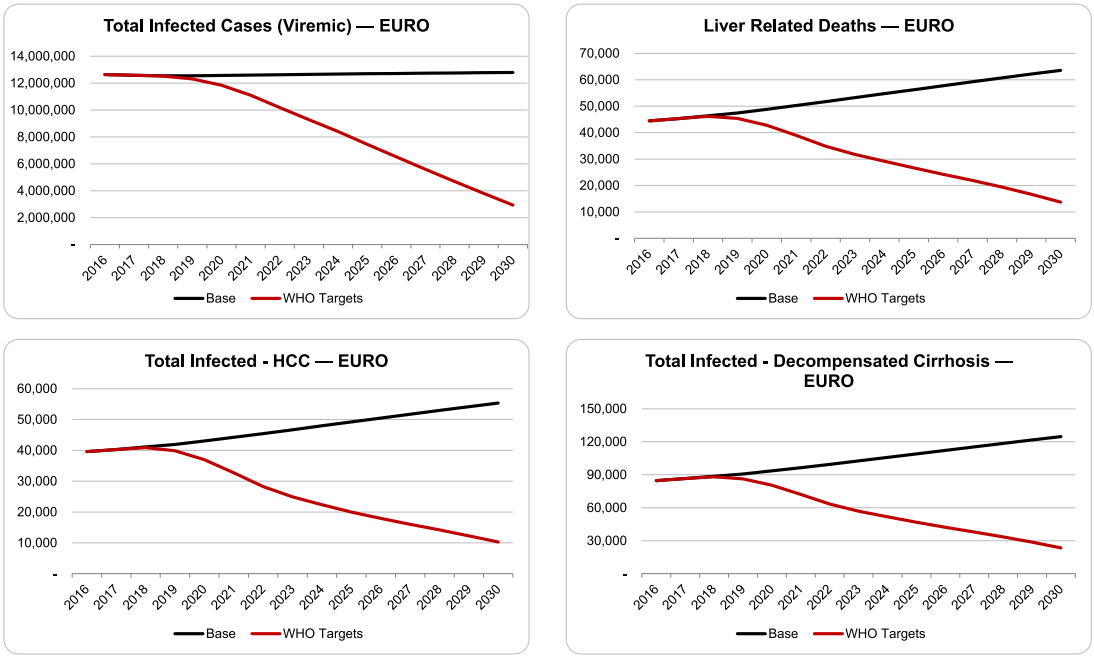


Figure 2: (abstract THU-057) Liver Related Morbidity and Mortality by Scenario, 2016–2030.

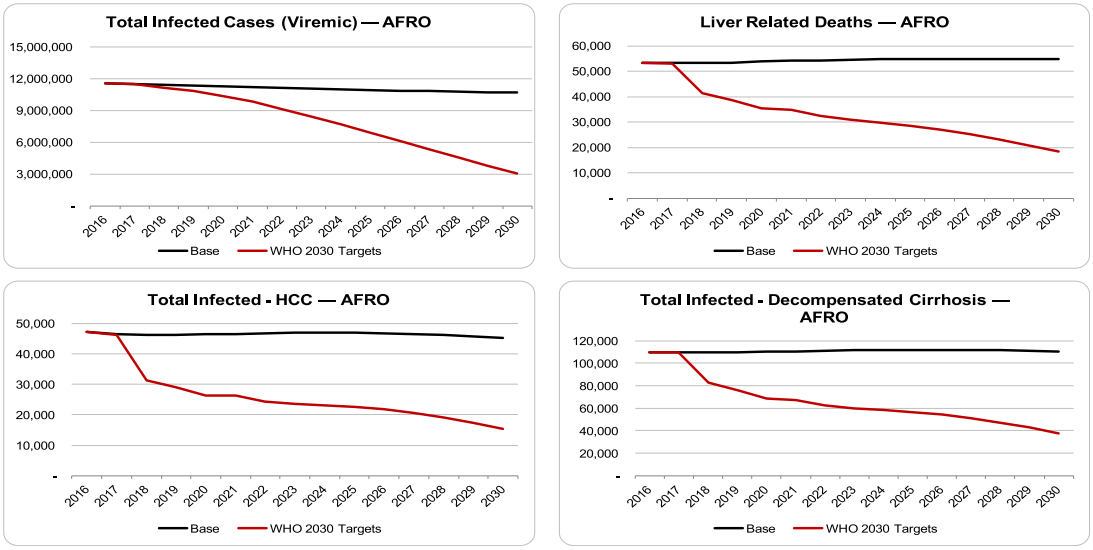


Figure 2: (abstract THU-058) Liver Related Morbidity and Mortality by Scenario, 2016–2030.

expected to decline by 5% over the next 15 years, while decompensated cirrhosis cases and liver related mortality will increase 1–2% by 2030.

To achieve the GHSS goals, a significant increase in total number of patients screened and linked to care is necessary. The number of individuals diagnosed annually would need to increase to 1.3 million by 2022 and the number of patients treated annually to 700,000 patients by the same year. Under this scenario, total viremic infections are forecasted to decline by 75% from 2015 to 2030; while decompensated cirrhosis, HCC, and liver related deaths will decline by 65% by the same year.

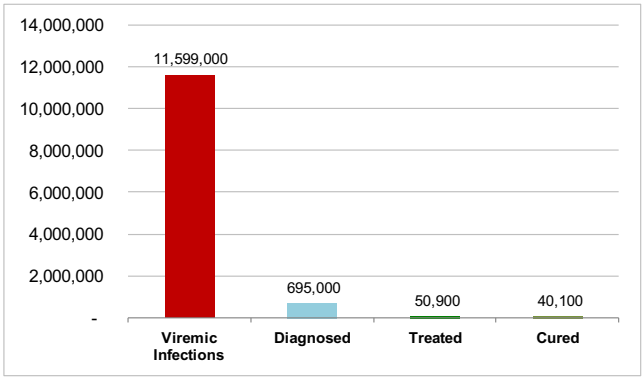


Figure 1: AFRO Cascade of Care, 2016.

Conclusion: Total viremic infections are expected to decline minimally in the African region over the next two decades. The WHO Goals can be achieved if drastic increases in the number of diagnosed and linked-to-care patients are met. Targeted screening strategies coupled with increased access to DAA therapy are needed to achieve these goals.

THU-059

Forecasting liver disease burden based on a real life cohort of the linked to care patients in Italy. Does the 'underwater portion of the iceberg' matter to reach the WHO HCV eliminating goals in the high HCV prevalent countries?

S. Robbins[1], L. Kondili[2], S. Blach[1], I. Gamkrelidze[1], A. Zignego[3], M. Brunetto[4], G. Raimondo[5], G. Taliani[6], A. Iannone[7], F.P. Russo[8], T.A. Santantonio[9], M.G. Zuin[10], L. Chessa[11], P. Blanc[12], M. Puoti[13], M. Vinci[14], E.M. Erne[15], M. Strazzabosco[16], M. Massari[17], P. Lampertico[18], M.G. Rumi[19], A. Federico[20], C. Ferrari[21], A. Ciancio[22], G. Borgia[23], P. Andreone[24], N. Caporaso[25], M. Persico[26], D. Ieluzzi[27], A. Gori[28], A. Gasbarrini[29], C. Coppola[30], G.B. Gaeta[31], A. Andriulli[32], S. Montilla[33], H. Razavi[1], M. Melazzini[33], S. Vella[2], A. Craxi[34]. *[1]Center for Disease Analysis, Polaris Observatory, Lafayette, United States; [2]Istituto Superiore di Sanità, Center for Global Health, Roma, Italy; [3]Azienda Ospedaliero-Universitaria Careggi, Firenze, Italy; [4]Azienda Ospedaliero-Universitaria Pisa, Gastroenterology; [5]University Hospital of Messina, Internal Medicine, Messina, Italy; [6]Policlinico Umberto I, Infectious Disease, Roma, Italy; [7]Università degli Studi di Bari Aldo Moro, Gastroenterology, Bari, Italy; [8]University Hospital Padua, Gastroenterology, Padua, Italy; [9]Ospedali Riuniti, Infectious Disease, Foggia, Italy; [10]Ospedale San Paolo, Gastroenterolgy/Hepatology, Milano, Italy; [11]Policlinico Universitario Monserrato, Liver Unit, Monserrato, Italy; [12]Ospedale Santa Maria Annunziata, Infectious Disease, Ponte a Niccheri, Bagno a Ripoli, Italy; [13]Niguarda Cà Granda Hospital, Infectious Disease, MIlano, Italy; [14]Ospedale Niguarda, Hepatitis Center, Milano, Italy; [15]Azienda Ospedaliero-Universitaria Padova, Infectious Disease; [16]Ospedale San Gerardo, Hepatology, Monza, Italy; [17]Santa Maria Nuova, Infectious Disease, Santa Maria Nuova, Italy; [18]IRCCS Ca' Granda Ospedale Maggiore Policlinico, Gatroenterology/Hepatology, Milano, Italy; [19]Ospedale San Giuseppe, Gastroenterolgy/Hepatology, Milano, Italy; [20]Università della Campania "L. Vanvitelli", Gastroenterolgy/Hepatology; [21]Università degli Studi di Parma, Infectious Diseases and Hepatology, Parma, Italy; [22]Ospedale Molinette, Gastroenterology, Torino, Italy; [23]Università Federico II, Infectious Disease, Napoli, Italy; [24]Alma Mater Studiorum - Università di Bologna, Hepatology, Bologna, Italy; [25]Università degli Studi di Napoli Federico II, Gastroenterology, Napoli, Italy; [26]Università degli Studi di Salerno, Internal Medicine and Hepatology, Fisciano, Italy; [27]Azienda Ospedaliero-Universitaria Verona, Gastroenterology; [28]Ospedale San Gerardo, Infectious Disease, Monza, Italy; [29]Università Cattolica del Sacro Cuore, Internal Medicine, Gastroenterology and Hepatology, Milano, Italy; [30]Ospedale Gragnano, Hepatology, Gragnano, Italy; [31]Università della Campania, Infectious*

Diseases, Infectious Diseases, Naples, Italy; [32]Ospedale Casa Sollievo della Sofferenza, Gastroenterology, San Giovanni Rotondo, Italy; [33]Agenzia Italiana del Farmaco, Roma; [34]Università degli Studi di Palermo, Gastroenterology, Palermo, Italy
Email: sarah.robbins@centerforda.com

Background and Aims: Recent advances in direct acting antiviral treatment of Hepatitis C virus (HCV) has reinvigorated public health initiatives aimed at identifying affected individuals. We forecasted the impact of different disease management scenarios on viremic infections, liver related morbidity and mortality through 2030 in order to identify a potential scenario to achieve the World Health Organization (WHO) Targets.
Method: Using data from the Italy PITER cohort and from the Italian Medicines Agency Monitoring Registry, we modelled the impact on HCV disease burden according to different linkage to care scenarios.
Results: There were an estimated 849,000 viremic individuals in 2015 in Italy. Considering the 2016 standard of care, liver related mortality is expected to decline by 65%, achieving the WHO mortality target. Under the 40% linked to care scenario, the impact on disease burden would be significant; however eligible patients to be treated will be depleted by 2025, resulting in a treatment rate decline moving forward. A targeted screening strategy in 2020–2025 in those individuals born in the years 1948–1978 could aliment the pool of diagnosed and treated patients by finding approximately 80% of asymptomatic infected F0-F3 cases. Under the PITER 60% linked to care scenario, viremic infections will decline by 70% by 2030, but the patients eligible for treatment are expected to run out in 2028. If treatment is to be maintained at 33,700 through 2028, a screening strategy focusing on individuals born in the years 1958–1978 could be useful to capture 60% of eligible infected patients for treatment. Under the PITER 80% linked to care scenario, total viremic infections are forecasted to decline by 80%, by 2030. The pool of eligible patients to be treated is expected to be depleted by 2031 and screening limited to those born in the years 1968–1978, which would capture 25% of infected cases, would be sufficient to sustain treatment at levels required to achieve the WHO decreased prevalence target.

Conclusion: Due to DAA access policies, Italy is meeting the WHO target of a 65% reduction in HCV liver related mortality by 2030, without requiring further interventions. In the three PITER linkage to care scenarios, the eligible pool of patients to be treated will run out between 2025 and 2031, leaving a significant proportion of infected individuals undiagnosed and without access to care. Targeted screening strategies are required in order to achieve the overall WHO targets.

THU-060

Outcomes of delaying hepatitis C treatment in persons who inject drugs: Dynamic modeling of C-EDGE CO-STAR trial cohort

J. Chhatwal[1], S. Samur[1], K. Li[2], A. Spaulding[3], C. Nwankwo[4]. *[1]Harvard Medical School, Massachusetts General Hospital, Boston, United States; [2]The University of Texas Health Science Center at Houston, Houston, United States; [3]Rollins School of Public Health, Emory University, Atlanta, United States; [4]Merck & Co., Inc., United States*
Email: jagchhatwal@mgh.harvard.edu

Background and Aims: Hepatitis C virus (HCV) mortality, morbidity and incidence continue to increase globally among persons who inject drugs (PWIDs). Oral direct-acting antivirals (DAAs) have been shown to be highly effective for treating HCV in PWID. However, treatment rates remain low because of concerns about re-infection and unknown long-term benefits of treatment. Our objective was to evaluate outcomes of not treating HCV versus immediate treatment to PWID with potential re-infection.
Method: We used a dynamic agent-based model, *TapHCV* (*treatment as prevention of HCV*), that simulated the natural history of HCV progression and incorporated transmission among PWID, treatment with oral DAAs, and re-infection after treatment. The natural history of HCV in the model was validated with multiple observational studies. The baseline population in the model was based on C-EDGE CO-STAR clinical study, a multinational trial of HCV treatment of PWID. Sustained virologic response (SVR) rates and re-infection rates were extracted from the C-EDGE CO-STAR trial using 3-year follow-up data. We simulated two scenarios—no treatment and immediate treatment of PWID. Under "no treatment" scenario, patients' disease

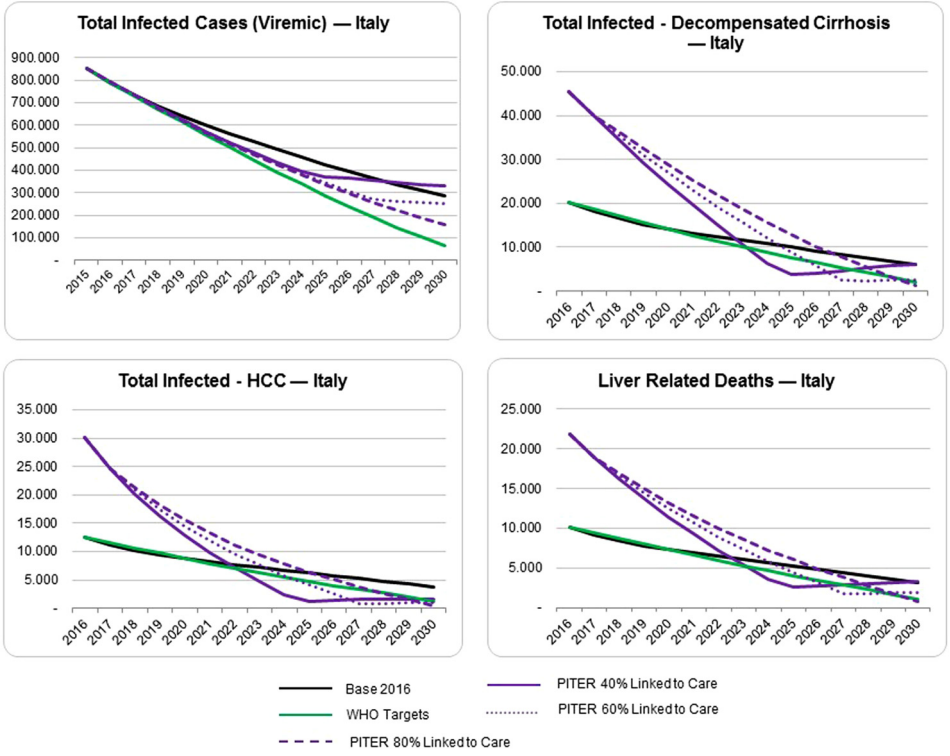


Figure: (abstract: THU_059)

continued to progress and HCV-positive PWID could infect non-HCV PWID. In "treatment" scenario, PWID could achieve SVR and get re-infected who could progress further to advanced stages of HCV. We ran our model for 6 years to compare the long-term outcomes.
Results: Among 10,000 treated PWID, it was estimated that 440 would get re-infected in 6 years. Despite this, compared with no treatment, treating 10,000 PWID with DAAs would prevent approximately 460 new infections in non-HCV PWIDs, 620 cases of decompensated cirrhosis, 580 hepatocellular carcinomas, 60 liver transplantations, and 590 liver-related deaths in 6 years.
Conclusion: Even after accounting for re-infections, immediate treatment of PWID offers substantial benefits between the time of treatment and re-infection. Providing HCV treatment with oral DAAs to PWID could reduce ongoing HCV transmission and HCV-associated diseases, both in treated PWID and non-HCV PWID. Such a strategy could also aid in HCV elimination efforts.

THU-061
Improved health outcomes from hepatitis C treatment scale-up in Spain's prisons: A cost-effectiveness study

J. Chhatwal[1], S. Samur[1], K. Li[2], T. He[3], S. Llerena[4], C. Cobo[5], T. Ayer[6], M. Roberts[7], A. Spaulding[8], J. Crespo[4]. *[1]Harvard Medical School, Massachusetts General Hospital, Boston, United States; [2]The University of Texas Health Science Center at Houston, Department of Biostatistics, Houston, United States; [3]Peking Union Medical College and Chinese Academy of Medical Sciences, Beijing, Bejing, China; [4]Marques de Valdecilla University Hospital, Santander, Spain; [5]El Dueso Penitentiary Centre, Santoña, Spain; [6]Georgia Institute of Technology, Atlanta, United States; [7]University of Pittsburgh, United States; [8]Rollins School of Public Health, Emory University, Atlanta, United States*
Email: jagchhatwal@mgh.harvard.edu

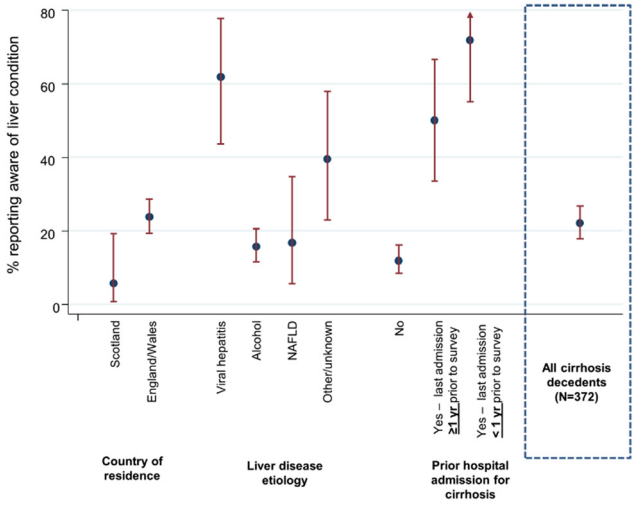
Background and Aims: Hepatitis C virus (HCV) infection is 15 times more prevalent among prison inmates in Spain compared with the general population. Direct-acting antivirals (DAAs) for HCV treatment can potentially reduce ongoing transmission, and eliminate HCV. Spain initiated an innovative pilot program, JAILFREE-C, to screen and treat HCV in prisons. Our aim was to identify a cost-effective strategy to scale-up HCV treatment to all Spain's prisons.
Method: We used a dynamic agent-based microsimulation model that considered HCV transmission, natural history of HCV progression, screening, treatment with oral DAAs, and simulation of prison and general population dynamics. The baseline population in the model represented Spain's population in the community and prisons in all regions stratified by age, prevalence of HCV, health states, HCV genotype, and injection drug use status. SVR rates and patient demographics in prisons were informed by published studies, including the JAILFREE-C study. Treatment capacity in prisons was assumed to be 2000/year. The long-term disease and cost outcomes of the following strategies in prisons were evaluated: (1) no treatment; (2) prioritize treatment of inmates by their health states (F4, F3, F2, F1, F0) irrespective of the prison/region; (3) prioritize inmates in prisons high HCV prevalence; and (4) prioritize inmates in prisons with high number of HCV-infected inmates.
Results: Under the current limited resources in prisons, scaling-up treatment by prioritizing patients based on their disease stage would yield the highest quality-adjusted life years (QALYs) – 7186 additional QALYs but cost €98.24 million more than that under no treatment. This strategy was also the most cost-effective strategy, yielding the incremental cost-effectiveness ratio of €5800/QALY when compared with the next effective strategy. Compared with no treatment, this strategy would prevent 70 new incident cases of HCV, 270 cases of decompensated cirrhosis, 450 cases of hepatocellular carcinoma and 670 HCV-related deaths in the next 25 years in Spain. The majority of these benefits would occur outside of prisons in the general community.
Conclusion: Scaling-up HCV treatment with DAAs to all prisons in Spain would reduce ongoing HCV transmission and HCV sequelae burden. Among the strategies considered, prioritizing patients with advanced disease stage in all prisons, irrespective of the region, HCV prevalence or size of the prison would be the most cost-effective strategy.

THU-062
Poor awareness of liver disease shortly before cirrhosis death: findings from a large community cohort in the UK

H. Innes[1], E. Aspinall[1], J. Morling[2], D. Goldberg[3], N. Guha[4,*], S. Hutchinson[1,*]. *[1]Glasgow Caledonian University, School of Health and Life Sciences, Glasgow, United Kingdom; [2]University of Nottingham, Division of epidemiology and public health, School of Medicine., Nottingham, United Kingdom; [3]Health Protection Scotland, Glasgow, United Kingdom; [4]NIHR Nottingham Digestive Diseases Biomedical Research Unit, Nottingham University Hospital NHS Trust and University of Nottingham., Nottingham, United Kingdom*
[*]Senior authors
Email: hamish.innes@gcu.ac.uk

Background and Aims: Death from liver cirrhosis typically occurs after decades of silent hepatitis and fibrogenesis triggered by a persisting liver insult. Early detection of progressive liver damage before serious complications emerge is critical to preventing cirrhosis mortality. In this study we investigated awareness of liver disease among cirrhosis decedents shortly before their death, using data from a large UK community sample.
Method: The study population comprised participants from the UK biobank cohort – a large community sample of middle aged men and women from UK, recruited in 2006–2010 – who died a cirrhosis-related death up to Nov 2016. Cirrhosis-related mortality was defined either as death: a) directly from liver cirrhosis (ICD 10: K70; K73; K74); or b) indirectly from cirrhosis via hepatocellular carcinoma (HCC), given that, by and large, cirrhosis is prerequisite for HCC in Western settings (ICD 10: C22.0). We inferred awareness of liver disease according to whether participants disclosed any liver-related condition when asked to report "serious medical conditions/disabilities" diagnosed by a doctor in their survey interview. We investigated determinants of liver disease awareness via univariate and multivariate logistic regression. Specifically, we assessed the association between awareness and the following patient factors: age, gender, deprivation score; country of birth; UK country of residence; year of interview; length of time between interview and death; type of cirrhosis death; previous hospitalisation for cirrhosis; comorbidity; abdominal pain in last month; and liver disease etiology.

Fig.1 Patient characteristics associated with awareness of liver disease at survey interview, shortly before cirrhosis death



Results: From 502,633 survey participants, there were 372 deaths from cirrhosis (the majority – 74% – due to alcohol etiology). The median time interval between survey interview and cirrhosis mortality was 4.2 years (IQR: 2.5–5.9). Of the 372 decedents, 82 (22.0%) reported awareness of a liver-related condition at baseline. Factors significantly associated with increased awareness in multivariate analysis were: viral hepatitis etiology; prior cirrhosis hospitalisation; and living in England/Wales (versus Scotland); see Fig. 1.
Conclusion: Less than a quarter of cirrhosis decedents reported awareness of liver disease 4.2 years (on average) prior to death. These data indicate suboptimal identification and/or communication of life-threatening liver disease among high risk individuals in the UK, and foreground the need for better diagnostic pathways in the community setting.

THU-063

Eradicate hepatitis C: A pilot of treatment as prevention in active drug users

J. Schulkind[1], F. Ahmad[2], B. Stephens[2], L. Johnston[2], M. Hickman[1], Z. Ward[1], J. Dillon[2]. [1]*University of Bristol, Population Health Sciences, Bristol, United Kingdom;* [2]*University of Dundee, Department of Molecular and Clinical Medicine, Dundee, United Kingdom*
Email: jasmine.schulkind@gmail.com

Background and Aims: To achieve WHO Hepatitis C virus (HCV) elimination targets by 2030, there needs to be significant scale-up of treatment among active injecting drug users – a concept known as "treatment as prevention" (TasP). Current EASL guidelines highlight active injectors as a priority group for HCV treatment. Our principal aim was to test whether active injectors can be recruited and treated successfully, and assess rates of re-infection.
Method: This prospective study recruited 104 HCV positive participants over 42 months from the largest Needle exchange (NE) centre in Tayside, Dundee. 94/104 individuals commenced treatment. Genotype 1 (G1) individuals (n = 37) were treated with peg-interferon + ribavirin+ Simepravir/Telaprevir. Genotype 2/3 (G2/3) (n = 57) received peg-interferon + ribavirin. Weekly study visits took place within the NE centre.
Results: Mean age of participants was 34.0 years (SD 6.9), 71.3% (61/94) were male. 1 in 5 (20/94) participants were homeless/living in unstable accommodation; 12.8% (12/94) were in prison at some point during the treatment period. Reported history anxiety/depression was high, 69.2% (65/94). Baseline data showed high rates of injecting: participants injected median 6.5 times/week, 54.3% (51/94) injected daily/more than once a day. In terms of clinical outcomes >80% treatment adherence was 71.3% (67/94). SVR12 data was available for 92/94 participants (Table 1). 2 participants died prior to 3-month follow-up. There was no difference in SVR12 rates between Genotype: 81.0% (30/37) for G1 and 85.5% (47/55) for G2/3. There was limited lost to follow-up at 6-months, 5.4% (5/92). Re-infection rates were 12.6/100 person-years (95% CI 5.3–30.4) (n = 5) at 6-months and 18.3/100 person-years (95% CI 11.1–30.4) (n = 15) at 18-months post-treatment.

Table 1: principal study outcomes

Study outcome	n = 92
SVR12, No. (%)	77 (83.7)
Lost to follow-up at 6-months, No. (%)	5 (5.4)
Died at 6-months, No. (%)	3 (3.2)
6-month reinfection rate, per 100-pyrs (95% CI	12.6 (5.3–30.4
18-month reinfection rate, per 100-pyrs (95% CI)	18.3 (11.1–30.4)

Conclusion: Active injectors were successfully recruited, treated and followed-up. However, we also report higher rates of re-infection than many other studies. These re-infection rates demonstrate this is a high-risk population, who should be considered a priority population for TasP. This pilot study provides a successful model for engaging active injectors in HCV treatment.

THU-064

HIV co-infection is associated with increased liver complications and reduced mental health among patients with chronic hepatitis B

M. Lu[1], N.P. Markowitz[2], Y. Zhou[1], K.-H. Wu[1], L.B. Rupp[3], S. Trudeau[1], J. Li[1], J.A. Boscarino[4], M.A. Schmidt[5], Y.G. Daida[6], S.C. Gordon[7]. [1]*Henry Ford Healthy System, Department of Public Health Sciences;* [2]*Henry Ford Healthy System, Department of Infectious Disease;* [3]*Henry Ford Healthy System, Center for Health Policy and Health Services Research;* [4]*Geisinger Clinic, Department of Epidemiology and Health Services Research;* [5]*Kaiser Permanente Northwest, Center for Health Research;* [6]*Kaiser Permanente Hawai'i, Center for Health Research;* [7]*Henry Ford Health System, Gastroenterology and Hepatology, Detroit, United States*
Email: mlu1@hfhs.org

Background and Aims: Most studies of hepatitis B (HBV) and HIV co-infection focus on HIV cohorts, and thus may not collect data regarding HBV-related treatment or outcomes. We used data from the Chronic Hepatitis Cohort Study (CHeCS)—a racially- and geographically-diverse sample from four large US health systems—to investigate the impact of HIV on the clinical characteristics and mental health of patients with chronic hepatitis B.

Table 1: HBV and HBV-HIV patients: demographics, current clinical status, and survey responses

Variable	Response	HBV (n = 4340)	HIV/HBV (n = 300)	p
Sex	Female	47%	9%	<0.001
	Male	53%	91%	
Age	<40	22%	14%	<0.001
	40 < 50	23%	29%	
	50 < 60	25%	37%	
	≥60	29%	20%	
Race	ASINPI	55%	9%	<0.001
	Black	13%	47%	
	White	23%	38%	
	Unknown	9%	6%	
Insurance	Medicaid	14%	26%	<0.001
	Medicare	20%	38%	
	Private	66%	36%	
Household Income	<$30 K	14%	36%	<0.001
	$30 < $50 K	41%	44%	
	≥$50 K	44%	19%	
Charlson-Deyo comorbidity score	0	69%	24%	<0.001
	1–2	17%	3%	
	≥3	14%	73%	
FIB4 Score		2.7 ± 11.7	4.1 ± 10.9	0.051
Antiviral med activity	Neither HIV nor HBV	70%	9%	<0.001
	HBV only	30%	6%	
	HIV only	0%	6%	
	Both HIV and HBV	0%	79%	
Cirrhosis	No	84%	77%	<0.001
	Yes	16%	23%	
Hepatocellular carcinoma	No	97%	98%	0.426
	Yes	3%	2%	
Deceased	No	88%	73%	<0.001
	Yes	12%	27%	
Survey response		n = 913	n = 67	
SF8 Mental health score		51.3 (8.8)	45.3 (12.3)	<0.001
SF8 Physical health score		50.6 (9.0)	47.4 (10.4)	0.007
High stress		14%	34%	<0.01
Any depression (PHQ9)		11%	37%	<0.01
Hx injection drug use		4%	13%	<0.001
Hx sex with multiple partners		43%	13%	0.019
Hx smoking		39%	64%	<0.01
Audit C: alcohol use		14%	25%	0.02
US or Canada born		35%	94%	<0.01
Married		13%	69%	<0.01

Method: Patient demographics and clinical status were collected from the electronic health record from date of diagnosis (HBV or HIV/

HBV co-infection) onward. A subgroup provided survey data regarding health-related behaviors and mental health. Chi-square tests and two-sample t-tests were used to compare categorical and continuous variables, respectively, between HBV mono-infected and HIV/HBV co-infected patients.
Results: Among a sample of 4640 HBV patients, 300 (6.5%) were HIV co-infected. HIV/HBV co-infected patients were significantly more likely to be male, African American or white, low-income, and publicly insured than HBV mono-infected patients. Despite high rates of antiviral treatment, co-infected patients also demonstrated increased comorbidities, fibrosis/ cirrhosis, and mortality. Among a subgroup of 980 survey respondents (913 HBV, 67 HIV/HBV), co-infected patients were significantly more likely to be depressed, to have lower mental health scores, and to report being "highly stressed".
Conclusion: HIV co-infection impacts a demographically distinct subset of HBV patients. Despite high rates of antiviral treatment, co-infected patients demonstrate increased rates of liver-related complications and report poor mental health outcomes.

THU-065
Australia on track to achieve WHO elimination targets following rapid initial DAA treatment uptake
J.A. Kwon[1], G. Dore[1], J. Grebely[1], B. Hajarizadeh[1], R. Guy[1], E.B. Cunningham[1], C. Estes[2], H. Razavi[2], R.T. Gray[1]. *[1]Kirby Institute, UNSW, Kensington, Australia; [2]Center for Disease Analysis (CDA), Lafayette, Colorado, United States*
Email: akwon@kirby.unsw.edu.au

Background and Aims: From March 2016, the Australian government made direct-acting antiviral (DAA) treatment available at a highly-subsidized cost to all adults living with chronic hepatitis C (HCV). An estimated 32,550 people initiated DAA treatment in 2016, equating to 14% of the 227,000 people living with chronic HCV. We estimated the initial and future impact of DAA treatment on prevalence, morbidity, and mortality of HCV to evaluate whether Australia can meet WHO HCV elimination targets by 2030.
Method: We used a mathematical model and assumed three different future treatment coverage scenarios over 2016–2030: optimistic, 32,550 people initiate DAA treatment each year 2016–2030; intermediate, treatment numbers drop moderately: 32,550 (2016), 27,900 (2017), 23,250 (2018), then 18,600 (2019–2030); and pessimistic, treatment drops markedly; 32,550 (2016), 18,600 (2017), 13,950 (2018), then 13,950 (2019–2030), with comparison to a status-quo scenario where treatment remains at 2015 levels (7,300 per annum). Treatment and testing rates were varied by disease stage, and reduced disease progression rates to decompensated (DC) and hepatocellular carcinoma (HCC) among the cured population. We assumed testing rates and current harm reduction programs remained in place from 2016 and only the impact of treatment uptake was analysed in this study.
Results: Under the intermediate DAA treatment scenario during 2016–2020, 28% (24–31%) of new HCV infections, 57% (46–67%) of DC, 59% (47–69%) of HCC, and 53% (42–63%) of liver-related deaths were averted. By 2030, the intermediate scenario would avert 57% (47–65%) of new HCV infections, 86% (70–91%) of DC, 89% (74–93%) of HCC, and 83% (64–88%) of liver-related deaths. The model estimates that under the intermediate scenario Australia will meet WHO targets of 80% reduction in HCV incidence in 2024, 80% eligible treated in 2025, and 65% reduction in liver-related mortality in 2020. The pessimistic scenario will delay meeting the targets by 3–5 years, and the optimistic scenario will bring it forward by 3–5 years.
Conclusion: Based on a realistic DAA treatment uptake scenario Australia should meet the WHO HCV elimination targets in 10–15 years even with moderate reductions in DAA treatment uptake from 2016 level. To achieve these targets requires a continuation of current harm reduction activities and HCV testing strategies to ensure anyone living with chronic HCV can receive treatment.

THU-066
Hepcare Europe: HepCheck; reaching vulnerable populations
J. Lambert[1], W. Cullen[2], C. Oprea[3,4], A. Story[5], J.M. Sanchez[6], J. Surey[7]. *[1]Mater Misericordiae University Hospital, Infectious Diseases Department, Dublin, Ireland; [2]University College Dublin, School of Medicine, Dublin, Ireland; [3]Carol Davila University of Medicine and Pharmacy, Bucharest, Romania; [4]Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania; [5]UCLH NHS Trust, London, United Kingdom; [6]Hospital Universitario de Valme, Infectious Diseases and Microbiology Unit, Seville, Spain; [7]University College London, Institute of Global Health, London, United Kingdom*
Email: alistairstory@gmail.com

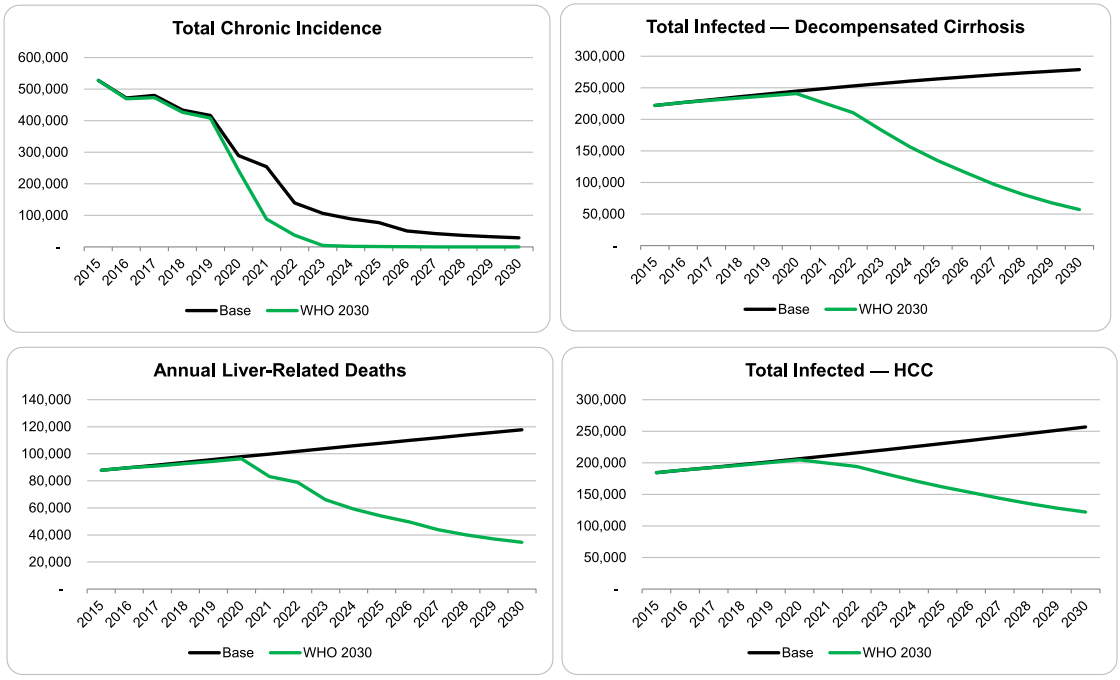
Background and Aims: HepCare Europe is a three year EU funded project involving collaboration with four member states. The vision for the project is to create an innovative, integrated system for HCV testing & treatment among key "at-risk" groups, including PWID's and the homeless, through outreach to the community and integration of primary and secondary care services. With clinical sites in Dublin, London, Seville and Bucharest, and economic evaluation in Bristol UK, the consortium has developed a number of work packages focused on operationalizing the multiple components of testing, care and cure that are key components of the strategy to eradicate HCV in the European Union. Consortium members include UCD (Ireland) SAS (Spain) SVB (Romania) University of Bristol (UK) and University College London (UK).
Method: The HepCheck component of the project offered screening across the four clinical sites in Dublin, London, Seville and Bucharest. Point of care testing was offered to "at-risk" groups who are frequently marginalized with respect to health service engagement. Screening was conducted in prisons, opioid substitution treatment clinics and in homeless services.
Results: A total of 1,749 individuals were screened, 31.2% (n = 559) tested HCV antibody positive. To date 40% (n = 222) individuals have attended a specialist appointment for HCV treatment. In-depth analysis of the data is ongoing including identification of risk factors for HCV infection, levels of HCV related liver disease, prevalence of blood borne viruses and linkage to care.

	Dublin	London	Bucharest	Seville	Total
Screened	569	310	469	401	1749
Ab Positive	24%	41.8%	35%	34%	31.2%

Conclusion: In order to achieve WHO HCV elimination targets by 2030 we need to identify and successfully treat the most vulnerable HCV individuals in the community. Community based screening intervention can enhance HCV diagnosis for at risk populations but referrals to/ attendance at secondary care remains a challenge for this cohort. The HepCheck data highlights the potential for developing interventions to enhance engagement with HCV screening and entry to the cascade of care required to cure HCV.

THU-067
Achieving World Health Organization targets for hepatitis B by 2030: Results from 17 WHO AFRO Countries
H. Nde, S. Robbins, D. Razavi-Shearer-Spink, S. Brandon, I. Gamkrelidze, H. Razavi. *Polaris Observatory, Lafayette, United States*
Email: hnde@cdafound.org

Background and Aims: The AFRO region has a perilously high burden of hepatitis B (HBV) but data to guide management strategies are lacking. Progression to decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver related death (LRD) makes the virus a main driver of morbidity and mortality in the region with HBV accounting for almost 88,000 deaths annually.
Method: Excel-based disease progression models, built with verified, published and/or extrapolated data were used to assess 2016–2030 trends in morbidity and mortality in 17 World Health Organization



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(WHO) AFRO countries: Burkina Faso, Burundi, Cameroon, Central African Republic (CAR), Chad, Ethiopia, Gabon, Gambia, Kenya, Madagascar, Malawi, Nigeria, Rwanda, Senegal, Tanzania, Uganda, Zimbabwe. After 2017, interventions were introduced with the aim to achieve WHO 2030 hepatitis targets of 90% diagnosed and 80% treated with a 65% reduction in mortality by 2030.

Results: 2016 saw approximately 42 million chronic cases in all 17 modeled countries with Nigeria alone accounting for ~50% of all infections. Ten modeled countries had over a million cases each, five countries (Burundi, CAR, Kenya, Malawi, Rwanda) had 200,000–700,000 cases while two (Gabon and Gambia) had under 100,000 cases. 65% of cases were aged 15–49, with a male predominance. By 2030, cases decrease in all countries but Chad, Central African Republic and Nigeria where they increase 8–20%. However, prevalent DC, HCC and annual LRD increase 20–40% for all countries with Ethiopia, Gabon and Gambia showing >30% increases in HCC cases. Meeting WHO 2030 targets from this base requires 40 million total diagnosed cases and 9 million treated annually by 2025. This represents an exponential increase in diagnosis and treatment respectively from 2016, and it reduces DC by 75% and HCC by 35%. Mortality, however, could only be reduced by 61% in this time frame, contrary to the expected 65% to meet WHO 2030 targets.

Conclusion: HBV is a neglected disease in the AFRO region. Continuing current conditions will lead to increases in end-stage outcomes by 2030. In light of the sizeable disease burden in the young population of these countries, diagnostic and treatment efforts will have to be radically expanded in the next 10 years to meet WHO 2030 targets, although such an expansion will likely be insufficient to meet mortality targets. Countries thus need to review strategies on how to best control the expected increase in disease burden.

THU-068

Achieving World Health Organization targets for hepatitis B in infants and 5-year olds by 2030: Results from 17 WHO AFRO countries

H. Nde, S. Robbins, D. Razavi-Shearer-Spink, S. Brandon, I. Gamkrelidze, H. Razavi. *Polaris Observatory, Lafayette, United States*
Email: hnde@cdafound.org

Background and Aims: 90% of children infected via perinatal transmission of the hepatitis B virus (HBV) become chronic carriers, while childhood transmission poses a 20–50% risk. Chronic infection is linked to severe end-stage outcomes, and averting perinatal infections is crucial to elimination. Few countries in the WHO AFRO region, however, have all perinatal prophylaxes options available in existing frameworks, raising the question of if the WHO 2030 target of 0.1% prevalence in 5-year olds can be met otherwise.

Method: Excel-based disease progression models were built with verified, published and/or extrapolated epidemiological data from 17 countries in the WHO AFRO region: Burkina Faso, Burundi, Cameroon, Central African Republic (CAR), Chad, Ethiopia, Gabon, Gambia, Kenya, Madagascar, Malawi, Nigeria, Rwanda, Senegal, Tanzania, Uganda, Zimbabwe. 2016–2030 infection trends in the infant (<1 year old) and 5 year old population were analyzed, assuming the current immunization paradigm from 2014 remained constant. Interventions were introduced to the models after 2017 first by expanding coverage rates for the 3-dose vaccine, then treatment of high viral load mothers, birth-dose and HBIG with the aim to achieve the WHO targets for HBV in 5-year olds by 2030.

Results: By 2030, 16 of 17 analyzed countries saw decreased infant cases. CAR alone, with no birth-dose and under 50% 3-dose, saw a 13% increase in the number of infants cases by 2030. Similarly, cases in 5-year olds decreased 12–57% for all analyzed countries except for Burkina Faso and CAR which saw increases of 8% and 68% respectively. Sustaining 3-dose coverage rates from 2014 in Kenya, Malawi and Rwanda (all >80%) was sufficient to meet the WHO targets. CAR required increases to both 3-dose coverage and treatment of mothers (99% by 2025), as well as to birth-dose coverage (35% by 2025). The Gambia, with birth-dose and 3-dose coverage at 96% in 2014, required 99% coverage in both therapies as well as in treatment of mothers by 2025, to meet targets. Nigeria could meet targets by keeping the 2014 birth-dose rate of 54% while expanding 3-dose coverage and treatment of mothers to 99% by 2025. Alternately, increasing both immunization rates to 99% by 2025 and treating 85% of mothers by the same time would meet goals. In the remaining countries, increasing the 3-dose coverage to 99% by 2025 and treating 40% (Ethiopia) to 99% (Chad) of mothers by 2025 was sufficient.

Conclusion: Early infection with HBV poses a threat in the AFRO region. Current efforts go a long way towards reducing HBV disease burden as some countries could achieve WHO 2030 HBV targets for 5-year olds with the existing 3-dose coverage rates. Even more countries, however, will need to expand access to 3-dose and birth-dose coverage as well as treatment for infected mothers. Carefully designed strategies are thus necessary to maximize resources.

THU-069

Impact of the hepatitis B vaccine birth-dose on perinatal incidence between 2017–2050: Results from 17 WHO AFRO Countries

H. Nde, S. Robbins, D. Razavi-Shearer-Spink, S. Brandon, I. Gamkrelidze, H. Razavi. *Polaris Observatory, Lafayette, United States*
Email: hnde@cdafound.org

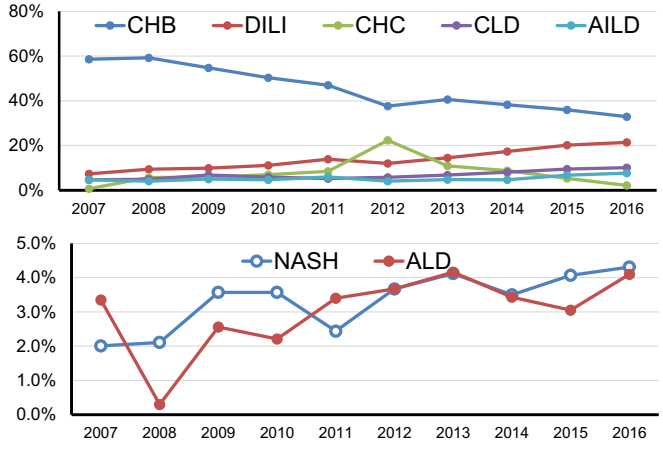
Background: Expanding access to the HBV vaccine birth-dose is recommended as an essential step towards preventing mother-to-child transmission of the virus as well as in elimination efforts. This is particularly the case in the WHO AFRO region where birth-dose coverage is still low. Few analyses exist, however, which investigate the impact of administering versus not administering birth-dose on future perinatal incidence.
Methods/Design: Excel-based disease progression models were seeded with verified, published and/or extrapolated epidemiological data from 17 countries in the WHO AFRO region (Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Ethiopia, Gabon, Gambia, Kenya, Madagascar, Malawi, Nigeria, Rwanda, Senegal, Tanzania, Uganda, Zimbabwe). The base model assumes no change in the country's current birth dose-coverage, with other parameters set to meet WHO 2030 targets for 5 year olds. The test model increased birth-dose coverage between 2017 and 2030 to match WHO target 3-dose coverage rates by 2030. The difference in perinatal incidence between 2017 and 2050 was then calculated.
Results: Expanding birth-dose to match 3-dose rates for WHO targets by 2030 in these 17 countries, results in ~200,000 total incident perinatal HBV cases prevented between 2017 and 2050. This ranged from 15 cases in The Gambia to ~44,000 cases in Ethiopia. Over 60% of all incident cases prevented occurred before 2030. Cameroon, Ethiopia, Nigeria, Tanzania and Uganda each prevented over 10,000 incident perinatal cases by 2030.
Conclusion: Expanding access to birth dose in the next 15 years will lead to reductions in incident perinatal HBV cases by 2050. This suggests that in the long term i.e., 2050 and beyond, the lack of a birth-dose might lead to more chronic cases and end stage outcomes, unless other measures are taken to manage disease burden.

THU-070

The 10-year chronic liver disease spectrum evolution in China: experience from the largest tartiary special hospital with 21382 liver biopsy cases

D. Ji[1,2], G. Chen[1,2], Y. Fu[1], C. Wang[3,4], J. Chen[3], Q. Shao[1,2], B. Li[1,2], F. Li[1,2], Z.B. Li[1], V. Wu[3], T. Wu[3], Y. Wang[3], G. Lau[2,5]. *[1]Beijing 302 Hospital, Second Liver Cirrhosis Diagnosis and Treatment Center, Beijing, China; [2]Beijing 302-Hong Kong Humanity and Health Hepatitis C Diagnosis and Treatment Centre, Beijing, China; [3]Humanity and Health Research Centre, Hong Kong, Hong Kong; [4]Nanfang Hospital, Southern Medical University, State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Guangzhou, China; [5]Humanity & Health Medical Centre, Division of Gastroenterology & Hepatology, Hong Kong, Hong Kong*
Email: gkklau@netvigator.com

Background and Aims: Beijing 302 hospital is the largest tertiary special hospital for liver diseases, which receives patients from all over the China. The patients visited our hospital is representative and we aimed to assess the pattern and evolution of Chinese people liver disease spectrum using data from our patients to provide the evidence for developing population–based effective strategy of chronic liver disease management.



Method: The clinical data of executive patients who underwent liver biopsy by any reasons from 2007 to 2016 were retrospectively collected, and the disease spectrum and biochemical parameters of each patient were recorded, such as sex, age, outcome, etc. Liver biopsy were guided by ultrasound, and HE, Masson and reticular fiber staining were performed routinely in liver tissues,

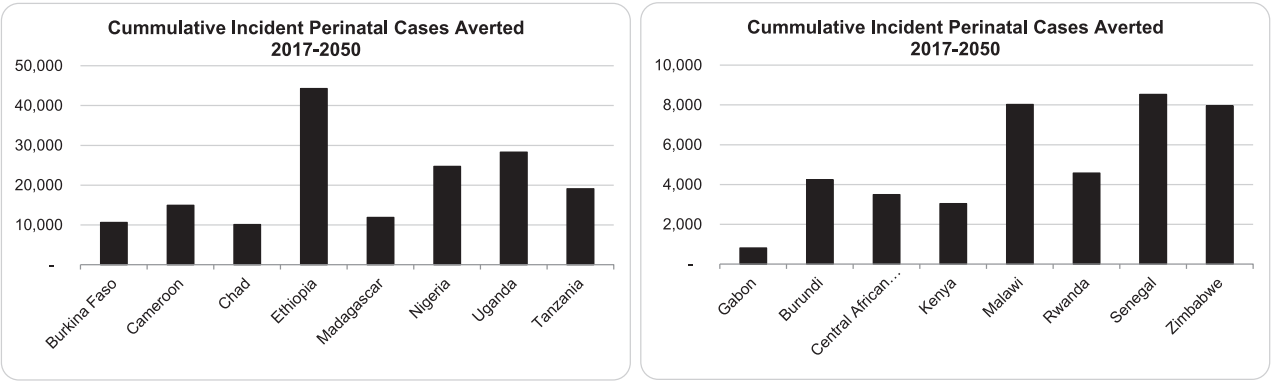


Figure: (abstract: THU_069)

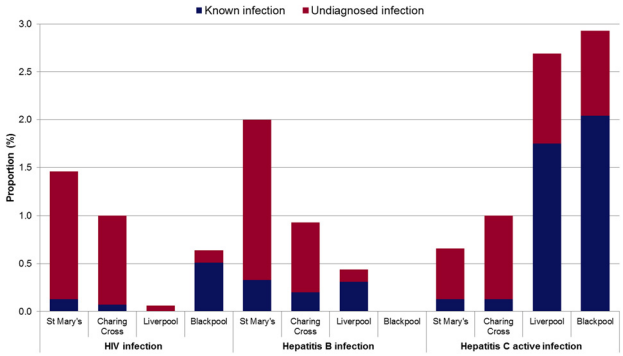
immunohistochemical staining and special staining, such as Congo red and PAS, were optional selected if necessary.
Results: In total, 21382 liver biopsy cases were enrolled and analyzed. The top 5 etiology were chronic hepatitis B (CHB) (44.1%), drug induced liver injury (DILI) (14.1%), chronic hepatitis C (CHC) (9.2%), cryptogenic liver disease (CLD) 6.9%, and autoimmune liver diseases (AILD) (5.2%). The rate of CHB patients decreased from 58.6% to 32.9%, DILI increased from 3.7% to 13.7%, CHC increased from 7% to 22.4%, and then decreased to 2.2%, CLD increased from 4.8% to 13.3%, and AILD increased from 6.3% to 13.3%. Besides, non-alcoholic steatohepatitis (NASH) increased from 4.1% to 11.4%.
Conclusion: Chronic liver disease spectrum in China has been changed, as the living standard of Chinese people rising recent decades. The incidences of DILI, CLD, NASH and AILD increased rapidly, while CHC decreased significantly, implying the DAAs therapy has achieved a great success.

THU-071

The ENABLE projects: Consistent high prevalence of undiagnosed active blood borne virus infection [HBV, HCV, HIV] across four urban emergency departments in England – Data for action?

M. Hopkins[1], S. Todd[2], M. Beadsworth[2], R. Vivancos[3], C. Anderson[4], D. Muir[5], Z. Mohamed[6], A. Brown[6], A. Guleri[7], R. Sharma[7], R. Palmer[7], D. Singleton[7], M. Ruf[8], A. Chawla[1]. *[1]Royal Liverpool University Hospital, Department of Clinical Virology, Liverpool, United Kingdom; [2]Royal Liverpool University Hospital, Tropical and Infectious Disease Unit, Liverpool, United Kingdom; [3]Public Health England, Field Service, National Infection Service, Liverpool, United Kingdom; [4]Public Health England, Field Service, National Infection Service, London, United Kingdom; [5]Northwest London Pathology, Infection & Immunity, London, United Kingdom; [6]Imperial College London, Hepatology, London, United Kingdom; [7]Blackpool Teaching Hospitals NHS Trust, Microbiology, Blackpool, United Kingdom; [8]Gilead Sciences, Medical Department, London, United Kingdom*
Email: hopkinsmj@gmail.com

Background and Aims: There is limited local epidemiological data on blood borne viruses [HBV, HCV, HIV] (BBV) infection in England. 18 million people attend emergency departments (EDs) in England each year, including marginalised groups at increased risk of BBV who may not regularly access healthcare. Routine BBV screening in EDs is uncommon. We estimated both diagnosed and undiagnosed active BBV prevalence in four busy urban EDs across England to inform BBV testing initiatives in this setting.
Method: Standardised triple blind unlinked anonymous BBV prevalence surveys using residual biochemistry blood samples of unselected ED attendees aged 16–65 years were undertaken at Liverpool (LP), Blackpool (BP) and two London hospitals (St Mary's and Charing Cross). Previously diagnosed BBV prevalence was estimated through interrogation of local hospital laboratory IT records. Samples were then irreversibly anonymised except for gender, age, and ethnicity; and screened for hepatitis B surface antigen (HBsAg), HCV antibody and HIV antigen/antibody. Positive results were confirmed using neutralisation, RNA and lineblot assays. Undiagnosed BBV was estimated by subtracting previously locally diagnosed from survey diagnosed prevalence.
Results: 5,383 samples collected from unique patients across the four sites between May and August 2017 were analysed. 53% were female. Pooled active BBV survey prevalence across sites was 3.33% (range 2.67–4.00%). Coinfection prevalence: 0.11%. Undiagnosed prevalence was estimated at 2.17% (range 1.02–3.53%).
Pooled survey prevalence stratified by virus was HCV-RNA: 1.69%, HBsAg: 0.95% and HIV: 0.80%. Undiagnosed prevalence for HCV-RNA: 0.80%, HBsAg: 0.71% and HIV: 0.67%.
HCV accounted for 82% and 84% of survey diagnosed local BBV infections in BP and LP, compared with 24% in the two London sites, although we found an HCV-RNA prevalence of 2.1% among 327 patients of black ethnicities in London. HBV and HIV prevalence were 1.47% & 1.23% in London, compared to 0.5% & 0.06% in LP and 0% & 0.64% in BP (Figure).



Conclusion: We demonstrated consistently high prevalence of active BBV infection in adults across four busy urban EDs; substantially higher than general population estimates. However, we also found marked geographical variation in BBV patterns. Our results suggest that targeted ED BBV testing initiatives, informed by local prevalence surveys, could provide a valuable contribution to improving diagnosis and linkage to care pathways for often marginalised populations.

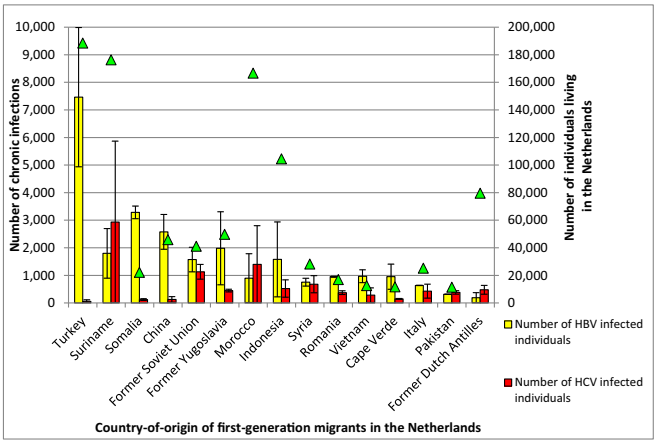
THU-072

Chronic hepatitis B and C infections in the Netherlands: estimated prevalence in risk groups and the general population

J. Koopsen[1,2], J. van Steenbergen[2], J.H. Richardus[3], M. Prins[4], E. Op de Coul[2], E. Croes[5], J. Heil[6], F. Zuure[4], I. Veldhuijzen[2]. *[1]Public Health Service of Amsterdam, Department of Infectious Diseases, Research and Prevention, Amsterdam, Netherlands; [2]National Institute for Public Health and the Environment, Center for Infectious Disease Control, Bilthoven, Netherlands; [3]Public Health Service of Rotterdam, Division of Infectious Disease Control, Rotterdam, Netherlands; [4]Public Health Service of Amsterdam, Department of Infectious Diseases, Research and Prevention, Amsterdam, Netherlands; [5]Netherlands Institute of Mental Health and Addiction (Trimbos Institute), Utrecht, Netherlands; [6]Public Health Service of South Limburg, Department of Sexual Health, Infectious Diseases and Environmental Health, Geleen, Netherlands*
Email: jkoopsen@gmail.com

Background and Aims: Worldwide, it is estimated that 248 million people are chronically infected with HBV and that 71 million are chronically infected with HCV. In the countries of the European Union (EU) and European Economic Area (EEA), approximately 4.7 million people live with chronic HBV and 5.6 million people are anti-HCV positive. Because chronic HBV and HCV infections are usually asymptomatic for decades, targeted screening is needed to diagnose infected individuals and prevent irreversible damage. Insight in the number of chronic HBV and HCV infections in the general population and in specific risk populations is needed to aid the design of screening programs.
Methods: Using a modified workbook method, originally designed for HIV estimations, the total number of ever chronically infected individuals in 2016 was determined for HBV and HCV. Population size and prevalence estimates were used, derived from studies in the general Dutch population and in populations at higher risk, including men who have sex with men (MSM), people who inject drugs (PWID), first-generation migrants from low-intermediate to high prevalence countries, sex workers and haemophilia patients. MSM and PWID were stratified by human immunodeficiency virus (HIV) status and first-generation migrants by country-of-origin.
Results: The estimated 2016 chronic HBV infection prevalence is 0.34% (low 0.22%, high 0.47%), corresponding to approximately 49,000 (low 31,000, high 66,000) HBV-infected individuals aged 15 years and older in the Netherlands. The estimated ever-chronic HCV

infection prevalence is 0.16% (low 0.06%, high 0.27%), corresponding to approximately 23,000 (low 8,000, high 38,000) ever HCV-infected individuals. First-generation migrants account for most infections with 81% and 60% of chronic HBV and HCV infections, respectively. The migrant groups that were estimated to harbor most chronic HBV infections in the Netherlands are migrants from Turkey, Somalia and China. The migrant groups that were estimated to harbor most chronic HCV infections in the Netherlands are migrants from Surinam, Morocco, and the former Soviet Union.



Conclusion: The prevalence of chronic HBV and HCV infections in the Netherlands is low. First-generation migrants are disproportionally affected, although about one fifth of HCV infections is found in the general population at low risk of infection. Targeted screening efforts are needed to diagnose and link infected persons to care. Our method could serve as an example of an accessible method to estimate risk group specific and overall HBV/HCV prevalences. Outcomes can be used to implement screening effectively and monitor progress towards elimination of chronic viral hepatitis.

THU-073

Transient elastography for screening of liver fibrosis in the population: A cost-effectiveness analysis using prospective databases from 6 countries in Europe and Asia

M. Serra[1], I. Graupera[2], L. Caballeria[3,4], M. Thiele[5], D. Roulot[6], W.S.V. Wong[7], N. Guha[8], N. Fabrellas[9,10], F. Lammert[11], R. Hernández[12], L.-H.G. Wong[7], A. Juanola[13], S.D. Murad[14], A. Krag[15], P. Angeli[16], P. Galle[17], P. Torán[3], C. Laurent[18], P. Ginès[1]. *[1]Centre de Recerca en Economia i Salut - Universitat Pompeu Fabra, Spain; [2]Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona; Spain; [3]Unitat de Suport a la Recerca Metropolitana Nord, Institut Universitari d'Investigació en Atenció Primària Jordi Gol (IDIAP Jordi Gol), Mataró, Barcelona; [4]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD); [5]University of Southern Denmark & Odense University Hospital, Department of Gastroenterology and Hepatology, Odense C, Denmark; [6]Unité d' Hépatologie, Hopital Avicenne, France; [7]Dept of Medicine and Therapeutics. The Chinese University of Hong Kong, Hong Kong, China; [8]NIHR Nottingham Digestive Diseases Biomedical Research Unit, University of Nottingham, Nottingham, UK; [9]Facultat of Medicine and Health Sciences. School of Nursing. University of Barcelona; [10]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS). Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD). Barcelona, Spain; [11]Department of Medicine II, Saarland University Medical Center, Homburg, Germany; [12]CAP La Marina, Institut Català de la Salut de Barcelona, Barcelona, Spain; [13]Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS); [14]Department of Gastroenterology and Hepatology, Erasmus Medical Center Rotterdam, Rotterdam, Netherlands; [15]Department of Gastroenterology and Hepatology, Odense Patient data Exploratory Network (OPEN), Odense University Hospital, Odense, Denmark; [16]of Internal Medicine and Hepatology, University and General Hospital of Padova, Padova, Italy; [17]Department of Internal Medicine, University Medical Centre of the Johannes Gutenberg-University Mainz, Germany; [18]Department of Hepatology, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; Université Paris VII, INSERM UMR 1149, Centre de Recherche sur l\'Inflammation, Paris, France*
Email: pgines@clinic.cat

Background and Aims: The global epidemic of obesity and diabetes leads to an increased incidence of nonalcoholic fatty liver disease (NAFLD) posing a challenge to current hepatic clinical pathways in our healthcare systems. The aim of the present study is to explore the cost-effectiveness of transient elastography (TE) as screening method to detect advanced liver fibrosis in the general population.
Methods: Microdata from 7 independent prospective databases from 6 countries (5 in Europe and one in Asia) (n = 6,295), mean age = 54.7 (12.2), mean BMI = 27.0 (4.9) with mean liver stiffness measurement (LSM) value = 5.6 kPa (5.0) was merged and analyzed with data mining techniques (conditional inference trees, logistic regression and Heckman sample-selection models) to explore the relationship between socio-demographics, comorbidities, LSM, and hepatic fibrosis, as assessed by liver biopsy in 295 patients. The results were used in the parameter tuning of one cost-effectiveness model (Tanajewski L et al., BJM 2017) for a risk-based community stratification strategy in each of the populations.
Results: Heckman's inverse Mills ratio was −0.23, p = 0.343, indicating that the biopsied subsample of patients is consistent with no selection bias. A LSM cut-off of 9.1 kPa was found to provide the best discriminatory accuracy (DA) for advanced fibrosis (stages ≥ F2), AUC = 77.46% (95%CI 0.71–0.83). 343 (5.45%) patients of the whole sample presented LSM values above the selected threshold. The mean incremental cost-effectiveness ratios (ICER) of the risk-stratification strategy ranged from 4,034€ (95%CI 4,531–2,853€) per quality-adjusted life-year (QUALY) to 849€ (95%CI 1,533–603€) per QUALY depending upon the targeted population. For comparison we used the ICER of hepatocellular carcinoma screening published in 2016 that was found to be 39,825USD (Kuo et al., WJG 2016).
Conclusion: The evidence presented suggests that community risk factor-based TE screening pathways performed at primary care centres is a highly cost-effective intervention and potentially cost-saving for health systems in need for better resource allocation within their provision of care. Compared to previous published in hepatocellular carcinoma screening, our findings suggest that an earlier detection of fibrosis associated with NAFLD leads to a 10-fold improvement in cost-effectiveness estimates in European and Asian contexts.

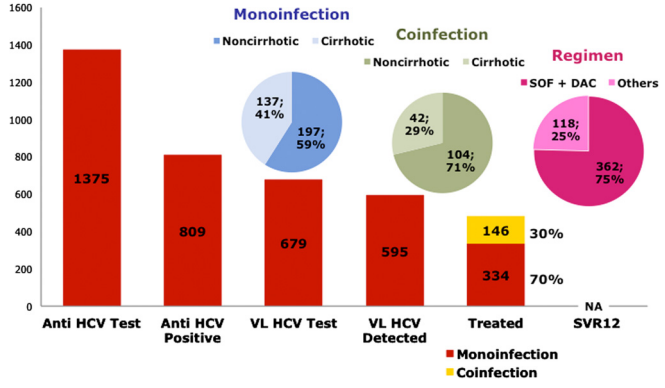
THU-074

Scale-up of the national HCV screening and treatment program in Indonesia: data from Jakarta, West Java and Central Java

A. Anartati[1], R. Kosasih[1], A. Budiman[1], J. Sacks[2], J. Tebor[2], C. Boeke[2], R. Sidjabat[3], S. Dwisangka[3]. *[1]Clinton Health Access Initiative, Jakarta, Indonesia; [2]Clinton Health Access Initiative, United States; [3]Indonesia Ministry of Health, Sub-directorate Hepatitis & Digestive Infection, Indonesia*
Email: aanartati@clintonhealthaccess.org

Background and Aims: HCV is a significant public health concern in Indonesia, with an estimated 1.28 million Indonesians living with chronic HCV. The government is committed to tackling the epidemic: a Ministerial Decree for hepatitis control was introduced in 2015, the 5 year Viral Hepatitis National Action Plan (2015–2019) was developed and the guidelines were updated to enable simplified diagnosis and treatment. The public program was launched in 2017, with the Government procuring diagnostics and DAAs (sofosbuvir/daclatasvir, sofosbuvir/simeprevir, and sofosbuvir/ribavirin) to treat up to 6,000 patients in 2017. Screening and treatment is currently

available across 7 provinces, with patients responsible for payment for visit fees and viral load consumables. Treatment is prescribed by specialists at hospitals, which are linked to primary health centers in the catchment area to expand access to screening. This analysis describes the initial scale-up in 3 provinces where the national program is most advanced.



Method: We conducted a retrospective analysis of routine programmatic data across 35 health facilities in Jakarta, West Java and Central Java for the first 1,375 patients who were screened. Screening targeted high risk groups, including people who inject drugs, people living with HIV, health care workers, and patients indicating they had been diagnosed previously. Data included analysis of serological markers, nucleic acid testing and assessment of fibrosis/cirrhosis through AST-to-platelet-ratio index (APRI).

Results: Out of 1,375 patients screened using anti-HCV rapid tests at 18 primary health centers and 17 hospitals, 809 (58.8%) were found to be positive. Of those who screened positive, 84% received a confirmatory HCV RNA test, of whom 88% were diagnosed with current HCV infection. 37% of all diagnosed were cirrhotic. As of October 2017, 81% of diagnosed patients had initiated treatment (n = 480), 30% of whom were HIV co-infected. The majority (362) of patients are being treated with SOF/DCV. Rates of treatment completion will be analyzed when data become available.

Conclusion: With strong political commitment and leadership, launching a public health HCV program in a high-burden middle-income country is feasible. Because direct patient payment is required, affordable diagnosis and treatment will be paramount to minimizing losses and achieving the public program's goal of diagnosis, treatment and cure for all Indonesians with chronic HCV.

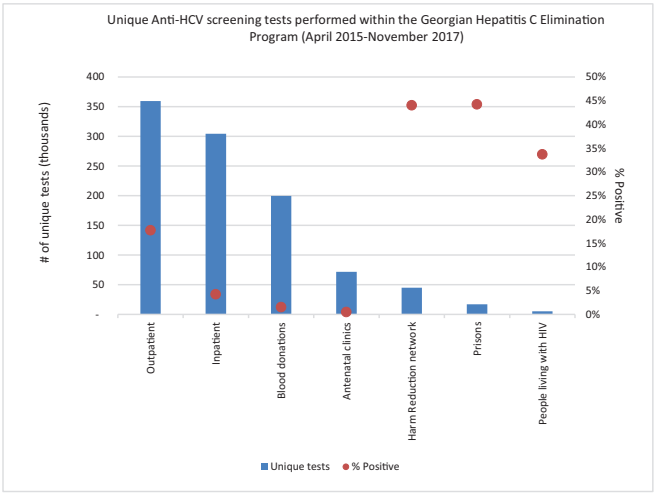
THU-075

Hepatitis C screening within the national elimination program in the country of Georgia

A. Gamkrelidze[1], A. Turdziladze[2], V. Getia[3], M. Alkhazashvili[4], M. Tsereteli[1], A. Aslanikashvili[5], D. Baliashvili[6], P. Imnadze[1]. [1]*National Center for Disease Control and Public Health, Director General, Tbilisi, Georgia;* [2]*National Center for Disease Control and Public Health, Tbilisi, Georgia;* [3]*National Center for Disease Control and Public Health, Department of State Programs, Tbilisi, Georgia;* [4]*National Center for Disease Control and Public Health, Lugar Center for Public Health Research, Tbilisi, Georgia;* [5]*National Center for Disease Control and Public Health, Department of Communicable Diseases, Tbilisi, Georgia;* [6]*Emory University, Rollins School of Public Health, Department of Epidemiology, Atlanta, United States*
Email: mtsereteli2002@yahoo.com

Background and Aims: Georgia is among the countries with high hepatitis C (HCV) prevalence. Based on the nationwide seroprevalence study conducted in 2015, 7.7% of the total population is hepatitis C antibody positive. In 2015, Georgia launched a large-scale public health program aiming to identify 90% of hepatitis C infected people, treat 95% of the identified individuals and achieve sustained virologic response in 95% of those treated. In order to achieve the set goals and eliminate hepatitis C by 2020, Georgia has significantly scaled up the screening activities during recent years.

Methods: Hepatitis C screening is provided free-of-charge by 602 testing centers across the country. Screening is performed according to the National Screening Protocol approved by the Georgian Government. The data are entered on-site into the electronic unified screening module, which is designed to capture results from all screening programs. Universal coverage with hepatitis C screening is ensured for certain population groups, such as pregnant women, blood donors and hospitalized patients. Screening-related data for these groups are entered in corresponding databases and imported into the module on a predefined regular manner.



Results: As of November 2017, 1,218,626 screening tests were registered in the electronic screening module, of which 9.3% were positive. 775,121 unique individuals were screened with 12.2% positive cases. The proportion of positive results were considerably higher in males compared to females with the positivity rates of 19.0% and 4.7%, respectively. Infection was mainly concentrated in 30–59 age group (79.0% of all screening positive cases) which reflects the 2015 seroprevalence study findings. The number of screening sessions and positivity rates among different population groups are shown in the figure.

Note: Figure shows only selected screening programs.

Conclusion: Georgia has markedly strengthened hepatitis C screening interventions and has already covered significant part of its population. Although, extending screening over the total population is still a challenge and requires a multi-sectoral approach.

THU-076

Inferring the migration routes of hepatitis C virus subtype 1a lineages identifies a need for pan-European prevention strategies

L. Cuypers[1,2], B. Vrancken[1], L. Fabeni[3], V.C. Di Maio[4], V. Cento[4], G. Baele[1], M. Parczewski[5], V. Chulanov[6], P. Gomes[7,9], A. Beloukas[11], A.M. Geretti[10], J. Dietz[11], C. Sarrazin[11], M. Neary[12], C. Degascun[12], S. Sierra[13], R. Kaiser[13], A.B.P. Jimenez[14], F.G. Garcia[14], M. Zazzi[15], A.-M. Vandamme[1,16], F.C. Silberstein[4]. [1]*KU Leuven - University of Leuven, Rega Institute for Medical Research - Department of Microbiology and Immunology, Leuven, Belgium;* [2]*Peter Medawar Building for Pathogen Research, Nuffield Department of Medicine, Oxford, United Kingdom;* [3]*National Institute for Infectious Diseases L. Spallanzani-IRCCS, Antiretroviral drug monitoring laboratory, Rome, Italy;* [4]*University of Rome Tor Vergata, Department of Experimental Medicine and Surgery, Rome, Italy;* [5]*Pomeranian Medical University, Department of Infectious, Tropical Diseases and Immune Deficiency, Szczecin, Poland;* [6]*Reference Center for Viral Hepatitis, Central Research Institute of Epidemiology, Moscow, Russian Federation;* [7]*Centro*

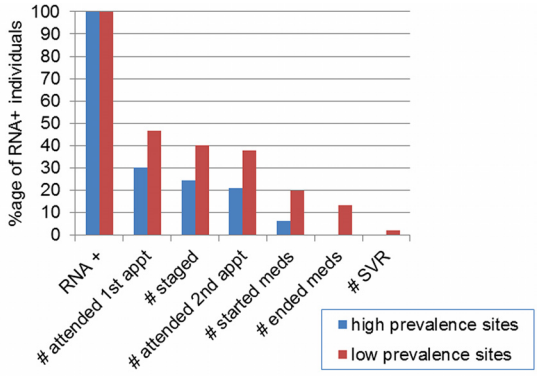
Hospitalar Lisboa Ocidental, Molecular Biology Laboratory, LMCBM, SPC, HEM, Lisbon, Portugal; [9]Centro de Investigação Interdisciplinar Egas Moniz, CiiEM, ISCSEM, Almada, Portugal; [10]University of Liverpool, Institute of Infection & Global Health, Liverpool, United Kingdom; [11]Goethe-University Hospital, Medical Clinic 1, Frankfurt, Germany; [12]University College Dublin, National Virus Reference Laboratory, Dublin, Ireland; [13]University of Cologne, German Center for Infection Research (DZIF), partner site Köln-Bonn, Institute of Virology, Cologne, Germany; [14]Clinical Microbiology Department, University Hospital San Cecilio Granada, Instituto de Investigación Ibs. Granada, Granada, Spain; [15]University of Siena, Department of Medical Biotechnology, Siena, Italy; [16]University de Nova Lisboa, Center for Global Health and Tropical Medicine, Microbiology Unit, Institute for Hygiene and Tropical Medicine, Lisbon, Portugal
Email: lize.cuypers@kuleuven.be

Background and Aims: Despite treatment response rates of nearly 100% for the majority of hepatitis C virus (HCV) infected patients, the virus can only be eradicated on a global scale through the combined effort of preventing new infections and curing diagnosed cases. As HCV1a constitutes a large part of recent infections, investigating by which migration routes it spreads, is of public health relevance.
Method: HCV1a genetic data from two viral proteins, NS3 (n = 2514) and NS5A (n = 1957), was used to reconstruct the virus migration pathways through time and space on a global and European level. Data from thirteen European countries was available, including nine (Belgium, Germany, Ireland, Italy, Poland, Portugal, Russia, Spain and the United Kingdom) for which 1825 sequences were newly generated. These and publicly available spatiotemporally annotated virus genetic data were used to infer the migration rates between geographical locations with a fast and scalable Bayesian approach. To counter the impact of potential sampling biases on the phylogeographic reconstructions, the among-location exchange rate matrix was shared between the gene datasets.
Results: Inferring migration pathways for both genes reveals extensive movements on a supra-continental scale, showing a dominant role for the United States in seeding HCV1a into Europe (74.6% of all migration links), as well as considerable migration within Europe. As only a small minority of outgoing migration events from Europe is directed to the United States (<5%), this suggests a scenario of one-way traffic to Europe. Within Europe, the migration network becomes increasingly complex and diffuse over time. Preliminary analyses to identify source-sink relations within Europe suggest that Germany functions as a hub for the spread of HCV1a lineages in Europe, exporting mainly viral strains to France, Italy, the United Kingdom and Spain.
Conclusion: Molecular epidemiology of the European HCV1a epidemic illustrates complex patterns of human migrations that are increasing in complexity over time. The presence of a pan-European migration network impairs the efficacy of national-based intervention programs. In turn, this indicates that a supra-national coordinated approach is needed to more quickly and more efficiently curb the HCV1a epidemic. Furthermore, similar analyses for HCV3a and HCV4, both additional important sources of new infections, are needed to support evidence-based European prevention strategies.

THU-077
Outcomes of hepatitis C testing, linkage to care, and treatment in a community based program in high versus low prevalence sites

L. Magaldi, N. Brown, C. Coleman, M. Dorshimer, J. Kostman, D. Zaret, T.-W. Preston, M. Reddy, R. Rivera, S. Trooskin. *Philadelphia FIGHT, C a Difference, Philadelphia, United States*
Email: lmagaldi@fight.org

Background and Aims: In order to identify individuals with chronic hepatitis C virus (HCV) infection who are not engaged in medical care, HCV testing needs to be done in community settings. However, approaches to screening and linkage to care may be different depending on the type of community site. We describe the linkage to care rates in comprehensive drug treatment programs ("high prevalence sites") and those in other community testing sites ("low prevalence sites") receiving HCV testing through the C a Difference program.
Method: Participants presented for rapid HCV testing at various community settings in Philadelphia, Pennsylvania, between 10/2016 and 9/2017. Participants who tested positive for HCV antibody using the Oraquick HCV antibody test via fingerstick were immediately offered HCV confirmatory PCR testing via blood draw and linkage to subspecialty HCV care at a Federally Qualified Health Centre (FQHC) with experienced HCV treaters. We defined engagement in care as attending two visits at the FQHC. Comparisons of linkage rates and rates of treatment initiation were made between those tested in high prevalence sites and those tested in low prevalence sites using Chi Square tests.



HCV Care Continuum in High vs. Low Prevalence Community Based Sites

Results: During the study period 2244 adults 1523(68%) from low prevalence sites and 721(32%) from high prevalence sites presented for rapid HCV testing. Compared to those tested in low prevalence sites, those tested in high prevalence sites were more likely to be antibody positive (5.52% vs 45.9% p = 0.0001), and more likely to accept confirmatory testing (79.76% vs 91.84% p = 0.0144). Those tested in low prevalence sites were more likely than those tested in high prevalence sites to engage in subspecialty care after chronic infection was confirmed (37.78% vs 21.05% vs p = 0.0162) and were more likely to begin HCV treatment after engaging in care (20% vs 6.58% p = 0.0037).
Conclusion: Our study suggests that HCV community-based testing and screening programs are important for engaging those at risk for HCV. However, although the prevalence of chronic HCV infection is significantly higher incomprehensive drug treatment centres, the rates of care engagement and treatment initiation are significant lower when compared to individuals found to be HCV infected from low prevalence testing settings. In order to improve the HCV care cascade for individuals from high prevalence sites, on site treatment or models of intensive addiction-informed navigation are needed.

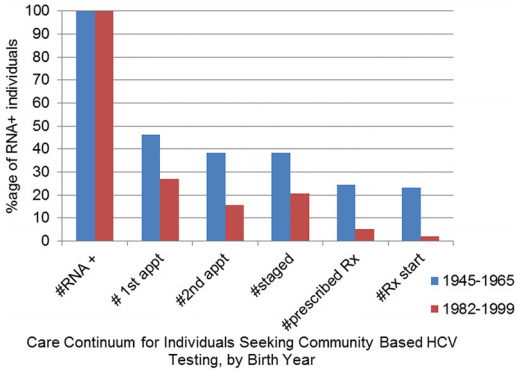
THU-078
Testing and linkage to care outcomes in baby boomers versus young adults tested in the community and linked to care at a Federally Qualified Health Center in the US

L. Magaldi, N. Brown, C. Coleman, M. Dorshimer, J. Kostman, D. Zaret, T.-W. Preston, M. Reddy, R. Rivera, S. Trooskin. *Philadelphia FIGHT, C a Difference, Philadelphia, United States*
Email: lmagaldi@fight.org

Background and Aims: While adults born between 1945–1965 (baby boomers) constitute the largest United States cohort with chronic hepatitis C infection (HCV) young adults born between 1982–1999, particularly those with a history of injection drug use, represent a growing population infected with HCV. Unfortunately, young adults often are not engaged in primary care and therefore are unlikely to be tested for HCV in this setting. Since community based testing can be used to identify members of these two cohorts with HCV infection,

we aimed to describe linkage to care rates of baby boomers versus young adults who were tested for HCV through C a difference, a community testing program.

Method: Participants include all adults born after 1945 presenting for point of care rapid HCV testing (Oraquick) at community settings in Philadelphia, Pennsylvania between 10/2016–9/2017. Participants testing positive for HCV antibody were immediately offered HCV confirmatory testing via phlebotomy and navigation to subspecialty HCV care in an FQHC setting. Care engagement was defined as attending at least two visits at the FQHC. We determined rates of antibody positivity, linkage to care, engagement in care and HCV treatment initiation and compared outcomes between baby boomers and young adults using Chi square tests.



Results: During the study period 1,349 adults, of whom 718 (53%) were baby boomers and 631 (47%) were young adults received community based HCV testing. Young adults were more likely to be antibody positive than baby boomers (23.3% vs 14.8% p = 0.0001), and more likely to accept immediate confirmatory testing (93.8% vs 85% p = 0.0341). However, young adults were less likely than baby boomers to engage in HCV care (19.1% vs 38.5% p = 0.0010) and baby boomers that engaged in care were more likely to begin HCV treatment (23.1% vs 4.8% p = 0.0001) (Figure).

Conclusion: Our results suggest that community-based programs are an important site for engaging and testing both baby boomers and young adults at risk for HCV and who may require assistance obtaining subspecialty care. Although young adults were more likely to be seropositive for HCV and to accept navigation services in an FQHC program, baby boomers were more likely to engage in care and start HCV treatment. Special care should be given to chronically infect young adults during the linkage process to be sure they enter and engage in subspecialty care and begin HCV treatment.

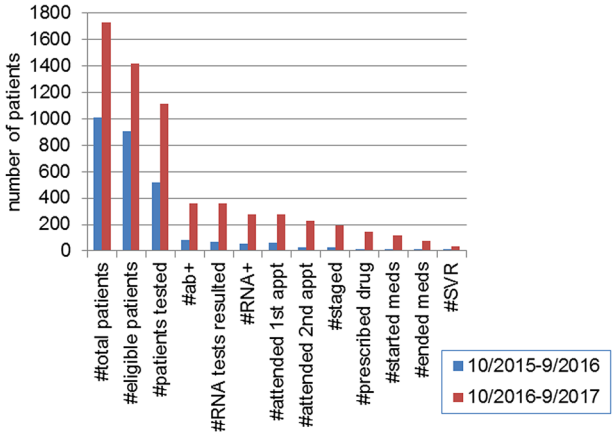
THU-079

The impact of EMR modification and a multi-disciplinary care team on the hepatitis C care cascade of a US Federally Qualified Health Center

L. Magaldi, N. Brown, C. Coleman, M. Dorshimer, J. Kostman, D. Zaret, T.-W. Preston, R. Rivera, M. Reddy, S. Trooskin. *Philadelphia FIGHT, C a Diffrence, Philadelphia, United States*
Email: lmagaldi@fight.org

Background and Aims: At least 50% of individuals infected with hepatitis C virus (HCV) are unaware of their status and 50% of individuals with a reactive antibody test never receive a confirmatory test; only a fraction of those engage in subspecialty care. Electronic Medical Record (EMR) lab order modifications for opt out HCV antibody testing with reflexive confirmatory PCR testing can increase rates of HCV testing and confirmatory testing. Implementing these EMR modifications in a Federally Qualified Healthcare (FQHC) setting where all providers also treat HCV and can be notified monthly of patients eligible for treatment may facilitate access to cure. We describe the impact of these EMR interventions on rates of HCV testing and treatment in a FQHC setting.

Method: Individuals seen between 10/2016 and 9/2017 with either no HCV testing recorded within one year or new FQHC patients had a lab order placed for automated HCV screening. Educational sessions were held for providers to reinforce implementation. Laboratory testing menus in the EMR were modified to include only HCV antibody tests with reflexive PCR testing on 7/12/2016. Data was collected through 5/11/2017. We compared points along the HCV care cascade with those at the same FQHC in the year prior (10/2015–9/2016). Since patients continue to progress through the care continuum, treatment and sustained virologic response (SVR) rates reflect interim outcomes.



Effect of EMR Modifications on the HCV Care continuum in an FQHC

Results: Prior to the EHR modifications, 57.3% (521 of 909) of eligible patients received antibody testing for HCV, and of those who were antibody positive (n = 81), 81% (n = 66) received confirmatory testing 45.5% of those (n = 25) received liver disease staging and 11 were treated for HCV. After EHR modifications, 78.4% (n = 1112) of eligible patients were tested, and of those who had a reactive antibody test, 99.7% (n = 358) had confirmatory reflexive testing. 98.6% of all RNA positive patients (n = 277) attended a subsequent HCV-specific provider visit; 68.6% (n = 190) received disease staging and 52.3% (n = 145) were prescribed HCV treatment. As of 4/11/2017, 42.6% (n = 118) began HCV treatment, 27.1% (n = 75) had completed treatment and 12% (n = 33) have achieved SVR.

Conclusion: Reflexive HCV testing via EMR modification resulted in significant increases in confirmatory testing rates. An FQHC setting where all providers are trained to treat HCV, results in improved treatment and SVR rates than reflected in the literature.

THU-080

Identifying patients with cirrhosis at high risk of readmission: a population-based data-linkage Australian study

P. Valery[1], L. Marquart[1], T. Rahman[2], P. Clark[3], S. Mcphail[4], R. Skoien[5], E. Powell[6]. *[1]QIMR Berghofer Medical Research Institute, Brisbane City, Australia; [2]The Prince Charles Hospital, Department of Gastroenterology and Hepatology; [3]Mater Hospital Brisbane, South Brisbane, Australia; [4]Queensland University of Technology, Institute of Health and Biomedical Innovation and School of Public Health & Social Work; [5]Royal Brisbane and Women's Hospital, Department of Gastroenterology and Hepatology; [6]Princess Alexandra Hospital, Department of Gastroenterology and Hepatology, Brisbane City, Australia*
Email: patricia.valery@qimrberghofer.edu.au

Background and Aims: While there are studies that have assessed predictors of readmission in decompensated cirrhosis, population-based Australian data are lacking. These data are essential to inform health work-force planning and strategies to reduce readmission. We describe the rates and associated risk factors of readmission within 1 year in patients with a first cirrhosis-related hospital admission.

Method: Hospital data on all patient admissions and deaths between Jul-2007 and Dec-2016 in the state of Queensland were obtained. Patient data were linked using deterministic and probabilistic methods. We identified index cirrhosis-related hospital admissions during 2012–2015 of patients ≥20 years of age, who did not have a liver transplant and were discharged alive. As ~50% of patients with decompensated cirrhosis die within 2 years, a look-back period of 4.5 years was used to identify the majority of *first* admissions with decompensation. We used Poisson regression to model the dichotomous outcome of readmission.
Results: Of 3,491 cases identified, most were male (66.7%), ≥50 years (77.2%), with the number of cases increasing by 38.4% between 2012 and 2015. The 1 year readmission rate was 32.7% (95%CI 31.1–34.2). Factors strongly associated with readmission included ascites (OR= 1.97, 95%CI 1.76–2.20; $p < 0.001$), hepatocellular carcinoma (OR = 1.58, 95%CI 1.11–2.60; $p = 0.012$), hepatorenal syndrome (OR = 1.57, 95%CI 1.00–2.45; $p = 0.049$), endoscopic banding procedure (OR = 1.52, 95%CI 1.34–1.74; $p < 0.001$) on the index admission, and history of alcohol consumption (OR = 1.22, 95%CI 1.08–1.37; $p = 0.002$). Having ≥2 cirrhosis-related complications (ascites, hepatic encephalopathy, gastroesophageal bleeding, jaundice, or hepatorenal syndrome), doubled the risk of readmission (OR = 1.95, 97%CI 1.56–2.44). Patients with one comorbidity vs. none were 1.79 (95%CI 1.60–2.00) times more likely to readmit, ≥2 comorbidities double the risk of readmission (OR = 2.02, 95%CI 1.63–2.52). A diagnosis of autoimmune liver disease was inversely associated with readmission (OR = 0.42 95%CI 0.23–0.76). Older age ($p = 0.019$) and male gender ($p = 0.048$) were weakly associated with readmission. No associations were seen with Indigenous status, rural residence, area-based socioeconomic status, year of admission, hospital sector, health insurance status, diagnosis of viral hepatitis (B/C) and/or NAFLD/NASH, and having gastroesophageal bleeding, hepatic encephalopathy, or jaundice on the index admission.
Conclusion: One-third of patients with cirrhosis are readmitted within 1 year. Opportunities exist to reduce readmissions via risk factor modification (e.g. alcohol consumption) and providing alternatives to re-hospitalization for management of ascites. The lack of association with Indigenous status, rural residence, and socioeconomic status needs further investigation.

THU-081

The role of a template-based assessment letter in the continuing education of general practitioners: a qualitative exploration of NAFLD educatioin

P. Valery[1], P. Patel[2], L. Horsfall[3], A. Russell[4], E. Powell[3], S. Williams[5].
[1]*QIMR Berghofer Medical Research Institute;* [2]*Princess Alexandra Hospital, Brisbane, Department of Gastroenterology and Hepatology;* [3]*Princess Alexandra Hospital, Department of Gastroenterology and Hepatology, Brisbane, Australia;* [4]*Princess Alexandra Hospital, Department of Diabetes and Endocrinology, Brisbane, Australia;* [5]*Inala Primary Care, Inala, Australia*
Email: patricia.valery@qimrberghofer.edu.au

Background and Aims: General practitioners (GPs) have a key role in identifying patients with non-alcoholic fatty liver disease (NAFLD) who are at risk of significant liver disease and may require specialist referral for further evaluation or management. However, many GPs under-recognize the clinical spectrum of NAFLD and how this is assessed.[1] On-line and other approaches have been used for providing continuing medical education for GPs across a range of diseases. Yet, acceptability and uptake has been limited, and research on learning opportunities about NAFLD by GPs is lacking. We aimed to investigate GPs' perspectives about the use of a template-based assessment letter ("template-letter") with educational content about NAFLD from hepatologists to referring GPs in routine care of patients with NAFLD.
Method: A qualitative study involving GPs from a primary care centre and specialists from an Endocrine clinic at a tertiary hospital in Queensland, Australia. Purposeful sampling was conducted to recruit GPs who took part in a focus group interview. Data were analyzed using a thematic analysis approach.
Results: GPs reported substantial benefits in the use of template-letters with educational content. Key themes that emerged for GPs included the consistency in the way patient information is presented in the template-letter (letters were "*accurate, concise, and consistent*"); information provided were practical and easy to follow ("*easy to understand, to the point*"), and the notes about the guidelines for management of NAFLD were "*very helpful*". While the GPs were unequivocal in their praise of the template-letters, suggestions to improve some dimensions of the template-letter were made e.g. having the key information about the patient upfront, i.e. patient follow up (what is expected from the GP vs. specialist follow up; long term plan for GP follow up, "*when to refer them* [patients] *back*") and no longer than 2 pages. Having a separate one-page document (and equivalent on-line version) with a simple algorithm for NALFD diagnosis, management and referral was seen as a helpful addition to the template-letter.
Conclusion: There is little published research into the influence of communication between primary and secondary care clinicians in the continuing education of GPs about NAFLD. A template-based assessment letter with an educational content generally had a positive impact on GP access to specialist expertise.

Reference

1. Patel *et al. Int Med J* 2017. doi: 10.1111/imj.13667

THU-082

The first large scale registry for non alcoholic fatty liver disease in Israel

I. Goldshtein[1], R. Oren[2], G. Chodik[1]. [1]*Maccabi Healthcaer Services, Epidemiology and Database Research, Research and Innovation Institute, Tel Aviv, Israel;* [2]*Institution of Gastrointestinal & Liver Diseases*
Email: goldst_in@mac.org.il

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a growing public health concern worldwide, due to its rising prevalence, excess morbidity and mortality. Many patients are not recognized despite abnormal liver enzymes and/or NAFLD related findings on abdominal imaging tests. A previous EASL publication (M. Alexander, 2017) described the incidence and prevalence of recorded NAFLD in European databases, with 135,912 identified cases out of 21.9 million adults. Given the poor disease documentation, we aimed to establish a comprehensive NAFLD registry, combining structured as well as unstructured data to increase capture rate.
Method: The registry was built using the computerized database of Maccabi Healthcare Services, a nationally representative payer-provider health fund in Israel, currently covering 2 million members. Cases were included by either NAFLD/cirrhosis recorded diagnoses, or high NAFLD fibrosis scores (>0.67) or at least 2 elevated liver enzymes measurements, or imaging indication of fatty infiltration. The latter was facilitated by natural language processing of 1 million text reports of ultrasonography, computed tomography and magnetic resonance tests conducted in the years 2006–2017. The resulting coded presence and level of fatty infiltration were validated by a random sample of n = 800 manually annotated text reports, indicating 96% accuracy. Patients with other causes of fatty liver were excluded (viral hepatitis or excess alcohol intake as detected by diagnoses, laboratory and dispensed medications).
Results: A total of n = 217,154 NAFLD patients were identified, with approximately 18,000 incident cases each year, and a mean age of 50.7 (SD 17.5) at NAFLD onset. In January 2017 the registry included 9% of the general population or 21% of those aged 45 years old or above. Most cases were either overweight (36%) or obese (43%) and 29% had diabetes mellitus. Only 44% had NAFLD diagnoses coded in their health records.
Conclusion: To the best of our knowledge this is the first large-scale NAFLD registry relying on population-based data. This infrastructure will be further studied to characterize patients' comorbidities or health care utilization and will serve in the future as a valuable

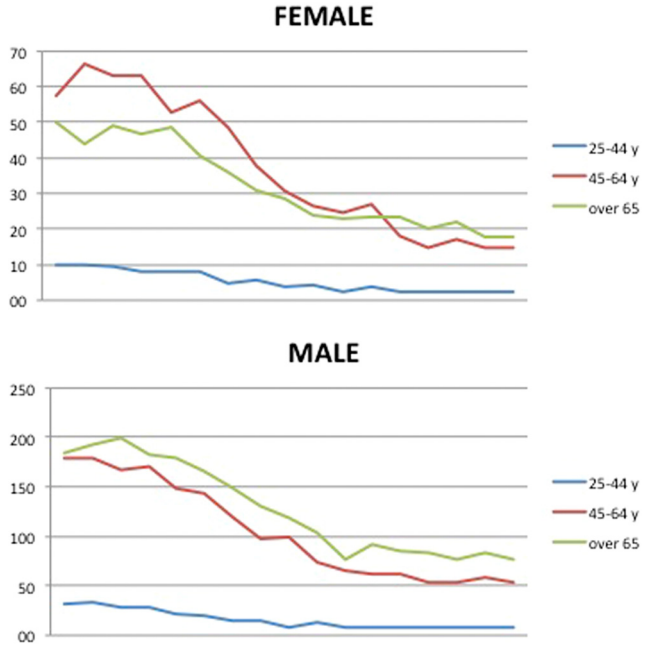
infrastructure to study real-world efficacy, safety and cost-effectiveness of evolving therapies.

THU-083

Hospitality discharge for alcohol related problems in north east Italy in a sixteen-years period: Influence of new population at risk

S. Vicario, M. Saia, D. Caroli, L. Scribano, F. de Lazzari, E. Rosa-Rizzotto, S. Lobello. *Gastroenterology*
Email: erik.rosarizzotto@aulss6.veneto.it

Background and Aims: WHO (2014) estimates a remarkable decline in per capita pure alcohol consumption in Italy, dropped from 18.1 to 7.1l in the period 1970–2013. Despite this, Italian Report on Alcohol 2016 showed an increase in drinking outside meals and a rise in consumption and binge drinking among young people (18–24, 14–17), particularly in males. The impact of these drinking styles on hospitalisation is still under-researched. This study aims to evaluate the trends of hospitality discharge for alcohol-related liver disease in the period 2000–2016 in Veneto Region in North Eastern Italy (4.8 million inhabitants).
Method: Retrospective cohort analysis based on Veneto Region anonymous computerised database of hospital discharges between 2000 and 2016. All Veneto residents discharge records with principal diagnosis of alcohol-related liver disease (cod. ICD9-CM: 571.0, 571.1, 571.2, 571.3) were included in the study. The principal diagnosis was chosen as it is considered the primary reason for hospital admission. Standardised Hospitalisation Ratio (SHR) per five-year age group (ref. pop. Veneto 2008) was calculated and expressed per 100.000 population.
Results: Over the period 2000–2016, 28.968 hospital admissions for alcohol-related diseases were recorded. Most part of subjects were males (74%) with a SHR more than double compared to females (53.3 vs. 18; OR:2.96; CI95%:2.89–3.04, $p < 0,05$). The longitudinal analysis of the hospitalisation trend shows a 7% increase on average age in both sexes (from 58.8 ± 9,2 to 62.6 ± 9,6) and a substantial decrease of 66% in SHR (X2 trend: 3933,326). In the last year of observation SHR tends to 19.5, and the greater risk for males is confirmed (30.2 vs. 8.8; OR:3.51; CI95%:3.05–4.10; $p < 0.05$). Considering the age groups, the highest decline in SHR can be found in the ranges 45–64 (from 69.2 to 34.1) and >65 (from 69.3 to 26.8). Interestingly, SHR shows a slightly rising trend in the group 25–44 between 2013 and 2016 ($p < 0.05$).



Conclusion: In Veneto Region, the reduction in alcohol intake over the last 30 years has lead to a marked decrease in hospitalisation for alcohol-related diseases. However, the changes in drinking styles occurred in the age range 25–44 may explain the upward SHR trend between 2013 and 2016. Thus, in the next few years it is likely to expect an increase in hospitalisation in this age group. Public Health strategies are needed to address the new styles of alcohol consumption, especially in young people.

THU-084

Is macro-elimination of HCV infection the right approach for Canada?

J. Holeksa, A. Alimohammadi, A. Bassi, A. Thiam, B. Conway. *Vancouver Infectious Diseases Centre*
Email: julie.holeksa@vidc.ca

Background and Aims: The World Health Organization has set a goal to eliminate HCV infection as a public health concern by 2030. Though some jurisdictions may implement country-wide macro-elimination strategies, this may not apply to many settings where health care delivery is a provincial/regional responsibility and where health care systems themselves are further divided to address the needs of local populations. A series of micro-elimination strategies may be more applicable in these circumstances. The inner city of Vancouver, British Columbia (BC) is home to a particularly vulnerable population with a 70% prevalence of HCV infection, and may be an ideal setting for the development of a pilot project for the control of HCV infection in the context of the development of a multidisciplinary model of care to address participants' needs, including optimized addiction care in the setting of the opioid crisis (3–4 opioid-related deaths/day in BC).
Method: We have developed a "four-legged chair" model to promote engagement with healthcare and social services. This model addresses the four main priorities of our population–medical, psychiatric, addictions, and social needs. This analysis was conducted to report on two principal outcomes: success of HCV therapy (SVR12), and opioid-related morbidity and mortality.
Results: Since 2014, 195 active/recent people who use drugs (PWUD) have received all-oral HCV treatment within this program. Key baseline characteristics were: median age 53 years; 78% male; 68/19% GT 1a/3; 20% F4; 68/59% using opiates/cocaine. Of patients with available SVR12 data, our overall success rate has been 140/149 (93%), with the remaining 7% experiencing a virologic relapse and requiring retreatment. Of the total cohort, 3% (n = 6) have been lost to follow up and will require novel strategies for reintegration in care. The remainder of the cohort is still in follow up and information will be updated appropriately. Over the past 2 years (almost 2,000 opioid-related deaths in BC), there have been only 22 medically significant overdose events and 2 opioid-related deaths within this cohort.
Conclusion: Given the broad range of health care delivery jurisdictions and target populations, a macro-elimination strategy for HCV infection in Canada will likely not be feasible. The model we have developed could be an ideal micro-elimination approach that will allow us to address both HCV infection as well as respond to the opioid crisis in a high-risk population. It is likely that Canada's optimal response to HCV infection will include a series of micro-elimination strategies, designed to optimize the social and healthcare needs of individual populations of interest.

THU-085

Low rates of prenatal testing for hepatitis B and C infections in Ontario, Canada

M. Biondi[1], A. Marchand-Austin[2], K. Sahdra[1], H. Janssen[1], T. Mazzulli[3], J. Feld[1]. [1]*Toronto General Hospital, Toronto Centre for Liver Disease, Toronto, Canada;* [2]*Public Health Ontario, Laboratory Surveillance and Data Management, Toronto, Canada;* [3]*Public Health Ontario, Toronto, Canada*

Email: mia.biondi@mail.mcgill.ca

Background and Aims: Prenatal testing is widely accepted for certain infections including syphilis, hepatitis B virus (HBV) and HIV, the latter of which has a testing uptake between 95% and 99% in Ontario. However, currently, universal prenatal testing for hepatitis C virus (HCV) is not recommended in most jurisdictions. The aim of our study was to examine HBV and HCV testing uptake, seroprevalence, and follow-up testing in women receiving prenatal care in Ontario, Canada, to identify potential gaps.

Methods: Anonymous, unlinked data from the provincial public health laboratory were collected to determine the number of women tested, and positive for HBsAg and anti-HCV from 2010–2017. As a result of unique identification numbers, we were able to link these individuals to results from subsequent tests completed for both HBeAg and HCV RNA. Data were compared by age and region.

Results: HBsAg prenatal testing occurred in 85% of live births with little year-to-year variation. Women ages 15–20 had the lowest prevalence at 0.1%, ages 21–25 at 0.5%, and those younger than 15, as well as ages 26–45 from 0.7–1%. Of the 2,326 women over 45 tested, 117 were positive, with a prevalence of 5%. From a regional perspective, the Greater Toronto Area had the highest rates ranging from 0.5% to 1.5%, whereas two regions in Northern Ontario had the lowest prevalence of 0.05%. Although HBeAg is a predictor of vertical transmission, only 8% of HBsAg-positive women received HBeAg testing within 259 days. With respect to HCV testing, 2% of all pregnant women from 2010 to 2017 were antibody tested using a prenatal requisition. Overall, 1.4% were HCV antibody positive, with the highest rates among pregnant women ages 21–25 at 2.5%. This is in comparison to younger (less than 21) at 2%, and older women (over 40) at 1.5%. Of women who tested HCV antibody positive, 56% had follow-up HCV RNA testing, with a positivity rate of 57%. HCV RNA was detected at the highest rates among those ages 21–30, at 61% of antibody positive individuals.

Conclusion: Our data demonstrate that HBsAg testing was frequent, but not universal, and that subsequent HBeAg testing was low; which may lead to missed opportunities for antiviral therapy. Acknowledging that some HCV screening may not be requested on a prenatal requisition, HCV testing uptake was also low, and only half of women received RNA follow-up testing. Knowing whether a woman is actively infected is essential to assess transmission risk and need for pediatric and maternal follow-up. These data point to the need for a streamlined approach to HBV and HCV prenatal screening and care.

THU-086

Scale up of hepatitis C virus treatment in the era of all-oral direct-acting antivirals: a 9-year Greek cohort study

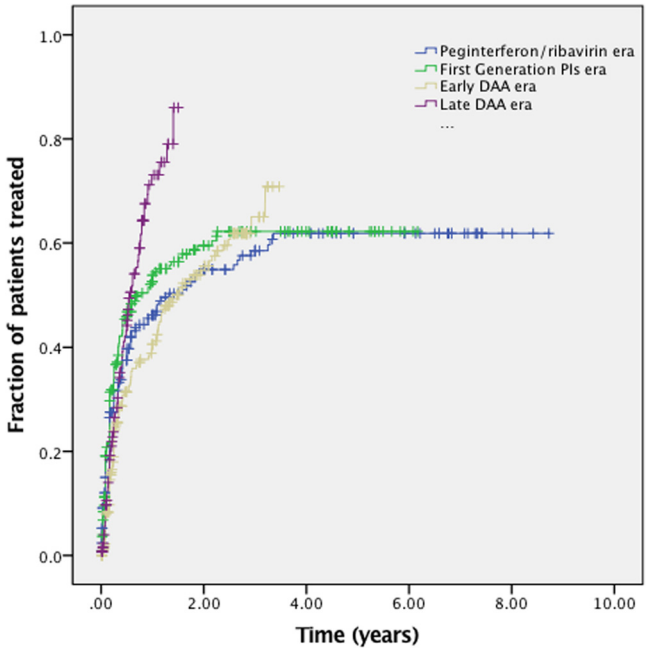
V. Papastergiou[1], M. Deutsch[1], M. Mela[2], C. Triantos[3], H. Kranidioti[1], C. Chatzievangelinou[2], K. Zisimopoulos[3], O. Anagnostou[4], G. Papatheodoridis[5], S. Manolakopoulos[6]. [1]*2nd Department of Internal Medicine, School of Medicine of National and Kapodistrian University of Athens, Athens, Greece;* [2]*Department of Gastroenterology, Evaggelismos General Hospital;* [3]*Department of Gastroenterology, University Hospital of Patras;* [4]*Greek Organisation Against Drugs (OKANA), Athens, Greece;* [5]*Academic Department of Gastroenterology, School of Medicine of National and Kapodistrian University of Athens;* [6]*2nd Department of Internal Medicine, School of Medicine of National and Kapodistrian University of Athens, Athens, Greece*

Email: vasi.pap@hotmail.com

Background and Aims: It is estimated that more than 80.000 people are living with hepatitis C virus (HCV) infection in Greece. A number of changes in direct-acting antivirals (DAA) reimbursement criteria have occurred during the last years, including prioritization of patients with ≥F2 fibrosis and those with hematological/kidney comorbidities since July 2017. However, the impact of these changes on HCV treatment initiation remains unknown. The aim of this study was to compare longitudinal HCV treatment initiation rates during 4 different periods: peginterferon/ribavirin (PR; January 2009–May 2011), first-generation protease inhibitors (PI; June 2011–December 2013), early DAA (January 2014–December 2015) and late DAA (January 2016–August 2017).

Method: Data were collected from 3 tertiary hospitals (5 physicians). A total of 832 HCV-viraemic adults were included (71.1% males, mean 46.5 ± 13.1 years, 56.3% intravenous drug users, 29.4% cirrhotics, 35.3% genotype-1, 74.9% treatment-naïve, PR/PI/early DAA/late DAA eras: 211/255/233/133), with at least one clinical visit between January 2009 and August 2017. Observation time was calculated from the day of first clinical visit to 31/10/17, initiation of antiviral treatment, last follow-up or death. Kaplan-Meier analyses were used to determine the cumulative incidence of start of antiviral therapy. Cox regression was used to estimate incidence rate ratios as relative risks (RR) with 95% confidence intervals (CI).

Results: Overall, 427 (51.3%) patients started treatment over a median (IQR) follow-up of 25.6 (8.6–73) weeks. The annual HCV treatment uptake remained stable from 2009 to 2013 fluctuating between 24.6%/year and 31.4%/year, dropped to 19.4%/year in 2014, and then raised again peaking to 32.7%/year in 2017. A steadily increasing trend was observed in the proportion of treated patients receiving all-oral DAAs, from 10.2% in 2014 to 89.9% in 2017. The overall cumulative probability of treatment across all periods was 50%, 64.3% and 66.3% at 1, 3 and 5 years respectively. Patients presenting in the late DAA era were significantly more likely to initiate therapy compared to those presenting in PR, PI, and early DAA eras (1-year cumulative treatment initiation: 73.1% vs 46.1%, 52.6% and 40.6% respectively; p = 0.006) (Figure). The probability of treatment was higher in the late (vs early) DAA period for non-cirrhotics (RR:2.43; 95%CI:1.51–3.90), treatment-naïve (RR:2.16; 95%CI:1.43–3.27), intravenous drug users (RR:3.05; 95%CI:1.92–4.82) and non-holders of public insurance (RR:4.87; 95% CI:2.63–8.70).



Conclusion: Our data show an increase in HCV treatment uptake after the introduction of new-generation DAAs and the expanded DAA

prioritization policies. However, as a substantial proportion of patients still remain untreated, more efforts are required in order to increase the HCV treatment uptake.

THU-087

Design and cost effectiveness of a hepatitis C virus elimination strategy based on an updated epidemiological study (ETHON cohort)

A. Cuadrado[1], C. Perello[2], S. Llerena[1], D. Escudero-García[3], M. Gómez[2], Á. Estébanez[1], L. Puchades[3], M. Serra[3], L. Rodríguez[2], J.C. Gonzalez[1], J.L.C. Panero[2], J. Crespo[1]. *[1]Marqués de Valdecilla University Hospital. IDIVAL. CIBERehd., Department of Gastroenterology and Hepatology; [2]Puerta de Hierro University Hospital, CIBERehd, Liver Unit; [3]University Hospital Clinic, Department of Medicine; University of Valencia, Service of Hepatology*
Email: acuadrado@humv.es

Background and Aims: Elimination of hepatitis C virus (HCV) is feasible in a country with universal access to direct acting antivirals, so hepatitis C screening in the general population is essential to achieve it. Our aim is to design a non-universal population screening strategy according to the results obtained in the ETHON study.
Method: Epidemiological, population and cross-sectional study carried out between July 2015 and March 2017 in three different communities of Spain (Madrid, Valencia and Cantabria). Two-stage cluster sampling was performed, with stratification by socio-economic status, rural/urban area and age. Anthropometric, demographic, analytical and serological data were collected. An analysis of the effectiveness of different HCV population screening settings was made. This analysis was carried out in 3 stages: Cost of the selection process, efficiency of the evaluation process and cost-effectiveness of the detection program + treatment.
Results: A total of 12,515 subjects were included (mean age 50.35 years, 41% men) (table). The prevalence of anti-HCV was 1.23%, and HCV-RNA were detectable in 0.32%. The prevalence was higher in males ($p < 0.001$), low educational level ($p < 0.001$) and with transmission risk factors ($p < 0.001$). 59% subjects knew the existence of the infection. The viremia positive was mainly between 45 and 59 years old (45–49: 0.30%, 50–54: 0.64%, 55–59: 0.46%), grouping more than 50% of cases. The strategy of HCV screening and its subsequent treatment has incremental cost-effectiveness ratios lower than 6,000 euros in any setting. The analysis by age cohorts shows that the screening strategy is cost-effective in any age cut, being especially effective between 45 and 49 years.
Conclusion: Our results show that a strategy of HCV screening and treatment aimed at subjects between 45 and 60 years old is highly cost-effective.

THU-088

Hepatitis C infection in the Pan American Health Organization Region: The current burden of disease and a road map for achieving the WHO Global Health Sector Strategy Goals

J. Schmelzer, S. Blach, S. Brandon, C. Estes, I. Gamkrelidze, H. Nde, D. Razavi-Shearer, S. Robbins, H. Razavi. *CDA Foundation, Polaris Observatory, Lafayette, United States*
Email: jonathan.schmelzer@centerforda.com

Background and Aims: The 69th World Health Assembly passed a resolution to eliminate viral hepatitis by 2030. Epidemiological assessment and predictive modeling are needed to develop strategies to achieve this goal. This study quantifies the current hepatitis C disease burden in the Pan American Health Organization (PAHO) and proposes a strategy for achieving the World Health Organization (WHO) Global Health Sector Strategy (GHSS) goals for Hepatitis by 2030.
Method: HCV disease burden models were developed for 24 countries and aggregated into a regional model which took into consideration new infections, disease progression, mortality and cured to estimate historic and future burden of disease. Regional averages were applied to country populations when country-specific data were not available. Intervention scenarios were developed within the regional model and projected outcomes related to the size of the HCV-infected population by disease stage were assessed from 2016 to 2030.

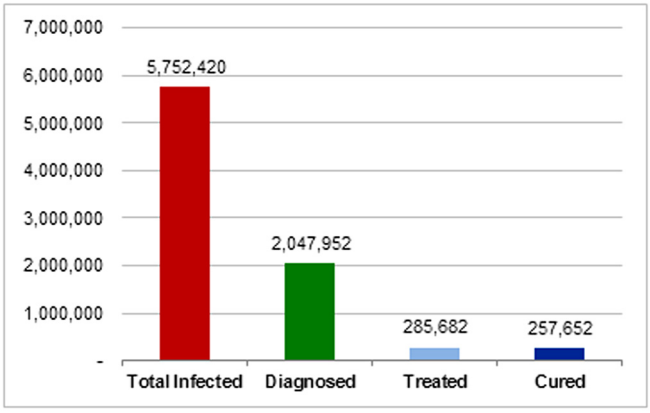


Figure 1: PAHO Cascade of Care, 2016.

Results: In 2016, there were an estimated 5.8 million viremic infections in the region, 36% of which had been previously diagnosed (163,000 newly diagnosed) and 286,000 of which had initiated treatment that year. Maintaining the current treatment and

Table: (abstract: THU-087)

Age range	n	Anti-HCV (+)	Prevalence of anti-HCV	HCV-RNA positive	Prevalence of HCV-RNA	Knowledge of HCV	RNA (-) by previous tratment	Spontaneous clearance	Spanish population estimated by SIN (2017)	Spanish anti-HCV population estimated (2017)	Spanish HCV-RNA (+) population estimated (2017)
20-24	368	1	0.27	1	0.27	1	0	0	2,261,020	6,105	6,105
25-29	409	1	0.24	1	0.24	1	0	0	2,518,366	6,044	6,044
30-34	668	4	0.59	1	0.14	0	0	2	2,961,043	17,470	4,145
35-39	1,237	6	0.48	2	0.16	6	3	1	3,716,570	17,840	5,947
40-44	1,592	9	0.56	3	0.18	5	0	3	3,960,335	22,178	7,129
45-49	1,638	25	1.52	5	0.3	17	4	14	3,742,512	56,886	11,228
50-54	1,706	33	1.93	11	0.64	19	8	10	3,524,707	68,027	22,558
55-59	1,519	28	1.84	7	0.46	18	6	6	3,151,461	57,987	14,497
60-64	1,299	20	1.53	4	0.26	11	6	8	2,636,543	40,339	6,855
65-69	1,124	9	0.8	2	0.17	5	0	5	2,370,045	18,960	4,029
70-74	686	11	1.6	1	0.29	5	1	6	2,058,779	32,940	5,970
75-79	269	7	2.6	2	0.74	4	2	1	1,537,204	39,967	11,375
TOTAL	12,515	154	1.23	40	0.32	92	30	56	34,438,585	384,744	105,882
						59,1%	26%	49%			

SNI, Statistics National Institute

diagnostic paradigm would result in an estimated 50% reduction in total HCV infections and 5% to 9% decrease in liver-related morbidity and mortality by 2030.
To achieve the GHSS goals of diagnosing 90% of total infections and reducing liver-related mortality by 65% by 2030, the region would need to treat an estimated 260,000 patients in 2017, gradually increasing to 280,000 in 2025, while gradually increasing the number diagnosed annually to 260,000 by 2025. Additional prevention efforts will need to be coordinated across the region in order to achieve the GHSS goal of a 90% reduction in new infections by 2030.

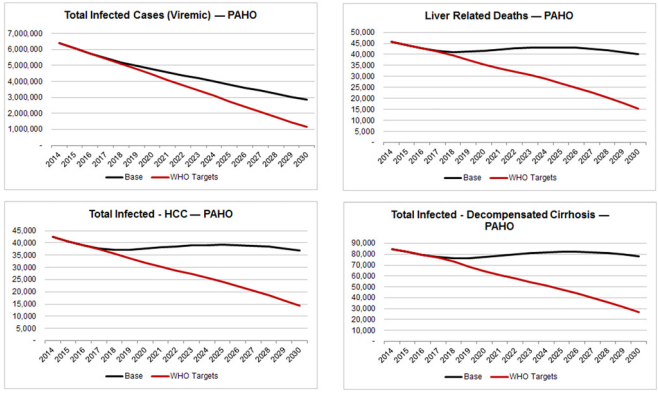


Figure 2: Liver Related Morbidity and Mortality by Scenario, 2016–2030.

Conclusion: Achieving the GHSS goals across the PAHO region is feasible with a slight increase in the number of annually diagnosed and treated cases. However, prevention efforts, easing age restrictions and the increased expansion of access to highly curative treatment will be necessary components.

THU-089
The current and future disease burden of hepatitis B in the general population and among five year olds in the Eastern Mediterranean Region

J. Schmelzer, D. Razavi-Shearer, S. Blach, S. Brandon, C. Estes, I. Gamkrelidze, H. Nde, S. Robbins, H. Razavi. *CDA Foundation, Polaris Observatory, Lafayette, United States*
Email: jonathan.schmelzer@centerforda.com

Background and Aims: Accurate national estimates of chronic hepatitis B (CHB) are needed to devise national and regional strategies. Previous studies have either provided prevalence estimates based on a literature review or have depended on regional models. This study quantifies the prevalence of CHB in the Eastern Mediterranean Region (EMRO) among the general population and five year olds from 2016 through 2030 using historical prevalence estimates combined with country level modeling.
Method: A literature review was conducted for hepatitis B surface antigen (HBsAg) prevalence among the general population (by age) and e-antigen prevalence among women of child bearing age. A dynamic country-level transmission and disease burden model was used to estimate the impact of vaccination, hepatitis B immune globulin, treatment of mothers, aging, disease progression and mortality in the infected population in each country. Regional averages were applied to populations of countries without available data and results were then aggregated to the region.
Results: HBsAg prevalence data were available and models were developed for 18 countries representing 92% of the region's population. In 2016, the regional CHB prevalence was estimated at 2.2% (CI:1.9–2.9%) corresponding to 14.9 million (CI:12.9–19.5 million) infections after the impact of perinatal prophylaxes was taken into consideration. There were an estimated 1.2 million total cases of cirrhosis, 111,000 cases of decompensated cirrhosis and 112,000 cases of hepatocellular carcinoma (HCC). Among five year olds, the regional prevalence was estimated to be 0.5% (CI:0.4–0.7%) corresponding to 76,100 infections (CI:67,300–110,000).
By 2030, total CHB infections in the EMRO region is projected to decline by 9% in the general population and 6% among five year olds. However, total cirrhosis, decompensated cirrhosis and HCC are expected to increase by 8%, 4% and 22% respectively.

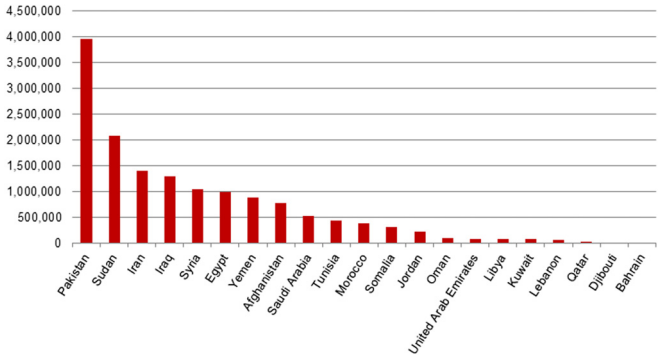


Figure 1: CHB Infections by EMRO Country, 2016.

Conclusion: While total CHB infections are expected to decline over the next 15 years in the EMRO region, advanced morbidity and mortality are projected to increase as the infected population ages. A CHB prevalence of 0.5% among five year olds and expected decline of only 6% suggests that higher perinatal prophylaxes coverage is needed to further reduce the prevalence among children.

THU-090
The covert "C"; prevalence: Risk factors and management of hepatitis C in psychiatric in-patients

J. Ramachandran[1], H. Slattery[2], S. Budd[2], T. Mohan[3], T. Cowain[4], A. Baas[5], L. Wigg[6], J. Alexander[6], K. Muller[1], B. Kaambwa[7], R. Woodman[8], A. Wigg[1]. *[1]Flinders Medical Centre, Flinders University, Department of Gastroenterology and Hepatology, Adelaide, Australia; [2]Flinders Medical Centre, Department of Psychiatry, Adelaide, Australia; [3]flinders medical Centre, Department of psychiatry, Adelaide, Australia; [4]the Jamie Iarcombe Centre, Glenside, veterans mental health, Adelaide, Australia; [5]Morier Ward, Noarlunga Hopsital, department of psychiatry, Adelaide, Australia; [6]gelnside campus, rural and remote mental health service, Adelaide, Australia; [7]flinders university, health economics unit, College of Medicine and Public health, Adelaide, Australia; [8]Flinders University, Flinders Centre for epidemiology and biostatistics, Adelaide, Australia*
Email: jeyamani.ramachandran@sa.gov.au

Background and Aims: Despite concerns about high prevalence of hepatitis C virus (HCV), psychiatry patients have been underserved due to neuropsychiatric adverse effects of interferon therapy. Directly acting antiviral (DAA) agents have made treatment of HCV in these patients feasible. In view of the paucity of information about prevalence of HCV in this group in Australia, and since an admission for mental illness may offer an opportunity for screening and treatment of HCV, this study was undertaken.
Aims of this study were to assess in patients admitted to hospital with mental illness: (1) HCV seroprevalence (2) prevalence of risk factors for HCV and (3) experience of treatment and follow-up.
Method: This was a point prevalence study including four inpatient psychiatric units. All inpatients from January 2017 to date were eligible to participate. After consent, HCV testing was performed and information about HCV risk factors obtained. Descriptive statistics for proportions were used to estimate HCV prevalence with 95% CI. Predictors of HCV prevalence were assessed using binomial logistic regression.

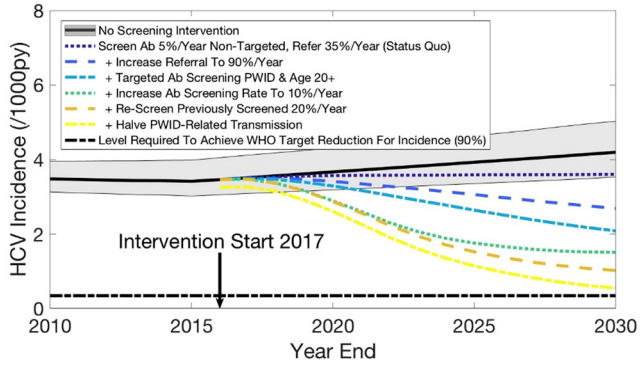
Results: 241 patients (70% male), median age 43 years (IQR 24) consented to the study, which was only 13% of patients admitted during the study period. Reasons for low recruitment included lack of interest, distrust and understanding by patients and busy schedule of medical staff.
Reasons for admission were major depression (26%), schizophrenia (17%), anxiety disorder (12%), bipolar affective disorder (10%), substance dependence (7%), personality disorder (3%) and other (14%). Prevalence of risk factors for HCV in the cohort were intravenous drug use (IVDU) (28%), exposure to custodial stay (20%), tattooing (63%), blood transfusion or organ transplantation (10%), sex workers (16%) and indigenous descent (8%). Period prevalence of HCV antibody was 10% (95%CI 7–15). Independent predictive factors for HCV seropositivity were IVDU (OR 15.60, 95%CI 4–61, $p < 0.001$) and custodial stay (OR 5.6, 95%CI 1.8–18, $p = 0.004$). HCV RNA was negative in 11/25 patients with positive antibody (prior treatment-5 and spontaneous clearance-6). Of the 14 patients with detectable HCV RNA, five were initiated on DAAs. Treatment was well tolerated, without significant non-adherence. One of them achieved viral clearance and results are awaited in the rest. The remaining 9 patients have proven difficult to engage with despite efforts by hospital and community care teams.
Conclusion: In view of high prevalence, psychiatric inpatients should be considered a high risk population for HCV and routine screening should be considered. Despite availability of well tolerated DAA therapy, engaging with this patient population remains a challenge. Non-traditional models of care involving community mental health teams, hepatitis nurses and primary care physicians require further investigation to improve treatment uptake.

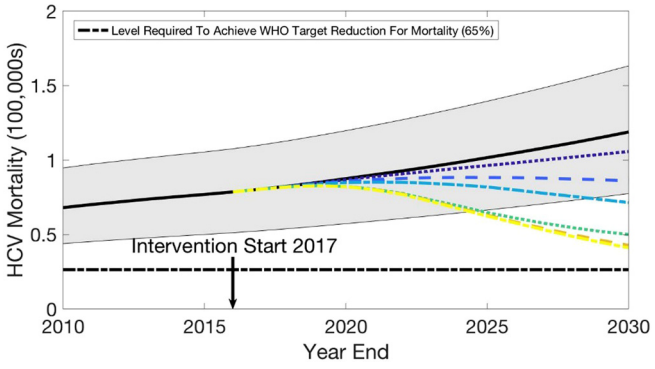
THU-091

Modelling the impact and efficiency of screening and treatment scale-up for hepatitis C virus in Pakistan: Working towards elimination

A.G. Lim[1], J. Walker[1], H. Qureshi[2], H. Mahmood[2,3], S.S. Hamid[4], F. Averhoff[5], P. Vickerman[1]. *[1]University of Bristol, Population Health Sciences, Bristol Medical School, Bristol, United Kingdom; [2]Pakistan Health Research Council (PHRC), Islamabad, Pakistan; [3]Centers for Disease Control and Prevention (CDC)/TEPHINET, Division of Viral Hepatitis, Atlanta, United States; [4]Aga Khan University, Karachi, Pakistan; [5]Centers for Disease Control and Prevention (CDC), Division of Viral Hepatitis, Atlanta, United States*
Email: aaron.lim@bristol.ac.uk

Background and Aims: Pakistan has the second-largest hepatitis C virus (HCV) burden worldwide. With increasing access to highly effective direct-acting antiviral (DAA) HCV treatment, Pakistan can now tackle the country's HCV epidemic and aim for the World Health Organization (WHO) HCV elimination targets. However, low levels of diagnosis and referral present challenges to treatment scale-up. We use modelling to project the impact of screening and treatment interventions in Pakistan to reduce HCV incidence by 90% and HCV-related mortality by 65% by 2030 compared with 2015.
Method: We developed a dynamic HCV transmission model for Pakistan incorporating screening and treatment, and calibrated to national HCV seroprevalence data from 2007 (4.8%), surveys among people who inject drugs (PWID, 56–69%), and HCV prevalence trends amongst blood-donors. Compared to a counterfactual of no treatment, we determine what screening coverage is needed from 2017 to sustain current treatment levels (150,000 annual treatments). We estimated the impact and costs of scaling-up screening, DAA treatment, and prevention interventions directed at achieving the WHO HCV-elimination targets.
Results: Current levels of treatment can be maintained by implementing general population screening with 5% of individuals screened annually (~10 million tested/year) and 35% of diagnosed individuals initiating treatment, resulting in 82 tests per treatment and 5 infections averted per 1000 antibody screenings (IA/1000Ab). However, incidence and mortality will rise by 6% and 38%, respectively, by 2030. Much greater impact is achieved by doubling annual screening to 10%, targeting adults (>20 years), increasing referral to 90%, and introducing re-screening every 5 years, with 56 tests per treatment, 10 IA/1000Ab, and the WHO mortality target reached by 2041. However, only with also halving HCV transmission risk in PWID will HCV incidence and mortality approach the WHO targets, now being reached by 2036. Preliminary costing estimates suggest that screening and treatment scale-up in Pakistan is likely to cost about USD$2,000 per cure, with the majority (70%) of costs coming from screening.





Conclusion: Substantial scale-up of screening and treatment interventions will be required to achieve the WHO HCV elimination targets. This can be optimised if referral rates are increased and screening is preferentially targeted toward priority groups with higher prevalence of HCV infection, but despite this, costs will be substantial.

THU-092

Characteristics and outcomes of patients with late presentation of hepatitis B among newly-diagnosed hepatocellular carcinoma: A national cohort study 2002–2013

D.H. Sinn[1], D. Kang[2], S.W. Paik[1], B.C. Yoo[3], J. Cho[2], G.-Y. Gwak[1]. *[1]Samsung Medical Center, Department of Medicine, Seoul, Korea, Rep. of South; [2]Samsung Medical Center, Department of Clinical Research Design and Evaluation, SAIHST, Seoul, Korea, Rep. of South; [3]Konkuk University Medical Center, Department of Medicine, Seoul, Korea, Rep. of South*
Email: sinndhn@hanmail.net

Background and Aims: Nowadays, effective and well tolerated treatments for hepatitis B virus (HBV) are available to treat and improve patient outcome, especially if diagnosed early. Consensus definition of late presentation of chronic viral hepatitis for medical

care has been recently suggested, yet, clinical implications on a population basis are lacking.
Method: We used a population-based, National Health Insurance Service-National Sample Cohort between January 1, 2002 and December 31, 2013 to assess presentation pattern among newly-diagnosed HBV-associated hepatocellular carcinoma (HCC) patients. Late presentation was defined when patients were diagnosed with HCC without prior clinic visit for HBV. For patients with prior clinic visit, they were categorized into "regular" or "irregular" visit based on the pattern of outpatient clinic visits before HCC diagnosis.
Results: Among 1,326 newly diagnosed HBV-related HCC patients, 424 (32.0%) cases were late presentation cases, while 557 (42.0%) and 345 (26.0%) patients belonged to the irregular and regular visit groups, respectively. Late presentation has declined from 45% in 2003 to 22% in 2013, while regular clinic visit has increased from 22% in 2003 to 35% in 2013, respectively. Lower economic status and young age were associated with late presentation. Late presentation was associated with higher mortality compared to regular visit group (multivariable-adjusted HR, 1.97; 95%CI, 1.59–2.44), as well as the irregular visit group (multivariable-adjusted HR: 1.42, 95%CI, 1.42–1.75).
Conclusion: Late presentation was associated with increased risk of mortality in HBV-related HCC patients, indicating that reducing late presentation is one of practical goals to decrease mortality for HBV-related HCC on a population level. Late presentation is a good surrogate to estimate clinical situation and monitor effectiveness of current health-care policy for hepatitis B and liver cancer on population level.

THU-093

Evaluation of the Xpert fingerstick HCV viral load assay

F. Lamoury[1,2], S. Bajis[1], B. Hajarizadeh[1], A. Marshall[1], M. Martinello[1], E. Ivanova[2], B. Catlett[3], Y. Mowat[1], P. Marks[1], J. Amin[4], J. Smith[5], N. Ezard[6], V. Cock[7], J. Hayllar[8], D. Persing[9], M. Kleman[10], P. Cunningham[11], G. Dore[1], T. Applegate[1], J. Grebely[12]. *[1]UNSW Sydney, The Kirby Institute, Sydney, Australia; [2]Foundation for Innovative Diagnostics, Geneva, Switzerland; [3]St Vincent's Centre for Applied Medical Research, Sydney, Australia; [4]Macquarie University, Sydney, Australia; [5]Matthew Talbot Hostel, St Vincent de Paul Society NSW Support Services, Sydney, Australia; [6]St Vincent's Hospital, Alcohol and Drug Service, Sydney, Australia; [7]Drug and Alcohol Services of South Australia, Adelaide, Australia; [8]Metro North Mental Health, Metro North Hospital and Health Service, Alcohol and Drug Service, Brisbane, Australia; [9]Cepheid, Sunnyvale, United States; [10]Cepheid AB, Solna, Sweden; [11]St Vincent's Centre for Applied Medical Research, Sydney, Australia; [12]UNSW Sydney, The Kirby Institute, Australia*
Email: jgrebely@kirby.unsw.edu.au

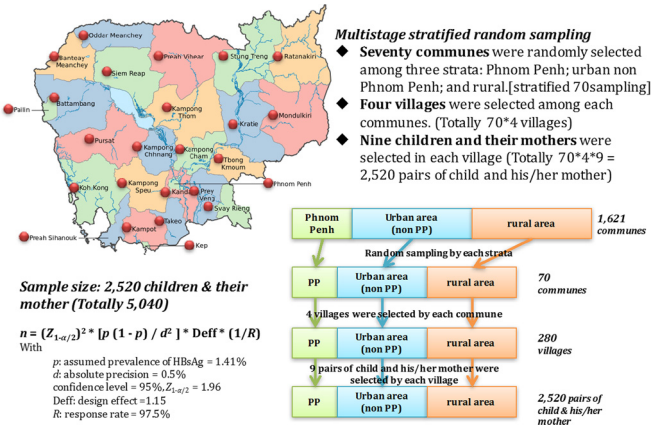
Background and Aims: Point-of-care hepatitis C virus (HCV) RNA testing is advantageous over antibody testing (which only indicates previous exposure), enabling diagnosis of active infection in a single visit. The aim of this study was to evaluate the performance of the Xpert® HCV Viral Load Fingerstick assay (Xpert HCV VL FS) from samples collected by finger-stick capillary whole-blood and the Xpert® HCV Viral Load Assay from plasma samples collected by venepuncture.
Method: Plasma and finger-stick capillary whole-blood samples were collected from participants in an observational cohort enrolled at four sites in Australia (three drug treatment clinics and one homelessness service). This study evaluated the sensitivity and specificity of the Xpert® HCV VL FS assay for HCV RNA detection (finger-stick) and the Xpert® HCV Viral Load Assay (plasma) compared with the Abbott RealTime HCV Viral Load assay by venepuncture (reference standard).
Results: Of 223 participants enrolled, 181 had HCV RNA testing results for the three assays tested. Participants receiving HCV therapy were excluded from analyses (n = 16). HCV RNA was detected in 36% ([95%CI 29–44], 60 of 165). Sensitivity of the Xpert® HCV Viral Load Assay for HCV RNA quantification in plasma collected by venepuncture was 100.0% (95%CI 93.9–100.0) and specificity was 100.0% (95%CI 96.5–100.0). Sensitivity of the Xpert® HCV VL FS assay for HCV RNA quantification in samples collected by finger-stick was 100.0% (95%CI 93.9–100.0) and specificity was 100.0% (95%CI 96.5–100.0).
Conclusion: The Xpert® HCV VL FS test can accurately detect active infection from a finger-stick sample in one hour allowing single-visit HCV diagnosis, representing an advance over current diagnostic algorithms which involve sequential antibody and RNA testing. This advance offers an opportunity to move towards a single-visit HCV diagnosis.

THU-094

Sero-prevalence of Hepatitis B surface antigen among 5–7 years old children and their mothers in Cambodia by nationwide multi-stage stratified random sampling strategy

J. Tanaka[1], J.V. Woodring[2], V. Ork[3], M. Bunsoth[4], S. Nagashima[1], C. Yamamoto[1], C. Chuon[1], K. Ko[1], S. Hossain[5]. *[1]Hiroshima University, Epidemiology Infectious Disease Control and Prevention, Hiroshima, Japan; [2]WPRO, Expanded Programme on Immunization, Manilla, Philippines; [3]Ministry of Health Cambodia, National Immunization Program, Phnom Penh, Cambodia; [4]University of Health Science, Phnom Penh, Cambodia; [5]WHO Country Office in Cambodia, Expanded Programme on Immunization, Phnom Penh, Cambodia*
Email: jun-tanaka@hiroshima-u.ac.jp

Background and Aims: HBV is highly endemic in Cambodia with an estimated HBsAg prevalence of 9%. Since 2005, HB vaccine has been launched as NIP at birth and then the regional goal of <1% HBsAg prevalence among >5 years old children was set to attain in 2017. The primary aim was to assess the impact of NIP by estimating HBsAg prevalence among children who were born after 2005. Additionally, this study determined the effectiveness of dried blood spots (DBS) sample in field settings.
Method: Nationwide cross-sectional sero-prevalence study among 5–7 years old children and their mother was conducted by collaboration among Hiroshima Univ, WPRO, WHO-Cambodia, US-CDC, NIP and UHS. Multistage stratified random sampling was used in which four villages were selected from each commune among total 70 communes in three strata. Thereafter, nine pairs of targeted children and their mothers were selected from each village. Demographic data and written or oral vaccination history were collected by questionnaires. The total of 2514 children and 2021 mothers were participated and tested for HBsAg by rapid testing and then additional blood samples were taken by DBS. Among them, total of 520 children and 408 mothers were undergone venepuncture for further investigation of HBV serological markers including anti-HBs, anti HBc as well as HBV DNA by Nested-PCR.
Results: The average age of mother was 32.5 ± 6.1 years. The prevalence of HBsAg among children was 0.6% [95%CI: 0.3–0.8%] by rapid test, 0.5% [0.2–0.8%] by DBS and 0.8% [0–1.5%] by venepuncture while 4.4%, 4.7% and 5.4% in mother respectively. By questionnaires, 1145(45.5%) children received birth-dose HB vaccine within 24 hours after birth, 791(31.4%) children received after 24 hours and 581 (23.1%) children did not. Among 95 HBsAg positive mothers, 9(9.5%) children become HBsAg positive in which 3(33.3%) children have already received HB birth-dose vaccine. Among 1,926 HBsAg negative mothers, 2(0.1%) children became HBsAg positive in which 1(50%) child has received HB birth-dose vaccine.
Conclusion: Since 9.5% of children born to positive mother were positive for HBsAg, it is indicated that mother-to-child transmission is not under control. Finally, <1% seroprevalence among children indicates that Cambodia has met the 2017 regional target. By this study, DBS with resultant sensitivity of 92% (24/26) and specificity of 100% (895/895) compared by venepuncture suggested that it is as useful in field setting.



THU-095

Burden of comorbidity in patients with advanced NASH-a retrospective analysis using a large US insurance claims database

T.D. Kou[1], L. Burns[2], Y. Qiu[3], T. Kansal[4], N. Ray[5]. [1]*Bristol-Myers Squibb, Global Pharmacovigilance and Epidemiology, Pennington, United States;* [2]*Bristol-Myers Squibb, CORDS, Hopewell, United States;* [3]*Bristol-Myers Squibb, Worldwide Health Economic and Outcome Research, Hopewell, United States;* [4]*Mu-sigma, Pennington, United States;* [5]*Mu-sigma, Hopewell, United States*
Email: tzuyung.kou@bms.com

Background and Aims: Patients diagnosed with nonalcoholic steatohepatitis (NASH) have a higher risk of cirrhosis, end stage liver disease, and liver transplantation. The presence of advanced fibrosis has been associated with increased mortality and liver-related events in NASH patients. Most NASH natural history studies relied upon relatively small cohorts of patients chosen from clinical practice. Elucidating which patient characteristics are associated with NASH, and with advanced fibrosis in a large, real-world setting, is critical for a more complete understanding of the natural history of NASH.

Method: Using the Optum insurance claims database, patients with relevant diagnosis code(s), with available liver enzyme test results, and with coverage enrollment between 2002 and 2015 were included in the analysis. FIB-4 score at time of index date was calculated. Burden of comorbid conditions based on diagnosis codes at baseline was described using the modified Charlson Comorbidity Index. Clinical and demographic characteristics of NASH patients with FIB-4 score ≥2.67 (indicative of advanced fibrosis) and no evidence of decompensation were compared to patients with FIB-4 score <2.67. Relevant statistical methods were used to test for significant difference ($p < 0.05$). Potential association was further evaluated using a multivariate logistic regression.

Results: NASH patients with available estimated FIB-4 score (n = 112,183) were included in the analysis. 5,964 or 5.3% had a FIB-4 score ≥2.67. Overall, NASH patients had higher a prevalence of pulmonary disease (28.5%), type 2 diabetes (T2DM) (37.6%), cardiovascular risk factors (8.2%), rheumatologic disease (6.8%), and other chronic disease compared to general population. Compared to NASH patients with FIB-4 score <2.67, NASH patients with FIB-4 score ≥2.67 were older (mean age 65.6 vs. 52.8), more frequently male (49.8 vs. 43.5%), and had a higher burden of comorbidities (Charlson comorbidity index score of 2.2 vs. 1.3). NASH patients with FIB-4 score ≥2.67 also had a higher prevalence of T2DM (49.2 vs. 37.0%), renal disease (14.9 vs. 7.0%), congestive heart failure (16.0 vs. 7.7%), and higher prevalence of malignancy (17.7 vs. 10.8%). Multivariate logistic regression controlling for potential confounders further confirmed these associations.

Conclusion: The overall NASH patient population has a higher comorbidity burden compared to the general population. NASH patients with advanced fibrosis (FIB-4 score ≥ 2.67) but without decompensation are more likely to have various comorbid conditions such as T2DM, renal disease, congestive heart failure, and malignancy compared to NASH patients without advanced fibrosis. Findings suggest that NASH patients with advanced fibrosis represent a unique subset of all NASH patients with a distinct natural history requiring different treatment considerations.

THU-096

Khat chewing increases the risk for developing chronic liver disease: A hospital-based case-control study

S. Orlien[1], I. Sandven[2], N. Berhe[3], N.Y. Ismael[4], T.A. Ahmed[4], K. Stene-Johansen[5], S.G. Gundersen[6,7], M. Morgan[8], A. Johannessen[1]. [1]*Oslo University Hospital Ullevål, Regional Centre for Imported and Tropical Diseases, Oslo, Norway;* [2]*Oslo University Hospital, Oslo Centre of Biostatistics and Epidemiology, Oslo, Norway;* [3]*Addis Ababa University, Aklilu Lemma Institute of Pathobiology, Addis Ababa, Ethiopia;* [4]*Haramaya University, College of Health and Medical Sciences, Harar, Ethiopia;* [5]*Norwegian Institute of Public Health, Department of Molecular Biology, Oslo, Norway;* [6]*University of Agder, Department of Global Development and Planning, Kristiansand S, Norway;* [7]*Sørlandet Hospital HF, Research Unit, Kristiansand S, Norway;* [8]*University College London, UCL Institute for Liver & Digestive Health, London, United Kingdom*
Email: stian@orlien.no

Background and Aims: The chewing of the leaves of *Catha edulis* (khat) is widespread at the Horn of Africa and Arabian Peninsula; the habit is perpetuated or even adopted by immigrant communities worldwide. Case reports from Europe, USA, Africa and Australia implicate khat in the development of liver disease but no controlled observations have been undertaken. The aim of the present study was to determine whether chewing khat is associated with the development of chronic liver disease (CLD).

Method: A case-control study was conducted at two public hospitals in Harar, Ethiopia, between April 2015 and April 2016. The cases comprised of 150 adult hospital attendees with evidence of CLD were included as cases. The controls comprised of 300 adult hospital attendees without clinical or laboratory evidence of CLD. Information on risk factors for liver disease was collected from cases and controls. Khat consumption was quantified in khat years; one khat year was defined as daily use of 200 grams of fresh khat for one year. A logistic regression model was used to control for confounders; interaction was pinpointed by stratification analysis.

Results: There was a significant association between chewing khat and the risk for developing CLD (crude odds ratio [OR] 2.64; 95% CI 1.56–4.58). After adjusting for age, alcohol consumption and viral hepatitis, the effect was strong in men (adjusted odds ratio [AOR] 5.67; 95% CI 1.85–17.37; p = 0.002), but not evident in women (AOR 1.04; 95% CI 0.49–2.19; p = 0.922). In men, a dose-response relationship was observed (Table). The findings were robust in a post hoc sensitivity analysis in which cases and controls with identifiable risk factors for CLD were excluded.

Table: Gradient effect of khat use on chronic liver disease, stratified by sex

	Men[1] (n = 280)			Women[1] (n = 170)		
Khat years (quartiles):	Cases (n = 108)	Controls (n = 172)	OR (95% CI)	Cases (n = 42)	Controls (n = 128)	OR (95% CI)
0	4	40	1	19	61	1
0.1–5.0	21	40	3.88 (1.11–13.56)	11	37	1.24 (0.48–3.17)
5.1–40.0	34	51	5.84 (1.73–19.65)	7	22	0.99 (0.32–3.12)
40.1–250.0	49	41	13.62 (3.71–50.05)	5	8	1.75 (0.38–8.16)
Test for trend:	p = 0.0007			p = 0.8805		

CI, confidence interval; OR, odds ratio.
[1]Adjusted for age, alcohol and viral hepatitis.

Conclusion: A significant association was observed between chewing khat and the risk for developing CLD. In men, the association was strong and dose-dependent, suggesting a causal relationship. These findings have significant public health implications given the widespread use of khat worldwide.

THU-097

The global prevalence of HBsAg by age in 2016 and the case for universal treatment in low and middle income countries

D. Razavi-Shearer, I. Gamkrelidze, S. Blach, S. Brandon, C. Estes, H. Nde, S. Robbins, J. Schmelzer, H. Razavi. *The Polaris Observatory, Lafayette, United States*
Email: hrazavi@cdafound.org

Background and Aims: For over thirty years, vaccination to protect against hepatitis B virus (HBV) has been available. The impact of rigorous vaccination programs have resulted in major reductions in the incidence of HBV and the prevalence in vaccinated cohorts. However, there are many countries that have yet to introduce birth dose, and HBV remains a major problem. Quantifying the age of the infected population is imperative, as it is evidence of the importance of vaccination, but also a harbinger for the coming burden of the later stages of the disease that will impact health systems globally.
Method: 120 country level PRoGReSs models were built based on literature review and consultation with country experts. The transmission and disease progression model was utilized use historical prevalence estimates to quantify the prevalence of HBsAg by age in 2016 after taking into account the impact of perinatal prophylaxes measures. Global age specific prevalence was estimated by extrapolating data from countries in each Global Burden of Disease Regions to countries without data and summing across all countries.
Results: In 2016, there were an estimated 284 (UI: 246–339) million individuals chronically infected with HBV. While the impact of vaccination can be seen in the 25–29 year cohort, it is the <25 year cohorts in which this impact is most visible (Figure). Unfortunately, even with availability of vaccines, there are an estimated 49 million under the age of 20 who are infected due to low or no birth or 3 dose vaccination. Although HBsAg prevalence stays relatively constant after age 25, the total number of infections declined as shown below due to mortality and declining population. Almost 70% of all infections (200 million) are found between the ages of 15 and 54 and this cohort has by and large yet to progress to the later and more expensive stages of the disease. Without treatment, many will progress to end stage liver disease as they age.

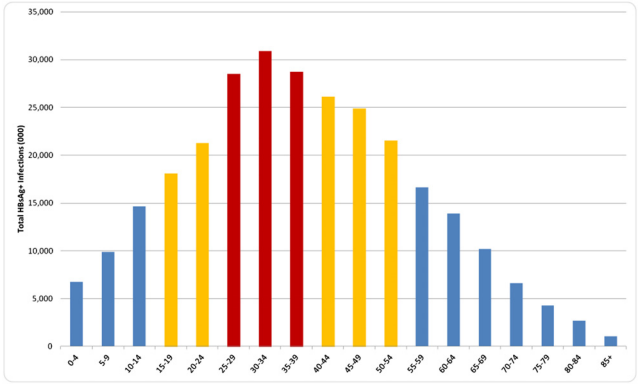


Figure 1: Global Distribution of HBsAg by Age, 2016.

Conclusion: Due to vaccination, the future prevalence of hepatitis B will be lower in the younger age cohorts. However, HBV related disease burden will continue to increase as the infected population ages. With limited availability and the cost of annual diagnostics and follow-ups in lower and middle income countries, universal treatment of all infected can aid in stopping transmission and disease progression. The low cost of antiviral treatments allows for a test and treat strategy in these countries.

THU-098

Influence of geographical origin on access to therapy and therapy outcomes in hepatitis C virus-infected persons: the Swiss Hepatitis C Cohort Study

M. Brezzi[1], B. Bertisch[1], D. Moradpour[2], A. Cerny[3], J.-F. Dufour[4,5], M. Heim[6], B. Müllhaupt[7], D. Semela[8], F. Negro[9], O. Keiser[1]. *[1]Institut of Global Health, University of Geneva, Geneva, Switzerland; [2]Division of Gastroenterology and Hepatology, University Hospital Lausanne, Lausanne, Switzerland; [3]Epatocentro Ticino, Lugano, Switzerland; [4]Hepatology, Department of Clinical Research, University of Bern, Berne, Switzerland; [5]University Clinic of Visceral Surgery and Medicine, Inselspital Bern, Berne, Switzerland; [6]Gastroenterologie & Hepatologie, Universitätsspital Basel, Basel, Switzerland; [7]Gastroenterology and Hepatology, University Hospital Zurich, Zurich, Switzerland; [8]Division of Gastroenterology and Hepatology, Kantonspital St.Gallen, St.Gallen, Switzerland; [9]Divisions of Gastroenterology and Hepatology and of Clinical Pathology, University Hospitals Geneva, Geneva, Switzerland*
Email: matteo.brezzi@gmail.com

Background and Aims: Hepatitis C (HCV) is an important health threat, and late diagnosis, limited access to care and poor adherence to treatment may increase morbidity and mortality. We explored whether their origin is associated with access to therapy and therapy outcomes in HCV-infected persons in the Swiss Hepatitis C Cohort Study (SCCS).
Method: We included all persons enrolled in the SCCS and analyzed the association between their origin and the following outcomes by univariable and multivariable logistic and Cox regressions: (a) antiviral treatment status (ATS), (b) sustained virologic response (SVR), (c) cirrhosis at enrolment, (d) incident cirrhosis during follow-up, (e) loss to follow-up (LTFU), and (f) mortality. Analyses were adjusted for the following baseline characteristics: gender, age, education, source of income, alcohol consumption, injection drug use (IDU), HCV genotype, HIV and/or HBV co-infection, duration of HCV infection, cirrhosis and center of enrolment.
Results: Among 5,356 persons of known origin, 1,752 (32.7%) were foreign-born. IDU was more frequent among Swiss (65.5%) compared to non-Swiss (37.7%). Figure 1 shows both crude and adjusted results. In adjusted analyses, persons of foreign origin were more likely to have cirrhosis at enrolment (odds ratio OR 1.29, 95%CI 1.06–1.56) and to be LTFU (hazard ratio HR 1.37, 95%CI 1.20–1.58). Mortality was lower in foreign-born persons (HR 0.69, 95%CI 0.54–0.87). There was no association for treatment status, sustained virologic response and incident cirrhosis. Part of the differences between persons of Swiss and foreign origin were attributable to particular countries. For example, LTFU was more frequent in persons from Germany, Eastern and Southern Europe as well as America; while baseline cirrhosis was more frequent in Italians.
Conclusion: There were substantial differences in access to therapy and therapy outcomes depending on the country of origin of the study participants, and the type of the outcome studied. The heterogeneity was only slightly reduced in the adjusted analyses, which suggests that additional unmeasured lifestyle factors associated with drug use, genetic factors, and physician-related factors may explain most of the difference.

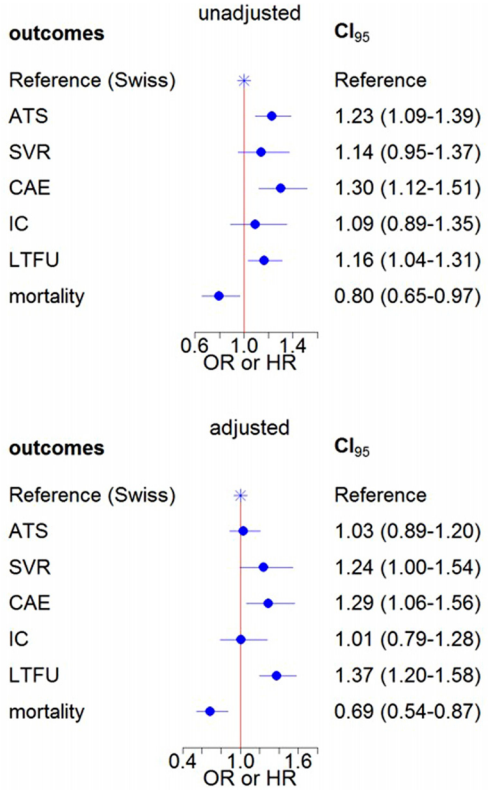


Figure 1: Univariable and multivariable logistic and Cox regression analyses for different outcomes by origin (Swiss versus foreign-born). Odds ratios (OR, with 95% confidence intervals) are shown for antiviral treatment status (ATS), sustained virologic response (SVR) and cirrhosis at enrolment (CAE). Hazard ratios (HR) are shown for incident cirrhosis (IC), loss to follow-up (LTFU) and mortality.

THU-099

Lowering the upper limit of serum alanine aminotransferase levels may detect significant liver disease in the elderly

H. Schmilovitz-Weiss[1,2], R. Gingold-Belfer[3], A. Gossman[4], N. Issa[2], D. Boltin[4], Y. Beloosesky[4], N. Koren-Morag[5], J. Meyerovitch[6], A. Weiss[4].
[1]Rabin Medical Center Golda Hasharon Campus, Gastroenterology, Petah Tikva, Israel; [2]Rabin Medical Center Golda Hasharon Campus, Petach Tikva, Israel; [3]Rabin Medical Center Beilinson, Gastroenterology, Petah Tikva, Israel; [4]Rabin Medical Center Beilinson, Petah Tikva, Israel; [5]Tel Aviv University, Sackler Faculty of Medicine, Tel Aviv, Israel; [6]Schneider Children 's Medical Center, Petah Tikva, Israel
Email: hemdaw1@017.net.il

Background and Aims: Serum alanine aminotransferase (ALT) levels above normal range are markers of liver injury. Studies recently suggested lowering the upper limit of normal (ULN) of ALT. This study aimed to investigate the prevalence of significant liver disease in elderly patients in whom ALT levels fall within the difference between the previous ULN the newly suggested ULN ("delta range").
Method: The database of a large HMO was searched for all individuals aged ≥ 65 years who underwent at least one measurement of ALT in 2002 and were followed until 2012 (n = 49,634). Fibrosis scores in the two groups were calculated with the FIB-4, AAR, and APRI. Prevalence rates of chronic liver disease (CLD) and particularly liver cirrhosis (fibrosis score ≥ 2) were compared between those with ALT levels in the delta range (42–45 IU/l for men, 26–34 IU/l for women) and those with ALT levels in the newly suggested normal range (15–42 IU/L for men, 10–26 IU/L for women).
Results: CLD was diagnosed in 2022 subjects (41% male, mean age 83 ± 6 years), and cirrhosis, in 366. Compared to subjects with ALT values in the newly suggested range, subjects with "delta-range" values had higher rates of CLD (men, 15.3% vs. 4.9%; women, 7.8% vs. 3.3%) and cirrhosis (men, 4.2% vs. 0.9%; women, 1.5% vs. 0.4%) and significantly higher mean fibrosis scores.
Conclusion: Lowering the current ULN of serum ALT may help to identify significant liver disease in the elderly.

THU-100

Hepatitis C patients with HIV co-infection demonstrate unique liver-related complications and health behaviors compared to HCV mono-infected patients

M. Lu[1], N.P. Markowitz[2], Y. Zhou[1], K.-H. Wu[1], L.B. Rupp[3], S. Trudeau[1], J.A. Boscarino[4], M.A. Schmidt[5], Y.G. Daida[6], S.C. Gordon[7]. *[1]Henry Ford Healthy System, Department of Public Health Sciences; [2]Henry Ford Healthy System, Department of Infectious Disease; [3]Henry Ford Healthy System, Center for Health Policy and Health Services Research; [4]Geisinger Clinic, Department of Epidemiology and Health Services Research; [5]Kaiser Permanente Northwest, Center for Health Research; [6]Kaiser Permanente Hawai'i, Center for Health Research; [7]Henry Ford Healthy System, Department of Gastroenterology and Hepatology*
Email: mlu1@hfhs.org

Background: Most studies of hepatitis C (HCV) and HIV co-infection focus on HIV cohorts, and may not collect data regarding liver-related outcomes. We used data from the Chronic Hepatitis Cohort Study to investigate the impact of HIV on clinical characteristics and mental health in HCV patients.
Methods: Patient demographics and clinical status were collected from the electronic health record from date of diagnosis (HCV or HIV/HCV co-infection) onward. A subgroup provided survey data regarding health-related behaviors and mental health. Chi-square tests and two-sample t-tests were used to compare categorical and continuous variables, respectively, between mono- and co-infected patients.
Results: Among 14545 patients, 584 (4.0%) were HIV co-infected. Compared to mono-infected patients, co-infected patients were significantly younger and more likely to be male, African American, low-income, and publicly insured; less likely to see a liver specialist or receive HCV treatment; and demonstrated increased comorbidities, fibrosis/ cirrhosis, hepatocellular carcinoma, and mortality. Among 5008 survey respondents (4885 HCV; 123 HIV/HCV), co-infected patients were significantly more likely to report drug/ alcohol use and sex with multiple partners.
Conclusion: HIV co-infection impacts a demographically distinct subset of HCV patients. Despite high rates of HIV treatment, co-infected patients were less likely to see a liver specialist or receive HCV-specific treatment than HCV mono-infected patients. Co-infected patients also demonstrated increased rates of liver complications and mortality, as well as high-risk behaviors.

Table: Demographics, current clinical status, and survey responses

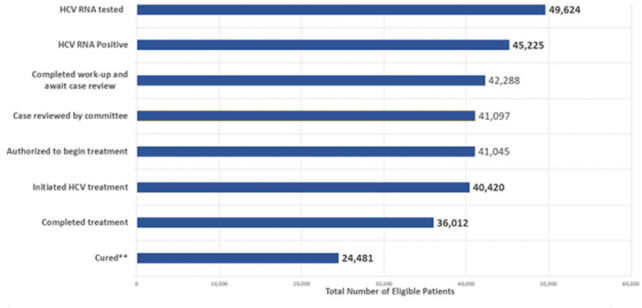
Variable	Response	n = 13961	n = 584	p
Sex	F	40%	25%	<0.001
	M	60%	75%	
Age	<40	8%	7%	<0.001
	40 < 50	9%	22%	
	50 < 60	32%	42%	
	≥60	51%	29%	
Race	ASINPI	6%	4%	<0.001
	Black	24%	43%	
	White	65%	49%	
	Unknown	5%	4%	
Insurance	Medicaid	17%	31%	<0.001
	Medicare	33%	39%	
	Private	49%	30%	
Income	<$30 K	23%	41%	<0.001
	$30 < 50 K	46%	43%	
	≥$50 K	32%	15%	
Charlson-Deyo comorbidity score	0	68%	29%	<0.001
	1–2	25%	9%	
	≥3	7%	62%	
Fibrosis-4 category	<1.21	20%	18%	<0.001
	1.21–5.88	34%	46%	
	>5.88	9%	8%	
	Unk	37%	28%	
Cirrhosis	No	62%	68%	0.005
	Yes	38%	32%	
Hepatocellular carcinoma	No	95%	98%	<0.001
	Yes	5%	2%	
Ever treated for HCV	No	45%	66%	<0.001
	Yes	55%	34%	
Ever treated for HIV	No	100%	21%	<0.001
	Yes	0%	79%	
Deceased	No	79%	64%	<0.001
	Yes	21%	36%	
Survey	*Response*	*HCV n = 4885*	*HIV/HCV n= 123*	*p*
Hx of alcohol use	No	25%	15%	0.021
	Yes	75%	85%	
Hx of injection drug use	No	97%	89%	<0.001
	Yes	3%	11%	
Hx of intranasal drug use	No	95%	89%	0.029
	Yes	5%	11%	
Hx sex with multiple partners	No	92%	66%	<0.001
	Yes	8%	34%	
Marital status	Single	48%	80%	<0.001
	Married	50%	19%	
Change/ stop HCV rx	No	68%	65%	0.447
	Yes	29%	29%	
	NA	3%	6%	
Liver specialist	No	14%	21%	0.049
	Yes	83%	75%	
	NA	1%	1%	
	Don't know	2%	3%	
Depression	No	70%	63%	0.069
	Yes	30%	37%	
Stress level	None	46%	41%	0.119
	Moderate	29%	37%	
	High	25%	22%	
Support level	Low	24%	26%	0.061
	Moderate	27%	35%	
	High	49%	39%	

THU-101

Progress toward hepatitis C virus elimination through provision of care and treatment services, Georgia, 2015–2017

D. Sergeenko[1], A. Gamkrelidze[2], T. Tsertsvadze[3], G. Kamkamidze[4], D. Metreveli[5], L. Sharvadze[6], M. Tsereteli[2], A. Aslanikashvili[2], E. Adamia[7], L. Gvinjilia[8], M. Nasrullah[9], T. Kuchuloria[8], F. Averhoff[9].
[1]Ministry of Labor, Health and Social Affairs of Georgia, Minister; [2]National Center for Disease Control and Public Health; [3]Infection Diseases, AIDS, and Clinical Immunology Research Center, Tbilisi, Georgia; [4]Neolab, Director; [5]Medical Center Mrcheveli; [6]Hepatology Clinic HEPA; [7]Ministry of Labor, Health and Social Affairs of Georgia, State Programs Department; [8]CDC Foundation; [9]Centers for Disease Control and Prevention
Email: mtsereteli2002@yahoo.com

Background and Aims: The country of Georgia has high burden of hepatitis C virus (HCV) infection. The nationwide seroprevalence survey conducted in 2015, indicated 5.4% of adults (approximately 150,000 persons) with active HCV infection (RNA positive). In April 2015, the Georgian government, in collaboration with CDC and other partners embarked on a national program to eliminate HCV by 2020, defined as decreasing prevalence of active infection by 90%; a key strategy is scaling up HCV treatment by ensuring access to free of charge treatment for all infected persons.
Method: Data from all screening and treatment sites are collected and analysed by the Georgia National Center for Disease Control and Public Health and Ministry officials. All data from treatment providers are entered into a web-based database. A unified electronic screening registry captures data from all national and local HCV screening programs throughout Georgia. Data from the screening and treatment programs are linked by a unique identification number; these data were analysed to describe the national cascade of care.
Results: From April 28, 2015 through October 31, 2017, more than 1.2 million people were screened for HCV, and 45,225 HCV infected (RNA positive) individuals were registered for the treatment program. Among those who registered, 40,420 (89.4%) individuals initiated treatment, approximately 27% of the estimated 150,000 persons living with HCV in the country. Of those who initiated treatment, 36,012 (81%) completed treatment. Among individuals with available data on sustained virologic response (SVR) i.e., cure (n = 32,835), the overall SVR was 98.2%.



** of **32,835** patients eligible for SVR assessment, **24,930–**were tested, 24,481 **(98.2%)** achieved SVR, 7.905 (24%) missing data

Conclusion: In the first 30 months of the HCV Elimination Program, Georgia has scaled up the screening and treatment services achieving impressive cure rates. These activities represent a key step towards reaching the established national HCV elimination goals.

THU-102

High prevalence of hepatitis delta virus in specimens from Cameroon

E. Butler[1], M. Rodgers[1], K. Coller[1], D. Barnaby[2], E. Krilich[2], A. Olivo[1], M. Cassidy[1], D. Mbanya[3], L. Kaptue[4], N. Ndembi[5], G. Cloherty[1]. [1]*Abbott Laboratories, Infectious Disease Research, Abbott Park, United States;* [2]*Franciscan University of Steubenville, Franciscan Institute for Science and Health, Steubenville, United States;* [3]*Université de Yaoundé I, Yaoundé, Cameroon;* [4]*Université des Montagnes, Bangangté, Cameroon;* [5]*Institute of Human Virology, Abuja, Nigeria*
Email: mary.rodgers@abbott.com

Background and Aims: Hepatitis Delta virus (HDV), an RNA satellite virus of Hepatitis B virus (HBV), infects an estimated 15–20 million people worldwide and confers a greater risk for accelerated progression to liver disease and death. However, limited HDV surveillance data are available in sub-Saharan Africa where HDV diversity is high. To determine the prevalence and diversity of HDV in Cameroon, serological and molecular characterization was performed on 1928 HBV surface antigen (HBsAg) positive specimens.
Method: HBsAg positive plasma specimens were selected from retrospective HIV and HBV viral surveillance studies conducted in Cameroon from 2010–2016. Samples were screened for HDV IgG antibodies on the Abbott ARCHITECT instrument and HDV RNA on the Abbott m2000 instrument by prototype research assays. HDV positive specimens with sufficient viral load were selected for sequencing of overlapping regions covering the 1.7 kb HDV genome.
Results: The seroprevalence of HDV in HBsAg positive samples from Cameroon was 46.73% [95%CI; 44.51–48.96%], with prevalence of active HDV infection being 34.2% [95%CI; 32.09–36.41%]. HDV antibodies were detected in 98.6% of HDV RNA positive samples. Within the HIV positive cohort (48.86% of all samples), HDV seroprevalence was 43.29%. HDV sequences were obtained from n = 211 specimens, including n = 145 complete or near complete genomes with HDV genotypes 1, 6, 7 and 8 and several subgenotype branches within 1 and 7 clades identified.

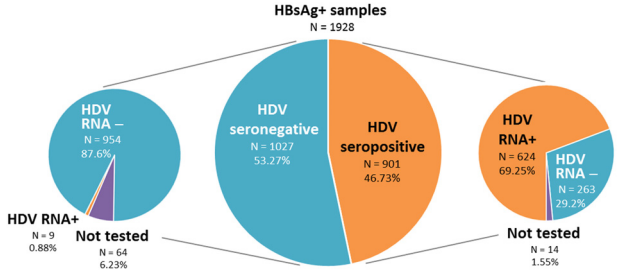


Figure: Pie charts summarizing results of serological testing (center) and RNA testing for HDV seropositive (left) and seronegative (right) for all HBsAg+ samples in the study.

Conclusion: HDV prevalence is high within the study cohort, indicating that a large portion of HBV infected individuals in Cameroon are at elevated risk for severe hepatitis and death. Collectively, these results emphasize the need for preventative measures like HBV vaccination and regular HDV testing of HBsAg positive patients in Cameroon.

THU-103

Achieving the World Hepatitis Organization global health sector strategies goals for hepatitis in the WHO Western Pacific Region: A modeling study

S. Brandon, C. Estes, H. Nde, J. Schmelzer, H. Razavi. *Center for Disease Analysis, Lafayette, United States*
Email: sbrandon@cdafound.org

Background and Aims: The Western Pacific Region (WPRO) region accounts for 20% of the burden of hepatitis C (HCV) globally, but data to guide management strategies are lacking. Progression to decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver related death (LRD) makes the virus a main driver of morbidity in the region. This study sought to quantify the burden of HCV in WPRO and identify a strategy to achieve the Global Health Sector Strategy Goals (GHSS) for Viral Hepatitis Elimination by 2030.
Method: Excel-based disease progression models, built with published data and/or expert consensus were used to assess 2016–2030 trends in HCV infection and morbidity in 16 WHO WPRO countries and Taiwan (Australia, Cambodia, China, Fiji, Hong Kong, Japan, Laos, Malaysia, Mongolia, New Zealand, Papua New Guinea, Philippines, Samoa, Singapore, South Korea, Vietnam).
Results: In 2016, there were an estimated 13.7 million viremic HCV infections, 21% have been diagnosed. Under today's treatment paradigm (300,000 treated annually), this is expected to decrease by 30%, to 10 million, by 2030. Liver related mortality is expected to increase 20%, from 102,000 deaths in 2016 to 124,000 in 2030. The number of patients with end-stage liver disease is also expected to increase 20%.

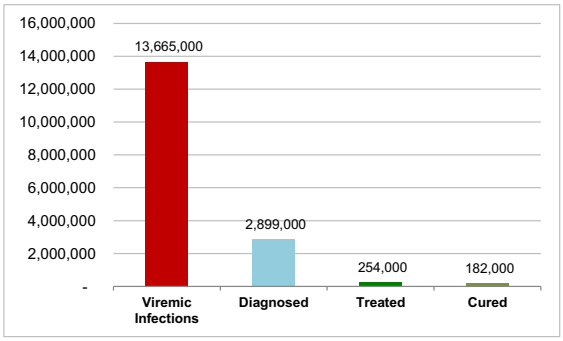


Figure 1: WPRO Cascade of Care, 2016

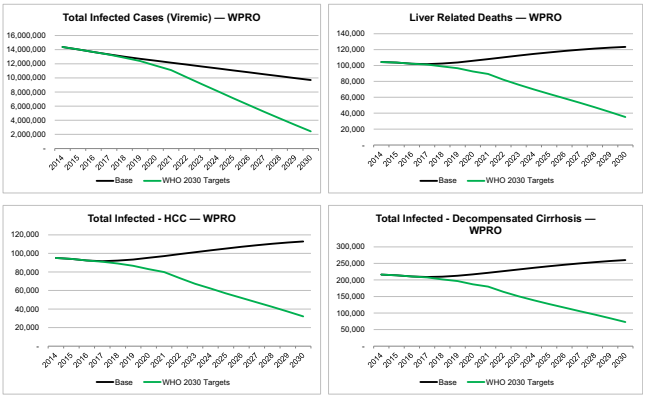


Figure 2: Liver Related Morbidity and Mortality by Scenario, 2016–2030.

In order to achieve GHSS goals of diagnosing 90% of the infected population and reducing liver related mortality by 65%, treatment in the region must be increased to 900,000 patients annually by 2030. Similarly, the annual number of newly diagnosed patients will need to increase to 750,000 by 2019 (from 350,000 in 2016). These actions will reduce total HCV infections by 90% and liver related morbidity and mortality by 70%. After 2031, the number of infections will decline and the number of treated patients can be scaled back accordingly.
Conclusion: Under the status quo, HCV prevalence in WPRO countries will decrease by 2030, but cases of advanced liver disease and liver-related deaths will continue at a high level. Increasing diagnosis and treatment can lead to significant reductions in total infections, mortality, and morbidity.

THU-104

The first result from the general population hepatitis screening in Mongolia: 38% of 40–65 year olds screened and anti-HCV prevence of 15.6% among 40–65 year olds

B. Dashtseren[1,2], U. Baatarsuren[2], T. Dagvadorj[3], A. Bungert[4], Z. Genden[4], D. Yagaanbuyant[2,3,4], N. Dashdorj[2,4], N. Dashdorj[2]. [1]*Liver Center, Mongolia;* [2]*Onom Foundation;* [3]*Mongolian National University of Medical Sciences, Department of Infecious Diseases;* [4]*Liver Center*
Email: d.bekhbold@onomfoundation.org

Background and Aims: Recent estimates show an HCV infection rate of 8.5% among Mongolian adults. As part of the Hepatitis Prevention, Control, and Elimination Program (HPCE) in Mongolia – Элэг бүтэн Монгол хөтөлбөр with the mission to eliminate HCV in Mongolia by 2020, all adult Mongolians are to be screened for HCV by 2018. The first stage, starting from June 2017 targets the age group of 40–65 years of age. As of October 1, 2017, 287,000 out of 741,000 (total Mongolian population in this age group) were tested for anti-HCV.
Method: The data presented is based on the official data from the Ministry of Health of Mongolia. Screening was conducted at primary health care centers through the country. On-site rapid diagnostic tests for anti-HCV from different manufacturers were used for screening. The data is compared to a recent prevalence study that we conducted in 2013 and published recently (*J Viral Hepat*. V. 24, Issue 9; 2017 pp: 759–767).
Results: In total, 26,200 participants were detected to be anti-HCV positive out of 287,000 people who were screened. HCV prevalence is higher in older age groups and these results are reflected to a high degree in the 2013 estimate. 116,092 or 15.6% of all Mongolians 40–65 are anti-HCV positive.

Age groups	Screened population in 2017 (Absolute number)	Anti-HCV(+) percentage 2017	Anti-HCV(+) percentage 2013 estimate	Total population in 2016 (Absolute number)	Total anti-HCV(+) population (Absolute number)
40–44	59,910	9.93%	8.5%	210,897	20,942
45–49	59,335	13.06%	6.5%	179,429	23,433
50–54	60,830	16.62%	16.9%	157,548	26,184
55–59	59,882	21.04%	22.4%	119,171	25,073
60–64	46,941	27.65%	30.4%	73,995	20,460
40–65	286,898	15.6%		741,040	116,092

Conclusion: These results show the progress of the General Population Hepatitis Screening, which has reached 38% of the target population in 4 months. Given the high outreach of the screening, the total number of 116,092 or 15.6% anti-HCV positives in this age group is a highly accurate estimate.

THU-105

Diagnosis of hepatitis C virus infection in Spain. On the correct side of the road?

F.G. Garcia[1,2], A.J.B. Bravo[3], P. Lazaro[3], A. Aguilera[4,5], F.J.G.-S. Rey[6], J.M. Eiros[7], J.L.C. Panero[8,9], J. Crespo[10]. [1]*Instituto Investigación Biosanitaria Ibs. Granada;* [2]*Servicio de Aparato Digestivo. Hosital Universitario San Cecilio, Granada., Granada, Spain;* [3]*Independent Health Services Researcher. Madrid., Madrid, Spain;* [4]*Servicio de Microbiología, Complejo Hospitalario Universitario de Santiago de Compostela, A Coruña;* [5]*Departamento de Microbiología, Universidad de Santiago de Compostela, A Coruña., Spain;* [6]*Hospital Universitario La Paz, CIBERehd, Madrid, Spain;* [7]*Servicio de Microbiología, Hospital Universitario Río Hortega, Valladolid., Valladolid, Spain;* [8]*Servicio de Aparato Digestivo, Hospital Universitario Puerta de Hierro, Majadahonda, Madrid;* [9]*CIBERehd, Universidad Autónoma de Madrid;* [10]*Servicio de Aparato Digestivo. Hospital Universitario Marqués de Valdecilla, Santander, Spain*
Email: plazaro@gmx.es

Background and Aims: Reflex testing of antibodies and viral load in the same sample for diagnosing active hepatitis C virus (HCV) infection, together with appropriate communication strategies, have shown to improve linkage to care and access to treatment. However, how HCV diagnostics is done in Spain is still unknown. The aim of the study is to describe resources and procedures for the diagnosis of HCV infection in Spanish hospitals.
Method: Cross-sectional study with data collection through a survey addressed to hospitals of the Hospitals National Catalogue with the following inclusion criteria: (1) general hospital (monographic, e.g., psychiatric hospitals are excluded); (2) with at least 200 beds; and (3) public, or teaching hospital if private. A questionnaire with the variables of interest, designed by a scientific committee composed of hepatologists and microbiologists, was sent to the selected hospitals. The field work was carried out in September and October 2017.
Results: Of the 160 hospitals that met inclusion criteria, 90 centers from 14/17 autonomous communities (regions) answered the survey (response rate: 56.3%). Two hospitals (2.2%) have no diagnostic resources, 15 (16.7%) can only test for anti-HCV (Ab), 9 (10.0%) for Ab and viral load (VL), 47 (52.2%) for Ab, VL and genotype (GT), 2 (2.2%) for Ab, VL and core antigen (Ag), and 15 (16.7%) can perform Ab, Ag, VL and GT tests. General practitioners (GP) can request VL testing to 35 (38.9%) hospitals, and GT to 24 (26.7%) hospitals. When an Ab test is positive, 34 (37.8%) hospitals perform reflex testing, being VL + GT (17 hospitals) the most frequent additional testing. When active infection is diagnosed, some communication strategy is used in 62 (68.9%) hospitals: the most frequent are a direct contact with the solicitor (in 39 hospitals) and an alert in the report (in 32). Thirty eight of 86 (44.2%) respondents believe that all determinations needed to reach a diagnosis should be done in a single blood sample, and 76 (88.4%) that some type of alert should be used when active infection is diagnosed.
Conclusion: Although 81% of Spanish hospitals have the resources to perform reflex testing, it is only done in 38%, and less than a half of respondents believe that the diagnosis should be done in a single sample. Nine out of 10 respondents believe that some kind of alert should exist when an active infection is detected, but almost a third of hospitals do not have any communication strategy. Educational programs are needed in Spain to implement reflex testing across the country and increase linkage to care.

THU-106

HepCARE: A tool enabling the identification, assessment and management of viral hepatitis. An integrated approach to the patient journey

B. Anthony[1], L. Smith[1], K. Childs[1], P. Troke[2], F. Sinan[1], K. Agarwal[1], G. Dusheiko[1], M.D. Cannon[1]. [1]*King's College Hospital NHS Foundation Trust, United Kingdom;* [2]*Gilead Sciences*
Email: benanthony@nhs.net

Background and Aims: HepCARE is an end to end viral hepatitis (HBV and HCV) patient management tool. HepCARE enables simple, automated, rapid identification and analysis of patient cohorts and provides a single system for management of patients during clinic visits. Funding for HepCARE at our centre was provided by a service to medicine grant from Gilead Sciences. HepCARE can also assist in the provision of an outreach service for the treatment of HCV and HBV, through the analysis of geographical and liver health data.
Method: All patients with a positive marker of HBV and/or HCV were identified through read code searches to create the database. All relevant lab test results were then extracted and uploaded to HepCARE. New patient diagnoses of HBV and/or HCV are instantaneously transmitted to HepCARE through the hospitals electronic patient records. In parallel, transient elastography (Fibroscan), CAP score and clinically relevant laboratory results are also transfer electronically to HepCARE. APRI and FIB-4 scores are automatically calculated.
Results: HepCARE has collated data on 9,816 patients with viral hepatitis attending Liver Services at our centre (HBV: 6524; HCV: 3292).

To date, 891 HCV treatment outcomes following direct-acting antiviral therapy have been identified by HepCARE. This includes 319 patients who have cirrhosis who have been identified for ongoing HCC surveillance and follow-up.
A further 1,506 individuals with untreated HCV infection have been identified, of these, 1,094 were previously known to the service but have not attended their clinic appointments in the past 18 months. Of these, 294 have cirrhosis based on FIB-4 and/or Fibroscan data. 26.9% are thought to be cirrhotic.
Of those with HBV, 3,375 are currently engaged with our viral hepatitis service, and 481 are cirrhotic.
Analysis of the geographic distribution of patients with HCV who are awaiting treatment is ongoing. Extraction of patients' geographic and liver health data is enabling service redesign to ensure the provision of HBV/ HCV treatment services are directed towards high prevalence areas. Data will be presented on the impact of HepCARE on the redesign of HCV outreach services.
Conclusion: The use of HepCARE has reformed local clinical management, and will enable large-scale patient reengagement with our service. It also facilitates in-depth analysis of the patient cohort attending the viral hepatitis service at our centre. Future strategies include linking raw patient data from primary care to assist with case finding, and mapping of geographic inequalities in diagnoses and treatment, to ensure equity in access to care.

THU-107
A tool to measure the impact of inaction towards elimination of hepatitis C virus: A case study in Germany

M. Cornberg[1], Y. Sanchez[2], A. Pangerl[2], H. Razavi[3]. *[1]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]AbbVie Inc., North Chicago, United States; [3]Center for Disease Analysis, Lafayette, United States*
Email: yuri.sanchezgonzalez@abbvie.com

Background and Aims: Chronic infection with hepatitis C virus (HCV) and its sequelae presents a significant source of economic and societal burden. Introduction of highly effective curative therapies has made elimination of HCV attainable. Our study aimed to develop a predictive model scalable at national, regional or local level to assess the clinical and economic impact of implementing screening and treatment policies towards HCV elimination, using Germany as a case study.
Method: A Markov disease progression model of HCV infection was developed to analyse the clinical and economic impact of delaying diagnosis and treatment of HCV using modules that quantified the disease burden and medical costs associated with CHC (chronic hepatitis C) and its sequelae. The model was built using national-level inputs, but the modelled population was scalable to support decision-making on a regional or treatment-facility level as well. In this analysis, the model compared the clinical outcomes of the national status quo in Germany of 13,125 treatments and 4,371 newly diagnosed HCV-infected cases annually, starting in 2017 to (1) a scenario that met WHO's diagnosis, incidence, and mortality targets for elimination of HCV by 2030, and (2) a scenario of delaying these interventions by two years. Modelled historical incidence of HCV was calibrated to match the reported prevalence of antibodies against HCV (0.5% in 2012) by sex and age group. Elimination scenario required 17,983 treatments and 9,811 newly diagnosed cases annually, starting in 2018, to reach the 2030 targets.
Results: Compared to base case, elimination would avert 9,995 incident cases of HCV, 1,219 cases of decompensated cirrhosis (DCC), 1,587 cases of hepatocellular carcinoma (HCC), 289 liver transplantations (LTs), and 1,329 liver-related deaths (LRDs) over the 2017–2030 period. Delaying treatment and diagnosis interventions for elimination until 2020 would avert 6,418 incident cases, 925 cases of DCC, 1,190 cases of HCC, 224 LTs, and 1,004 LRDs versus base case.
Conclusion: The Markov model is a tool to visualize the impact of screening and treatment interventions and track their progress towards WHO targets. In this example for Germany, HCV elimination would avert a significant portion of incident cases, as well as new cases of end-stage liver disease (ESLD) and LRDs due to HCV. Postponing this intervention by just two years would fail to avert over 3,500 new HCV infections, nearly 700 cases of ESLD, 65 liver transplantations, and 325 LRDs by 2030.

Scenario	Base case	Elimination	Delay of elimination
	Total new cases, 2017–2030		
Incident cases of HCV	54,911	44,916	48,493
New cases of DCC	2,200	981	1,276
New cases of HCC	3,008	1,421	1,818
Liver transplantations	479	190	254
Liver-related deaths	2,479	1,150	1,475

HCV—hepatitis C virus; DCC—decompensated cirrhosis; HCC—hepatocellular carcinoma.

THU-108
Linkage to HCV care and reincarceration following release from New York City jails

M. Akiyama[1], R. Macdonald[2], A. Jordan[2], D. Columbus[3], J. Schwartz[4], A. Litwin[1], B. Eckhardt[3], E. Carmody[3]. *[1]Montefiore Medical Center/ Albert Einstein College of Medicine; [2]New York City Health and Hospitals, Correctional Health Services; [3]New York University School of Medicine; [4]New York City Department of Health and Mental Hygiene, United States*
Email: makiyama@montefiore.org

Background and Aims: Hepatitis C virus (HCV) is an international public health problem in correctional settings. HCV treatment is often not possible in US jails due to short lengths of stay. Linkage to care (LTC) is crucial in these settings, but competing priorities complicate post-release LTC. Reincarceration is also a common outcome following release; however, its impact on LTC for HCV is lesser known. We present rates of linkage, reincarceration, and other barriers to HCV care associated with a care coordination program (CCP) for patients with HCV following release from New York City jails.
Method: We conducted a one-armed clinical trial to assess rates of linkage associated with the CCP. The CCP consists of a needs assessment, discharge planning by jail-based transitional care coordinators, HCV education, appointment scheduling, reminder calls, and appointment accompaniment by a community patient navigator after reentry. Enrolment in the CCP began 5/16/15, was complete 4/14/2017, and follow-up is ongoing. We determined predictors of linkage using the Addiction Severity Index at enrolment. Statistical significance was determined using Fisher's exact tests. We used the EventFlow data visualization tool to visually inspect the data and identify relevant temporal event sequences.
Results: Among 100 eligible participants, the mean age was 45 (SD 13); 59 were male, 52 were Hispanic, 23 were non-Hispanic (NH) white, 19 were NH black, 6 were other. In terms of disposition, 88 have been released to the community, 4 initiated HCV treatment prior to release, 1 is pending release, 7 are in state prison. Of those released, 35 (40%) were reincarcerated ≥1 time within 1 year of release. Reincarceration was the initial event for 31 (36%) within a median of 109 days. 26 (30%) participants have linked to HCV care within a median of 25 days, 16 (18%) of whom have initiated HCV treatment, and 35 (38%) have been lost to follow up. Having an existing primary care provider ($p = 0.05$), being on methadone ($p = 0.01$), and feeling supported socially (0.03) prior to incarceration were all associated with LTC.
Conclusion: These data provide preliminary evidence that an integrated community-based CCP with jail-based transitional care coordinators may be effective in improving timely LTC. Despite encouraging linkage rates, additional multicomponent interventions aimed at intervening on cycles of reincarceration and increasing

social support, linkage to primary care, and opioid agonist therapy could lead to improvement in linkage to HCV care.

THU-109

Impact of elevated coffee intake on the risk of advanced liver fibrosis in HIV-HCV co-infected patients of the French ANRS CO13 HEPAVIH cohort: a sex-based analysis

I. Yaya[1], C. Protopopescu[1], F. Marcellin[1], L. Esterle[2], L. Wittkop[2], C. Duvivier[3], L. Piroth[4], P. Sogni[5], D. Salmon-Ceron[6], M.P. Carrieri[7].
[1]SESSTIM ORS-PACA, INSERM, IRD, SESSTIM, Marseille, France; [2]Univ. Bordeaux, ISPED, Inserm, Bordeaux Population Health Research Center, Bordeaux, France; [3]AP-HP-Necker Hospital, Infectious Diseases Department, Paris, France; [4]CHU de Dijon, Infectiologie, Dijon, France; [5]Assistance Publique des Hôpitaux de Paris, Hôpital Cochin, Service d'Hépatologie, Paris, France, Paris, France; [6]AP-HP, Hôpital Cochin, Service Maladies infectieuses et tropicales, Paris, France; [7]Aix Marseille Univ, INSERM, IRD, SESSTIM, Marseille, France
Email: issifou.yaya@inserm.fr

Background and Aims: Hepatic fibrosis remains one of the most common manifestations of the HIV-HCV co-infection. Several studies reported that coffee consumption is inversely associated with the progression of liver disease, including hepatic fibrosis. The aim of this longitudinal study was to analyze the sex-specific effect of elevated coffee consumption on advanced liver fibrosis in HIV-HCV co-infected patient.
Method: A longitudinal analysis was performed using 5-year follow-up data from patients included in the French national cohort ANRS CO13-HEPAVIH. Data from annual biological/clinical records and socio-behavioral characteristics were used. The outcome, advanced liver fibrosis, was defined as a FIB-4 index >3.25. We used mixed logistic regression models to examine the association between elevated coffee consumption (≥3 cups/day) and advanced liver fibrosis, after adjustment for other correlates.
Results: Overall 1019 HIV-HCV co-infected patients were included in the study. At the last visit available, 27.4% of them reported elevated coffee consumption during the previous six months and 15.2% had an advanced liver fibrosis. In the multivariable analysis, adjusted for significant clinical (CD4 count, HCV clearance, BMI), socio-demographic (age) and behavioral factors (alcohol consumption, IV drug use), men with elevated coffee intake were 64% less likely to have an advanced liver fibrosis; while elevated coffee intake was not significantly associated with advanced liver fibrosis in women (table).
Conclusions: In the ANRS CO13-HEPAVIH cohort, elevated coffee consumption was not associated with advanced liver fibrosis in HIV-HCV co-infected women.

THU-110

High agreement with HCV RNA in screening and DAA treatment monitoring indicates that cost-effective HCV core Ag test can also be enlisted in the fight to eliminate hepatitis C

N. Chitadze[1], M. Alkhazashvili[2], G. Chanturia[3], A. Gamkrelidze[4], B. Skaggs[5], J. Drobeniuc[6], G. Cloherty[7], G. Kamkamidze[8], R. Sukhiashvili[1], F. Averhoff[9]. *[1]National Center for Disease Control and Public Health of Georgia, Department of Virology, Molecular Biology and Genome Research, Tbilisi, Georgia; [2]National Center for Disease Control and Public Health of Georgia, Manager Lugar Center, Tbilisi, Georgia; [3]National Center for Disease Control and Public Health of Georgia, Head of Department of Virology, Molecular Biology and Genome Research, Tbilisi, Georgia; [4]National Center for Disease Control and Public Health of Georgia, Director General, Tbilisi, Georgia; [5]Division of Global Health Protection, Centers for Disease Control and Prevention, Country Director, Tbilisi, Georgia; [6]Division of Viral Hepatitis, Centers for Disease Control and Prevention, United States; [7]Abbott Diagnostics, Abbott Park, United States; [8]Clinic NeoLab, Tbilisi, Georgia; [9]Division of Global Health Protection, Centers for Disease Control and Prevention, United States*
Email: chitadzenuki@gmail.com

Background and Aims: HCV core antigen (HCVcAg) is a serologic marker of HCV infection highly concordant with HCV RNA testing-the current standard of care. The aim of this study was to assess feasibility of the HCVcAg test as a high throughput and cost-effective alternative to HCV NAT to determine active HCV infection in screening and DAA treatment monitoring program.
Method: The study consisted of two arms: 1) Evaluation of a new HCV screening algorithm that will include reflex HCVcAg testing for confirmation of active infection in anti-HCV-positive participants; and 2) Feasibility of HCVcAg test for monitoring patients on DAA therapy.
The first arm included 4,235 samples obtained from regular screening sites of the hepatitis C elimination program in Georgia- Blood Banks, Harm Reduction Networks (HRN), Provider Clinics, Screening centers, and from the National Seroprevalence Survey (NSS).

Table 1: (abstract: THU-109): Effect of elevated coffee intake on risk of advanced liver fibrosis in HIV-HCV co-infected patients (ANRS CO13 HEPAVIH cohort)

	Characteristics at the last visit in the cohort		Mixed logistic regression[1] (dependent variable = advanced hepatic fibrosis) AOR [95%CI]		
	Total (1019)	Advanced liver fibrosis, n = 147 (15.2%)	Men, n = 710 (69.7%)	Women, n = 309 (30.3%)	All patients, n = 1019
Age		**0.0118****			
<50 years	652 (64.0)	82 (55.8)	**1**	**1**	**1**
≥50 years	367 (36.0)	65 (44.2)	**2.02[1.30–3.15]**	**2.03[1.13–3.64]**	**2.01[1.41–2.86]**
CD4/100 (cells/mm^3)		**<0.0001***			
Mean (±SD)	5.6 (± 3.1)	3.9 (± 2.4)	**0.56[0.51–0.63]**	**0.57[0.50–0.65]**	**0.57[0.53–0.62]**
Median (IQR)	5.2 (3.4–7.3)				
HCV clearance		**<0.0001****			
No	813 (79.8)	142 (96.6)	**1**	**1**	**1**
Yes	206 (20.2)	5 (3.4)	**0.07[0.04–0.15]**	**0.006[< 0.001–0.047]**	**0.05[0.03–0.10]**
Elevated coffee intake		**0.0002****			
No	713 (72.6)	122 (85.9)	**1**	**1**	**1**
Yes	269 (27.4)	20 (14.1)	**0.36[0.22–0.58]**	0.88[0.41–1.88]	**0.44[0.30–0.66]**
Alcohol consumption		**0.0079***			
(Number of drinks per month)					
Mean (± SD)	25.3 (± 51.5)	38.9 (± 67.3)	1.003[0.999–1.007]	**1.01[1.003–1.02]**	**1.004[1.002–1.008]**
Median (IQR)	4 (0–20)				

*t-test.
**khi-2.
[1]Multivariable model adjusted for age, CD4, HCV clearance, BMI, alcohol consumption and IV drug use.

In the second arm a total of 976 samples were collected at Baseline, Week 4, End of Treatment (EOT), and 12 weeks post treatment, submitted by three provider clinics in Georgia. HCV RNA and genotype testing was conducted at the clinics using standard of care Nucleic Acid Test (NAT).
Specimens were tested with the ARCHITECT HCVcAg assay at the Georgia NCDC R. Lugar Center for Public Health Research. Percent agreement between HCVcAg and HCV RNA results was calculated based on qualitative results.
Results: Overall agreement between HCVcAg and HCV RNA among participants subjected to HCV screening was 97.14% (1258/1294) which concordance in samples with quantifiable viral load >3,000 IU/mL (estimated LOD for HCVcAg) excluding HCVcAg grey zone not-repeated (n-=10) was 99.68% (1258/1,262).
The agreement between HCVcAg and HCV RNA in the Pre-Treatment specimens was 98.3% (414/421), and in specimens from the 4 week monitoring point was 96.5% (334/346). At EOT and 12 weeks post treatment, the agreement between HCVcAg and HCV RNA was 98.9% (186/188) and 100% (21/21), respectively.
Conclusions: The observed percent agreement between HCV RNA and HCVcAg in the new HCV screening algorithm, and among patients who underwent Pre-Treatment testing selected for DAA therapy, were similar – 98.3% and 97.14% respectively. Among patients who received DAA therapy, the agreement between HCVcAg and HCV RNA exceeded 98% at the EOT, and reached 100% at the 12 week post treatment. These data suggest that the HCVcAg can be used as an alternative to HCV RNA to determine active infection in anti-HCV screening positive population, and for the DAA treatment monitoring.

THU-111

Elimination of hepatitis C in two different Swiss regions – A model-based microelimination scenario

U. Rusch[1], S. Robbins[2], S. Blach[2], H. Razavi[2], P. Vernazza[3], F. Negro[4], D. Semela[1]. *[1]Cantonal Hospital St. Gallen, Division of Gastroenterology and Hepatology, St. Gallen, Switzerland; [2]Center for Disease Analysis, Louisville, United States; [3]Cantonal Hospital St. Gallen, Division of Infectious Diseases, St. Gallen, Switzerland; [4]University Hospital Geneva, Divisions of Gastroenterology and Hepatology and of Clinical Pathology, Geneva, Switzerland*
Email: ursrusch88@hotmail.com

Background and Aims: The high effectiveness of direct-acting antivirals (DAAs) make global elimination of hepatitis C virus (HCV) possible. In Switzerland, only a minority of HCV patients has been cured this far and estimated >50% of the Swiss HCV population has not been diagnosed yet. Since 10/2017, all HCV patients in Switzerland have access to DAAs. According to the WHO goals, the Swiss hepatitis strategy aims to reduce morbidity and mortality caused by HCV and eliminate it by 2030. Our aim is to model micro-elimination scenarios for two distinct regions.
Method: A previously described HCV disease burden model (*Razavi H et al. 2014*) was used to develop two elimination scenarios to achieve the Swiss hepatitis strategy goals in Eastern Switzerland and Geneva. Hospital-based data gathered from retrospective analysis of electronic medical records and current reported data from the federal office of public health (FOPH) with proportional adjustments were used as input data for the model. Two scenarios were developed. The "Base 2016" scenario continues the current standard of care (before general DAA access with limitation to fibrosis stage 2) in the individual cantons through 2030 while the "Swiss Hepatitis Strategy" scenario increases diagnosis and treatment, in order to achieve a 30% reduction in new infections, total viremic infections, liver transplants, and HCC cases by 2020 and a further 90% reduction by 2030.
Results: *2016 Scenario:* The Eastern Switzerland model shows a reduction of liver related death by 55%, while liver cancer due to HCV was reduced by 60% in 2030. The model shows also a reduction of chronic infections by 55% in 2030. By retaining a rate of 95 new diagnosed patients per year, 85% of all infected patients could be detected in 2030. In Geneva, the model estimates similar declines in liver related morbidity and mortality. The model estimates a reduction of liver related death and liver cancer due to HCV by 80% in 2030. There is also forecasted a reduction of chronic infections by 65% in 2030. By retaining a rate of 140 new diagnosed patients per year, 48% of all infected patients could be detected in 2030.
Swiss Hepatitis Strategy: To achieve these goals in Eastern Switzerland treatment had to be expanded to a maximum of 430 patients in 2020 and 195 treated patients per year during the following ten years. In Geneva, with 450 treated patients per year starting in 2018 all the goals can be achieved.
Conclusion: Elimination of chronic HCV infection in Eastern Switzerland and Geneva by 2030 is possible, but higher treatment and diagnosis rates are necessary to meet the 90% elimination goal.

THU-112

Role of physician specialties to close gaps in the care cascade of hepatitis C: Evidence from paid claims in the United States from 2010 to 2016

D. Mehta[1,2], J. Mccombs[1], Y. Sanchez[2], S. Marx[2], S. Sammy[3]. *[1]University of Southern California, Schaeffer Centre for Health Policy and Economics, Los Angeles, United States; [2]AbbVie Inc., Health Economics and Outcomes Research, Mettawa, United States; [3]University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, United States*
Email: darshanm@usc.edu

Background and Aims: US estimates report that 50% of people with chronic hepatitis C virus (HCV) infection have been screened, and 16% have been linked to care. The role of physician specialty to close such gaps in the care cascade from screening to treatment is not well understood. This study assesses antibody (AB) screening rates and AB+ detection rates by physician specialty, and evaluates the impact of physician specialty on linking infected patients to care.
Method: Claims data from Optum Clinformatics® Data Mart, a de-identified claims database from the US, were analyzed for 2010–2016. HCV screening was identified by paid claims for Current Procedural Terminology (CPT) codes 86803, 86804, or G0742. Physician specialty was determined based on the physician's order or bill for the index AB test. Screened patients who were AB+ were identified and their linkage to care was assessed. Descriptive statistics were generated for screening rates, AB+ detection rates and treatment rates by physician specialty. Logistic regressions were used to estimate the effect of physician specialty and time trend on the likelihood of testing positive and being linked to care, controlling for patient characteristics.
Results: Among the 1,058,207 total patients tested, most HCV AB tests were ordered by primary care physicians (PCPs; 29.7%), obstetricians/gynecologists (OB/GYNs; 19.1%) and nurses/physician assistants (PAs; 5.3%). The mean AB+ detection rate across all studied specialties was 3% of screened patients, higher than the national AB+ prevalence of 1.7%. While gastroenterologists, oncologists, and infectious disease specialists did not screen more than 3% of total sample, their tests resulted in the highest observed rate of AB+ results (3.9–5.3%). Linkage to care was low for AB+ patients at 13.8% overall, and hospitalist and gastroenterologists had the highest linkage rates (19.9–25.0%). Among the top three specialties ordering AB screening, OB/GYN had the lowest linkage to care rate at 4.7%. Logistic regressions showed that being screened by gastroenterologists (56.7%) significantly increased treatment rate compared to PCPs. The availability of curative therapies increased the treatment rate for AB+ patients by 25.6%.
Conclusion: PCPs and OB/GYNs emerged as the gatekeepers for AB screening accounting for nearly half of total tests. In spite of high AB+ detection rates across specialties, increased efforts are needed to improve linkage to care, especially in PCP and OB/GYN settings.

THU-113

Effectiveness of hepatitis C virus screening laws in United States: Evidence from paid claims data from 2010 to 2016

D. Mehta[1,2], J. Mccombs[1], Y. Sanchez[2], S. Marx[2], S. Sammy[3]. [1]*University of Southern California, Schaeffer Centre for Health Policy and Economics, Los Angeles, United States;* [2]*AbbVie Inc., Health Economics and Outcomes Research, Mettawa, United States;* [3]*UCLA, David Geffen School of Medicine, Los Angeles, United States*
Email: darshanm@usc.edu

Background and Aims: The World Health Organization [WHO] has set a goal of having 90% of the world's population screened for chronic hepatitis C (HCV) infection by 2030. Starting from 2014 in the United States (US) 5 states (NY, CA, CT, MA, CO) implemented new HCV screening policies. This study assesses the effectiveness of these screening laws and projects states' progress toward the WHO target.
Method: Claims data for 2010–2016 from Optum Clinformatics® Data Mart, a de-identified claims database from the US were analyzed. HCV screening was identified by paid claims for CPT codes 86803, 86804, or G0742. Logistic regression models of the likelihood of a patient being screened were estimated, controlling for patient demographic and clinical characteristics. Three time periods [2010; 2011–13 and 2014–16] were used to measure the effect on screening of the availability of the newer curative agents. Variables identifying states with screening policies were entered as interaction terms with the post-2014 time period to test if new screening policies enhanced screening rates, independent of the availability effect of the newer agents. Further, the proportion of the population screened in each state was extrapolated to 2050 using each state's 2014–16 screening rates applied to an assumed baseline diagnosis rate of 50%.
Results: Relative to the annual screening rate in 2010, annual screening rates were increased by 19.9% post 2014. In the states that passed screening laws, the annual post 2014 screening rates were increased by an additional 6.4%. Among the states that passed screening laws, MA and CT increased annual screening rates but policies in NY, CA and CO had no significant effect. Other factors that increased the likelihood of a patient being screened were female gender, Medicare enrollment and presence of comorbidities like chronic kidney disease, mixed cryoglobulinemia, fatigue and coinfection with HIV and/or HBV. Projections of screening rates suggest that NY and 4 other states without screening laws were on track to reach the WHO target by 2030 with 8 additional states attaining WHO target by 2040. 29 states would not attain this target by 2050.

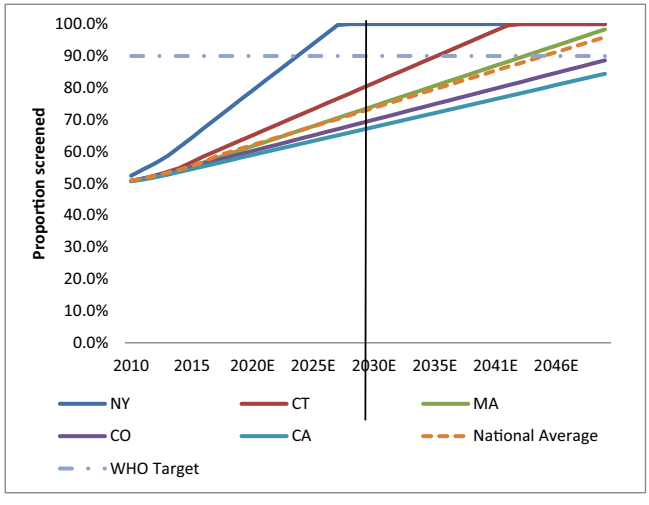


Figure 1: Projected screening rates in US states implementing HCV screening policies: 2010–2050.

Conclusion: The availability of curative therapies has increased the likelihood of screening for HCV. While current efforts to increase annual HCV screening have had positive impact, over 90% of states in the US are still not on track to reach WHO target by 2030.

THU-114

Development of a clinical prediction score for targeted hepatitis C screening in a low-risk HIV cohort in Cambodia

A. De Weggheleire[1], J. Buyze[1], S. An[2], S. Thai[2], J. van Griensven[1], S. Francque[3], L. Lynen[1]. [1]*Institute of Tropical Medicine Antwerp, Clinical Sciences;* [2]*Sihanouk Hospital Center of Hope, Infectious Diseases, Phnom Penh, Cambodia;* [3]*UZA, Gastroenterology Hepatology, Edegem, Belgium*
Email: adeweggheleire@itg.be

Background and Aims: WHO guidelines recommend screening all people living with HIV for hepatitis C virus (HCV). Considering the limited resources for health in Cambodia, and data indicative of low-to-intermediate HCV/HIV coinfection rates (3.5%), targeted HCV screening is potentially more feasible and cost-effective in the current phase of initial HCV care scale-up. We developed a clinical prediction score (CPS) for targeted screening combining age and factors linked to liver disease severity.
Method: We analyzed data of a cross-sectional HCV diagnostic study in the HIV cohort of Sihanouk Hospital Center of Hope in Phnom Penh, Cambodia (clinical trials.gov NCT02361541). Score development relied on the Spiegelhalter and Knill-Jones method. Predictors independently associated with current HCV infection (HCV RNA detected) with likelihood ratio ≥1.5 or ≤0.67 were retained, and transformed to their natural logarithm and rounded to the nearest integer to calculate the score. CPS performance was evaluated by the area-under-the-ROC curve (AUROC) with 95% confidence intervals (CI), and diagnostic accuracy at the different cut-offs of the score. As clinically useful threshold-to-screen, we considered a 1% probability of having a current HCV/HIV coinfection.
Results: Data of 3045 HIV patients of whom 106 with current HCV infection were available for analysis. The predictors identified for the CPS were: age 50 or above (+1 point), diabetes mellitus (+1), partner or household member with liver disease (+1), generalized pruritus (+1), platelet count $<200 \times 10^9$/l (+1), aspartate aminotransferase (AST) <30 IU/l (−1), AST-to-platelet ratio index (APRI) ≥0.45 (+1), and APRI <0.45 (−1). The CPS yielded an AUROC of 0.84 (95% CI: 0.80–0.89), indicating good discrimination between HCV/HIV coinfection and HIV mono-infection. A score ≥0 fitted best as threshold-to-screen with a negative predictive value (NPV) of 99.2% (95%CI: 98.8–99.6). Applying this cut-off (≥0), 30% (n = 926) would have needed screening, and 16 coinfections been missed, but none with advanced fibrosis (details in Tables 1 and 2).

Table 1: HCV coinfection rate by score

Score	HCV coinfection rate n/N (%)
−2	7/1174 (0.60)
−1	9/945 (0.95)
0	11/256 (4.30)
1	16/345 (4.64)
2	28/222 (12.61)
3	24/85 (28.24)
4	8/14 (57.14)
5	3/4 (75.00)

Table 2: Diagnostic accuracy of the prediction score at different cut-offs

Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥−1	93.4	39.7	5.3	99.4
≥0	84.9	71.6	9.7	99.2
≥1	74.5	79.9	11.8	98.9
≥2	59.4	91.1	19.4	98.4
≥3	33.0	97.7	34.0	97.6
≥4	10.4	99.8	61.1	96.9
≥5	2.8	99.97	75.0	96.6

Conclusion: The CPS for targeted HCV screening performed well in the derivation cohort and bears potential to identify most patients with active HCV/HIV coinfection in contexts of low-to-intermediate prevalence whilst substantially decreasing the number to test. The score requires further validation before it can be recommended for wider use.

THU-115

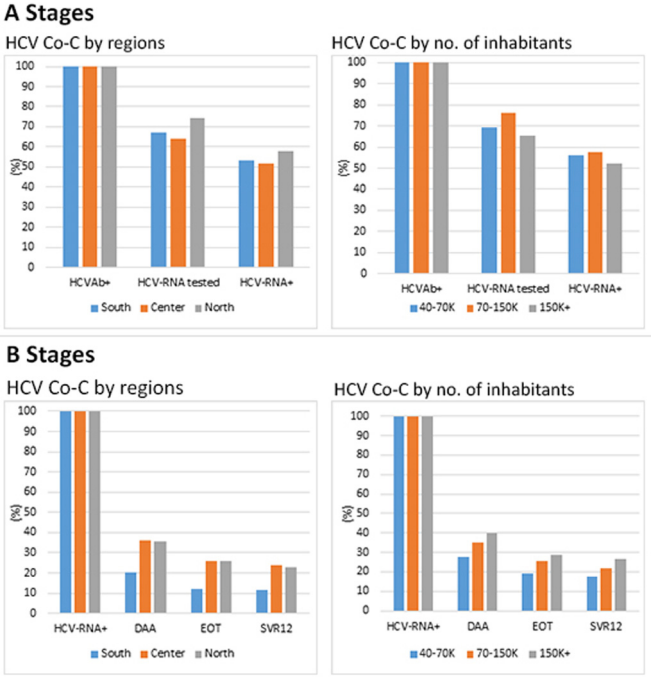
The hepatitis C continuum of care among HIV infected individuals in the Icona study network

E. Girardi[1], M. Puoti[2], C. Mussini[3], A. Tavelli[4], I. Mastrorosa[1], F.C. Silberstein[5], G. Madeddu[6], C. Molteni[7], P. Nasta[8], A. Antinori[1], A.D'arminio Monforte[9], A. Cozzi-Lepri[10]. *[1]National Istitute for Infectious Diseases "Lazzaro Spallanzani" IRCCS, Rome, Italy; [2]Infectious Diseases Unit, ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [3]Infectious Disease Clinic, Modena University Hospital, University of Modena and Reggio Emilia, Department of Medical and Surgical Sciences for Children & Adults, Modena, Italy; [4]Icona Foundation, Milan, Italy; [5]University of Rome Tor Vergata, Department of Experimental Medicine and Surgery, Rome, Italy; [6]University of Sassari, Infectious diseases Department, Sassari, Italy; [7]ASST Lecco, A Manzoni Hospital, Department of Infectious and Tropical Diseases, Lecco, Italy; [8]University of Brescia and Brescia Spedali Civili General Hospital, University Department of Infectious and Tropical Diseases, Brescia, Italy; [9]Clinic of Infectious and Tropical Diseases, ASST Santi Paolo and Carlo, University of Milan, Department of Health Sciences, Milan, Italy; [10]Institute for Global Health, University College London, Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), London, United Kingdom*
Email: a.cozzi-lepri@ucl.ac.uk

Background and Aims: It is estimated that there are currently 20,000 HIV/HCV+ persons in Italy. WHO has the goal of eliminating viral hepatitis by 2030. We aimed to develop and evaluate a HCV continuum of care (CoC) in HIV/HCV+ individuals across Italy and to describe differences by region and population density.

Method: We included HIV/HCV+ individuals in the Icona cohort under active follow-up at January 2015. This population was used to describe the first stages of CoC: A1 = "tested for HCV-RNA" and A2="HCVAb+ with HCV-RNA+". People in Icona who were ever HCV-RNA+ and those in HepaIcona (with HCV-RNA+ and DAA-naïve) were used to describe the subsequent stages: B1= "started IFN-free DAA"; B2 = "with available HCV-RNA after end of treatment (EOT)"; B3 = "achieved sustained virologic response (SVR)". Stage B1 was stratified by level of Fib4 ($\leq$3.25 vs. >3.25). CoC stages were described by region of Italy (North, Center, South) and density of population in surrounding urban area (SUA, 40k–70k, 70k–150k, >150k inhabitants). Predictors of HCV-RNA testing in HCVAb+ (stage A1) were identified by means of multivariable logistic regression.

Results: We included 1,212 HIV/HCV+, the majority were PWID (62%) and 34% sexual contacts (17% MSM), 25% females. Median age was 50 (IQR:43–54) years, CD4 count 632 (445–885)cells/mm^3, 83% with a HIV-RNA $\leq$50 copies/ml. 853 (70%) had a HCV-RNA test result available and 671 (55% of total and 76% of HCV-RNA tested) were HCV-RNA +. Overall, there were significant differences by regions ($p = 0.0006$) and population density ($p < 0.0001$) across A stages (Figure A Stages). For B stages we included 3,241 subjects (1,108 Icona and 2,133 HepaIcona). 1,109 of these (34%) started DAA. This percentage was 33% (888/720) in those with Fib4 $\leq$ 3.25 and 42% (221/521) in those with Fib4 > 3.25. Overall, 788 (24% of total and 71% of those who started DAA) had a HCV-RNA available 12 weeks after EOT and 707 (22% of total and 90% of those evaluable) achieved SVR. There were significant differences by regions ($p < 0.0001$) and by population density ($p < 0.0001$) across B stages (Figure B Stages). Large SUA cities (OR = 0.47 vs. intermediate, $p = 0.0001$), younger age (OR = 0.70, $p < 0.0001$), higher current HIV-RNA (OR = 0.72, $p < 0.0001$) and heterosexual HIV transmission (OR = 0.57 vs. PWID, $p = 0.003$) were all associated with a reduced chance of HCV-RNA testing.



Conclusion: Currently only 22% of our HIV/HCV-RNA+ population is cured. Although DAA access/SVR rates were higher in large SUA cities, the opposite was seen for HCV-RNA testing. It is crucial to identify and address leaks in the CoC to ensure individuals' transition through all stages.

THU-116

One-step diagnostic strategy of viremic hepatitis C virus infection from dried-blood spots: feasibility and usefulness in people who inject drugs

V. Saludes[1,2], C. Folch[2,3], A.A. Torres[1], N. Ibáñez[4], V. Monotya[5], R. Harrigan[5], J. Colom[4], J. Casabona[2,3], E. Martró[1,2]. *[1]Germans Trias i Pujol University Hospital and Research Institute (IGTP), Microbiology Service, Badalona (Barcelona), Spain; [2]Biomedical Research Networking Centre in Epidemiology and Public Health (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain; [3]Centre for Epidemiological Studies on Sexually Transmitted Infections and HIV/AIDS of Catalonia (CEEISCAT), Catalonia Public Health Agency (ASPCAT), Badalona (Barcelona), Spain; [4]Catalonia Public Health Agency (ASPCAT), Program on Substance Abuse, Barcelona, Spain; [5]BC Centre for Excellence in HIV, Vancouver, Canada*
Email: emartro@igtp.cat

Background and Aims: Simplified strategies are needed to improve the diagnosis of active HCV infection in people who inject drugs (PWID). For the first time in Spain, we aimed to: (i) assess the feasibility and usefulness of an alternative one-step screening and confirmatory assay based on HCV-RNA detection in dried-blood spots (DBS), (ii) estimate the prevalence of active HCV infection and its determinants, (iii) epidemiologically characterize the infections, and (iv) assess self-knowledge of HCV infection and linkage-to-care among PWID attending harm-reduction centers (HRC).

Methods: A cross-sectional study of current injectors attending four HRC in Barcelona was conducted (n = 410). Epidemiological and behavioral data were compiled, rapid HCV antibody (Ab) testing was performed, and fingerprick DBS were collected. DBS were shipped to the laboratory at room temperature and HCV-RNA was assessed using a previously developed in-house RT-PCR assay (LOD, 541 IU/ml of blood). Plasma was collected in one center (n = 300) for viral load quantification (Abbott), and for next-generation sequencing and phylogenetic analysis to evaluate HCV intra and inter-host variability.

Results: DBS testing was easily implemented at HRC. Participants were mostly male (85.4%) of Spanish origin (70.5%), with an average age of 40.5 years and 17.7 years of injection, 19.0% being recent injectors (<5 years). HCV seroprevalence was 79.8%, and the prevalence of active infection was 58.5%. Among the latter, 14.0% were not aware of their disease (38.2% in recent injectors), and 24.3% were co-infected with HIV. Of those with a viremic infection and previously diagnosed, 31.9% were linked to care, and 18.6% reported having received therapy. Having shared injection equipment (OR, 2.7; 95%CI: 1.4–5.1) and the injection of cocaine (4.6; 95%CI: 1.6–13.0) were associated with HCV infection. The DBS assay was 95% sensitive and 100% specific in comparison with the conventional two-step algorithm (rapid Ab test followed by viral load if positive; Figure). Circulating genotypes, transmission networks and recent infections were virologically identified.

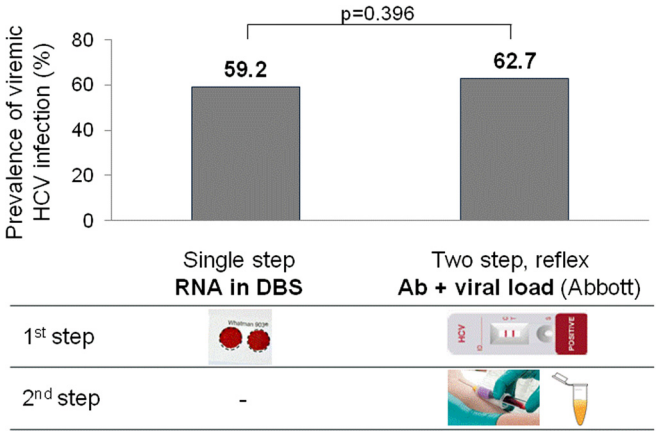


Figure 1: Comparison between diagnostics strategies.

Conclusions: This one-step diagnosis strategy presents a simple and reliable way of increasing the identification and self-knowledge of viremic HCV infections among PWID attending HRC. To improve access to care and fulfill the elimination goals set by the World Health Organization, DBS testing could enable decentralized diagnosis and treatment monitoring in this setting.

THU-117

The contribution of injecting drug use to Hepatitis C virus transmission globally, regionally, and at country level: a modelling study

A. Trickey[1], H. Fraser[1], A.G. Lim[1], J. Walker[1], A. Peacock[2], S. Colledge[2], J. Leung[3], J. Grebely[2], S. Larney[2], L. Degenhardt[2], M. Hickman[1], P. Vickerman[1]. [1]*University of Bristol, Population Health Sciences, Bristol, United Kingdom;* [2]*University of New South Wales, Sydney, Australia;* [3]*University of Queensland, Faculty of Medicine, Australia*
Email: adam.trickey@bristol.ac.uk

Background and Aims: Injecting drug use is an important risk factor for Hepatitis C virus (HCV) transmission. HCV prevalence amongst people who inject drugs (PWID) is generally high but the prevalence of PWID in most countries is <1% of adults. To assist policy-makers in prioritising resources to enhance HCV prevention, modelling was undertaken to estimate the degree to which injecting drug use contributes towards HCV transmission at country, regional and global levels.
Method: A dynamic, deterministic HCV transmission model was used to simulate the country-level HCV epidemic amongst PWID and the general population. The model for each country was calibrated using country-specific data from UN datasets and recent systematic reviews on HCV prevalence amongst PWID and the general population, and the proportion of adults that are PWID. We estimated the dynamic population attributable fraction (PAF) due to injecting drug use, defined as the proportion of all new HCV infections within each country that would be prevented if HCV transmission due to injecting drug use was set to zero for the period 2017–2037. Regional and global PAF averages were produced by weighting the PAFs for each country by their relative burden of HCV compared to the regional or global burden.
Results: The model was successfully calibrated to 82/83 of the included countries comprising 84% of the global population. Although the model predicts 0.2% of individuals will be injecting drug users in 2037, 6% of prevalent HCV in 2037 is among recent PWID. Globally, if the risks due to injecting drug use were removed, then an estimated 31% (the PAF) of all incident HCV infections would be prevented from 2017 to 2037, varying from 7% in South Asia to 74% in North America (figure). Injecting drug use contributes most to HCV transmission in high-income settings, where 62% of new HCV infections could be prevented from removing the risk due to injecting drug use, whereas in some countries (Egypt, Ghana, Maldives, Nigeria, Senegal, and Uzbekistan) this is less than 5%.

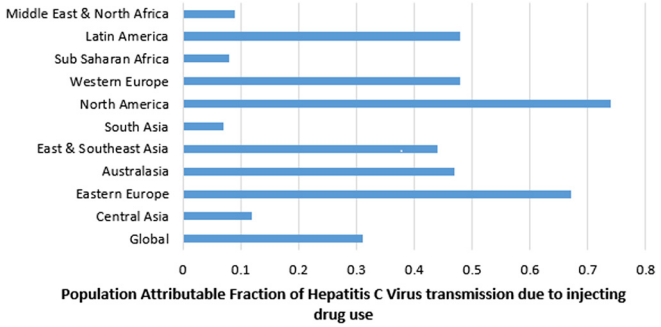


Figure 1: The population attributable fraction of HCV infections due to injecting drug use, by region.

Conclusion: Injecting drug use is a major contributor to the global burden of HCV, but this varies widely within and across regions. Scaling up HCV prevention interventions for PWID, including needle and syringe programmes, opioid substitution therapy, and HCV treatment will be essential to meet WHO elimination targets in many settings.

THU-118

Comparing the prevention gains of different treatment strategies at the global, regional, and country level: a modelling study

A. Trickey[1], H. Fraser[1], A.G. Lim[1], J. Walker[1], A. Peacock[2], S. Colledge[2], J. Leung[3], J. Grebely[2], S. Larney[2], L. Degenhardt[2], M. Hickman[1], M. May[1], P. Vickerman[1]. [1]*University of Bristol, Population Health Sciences, United Kingdom;* [2]*University of New South Wales, Sydney, Australia;* [3]*University of Queensland, School of Public Health, Australia*
Email: adam.trickey@bristol.ac.uk

Background and Aims: To meet the World Health Organization's 2030 hepatitis C virus (HCV) elimination targets, countries must efficiently allocate their resources to prevent and treat HCV infections. Policy makers need data on who to target for treatment to reduce morbidity and prevent new infections. We estimated the prevention gains of four treatment strategies in terms of infections averted (IA) across different countries, and consider how they depend on country-level factors.
Method: To simulate country-level HCV epidemics a dynamic, deterministic HCV transmission model was used, incorporating age demographics, population growth, and HCV progression. Country-specific data from systematic reviews and UN datasets were used to calibrate the model to each country's HCV epidemic. We evaluated the impact of treating 1000 infected individuals in 2017, either selected randomly, or selected amongst people who inject drugs (PWID), people age ≥30, or those with cirrhotic infection. We estimated the number of infections from 2017 to 2037 compared to if no treatment had occurred, weighting country estimates by HCV

burden for regional and global averages. Linear regression was used to identify associations between IA per treatment and a country's population growth rate, the population attributable fraction of injecting drug use to HCV transmission (PAF; defined as the percentage of a country's new HCV infections that would be prevented from 2017–2037 if risk due to injecting drug use was removed), and HCV prevalence amongst PWID.

Results: Countries (83) amassing 84% of the global population were included. Globally, the model estimates on average 0.59 IA per randomly allocated treatment 2017–2037, varying across regions (figure). Similar IA are achieved through treating cirrhotics or those aged ≥30. Overall, treating PWID is the most effective strategy globally with 1.21 IA per treatment, although this effect is reversed in countries with high chronic HCV prevalence (>50%) amongst PWID. The IA per randomly allocated treatment is positively associated with the growth rate of a country, and negatively associated with the PAF of PWID to HCV and the HCV prevalence amongst PWID.

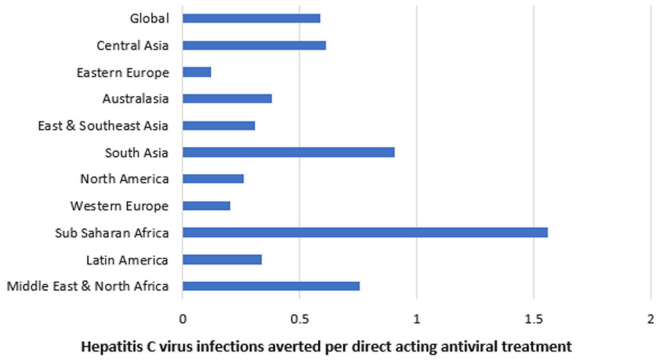


Figure 1: Hepatitis C virus infections averted per randomly allocated HCV treatment over 20 years globally, and by region.

Conclusion: The number of HCV infections averted per randomly allocated treatment is likely to be greatest in settings with high population growth, and less contribution of injecting drug use to HCV transmission. In settings where PWID drive the HCV epidemic, high treatment rates are needed to avert infection.

THU-119

Factors associated with self-reported HCV infection among people who inject opioids: the role of incarceration

P. Roux[1], N. Khadim[1], M. Salim[1], B.M. Laélia[1], L. Virginie[2], M. Marion[1], M. Stéphane[2], R.C. Daniela[2], C. Patrizia[1]. [1]*INSERM, SESSTIM, Marseille, France;* [2]*AIDES, Tour Essor, Pantin, France*
Email: perrine.roux@inserm.fr

Background and Aims: While access to opioid substitution treatment and needle exchange programs have dramatically decreased HIV epidemic among people who inject drugs, HCV infection is still highly prevalent among this population. Sharing injecting material is recognized as the major source of HCV but when this occurs in specific contexts (e.g. prison, street etc…) the risk can be even higher. We used a community-based survey among people who inject opioids to identify individual and contextual factors (prison in particular) associated with self-reported HCV infection.

Method: This cross-sectional community-based survey was conducted in harm reduction centers, in primary care practices and in medical/addiction centers, as well as through an online questionnaire (Psychoactif.org), between May and August 2015. We collected information regarding socio-demographic and behavioral profiles and self-reported HCV serostatus. Among the 557 PWID enrolled, we selected 552 respondents who had no missing data. We used a logistic regression model to identify factors associated with self-reported HCV infection.

Results: Among the selected 552 participants, 164 (29,7%) reported being HCV positive. Women represented 19% of the sample and median [IQR] age was 34[28; 41] years. Twenty-nine percent of participants reported being employed and 41% having already been incarcerated during lifetime. The main opioid regularly used by injection was buprenorphine (53%) after heroin (19%) and morphine sulfate (18%). After adjustment for known correlates (being female, unemployed, history of overdose), we found that with respect to individuals who were never incarcerated, those reporting incarceration but no drug injection in prison (OR[IC95%] = 1.84[1.14; 2.97]) and those who have injected drugs while incarcerated (OR[IC95%] = 2.17[1.17; 4.02] were more likely to report to be HCV infected. In addition, heroin injectors report being less HCV infected compared with prescription opioids injectors.

Conclusion: Our findings showed that prison experience is associated with HCV infection and that such risk is higher for those who injected in prison. Though the recent French law states equity in access to prevention and care in prison as in the general population, this principle is not yet followed. Promoting a rapid scale up of access to sterile equipment, harm reduction information and HCV treatment is urgent to reduce HCV risk in the most criminalized groups such as people who inject drugs.

THU-120

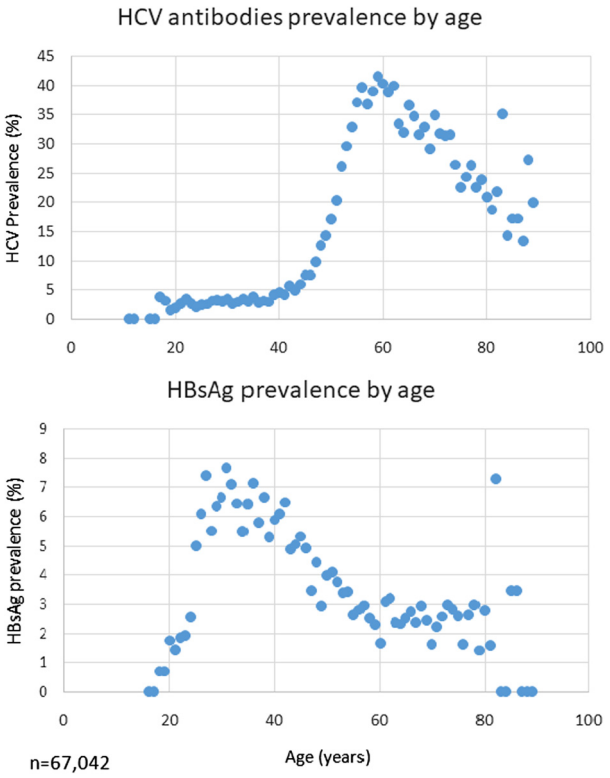
Mass screening for hepatitis B and C in South Upper Egypt: lessons learned from a real life experience

G. Soliman[1], M. Elzalabany[2], T. Hassanein[3], D. Miller[4]. [1]*Faculty of Medicine, Al-Azhar University, Tropical Medicine, Gastroenterology and Hepatology Department, Cairo, Egypt;* [2]*Ahmed Maher Teaching Hospital, Internal Medicine Department, Cairo, Egypt;* [3]*Southern California Liver Centers, Coronado, CA, United States;* [4]*John A. Burns School of Medicine, University of Hawaii, Department of Tropical Medicine, Medical Microbiology and Pharmacology, Honolulu, Hawaii, United States*
Email: dr_msf@hotmail.com

Background and Aims: Egypt has the highest HCV prevalence in the world, estimated to be up to 10% in the last 2015 Egyptian Health Issues Survey (EHIS). In an effort to control HCV infection, treatment centers were established across the country. The first center in Luxor was inaugurated in June 2016 and implemented a free screening program in South Upper Egypt (Luxor and Qena governorates), funded by Tahya Misr Fund, the Ministry of Health and local NGOs.

Method: Free screening for HCV and HBV was offered to individuals older than 16 years. Demographic data and a blood specimen were collected. Sera were tested for HCV antibodies and HBsAg using third generation enzyme immunoassays (Enzygnost® Anti-HCV and HBsAg, Siemens, Germany). Between June 2016 and May 2017, 71,952 individuals were screened and positive patients were referred to treatment centers.

Results: At the time of this analysis, data was available for 67,042 participants. 31,965 males (47.7%) and 35,077 females (52.3%) were screened with a mean age of 43.6 ± 14.3 years. 9701 patients (14.5%) were positive for HCV antibodies and 2950 (4.4%) for HBsAg. Prevalence of HCV antibodies was significantly higher in males than females (19.67% vs. 9.73% OR = 2.27; CI 2.2 to 2.4; $p < 0.001$) and the same for HBsAg (6.2% vs. 2.8% OR = 2.3; CI 2.2 to 2.5; $p < 0.001$). The prevalence of HCV antibodies was significantly associated with age ($p < 0.001$) and ranged between 1% and 4% in individuals below the age of 40 years, then increased steadily until age 59 (41.6%). In contrast, HBsAg prevalence was lower than 2% in individuals younger than 25 years, and increased to 6% in the 25–44 years age group. Above 45 years of age the prevalence was 2–4% (Figure). HCV/HBV co-infection was found in 0.16% of individuals (107/67,042). HBsAg was positive in 1.1% of HCV positive patients versus 5% in negative individuals.



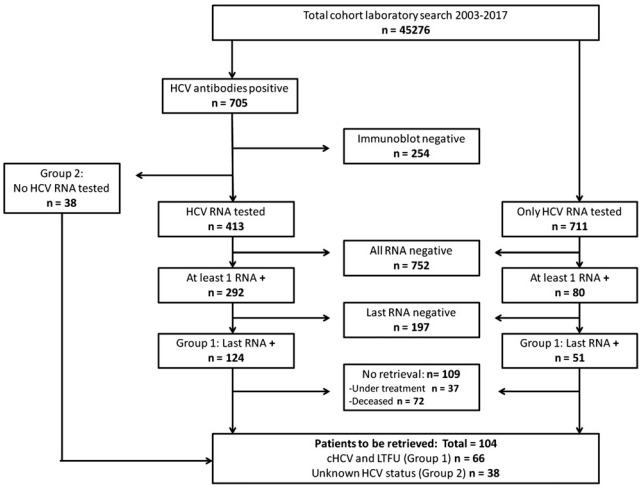
Conclusion: This screening program in South Upper Egypt rural areas showed: (1) a higher prevalence of HCV (14.5%); (2) higher prevalence of HBsAg (4.4%) than the reported prevalence in the 2015 EHIS; (3) HCV prevalence was higher in males and in patients older than 40 years. In summary, this new data underscores the importance of extending infection control efforts and screening to rural areas.

THU-121

Track, Trace & Treat: Results from a retrieval strategy to identify lost to follow-up chronic hepatitis C patients

I. Munsterman[1], J. Rahamat-Langendoen[2], J.P.H. Drenth[1], E.T.T.L. Tjwa[1].
[1]Radboud University Medical Center, Gastroenterology and Hepatology, Nijmegen, Netherlands; [2]Radboud University Medical Center, Medical Microbiology, Nijmegen, Netherlands
Email: isabelle.munsterman@radboudumc.nl

Background and Aims: There are an estimated 19.000 chronic Hepatitis C infected patients in the Netherlands. An unknown proportion has been lost to follow-up and received no adequate treatment. The advent of direct antivirals offers the prospect of safe and efficacious therapy. We designed this study to examine a retrieval strategy that identifies chronic HCV patients lost to follow up and brings them back into care.
Method: We analysed data files from the virology laboratory of the Radboud university medical centre Nijmegen to identify chronic hepatitis C (cHCV) infected patients. The laboratory serves applicants from two hospitals: a tertiary referral and liver expert centre and a rehabilitation clinic. Patients with positive HCV antibodies, immunoblot and/or HCV quantitative RNA PCR measurements between 2003 and 2017 were acquired and linked to personal data. Chart review was performed to assess possibility of loss to follow-up. Identification data was checked with the governmental citizen administration to adjust for death or change of municipality.
Results: In 1124 patients HCV RNA was tested, of which in 372 (33%) individuals at least one RNA was positive. Prevalence of HCV infection in this cohort would be estimated at 0.22%, which is similar to the prevalence in the Netherlands. In 175/372 patients (47%) the last measured RNA was still positive. Of these cHCV patients, 35/175 (20%) were still in care and 72/175 (41%) deceased. A total of 66/372 (18%) of cHCV patients is lost to follow-up and could benefit from linkage to care (group 1). Secondly, we assessed all individual HCV antibodies tested in this time period: 705/44.565 patients had positive HCV antibodies (1.6%), of which 254 (36%) could be excluded due to a negative immunoblot. In 38 patients with confirmed antibodies no HCV RNA was tested, none of them were adequately followed up (group 2). Together with group 1 they will be contacted for re-evaluation of HCV status, disease severity, and treatment if indicated.



Conclusion: Identification of patients through analysis of archival laboratory results is feasible and leads to identification of the target cHCV population. Prevalence of HCV infection in this cohort is representative of our country. The percentage of lost to follow-up cHCV patients in our tertiary referral centre emphasize the need for nationwide retrieval projects to get this group back in to care.

THU-122

Community interventions and peer support for active case finding and treatment support for underserved populations with hepatitis C in the UK, Ireland, Romania and Spain as part of the HEPCARE programme

J. Surey[1], D. Menezes[2], A. Story[3], J.M. Sanchez[4], O.A. Cristiana[5], P. Vickerman[6], W. Cullen[7], J. Lambert[8]. *[1]University College London, Institute of Global Health, London, United Kingdom; [2]University College London, The Farr Institute of Health Informatics Research, London, United Kingdom; [3]UCLH NHS Trust, Find&Treat, London, United Kingdom; [4]Hospital Universitario de Valme, Infectious Diseases and Microbiology Unit, Sevilla, Spain; [5]Victor Babes Clinical Hospital for Infectious and Tropical Diseases, Bucharest, Romania; [6]University of Bristol, School of Social and Community Medicine, Oakfield House, Bristol, United Kingdom; [7]University College Dublin, School of Medicine, Dublin, Ireland; [8]Mater Misericordiae University Hospital, Infectious Diseases Department, Dublin, Ireland*
Email: j.surey@ucl.ac.uk

Background and Aims: Hepatitis C disproportionately affects vulnerable groups such as the homeless, PWIDs and prison populations. In the age of DAAs community interventions are vital to reach these underserved populations if there is to be a chance of reducing prevalence and eventual elimination. The four EU HepCare sites (Ireland, UK, Spain, Romania) aim to improve identification and treatment of HCV, especially focusing on vulnerable populations with a commitment to sharing knowledge and practice. The HepFriend workpackage aims to utilise peer support in the community to increase awareness of the risk of HCV, the importance of testing, disease severity and provide treatment support. Peers, with their lived experience, can connect with underserved populations in a way traditional treatment services cannot.

Method: Peers were recruited and trained in HCV awareness raising and testing using a standardised method developed by the Hepatitis C Trust (UK). They were taught to deliver three simple messages: the importance of getting tested; the effectiveness of current treatment; how to avoid infection. Each site then adapted the training to meet local needs and peer networks were developed locally with NGO partners to feed into specialist HCV services. One site (London) trained peers in Fibroscan alongside the clinical team. Training was also provided in other diseases such as TB, HIV and linkage to care.
Results: To date, a total of 27 peers received training: Dublin n = 12, London n = 6, Bucharest n = 3 and Sevilla n = 6. These peers have collectively carried out 216 tests and (re-)engaged 168 patients with clinical services. Of these 82 (48.8%) were started on treatment. Three sites (Dublin, London, Bucharest) made linkages with TB services, two also with HIV advocacy NGOs (Bucharest, Sevilla). The London site offered peer support linked with a mobile health unit with trained peers carrying out 70 Fibroscans. Peers have been also incorporated into OST delivery sites (Dublin n = 4, London n = 3) and the local hospital treatment network (Bucharest, Sevilla).
Conclusion: Peers have a unique role in engaging with underserved populations and we have shown they can be successfully integrated into community interventions to improve case finding and treatment outcomes. Peers can also be a powerful resource to empower patients to access treatment, which is vital if we are to eliminate HCV as a public health concern, where traditional medical models have failed.

THU-123

Virological and clinical characterization of a hepatitis A outbreak in Barcelona involving primarily men who have sex with men

S. Rodríguez-Tajes[1,2], E. Perpiñan[1,2,3], B. Caballol[2], S. Lens[1,2,3], Z. Mariño[1,2,3], J. Costa[2,3], A. Vilella[2], S.P. del Pulgar[1,2,3], X. Forns[1,2,3], G. Koutsoudakis[1,2,3]. *[1]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [2]Hospital Clínic, Barcelona, Spain; [3]CIBER - Centro de Investigación Biomédica en Red, Madrid, Spain*
Email: sergio.tajes@gmail.com

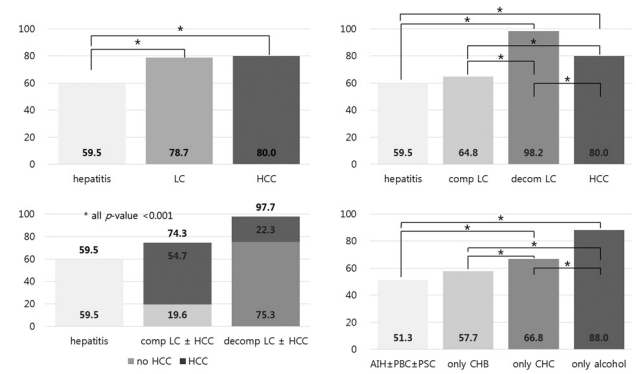
Background and Aims: Acute hepatitis A (AHA) transmission occurs mainly through the faecal-oral route and/or via contaminated food or water. Moreover, men who have sex with men (MSM) are considered a high risk population and thus, vaccination is strongly recommended. Strikingly, an increasing number of cases of AHA in different European countries have been reported since the second half of 2016. Here, we aimed to evaluate the clinical and virological characteristics of the ongoing hepatitis A outbreak in our area (Barcelona).
Method: We prospectively analyzed all cases of AHA diagnosed in our hospital between January and October 2017. We evaluated demographic data, risk factors, clinical symptoms, sexual orientation, comorbidities and further sexually transmitted diseases (STD). Phylogenetic correlation of the current circulating viruses among them and previously hepatitis A reported strains in our area was assessed by sequencing the VP1/P2A viral region.
Results: So far, 64 patients have been included. Most were male (62, 97%) with a median age 32 years (range 28–39). Twenty-three (39%) patients required hospitalization, 11 (17%) due to severe acute hepatitis and the remaining patients due to severe gastrointestinal symptoms. Except for 2 patients, all had a full recovery in less than 3 months. Of note, 42 (66%) patients self-reported to be MSM. Compared with the non-MSM group, MSM reported more frequent risk sexual contacts (78% vs 10%, p = 0.00), active drug consumption during the previous month (39% vs 11%, p = 0.05) and were diagnosed with others STD (36% vs 14%, p = 0.05).
Molecular phylogenetic analyses revealed that all patients were infected by hepatitis A subgenotype IA strains, which comprised 3 distinct clusters previously reported in other ongoing outbreaks in the United Kingdom, Berlin and the Netherlands. However, these strains were not phylogenetically related to those previously reported in Barcelona during the last decades.
Conclusion: The ongoing hepatitis A outbreak in Barcelona affects primarily the MSM community and is phylogenetically linked to current hepatitis A outbreaks described in other European countries. Because of the high admission rate, these outbreaks may impact the admission pattern of referral liver units. Control measures such as vaccination programs tailored to the MSM community must be implemented to control further spreading.

THU-124

Anemia in chronic liver disease

S.J. Suh[1], H.A. Lee[2], T.H. Kim[3], Y.-S. Lee[3], Y.K. Jung[3], J.H. Kim[3], Y.S. Seo[4], H.J. Yim[3], J.E. Yeon[3], S.H. Um[3], K.S. Byun[3]. *[1]Korea University Ansan Hospital, Department of Internal Medicine, Ansan-si, Gyeonggi-do, Republic of South Korea; [2]Korea University Anam Hospital, Department of Internal Medicine, Seoul, Republic of South Korea; [3]Korea University Medical College, Internal Medicine, Seoul, Republic of South Korea; [4]KUMC Anam Hospital, Internal Medicine, Republic of South Korea*
Email: mothpickle@naver.com

Background and Aims: The anemia in liver disease is common and the prevalence is various according to the stage of liver diseases. It is reported as 21% in compensated liver cirrhosis (LC), 50–70% in alcoholic or non-alcoholic liver cirrhosis, and 67% in hepatocellular carcinoma (HCC) patients. The prevalence in chronic liver disease is difficult to describe because various stages of liver disease are included in studies. According to WHO report at 2008, global prevalence of anemia in general population is about 24.8%.
The aim of study is to investigate the prevalence of anemia according to the stage of liver disease, and the causes of anemia in chronic liver disease.
Method: The patients who visited to Korea university ansan hospital were reviewed by medical record. From January 2012 to December 2016, 2357 patients visited for liver disease. The anemia was defined as hemoglobin level <13.0 g/dl (men) or <12.0 g/dl (women) by WHO's threshold.
The causes of anemia is classified as hemorrhage (definite gastrointestinal bleeding is noted by endoscopic exam), renal diseases (eGFR, MDRD < 30 ml/min/1.73 m^2), inflammatory disorder (CRP > 3 g/dl), iron deficiency anemia (Fe/TIBC < 15% or ferritin < 18 ng/ml), direct toxicity of ethanol (alcohol etiology and MCV > 100), hypersplenism (spleen size ≥ 13 cm), and others as undetermined. This classification is modified from "the algorithm of the physiologic classification of anemia" of Harrison's Principal of Internal Medicine.
Results: 2357 patients visited for liver disease, and 1961 patients had chronic liver disease. 1317 patients had anemia. The prevalence of anemia in chronic liver diseases were 69.8% [1317/ (1961–75 missing haemoglobin data)]. Female patients had more anemia (75.5% vs. 68.2%, p = 0.048).
As the chronic liver disease worsened, more anemia was observed (chronic hepatitis 59.5%, compensated LC 64.8%, decompensated LC 98.2%, HCC 80.0%). The progression of liver disease rather than HCC was associated with anemia (hepatitis 59.5%, compensated LC ± HCC 74.3%, decompensated LC ± HCC 97.7%, p < 0.001).
The proportion of anemia was different according to the etiology of liver disease (AIH ± PBC ± PSC 51.3%, CHB 57.7%, CHC 66.8%, and alcohol 88.0%). The alcoholic patients had more anemia (alcohol 84.8% vs. non-alcohol 62.0%, p < 0.001).
The causes were hemorrhage 19.1%, renal diseases 6.4%, iron deficiency anemia, 22.3%, inflammatory 15.3%, drug side effect 2.5%, direct toxicity of ethanol 17.8%, hypersplenism 11.5%, and undetermined 5.1%.
Conclusion: The prevalence of anemia in chronic liver disease was 69.8%, higher than general population 24.8%. Attention should be paid more to the patients with progressed liver disease. The proportion of anemia was larger in alcoholic liver disease than viral or inflammatory liver disease. Because of the variety of causes, different treatment is needed for each causes.



THU-125

Increasing access to treatment for hepatitis C by vulnerable, high risk patients through community pharmacy: The SuperDOT-C study in Scotland

A. Radley[1,2], L. Beer[3], C. Byrne[3], S. Inglis[3], A. Eriksen[1], S. Barclay[4], A. Fraser[5], J. Dillon[6]. [1]*NHS Tayside, Directorate of Public Health, Dundee, United Kingdom;* [2]*University of Dundee, Molecular and Clinical Medicine, Dundee, United Kingdom;* [3]*University of Dundee, Tayside Clinical Trials Unit (TCTU), Dundee, United Kingdom;* [4]*NHS Greater Glasgow and Clyde, Department of Gastroenterology, Glasgow, United Kingdom;* [5]*NHS Grampian, Summerfield House, Aberdeen, United Kingdom;* [6]*University of Dundee, Molecular and Clinical Medicines, Dundee, United Kingdom*
Email: Andrew.Radley@nhs.net

Background and Aims: New care pathways for Hepatitis C (HCV) are required to increase access to treatment among people prescribed opioid substitution therapy (OST). Existing pathways are often poorly utilised by this vulnerable group because of barriers to care including issues with stigma and health literacy and complexity of service design. This is despite OST patients having regular contact with a pharmacist. Highly effective direct-acting antiviral therapy (DAAs) for HCV have a much smaller burden of treatment than interferon-based regimes, require less monitoring and have improved adherence, making a community pharmacy treatment pathway potentially viable. The SuperDOT-C trial compares an established standard of care pathway (conventional care). with a community pharmacy-led pathway utilising directly observed therapy.
Method: Fifty-five community pharmacies have been recruited from the Tayside, Grampian and Glasgow regions of Scotland. and have been randomised to either provide HCV treatment on site (pharmacy-led arm), or refer patients to the conventional care pathway At the beginning of the study, pharmacists and support staff were trained to provide dried blood spot testing for HCV to OST recipients and to evaluate laboratory test results to determine suitability for treatment within the community pharmacy. Individuals suitable for treatment either receive therapy within their pharmacy or are referred to the conventional care pathway.
Results: To date, 280 HCV positive patients have been consented into the two SuperDOT-C treatment arms and 113 have initiated therapy. No problems have been encountered with the testing or assessment of patients for treatment. Pharmacy staff report that the opportunity to offer testing and treatment for HCV has enhanced the relationship with patients.
Conclusion: The SuperDOT-C study has shown initial promise, in terms of the ability of pharmacy staff to recruit OST patients and encourage them to initiate treatment. The study is scheduled to complete recruitment by the end of 2018.

THU-126

Drug utilization in patients with liver cirrhosis in ambulatory care

R. Weersink[1,2], T. Katja[2], S. Borgsteede[1]. [1]*Health Base Foundation, Dept. Clinical Decision Support, Houten, Netherlands;* [2]*University of Groningen, Unit PharmacoTherapy, Epidemiology & Economics, Groningen, Netherlands*
Email: sander.borgsteede@healthbase.nl

Background and Aims: Patients with liver cirrhosis are at risk to develop adverse events because of altered pharmacokinetics and pharmacodynamics. Some drugs have known safety risks in patients with cirrhosis, such as NSAIDs and benzodiazepines. There is not much known about drug use in these patients in ambulatory care, where drug use might be more risky because of less monitoring. Therefore, we aim to explore which drugs patients with liver cirrhosis use in ambulatory care.
Method: In this retrospective longitudinal cohort study, data from an out-patient pharmacy database were combined with hospitalization data (PHARMO Database Network). Patients with a clinical diagnosis of cirrhosis (ICD-9 code 571.2 or 571.5) between January 1998 and December 2015 were included in the study. The index date was the first day of discharge from hospital with the diagnosis of cirrhosis. Data on drug dispensions were analyzed during the total follow-up of a patient.
Results: In total 5,618 patients (59% males) were included with a mean age at the index date of 60.7 ± 12.5 years. Patients were followed for a median of 3 years (interquartile range (IQR) 3) after the index date. In 179 patients (3.2%) follow-up ended because of a liver transplantation. During the total follow-up, 102,297 drugs were prescribed. General practitioners prescribed 61.5% of these drugs, specialists 36.4% and the prescriber was unknown in 2.2%. Patients used a median of 6.8 unique drugs per person per year (IQR 8.4). Drugs for acid related disorders (mainly proton pump inhibitors) were the most frequently used therapeutic group (70.9% of patients) followed by diuretics (63.5%) and antibacterials for systemic use (61.9%). For individual drugs, spironolactone (48.7%), furosemide (44.0%) and pantoprazole (34.9%) where used most often. Temazepam (23.2%), diclofenac (22.2%) and paracetamol (21.3%) were the most frequently used drugs for non-liver related co-morbidities. Looking at the group of benzodiazepines and NSAIDs; they were used by respectively 46.2% and 37.1% of patients during the total follow-up.
Conclusion: Patients with cirrhosis frequently use drugs in ambulatory care. A substantial proportion of patients used drugs with known safety risks in cirrhosis, such as NSAIDs and benzodiazepines. Attention is needed for both specialists and general practitioners when prescribing drugs to these fragile patients to prevent adverse events.

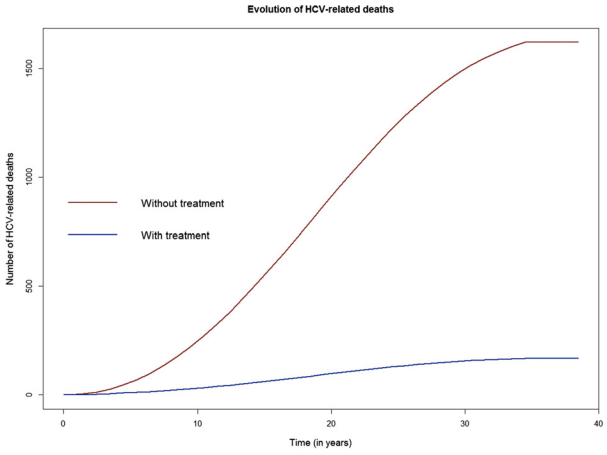
THU-127

Long-term effectiveness of Sofosbuvir-based hepatitis C regimens in Central and West Africa (ANRS 12342)

S. Boyer[1], M. Baudoin[1,2], M. Nishimwe[1,2], M.E. Woode[3], G. Maradan[1,2], M. Lemoine[4], B. Sylla[5], C. Kouanfack[6], B. Spire[1,2], N. Rouveau[7], R. Moh[8], M. Seydi[9], A. Attia[10], K. Lacombe[11]. [1]*Aix Marseille Univ, INSERM, IRD, SESSTIM (Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale) Marseille France;* [2]*ORS PACA (Observatoire Régional de la Santé Provence-Alpes-Côte d'Azur) Marseille France;* [3]*Liverpool School of Tropical Medicine;* [4]*Imperial College, London;* [5]*IMEA, Paris, France;* [6]*Hôpital Central de Yaoundé, Hôpital de jour, Yaoundé, Cameroon;* [7]*ANRS, Paris, France;* [8]*Mereva, PACCI Abidjan, Abidjan, Côte d'Ivoire;* [9]*CHU Fann, Service des Maladies Infectieuses, Dakar, Senegal;* [10]*CHU Yopougon, Service d'hépatologie, Abidjan, Côte d'Ivoire;* [11]*INSERM UMR-S1136, Université Paris VI-APHP, Paris, France*
Email: sylvie.boyer@inserm.fr

Background and Aims: Chronic hepatitis C (CHC) is a global public health problem with long-term consequences including the development of liver cirrhosis and hepatocellular carcinoma (HCC). The short-term effectiveness of Direct Anti-Viral Agents (DAA) has been assessed for the first time in the setting of sub-Saharan Africa within the multicenter, non-randomized, open-label ANRS 12311 TAC trial.

We assessed the long term clinical benefits of treating hepatitis C patients with sofosbuvir-based treatment in Cameroun, Senegal and Côte d'Ivoire.
Method: Using a Markov cohort model, we simulated CHC with and without treatment in a cohort of 10,000 chronically infected patients. CHC treatment efficacy and costs were derived from the TAC trial, which treated a total of 120 CHC adult patients either with sofosbuvir/ribavirine (for genotype 2, n = 40) or sofobuvir/ledispavir (for genotypes 1 and 4, n = 40 and 40, respectively) in the three study countries. An extensive literature review was carried out to obtain disease progression probabilities without treatment and after cure. We compare life-years gained over the life time, as well as number of individuals with compensated cirrhosis, decompensated cirrhosis and HCC 10 and 20 years after diagnosis, with and without treatment. Sensitivity analysis were performed to evaluate model robustness.
Results: The total number of life years was 228,600 with treatment and 207,736 without treatment, i.e. 20,864 life years gained with treatment. Figure 1 shows the impact of CHC treatment on the liver-related mortality over time. Treatment prevented 1452 HCV related deaths. Disease progression outcomes showed that after 10 (20) years, 9.45% (resp. 7.36%) of the treated cohort had a compensated cirrhosis versus 24.40% (resp. 23.80%) of the non-treated cohort. Similarly, after 10 (20) years, only 0.41% (resp. 0.53%) of the treated cohort had decompensated cirrhosis versus 3.98% (resp. 5.32%) of the non-treated cohort. HCC cases represented 0.01% of the treated cohort (resp. 0.02%) and 0.10% (resp. 0.16%) of the non-treated cohort after 10(20) years.



Conclusion: Sofosbuvir-based treatment significantly reduces HCV-related mortality and allows controlling the evolution of liver disease in the setting of sub-Saharan Africa which presently pays a high burden to the global liver associated mortality. These results highlight the necessity of increasing the access to DAAs that offer large long-term health benefits in resource-limited settings.

THU-128
Cost-effectiveness of Sofosbuvir-based hepatitis C regimens in Central and West Africa (ANRS 12342)

S. Boyer[1], M. Baudoin[1,2], M. Nishimwe[1,2], M.E. Woode[3], G. Maradan[1,2], M. Lemoine[4], B. Sylla[5], C. Kouanfack[6], P. Carrieri[1,2], N. Rouveau[7], R. Moh[8], M. Seydi[9], A. Attia[10], K. Lacombe[11]. *[1]Aix Marseille Univ, INSERM, IRD, SESSTIM (Sciences Economiques & Sociales de la Santé & Traitement de l'Information Médicale); [2]ORS PACA (Observatoire Régional de la Santé Provence-Alpes-Côte d'Azur); [3]Liverpool School of Tropical Medicine, London, United Kingdom; [4]Imperial College, London, London, United Kingdom; [5]IMEA, Paris, France; [6]Hôpital Centrale de Yaoundé, Hôpital de Jour, Yaoundé, Cameroon; [7]ANRS; [8]MEREVA, PACCI Abidjan, Abidjan, Côte d'Ivoire; [9]CHU Fann, Service des Maladies Infectieuses, Dakar, Sénégal; [10]CHU Yopougon, Service d'hépatologie, Abidjan, Côte d'Ivoire; [11]INSERM UMR-S1136, Université Paris VI-APHP*
Email: sylvie.boyer@inserm.fr

Background and Aims: While low-income countries (LICs) bear the highest burden of Chronic Hepatitis C (CHC), treatment is poorly accessible in these countries mainly due to cost consideration. As part as the open-label trial for CHC treatment in Africa (TAC-ANRS 12311), we assessed the cost-effectiveness of an interferon-free regimen in patients with CHC living in Senegal, Cameroon and Cote d'Ivoire.
Method: Using a Markov cohort model, we simulated CHC with and without treatment in a cohort of 10,000 chronically infected patients. CHC treatment efficacy and costs were derived from the TAC trial, which treated a total of 120 CHC adult patients either with sofosbuvir/ribavirine (for genotype 2, n = 40) or sofobuvir/ledispavir (for genotypes 1 and 4, n = 40 and 40, respectively) in the three study countries. An extensive literature review was carried out to obtain disease progression probabilities and costs without treatment and after cure. We estimated quality adjusted life-years (QALY) gained over the life time, incremental costs and incremental cost-effectiveness ratio (ICER) of sofosbuvir-based treatment compared with the situation without treatment. We assessed uncertainty with probabilistic sensitivity analysis and cost-effectiveness acceptability curves.
Results: Sofosbuvir-based treatment increased costs by a mean of €822.5, €997.5 and €1173.2 per patient in Senegal, Ivory Coast and Cameroon, respectively. It saved 1.4, 1.2 and 1.3 QALY per patient compared with the situation without treatment. Corresponding ICER (95% Confidence Intervals) were €588.4 [330.7–1327.6], €806.6 [480.1–1533.4] and €870.8 [536.2–1760,1] per QALY in the study countries (Senegal, Ivory Coast and Cameroon, respectively). At a cost-effectiveness threshold of three times the GDP per capita, the probability to be cost-effective reached near 100% in all three countries (See Figure).

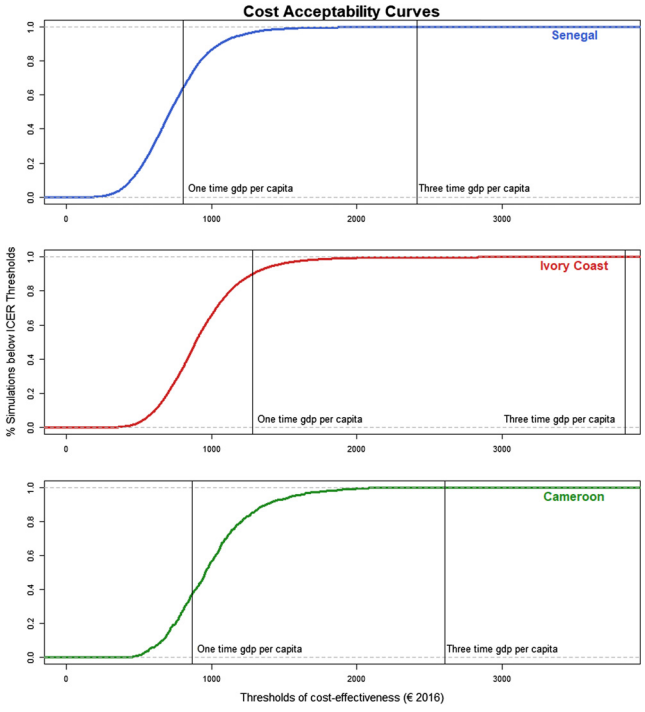


Figure 1: Cost-effectiveness acceptability curves of sofosbuvir-based treatment in West and Central Africa.

Conclusion: Our findings suggest that sofosbuvir-based treatment is cost-effective in the setting of the study countries at the cost-effectiveness threshold of three times the GDP per capita. As large reductions in DAA prices are expected with the development of generics, this treatment may even become very cost-effective in the short term. These results highlight the necessity of increasing access to DAAs that offer large long-term health benefits at additional acceptable costs in resource-limited settings.

THU-129

HCV screening in the adult general population of a basic health area in the Valencian Region (Spain)

L.G.-E. Viejo[1], A.G. Herola[1], I.S. Lloret[2], I. Clemente[2], F. Sanchez-Ruano[3], C.Q. Ivorra[1], I.A. Saavedra[1], J. Valverde[1]. *[1]Hospital Marina Baixa, Seccion Medicina Digestivo, Villajoyosa (Alicante), Spain; [2]Departamento de Salud Marina Baixa, Centro de Salud Publica Benidorm, Benidorm (Alicante), Spain; [3]Centro de Salud Callosa d'en Sarria, Departamento Salud Marina Baixa, Callosa d'en Sarria (Alicante), Spain*
Email: agherola@gmail.com

Background and Aims: Data on seroprevalence of hepatitis C (HCV) in the general population in Spain is scarce. A national cross-sectional, population-based study (PREVHEP study) recently estimated HCV seroprevalence (1.2%) and viremia prevalence (0.31%). Aim: to estimate HCV seroprevalence and prevalence of HCV viremia in the adult (25–70 years-old) general population of a basic health area in the Valencian Region.

Method: Design: observational, cross-sectional, population-based study.

Population: All 25–70 years-old adults living in a basic health area (Callosa d'En Sarrià) with universal population covering and registered in the Valencian Health Service (VHS) database.

Variables: (1) outcome: HCV serology, HCV viremia. (2) descriptive: id number, age.

Data collection: Study subjects were invited to participate and sign the study informed consent by mail. HCV serology was obtained amongst those who agreed to participate using a rapid anti-HCV finger stick blood test (Core HCV). Subjects were encouraged to contact investigators in order to communicate HCV serology status if previously known. An attempt to confirm HCV serology and HCV viremia status was done, using ELISA and PCR, respectively. Information on descriptive variables was obtained from the VHS database, whilst on risk factors associated to HCV infection were collected through personal interviews.

Analysis: descriptive analysis.

Results: 5,849 subjects were invited to participate in the study by mail. 143 subjects were excluded due to mailing address errors (study population = 5,706). Between February and April 2017, 2,637 out of 5,706 subjects directly participated in the study (46.2%). Of all the subjects to whom the rapid HCV test was performed, seven were positive; none of them were aware of their HCV infection status. Twenty-three subjects had a history of HCV infection, some of whom had been treated and/or were being followed by hepatologists. In all, 30 subjects (mean age 54.9, range: 37–71) were anti-HCV positive, resulting in an estimated prevalence of 1.1% (30/2637). All of the 30 anti-HCV positive subjects were tested for RNA-HCV (13 positive), and HCV viremia prevalence has been estimated as 0.49% (13/2637).

Conclusion: (1) HCV seroprevalence (1.1%) in the general population of the study area was similar and viremia (0.49%) was higher than those recently reported in Spain. (2) Most anti-HCV positive patients were born in 1950 to 1970. (3) The majority of patients with positive viremia were aware of their HCV status. (4) Participation in the study was very high (46.2%).

THU-130

The nature and impact of stigma in patients with chronic hepatitis B: a systematic literature review

J. Smith-Palmer[1], R. Pollock[1], K. Bonroy[2], U. Sbarigia[2], W. Valentine[1], K. Cerri[2]. *[1]Ossian Health Economics and Communications, Basel, Switzerland; [2]Janssen Pharmaceutica N.V., Beerse, Belgium*
Email: smith-palmer@ossianconsulting.com

Background and Aims: People with chronic infectious diseases can face stigma, which can negatively impact quality of life and quality of care, as well as influence treatment seeking and disclosure behavior. Stigma can be defined as a social process characterized by exclusion, rejection, blame or devaluation due to experience or anticipation of adverse social judgement of a person/group and can be classified as internalized, social or structural/institutional. A systematic literature review was performed to characterize the level and type of stigma experienced by people infected with hepatitis B virus (HBV) as well as the extent to which these influences treatment seeking, disclosure and quality of life in this patient population.

Method: A systematic literature review was performed in November 2016 using the PubMed, EMBASE and Cochrane databases to identify studies describing (quantitatively or qualitatively) stigma related to HBV. For inclusion, articles were required to be published in full text form, in English and contain data from which qualitative or quantitative data on HBV-related stigma could be extracted. No time limits were applied to the search.

Results: A total of 23 (17 quantitative and 6 qualitative) articles examined HBV-related stigma, these were almost exclusively conducted in Asian or Asian Immigrant populations, with some utilizing tools that allow the quantitative assessment of HBV-related stigma, including the HBV Stigma Instrument (n = 3) and the Hepatitis B Quality of Life Questionnaire 1.0 (n = 2). Qualitative studies were primarily conducted via patient interview. Internalized and social stigma were common in HBV-patients with >30% respondents in some studies believing that HBV brought trouble/shame to their families and that people with HBV should avoid kissing/hugging others. There was some evidence that stigma was partly attributable to lack of knowledge around transmission routes, which led to a fear of infection. HBV patients, also perceived structural/institutional stigma, with up to 20% believing that they may be denied healthcare and up to 30% stating that they may face workplace discrimination due to HBV.

Conclusion: Stigma towards patients with HBV is common and deeply entrenched in Asia and among Asian immigrant communities in North America, and is poorly characterized in non-Asian populations. Initiatives are needed to measure and document HBV-related stigma, as well as its clinical and socioeconomic consequences.

THU-131

Cost-effectiveness of scaling up Hepatitis C virus prevention, testing and treatment interventions among people who inject drugs in the US

C. Barbosa[1], H. Fraser[2], T. Hoerger[1], A. Leib[1], J. Evans[3], J. Havens[4], L. Nerlander[5], K. Page[3], A. Young[6], A. Kral[1], J. Zibbell[1], S. Hariri[5], C. Vellozzi[5], J. Ward[5], P. Vickerman[2]. *[1]RTI International; [2]University of Bristol, Population Health Sciences; [3]University of California, San Francisco; [4]University of Kentucky College of Medicine; [5]Centers for Disease Control and Prevention; [6]University of Kentucky College of Public Health*
Email: hannah.fraser@bristol.ac.uk

Background and Aims: HCV prevention and treatment interventions need to be scaled-up for people who inject drugs (PWID) to tackle the increasing HCV epidemic in the US; we undertake the first cost-effectiveness of this strategy.

Method: We calibrated two HCV-transmission and disease progression models among PWID and ex-PWID to data from rural Perry County, Kentucky (PC) and urban San Francisco (SF). Compared to PC, SF has a greater proportion with recent (last 3–6 months) access to

MAT (6% vs 12%) or SSP (0% vs 85%), which are both assumed to reduce HCV-transmission risk by about 50%, and 70% combined, based on a recent Cochrane review. HCV-treatment of PWID is currently negligible in both settings. Intervention scenarios considered: (HR) Scale-up of SSP and MAT to 50% coverage (SSP coverage at baseline is high in SF) with no HCV-treatment scale-up; and HR (50% coverage for both) plus 90% of PWID HCV-screened annually and 90% of HCV-infected PWID treated annually. Using a health-care perspective and measuring benefits in terms of quality adjusted life years (QALYs), we determined the incremental cost-effectiveness ratio (ICER) of each intervention compared to existing baseline.

Results: In PC, intervention HR would cost $14 million, gaining 782 QALYs, for an ICER of $17,698 per QALY gained, whereas HR + PWID HCV-treatment could cost $35 million, gaining 3,182QALYs, for an ICER of $11,037 per QALY gained. Conversely, the interventions were less cost-effective in SF; HR would cost $383 million, gaining 7,958QALYs, for an ICER of $48,098 per QALY gained, whereas HR + PWID HCV-treatment would cost $1,484 million, gaining 75,019 QALYs, for an ICER of $19,787 per QALY gained. Assuming a $50,000 willingness to pay threshold, both interventions are cost-effective in 100% of simulations for PC, but in SF, only for 64% of simulations for HR and 99% for HR + PWID HCV-treatment.

Conclusion: The scale-up of HCV prevention, screening and treatment interventions for PWID could be cost-effective in both rural and urban US settings.

THU-132

HEV positivity in domesticated pigs and a relative risk of HEV zoonosis among occupationally exposed individuals in Vietnam

X.H. Nghiem[1,2,3], X.H. Pham[4], V.S. Trinh[3,5], P.G. Dao[3,6], T.B. Mai[3,7], T.A. Dam[8], H.S. Le[3,6], C.-T. Bock[9], T. Hoang[3,4], L.T. Nguyen[3,4], T.P. Velavan[1,3]. *[1]Institute of Tropical Medicine, University of Tuebingen, Tuebingen, Germany; [2]108 Military Central Hospital, Institute of Clinical Infectious Diseases, Hanoi, Viet Nam; [3]Vietnamese - German Center of Excellence in Medical Research (VG-CARE), Hanoi, Viet Nam; [4]Vietnam Military Medical University, Department of Pathophysiology, Hanoi; [5]Institute of Clinical Infectious Diseases, Hanoi, Viet Nam; [6]108 Military Central Hospital, Institute of Clinical Infectious Diseases, Hanoi, Viet Nam; [7]Institute of Tropical Medicine, Tuebingen, Germany; [8]Hanoi Medical University, Pathophysiology, Hanoi, Viet Nam; [9]Robert Koch-Institute, Viral Gastroenteritis and Hepatitis Pathogens and Enteroviruses, Berlin, Germany*
Email: nghiemxuanhoan@108-icid.com

Background and Aims: Hepatitis E virus (HEV) infections by zoonosis is well documented in developed countries, and seldom known in developing countries. HEV infection can occur from eating undercooked pork or by exposure to animal faeces. HEV infection in domesticated pigs sold at markets in Hanoi metropolitan area were investigated to understand, if pigs were a potential source of HEV exposure. Additionally, we investigated on the seroprevalence of HEV exposure in general population, butchers, pig-farmers and individuals working at slaughterhouses.

Method: Liver tissues from domesticated pigs (n = 210) were screened for HEV RNA by reverse transcriptase polymerase chain reaction (rT-PCR). Serum samples from occupational workers (n = 182) and from general population (n = 340) were subjected to HEV IgG and IgM specific ELISAs, and the presence of HEV RNA was investigated by rT-PCR. Additionally, sequence analysis of HEV were done to address HEV genotypes in circulation in the region.

Results: Of the investigated pig liver tissues, 26/210 (12.4%) were positive for HEV-RNA and were characterized to be HEV Genotype 3. HEV seroprevalence was high among occupationally exposed population than the general population (anti-HEV IgM: 12% vs. 5%; p = 0.0065 and anti-HEV IgG: 67% vs. 31%; p < 0.0001, respectively). In particular, pig farmers had the highest anti-HEV IgG (92%), followed by slaughterers (66%) and butchers (49%). A similar trend for anti-HEV IgM was observed. The pig farmers had the highest anti-HEV IgM (14%), followed by slaughterers (10%) and the butchers (8%).

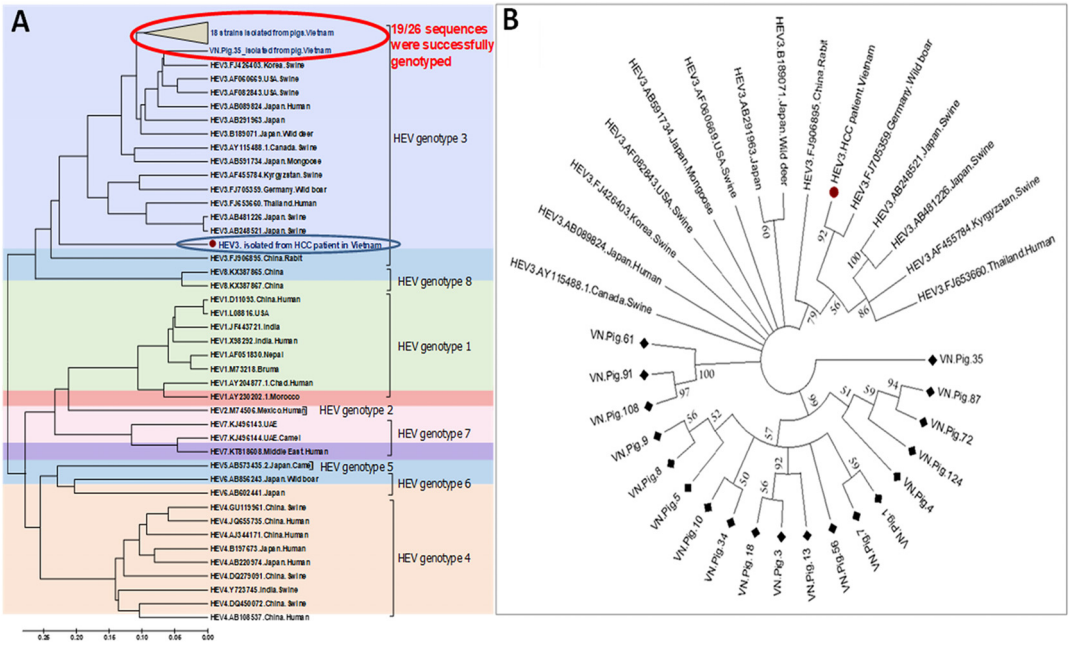


Figure 1: (abstract: THU-132): Phylogenetic analysis of HEV strains isolated from domesticated pigs. (A) Phylogenetic analysis of 19 HEV strains isolated from domestic pigs: Phylogenetic tree was reconstructed based on the alignment of 306 bp of the HEV RdRp region (ORF1), one HEV strain isolated from liver cancer patient coinfected with hepatitis B virus in Vietnam. A total of 40 full-length HEV genomes were included (all genotypes HEV-1 to HEV-8), as retrieved from NCBI database. Genetic distances were computed using the Kimura-parameter and a neighbor-joining tree was constructed with 1000 bootstrap replications. The scale indicates nucleotide substitutions per base pair. (B) Phylogenetic clade reconstructed with all available HEV 3 genotypes: The analysis involved 34 nucleotide sequences, including 19 HEV strains isolated from domestic pigs. Bootstrap analysis values (in percentage) are shown on the branches.

Conclusion: This first study reports that, HEV is circulating in domesticated pigs in Northern Vietnam. High HEV seroprevalence indicates an associated relative risk to HEV exposure. Taken together, this study provides insights on HEV transmission dynamics and domesticated pigs remain a zoonotic reservoir for HEV infection in Vietnam.

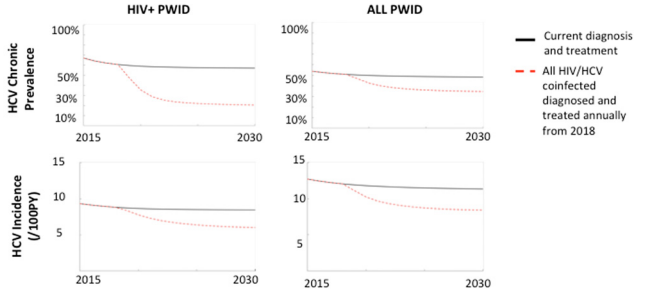
THU-133

Is HCV elimination among HIV-infected people who inject drugs possible through HCV treatment targeting HIV/HCV coinfection? A modeling analysis for Andalusia, Spain

B. Skaathun[1], A. Borquez[1], A. Rivero-Juarez[2], F. Tellez[3], M. Castano[4], D. Merino[5], J. Santos[6], J.M. Sanchez[7], A. Rivero[2], N. Martin[8,9].
[1]University of California, San Diego, Medicine, La Jolla, CA, United States; [2]Instituto Maimonides de Investigaciones Biomedicas do Cordoba, Hospital Universitario Reina Sofia de Cordoba, Universidad de Cordoba, Cordoba, Spain; [3]Universidad de Cadiz, Instituto de Investigacion e Innovacion en Ciencias Biomedicas de la Provincia de Cadiz, Cadiz, Spain; [4]Hospital Regional Universitario de Málaga, Infectious Diseases Unit, Malaga, Spain; [5]Hospitales Juan Ramon Jimenez e Infanta Elena de Huelva, Infectious Diseases Unit, Huelva, Spain; [6]Hospital Universitario Virgen de la Victoria, Infectious Diseases Unit, Malaga, Spain; [7]Hospital Universitario de Valme, Instituto de Biomedicina de Sevilla, Sevilla, Spain; [8]University of California, Medicine, San Diego, United States; [9]University of Bristol, School of Social and Community Medicine, Bristol, United Kingdom
Email: natasha-martin@ucsd.edu

Background and Aims: Scale-up of HCV treatment for HIV/HCV coinfected individuals is occurring in Spain, the majority with a history of injecting drug use (IDU). However, it is unclear if this scale-up will achieve the WHO elimination target (90% reduction in incidence by 2030) among HIV-infected people who inject drugs (HIV + PWID). We assess the population impact of HCV treatment scale-up to HIV+ individuals, and its implications for elimination among HIV+ PWID in Andalusia, Spain, using dynamic modeling.
Method: A joint HIV and HCV transmission model among PWID was developed and stratified by HIV stage, HCV stage, diagnosis, and PWID status (PWID, exPWID). The model was calibrated to Andalusia (55%/70% chronic HCV prevalence among PWID/HIV+ PWID in 2010, respectively, 30% HIV prevalence among PWID in 2010, 6700 PWID in 2010, 370/2300 diagnosed coinfected PWID/exPWID in 2015). We assumed HCV treatment among diagnosed coinfected PWID and exPWID of 10.5%/year from 2004–2014, and 33%/year from 2015 (estimated from the HERACULES cohort, HIV/HCV coinfected individuals from 21 hospitals in Andalusia). We examine the impact of: (1) current treatment rates and (2) 100% screening and treatment of coinfected PWID from 2018 on HCV chronic prevalence and incidence among HIV+ PWID and PWID.
Results: Our model estimated that in 2015, 36% and 47% of HCV infected PWID and exPWID, respectively, in Andalusia were HIV/HCV coinfected. Among them, 26.8% and 60.5% of coinfections, respectively, were diagnosed. Current treatment rates could dramatically reduce the prevalent number of diagnosed coinfected people with a history of IDU (by a relative 77% from 2015–2030). However, this would only reduce HCV chronic prevalence by a relative 15% and 10% from 2015–2030 among HIV+ PWID and all PWID, respectively, due to transmission from PWID with HCV monoinfection and undiagnosed coinfection (Figure). If all coinfected PWID are diagnosed and treated annually from 2018, this could reduce chronic prevalence among HIV+ PWID by a relative 69% in 2030, but incidence by only 35% (Figure).
Conclusion: Increased HCV treatment of HIV+ individuals in Andalusia will dramatically reduce the diagnosed coinfection population, and scale-up could moderately reduce HCV incidence among HIV+ PWID, but elimination among HIV+ PWID will not be achieved through treating coinfected PWID alone. Elimination efforts among HIV+ PWID should focus on HCV diagnosis and treatment among both coinfected and monoinfected PWID.

Figure 1: Modeled HCV chronic prevalence (top panels) and incidence (bottom panels) among HIV+ PWID (left panels) and all PWID (right panels) in Andalusia, Spain. Simulations show model projections with current diagnosis and treatment rates (black lines) and scaled-up so all HIV/HCV coinfected PWID are diagnosed and treated annually from 2018.



THU-134

Incidence of hepatitis C virus infection in four prisons in New South Wales, Australia: The SToP-C study

B. Hajarizadeh[1], J. Grebely[1], M. Byrne[1], P. Marks[1], J. Amin[1], T. Butler[1], P. Vickerman[2], N. Martin[2,3], J.G. Mchutchison[4], D. Brainard[5], C. Treloar[6], A. Lloyd[1], G. Dore[1]. *[1]UNSW Sydney (University of New South Wales), The Kirby Institute, Sydney, Australia; [2]University of Bristol, School of Social and Community Medicine, Bristol, United Kingdom; [3]University of California San Diego, Division of Global Public Health, San Diego, United States; [4]Gilead Sciences Inc, Foster City, United States; [5]Gilead Sciences, Gilead Sciences, Foster City, United States; [6]UNSW Sydney (University of New South Wales), Centre for Social Research in Health, Sydney, Australia*
Email: bhajarizadeh@kirby.unsw.edu.au

Background and Aims: The Surveillance and Treatment of Prisoners with hepatitis C (SToP-C) study assesses HCV treatment as prevention in 4 prisons, in New South Wales, Australia. SToP-C consists of: (i) Surveillance phase, HCV status and risk behaviour are evaluated at study entry and monitored longitudinally; (ii) Treatment scale-up phase, participants with detected HCV RNA are offered 12 weeks sofosbuvir/velpatasvir. This analysis assessed HCV incidence before treatment scale-up.
Method: Surveillance phase data of participants enrolled before treatment scale-up (Oct 2014 to Sept 2017) was used. Participants were screened for HCV antibody (Ab) and RNA at enrolment. HCV Ab or RNA negative participants were tested 6-monthly. Those HCV Ab negative and HCV Ab positive/RNA negative were considered at risk of HCV primary infection and reinfection, respectively.
Results: Among 1,569 participants screened, 392 had detected HCV RNA (25%) and 1175 were at risk of HCV, among whom 482 had at least one follow-up visit (included in analysis, 356 and 126 at risk of primary infection and reinfection, respectively). During 388 person-years (py) of follow-up, HCV incidence was 7.9/100 py (95%CI: 5.6, 11.3). Incidence of primary infection and reinfection was 6.4/100 py (95%CI: 4.0, 10.1), and 12.3/100 py (95%CI: 7.2, 21.2), respectively. HCV incidence differed among prisons [prison A: 9.8/100 py (95%CI: 6.2, 15.3); prison B: 3.9/100 py (95%CI: 1.4, 10.3); prison C: 0/100 py (95% CI: 0, 64.2); prison D (female prison): 24.0/100 py (95%CI: 12.0, 48.0); $p < 0.001$]. HCV incidence among those with a history of injecting drugs, but not reported in the current imprisonment and among those injecting in the current imprisonment was 11.4/100 py (95%CI: 5.4, 23.9), and 21.5/100 py (95%CI: 14.1, 32.6), respectively. In a Cox proportional hazard model, adjusted for prison site, younger age (aHR per 10 years: 1.65, 95%CI: 1.35, 1.81), history of injecting, but not in the current imprisonment (vs. no injecting, aHR: 8.16, 95%CI: 1.64, 40.76), and injecting in the current imprisonment (vs. no injecting, aHR: 12.29, 95%CI: 2.82, 53.69) were associated with greater risk of HCV infection.
Conclusion: Before treatment scale-up, HCV incidence (both primary infection and reinfection) was high in SToP-C prisons and varied across prisons. HCV infection was associated with younger age and a history of injecting drugs, while those injecting in the prison were at greatest risk. These findings support the need for HCV screening and

comprehensive prevention strategies, including harm reduction and a HCV treatment as prevention evaluation.

THU-135

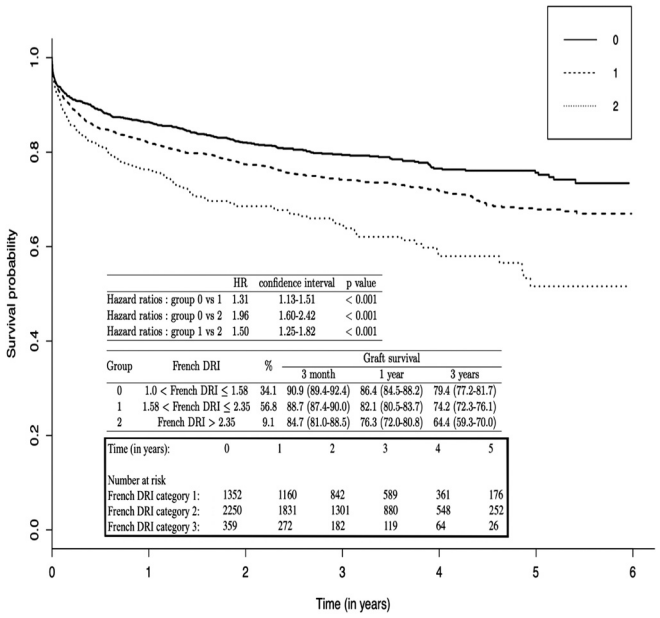
The French donor risk index for liver transplantation: development, internal and external validation

A. Winter[1], C. Feray[2], C. Antoine[3], O. Group[4], J.P. Daures[1], L. Paul[1].
[1]*Clinical Research University Institute, Biostatistics, Montpellier, France;* [2]*CHU Henri-Mondor, Hepatology, Créteil, France;* [3]*Agency of Biomedecine, Saint-Denis, France;* [4]*PHRC, France*
Email: audrey.winter89@gmail.com

Background and Aims: A major limitation to liver transplantation (LT) is organ shortage, leading to the use of non-optimal liver grafts. Finding the best match between a graft and its recipient is a challenge. Within the scope of a national project called OPTIMATCH, the aim was to optimize the current liver allocation system in France. A donor score, which scores the characteristics of the graft, is one of the key factors for a better matching. To determine the quality of the graft, scores such as the Donor Risk Index (DRI) or the Eurotransplant-DRI have been proposed. None of them have been validated on the French national database [*Liver Int*. 2017;37:1229–1238] possibly due to important donors' and candidates' differences between the databases.

The aim was to propose a French DRI using a derivation data from 3961 liver transplantations performed in France between 2009 and 2013, with an external validation based on a validation dataset from 1,048 French transplantations performed in 2014.

Methods: We used a Cox model, in the derivation dataset, with adjustment on recipient and transplant characteristics to create the score. We developed the French DRI score, using three different methods of selection, which we applied to construct groups at risk. Model performance was assessed through three measures of discrimination corrected by the optimism, through an internal validation. We plotted three calibration plots at months 3, 6 and 12 to evaluate the calibration of the score in the derivation dataset. An external validation [BMC 2013, 13:33] was also performed in order to evaluate calibration and discrimination of this new score in the validation dataset.



	HR	confidence interval	p value
Hazard ratios : group 0 vs 1	1.31	1.13-1.51	< 0.001
Hazard ratios : group 0 vs 2	1.96	1.60-2.42	< 0.001
Hazard ratios : group 1 vs 2	1.50	1.25-1.82	< 0.001

Group	French DRI	%	Graft survival 3 month	1 year	3 years
0	1.0 < French DRI ≤ 1.58	34.1	90.9 (89.4-92.4)	86.4 (84.5-88.2)	79.4 (77.2-81.7)
1	1.58 < French DRI ≤ 2.35	56.8	88.7 (87.4-90.0)	82.1 (80.5-83.7)	74.2 (72.3-76.1)
2	French DRI > 2.35	9.1	84.7 (81.0-88.5)	76.3 (72.0-80.8)	64.4 (59.3-70.0)

Time (in years):	0	1	2	3	4	5
Number at risk						
French DRI category 1:	1352	1160	842	589	361	176
French DRI category 2:	2250	1831	1301	880	548	252
French DRI category 3:	359	272	182	119	64	26

Figure: Survival curves using Kaplan Meier estimate for the three risk groups of the French DRI score. Graft survival at month 3, year 1 and 3, estimated using Kaplan Meier and hazard ratios through French DRI risk groups.

Results: Five donor covariates were retained: age, cause of death, intensive care unit stay, lowest MDRD clearance creatinine, liver type (split/total). The score had good properties and discriminated three groups at risk (Figure). Calibration plots showed a slight over-estimation. The performance of the model remained satisfactory even after correction by the optimism. Discrimination and calibration were preserved in the validation dataset.

Conclusion: This French DRI has good properties and is expected to be of interest for liver transplantation. The next step is to use this new DRI to explore the optimal matching between donor and recipient, taking into account the ⟪extended criteria donor⟫ graft attribution. This score will be reassessed yearly to take into account the modifications of the graft allocation system.

THU-136

Looking for the best matching between donor and recipient in liver transplantation: a sequential stratification approach

A. Winter[1], C. Feray[2], Optimatch Group[3], J.P. Daures[1], L. Paul[1]. [1]*Clinical Research University Institute, Biostatistics, Montpellier, France;* [2]*CHU Henri-Mondor, Hepatology, Créteil, France;* [3]*PHRC*
Email: audrey.winter89@gmail.com

Background and Aims: Liver transplantation (LT) is a life saving procedure for patients with end stage liver disease. The grafts are distributed according to a score calculated by recipients. The Model for End-stage Liver Disease (MELD) is the most use. The donor risk can be measured through a score: the French Donor Risk Index (DRI). Persistent shortage of donors has encouraged the use of "lower quality" grafts often accompanied with higher risk of graft loss. To whom should those grafts be given? What kind of matching would be optimal? We developed a model to explore the optimal matching. A graft, with a specific French DRI, is given to a recipient, with a known MELD. Would it be better to wait on the list for a better graft (i.e. with a lower French DRI) given the risk of clinical deterioration or death? From 8,526 patients listed between 2009 and 2014, our aim was to explore the optimal matching between donors and recipients and the use of Extended Criteria Donor (ECD) grafts according to the sequential stratification approach.

Methods: We estimated the survival benefit associated with LT in different categories of MELD and French DRI using Sequential Stratification derived from Schaubel [AJT 2008, 8:419–425.]. Briefly, this method reorganizes the observed data, and, as far as possible, reproduces a randomized controlled trial dataset. For each transplant, a stratum is created. The index patient is the patient receiving the graft, the control group is composed of all the matching waitlisted control patients. Then strata were combined and a stratified Cox regression model used. Several matching and adjustment covariates are considered in the model. The survival benefit is estimated through hazard ratios.

Results: As presented (Figure), a significant survival benefit was observed for all MELD and French DRI categories, except for low MELD and high French DRI category (i.e. ECD graft). For the latter occurrence, waiting for a graft, with a lower French DRI than the one received by the index patient, appears more appropriate.

Conclusion: In the current allocation system, high-risk grafts (or ECD graft) only provide a survival benefit to patients with medium or high MELD. In current practice, it would appear that only low MELD patients would not have a survival benefit with a high-risk transplant.

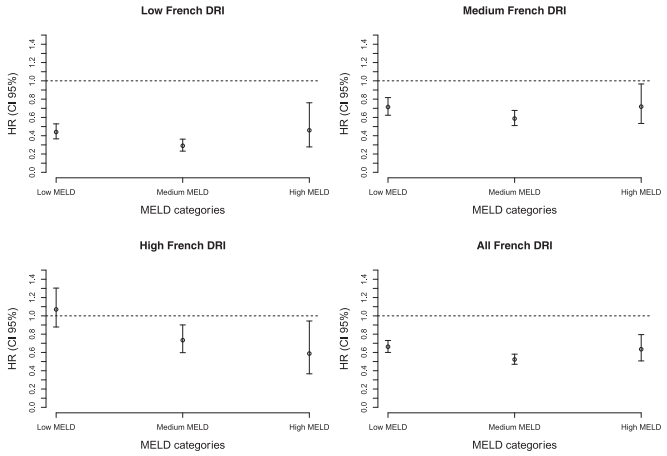


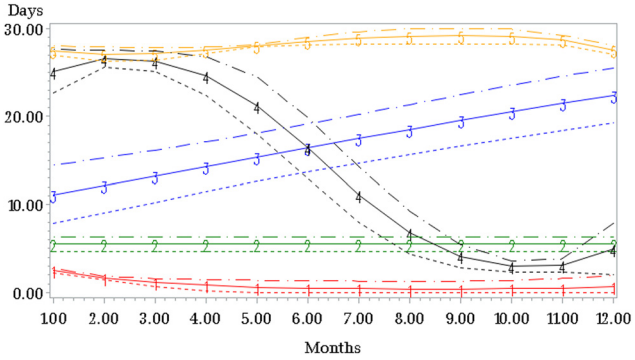
Figure: HRs through MELD and French DRI categories. With low French DRI: 1.0 < French DRI ≤ 1.58, medium French DRI: 1.58 < French DRI ≤ 2.35, high French DRI: 2.35 < French DRI, low MELD: 6 ≤ MELD ≤ 15, medium MELD: 15 < MELD ≤ 30 and high MELD: 30 < MELD.

THU-137

One-year injecting frequency trajectories as predictors of hepatitis C acquisition: findings from an observational cohort study of people who inject drugs in Montréal, Canada

E. Fortier[1,2], M.-P. Sylvestre[1,3], A.A. Artenie[1,3], D. Justras-Aswad[1,4], R. Élise[5,6], J. Grebely[7], J. Bruneau[1,2]. *[1]CHUM Research Centre, Montréal, Canada; [2]Université de Montréal, Department of Family and Emergency Medicine, Montréal, Canada; [3]Université de Montréal, Department of Social and Preventive Medicine, Montréal, Canada; [4]Université de Montréal, Department of Psychiatry, Montréal, Canada; [5]Institut national de santé publique du Québec, Montréal, Canada; [6]Université de Sherbrooke, Addiction Research and Study Program, Longueuil, Canada; [7]UNSW Australia, The Kirby Institute, Sydney, Australia*
Email: Julie.bruneau@umontreal.ca

Background and Aims: Injecting frequency is a well-established risk factor for hepatitis C virus (HCV) infection, yet few studies have assessed injecting frequency variations as predictors of HCV acquisition. This investigation aimed to identify one-year injecting frequency trajectories and examine their relation with subsequent HCV acquisition among people who inject drugs (PWID).
Method: HCV-uninfected PWID enrolled in the HEPCO study (Montréal, Canada) between March 2011 and June 2016 were tested for HCV and completed an interviewer-administered questionnaire at three-month intervals. In order to examine injecting frequency, participants were questioned at each visit on the number of days during which they used injecting drugs in each of the past three months. Group-based trajectory modelling was performed to identify injecting frequency trajectories over a 12-month period and estimate probabilities of group membership (using a censored normal model). Participants were assigned a trajectory using maximum posterior probabilities. HCV incidence and confidence intervals were estimated for all trajectory groups using Poisson distribution.
Results: For trajectory modelling, 386 participants contributed 3,725 observations over 12 months (mean age 40, 82% male, 52% HCV antibody positive). Five trajectories were identified and are depicted in the figure below: sporadic injecting (group #1, 26%), infrequent injecting (group #2, 34%), increasing injecting (group #3, 15%), decreasing injecting (group #4, 11%), and frequent injecting (group #5, 13%). For subsequent HCV incidence analyses, 273 participants with at least one follow-up assessment following the 12-month period contributed 565.6 person-years of follow-up (mean age 41, 83% male, 54% HCV antibody positive). Overall, HCV incidence was 5.7 per 100 person-years (95%CI 3.9–7.9). Participants were assigned to trajectory groups as follows: sporadic injecting (n = 70, 26%), infrequent injecting (n = 103, 38%), increasing injecting (n = 41, 15%), decreasing injecting (n = 27, 10%), and frequent injecting (n = 32, 12%). HCV incidence per 100 person-years was 2.7 (95%CI 0.9–6.4) for sporadic injecting, 3.8 (95%CI 1.9–7.0) for infrequent injecting, 12.1 (95%CI 5.9–22.2) for increasing injecting, 15.6 (95%CI 6.3–32.5) for decreasing injecting, and 5.9 (95%CI 1.9–14.3) for frequent injecting.



Conclusion: Trajectories with varying injecting frequencies (increasing and decreasing injecting) were more likely to predict HCV acquisition than stable trajectories, including frequent injecting. Injecting frequency trajectories could potentially help identify most-at-risk PWID, inform harm reduction interventions, and tailor clinical care.

THU-138

Cost-effectiveness of elbasvir/grazoprevir + sofosbuvir for the treatment of chronic HCV genotype 3 infection in Argentina

E. Bissio[1], C. Nwankwo[2], S. Corman[3], H. Monsanto[4], J.L. Montes[1]. *[1]MSD Argentina, Medical Affairs, Munro, Argentina; [2]Merck & Co., Inc., United States; [3]Pharmerit International, United States; [4]Merck Sharp & Dohme (I.A.) LLC, Latin America Health Outcomes Research, Carolina, Puerto Rico*
Email: ebissio@gmail.com

Background and Aims: EBR/GZR is indicated for use in combination with sofosbuvir (SOF) for the treatment of previously untreated chronic hepatitis GT3 infections in adults in Argentina. The objective of this model was to evaluate the cost-effectiveness of treatment with EBR/GZR plus SOF compared to no treatment and to daclatasvir (DAC) plus SOF, with or without ribavirin (RBV), in treatment-naïve GT3 patients.
Method: A Markov model created to simulate the natural history of HCV and estimate the lifetime cumulative incidence of advanced liver-related diseases was used. The structure of the model is based on other published health economic models of HCV disease. The model evaluates non-cirrhotic and cirrhotic patients separately from the perspective of the healthcare system. Information concerning the treatment regimens was derived from the clinical trials and the published literature. Comparators used in this model were SOF + DAC (non-cirrhotic) and SOF + DAC + RBV (cirrhotic). Outcomes generated include total costs and QALYs associated with each treatment strategy and the incremental cost-utility ratio (ICUR) over a 30-year time horizon. A deterministic and probabilistic sensitivity analysis was conducted for key model inputs.
Results: In the base case analysis, EBR/GZR + SOF was associated with lower lifetime costs and greater QALYs compared to both SOF + DAC and no treatment in GT3 treatment-naïve, non-cirrhotic patients, and thus was economically dominant (Table). EBR/GZR + SOF was also economically dominant over both SOF + DAC + RBV and no treatment in GT3 treatment-naïve, cirrhotic patients (Table). Deterministic, one-way sensitivity analyses showed that ICURs were sensitive only to SVR for EBR/GZR + SOF in non-cirrhotic patients. The probabilistic sensitivity analysis showed that EBR/GZR + SOF was cost-effective in

more than 85% of iterations in non-cirrhotic and 99% of cirrhotic patients, regardless of willingness to pay threshold.

Table 1: Treatment-Naïve, Non-Cirrhotic

Treatment Regimen	Total Discounted Costs (ARS)	Total Discounted QALYs	Incremental Costs (ARS)	Incremental QALYs	ICUR
EBR/GZR + SOF	187,143.32	10.4713	–	–	–
DAC + SOF	193,994.71	10.4451	−6,851	0.0263	EBR/GZR + SOF dominant
No treatment	425,911.68	9.4867	−236,786	0.9846	EBR/GZR + SOF dominant
Treatment-Naïve, Cirrhotic					
EBR/GZR + SOF	282,647.87	9.8371	–	–	–
DAC + SOF	360,215.44	9.3740	−77,568	0.4631	EBR/GZR + SOF dominant
No treatment	712,929.19	7.0981	−430,281	2.7390	EBR/GZR + SOF dominant

Conclusion: EBR/GZR + SOF is cost-saving in HCV patients with GT3 infection with and without cirrhosis when compared to DAC + SOF ± RBV and no treatment.

THU-139

Molecular epidemiology of hepatitis B and D in the Pacific Islands of Kiribati

K. Jackson[1], R. Tekoua[2], A. Tonganibeia[2], M. Littlejohn[1], T. Holgate[1], S. Nicholson[3], R. Edwards[3], S. Locarnini[1]. *[1]Victorian Infectious Diseases Reference Laboratory, The Doherty Institute, Research and Molecular Development, Melbourne, Australia; [2]Ministry of Health and Medical Services, Tungaru Central Hospital, Tarawa; [3]Victorian Infectious Diseases Reference Laboratory, The Doherty Institute, Serology Department, Melbourne*
Email: kathy.jackson@mh.org.au

Background and Aims: The Pacific island of Kiribati is endemic for Hepatitis B virus (HBV) and Hepatitis D virus (HDV). Despite the introduction of HBV immunization in 1989, studies performed on serum collected in 1998 showed a HBsAg prevalence as high as 27.4% in students and 15.1% in mothers. 37.5% of these individuals also had HDV RNA detected. A 2015 review of viral hepatitis in Kiribati was carried out by the Western Pacific Regional Office of the WHO. A key recommendation of the review was the establishment of a treatment program for HBV. The aims of this study were to determine the current status of HBV and HDV infections in Kiribati with a view to enabling the provision of treatment for those that require it; and to characterize the current strains circulating in Kiribati.
Method: 219 serum samples collected in 2017 from Kiribati's Tungaru Central Hospital were sent to VIDRL for HBV and HDV serological and molecular testing. 98 matching dried blood spots (DBS) were also collected. Serum HBsAg positivity was confirmed before testing for HBeAg serology and anti-HDV. All sera were tested for liver function tests, HBV DNA load, and anti-HDV positive samples were reflexed into a HDV PCR and load assay. Sequencing and phylogenetic analysis of the HDV strains was performed. Detection of HBsAg, HBV DNA and HDV RNA was attempted from the DBS and results compared to matched sera.
Results: HBsAg was detected in 200/219 (91%) samples, however 11 of the HBsAg negative samples were positive for either anti-HBc or anti-HBe. 43/200 (21.5%) were HBeAg positive and 144 (72%) had quantifiable HBV DNA. 52/96 (54.2%) HBsAg positive subjects also had positive anti-HDV serology. 36/52 (69.2%) of these had detectable HDV RNA. HBV DNA was able to be reliably detected from DBS in subjects with a serum HBV DNA load greater than 200 IU/mL. HDV RNA was only detected from DBS in 19/35 samples where matched sera was positive. The HBV strains were confirmed as the Polynesian genotype D4 and the HDV was the unique Pacific clade of genotype 1.
Conclusion: HBV and HDV are still highly endemic in Kiribati. Provision of the laboratory results will enable the linking of care and antiviral therapy to eligible individuals. Serological and molecular testing is on-going at VIDRL however laboratory capability in Kiribati will be assessed and reinforced to facilitate the establishment of a feasible diagnostic and monitoring program on the Island.

THU-140

Screening and treatment of hepatitis C virus infection of adult general population in Spain is cost-effective

M.B. Ferret[1], R. Domínguez-Hernández[2], M. Ángel Casado[2], E. Sabater[2], R. Esteban[1]. *[1]Hospital Universitario Vall d'Hebron, Barcelona, Spain; [2]Pharmacoeconomics & Outcomes Research Iberia (PORIB), Pozuelo de Alarcón, Spain*
Email: rdominguez@porib.com

Background and Aims: Elimination of infection by hepatitis C virus (HCV) requires high diagnostic rates and universal access treatment. Approximately 40% of infected are unaware of their infection. It is necessary to set up effective screening strategies to detect this population. We analyze the efficiency (incremental cost-utility ratio, ICUR) of three HCV screening strategies: adults of general population (1938–1997 born), adults belonging to high-risk groups and the highest HCV prevalence (1938–1967 born).
Method: An analytical decision model was used to establish the susceptible population for screening and diagnosis of chronic hepatitis C (CHC) and to project the progression of disease over lifetime. Screening was performed by a single blood test to 100% of the population evaluated and HC diagnosis by the RNA-HCV presence. Epidemiological data were obtained from the literature: anti-HCV prevalence (0.56–1.54%), viremic patients (31.5%) (*Cuadrado 2017*) and percentage of total undiagnosed (35%). Diagnosed and linked to care chronic patients were assumed to be treated (82%). Response rates (>98% SVR), transition probabilities, utilities and disease management annual costs were obtained from literature. Efficiency, under the National Health System perspective, throughout the life of patients was measured as quality-adjusted life years (QALY) and total costs (screening, diagnosis, pharmacological and disease management). A discount rate of 3% was applied to costs and results.
Results: General population screening strategy identified more additional cases of chronic HCV infection compared to high-risk groups and the highest prevalence population. ICUR value was below the accepted efficiency threshold in Spain (€30,000/QALY) comparing general population vs high-risk groups or general population vs the highest prevalence population (Table).

Table 1: Analysis results

	Strategies		Strategies	
	General population	High-risk groups	General population	Highest prevalence population
Population	34,529,609		15,197,719	
Screened individuals	12,085,363	134,069	12,085,363	5,319,202
CHC patients identified	52,694	17,132	52,694	23,668
Results per patient				
Incremental QALY	2.0 (18.7 vs 16.7)		3.8 (18.7 vs 14.9)	
Incremental cost (€, 2017)	€18,157 (€35,497 vs €17,339)		€857 (€35,497 vs €34,640)	
ICUR (€/QALY)	€8,914		€226	

Conclusion: HCV screening and treatment of all adults of general population is cost-effective compared to the screening in high-risk groups or in adult population with the highest prevalence.

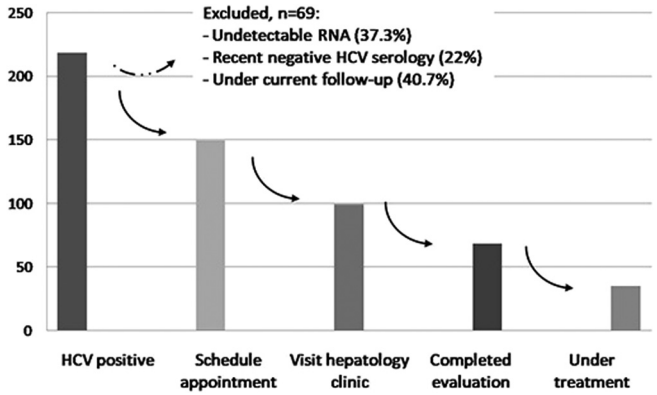
THU-141

Efficacy of a program based on on-site dried blood spot testing for hepatitis C to improve linkage to care and treatment uptake for people who injected drugs

D.M. Arraez[1], F. Gutierrez[2], E. Quintero[3], V. Casañas-Sanchez[4], A. De Vera[5], L.G.S. Gutierrez[6], E. Cuisido[7], Z.R. Marrero[6], V.P. Perez[7], A.R. Perez[6], M.J.M. Alonso[7], E.M. Carballo[8], F. Diaz-Flores[9], J.N. Casariego[4], M. Hernandez-Guerra[1]. *[1]Servicio de Aparato Digestivo. Hospital Universitario de Canarias, Hospital Universitario de Canarias, La Laguna, Spain; [2]Hospital Universitario de Canarias, Servicio de Farmacia, La Laguna, Spain; [3]Hospital Universitario de Canarias, Servicio de Aparato Digestivo, Spain; [4]Hospital Universitario de Canarias, Servicio de Farmacia, Spain; [5]Hospital Universitario de Canarias, Laboratorio Central, La Laguna, Spain; [6]Centro de Atencion a las Drogodependencias, San Miguel Adicciones Tenerife, Spain; [7]Centro de Atencion a las Drogodependencias, ANTAD Tenerife, Spain; [8]Centro de Atencion a las Drogodependencias, Proyecto Hombre Tenerife, Spain; [9]Hospital Universitario de Canarias, Laboratorio Central, Spain*
Email: mhernandezguerra@gmail.com

Background and Aims: People who injected drugs (PWID) face health and social barriers to accessing healthcare services resulting in poor engagement in hepatitis C virus (HCV) care challenging Public Health. Dried blood spot (DBS) testing has been shown to be efficacious to diagnose HCV and is recommended in this particular setting. However, facilitated referral for HCV assessment and scheduling of specialist appointments after on-site DBS on the PWID community has not been conveniently evaluated. The objective of this pilot study was to determine characteristic of PWID, rates of HCV prevalence and the engagement-in-care cascade after DBS testing. In addition, the diagnostic accuracy of DBS was evaluated.

Method: The intervention targeted subjects attending six drug clinics that serve a population of 400,000 inhabitants, from Jan-Oct/2017. Subjects were invited to participate in the program and on-site DBS testing (Whatman 903; ELISA Dia.Pro HVC AB) was performed, independently of previous HCV serum testing. A questionnaire about previous viral testing, risk factors, social and demographic variables was administered. Subjects testing positive were studied by a case manager with access to the electronic medical records and an appointment at hepatology clinic was scheduled directly to evaluate viral load, genotype and fibrotic grade.



Results: A total of 446 subjects (84.4% male, median 45.3 age [16.3–73.6]) were enrolled and 411 (92.2%) signed consent form and participated. In a sample of 336 subjects, DBS test obtained a sensibility, specificity, positive/negative predictive value, pos/neg likelihood ratio of 96.7%, 97.4%, 96.7%, 97.4%, 37.1, y 0.03, respectively. Overall 218 out of 411 (53.0%) tested positive to DBS testing. In 87% (n = 189) a HCV result was previously available in the record system (median 7.6 years [0.3–27.3]), of which 146 had a positive result. In addition, in 61.6% of subjects at least one viral load result was available. After an individualized case study, an appointment was scheduled in 149 out of 218 subjects. Figure shows the engagement-in-care cascade. At present, 23.4% of the potential candidates for treatment are under antiviral regimens.

Conclusion: On-site DBS testing in drug clinics is a feasible method for HCV diagnosis and facilitates linkage to care of previously diagnosed HCV patients without adequate care and treatment. This pilot study opens the rationale to expand our program to other drug clinics.

THU-142

Hepatitis B changes in epidemiological and molecular features of Afro-Brazilian communities, Central Brazil

A.R. Motta-Castro[1], B. Lago[2], L. Guedes[3], S. Weis[3], L. Bandeira[3], G. Rezende[3], T. Tanaka[3], G. Cesar[3], C. Niel[2], S. Gomes[2]. *[1]Federal Universitiy of Mato Grosso do Sul and Oswaldo Cruz Foundation – Virology, Campo Grande, Brazil; [2]Oswaldo Cruz Foundation – Virology, Rio de Janeiro, Brazil; [3]Federal Universitiy of Mato Grosso do Sul, FACFAN – Virology, Campo Grande, Brazil*
Email: arcm.castro@hotmail.com

Background and Aims: Hepatitis B virus (HBV) is a major cause of liver disease worldwide and persists as an important public health problem in vulnerable populations. Over ten years ago, previous studies conducted in two Afro-Brazilian communities, Furnas dos Dionisios (FD) and São Benedito (SB), detected high prevalence rates of HBV infection (42.7% and 16.0%), susceptible individuals (55.3% and 63.0%) and a low prevalence of anti-HBs alone (2.0% and 21.0%). These findings resulted in actions for health promotion such as HBV vaccine supply and referral of active hepatitis B cases for clinical care. Reassessing the epidemiological situation of HBV infection nowadays in these communities is essential to qualify the effectiveness of the measures adopted and to design future interventions.

Method: Between October 2015 and July 2016, blood samples were collected from 331 Afro-descendants (207 from FD and 124 from SB) previously interviewed regarding socioeconomic and behavioral characteristics. All serum samples were tested for HBV serological markers by enzyme-linked immunosorbent assay, screened for the presence of HBV-DNA, sequenced and phylogenetically analyzed.

Results: Considering the two communities together, the overall prevalence of HBV infection and the chronic carriers remained respectively around 30% and 5.5%. All subjects presented HBeAg-/anti-HBe+ status. After more than one decade of the first interventions, the proportion of individuals susceptible to HBV infection fell from 58.9% to 26.3% ($p < 0.0001$), while the vaccinated individuals increased from 10.7% to 43.5% ($p < 0.0001$). In FD community the proportion of vaccinated individuals increased from 2% to 45.9% ($p < 0.0001$), while of individuals susceptible to HBV infection fell from 55.3% to 18.8% ($p < 0.0001$). In SB, the proportion of vaccinated individuals increased from 21.0% to 39.5% ($p < 0.001$) and of susceptible individuals fell from 63.0% to 38.7% ($p < 0.001$), Compared to SB, FD has a lower proportion of individuals who are still susceptible to HBV (18.8% *vs* 38.7%, $p < 0.0001$), however it has a higher overall prevalence of this infection (35.3% *vs* 21.8%, $p < 0.013$). After multivariate analysis, history of family hepatitis and increasing age were factors associated with exposure to HBV infection. All samples clustered with sequences from the Asian-American clade of the HBV subgenotype A1. Genetic distances (0.8 ± 0.3%) among isolates from the communities were smaller than the intragroup divergence found among A1 Brazilian sequences.

Conclusion: These results demonstrate a significant decrease in the number of individuals susceptible to HBV infection in FD and SB communities, but also the maintenance of high levels of chronic hepatitis B infection. Epidemiological and molecular studies in

Afro-descendant communities are needed for the design of effective strategies to prevent and control HBV vulnerable populations.

THU-143

Screening for hepatitis C in Ontario, Canada: Exploring antibody positivity in the federal and provincial correctional systems

K. Beck[1], A. Majury[2,3], T. Mazzulli[4,5,6], W. Wobeser[1]. [1]*Queen's University, Department of Medicine, Kingston, Canada;* [2]*Public Health Ontario, Kingston, Canada;* [3]*Queen's University, Department of Biomedical and Molecular Sciences, Kingston, Canada;* [4]*Mount Sinai Hospital, Department of Microbiology, Toronto, Canada;* [5]*Public Health Ontario, Toronto, Canada;* [6]*University of Toronto, Toronto, Canada*
Email: k.beck@queensu.ca

Background: Hepatitis C (HCV) has been a reportable infection in Ontario, Canada, since 1991. In 2012, it was estimated to be the most burdensome infectious disease in the province. Approximately 44% of HCV-positive (HCV+) Canadians are unaware of their infection status. The potential for population-based screening is currently under discussion. Correctional settings remain a high-risk environment for HCV transmission. Thus, elimination will require attention to the unique correctional barriers that hinder quality public health programming.
Method: HCV testing data from Public Health Ontario was analysed from 1999 to 2014, inclusive, with a focus on activities undertaken in correctional facilities. A novel view of HCV screening in Ontario is presented where year of test, age, sex, HCV test result, and incarceration status are examined using the chi-square and Kruskal-Wallis tests. Odds ratios are calculated. Persons are determined HCV+ based on a positive antibody or, for a small fraction, a positive viral RNA result. Persons are defined as ever-incarcerated (EI) if at least one test result was submitted from one of 60 correctional facilities; otherwise, they obtain a community status.

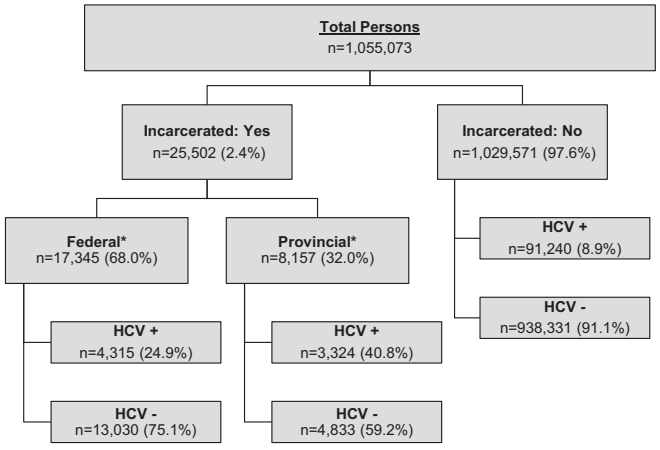


Figure 1: HCV positivity by incarceration status among persons tested in Ontario, 1999–2014.
Incarcerated HCV+: 7,639 (30.0%); Incarcerated HCV–: 17,863 (70.0%)
*Persons are defined as Federal or Provincial based on the location of their first correctional-submitted HCV test result.

Results: From 1999 to 2014, 1,729,869 tests were undertaken among 1,055,073 persons in Ontario. Of these, 44,355 (2.6%) results were submitted by correctional facilities. Of the 25,502 persons in the EI group, 30.0% are HCV+, compared to 8.9% HCV+ among those tested in the community (OR = 4.40[4.28–4.52], $p < 0.0001$). EI women are at a higher risk for HCV ($p < 0.0001$). The median age at first HCV+ test was lower among the EI group at 35(29–42) years, as opposed to 46 (37–54) years in the community ($p < 0.0001$). In addition, 68.0% (17,345) of persons had their first correctional HCV test result submitted from a federal facility. A higher proportion of persons first tested in provincial facilities are HCV+ (40.8%) than those first tested in federal facilities (24.9%) ($p < 0.0001$).
Conclusion: These results support an increased risk for HCV transmission among the incarcerated population in Ontario, with a significantly higher proportion HCV+ among those who have been incarcerated. In addition, significantly more test results are submitted from federal facilities than provincial, perhaps accounting for a lower proportion of positivity due to a larger sample size. Further research will be conducted using this data to examine trends in confirmatory testing, viral RNA testing following a positive antibody test, and the genotype distribution of positive cases.

THU-144

Can HCV be eliminated among HIV-infected MSM in Berlin? Modeling a setting with increasing incidence and high treatment rates

N. Martin[1], K. Jansen[2], M. an der Heiden[2], C. Boesecke[3], A. Boyd[4], K. Schewe[5], A. Baumgarten[6], T. Lutz[7], S. Christensen[8], A. Thielen[9], S. Mauss[10], J. Rockstroh[3], P. Ingiliz[6]. [1]*University of California, San Diego, Medicine, La Jolla, CA, United States;* [2]*Robert-Koch-Institut, Berlin, Germany;* [3]*University of Bonn, Medicine, Bonn, Germany;* [4]*Institut Pierre Louis d'Epidemiologie et de Sante Publique, INSERM, UMR_S1136, Paris, France;* [5]*ICH Hamburg, Hamburg, Germany;* [6]*Center for Infectiology, Berlin, Germany;* [7]*Infektiologikum, Frankfurt, Germany;* [8]*Centrum für Innere Medizin, Munster, Germany;* [9]*Institute for Immunology and Genetics, Kaiserslautern, Germany;* [10]*Center for HIV and Hepatogastroenterology, Dusseldorf, Germany*
Email: natasha-martin@ucsd.edu

Background and Aims: Despite widespread access to HCV direct-acting antiviral (DAA) therapy, there is a hepatitis C virus (HCV) epidemic among HIV-infected men who have sex with men (HIV+ MSM) in Germany. We use epidemic modeling to assess the impact of scaling-up DAAs on HCV incidence among HIV+ MSM in Berlin, and what DAA scale-up and behavioral risk reduction are required for HCV elimination.
Method: A dynamic HCV transmission model among HIV+ MSM was developed and calibrated to the Berlin MSM epidemic: rising HCV incidence from 0.56 per 100 person-years(/100 py) in 1996–1999 to 2.76/100 py in 2008–2012; 9.8% HCV seroprevalence in 2012, 8.2/100 py reinfection rate 2002–2014, 0.65% HCV seroprevalence among MSM at HIV diagnosis, annual number HIV-diagnosed MSM 2001–2015). Based on Berlin data, we incorporated high rates of HCV testing (twice/year) and treatment (80% initiated within 6 months of diagnosis from 2002). We assumed IFN-based SVR rates of 70%/30% for acute/chronic infection, respectively, and 95% SVR with DAAs from 2015. We modelled HCV incidence among HIV+ MSM in Berlin until 2030 under the following scenarios: (1) no change in treatment rates from 2018 on, (2) scale-up to 100% treated within 6 months of diagnosis, and 25%/year of previously diagnosed and untreated from 2018 on, (3) scale-up as in (2) and DAAs within 3 months of diagnosis. We evaluate what treatment and level of HCV transmission risk reduction among the HIV+ MSM population can achieve the WHO elimination target of 90% reduction in HCV incidence from 2016 to 2030.
Results: Modeling estimated that among the ~11,300 HIV-diagnosed MSM in Berlin in 2016, 1125 [95%CI 1025–1250] had chronic HCV and there were 342 [95%CI 307–380] incident HCV infections (3.18/100 py incidence [95%CI 2.77–3.60] in 2016). Continuing current treatment rates will marginally reduce incidence (by relative 3%) by 2030. Scaling-up to treat 100% within 6 months of diagnosis and 25%/year of those previously diagnosed and untreated could reduce incidence by 71% in 2030. This scale-up combined with DAAs within 3 months

of diagnosis could reduce prevalence by 78%. Achieving 90% incidence reduction by 2030 requires DAA scale-up plus an additional HCV transmission risk reduction among HIV-infected MSM of 35%.

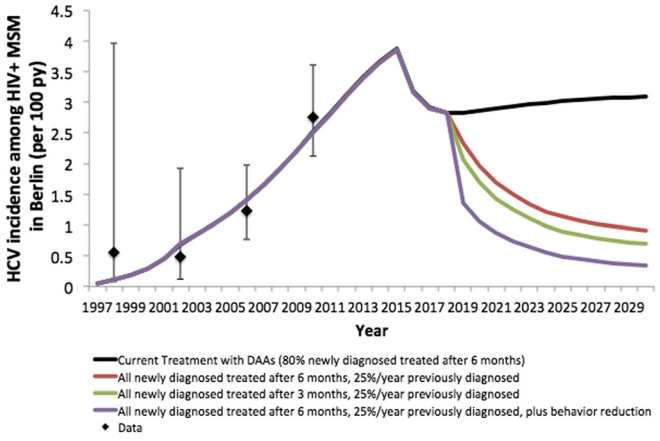


Figure: Modeled HCV incidence among HIV+ MSM in Berlin, Germany.

Conclusion: Due to escalating incidence despite high treatment rates, HCV elimination among HIV+ MSM in Berlin likely requires a combination of treatment scale-up and behavioral interventions to reduce the risk of infection.

THU-145

Hepatitis C elimination by 2030 is feasible in Brazil: a mathematical modelling approach

A. Benzaken[1], E. Catapan[1], R. Girade[1], H. Razavi[2], J. Schmelzer[2], M. Pessoa[3], M.L. Ferraz[4], P. Ferreira[5], A. Martinelli[6], M.C.M. Correa[1,7]. *[1]Ministry of Health, Brasília, Brazil, Department of Surveillance, Prevention and Control of STI, HIV/AIDS and Viral Hepatitis, Ministry of Health, Brasilia, Brazil; [2]Polaris Observatory, Center for Disease Analysis, Lafayette, CO, United States; [3]Sao Paulo University Medical School, Hospital das Clinicas, Division of Gastroenterology and Hepatology, Sao Paulo, Brazil; [4]Federal University of São Paulo, Gastroenterology Department, São Paulo, Brazil, Sao Paulo Brazil; [5]Federal University of São Paulo, Infectious Diseases Department, Sao Paulo, Brazil; [6]Ribeirão Preto School of Medicine, University of Sao Paulo, Department of Medicine, Ribeirão Preto/SP, Brazil; [7]Sao Paulo University Medical School, Tropical Institute Medicine, LIM 52, Sao Paulo, Brazil*
Email: maria.cassia@hc.fm.usp.br

Background and Aims: It is estimated that around 700,000 people are chronically infected with hepatitis C virus (HCV) in Brazil. The aim of this study is to explore potential strategies to manage the HCV disease burden in Brazil in the future.
Method: A previously described model was used to project the future disease burden up to 2030 under two different strategies: 1 – If no change is made to the HCV treatment program in Brazil; 2 – Where the World Health Organization (WHO) targets for 2030 elimination are met with diagnosis and treatment peaking before 2024. The mathematical model was calibrated using Brazilian data obtained through a literature search and prevalence data from a large national screening program conducted by the Ministry of Health of Brazil. A Delphi process was applied to gain expert consensus and validate inputs.
Results: The tables below detail the number of people that must be treated and newly diagnosed annually and the number of rapid tests that will be needed to meet the diagnosis targets for each year if screening continues to find positive cases at the current prevalence rate (0.71% anti-HCV) (Table 1a) or if high prevalence populations (defined as having five times higher prevalence than the current rate) are exclusively targeted for screening (Table 1b).

Table 1a: The number of people that need to be screened, diagnosed and treated in each different strategy

		2016	2017	2018	2019	2020	2025
Base	Treatment	36,600	25,000	19,000	12,900	12,500	12,500
	Newly Diagnosed	18,800	18,800	18,800	18,800	18,800	18,800
	Number needed to screen (gen. pop.)	3,889,000	4,040,000	4,205,000	4,305,000	4,576,000	5,818,000
Increase early efforts	Treatment	36,600	25,000	50,000	50,000	54,000	23,000
	Newly Diagnosed	18,800	24,800	40,000	50,000	52,800	25,000
	Number needed to screen (gen. pop.)	3,889,000	5,401,000	9,448,000	13,216,000	16,001,000	20,295,000

Table 1b: The number of people that need to be screened—if targeting high risk groups

	2016	2017	2018	2019	2020	2025
Base	778,000	808,000	841,000	861,000	915,000	1,164,000
Increase early efforts	778,000	1,080,000	1,890,000	2,643,000	3,200,000	3,735,000

Conclusion: Achieving the WHO Targets is feasible in Brazil with a scale-up of treatment and diagnosis over time, beginning in 2018. A major challenge will be to maintain these treatment levels into the future as the number of individuals needed to be screened increases exponentially over time. In order to continue this treatment rate in Brazil, efforts will need to be made to increase the number of diagnosed patients in order to maintain a pool of patients eligible for treatment. Screening programs targeting high prevalence populations would be an effective way to identify more cases with fewer tests.

THU-146

Micro-elemination of hepatitis C among patients with congenital bleeding disorders in Slovenia

M. Maticic[1,2], A. Lekše[2], M. Kozinc[1], M.B. Dolničar[3], D. Andoljšek[4], I. Preložnik Zupan[4], B. Faganel[5], M. Poljak[6], J. Lazarus[7,8]. *[1]Clinic for Infectious Diseases and Febrile Illnesses, University Medical Centre Ljubljana, Slovenia; [2]Faculty of Medicine, University of Ljubljana, Slovenia; [3]Slovenian Haemophilia Association; [4]Department of Haematology, University Medical Centre Ljubljana, Slovenia; [5]Department of Haematology and Oncology, University Children's Hospital, University Medical Centre Ljubljana, Slovenia; [6]Institute of Microbiology and Immunology, Faculty of Medicine, University of Ljubljana, Slovenia; [7]Barcelona Institute for Global Health (ISGlobal), Hospital Clínic, University of Barcelona, Spain; [8]CHIP, Rigshospitalet, University of Copenhagen, Denmark*
Email: mojca.maticic@kclj.si

Background and Aims: In Slovenia, management of hepatitis C virus (HCV) infection in patients with congenital bleeding disorders (PCBD) infected before 1992 has been organized systematically for over two decades with all of them screened for HCV in the mid-1990s. With the advent of direct acting antivirals (DAAs), national strategy for HCV elimination in this sub-population was prepared by a multidisciplinary expert team. Aim of the study was to evaluate the strategy in the PCBD population at national level.
Method: All PCBD who tested anti-HCV positive during Slovene screening program in the 1990s were identified from national register of haemophiliacs and included in study retrospectively. Active infection was defined with HCV RNA positivity. Demographic, virological and clinical data of HCV RNA-positive patients were extracted from patients' medical documentation and analysed.

Results: Overall, 105 patients were anti-HCV positive. Seven were excluded since they died before tested for HCV RNA. 25/98 (25%) eliminated virus spontaneously leaving 73/98 (75%) HCV RNA positive. Of them, 7 died before initiating HCV treatment. 63/66 received HCV treatment, 2/66 are currently on it and treatment is being delayed in 1/66 due to severe co-morbidity. Among 63 treated patients, all were male, presenting genotypes 1, 2 and 3 in 44 (70%); 5 (8%); and 12 (19%) cases, respectively. Sustained virological response (SVR) was achieved in 62/63 (98%) as 1 died prior to treatment completion. Average age at HCV diagnosis, first treatment initiation and SVR was 26.1, 38.1 and 42.0, respectively. In 37 cases SVR was achieved after first treatment attempt (59%); SVR after second, third and fourth attempts was noted in 12 (19%), 9 (15%) and 4 (6%) patients, respectively. Treatment included interferon (IFN) (SVR 3/20; 17%), IFN/ribavirin (SVR 10/20; 50%), pegIFN/ribavirin (SVR 26/39; 67%), and regimens with DAAs including boceprevir (SVR 2/2; 100%), telaprevir (SVR 4/6; 67%), simeprevir (SVR 1/1; 100%), sofosbuvir (SVR 1/1; 100%), ombitasvir/paritaprevir/dasabuvir (SVR 6/7; 86%), ledipasvir/sofosbuvir (SVR 5/5; 100%), elbasvir/grazoprevir (SVR 2/2; 100%), and sofosbuvir/velpatasvir (SVR 2/2; 100%), all being prioritised in PCBD.

Conclusion: This study demonstrates that in Slovenia, micro-elimination of HCV in sub-population of PCBD was achieved as result of national strategy and availability of new treatments which is in line with the strategy towards viral hepatitis elimination.

THU-147

Hepatitis E in pigs in Israel: seroprevalence, molecular characterization and potential impact on humans

R. Shirazi[1], S.P. Pozzi[2], M. Wax[1], I. Bar-Or[1], E. Asulin[1], E. Mendelson[1], Z.B. Ari[3], O. Mor[1]. *[1]Sheba Medical Center, Ramat Gan, Israel; [2]Veterinary Service, Rishon LeZion, Israel; [3]Sheba Medical Center at Tel Hashomer, Center of Liver Diseases, Tel Aviv, Israel*
Email: orna.mor@sheba.health.gov.il

Background and Aims: Hepatitis E virus (HEV) is a major causative agent of acute viral hepatitis worldwide. In recent years, reports on HEV-3 infections in Europe have accumulated, and undercooked pig products were found to be a source. In Israel, while clinical cases of HEV-3 infection have not been identified, HEV-3 sequences have been identified in 14 of 169 urban sewage samples collected between 2015 and 2016 from different regions in the country. In Israel, of the 90,000 pigs farmed at any given time, 80,000 are located in 23 farms in the north (West Galilee) and 10,000 in a single farm in the south (Negev). About 200,000 pigs are slaughtered yearly, exclusively for local consumption, yet, the distribution of the virus is unknown. In this pioneer study, we aimed to assess the status of HEV in the swine population and among swine farmers in the country.

Method: Serum samples from 141 pigs, representing different age groups, from 4 breeding farms (3 of which were northern farms) were collected between 2016 and 2017. Pig faeces (n = 39) and 5 raw sewage samples (4 from the sewage pipeline serving all northern farms and 1 from the southern farm) were also collected. Blood samples from 24 swine farmers were assessed. Serum anti-HEV immunoglobulin IgG was detected using the Wantai total IgG (pigs) or IgG (humans) HEV ELISA assays (Wantai Biopharmaceutical, Inc. Beijing, China). Total nucleic acids were extracted from blood (pigs and humans), pig faeces and sewage with NucliSENS EasyMag (bioMérieu, France). HEV RNA was analysed with the RealStar HEV RT-PCR kit, version 1.0 (Altona Diagnostics GmbH, Hamburg, Germany) HEV genotype was assessed in all HEV-RNA-positive samples.

Results: The overall prevalence of antibodies to HEV in pigs was 75.1% (106/141) Seroprevalence was age-dependent, with 85% (17/20) of young pigs (1.5 months old; maternal antibodies) and 97.4% (74/76) of pigs at slaughter (>5 months) but only 34.1% (15/44) of 2–4-month-old pigs, exhibiting seropositivity (Figure 1a). HEV RNA was detected in 2.1% (3/141) of serum samples, 40% (2/5) of sewage samples (from both northern and southern pipelines) and 5.1% (2/39) of faecal samples. All HEV RNA-positive samples were from the 2–4 month-old age group. HEV RNA was not detected in samples from pigs entering the food chain (n = 60, age > 5 months). Sequencing was successful in two of the serum samples and revealed clustering with HEV-3 sequences previously identified in sewage samples (Figure 1b). All farmers (median age 42.9) were HEV IgG-positive but RNA-negative.

Conclusion: HEV-3 is endemic in local pigs. The high force of infection yields anti-HEV-positive, HEV RNA-free animals in the age group used for meat consumption. All farmers demonstrate past HEV infections. As no clinical symptoms were ever noted, continuous monitoring of HEV-3 RNA in pig farms should be considered and the potential impact on farmers and on public health should be further explored.

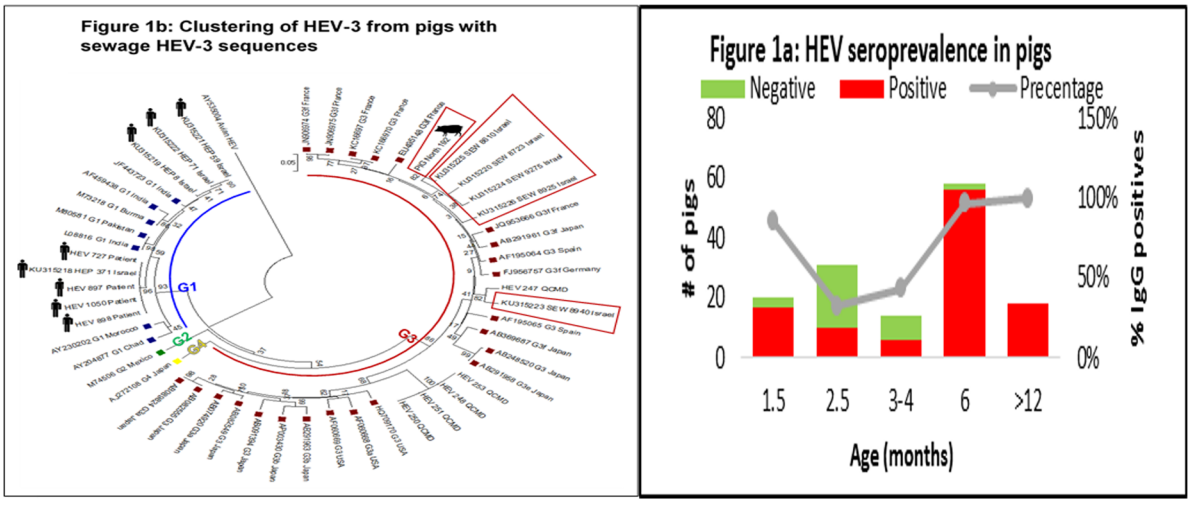


Figure: (abstract: THU-147)

Liver tumours: Therapy

THU-151

Results of the Phase II randomized French trial PRODIGE 21 comparing sorafenib vs pravastatin vs sorafenib and pravastatin vs best supportive care for the palliative treatment of HCC in CHILD B cirrhotic patients

J.-F. Blanc[1], F. Khemissa[2], J.-P. Bronowicki[3], C. Monterymard[4], J.-M. Perarnau[5], V. Bourgeois[6], S. Obled[7], M.B. Abdelghani[8], I. Mabile-Archambeaud[9], R. Faroux[10], J.-F. Seitz[11], C. Locher[12], H. Senellart[13], A.-L. Villing[14], F. Audemar[15], C. Costentin[16], G. Delplanque[17], S. Manfredi[18], J. Edeline[19]. *[1]CHU Bordeaux, Bordeaux, France; [2]CH Perpignan, Perpignan, France; [3]CHU Brabois, Vandoeuvre les Nancy; [4]FFCD, Dijon; [5]CHU Trousseau, Tours, France; [6]CH Boulogne sur Mer; [7]CHU Nimes; [8]CAC Strasbourg; [9]CHU Nantes; [10]CH La Roche Sur Yon; [11]CHU La Timone Marseille; [12]CH Meaux; [13]CAC Saint-Herblain; [14]CH Auxerre; [15]CH Bayonne; [16]CHU Henri Mondor Créteil; [17]Hôpital Privé Saint-Joseph Paris; [18]CHU Dijon; [19]CAC Eugène Marquis Rennes*
Email: jean-frederic.blanc@chu-bordeaux.fr

Background and Aims: Although sorafenib may be prescribed for the palliative treatment of HCC in patients with CHILD B cirrhosis, there is no evidence of its efficacy and safety in this indication. On the other hand, pravastatin has a good safety profile, even in patients with impaired liver function, and its benefit in the treatment of HCC was suggested by phase II studies. The aim of this study was to clarify the interest of sorafenib and pravastatin alone or in combination in the treatment of HCC developed on CHILD B cirrhosis.
Method: This phase II randomized, multicenter, national, open-label, four-arm parallel trial was planned to include 40 CHILD B cirrhotic patients with HCC in each arm for receiving sorafenib (800 mg/day) or pravastatin (40 mg/day) or pravastatin (40 mg / day) – sorafenib (800 mg/day) combination or best supportive care. The main objective was to evaluate the impact of treatments on time to radiological progression (TTP). Secondary objectives were overall survival (OS), progression free survival (PFS) and safety profile.
Results: 157 patients were included: 41 in group A (sorafenib), 39 in group B (pravastatin), 40 in group C (pravastatin and sorafenib) and 37 in group D (best supportive care). The characteristics of the patients are shown in the table.

	A (Sorafenib) n = 41	B (Pravastatin) n = 39	C (Prava-Sorafenib) n = 40	D (BSC) n = 37
Age (median)	67.5	63.7	66.3	66.4
CHILD A/B/C	2/38/1	0/39/0	1/39/0	0/36/1
ALBI = 3	97%	100%	100%	97%
BCLC A/B/C/D	0/4/37/0	0/6/33/0	0/5/35/0	0/4/31/2
OMS 0/1/2	5/30/6	10/20/9	6/23/11	6/22/9
Macrovascular invasion	41%	56%	60%	62%
Extra-hepatic spread	14.6%	18%	22.5%	10.8%

The safety profiles of sorafenib and pravastatin were similar to those observed in CHILD A patients. The occurrence of grade 3/4 toxicities was similar in each group (82%).
The median progression-free survival was 3.2, 2.2, 3.4 and 2.4 months in groups A, B, C and D respectively. The time to treatment failure (date of treatment discontinuation) was 3.0, 2.2 and 1,1 months in arm A, B and C and the median overall survival (OS) was 3.8, 3.1, 4.0 and 3.5 in groups A, B, C and D. In per-protocol analysis, OS was 6.5, 4.3, 5.4 and 3.5 months and PFS was 5.9, 3.6, 5.2 and 2.5 months in groups A, B, C and D.

Conclusion: In this population of patients with HCC and severe impairment of liver function, the prognosis is poor and not modified by pravastatin. The benefit of sorafenib in this population seems also limited.

THU-152

Systematic review and metanalysis establish dermatologic adverse events as a positive predictor of survival in hepatocellular carcinoma patients treated with sorafenib

A. Diaz-Gonzalez[1], M. Sanduzzi-Zamparelli[1], V. Sapena[2], F. Torres[2], N. Llarch[1], G. Iserte[1], A. Forner[1], L.G. Da Fonseca[1], J. Ríos[3], J. Bruix[4], M. Reig[1]. *[1]Hospital Clínic i Provincial de Barcelona, Barcelona Clínic Liver Cancer (BCLC) Group. Liver Unit., Barcelona, Spain; [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Medical Statistics Core Facility, Barcelona, Spain; [3]Universitat Autònoma, Biostatistics Unit, Faculty of Medicine, Spain; [4]BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain*
Email: mreig1@clinic.ub.es

Background and Aims: Sorafenib is the established 1st-line systemic therapy for hepatocellular carcinoma (HCC) but, in an era of new options for 1st and 2nd line, it is key to fully understand the treatment related events that may drive a better outcome and thus, should prime a careful decision to interrupt therapy and move to other options because of perceived impairment of quality of life and/or irrelevant disease progression. In this regard, dermatologic adverse events (DAEs) have been suggested to be a marker of better outcome in sorafenib treated patients. The aim of this systematic review and metanalysis is to explore the impact of DAEs in HCC patients treated with sorafenib in order to unequivocally define if DAEs, as an early evolutionary event, are associated to an improved outcome.
Method: The study was done according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Two authors retrieved all data and a 3rd one solved discrepancies. DAEs were defined as the presence of any kind of skin symptoms that are congruent with sorafenib side effects and maintain a reasonable temporary relationship.
Results: 313 studies were identified until July/2017. 10 studies were full-text manuscripts and met the inclusion criteria. They included 926 patients (82.5% Child-Pugh A, 84% BCLC-C, and 30% ECOG-0), 2 were prospective, 7 retrospective and 1 not disclosed. Only 2 studies were focused on early DAEs. 45% of the patients developed hand foot skin reaction and 24% other dermatologic adverse events. The presence of DAE was associated with a higher probability of overall survival when compared with those patients without DAEs. The pooled Hazard Ratio was 0.49 (CI-95%; 0.41–0.58) and there was no heterogeneity for the analysis ($p = 0.307$; I^2=14.8%).
Conclusion: This metanalysis demonstrates the positive association between the development of DAEs and better prognosis in patients with HCC treated with sorafenib. This association indicates the need to investigate the mechanism underlying the pathophysiology of DAEs and how this may help to define the mechanism for a less malignant tumor progression. At the same time, development of DAEs should not be seen as a disadvantage as compared with drugs with lower rate of DAEs, but rather become part of the decision process to sense the risk/benefit balance of HCC therapy across different options.

THU-153

Comparison of the prognosis between non-viral HCC and viral HCC

N. Izumi, M. Kurosaki, K. Takaura, K. Tsuchiya, J. Itakura, H. Nakanishi. *Musasino Red Cross Hospital, Musasinoshi, Tokyo, Japan*
Email: tuf029@gmail.com

Background and Aims: The most prevalent etiology of hepatocellular carcinoma (HCC) in Japan is hepatitis C, followed by of non-viral, and hepatitis B. Recently, due to decrease in HCC caused by hepatitis

C, the prevalence of non-viral HCC patients is increasing. This study aimed to investigate the prognostic differences of HCC with different etiologies stratified by the stage of HCC.

Method: We enrolled 759 consecutive HCC patients treated by radio-frequency ablation (RFA) at Musashino Red Cross Hospital from January 1998 to December 2016. The eligible criteria for RFA treatment was liver function of Child-Pugh class A, maximum of 3 HCC nodules, and maximum diameter of 5 cm if single nodule HCC, and 3 cm if multiple nodules. The etiology was viral (hepatitis C or B) in 573 patients, and non-viral in186 patients. The overall survival and recurrence free survival was compared between viral vs. non-viral HCC after stratification by tumor factors.

Results: The overall survival was significantly better in non-viral HCC compared to viral HCC. The 5- and 10-year survival was 71.7% and 55.7% in non-viral HCC and 55.0% and 14.7% in viral HCC ($p < 0.01$). Furthermore, recurrence free survival was significantly higher in non-viral HCC compared to viral HCC. The 1-, 3- and 5-year recurrence free survival was 66.3%, 30.2% and 16.3% in non-viral HCC and 54.9%, 22.6% and 8.4% in viral HCC ($p = 0.01$). In single nodule HCC, 5- and 10-year survival was 68.4% and 54.4% in non-viral and 42.6% and 11.5% in viral ($p < 0.01$). The 1-, 3- and 5-year recurrence free survival was 68.1%, 36.1% and 20.2% in non-viral and 62.4%, 25.2% and 9.7% in viral ($p = 0.01$). However, there was no such difference in prognosis or recurrence in patients with multiple HCC nodules. By multivariate analysis, factors related with survival were non-viral etiology (hazard ratio (HR) 1.89, 95% confidence interval (CI) 1.33–2.68), ALBI grade >2 (HR 1.54, 95%CI 1.18–2.01), serum des-gamma-carboxy prothrombin (DCP) >100 mAU/ml (HR1.62, 95% CI 1.21–2.17), and serum alpha-fetoprotein >100 ng/ml (HR 1.59, 95% CI 1.20–2.10) whereas factors related to recurrence were non-viral etiology (HR1.32, 95% CI 1.04–1.68), male gender (HR 1.26, 95% CI 1.02–1.55), multiple HCC nodules (HR 1.52, 95% CI 1.22–1.89), ALBI grade >2 (HR 1.31, 95% CI 1.06–1.62), and serum DCP >100 mAU/ml (HR1.62, 95% CI 1.21–2.17).

Conclusion: In patients with early stage HCC of single nodule and treated by RFA, prognosis was better and recurrence was lower in non-viral etiology compared to viral HCC. These results suggest the need of strategy for early detection of HCC in patients with non-viral liver disease.

THU-154

Risk-stratified management of advanced hepatocellular carcinoma (HCC)

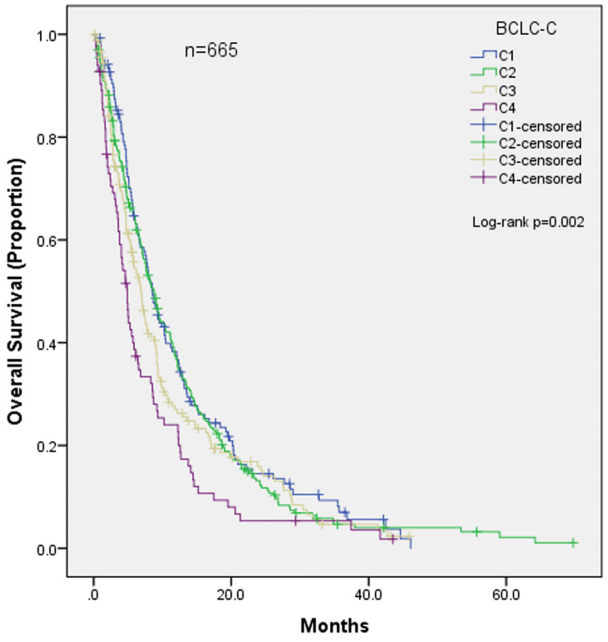
D.J. Pinato[1], D.E. Kaplan[2], C. Yen[1], L. Rimassa[3], B. Dominik[4], T. Pressiani[3], R. Thimme[4], M. Pirisi[5], M. Burlone[5], T. Arizumi[6], M. Kudo[6], J.W. Park[7], T.H. Taddei[8], P. Johnson[9], R. Sharma[1]. *[1]Imperial College London, Surgery & Cancer, London, United Kingdom; [2]Philadelphia Veterans Affairs Medical Center & University of Pennsylvania; [3]Humanitas Cancer Center, Medical Oncology & Haematology Unit, Italy; [4]University of Freiburg, Department of Medicine II, Germany; [5]Università degli Studi del Piemonte Orientale "A. Avogadro", Department of Translational Medicine, Italy; [6]Kindai University School of Medicine, Department of Gastroenterology and Hepatology, Japan; [7]National Cancer Center Hospital, Centre for Liver Cancer, Korea, Rep. of South; [8]Yale University School of Medicine, Department of Medicine; [9]University of Liverpool, Molecular and Cancer Medicine, United Kingdom*

Email: david.pinato09@imperial.ac.uk

Background and Aims: The Barcelona Clinic Liver Cancer (BCLC) algorithm states that patients with extra-hepatic spread (EHS), macro-vascular invasion (MVI) and ECOG performance status (PS) 1–2 are advanced stage HCC (BCLC-C). Combined use of these clinical features has been suggested, but not validated, to sub-classify BCLC-C HCC and improve treatment allocation (Giannini EG, Hepatology 2017), a clinically desirable aim now that treatment options are expanding to include immunotherapy and second-line targeted agents.

Method: We evaluated the prognostic accuracy of the BCLC-C stage sub-classification according to the following variables: C1 (PS1-2, EHS-, MVI-) C2 (any PS, EHS+, MVI-), C3 (any PS, EHS-, MVI+), C4 (any PS, EHS+, MVI+). The model was tested in a dataset of 665 patients treated with sorafenib across 6 centres in Europe and Asia (2008–2016) and validated in a cohort of 2241 patients with similar features treated at Veterans Health Administration hospitals (2006–2015) and a separate dataset of 1394 patients receiving sorafenib for advanced HCC as part of international clinical trials.

Results: In the training set, patients were 82% males, 70% HCV-positive, with a median age of 65 years. Median sorafenib duration was 2.3 months and disease progression was the most common cause of discontinuation, 72%. Median tumour size was 5.5 cm. The proportion of isolated EHS and MVI was 40% and 27% respectively, with 12% of patients being EHS+/MVI+. Median overall survival (OS) was 8.6 months in C1 and 8.8 months in C2 and significantly worse in C3 6.9 months and C4 4.9 months (Log-rank $p = 0.002$). Survival estimates were confirmed in the validation dataset ($n = 2241$) where deteriorating OS figures were observed across sub-classes: C1 ($n = 249$) 7.0 months, C2 ($n = 995$) 5.5 months, C3 ($n = 728$) 5.9 months, C4 ($n = 260$) 3.3 months (Log-rank $p = 0.001$). Despite longer survival in each subclass, the BCLC-C sub-classification retained stratifying potential in clinical trial patients: C1 ($n = 127$) 18.1 months, C2 ($n = 742$) 22.2 months, C3 ($n = 72$) 10.8 months, and C4 ($n = 414$) 10.6 months (Log-rank $p < 0.001$).



Conclusion: Advanced HCC is highly heterogeneous in routine practice and in clinical research. Combination of staging variables may facilitate risk-stratified patient management, aiding clinicians in treatment sequencing optimisation on the basis of poor prognostic features.

THU-155

A novel post-surgical prognostic system for colorectal liver metastases treated by preoperative systemic treatment, using tumoral and non tumoral pathological changes, Ras mutation and immunoscore

P. Baldin[1], M. Van Den Eynde[2], B. Mlecnik[3], G. Bindea[3], G. Beniuga[4], J. Carrasco[5], C. Hubert[6], B. Navez[6], A. Jouret-Mourin[1], J. Galon[3], M. Komuta[1]. *[1]Cliniques Universitaires Saint-Luc/Université Catholoque de Louvain (UCL), Department of Pathology, Woluwe Saint Lambert, Belgium; [2]Cliniques Universitaires Saint-Luc/Université Catholoque de Louvain (UCL), Department of Medical Oncology, Woluwe Saint Lambert,*

Belgium; [3]INSERM, UMRS1138, Laboratory of Integrative Cancer Immunology, Paris, France; [4]Institut of pathology and genetics (IPG), Department of Pathology, Charleroi, Belgium; [5]Grand Hôpital de Charleroi (GHdC), Department of Medical Oncology, Charleroi, Belgium; [6]Cliniques Universitaires Saint-Luc/Université Catholoque de Louvain (UCL), Hepatobiliary Surgery Unit, Department of Abdominal Surgery and Transplantation, Woluwe Saint Lambert, Belgium
Email: pamela.baldin@uclouvain.be

Background and Aims: Surgical control of colorectal liver metastasis (CRLM) combined with systemic treatment in patients aims to maximize survival. However, around 40% of patients develop recurrence in one-year post operation. Moreover, chemotherapy-related liver injury (CALI), such as sinusoidal obstruction syndrome (SOS), nodular regenerative hyperplasia (NRH), and steatohepatitis, have been reported to worsen operative mortality and morbidity rates. We aim to develop a prognostic scoring system to stratify patient prognosis post-hepatetomy by identifying the significant prognostic clinico-pathological-molecular factors in patients with resected CRLM.
Method: We investigated 143 patients with 403 CRLM operated from 2005–2013, including patients untreated (19 patients with 29 lesions) and treated with chemotherapy alone (33 patients with 91 lesions), chemotherapy with anti-VEGFR (47 patients with 157 lesions), and chemotherapy with anti-EGFR (44 patients with 126 lesions). All specimens were reviewed to assess tumor regression grading (TRG), histological growth pattern (HGP), and CALI. Genomic DNA from the lesions was extracted and purified from Formalin-fixed, paraffin-embedded slides. Immunoscore was assessed by the immune densities (cells/mm2) of CD3- and CD8 positive lymphocytes in the center and the invasive margin of the tumor by using morphometry. Comparisons were made using the Wilcoxon-Mann-Whitney test. Cumulative disease-free (DFS) and overall survival (OS) were analyzed using the Kaplan-Meier estimator and compared by log-rank tests. Cox proportional hazards models were used for uni- and multi-variate analysis. P value of less than 0.05 was considered statistically significant.
Results: Multivariate analysis showed that a high TRG (TRG 3–5), the worst HGP (replace growth pattern, mixed pattern), ≥ 4 lesions, positive surgical margin, CALI (steatohepatitis, NRH), RAS mutation and the worst Immunoscore were the significant prognostic factors. The prognostic scoring system combining these parameters significantly stratified post-operatively treated patients' prognosis into three groups (high risk group: 81.3% (63.1–90.3% 95CI) one-year recurrence rate, intermediate risk group: 41.3% (26.8–52.9% 95CI) one-year recurrence rate, low risk group: 13.8% (0.3–25.5% 95CI) one-year recurrence rate).
Conclusion: Our novel prognostic scoring system of CRLM assessed by tumor and non-tumor pathological changes, Ras mutation and Immunoscore, allowed us to identify the patient population with high risk of recurrence post-hepatectomy.

THU-156
Towards personalised approach in systemic treatment for hepatocellular carcinoma. The value of AGT M235T gene polymorphism

M. Reig[1], L. Boix[1], F. Torres[2], A. Darnell[3], A. Diaz-Gonzalez[1], N. Llarch[1], E. Belmonte[3], V. Sapena[4], M.S. Zamparelli[1], J. Corominas[5], A. Forner[1], C. Ayuso[6], J. Bruix[7]. *[1]Hospital Clinic de Barcelona., BCLC group. Liver Unit. Hospital Clínic de Barcelona. CIBERehd; [2]Hospital Clinic de Barcelona. IDIBAPS.Universitat Autònoma de Barcelona, Biostatistics Unit, Faculty of Medicine; [3]Hospital Clinic de Barcelona., BCLC group. Radiology department. [4]Hospital Clinic de Barcelona., BCLC group. Liver Unit. Hospital Clínic de Barcelona; [5]Hospital Clinic de Barcelona., BCLC group. Liver Unit. FCRB; [6]Hospital Clinic de Barcelona. IDIBAPS. CIBERehd., Barcelona Clinic Liver Cancer (BCLC) group. Radiology Department. Hospital Clínic de Barcelona. Universitat de Barcelona; [7]BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBEREHD, Barcelona, Spain*
Email: mreig1@clinic.ub.es

Background and Aims: Up to now there is no biomarker that may stratify patients with hepatocellular carcinoma (HCC) treated with sorafenib according to their expected outcome. In 2013 we showed that the development of Dermatology Adverse Events (DAEs) early after treatment initiation is associated to a delayed tumor progression and improved survival. Hence, identification of predictive biomarkers for early DAEs (eDAE) would be instrumental to define a population with a major treatment impact on survival. **Aim:** To assess the value of genetic profile and baseline characteristics of sorafenib treated patients to predict the development of eDAEs, and to evaluate the potential of the identified parameters to become surrogate markers of long term survival.
Method: We prospectively included all HCC patients who started sorafenib and accepted to be included in a pharmacokinetic/genetic study at the BCLC. All patients started with 800 mg/day. Clinical and laboratory assessments were done monthly, besides of a radiologic tumour evaluation at week 4, and every 8 weeks afterwards. Genetic polymorphisms tested included: UGT1A8, CYP3A5, CYP3A4, UGT1A9, MRP2, IL23R, IL17, FOXP3, VEGF, AGT, PLA2G12A, IL-8,AT1R,ANGPT2, TNF-a, GNB3, IL-6 gens. Treatment was maintained until symptomatic progression, second-line trial initiation, significant toxicity or patient decision.
Results: We included 82 patients with a median follow-up of 18.6 months. Sixty-eight patients (83%) died, thirty-two (39%) presented eDAES, thirteen (15.9%) suffered gastrointestinal events and 10 showed (12%) performance status deterioration. Other events were registered in < 10 patients. An Angiotensinogen (AGT) gene polymorphism, AGT M235T, was the sole parameter associated to eDAE development: with AA [prevalence: 32%] as the genotype used as ref. category, the HR (95%CI) were for AG [41%]: 0.34 (0.15–0.8) and for GG [27%]: 0.97 (0.41–2.31); p = 0.0335.
Conclusion: These data show that evaluation of the AGT M235T gene polymorphism could become instrumental to evolve to precision and personalised treatment decision in patients with HCC at a time when several systemic therapies with survival benefit are expected to be available.

THU-157
A statistical model for survival risk prediction in patients with advanced hepatocellular carcinoma undergoing sorafenib treatment

S. Berhane[1], R. Fox[2], S.L. Chan[3], T. Yau[4], P. Johnson[1]. *[1]University of Liverpool, Department of Molecular and Clinical Cancer Medicine, Liverpool, United Kingdom; [2]University of Birmingham, Cancer Research UK Clinical Trials Unit, Birmingham, United Kingdom; [3]The Chinese University of Hong Kong, Department of Clinical Oncology, Hong Kong, Hong Kong; [4]The University of Hong Kong, Department of Surgery, Hong Kong, Hong Kong*
Email: sarahberhane1@gmail.com

Background and Aims: Sorafenib is the current standard of care for patients with advanced hepatocellular carcinoma (aHCC). The aim of this study is to identify baseline clinical features that influence survival in patients undergoing sorafenib treatment and thereby build a statistical model that predicts risk.
Method: We had access to 1130 sorafenib patients from control arms of two phase III randomised clinical trials – RCT1 and RCT2 – as well as 364 non-trial sorafenib patients from Hong Kong, China. Model was built using RCT1 and validated on RCT2 and Hong Kong cohorts. Univariable and multivariable analyses were undertaken using flexible parametric survival models. Risk was stratified into four groups by identifying cut-points in the linear predictor of the training

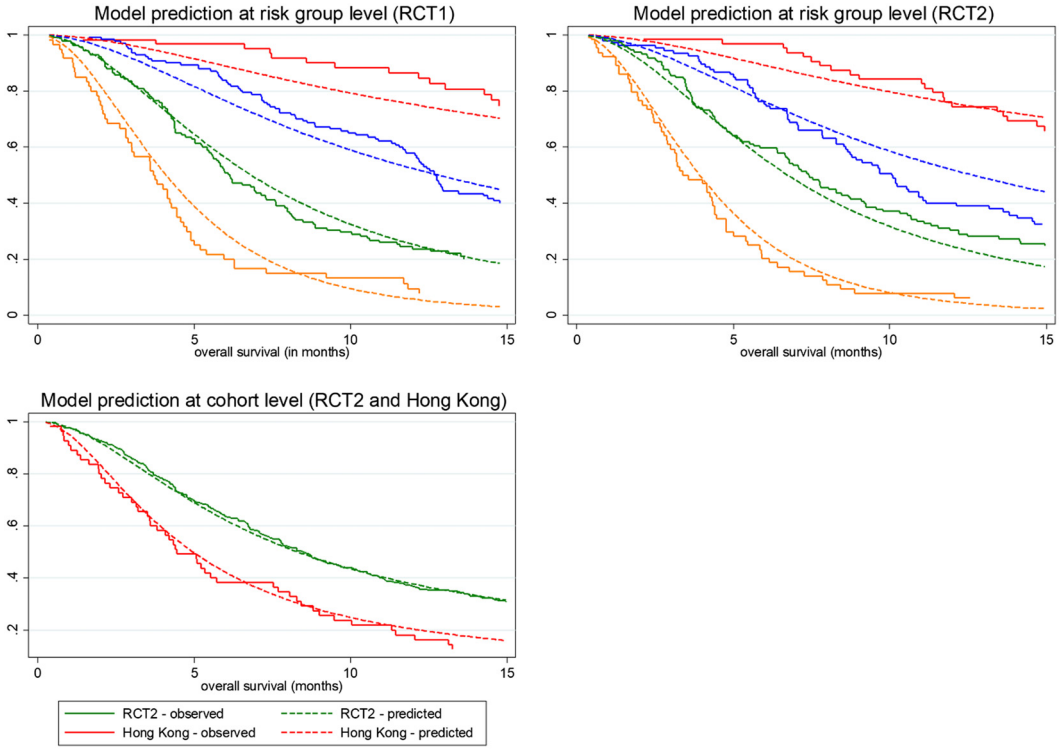


Figure: (abstract: THU-157)

set, and subsequent model predictions were grouped according to this classification. Model performance was assessed through Harrell's C statistic and comparison of observed and model-predicted survival curves and median survival times.

Results: Baseline factors that influenced survival in the multivariable model were vascular invasion, ECOG, log(AFP), albumin, log(AST), aetiology, extra-hepatic spread and tumour number. In both RCT1 and the validation sets, the model-predicted survival was very similar to the observed survival (figure). The Harrell's C indices for RCT1, RCT2 and Hong Kong cohorts were 0.73, 0.70 and 0.69 respectively indicating good prediction. The corresponding predicted and observed median overall survival for the same cohorts were 8.8, 8.3, 4.8 and 9.2, 8.5, 4.4 months respectively.

Conclusion: Model predicts survival similar to the observed. However, the model will require further validation on independent datasets.

THU-158

The ALBI and p-ALBI grades predict survival in patients with hepatocellular carcinoma undergoing transarterial chemoembolization (TACE)

C. Campani[1], G. Dragoni[1], S. Aburas[1], A. Vitale[2], E.G. Giannini[3], F. Trevisani[4], F. Marra[1] and For Ita.LI.Ca. Group[4]. [1]*Hepatology, Medicina Sperimentale e Clinica, Florence, Italy;* [2]*Surgery, Department of Surgery, Oncology and Gastroenterology, Padova, Italy;* [3]*Gastroenterology, DIMI, Genova, Italy;* [4]*Semeiotica Medica, Dipartimento di Scienze Mediche e Chirurgiche, Bologna, Italy*
Email: fabio.marra@unifi.it

Background and Aims: The prognosis of hepatocellular carcinoma is not solely influenced by the extent of the anatomic spread of the cancer but also by the severity of liver dysfunction. This makes the assessment of prognosis in individual patients difficult. Child-Pugh (CPS) and model for end-stage liver disease (MELD) scores are widely used but have considerable limitations. Recently, the prognostic value of albumin-bilirubin (ALBI) grade has been evaluated in patients undergoing resection of HCC or treatment with different modalities. Nonetheless, its predictive role specifically in patients undergoing TACE has not been evaluated. Another score based on the ALBI grade has recently been proposed, the pALBI grade that includes blood platelet count as a surrogate marker of portal hypertension.

Method: We retrospectively evaluated the prognostic significance of ALBI and pALBI in patients undergoing TACE recorded in the Ita.Li.Ca. database, and compared it with other prognostic systems, including MELD, CPS, hepatoma arterial-embolization prognostic (HAP) and mHAPII.

Results: 2283 TACE performed in 1012 consecutive patients between January 2008 and December 2016 were evaluated. Patients had a median MELD of 9 and belonged to all BCLC stages. 1168 TACE were performed in BCLC-A, 696 in BCLC-B and 419 in the BCLC-C stage. Median overall survival in the whole population was 33.9 months. Considering all TACE procedures, irrespective of the BCLC stage, the ALBI and pALBI grades were significant predictors of overall survival (P 0.001 and p < 0,0001 respectively), similar to the HAP and the mHAP scores (P < 0.0001). When patients in different BCLC stages were considered, ALBI was a significant predictor of OS only in BCLC-C (p < 0.001) patients treated with TACE, while pALBI was a significant predictor of OS in BCLC-B (p 0.001) and BCLC-C (p < 0.001) similarly to HAP and mHAPII.

Similar data were obtained when only the first TACE procedure was considered in each patient (total of 1012 patients, 520 BCLC-A, 299 BCLC-B and 193 BCLC-C). Considering all BCLC stages, ALBI was a significant predictor of overall survival (p 0,001) similar to the pALBI, HAP and mHAPII scores (p 0,003). When different BCLC stages were considered, ALBI, pALBI and HAP were significant predictors of OS in BCLC-C (p 0.008, p 0.003 and 0.008 respectively), whereas mHAPII was not significant. pALBI was also a significant predictor of OS in BCLC-B (p 0,005).

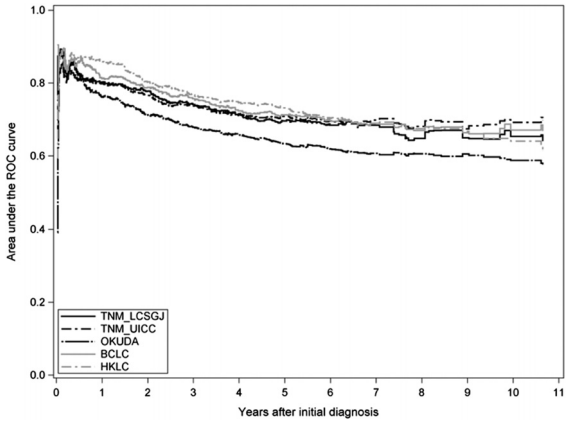
Conclusion: ALBI and pALBI offer additional simple and objective methods of assessing liver function in HCC and may be useful for selecting patients more likely to survive after TACE, especially ALBI in the BCLC –C stage and pALBI in BCLC-B and BCLC-C stages.

THU-159

Verification of staging systems and treatment algorithms for hepatocellular carcinoma: perspectives from a Japanese field practice

S. Ogasawara[1], Y. Ooka[1], M. Inoue[1], T. Chiba[1], E. Suzuki[1], M. Yokoyama[1], T. Maeda[1], T. Wakamatsu[1], K. Kobayashi[1], S. Kiyono[1], M. Nakamura[1], T. Saito[1], S. Nakamoto[1], S. Yasui[1], A. Tawada[1], M. Arai[1], H. Maruyama[1], S. Kuboki[2], M. Miyazaki[2], M. Ohtsuka[2], N. Kato[1]. *[1]Chiba University, Graduate School of Medicine, Department of Gastroenterology, Chiba; [2]Chiba University, Graduate School of Medicine, Department of General Surgery, Chiba, Japan*
Email: sadahisa@me.com

Background and Aims: In 1984, Okuda presented the first staging system for patients with hepatocellular carcinoma (HCC) which attempted to incorporate both tumor burden and liver function. The BCLC staging classification for HCC was first published in 1999 and included recommendations for first-line treatment for each stage. In 2017, the APASL and the Japanese guideline (JSH), which are not based on staging systems, were updated. The aim of this study was to verify staging systems and treatment algorithms used for HCC in a cohort of Japanese patients.
Method: Time-dependent ROC analysis was performed to determine survival outcomes in patients according to various staging systems (Okuda, BCLC, LCSGJ, AJCC/UICC, and HKLC). We also compared the prognosis of patients with HCC who received recommended treatment according to the treatment algorithms (BCLC, HKLC, APASL, and JSH) with that of patients who received non-recommended treatment.
Results: A total of 1161 new cases of HCC diagnosed between 2003 and 2015 were identified from the database of our Hospital. Among the staging systems, Okuda was found to have significantly poor predictive value with respect to survival outcomes compared with other staging systems (Figure). In terms of treatment algorithm, percentages of patients who received the recommended treatment based on BCLC, HKLC, APASL, and JSH were 72.8%, 69.1%, 86.1%, and 85.6%, respectively. Overall survival (OS) of patients who received the recommended treatment according to all four algorithms was significantly better than that of patients who received non-recommended treatment. According to BCLC, the percentages of patients with BCLC 0/A, B, and C disease who received the recommended treatment were 88.3%, 75.4%, and 11.1%, respectively. OS of patients with BCLC C who received recommended treatment was significantly poor compared with that of patients who received non-recommended treatment. Among patients with BCLC C disease, 59.8% and 60.8% patients received the recommended treatment based on APASL and JSH, respectively.



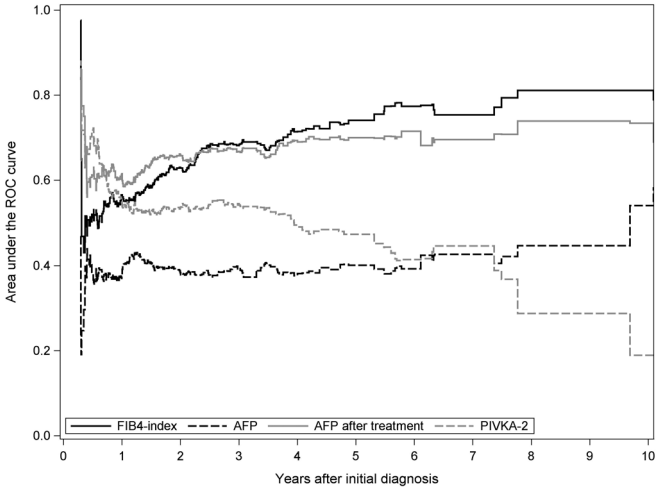
Conclusion: The prognostic relevance of Okuda was found to be poor because it created the era in which OS of majority of the patients with HCC was <1 year. Although both tumor status and liver function of patients with advanced HCC show considerable heterogeneity, diverse treatments were selected in the Japanese field practice.

THU-160

Temporal changes in recurrent incidences after curative therapies in early stage hepatocellular carcinoma

A. Kurosugi[1], S. Ogasawara[1], Y. Ooka[1], M. Inoue[1], T. Chiba[1], E. Suzuki[1], M. Yokoyama[1], T. Maeda[1], T. Wakamatsu[1], K. Kobayashi[1], S. Kiyono[1], M. Nakamura[1], T. Saito[1], S. Nakamoto[1], S. Yasui[1], A. Tawada[1], M. Arai[1], T. Kanda[1], H. Maruyama[1], S. Kuboki[2], M. Miyazaki[2], O. Yokosuka[1], M. Ohtsuka[2], N. Kato[1]. *[1]Chiba University, Graduate School of Medicine, Department of Gastroenterology, Chiba, Japan; [2]Chiba University, Graduate School of Medicine, Department of General Surgery, Chiba, Japan*
Email: sadahisa@me.com

Background and Aims: Several studies have previously reported the risk factors associated with early and late phase after curative therapies (resection/local ablation) in patients with hepatocellular carcinoma (HCC). However, a majority of the results were based on single modalities and included patients who extended from early stage HCC. During the past decade, antiviral therapies against both hepatitis B virus (HBV) and hepatitis C virus (HCV) have dramatically improved, resulting in an increase in non-viral HCC. The background of patients with HCC has varied from those reported in previous studies. The present study aimed to identify the risk factors associated with early and late recurrences in patients with HCC after receiving curative therapies and confirm temporal changes in recurrent incidences based on time-dependent receiver operating characteristic (ROC) analysis.
Method: We retrospectively retrieved the database of patients with HCC at our institution between January 2003 and December 2015. We performed multivariate analysis using Cox proportional hazard model to detect independent incidence factors of recurrence before and after 2 yeas from curative therapy. And we also analyzed the influence of each factors to recurrence in every elapsed time from curative therapy by using time-dependent ROC analysis.



Results: Of the 1161 newly diagnosed patients with HCC, 671 patients received curative therapies in early-stage HCC (resection; 225 patients, local ablation; 446 patients). Based on multivariate analysis using Cox proportional hazard model, the tumor size and number, alfa fetoprotein (AFP) before treatment, des-gamma-carboxy prothrombin (DCP), and treatment (resection vs. local ablation) were independent incidence factors of recurrence before 2 years from curative therapy. Similarly, AFP after treatment and the fibrosis-4 (FIB-4) index were independent incidence factors after 2 years. The figure shows the time-dependent ROC analysis of

recurrence of AFP before and after treatment, DCP, and the FIB-4 index.
Conclusion: Using time-dependent ROC analysis, we clarified that there were some differenced in the influential risk factors of recurrence between early and late period after curative therapy. In the early phase, tumor-related factors were mostly associated with recurrence in patients with early-stage HCC receiving curative therapies. In contrast, the FIB-4 index, which correlated with fibrosis, was related to recurrence and increased risk in a time-dependent manner. FIB-4 index appears as the most useful meter of surveillance during late phase after curative therapies.

THU-161

The predictive role of procalcitonin for guiding use of antibiotics in HCC patients with post TACE/RFA fever

S.B. Cho[1], S.-J. Kang[2], C.H. Jun[3], S. Choi[1]. *[1]Chonnam National University Hospital, Division of Hepatology, Internal Medicine, Gwangju; [2]Chonnam National University Hospital, Divison of infection, Internal Medicine, Gwangju, Rep. of South Korea; [3]Chonnam National University Hospital and Medical School, Department of Gastroenterology, Gwangju, Rep. of South Korea*
Email: portalvein@naver.com

Background and Aims: The overlap of clinical findings between inflammation and bacterial infection leading to antibiotics overuse in patients with fever after intervention for treating hepatocellular carcinoma. A procalcitonin is a serum biomarker expressed by epithelial cells in response to bacterial infection, but the roles of procalcitonin have not been elucidated in HCC patients for predicting bacterial infection.
Method: A prospective study was performed for a 97 HCC patients with fever (≥38°C) after transarterial chemoembolization (TACE) or radiofrequency ablation (RFA) among the 563 patents between Jan 2016 and Dec 2016. A inflammatory serum markers including C-reactive protein and procalcitonin, blood culture were measured on the fever day and 3 day and 7 day later after TACE or RFA in a enrolled 97 patients.
Results: Bacterial infection and chemical inflammation accounted for 9 (9.3%) and 88 (90.7%) respectively. Of total 9 cases of proven bacterial infection, hepatobiliary infection was most common (3 cases) followed by urinary tract infection, pneumonia (2 cases each), RFA site cutaneous abscess and bacteremia with unknown primary focus (1 case each). Serum PCT levels measured on the day of fever were significantly higher in patients with bacterial infection (median 0.2 ng/dl, interquartile range (IQR) 0.2–1.4) than those with chemical inflammation (median 0.1 ng/dl, IQR 0.1–0.3) (p = 0.035). The AUC of PCT on day of fever was 0.715 (95% CI 0.538–0.892), which was higher than that of CRP [AUC, (95% CI): 0.598 (0.368–0.828)], leukocytes count [AUC, (95% CI): 0.502 (0.307–0.697)] and neutrophil percentage [AUC, (95% CI): 0.647 (0.445–0.849)]. When the ROC curves were constructed based on peak value of inflammatory markers, AUC of peak PCT was 0.840 (95% CI 0.712–0.968), while other inflammatory markers showed relatively lower accuracy to predict the bacterial infection [CRP: AUC, (95% CI): 0.699 (0.563–0.834), leukocytes count: 0.576 (0.357–0.796), neutrophil percentage: 0.713 (0.565–0.862)] compared to PCT.
Conclusion: A procalcitonin is useful serum marker for differentiating bacterial infection and chemical inflammation in a HCC patients with post TACE/RFA fever. The serum level of procalcitonin is helpful for preventing overuse antibiotics.

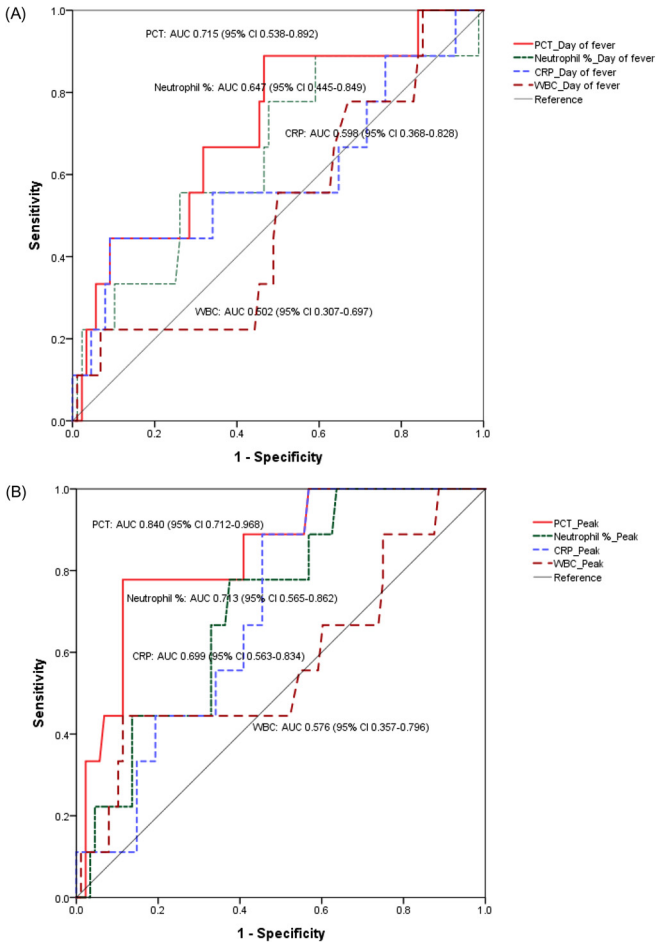


Figure 1: Receiver operating characteristics (ROC) curves and area under the curve (AUC) determined to predict the bacterial infection in patients with fever after TACE and/or RFA based on initial (day of fever) (A) and peak (within 7days of fever) (B) level of PCT, CRP, leukocytes and neutrophil percentage.

THU-162

Combined therapy of transarterial chemoembolizatoin and stereotactic body radiotherapy versus transaterial chemoembolizatoin for < 5m hepatocellular carcinoma: A propensity score matching analysis

B.G. Jun[1], Y.D. Kim[1], G.J. Cheon[1], S.G. Kim[2], Y.S. Kim[2], S.W. Jeong[3], J.Y. Jang[3], S.H. Lee[4], H.S. Kim[4]. *[1]University of Ulsan College of Medicine, Gangneung Asan Hospital, Internal Medicine, Gangneung-si; [2]Soonchunhyang University College of Medicine Bucheon Hospital, Internal Medicine, Bucheon, Rep. of South Korea; [3]Soonchunhyang University College of Medicine Seoul Hospital, Internal Medicine, Rep. of South Korea; [4]Soonchunhyang University College of Medicine Cheonan Hospital, Internal Medicine, Rep. of South Korea*
Email: khskhs@schmc.ac.kr

Background and Aims: Patients are often ineligible for resection or local ablation due to poor liver function and/or difficult location. The aim of this study is to compare therapeutic outcomes of stereotactic body radiotherapy (SBRT) combined with transarterial chemoembolization (TACE) and TACE only for ≤5 cm hepatocellular carcinoma (HCC).
Method: We reviewed data of eighty five patients who received SBRT with TACE (SBRT + TACE group) and one hundred fourteen patients who underwent TACE only (TACE group) in four tertiary hospital between March 2011 and December 2016. Local control rate (LCR), progression free survival (PFS) and overall survival (OS) were compared after propensity score matching (1:1 ratio).

Results: The SBRT + TACE group showed significantly higher 1-, 3- and 5-year LCR than the TACE group (91.1%, 89.9% and 89.9%, respectively, vs 69.9%, 44.8% and 44.8%, respectively; p < 0.001). The SBRT+ TACE group showed better 1- and 3-year PFS than the TACE group (56.5% and 32.3%, respectively, vs 42.2% and 21.6%, respectively; p = 0.050). However, 1-, 3- and 5-year OS was not different between the SBRT+ TACE and TACE group (98.8%, 89.1% and 80.7%, respectively, vs 99.7%, 83.3% and 71.0%, respectively; p = 0.417). Tumor size (HR = 1.266, p = 0.005), number of tumor (HR = 3.081, p < 0.001) and Child-pugh (CP) class B (HR = 2.005, p = 0.006) were associated with PFS. CP class B (HR = 2.462, p = 0.024) was independent prognostic factor of OS.
Conclusion: SBRT-TACE is superior to TACE in terms of LCR and PFS. SBRT-TACE may be an alternative treatment for patients with ≤5 cm HCC which is unsuitable for resection or local ablation.

Table 1: Baseline characteristics before and after propensity score matching

Variable	Before propensity matching			After propensity matching	
	SBRT + TACE (n = 85)	TACE (n = 114)	P-value	TACE (n = 85)	P-value
Sex					
Male	65	88	0.905	64	0.858
Female	20	26		21	
Age (mean ± SD)	62.64 ± 10.08	63.32 ± 10.10	0.639	62.85 ± 10.65	0.894
Number			0.045		0.816
1	55	55		51	
2	20	33		23	
3	10	26		11	
Tumor size (mean ± SD)	2.23 ± 1.17	2.54 ± 1.35	0.095	2.29 ± 1.17	0.753
Child-pugh score (mean ± SD)	5.52 ± 0.85	5.57 ± 1.18	0.183	5.59 ± 1.06	0.633
Child-pugh class					
A	71	96	0.897	74	0.516
B	14	18		11	
The etiology					
Alcohol	22	27	0.920	18	0.778
Hepatitis B virus	47	65		51	
Hepatitis C virus	11	13		9	
others	5	9		7	
ALT (mean ± SD)	27.7 ± 24.3	29.4 ± 18.8	0.674	29.1 ± 18.1	0.666
Total bilirubin (mg/dl) (mean ± SD)	0.94 ± 0.56	0.95 ± 0.65	0.857	0.90 + 0.63	0.654
Platelet count (×10^9/L) (mean ± SD)	128 ± 63.5	116 ± 53	0.160	118 ± 53	0.261
Prothrombin time (INR) (mean ± SD)	1.14 ± 0.20	1.17 ± 0.18	0.283	1.15 ± 0.19	0.651

ALT, alanine transaminase; INR, International Normalized Ratio.

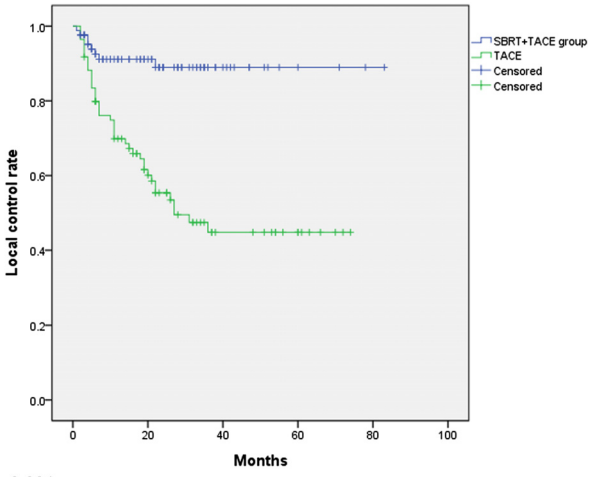


Figure 1: Comparison of the local control rate between SBRT-TACE group and TACE group.

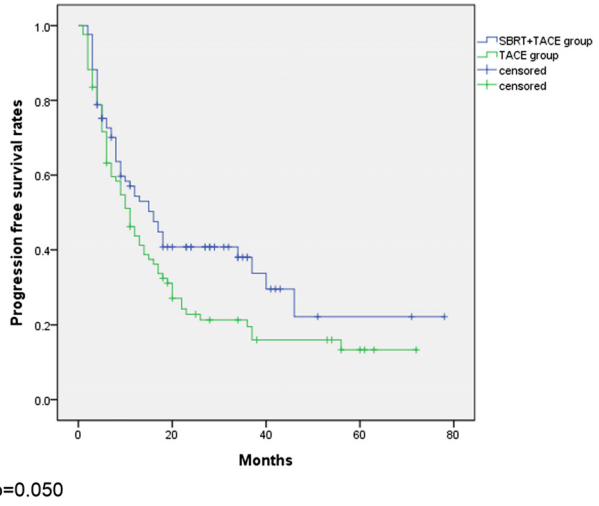


Figure 2: Comparison of the progression free survival rate between SBRT-TACE group and TACE group.

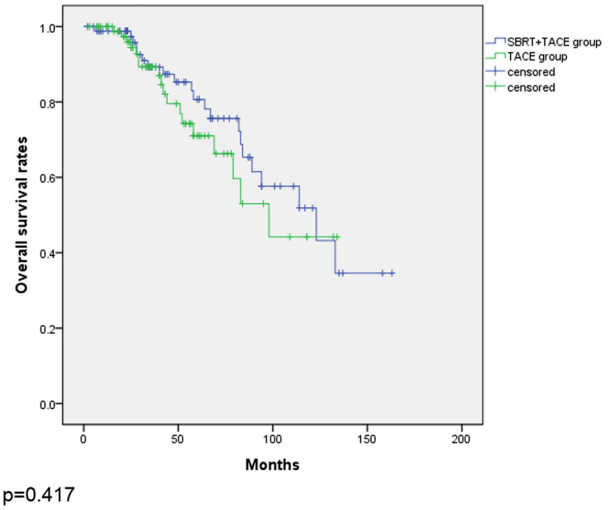


Figure 3: Comparison of the overall survival rate between SBRT-TACE group and TACE group.

THU-163

Out of Milan criteria and worse intetion to treat results at large liver transplant center

J.H. López[1], Ángel Rubín[1], C. Viaixa[1,2], Ángel Moya[3], M. Prieto[1,4], R. López[3], M.B. Haym[1,4]. *[1]Hospital Universitario y politécnico la Fe, Hepatology and Liver Transplant Section, Digestive Medicine Department, Valencia, Spain; [2]Instituto Carlos III, Networking Biomedical Research Centre Inhepatic and Digestive Disease (CIBEREHD), Valencia, Spain; [3]Hospital Universitario y politécnico la Fe, Hepato-Biliary -Pancreatic Surgery and Transplantation Unit, Valencia, Spain; [4]Hospital Universitario y politécnico la Fe, Networking Biomedical Research Centre Inhepatic and Digestive Disease (CIBEREHD), Valencia, Spain*
Email: herreras.julia8@gmail.com

Background and Aims: Milan criteria are widely used for LT selection but have been recognized to be restrictive. Although extra-Milan criteria are increasingly being adopted, intention-to-treat analyses are still lacking. **Aim:** To analyse if patients with extra-Milan hepatocellular carcinoma (HCC) included in a waiting list (WL) for LT have different outcome than Milan patients.
Method: Retrospective study analysing the outcome of 177 HCC patients waitlisted for LT between 2012 and 2015 at a single LT centre.

Patients were included in the waiting-list (WL) for LT if they were within-Milan from time of diagnosis or had been successfully downstaged from extra to within Milan. At time of WL inclusion, all patients were within Milan criteria and started and/or continued LRT if considered necessary until LT. Patients were followed up until death or January 2017. Patient, liver, tumour (including lorcorregional therapies-LRT) and surgical variables were recorded. LT-treatment failure was defined by a combined end-point including WL death due to liver disease, WL exclusion due to tumour progression and/or HCC recurrence post-LT.

Results: 177 patients, mostly men (87%) were included. Median age was 58 years old (51–63). Hepatitis C (51%) and alcohol (41%) were the main causes of liver disease. At time of HCC diagnosis, most patients (73%) were Child Pugh score (CTP) A with a median MELD score of 9(6–27) and median alpha-fetoprotein levels at diagnosis were 3.6 mg/dL. Most HCC cases were within Milan (n = 148, 84%). The median size of the nodules was 35 (10–80 mm). Downstaging was performed in all extra-Milan cases (n = 34) with 2 (1–4) local therapy before enter waiting list. LT was eventually performed in 146 patients after a median waiting time of 6 months LT-treatment failure occurred in n patients (20%) due to WL-death due to liver disease in 44% of these, WL exclusion due to tumour progression in 20% and HCC recurrence in the remainder 36% of patients. In the univariate analysis, extra- Milan criteria, high levels of alpha-fetoprotein at diagnosis, and number of LRT were predictive variables associated with treatment failure. Extra Milan criteria was the only variable remaining in the multivariate analysis with a HR of 3,3 (95% CI 1,34–7,4 p = 0.01).

Conclusion: According to our data, out-of-Milan criteria is associated with a higher intention-to-treat LT failure from time of inclusion in the WL.

THU-164

Real-world data in patients with hepatocellular carcinoma treated with transarterial chemoembolization: the second interim analysis of OPTIMIS

M. Peck-Radosavljevic[1,2], M. Kudo[3], H.C. Lee[4], A.-LII Cheng[5], K. Nakajima[6], J.-L. Raoul[7]. *[1]Medical University of Vienna, Vienna, Austria; [2]Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria; [3]Kindai University Faculty of Medicine, Osaka, Japan; [4]Asan Medical Center, Seoul, Rep. of South Korea; [5]National Taiwan University Hospital, Taipei, Taiwan; [6]Bayer HealthCare Pharmaceuticals, Whippany, NJ, United States; [7]Institut de Cancérologie de l'Ouest, Digestive Oncology, Nantes, France*

Email: markus@peck.at

Background and Aims: Transarterial chemoembolization (TACE) is commonly used for patients with unresectable hepatocellular carcinoma (HCC). However, there are no universally accepted criteria for TACE use and in clinical practice it is often used in broader populations outside of recommended international guidelines. Retrospective studies suggest TACE treatment for unsuitable patients may cause liver function deterioration and worse overall survival. The OPTIMIS study was designed to characterize TACE utilization, post-TACE treatments, and outcomes in real-world clinical practice settings.

Method: OPTIMIS is an international, prospective, observational study of patients with HCC who were treated with TACE. The study enrolled patients classified as BCLC stage B or higher and for whom a decision to treat with TACE was made at the time of study entry. Other treatments for HCC were also documented before, during, and after TACE, including sorafenib (SOR).

Results: In this interim analysis, 977 patients had received TACE. At inclusion, 153 patients (16%) had received other prior therapeutic procedures (10% hepatectomy) and 115 (12%) had prior local anti-cancer therapy excluding surgery (9% radio-frequency ablation). Overall, 431 (44%) were deemed ineligible for TACE at inclusion according to international guidelines (40% Europe; 55% Asia; 15% Japan; 82% China; 38% Korea). At study inclusion, 227 patients (23%) were BCLC C and 9 (1%) BCLC D (Table). Of the 333 patients with available STATE scores, 97 (29%) had scores ≤18 (% by region: 44% Europe; 56% Asia; 11% Japan; 73% China; 17% Korea) and 236 (71%) had >18. Overall, 267/977 patients (27%) received SOR (% by region: 25% Europe; 29% Asia; 24% Japan; 50% China; 12% Korea). In the SOR treated population, around one-third of patients received ≥3 TACE treatments and treatment-emergent adverse events (all grade) were reported in 148/267 patients (55%).

HCC at inclusion visit

	Europe n = 318	Asia n = 208	Japan n = 172	China n = 138	Korea n = 141	Total n = 977
BCLC stage*, %						
B	73	71	94	31	71	70
C	13	25	5	67	26	23
D	1	2	0	1	1	1
Child–Pugh score†, %						
A	60	67	78	82	84	71
B	21	19	21	15	14	19
C	<1	1	0	1	0	1

*Missing n = 55; †Missing n = 90.

Conclusion: In this interim analysis of OPTIMIS, a significant number of patients were considered for TACE, despite not being adequately indicated. Results also suggest that systemic therapy is not commonly used in the real-world setting. Further observation is necessary to confirm these findings.

THU-165

Comparision of long-term outcome for single small hepatocellular carcinoma between different treatment modalities by size and tumor marker

D.H. Sinn[1], S.-G. Lee[1], D. Hyun[2], S.W. Shin[2], G.-S. Choi[3], J.M. Kim[3], T.W. Kang[2], M.W. Lee[2], W. Kang[1], G.-Y. Gwak[1], Y.-H. Paik[1], M.S. Choi[1], J.H. Lee[1], K.C. Koh[1], S.W. Paik[4], B.C. Yoo[5]. *[1]Samsung Medical Center, Department of Medicine, Seoul, Republic of South Korea; [2]Samsung Medical Center, Department of Radioogy and Center for Imaging Science, Seoul, Republic of South Korea; [3]Samsung Medical Center, Department of Surgery, Seoul, Republic of South Korea; [4]Samsung Medical Center, Department of Medicine, Seoul, Republic of South Korea; [5]Konkun University Medical Center, Department of Medicine, Seoul*

Email: sinndhn@hanmail.net

Background and Aims: For single small hepatocellular carcinoma (HCC), radiofrequency (RF) ablation can be a first-line option for patients with preserved liver function. We tested whether size and tumor marker should be considered in selecting RF ablation as a first-line option.

Method: We used a retrospective cohort of 896 consecutive, treatment-naïve, single, small sized (<3 cm) HCC who were treated with resection (n = 319), radiofrequency (RF) ablation (n = 425) or transarterial chemoembolization (TACE) (n = 152) as a first-line therapy between 2010 and 2013. Patients were grouped into three based on tumor size and PIVKA-II levels; (1) tumor sized ≤2 cm with low PIVKA-II levels (<30 mAU/ml), (2) tumor sized 2–3 cm with low PIVKA-II levels (<30 mAU/ml) or tumor sized ≤2 cm with elevated PIVKA-II levels (≥30 mAU/ml); (3) tumor sized 2–3 cm with elevated PIVKA-II levels (≥30 mAU/ml). Long-term outcome was compared between treatment modality in each group.

Results: For group 1, compared to RF ablation, resection showed similar risk of overall mortality (adjusted hazard ratio (HR), 0.29, 95% confidence interval (CI), 0.06–1.45, adjusted for age, sex, etiology, albumin-bilirubin grade, ECOG performance, and AFP levels), while TACE showed increased risk of overall mortality (adjusted HR, 2.10, 95% CI, 1.10–4.02). For group 2, resection showed similar risk of overall mortality to RF ablation while the risk was higher for those who underwent TACE. For group 3, resection showed reduced risk of

overall mortality (adjusted HR, 0.46, 95% CI, 0.01–0.26) compared to RF ablation, while the risk was similar between TACE and RF ablation (adjusted HR, 0.60, 0.14–2.54).
Conclusion: RF ablation showed comparable efficacy in terms of overall survival to surgical resection for single, small tumor when PIVKA-II level was low. However, when PIVKA-II level was elevated, RF ablation showed worse survival than resection when tumor size exceeded 2 cm. Size and PIVKA-II levels should be considered when considering RF ablation as a first-line treatment option for single small HCC.

THU-166
Multimodal and sequential treatmente for hepatocellular carcinoma: how "real-life" complies with international recommendations
M. Triolo[1,2], A. Sangiovanni[1], M. Iavarone[1], L.V. Forzenigo[3], A. Nicolini[4], G. Rossi[5], V. La Mura[2], M. Colombo[6], P. Lampertico[1].
[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milano, Italy; [2]Policlinico S. Donato, University of Milan, Division of Internal Medicine, San Donato, Italy; [3]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Division of Radiology, Milano, Italy; [4]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Division of Interventional Radiology; [5]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, HBP Surgery and Liver Transplantation Unit, Milano, Italy; [6]Humanitas Clinical and Research Center, Rozzano, Italy
Email: pietro.lampertico@unimi.it

Background and Aims: Management of hepatocellular carcinoma (HCC) is framed within standardized protocols released by Scientific Societies, whose applicability and efficacy in field practice need refining.
We evaluated the applicability and effectiveness of guidelines for the treatment of HCC of the American Association for the Study of the Liver (AASLD).
Method: Between January 2007 and December 2011, 370 consecutive cirrhotic patients (250 viral hepatitis/41 ethanol/79 other etiologies, median age 68 yy, 272 males, 250 Child-Pugh A) with de-novo HCC in different stages (253 BCLC A, 66 BCLC B, 51 BCLC C) received treatment through a multidisciplinary team (MDT) decision. Patients were followed until death or last follow-up up to December 2016. Patients with a previous diagnosis of liver cancer and those with poor liver function (Child–Pugh C) were excluded.
Results: HCC treatment was adherent to AASLD recommendations in 205 (81%) BCLC A patients, 36 (54%) BCLC B, and 27 (53%) BCLC C. Overall, a radiological complete response was obtained in 185 (50%) patients, 165/370 (45%) after a first-line treatment, 25/117 (21%) after a second-line treatment, and 6/39 (15%) after a third-line treatment. Eleven patients (3%) achieved a complete response more than once.
During 58 (range 1–108) months, 105 (28%) patients died, 41 (16%) BCLC A, 25 (38%) BCLC B and 39 (74%) BCLC C. In BCLC A the mean mortality rate was lower in patients treated according to AASLD recommendations than in patients otherwise treated (5.0% vs 10.4%, $p = 0.004$), corresponding to a 1, 3, 5 year survival of 100%, 86%, 77% vs 93%, 75%, 47%, respectively; whereas the upward treatment stage migration was associated to a lower mortality rate as compared to standard of treatment in BCLC B (8.6% vs 20.7%, $p = 0.029$) corresponding to a 1, 3, 5 year survival of 100%, 74%, 67% vs 100%, 43%, 23%, respectively, as well as in BCLC C (42.6% vs 59%, $p = 0.04$) corresponding to 1, 3, 5 yr survival 79%, 39%, 0% vs 42%, 1%, 0%, respectively.
Conclusion: HCC multimodality treatment including other than first-line therapy is common in clinical practice and impacts on the achievement of complete response. Personalized treatment provided survival benefits to patients whose profile is not accounted for by international recommendations.

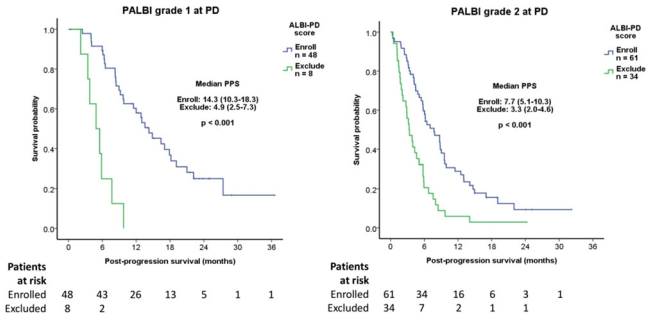
THU-167
Surgical resection is considered in resectable solitary hepatocellular carcinoma with portal vein tumor thrombosis of patients with Child A
J.M. Kim[1], C.H.D. Kwon[2], J.-W. Joh[3], G.-S. Choi[4], D.H. Sinn[5], Y.-H. Paik[4], J.H. Lee[4]. *[1]Sungkyunkwan University School, Samsung Medical Center, Seoul, Republic of South Korea; [2]Samsung Medical Center, Seoul, Republic of South Korea; [3]Sungkyunkwan University School of Medicine, Samsung Medical Center, Republic of South Korea; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of South Korea; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul*
Email: yjongman21@gmail.com

Background and Aims: Sorafenib is recommended in the hepatocellular carcinoma with portal vein tumor thrombosis. However, surgical resection and locoregional therapies such as combination transarterial chemoembolization (TACE) and/or radiation therapy (RT) are commonly used in those patients. The aim of present study is to compare the outcomes between surgical resection and combination therapy included TACE and RT in resectable solitary HCC with PVTT.
Method: We prospectively enrolled in resectable solitary HCC with PVTT between 2010 and 2015. Some hepatologists favored surgical resection and others favored locoregional therapies. Resectability was defined by three experienced surgeons. Patients were selected using propensity score matching (1:2).
Results: One-hundred sixteen patients enrolled in the study because of resectable solitary HCC with PVTT. All patients were Child-Pugh class A and ECOG performance grade $\leq$1. Forty-four patients underwent surgical liver resection (SR group) and 72 patients received combination therapies (Combination group). Age, AFP, PIVKA-II, and tumor size were significantly different between the two groups. Therefore, propensity score matching used four variables. Thirty-five patients in the SR group and 45 patients in the combination group were selected after propensity score matching. The 1-year, 2-year, and 3-year patient survival rates were 85.7%, 71.3%, and 68.2% in the SR group and 68.9%, 53.2%, and 38.1% in the combination group ($p = 0.008$). Multivariate analysis showed that surgical resection, low platelet counts, and male are closely associated patient survival in solitary HCC with PVTT.
Conclusion: Surgical resection may improve patient survival in solitary resectable HCC wih PVTT patients. Surgical liver resection is always considered as curative treatment in solitary resectable HCC with PVTT in patients with Child A.

THU-168
Performance of ALBI-PD Model and PALBI Grade in Sorafenib-failed Hepatocellular Carcinoma
P.-C. Lee[1], Y.-T. Chen[2], Y. Chao[3], T.-I. Huo[1], C.-W. Su[1], M.-C. Hou[1], Y.-H. Huang[1]. *[1]Taipei Veterans General Hospital, Gastroenterology and Hepatology, Taipei, Taiwan; [2]Taipei Veterans General Hospital, Nursing, Taipei, Taiwan; [3]Taipei Veterans General Hospital, Medical Oncology, Taipei, Taiwan*
Email: tympanum3688@gmail.com

Background and Aims: Albumin-bilirubin (ALBI) grade is superior to Child-Turcotte-Pugh (CTP) classification in prediction the survival of hepatocellular carcinoma (HCC) across all cancer stages. ALBI grade derived models, ALBI-PD and platelet-albumin-bilirubin (PALBI) grade seems to have better performance in prediction the survival of HCC. We aim to compare the performance of ALBI-PD model and PALBI in prediction the outcomes of sorafenib-failed HCC.
Method: From August 2012 to October 2015, 432 consecutive patients who received sorafenib treatment for advanced HCC in Taipei Veterans General Hospital were retrospectively reviewed. Of them, 328 experienced radiology-proved progressive diseases (PD) were enrolled into the analysis. The area under receiver-operator-

characteristic curve (AUROC), homogeneity and corrected Akaike information criterion (AICc) were compared between each system.
Results: During the median follow-up of 5.9 months, 294 deaths occurred. The median overall survival was 6.0 (95% confidence interval [CI], 5.2–6.7) months; and the post-progression survival (PPS) was 4.0 (95% CI, 3.5–4.4) months. ALBI-PD model and PALBI grade performed better in prediction the PPS than ALBI grade (AUROC of each model: 0.766, 0.757, 0.712 at 6 months and 0.766, 0.732, 0.723 at 9 months for ALBI-PD, PALBI and ALBI, respectively). ALBI-PD score had the highest homogeneity and the lowest AICc value among the three models. ALBI-PD score could further discern PPS across PALBI grades. In PALBI grade 1 patients beyond ALBI-PD criteria, the median PPS was only 4.9 month. Noteworthily, 61 (64.2%) of the 95 PALBI grade 2 patients were still within the ALBI-PD criteria, whose median PPS could achieve 7.7 months.



Conclusion: ALBI-PD, and PABLI are superior to ALBI to predict PPS after sorafenib failed. ALBI-PD model can further discriminate PPS in PALBI grade 1 and 2 sorafenib-failed HCC, and is a practical criterion to select eligible patients into second-line therapy.

THU-169

Feasibility of dynamic risk assessment for patients with repeated tras-arterial chemoembolization for hepatocellular carcinoma

M.I.Y. Jeon[1], Y. Park[1], B.K. Kim[2], J.Y. Park[1], D.Y. Kim[1], S.H. Ahn[1], K.-H. Han[1], H. Kim[1], S.U. Kim[1]. *[1]Yonsei University College of Medicine, Department of Interna Medicine, Seoul, Republic of South Korea; [2]Severance Hospital, Internal Medicine, Gastroenterology, Seoul, Republic of South Korea*
Email: ksukorea@yuhs.ac

Background and Aims: The hepatoma arterial-embolization prognostic (HAP) score and its modifications (modified HAP [mHAP] and mHAP-II) predict outcomes after trans-arterial chemoembolization (TACE) for hepatocellular carcinoma (HCC). We investigated the feasibility of using HAP-related risk scores for dynamic risk assessment during repeated TACE.
Method: A total of 619 HCC patients treated with TACE from two institutions between 2003 and 2010 were included.
Results: Patients with A-B class risk scores showed significantly better survival than those with C-D class at the first (median 43.7 vs. 21.5 months for mHAP-II, 35.2 vs. 10.2 months for mHAP, and 39.8 vs. 18.6 months for HAP; all $p < 0.001$) and the second TACE (38.6 vs. 17.2 months for mHAP-II, 30.0 vs. 8.5 months for mHAP, and 32.6 vs. 17.3 months for HAP; all $p < 0.001$). Sequential assessment of risk scores at the second TACE was applied for patients with A-B class risk scores at the first TACE, which further identified two subgroups of A-B and C-D class risk scores with different outcomes (median survival 40.6 vs. 19.6 months for mHAP-II, 31.2 vs. 16.9 months for mHAP, and 35.8 vs. 21.0 months for HAP; all $p < 0.001$). The mHAP-II, compared with mHAP and HAP, showed the highest likelihood ratio (22.61 vs. 14.67 and 13.97, respectively), highest linear trend (24.43 vs. 19.67 and 14.19, respectively), and lowest Akaike information criteria value (1432.51 vs. 3412.29 and 2296.98, respectively).
Conclusion: All HAP-related risk scores dynamically predicted outcomes during repeated TACE. Sequential risk assessment using mHAP-II best identified optimal candidates for repeated TACE.

THU-170

Surgical resection vs radiofrequency ablation for hepatocellular carcinoma: a propensity score matching analysis

G. Scialandrone, M.F. Valentini, S. Roselli, P. Panzera, R. Memeo, L.G. Lupo. *U.O. Chirurgia Generale "M.Rubino", DETO-Dipatimento Emergenza Trapianto D'Organi,Bari, Italy*
Email: grazisa.scialandrone@gmail.com

Background and Aims: Hepatocellular carcinoma (HCC) is the 5th cause of death among cancer. Surgical resection and local ablative therapies represent the most frequent firstline treatment adopted when liver transplantation is not indicated or not immediately applicable. Unfortunately, in literature, a lot of studies that directly compared Hepatic Resection (HR) and Radiofrequency Ablation (RFA) reports discrepant results. When comparing the efficacy of two different therapies for HCC, a major limitation is the causal inference problem.
Method: In this retrospective study we enrolled 411 patients undergoing to RFA and 147 patients undergoing to HR between January 2006 and August 2017. The Outcomes in terms of Overall Survival and Disease free Survival were analyzed using a Propensity Score Matching (PSM) method.
Results: The comparison between HR group and RFA group reveals significant differences as regards demographic characteristics, liver function and underlying disease, tumor features (number and size), Overall Survival rates (OS, $p < 0.0001$), or Recurrence-Free Survival rates (RFS, $p < 0.0001$). For the 81 patient pairs selected from the PSM analysis, the RFA group shows better OS and RFS than HR group (5yOS 49.9% vs 35.8%, $p = 0.003$ and 5y RFS 58.3% vs 30.6%, $p = 0.012$, respectively). A Cox proportional Hazard analysis demonstrates that choosing Treatment ($p = 0.004$), total Bilirubin ($p = 0.032$) and Neutrophil-Limphocyte Ratio (NLR, $p = 0.016$) were indipendent prognostic factors for OS; Treatment ($p = 0.001$), total Bilirubin ($p = 0.008$), NLR ($p = 0.003$) and HCV-rna ($p = 0.001$) were indipendent prognostic factors for RFS.
Conclusion: This study suggests that Local Ablation is equivalent to or better treatment option than Surgical Resection in patients with primitive HCC within Milan Criteria, a reliable alternative to hepatic resection in patients with functional and anatomical limitation, a first-line treatment for Downstaging and Bridge.

THU-171

Impact of the alpha-Fetoprotein model for patient selection for Liver Transplantation for Hepatocellular Carcinoma, a French experience

B. Brusset[1], Q.J. Louis[1], J. Dumortier[2], D. Cherqui[3], G.-P. Pageaux[4], S. Dharancy[5], S. Radenne[6], D. Samuel[7], D. Thomas[1]. *[1]CHU Grenoble, Grenoble, France; [2]Unité de Transplantation hépatique, Lyon, France; [3]Centre Hepatobiliaire Paul Brousse, Villejuif, France; [4]CHU Montpellier, Montpellier, France; [5]Liver Unit, CHRU Lille, Lille, France; [6]Hospices Civils de Lyon, Hepatology Department, Lyon, France; [7]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, France*
Email: bbrusset@chu-grenoble.fr

Background and Aims: The French organization for organ Sharing changed the allocation criteria for Liver transplantation (LT) in Hepatocellular carcinoma (HCC) on January 2013. The AFP Model replaced Milan criteria. Since then, only patients with an AFP score $\leq$2 access to LT. The aim of this study was to analyze the respect of the criteria and the results of LT with an intention-to-treat design since the adoption of the AFP model, and to compare them to the results before its adoption.
Method: 523 patients consecutively listed for LT for HCC between March 2011 and March 2014 in five French centers have been

included, whether they have been transplanted (n = 364) or not (n = 159). The Milan group (n = 199) consisted in patients transplanted or dropped out of list before the concrete adoption of the AFP model. The AFP group (n = 324) consisted in patients transplanted or dropped out of list since its application.

Results: In the AFP group, patients had less advanced cirrhosis and more bridging therapies than in the Milan group. Median waiting time was 7.7 months in the Milan group vs. 12.3 months in the AFP one ($p < 0.001$), mainly due to the establishing of "temporary contraindications".

The non-respect of the AFP score on the explants was highly predictive of recurrence (SHR 6.85, $p < 0.001$) and post-transplant death (HR 3.44, $p < 0.001$). There was no difference in the histological AFP score between groups ($p = 0.838$) with a global respect in 88% of patients. Independent factors predicting a non-respect of this score were a downstaging policy and an AFP score >2 on the last imaging. Dropout of list, 3-year post-listing survival and 2-year post-transplantation were similar between the groups (respectively 26.3% in Milan vs. 30.6% in AFP, $p = 0.086$; 68.2 vs. 66.7%, $p = 0.447$ and 87.4 vs. 82.7% $p = 0.100$).

However despite no significant difference in the rate of recurrence (9.2% vs. 13.2%, $p = 0.239$), the multivariate analysis showed that belonging to the AFP group, as well as the non-respect of the AFP model, a downstaging policy and preceding treatments to avoid LT, were predictors of post-LT tumor recurrence.

Conclusion: The adoption of the AFP model in France did not change the histological results but allowed a better respect of the allocation rules in comparison to Milan criteria, without significant increase in the dropout rate. A high rate of recurrence was observed in the most recent cohort, probably due to the lengthening of the waiting list and an increase of treatments. This study raises the necessity to discuss the principles of temporary contraindications and to develop solutions to cope with the organ shortage.

THU-172

Transarterial-chemoembolization and hepatocellular carcinoma. A regular interval approach avoids the 10% of the procedures and an optimal survival with the transition to systemic therapy in 80% of the patients

M.S. Zamparelli[1], M. Burrel[2], A. Darnell[3], V. Sapena[1], M. Barrufet[2], A. Sotomayor[2], N. Llarch[1], G. Iserte[1], A. Diaz-Gonzalez[1], E. Belmonte[4], A. Forner[1], J. Rimola[3], C. Ayuso[3], M. Reig[1], J. Bruix[1]. *[1]Hospital Clínic de Barcelona. BCLC group. Liver Unit. IDIBAPS. CIBERehd, Barcelona; [2]Hospital Clínic de Barcelona. BCLC group. Radiology department, Barcelona; [3]Hospital Clínic de Barcelona. BCLC group. Radiology department. Universitat de Barcelona, Barcelona, Spain; [4]Hospital Clínic de Barcelona. BCLC group. Radiology department. IDIBAPS. CIBERehd, Barcelona, Spain*

Email: jbruix@clinic.cat

Background and Aims: Chemoembolization (TACE) is the recommended treatment for patients with hepatocellular carcinoma (HCC) at BCLC-B stage or BCLC-0/A without other options. After initial response, TACE can be performed "on-demand" based on the tumor evolution or at regular intervals. Usually, TACE is performed at 0, 2 months and then at 6 months, but solid data on the benefit/needs/applicability of TACE at month 2 or on the possibility to avoid the second TACE after registering radiologic complete response (CR) after the 1st session are still lacking. Furthermore, it is controversial if a 6 months interval is appropriate or what amount of patients cannot be treated because of exceeding the criteria for the treatment. The aim of this study was to evaluate -if CR after the 1st TACE predicts the tumor de-vascularization and the futility of the 2nd TACE at month 2, -if the 1st TACE induces vascular lesions hampering the 2nd treatment, -the percentage of patients who develop untreatable-progression revealed by the regular interval schedule and -validation of the currently expexted overall survival (OS).

Method: Between 01/2014–3/2017, 106 patients (HCV 51.89%, Child-Pugh-A 92.45% y BCLC-A/B 43.4/56.6%) were included. For all patients 3 TACE (0/2/6 months) were scheduled and performed according to the radiologic and angiographic findings during the follow-up.

Results: The median follow-up was 19.3 months. Seven patients were transplanted and 39 had untreatable-progression [20.8% BCLC-B stage (n = 22), 10.3% en BCLC-C stage (n = 11) and 5.6% BCLC-D stage (n = 6)]. Two patients developed a hepatic abscess. Ninety-six patients (90.6%) had at least 1 TACE. The most common reasons for performing the angiography in spite of the 1st, 2nd and 3th TACE were: untreatable disease (6/10) for the 1st angiography, no treatable lesions for the 2nd and 3th angiography, [85.3% (n = 13/16)] and [73.7% (n = 14/19)] respectively. Twenty-one patients died during the follow-up and the median OS censoring at application of other treatment or liver transplantation was 44 months (42.6 months without censoring). Thirty-five of 44 patients (80%) who suspended TACE started systemic treatment with sorafenib.

Conclusion: 10% of the patients had CR by dynamic imaging and angiography after the first TACE and thus, may avoid a 2nd session at 2 months. The evaluation and treatment according to the regular interval schedule allowed that 80% of the patients with untreatable-progression may benefit from systemic treatment and this sequence translates into a median OS ≥ 40 months.

THU-173

Impact of regorafenib in the clinical practice and identification of second-line treatment orphan patients

M.S. Zamparelli[1], V. Sapena[1], A. Diaz-Gonzalez[1], A. Darnell[2], N. Llarch[1], E. Belmonte[3], L. Boix[1], G. Iserte[1], A. Forner[1], J. Corominas[1], L.G. Da Fonseca[1], C. Ayuso[2], J. Bruix[1], M. Reig[1]. *[1]Hospital Clinic, BCLC group. Liver Unit. IDIBAPS. CIBERehd, Barcelona, Spain; [2]Hospital Clinic, BCLC group. Radiology department. Universitat de Barcelona, Barcelona, Spain; [3]Hospital Clinic, BCLC group. Radiology department. IDIBAPS. CIBERehd., Barcelona, Spain*

Email: mreig1@clinic.cat

Background and Aims: The RESORCE study showed that regorafenib provides a significant benefit in terms of overall survival (OS) to patients with hepatocellular carcinoma (HCC) who tolerated sorafenib (400 mg/day) and presented radiologic progression. Data on regorafenib treatment in clinical practice are scarce and the percentage of patient candidates or orphans of effective second-line treatment is unknown. The purpose of this study was to investigate the feasibility and tolerance of regorafenib in clinical practice and to evaluate the proportion of patients who can benefit from it.

Method: we analysed a prospective database of patients with HCC treated with sorafenib to investigate the regorafenib applicability and assessed the outcome of patients that have received this novel option. This includes 19 patients [5 within the research trials and 14 under compassionate use]. All patients started at 160 mg/day. Treatment was continued until symptomatic progression, unacceptable adverse events or patient decision.

Results: Eighty of the 299 patients treated with sorafenib were alive at the time of regorafenib availability, 21/80 continued on sorafenib and 59 definitively discontinued (41 due to toxicity, 17 for tumor progression and 1 because of patient decision). 23% (14/59) of the patient who discontinued sorafenib started regorafenib and 14/17 (82.35%) with tumor progression started regorfenib. Among all the patients treated with regorafenib 85% were BCLC-C with the tumor progression pattern of: 15% BCLCp-B (n = 3), 35% BCLCp-C1 (n = 7) and 50% BCLCp-C2 (n = 10). The median follow-up was 19.9 and 5.6 months for the research and clinical practice patients respectively. 11/20 patients have died (range 3–32 months). The median time to 1st dose modification was 13.8 days and modifications were due to: fatigue (n = 4), skin reaction (n = 4) and diarrhoea (n = 3). Seven of the 8 patients who discontinued regorafenib did so because of symptomatic progression.

Conclusion: Since regorafenib approval for HCC, the number of patients treated with regorafenib is low but data on the tolerability and survival reproduce the RESORCE results even if presenting the poor prognosis pattern (50% BCLCp-C2). More than half of the patients treated with sorafenib are a potential candidate for regorafenib, although a relevant number of patients remains orphan for effective second-line treatment.

THU-174

Combined photodynamic therapy with systemic chemotherapy improves survival of patients with irresectable cholangiocarcinoma

M.A. Gonzalez-Carmona[1], M. Bolch[1], C. Jansen[1], A. Vogt[1], M. Sampels[1], K. van Beekum[1], R. Mahn[1], M. Praktiknjo[1], J. Nattermann[1], J. Trebicka[1], V. Branchi[2], H. Matthaei[2], S. Manekeller[2], J. Kalff[2], C.P. Strassburg[1], T. Weismüller[1]. *[1]University Hospital Bonn, Internal Medicine I, Bonn, Germany; [2]University Hospital Bonn, Visceral Surgery, Bonn, Germany*
Email: maria.gonzalez-carmona@ukbonn.de

Background and Aims: Systemic chemotherapy (SC) with gemcitabine and cisplatin is the current standard therapy for patients with irresectable cholangiocellular carcinoma. Photodynamic therapy (PDT), a local ablative procedure, has also been shown beneficial in patients with irresectable extrahepatic cholangiocarcinoma. However, the benefit of combined SC with PDT is still unclear. This retrospective study evaluated the benefit of PDT—alone or in combination with SC—compared to SC alone in patients with irresectable extrahepatic cholangiocarcinoma.
Method: 353 patients diagnosed of cholangiocarcinoma between 2004 and 2016 were treated at the University Hospital of Bonn, Germany. 96 patients suffering from irresectable extrahepatic cholangiocarcinoma were included in this study and retrospectively analyzed. Patients were stratified according to treatment: PDT-SC combination (n = 36), PDT alone (n = 34) and SC alone (n = 26).
Results: Combined PDT with SC resulted in significantly longer overall survival than SC alone (log-rank p = 0.022). Median survival was 20 months in the PDT-SC treatment group (95%CI:16.38–23.62 months), 15 months in the PDT group (95%CI:10.02–19.98) and 10 months in the SC group (95%CI:8.45–11.55 months). A multivariate analysis identified PDT-SC and PDT (hazard ratio [HR], 0.41, 95%CI: 0.22–0.77, p = 0.006), but also other local therapies, such as metal stenting and application of RFA as significant independent predictors for longer survival. Interestingly, patients with metastatic disease appeared to benefit highly of combined therapy, compared to SC alone (log-rank p = 0.014). Finally, combined therapy was well-tolerated, and adverse events were similar among the different groups (p < 0.05).
Conclusion: Combination of PDT with SC was feasible, well-tolerated and resulted in significantly longer overall survival compared to SC alone. Application of PDT significantly correlated with longer survival. This study strongly points out a relevant role of PDT but also of other local therapies in the control of advanced cholangiocarcinoma and should be evaluated in the therapy decision for this disease.

THU-175

Outcomes of single or sequential dual modality loco-regional therapies in Hepatocellular carcinoma

V.K. Balachandrakumar[1], M. Swaminathan[2], J. Evans[3], N. Kibriya[3], D. Palmer[1], T. Cross[2]. *[1]Liverpool University, Institute of Translational Medicine, Liverpool; [2]The Royal Liverpool Hospital, Hepatology, Liverpool; [3]The Royal Liverpool Hospital, Interventional Radiology, United Kingdom*
Email: vinayb96@yahoo.co.uk

Background and Aims: Hepatocellular carcinoma (HCC) in western populations commonly occurs in the context of cirrhosis. Staging of disease has been based primarily on the Barcelona Clinic Liver Cancer (BCLC) classification in the UK. Patients not fit for Orthotopic Liver Transplantation (OLT) or liver resection in stage A disease have been offered ablations whilst patients with intermediate stage B disease have been offered trans-arterial chemoembolization (TACE). The aim was to assess outcomes from patients offered single modality or dual modality therapy for HCC, and to identify prognostic factors.
Method: A single centre study of patients from the Royal Liverpool Hospital from 2003 to 2016 was analysed. Patients receiving loco-regional therapy were identified from the departmental HCC database. Patient characteristics collected included age, gender, etiology, standard biochemistry, BCLC stage, performance status, tumour size and number, and treatments offered: Radiofrequency ablation (RFA) alone, RFA-TACE, TACE alone and TACE -RFA. The primary outcome measure was survival, calculated using the log-rank method.
Results: Out of 295 patients in our cohort, 96 patients were identified who had ablation (RFA (pre-2010) or microwave ablation (from 2010)), TACE, or a combination of the 2. The median age was 67 (57–74), the BCLC grade was 0 = 9 (9%), A = 42 (44%), B = 35 (36%), C = 9 (9%), D = 1 (1%). Disease etiology was Alcoholic Liver Disease (ALD) = 27, Hepatitis B = 4, Hepatitis C = 21, Non-Alcoholic Steatohepatitis = 27, Haemochromatosis = 5, ALD + viral = 5, others = 7. Hepatoma arterial-embolization prognostic (HAP) score was available in 85 patients; HAP A = 38, B = 24, C = 21, D = 2. A total of 143 TACE and 154 ablation procedures were performed. The median survival for ablation alone was 37 months (26–48), RFA-TACE was 38 months (33–43), TACE alone was 16 months (15–17) and TACE-RFA was 34 months (22–46), log rank 13.3, p = 0.004. Survival using HAP score was; HAP A = 8 months (24–52), HAP B = 35 months (20–50), HAP C = 12 months (7–17), HAP D = 2 months (1–3), log rank 68.1, p < 0.0001.
Conclusion: Our data suggests that patients who cannot be down-staged with TACE to receive ablation do worse than patients with earlier stage disease who progress after ablation alone or who receive TACE following an ablation. This supports the use of dual sequential therapy where indicated. The HAP score is a useful tool to identify patients most likely to benefit from loco-regional treatments.

THU-176

Clinical features and prognosis of advanced stage hepatocellular carcinoma; verification of diverse progression processes

M. Yokoyama[1], S. Ogasawara[1], Y. Ooka[1], M. Inoue[1], T. Chiba[1], E. Suzuki[1], T. Maeda[1], T. Wakamatsu[1], K. Kobayashi[1], S. Kiyono[1], M. Nakamura[1], T. Saito[1], S. Nakamoto[1], S. Yasui[1], A. Tawada[1], M. Arai[1], T. Kanda[1], H. Maruyama[1], S. Kuboki[2], M. Miyazaki[2], O. Yokosuka[1], M. Ohtsuka[2], N. Kato[1]. *[1]Chiba University, Graduate School of Medicine, Department of Gastroenterology, Chiba, Japan; [2]Chiba University, Graduate School of Medicine, Department of General Surgery, Chiba, Japan*
Email: sadahisa@me.com

Background and Aims: Some of the hepatocellular carcinoma (HCC) patients progress to advanced stage during their clinical course regardless of early detection. However, because of variations in the process of progression to advanced stage HCC, its diversity in terms of clinical features and prognosis remains controversial, especially in patients who have received several treatments during their clinical courses from initial diagnosis to advanced stage HCC. The purpose of this study was to inspect the clinical courses of HCC patients and identify variations in the clinical features and prognosis of advanced HCC.
Method: We retrieved whole clinical courses of newly diagnosed HCC patients between January 2003 and December 2015. Progression process from initial diagnosis from advanced stage HCC were identified and survival outcomes were assessed from the time of diagnosed as advanced stage HCC.
Results: Of 1,161 patients, 783, 237, and 141 patients were initially diagnosed with early, intermediate, and advanced stage HCC, respectively. During the follow-up period, 57 early stage patients (7.3%) progressed to the advanced stage through the intermediate

stage and 79 (10.1%) reached the advanced stage directly from the early stage. Similarly, 130 of 408 patients (31.9%) who were diagnosed as being in the intermediate stage progressed to the advanced stage. Cumulative 3-, 5-, and 10-year incidence rates of advanced stage from the early stage were 12.5%, 22.8%, and 44.8%, respectively. Likewise, cumulative incidence rates of patients progressing to the advanced stage of the disease from the intermediate stage were 45.7% (3-year), 57.6% (5-year), and 77.8% (10-year). Of 350 patients who were diagnosed as bring in the advanced stage of HCC, 20 patients (5.7%) had only extrahepatic metastasis (EHM) and no intrahepatic lesions (IHL). With regard to patients with IHL, macrovascular invasion (MVI) could not be detected in 109 patients (31.1%) with EHM. Of the remaining patients with MVI, 169 patients (48.0%) were not identified EHM, and 51 patients (14.6%) had EHM. There were significant differences in overall survival between the four variations of advanced stage HCC [EHM only (no IHL and no MVI): 20.3 months, IHL with MVI (no EHM): 10.5 months, IHL with EHM (no MVI): 9.7 months, and IHL with both MVI and EHM: 4.2 months] ($p < 0.001$).
Conclusion: We confirmed several variations in the disease progression of HCC to its advanced stage. Although this was not a common pattern, a few patients progressed to the advanced stage without IHL and those patients had a significantly better prognosis compared with other variations. These differences in prognosis seem to be helpful to not only understand the clinical course of HCC but also to design clinical trials for advanced HCC patients.

THU-177
Soluble urokinase plasminogen activator receptor (suPAR) represents a novel serum biomarker for patients undergoing resection of colorectal liver metastases

S. Loosen[1], F. Tacke[2], M. Binnebösel[2], C. Klink[2], T.F. Ulmer[2], C. Trautwein[2], C. Roderburg[2], U. Neumann[2], T. Lüdde[2]. [1]*University Hospital RWTH Aachen, Department of Internal Medicine III, Aachen, Germany;* [2]*University Hospital RWTH Aachen, Department of Surgery, Aachen, Germany*
Email: tluedde@ukaachen.de

Background and Aims: In colorectal cancer (CRC), the liver is the most common site of metastasis. Surgical resection represents the standard potentially curative therapy for patients with colorectal liver metastases (CRLM). However, 5-year survival rates after resection do not exceed 50%, and despite existing preoperative stratification algorithms it is still not fully understood which patients benefit most from surgery. The soluble urokinase plasminogen activator receptor (suPAR) has recently evolved as a promising biomarker for distinct clinical conditions. Here, we examined a potential role of circulating suPAR as a biomarker in patients undergoing resection of CRLM.
Method: Expression levels of uPAR, the membrane-bound source of circulating suPAR, were analysed in tissue samples of CRLM using RT-PCR and IHC. SuPAR serum levels were measured by ELISA in 104 patients undergoing surgical resection of CRLM as well as 50 healthy controls. Results were correlated with clinical data.
Results: In line with an upregulation of uPAR in the CRLM tissue, serum levels of suPAR were significantly elevated in patients with CRLM compared to healthy controls. Patients with preoperative suPAR serum levels above our defined ideal cut-off value of 4.83 ng/ml showed a strikingly reduced overall survival after resection of CRLM, which could be confirmed for right- and left-sided primary CRC. Importantly, none of these patients reached long-term survival compared to patients with preoperative suPAR serum concentrations below the cut-off value. Moreover, multivariate Cox-regression analysis revealed preoperative suPAR serum levels as an independent prognostic factor in this setting. Additionally, elevated preoperative suPAR but not creatinine levels were a predictor of acute kidney injury after CRLM resection, correlating with a longer postoperative hospitalization.

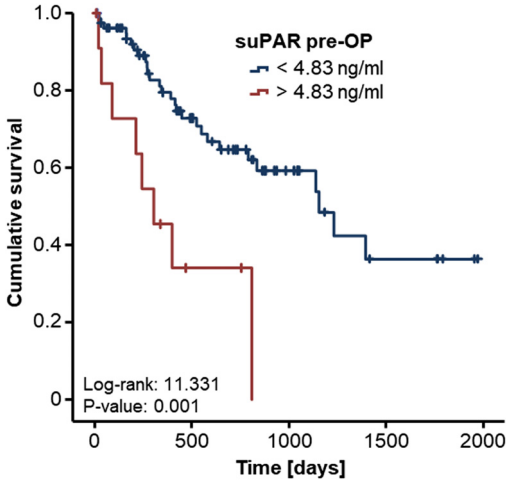


Figure 1: When applying the ideal cut-off value of 4.83 ng/ml, patients with initial suPAR serum above this cut-off show a strikingly reduced OS (median OS: 304 days) compared to patients with serum suPAR levels below this cut-off (median OS: 1154 days).

Conclusion: Serum levels of suPAR represent a promising novel biomarker in patients with resectable CRLM that might help to guide preoperative treatment decisions with regards to patients' outcome and the identification of patients particularly susceptible to post-operative acute kidney injury.

THU-178
Sarcopenia predicts survival in patients with advanced hepatocellular carcinoma treated with Sorafenib

G. Antonelli[1], E. Gigante[1], M. Iavarone[2], P. Begini[1], P. Biondetti[3], A.M. Pellicelli[4], A. Sangiovanni[2], P. Lampertico[5], M. Marignani[6]. [1]*Digestive and Liver Disease Unit, Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy;* [2]*Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy;* [3]*Radiology Unit, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Milan;* [4]*Liver Unit, San Camillo - Forlanini Hospital;* [5]*"A. M. and A. Migliavacca" Center for Liver Disease, Division of Gastroenterology and Hepatology, Università degli Studi di Milano;* [6]*Digestive and Liver Diseases Unit, Sapienza University of Rome, Roma, Italy*
Email: giulio.antonelli@gmail.com

Background and Aims: Sarcopenia, a condition characterized by muscle wasting and considered a parameter of malnutrition, has been associated with poor outcomes in patients with cirrhosis and solid tumors. We analyzed the influence of sarcopenia on the survival of patients with advanced hepatocellular carcinoma (HCC) treated with sorafenib, the standard of care for this stage.
Method: We conducted a multicenter, retrospective study on 96 patients with advanced HCC treated with sorafenib. Patients with an abdominal computed tomography (CT) scan within 30 days from treatment start were enrolled. Data on pre-treatment anthropometric features, baseline laboratory findings, toxicity, treatment duration and overall survival (OS) were collected. Transverse CT images corresponding to third lumbar vertebrae (L3) were collected to calculate the skeletal muscle index, defining the presence of sarcopenia.
Results: In our cohort, patients were mainly males (78%) and sarcopenia was present in 49% of patients, with a significant major prevalence in women (M 37, 3% vs F 90,5% p = 0,00001). Patients were divided into two groups according to sarcopenia and compared: age was significantly higher in the sarcopenic group [66 years (31–87) *vs* 72 years (30–84)], while all other baseline features were similar, without significant difference in albumin levels, INR, body max index, serum sodium, creatinine, bilirubin and MELD score. Patients with

sarcopenia showed a significantly shorter OS [39 (95% CI 26–50) *vs* 61 (95% CI 47–77) weeks (p = 0.02)], as well as time on treatment of sarcopenic patients [12,3 (95% CI 8–19) vs 25,9 (95% CI 15–33) weeks], while no significant differences in the cause of drug interruption were detected. At multivariate analysis, sarcopenia was found to be an independent predictor of reduced OS (p = 0.028), and of a reduced time on treatment (p = 0.0032).
Conclusion: Sarcopenia measured with CT-scan is present in nearly half of patients with advanced HCC, and it can be used as a predictor of mortality and worse response to sorafenib.

THU-179

The prognostic factors between different viral etiologies among advanced hepatocellular carcinoma patients receiving sorafenib treatment

M.-L. Yeh, J.-F. Huang, M.-L. Yu, C.-Y. Dai, C.-F. Huang, S.-C. Chen, W.-L. Chuang. *Kaohsiung Medical University Hospital, Hepatobiliary Division, Department of Internal Medicine, Kaohsiung, Taiwan*
Email: jf71218@gmail.com

Background and Aims: Sorafenib currently is the first-line therapy for advanced hepatocellular carcinoma (aHCC) patients. However, the outcomes and prognostic factors of sorafenib therapy have not been well investigated. We aimed to investigate the pre-treatment factors and outcomes among Taiwanese aHCC patients receiving sorafenib treatment.
Method: A total of 347 patients with aHCC and well-compensated liver cirrhosis (Child-Pugh A) status receiving sorafenib were consecutively enrolled from Mar 2013 through Dec 2016. Pre-treatment clinical data and viral hepatitis markers were collected and analyzed with their outcomes. The primary endpoint of the study was overall survival. The factors associated with overall survival were also investigated.
Results: The median overall survival of all the patients was 238 days (range, 9–1,504 days) with a one-year overall survival of 43.2%. Positive hepatitis B surface antigen, portal vein thrombosis, receiving other therapeutic strategies, and pre-treatment alpha fetoprotein level ≥ 3,500 ng/ml were independent factors associated with overall survival. The median duration of sorafenib therapy was 93.0 days (range, 4–1,504 days). In chronic hepatitis B patients, total bilirubin level was the only independent factor associated with overall survival, whereas HBV DNA level did not play a significant role in it. HCVRNA negativity, tumor size, portal vein thrombosis, and white blood cell count were the independent factors associated with survival among those chronic hepatitis C patients.
Conclusion: There were different prognostic factors stratified by viral etiologies in aHCC patients receiving sorafenib. Viral eradication increased survival in chronic hepatitis C patients.

THU-180

Analyses of intermediate stage hepatocellular carcinoma patients from the point of view of designing clinical trials comparing transarterial chemoembolization and systemic therapies

K. Koroki[1], S. Ogasawara[1], Y. Ooka[1], M. Inoue[1], T. Chiba[1], E. Suzuki[1], M. Yokoyama[1], T. Maeda[1], T. Wakamatsu[1], K. Kobayashi[1], S. Kiyono[1], M. Nakamura[1], T. Saito[1], S. Nakamoto[1], S. Yasui[1], A. Tawada[1], M. Arai[1], T. Kanda[1], H. Maruyama[1], S. Kuboki[2], M. Miyazaki[2], O. Yokosuka[1], M. Ohtsuka[2], N. Kato[1]. *[1]Chiba University, Graduate School of Medicine, Department of Gastroenterology, Chiba, Japan; [2]Chiba University, Graduate School of Medicine, Department of General Surgery, Chiba, Japan*
Email: sadahisa@me.com

Background and Aims: Intermediate stage hepatocellular carcinoma (HCC) patients, particularly those who have low tumor burden, are able to achieve durable tumor control by transarterial chemoembolization (TACE). On the other hand, high tumor burden patients have a high frequency of recurrence and progression to advanced stage HCC. Several promising compounds or combinations thereof, including immune oncology, have shown favorable results for HCC in early phase clinical trials. Specifically, upcoming novel systemic therapies may have the potential to replace TACE, in particular for high tumor burden intermediate stage HCC patients. The goal of the present study was to assess the outcomes of TACE from the viewpoint of designing clinical trials comparing TACE and systemic therapies.
Methods: We retrospectively retrieved whole clinical courses of HCC patients who were initially diagnosed and identified intermediate stage HCC with high tumor burden at Chiba University Hospital between January 2003 and December 2015. The outcomes of TACE of these patients were assessed according to three definitions.
Results: Of 1161 patients, 408 were diagnosed as having intermediate stage HCC during their clinical course. According to the three definitions, 143 and 265 patients (largest tumor diameter [cm] + number of tumors >7: out of up to 7 criteria), 257 and 151 patients (≥4 lesions of size ≥ 5 cm or ≥ 8 lesions), and 279 and 129 patients (≥8 lesions) were identified as having intermediate stage HCC with low and high tumor burden, respectively, at the time of their initial diagnosis as intermediate stage HCC. The fractions of patients (according to all three definitions) who progressed from low to high tumor burden stage in intermediate stage HCC were 25.9% (out of up to 7 criteria, 37 patients), 21.4% (≥4 lesions of size ≥5 cm or ≥8 lesions, 55 patients), and 21.9% (≥8 lesions, 61 patients), respectively. Overall survival of patients receiving TACE for high tumor burden intermediate stage HCC of Child–Pugh class A were 28.2 months (up to 7 out, 203 patients), 22.1 months (≥4 lesions of size ≥5 cm or ≥8 lesions, 143 patients), and 21.5 months (≥8 lesions, 132 patients), respectively. There were no significant differences between patients who progressed from low to high burden and diagnosed as high burden at the time of initial diagnosed as intermediate stage HCC.
Conclusions: Because our results indicated that outcomes of TACE in high tumor burden intermediate stage HCC were related to tumor status and not associated with previous clinical courses in intermediate stage HCC, identifying a suitable population for comparison might be significant when designing clinical trials of TACE versus systemic therapies.

THU-181

Impact of BCLC treatment stage migration in the survival of patients with hepatocellular carcinoma

S. Acosta-López[1], D.D. Bethencourt[1], J. Plata-Bello[2], E.B. Garrido[1], F.A.P. Hernández[1], A.G. Rodríguez. *[1]Hospital Universitario Nuestra Señora de la Candelaria, Liver Unit, Santa Cruz de Tenerife, Spain; [2]Hospital Universitario de Canarias, La Cuesta, Spain*
Email: sacostalopez9@gmail.com

Background and Aims: The Barcelona-Clinic Liver Center (BCLC) classification determines the best therapeutic option in each liver cancer stage. However, some clinical conditions may lead to a migration in the first-line treatment to other therapeutic option. This situation seems to be usual, but the impact of this treatment-migration has not been entirely studied. The aim of the present work is to analyze the causes and impact of treatment migration in each BCLC stages in terms of overall survival.
Method: A prospective registry of patients with a diagnosis of hepatocellular carcinoma have been performed since January 2011. One-hundred and thirty-eight patients were included in the study. The BCLC classification system was used to identify the first-line-treatment that corresponded for each stage. Treatment stage migrations were also identified and analyzed. Non-parametric tests were used to identify differences between first-line vs. migration treatment groups in each BCLC stage. Survival analysis in each BCLC stage was performed. Statistical significance was considered when p-value was below 0.05.

Results: Thirty-three percent of patients had a treatment stage migration (43.5% of patients in BCLC A; 18.9% in BCLC B; and 50% in BCLC C).
Regarding BCLC A patients, migration-treatment patients were significantly older than the patients who receive the first-line-treatment (p < 0.001). OS was significantly higher in the last group (median survival of 90.0 months vs. 24.3 months) (p < 0.001). Hazard ratio (HR) for migration-treatment group (adjusted by age) in BCLC A patients was 3.11 (95% C.I. of 1.2–7.7) (p = 0.015).
Bearing in mind BCLC B patients, migration-treatment group presented a higher number of lesions than first-line-treatment group (p = 0.01). The OS was also significantly higher in the first-line-treatment patients (median survival of 31.8 vs. 7.9 months) (p = 0.003). HR for migration-treatment was 4.9 (95% C.I. of 1.3–17.8).
Finally, BCLC C patients showed a different distribution of CHILD categories between the treatment groups. All patients in the first-line treatment group of BCLC C patients were classified as CHILD A, while only 33% of migration-treatment presented such categorization. No differences in OS were identified between both treatment groups (p = 0.225).

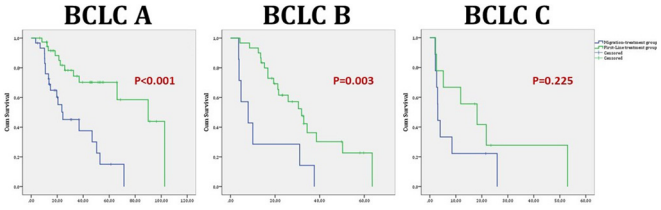


Figure 1: Kaplan-Meier survival analysis for both treatment groups in each BCLC stages where migration stage treatment was present.

Conclusion: BCLC A and BCLC B hepatocellular carcinoma patients with a treatment stage migration present a significant worse prognosis than patients with first-line-treatment options.

THU-182
ALBI is an independent predictor ofsurvival in resected patients with HCC

P. Kolly[1,2], L. von Köckritz[2], V. Isabelle[1], B. Vanessa[2], J.-F. Dufour[1,2].
[1]Hepatology, Department for BioMedical Research, University of Bern, Bern, Switzerland; [2]University Clinic for Visceral Surgery and Medicine, Inselspital, Switzerland
Email: philippe.kolly@students.unibe.ch

Background and Aims: Hepatic functional reserve is assessed by the Child-Pugh score which is a predictive factor for survival in HCC patients. In those undergoing surgical resection, the Child-Pugh score is of low significance, since most of those patients are Child-Pugh grade A. Furthermore, Child-Pugh score should not be used in non-cirrhotic patients, who mostly undergo surgical resection. We investigated whether the Albumin-Bilirubin (ALBI) score which is based on bilirubin and albumin is predictive of survival after HCC resection.
Method: Patients of the prospective Bern HCC Cohort at the University Hospital Bern, Switzerland were analyzed. The ALBI score and grade (A1-A3) was calculated for every patient. The association between overall survival (OS) and the ALBI score was assessed and multivariate Cox regressions were used to control for confounding variables. The Log-Rank statistic was used to assess the difference in survival of the ALBI grade. Additionally, the ability to predict OS was compared between the ALBI score and the total bilirubin using Nagelkerke's pseudo R2.
Results: Of 375 eligible HCC patients, 62 underwent a surgical resection. Mean ALBI score was –2.32, SD 0.56. Univariate cox regression analysis showed that the ALBI score was strongly associated with the overall survival (HR: 5.476, 95% CI: 2.137–14.031, p < 0.001). The different ALBI grades showed significant difference in their survival (p < 0.001) with a mean OS of 2309 (95% CI: 1788–2823), 1345 (95% CI: 1127–1563) and 505 (95% CI: 486–524) days for A1, A2, A3, respectively. Furthermore, the ALBI score remained independently predictive when controlling for age, sex, tumor size, number of nodules, AFP and comorbidities (alcohol consumption and diabetes). Nagelkerke's pseudo R2 was 0.49 for ALBI score and 0.28 for bilirubin.
Conclusion: The ALBI score is an independent predictor of survival in resected HCC patients. The ALBI score predicts 49% of the variance and bilirubin only 28%. Therefore, the ALBI score is a better predictor of OS than bilirubin. The different ALBI grades show significantly different mean OS and could be used in treatment allocation algorithms for surgical resection of HCC patients.

THU-183
Portal vein tumor thrombosis has a direct impact on liver function

R. Kloeckner, A. Maehringer-Kunz, D.P. Dos Santos, S. Schotten, D. Graafen, F. Meyer, S. Koch, C. Düber, P. Galle, A. Weinmann. *Medical Center of the Johannes Gutenberg University, Department of Diagnostic and Interventional Radiology, Mainz, Germany*
Email: roman.kloeckner@gmail.com

Background and Aims: Portal vein tumor thrombosis (PVTT) has a significant impact on the prognosis of patients with hepatocellular carcinoma (HCC). However, the mechanisms leading to shorter survival of such patients are still unknown. According to our clinical experience, the liver function deteriorates in such patients, considerably limiting treatment options. Aim of this study was to quantify liver function impairment due to newly diagnosed PVTT.
Method: A total of 1478 patients with proven HCC were treated in our tertiary referral center between 01/2005 and 01/2017. As we aimed for an intraindividual comparison to minimize confounding factors, we only included patients with a newly diagnosed PVTT during the observation period. Inclusion criteria were: proven HCC; PVTT-negative CT or MRI followed by at least one PVTT-positive CT or MRI; availability of all laboratory values needed to calculate Model for End-Stage Liver Disease (MELD)-, and Albumin-Bilirubin (ALBI)-score. Albumin, AST, bilirubin, MELD-, and ALBI-score were calculated before and after the diagnosis of PVTT. PVTT was diagnosed in consensus by re-evaluation of all available CT- or MRI-studies by two board certified radiologists experienced in abdominal oncologic imaging.
Results: In total, 134 patients developed a new PVTT during the observation period. Between the last PVTT-negative imaging and the first PVTT-positive imaging, AST increased from 74.8 to 95.4 U/l (p = 0.005), bilirubin from 1.53 to 2.04 mg/dl (p = 0.004), MELD from 10.4 to 11.3 points (p = 0.006), and ALBI from 2.0 to 2.2 points (p = 0.026). Albumin decreased from 32.8 to 30.4 g/l (p = 0.002).
Conclusion: New PVTT is associated with a significant impairment of liver function, considerably limiting treatment options. Therefore, meticulous evaluation of cross-sectional imaging is crucial for the clinical management of patients with HCC.

THU-184
A novel model for the outcome prediction of transarterial chemoembolization in patients with unresectable hepatocellular carcinoma with or without impaired hepatic function

H.Y. Kim[1], A.R. Choi[1], H.A. Lee[2], T.H. Kim[1], K. Yoo[1], M. Kim[3], S.Y. Choi[3].
[1]Ewha Womans University College of Medicine, Department of Internal Medicine, Seoul, Republic of South Korea; [2]Ewha Womans University Mokdong Hospital, Clinical Trial Center, Seoul, Republic of South Korea; [3]Ewha Womans University College of Medicine, Department of Radiology, Seoul, Republic of South Korea
Email: hwiyoung@gmail.com

Background and Aims: There are several prognostic systems for the assessment of patient suitability of transarterial chemoembolization (TACE) for unresectable hepatocellular carcinoma (HCC). However,

the decision of first TACE still remains challenging, especially in those with impaired hepatic function. The aims were (i) to identify prognosticators in patients undergoing TACE, (ii) to develop a prognostic scoring system, and (iii) to investigate the outcomes according to the scores in patients with/without impaired hepatic functional reserve.

Method: Between January 2006 and December 2015, a total of 240 consecutive HCC patients with baseline Child-Pugh score ≤ 8 were enrolled, who underwent TACE as an initial treatment for unresectable tumors without macrovascular invasion or extrahepatic spread. Tumor- and liver function-related risk factors for overall survival were explored using Cox model.

Results: Median age was 68.5 years, and 186 patients were male (77.5%). Etiologies of underlying liver diseases were mostly viral (n = 165, 68.8%) or alcoholic (n = 30, 12.5%). Multiple tumors were found in 120 patients (50.0%), and median maximal tumor diameter was 3.0 cm (interquartile range [IQR], 1.7–5.5). Median alpha-fetoprotein (AFP) was 19.5 ng/ml (IQR, 6.0–252.0). Child-Pugh classes were A in 194 patients (80.8%) and B in 46(19.2%), respectively. Median neutrophil-to-lymphocyte ratio (NLR) was 1.92(IQR, 1.34–3.12). Median AST and ALT were 43.5 IU/l (IQR, 32.0–64.0), and 33.0 IU/l (23.0–51.0), respectively. Hepatoma arterial-embolisation prognostic (HAP) score D and modified HAP score D were in 99 patients (41.3%) and in 49(20.4%), respectively. Albumin-bilirubin (ALBI) grades were 1 in 59 patients (24.6%), 2 in 162(67.5%) and 3 in 19(7.9%), respectively. Multivariable Cox model identified the following prognostic factors: number of tumors (hazards ratio [HR], 1.484; $p = 0.001$); ALBI grade (HR, 1.696; $p = 0.002$); Log AST (HR, 1.914; $p < 0.001$); Log NLR (HR, 1.675; $p < 0.001$); Log AFP (HR, 1.104; $p = 0.038$). A scoring system (A3N2) was developed by assigning points as shown in Table 1. C-index for the prediction of overall survival (OS) was 0.75 (95% confidence interval, 0.70–0.78, by bootstrapping [n = 100]). For all patients, median OS were 45 mo with A3N2 < 3 vs. 13 mo with A3N2 ≥ 3, respectively ($p < 0.001$). For Child-Pugh class B patients, median OS were 36 mo with A3N2 < 3 vs. 9 mo with A3N2 ≥ 3, respectively ($p = 0.030$). However, no significant differences in OS were observed in Child-Pugh class B patients using HAP score ($p = 0.709$) or modified HAP score ($p = 0.745$).

Table 1: A3N2 scoring system

	SCORE			
	0	1	2	3
ALBI grade	0	1		2
AST (IU/l)	<80	≥80		
AFP (ng/ml)	<200	≥200		
Number of tumors	1	2–3	>3	
NLR	<2	≥2		

Conclusion: A novel scoring system (A3N2) may be helpful in treatment selection in patient with unresectable HCC undergoing TACE, especially those with impaired hepatic function.

THU-185

Randomized trial of preoperative administration of oral pregabalin for postoperative analgesia in patients scheduled for radiofrequency ablation of focal lesions in the liver

S. Abd-Elsalam[1], A.S. Hanafy[2]. [1]*Tanta University, Tropical Medicine Department, Tanta, Egypt;* [2]*Zagazig University, Internal Medicine Department*
Email: sheriefabdelsalam@yahoo.com

Background and Aims: The aim of this study was to evaluate the effect of preoperative pregabalin on postoperative analgesia in patients presented for radiofrequency ablation of hepatic focal lesions.

Method: This randomized controlled study was carried out on 70 adult patients with hepatocellular carcinoma presented to Tanta University Hospital for radiofrequency ablation of hepatic focal lesions. They were randomized into two groups, 35 patients in each group: Group I: Patients in this group received placebo and Group II: patients in this group received 150 mg of oral pregabalin one hour before the procedure. The primary outcome was the analgesic effect in the form of the severity of postoperative pain and the need of opioid analgesics. Our secondary outcome was the safety of the drug in the form of incidence of side effects.

Results: Regarding pain assessed by visual analogue pain scale (VAS Pain) post operatively, there were no significant differences between both groups immediately postoperative ($p = 0.84$), then a highly significant difference in pain ($p = 0.00$) between two groups had been noticed as pregabalin showed high efficacy in decreasing pain in group II compared to group I, also patients received pregabalin had decreased requirements for the use of post operative analgesics. Regarding side effects, there was no significant difference regarding blood pressure ($p = 0.74$) nor oxygen saturation ($p = 0.53$) between the two studied groups, on the other hand patients in pregabalin group showed fewer side effects as nausea, vomiting ($p = 0.01$) and bradycardia ($p = 0.02$) and were discharged earlier when compared with the other group ($p = 0.01$).

Conclusion: Oral pregabalin is safe and effective for postoperative analgesia in patients scheduled for radiofrequency ablation of focal lesions in liver.

[ClinicalTrials.gov Identifier: NCT03151213]

Keywords: Pregabalin, Analgesia, Liver cancer, HCC, Radiofrequency Ablation.

THU-186

Comparison of efficacy between sorafenib monotherapy vs. transarterial chemoembolization – sorafenib sequential therapy in hepatocellular carcinoma patients with extrahepatic metastatis – An interim analysis of randomized controlled trial

H.J. Yim[1], S.J. Suh[1], Y.K. Jung[1], S.B. Cho[2], W.J. Chung[3], Y.S. Kim[4], S.H. Bae[5], J.Y. Park[6]. [1]*Korea University College of Medicine, Internal Medicine;* [2]*Chonnam National University Medical School, Internal Medicine;* [3]*Keimyung University College of Medicine, Internal Medicine;* [4]*Soonchunghyang University College of Medicine, Internal Medicine;* [5]*College of Medicine, The Catholic University of Korea, Internal Medicine;* [6]*Yonsei University College of Medicine, Internal Medicine*
Email: gudwns21@korea.ac.kr

Background and Aims: Sorafenib is the standard therapy for hepatocellular carcinoma (HCC) with extrahepatic metastasis (EHM). However, transarterial chemothembolization (TACE) which is a standard therapy for intermediate stage may be beneficial for controlling intrahepatic tumour, thereby providing chance of improving survival in HCC patients with EHM.

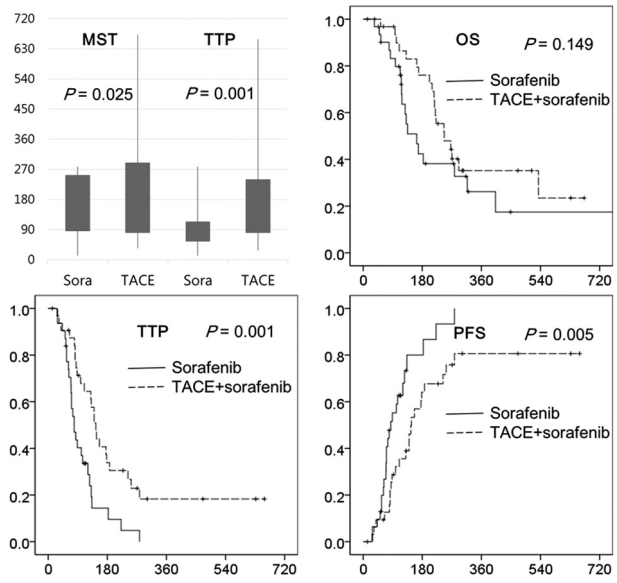
We aimed to compare the efficacy between the sorafenib monotherapy and TACE-sorafenib sequential therapy in HCC patients with EHM.

Method: This study is a prospective randomized controlled study conducted at 6 tertiary hospitals in South Korea. HCC patients with EHM were enrolled and randomized into sorafenib monotherapy or TACE-sorafenib sequential therapy group. Patients with main portal vein invasion, Child-Pugh class B or C, and history of TACE or previous systemic therapy were excluded. The sorafenib monotherapy group received sorafenib immediately after randomization while the TACE-sorafenib group received 2–4 times of TACE before starting sorafenib. Response evaluation was performed every 2 months, and time to progression (TTP), progression free survival (PFS), median survival time (MST), and overall survival (OS) were compared. We initially planned 130 patients for the present study, and the results of interim analysis are presented.

Results: A total of 64 patients were enrolled currently: 32 patients into the monotherapy and 32 into the sequential therapy group. Baseline characteristics of the patients such as gender, age, aetiology of liver disease, Child-Pugh score, HCC stage, and tumour burden were not significantly different between the groups. Median TTPs

were 77 days in the monotherapy group and 140 days in the sequential therapy group (p = 0.001). In addition, MST was longer in the sequential therapy group (117 vs. 225 days, respectively, p = 0.025).

The probability of survival rates were plotted by Kaplan-Meier curve and compared by log-rank test. The OS was not different in both groups (p = 0.149). However, the TTP rates were longer in sequential therapy group than monotherapy group (p = 0.001), and the PFS rates were also better in the sequential therapy group (p = 0.005).



Conclusion: The TACE-sorafenib sequential therapy would be a better strategy than sorafenib monotherapy for the treatment of HCC patients with EHM, especially, in controlling tumour progression.

THU-187

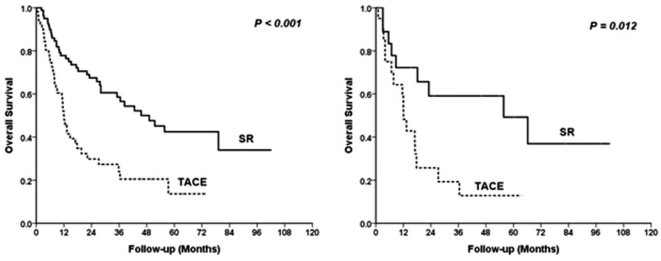
A comparison of surgical resection and transarterial chemoembolization for solitary hepatocellular carcinoma larger than 10 cm: A propensity score matching analysis

H.-S. Lu[1], C.-W. Su[1,2], W.-Y. Kao[2,3], T.-I. Huo[1,4], Y.-H. Huang[1,2,5], M.-C. Hou[1,2], H.-C. Lin[1,2], J.-C. Wu[5,6]. *[1]Taipei Veterans General Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [2]National Yang-Ming University, Faculty of Medicine, School of Medcine, Taipei, Taiwan; [3]Taipei Medical University Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [4]National Yang-Ming University, Institute of Pharmacology, Taipei, Taiwan; [5]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan; [6]Taipei Veterans General Hospital, Department of Medical Research, Taipei, Taiwan*
Email: cwsu2@vghtpe.gov.tw

Background and Aims: The optimal staging (early vs. intermediate) and treatment for patients with single large hepatocellular carcinoma (HCC) is not fully elucidated. We aimed to compare the treatment efficacy and prognosis between surgical resection (SR) and transarterial chemoembolization (TACE) for patients with solitary huge HCC.

Method: We retrospectively enrolled 135 patients with treatment-naïve solitary HCC ≥ 10 cm in size, with good performance status and liver functional reserve, and without vascular invasion or extra-hepatic metastasis from 2007 to 2013. Baseline characteristics were collected to identify the risk factors determining poor overall survival (OS) after therapy by multivariate Cox proportional hazards models. Moreover, to minimize the potential selection bias between SR and TACE, we further performed a propensity score matching analysis by one-to-one nearest-neighbor matching method.

Results: A total of 84 patients and 51 patients underwent SR and TACE, respectively. The SR group were younger, higher hemoglobin level, higher serum albumin, higher BUN, and lower glucose level than the TACE group. After a median follow-up of 17.0 (interquartile range 7.3–36.9) months, 75 patients had died. The cumulative 1, 3, and 5-year OS rate were 93.7%, 73.6%, 52.2% for the SR group and 76.5%, 34.8%, 13.7% for the TACE group, respectively (p < 0.001, Figure A). A multivariate analysis showed that TACE (Hazard ratio, HR 2.764, 95% confidence interval, CI 1.707–4.475, p < 0.001), serum AFP levels > 400 ng/ml (HR 2.065, 95% CI 1.283–3.322, p = 0.003) and albumin-bilirubin grade > 1 (HR 1.688, 95% CI 1.033–2.759, p = 0.036) were the independent risk factors associated with poorer OS. After propensity score matching analysis to adjust for baseline differences, 20 pairs of matched patients were selected from each treatment arm. Patients who underwent SR still had a significantly better survival than patients who underwent TACE (p = 0.012, Figure B).



Conclusion: SR provided a better long-term survival than TACE for patients with solitary huge (≥10 cm) HCC. SR is recommended as the therapeutic priority for these patients.

THU-188

Phase II trial using combination of TACE and SBRT for unresectable single large HCC: preliminary report

M. Buckstein[1], E. Kim[2], A. Fischman[2], M. Facciuto[3], M. Sung[4], B. Taouli[2], J. Llovet[5], M. Schwartz[5], K. Rosenzweig[1]. *[1]Icahn School of Medicine at Mount Sinai, Radiation Oncology, New York, United States; [2]Icahn School of Medicine at Mount Sinai, Radiology, New York, United States; [3]Icahn School of Medicine at Mount Sinai, Surgery, New York, United States; [4]Icahn School of Medicine at Mount Sinai, Medicine, New York, United States; [5]Icahn School of Medicine at Mount Sinai, Liver Medicine, New York, United States*
Email: michael.buckstein@mountsinai.org

Background and Aims: Patients with hepatocellular carcinoma (HCC) stage A not suitable for surgical therapies are first considered for local ablation. Nonetheless, objective responses and long-term results for ablation in large tumors (i.e. those >3 cm) are suboptimal. This pilot phase II trial studies combination transarterial chemoembolization (TACE) and Stereotactic Body Radiation Therapy (SBRT) for BCLC A patients with HCC from 4 to 7 cm.

Method: Patients were eligible if they were BCLC A, Child-Pugh score ≤7, had a single HCC from 4 to 7 cm, no evidence of macrovascular invasion, no evidence of metastatic disease, ECOG 0, and were not suitable for resection or liver transplantation. Treatment consisted of drug-eluting bead (DEB)-TACE at time 0 and 1 month followed by SBRT completed within 2–3 weeks following TACE. Each DEB-TACE treatment utilized 1 vial of 100–300 micron LC Beads (BTG) loaded with 50 mg of doxorubicin. SBRT was delivered from 35 to 50 Gy in 5 fractions. The primary end-point of the study was best objective response by mRECIST (measured 1 month post-treatment and every 3 months thereafter). Secondary endpoints were progression free survival (PFS), cancer specific survival (CSS), overall survival (OS) assessed using the Kaplan-Meier method.

Results: From 2014 to 2017, 20 patients were enrolled in a single institution with a median follow of 13 months (range 1–30). Baseline patient characteristics are shown in Table 1. Every patient completed

the protocol as planned except one who only received DEB-TACEx1 before SBRT. 19 patients had at least one post treatment scan to assess mRECIST response (one patient lost to follow up). Best objective response in the target lesion was 95%: 74% complete response (n = 14), 21% partial response (n = 4), 0%stable disease, and 5% progression of disease (n = 1). PFS at 1 year was 66%, CSS at 1 year was 88%, and OS at 1 year was 69%.

Baseline characteristic	N (% or range)
Median age (yrs)	68 (52–88)
Child-Turcott-Pugh Score	
A	18 (90)
B	2 (10)
Etiology	
HCV	13 (65)
HBV	1 (5)
Other (NASH, alcohol, unknown)	7 (35)
Median tumor size (cm)	4.6 (4–6.9)
Median baseline AFP (ng/mL)	18 (2–1923)
Median SBRT dose (Gy)	45 (35–50)

Conclusion: Preliminary results from this Phase II trial show very promising response rates when combining TACE + SBRT in large, unresectable HCC with excellent PFS and CSS at one year. These preliminary data are currently being confirmed in an expanded cohort.

THU-189

Real life experience with selective internal radiation therapy (SIRT) as part of multimodality treatment of advanced hepatocellular carcinoma (HCC)

F. van Boemmel[1], M. Asmus[1], T.-O. Petersen[2], T. Kahn[2], T. Lincke[3], S. Purz[3], S. Osama[3], D. Forstmeyer[4], F. Lordick[4], C. Domaratius[5], F. Gerhardt[5], D. Seehofer[6], R. Sucher[6], T. Berg[5]. *[1]University Hospital Leipzig, Section of Hepatology, Department of Gastroenterology, Leipzig, Germany; [2]University Hospital Leipzig, Klinik für Diagnostische und Interventionelle Radiologie, Germany; [3]University Hospital Leipzig, Klinik und Poliklinik für Nuklearmedizin, Germany; [4]University Hospital Leipzig, Onkologisches Zentrum am Universitären Krebszentrum, Leipzig, Germany; [5]University Hospital Leipzig, Section of Hepatology, Department of Gastroenterology, Germany; [6]University Hospital Leipzig, Hepatobiliäre Chirurgie und viszerale Transplantation, Germany*
Email: florian.vanboemmel@medizin.uni-leipzig.de

Background and Aims: Radioembolization by Yttrium-90 Selective Internal Radiotherapy (^{90}Y SIRT) has is associated with a similar survival as the multikinase inhibitor sorafenib in the treatment of patients with intermediate- to advanced-stage hepatocellular carcinoma (HCC). However, the role of SIRT in the multimodal treatment for HCC is not well defined. We have retrospectively assessed the efficacy and safety of SIRT in patients with advanced HCC receiving different sequential interventional or systemic treatments.
Method: 109 patients (87 male, mean age 64 ± 0.9 (range, 36–85) years, 73 with liver cirrhosis Child-Pugh A (n = 60), B (n = 12) or C (n = 1)) with advanced HCC who had received SIRT (1, 2 and 3 applications in 89, 19 and 1 patient; mean dose, 3,365 ± 1,902 GBq, 90Y glass microspheres) in terms of a multimodal HCC treatment approach between 2012 and 2016 in one center were retrospectively analysed. Before SIRT, BCLC scores A1, A2, A4, B and C applied to 2, 6, 5, 67 and 25, ECOG scores 0–3 in 56, 27, 8 and 1, ALBI scores 1–3 in 55, 47 and 5 and CLIP scores 1 to 3 in 12, 74 and 11 patients, respectively. HCC was present in the left, right or in both liver lobes in 12, 40, and in 52 patients. Before or after SIRT, transarterial chemoembolization was performed in 44 and 19 patients, and sorafenib treatment in 25 and 24 patients, respectively. Three patients received liver transplantation after SIRT.
Results: The mean overall survival (OS) after first diagnosis of HCC was 21 ± 1.5 (range, 2–78) months, as compared to 19 months estimated by CLIP score, and 12 patients survived longer than 36 months. After first SIRT the mean OS was 10 ± 0.96 (range, 0–54) months, and 45 patients (49%) showed radiological response. The mean time to progression after SIRT was 5.9 ± 0.7 (range, 0–54) months. Risk factors for shorter OS were liver adverse events (increase in ALT >5 times over baseline or worsening in Child-Pugh score) (p = 0.002) and an ALBI score of 3 at baseline (p = 0.004). Liver toxicity was diagnosed in 6 patients (7%), and associated with elevated gGT (p = 0.027) or ALT (p= 0.023) before, and an ALBI score of 3 after SIRT (p = 0.032).
Conclusion: SIRT as part of a multimodal treatment approach was safe and associated with a promising OS when compared to predicted survival by the CLIP score. Further studies may identify patients who benefit from SIRT and should investigate the potential of concomitant and sequential interventional and novel systemic treatment approaches.

THU-190

Ubr Ubiquitin ligases as modulators of inflammation in hepatocellular carcinoma

D. Leboeuf[1], M. Nesterchuk[1], E. Smekalova[2], A. Mikaelyan[1], D. Anderson[2], T. Zatsepin[1], K. Piatkov[1]. *[1]Skoltech, Translational Biomedicine, Moscow, Russian Federation; [2]MIT, Koch Institute for Integrative Cancer Research, Cambridge, United States*
Email: dominique.leboeuf@skoltech.ru

Background and Aims: The N-end rule pathway is an emerging player in the field of cancer biology, because of its capacity to positively regulate many hallmarks of cancer including angiogenesis, cell proliferation, motility and survival, offering the potential to be a target for an effective anti-tumor treatment. Hepatocellular Carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer-related deaths in the world. HCC is an aggressive cancer resistant to all conventional chemotherapies, highlighting the need to look for new therapeutic options. Therefore, the aim of this study is to investigate the role of the N-end rule pathway in the context of hepatocellular carcinoma in vivo, using an siRNA-mediated RNA interference approach for selective down-regulation of the four N-end rule-dependent ubiquitin ligases: UBR1, UBR2, UBR4 and UBR5.
Method: Downregulation of Ubrs was achieved using siRNA formulated into lipid nanoparticles (LNP). *In vitro* phenotyping was performed using proliferation assays, migration assays, and TUNEL assays. Then, LNPs were injected into mice for toxicity and efficacy studies. Blood biochemistry analysis, histology, flow cytometry, qPCR and Western Blot were used to assess toxicity and efficacy.
Results: We obtained successful downregulation of Ubrs *in vitro* and demonstrated that knock down of these four Ubr proteins negatively affects cell migration and proliferation, and renders cells more susceptible to apoptosis. Bi-weekly injections of the LNPs in mice for a period of up to 6 weeks efficiently downregulates the expression of *Ubrs* without any significant toxic effects. However, we observed a significant increase in the spleen/body weight ratio in mice treated with Ubr-LNPs, as well as an infiltration of neutrophils in the livers of these same mice. Treatment of HCC bearing mice with Ubr-LNPs worsened the tumor load due to the increased inflammation in the liver.
Conclusion: Downregulation of Ubrs leads to impaired proliferation, migration, and an increased susceptibility to apoptosis, in vitro. However, long-term downregulation of these same proteins in the liver recruits the immune system and induces inflammation. In the context of liver cancer, this leads to an increased tumor load. Using a combination of Ubr-LNPs at lower doses with chemotherapeutic drugs could harness the potential to increase apoptosis susceptibility in cancerous cells while reducing doses of chemotherapeutic drugs and their subsequent side effects.

Autoimmune and chronic cholestatic liver disease: Clinical aspects

THU-191

Extrahepatic autoimmune diseases in patients with autoimmune hepatitis and their relatives: a Danish nationwide family cohort study

L. Grønbæk[1], H. Vilstrup[2], L. Pedersen[3], P. Jepsen[3]. *[1]Aarhus University Hospital, Clinical Epidemiology, Aarhus, Denmark; [2]Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark; [3]Aarhus University Hospital, Department of Clinical Epidemiology, Aarhus, Denmark*
Email: groenbaek.lisbet@gmail.com

Background and Aims: It is widely accepted that patients with autoimmune hepatitis (AIH) have an increased prevalence of extrahepatic autoimmune diseases, and it is widely believed that their relatives share this trait, but it has not been epidemiologically studied in a satisfactory setting. We therefore conducted a nationwide registry-based family cohort study on this issue.
Method: From the Danish healthcare registries for 1994–2015 we included 2,745 patients with AIH, 17,812 of their first- and second-degree relatives, and 27,450 general population controls age- and gender-matched to the patients. We compared the gender- and -age-specific prevalence of extrahepatic autoimmune diseases between the patients with AIH, their first- and second-degree relatives, and the controls. We computed the prevalence ratio of extrahepatic autoimmune diseases relative to the controls.
Results: In the patients with AIH, the prevalence ratio of extrahepatic autoimmune diseases ranged from 7 to 10 up to age 30 years (prevalence ratio at age 20 = 9.92, 95% confidence interval 6.21–15.83), after which it declined to about 2 in old age (prevalence ratio at age 80 = 2.37, 95% confidence interval 1.89–3.00). In the patients' families, neither first- nor second-degree relatives had an increased prevalence of extrahepatic autoimmune diseases (prevalence ratio for first- and second-degree relatives at age 20 = 1.11, 95% confidence interval 0.72–1.70; and prevalence ratio at age 80 = 0.96, 95% confidence interval 0.70–1.31).
Conclusion: These population-based findings confirm that patients with AIH are highly prone to extrahepatic autoimmune diseases, but their relatives are not. Our data do not support the notion that patients with AIH and their family members share a general autoimmune predisposition.

THU-192

Pregnancy and birth outcomes in a Danish nationwide cohort of women with autoimmune hepatitis and matched population controls

L. Grønbæk[1,2], H. Vilstrup[2], P. Jepsen[1,2]. *[1]Aarhus University Hospital, Department of Clinical Epidemiology, Aarhus N, Denmark; [2]Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus C, Denmark*
Email: groenbaek.lisbet@gmail.com

Background and Aims: Many patients with autoimmune hepatitis (AIH) are women of fertile age. Some major concerns for these patients are related to pregnancy. We conducted a nationwide study on risk of miscarriage, birth rate, and birth outcomes in women with AIH.
Method: We collected data from Danish healthcare registries for 1994–2015. We included 1,947 women with AIH and 19,470 age- and gender-matched population controls. We calculated the risk of miscarriage and the birth rate in premenopausal women with AIH and controls. We used logistic regression to compare the odds of adverse birth outcomes (preterm birth, small for gestational age, congenital malformations, and stillbirth) between women with AIH and controls. We adjusted for mother's age and smoking habits, and we conducted separate analyses for AIH patients on vs. off immunosuppressive treatment and with vs. without cirrhosis.
Results: The risk of miscarriage was similar in women with AIH and controls: risk ratio 1.16 (95% confidence interval [CI] 0.80–1.69). At first-time birth, the age was similar in women with AIH and controls. The first-time birth rate per 1000 person-years in women with AIH was 37 (95% CI 29–46), in controls 32 (95% CI 30–35). In women with AIH there were 176 births, 70 of which were first-time births. The women with AIH had an increased risk of preterm birth (adjusted odds ratio 3.29, 95% CI 1.62–6.67) and small for gestational age children (adjusted odds ratio 4.65, 95% CI 0.83–26.04) but not of other adverse birth outcomes. Birth outcomes were similar in AIH patients on vs. off immunosuppression and with vs. without cirrhosis.
Conclusion: In this Danish cohort of women with AIH, fertility was unaffected. The women with AIH had an increased risk of preterm birth and small for gestational age children but not of other adverse birth outcomes.

THU-193

Autoantibodies against Huntingtin-interacting protein 1-related protein are superior to conventional autoantibodies in diagnosing autoimmune hepatitis in children

R. Taubert[1], J. Diestelhorst[2,3], N. Junge[2], N.T. Baerlecken[4], M. Yüksel[5], M. Hussain[5], Y. Ma[5], M.P. Manns[1], T. Witte[4], U. Baumann[2], E. Jaeckel[3]. *[1]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [2]Hannover Medical School, Pediatric Gastroenterology and Hepatology, Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover, Germany; [3]Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [4]Hannover Medical School, Clinical Immunology, Hannover, Germany; [5]King's College London, Liver Sciences; Faculty of Life Sciences & Medicine, School of Immunology and Microbial Sciences, London, United Kingdom*
Email: taubert.richard@mh-hannover.de

Background and Aims: Autoantibodies are key parameters in the diagnostic of paediatric autoimmune hepatitis (pAIH) among those with chronic liver diseases. However, conventional autoantibodies such as anti-nuclear (ANA), anti-smooth muscle (SMA), anti-liver kidney microsomal antibodies (LKM) and antibodies against soluble liver antigen (SLA) either lack high sensitivity or high specificity. We screened for alternative autoantibodies with a better clinical performance.
Method: Antibodies against Huntingtin-interacting protein 1-related protein (HIP1R) were identified via a protein macroarray in adult patients with AIH. Next, antibodies against a HIP1R fragment, measured with an ELISA, were compared to conventional autoantibodies in two independent retrospective cohorts from two center both including children with untreated AIH (total number: 67), other chronic liver disease (total number: 69) or without liver diseases (total number: 35).
Results: Children with untreated pAIH (type I and II) had the highest IgG antibody concentrations against HIP1R compared to AIH overlap syndromes, non-AIH liver diseases and children without liver diseases ($p < 0.001$ for all comparisons).
With the receiver operating characteristic the optimal cut-off for the distinction between untreated pAIH and other liver diseases was identified (43.3 arbitrary units), which is lower than in adults (52.7 arbitrary units). For the identification of untreated pAIH anti-HIP1R antibodies with this cut-off (AUC: 0.95 (confidence interval: 0.90–0.99); OR: 87.7; 21.3–362.4) achieved a significantly higher sensitivity (0.94; 0.82–0.98) and negative predictive value (0.93; 0.80–0.98) with the highest overall accuracy (0.90; 0.80–0.98) compared to ANA (0.81; 0.72–0.88), SMA (0.72; 0.62–0.80), LKM (0.51; 0.41–0.61) and SLA (0.48; 0.37–0.59) antibodies in the training cohort from Hannover/Germany (n = 96). The specificity (0.85; 0.72–0.94) and positive predictive value (0.87; 0.74–0.94) from anti-HIP1R

antibodies were not significantly different from ANA and SMA in this cohort.
In the external validation cohort from London/UK (n = 40) untreated pAIH had a bit lower anti-HIP1R antibody concentrations but still achieved the highest OR (34.3; 3.8–313.8) and overall accuracy (0.80; 0.64–0.90) compared to ANA and SMA. Due to the smaller sample number in the validation cohort only the specificity of anti-HIP1R (0.95; 0.74–1.00) was significantly higher than for SMA ($p < 0.05$).
Conclusion: Anti-HIP1R autoantibodies seem superior to conventional autoantibodies (ANA, SMA, LKM) by a better clinical prediction of AIH and by a simpler ELISA assay compared to the demanding immunofluorescence titration on rodent tissue section.

THU-194
Time trends in liver transplantation for primary biliary cholangitis in Europe over the past three decades
M. Harms[1], Q. Janssen[1], R. Adam[2], C. Duvoux[3], H.V. Buuren[1], B. Hansen[1,4], H. Metselaar[1]. *[1]Erasmus University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; [2]AP-HP Paul-Brousse Hospital, Paris Sud University, Hepato- Biliary Center, Villejuif, France; [3]European Liver Transplant Registry, Paul Brousse Hospital, France; [4]Toronto General Hospital, Toronto Centre for Liver Disease, Toronto, Canada*
Email: m.h.harms@erasmusmc.nl

Background and Aims: Primary biliary cholangitis (PBC) has long been a leading indication for liver transplantation (LT). Changes in selection criteria for LT and in the epidemiology of PBC, as well as the introduction of ursodeoxycholic acid as an effective treatment may be important factors that have changed the relative importance and actual performance of LT for PBC over time. The aims of this study were to assess trends in LT for PBC over the past 30 years in Europe, including potential changes in the relevant patient population.
Method: Patients receiving LT between 1986 and 2015 in centres reporting to the European Liver Transplantation Registry (ELTR) were included. We excluded patients in case of combined organ transplantation or when aged <18 years. For PBC, annual absolute and proportional numbers of LTs, and patient characteristics were assessed over time using linear regression models and chi-square tests. Secondly, detailed subgroup analyses were performed on all PBC patients listed for LT in the Netherlands from 1986–2015.
Results: During our 30-year study period, 112,874 patients underwent LT. In 6029 patients (5.3%) PBC was the primary indication. After an initial annual increase of 21.5 patients from 1986 to 1995, the absolute number of LTs for PBC reached a relatively steady state from 2006 onwards at approximately 200 LTs annually. The percentage of LT for PBC as compared to other aetiologies fell from 20.3% in 1986 to 3.6% in 2015 (Figure). PBC was the only indication showing a constant proportional decrease over three decades. In patients with PBC, median age at LT increased from 53.9 years (IQR47.3–59.4) in the first decade to 56.1 (IQR48.4–62.4) after 2006 ($p < 0.001$). The proportion of males increased from 11.0% in the first to 15.1% in the third decade ($p < 0.001$). Median MELD scores increased from 15.3 (IQR12.2–19.2) in 1996–2005 to 16.8 (IQR12.8–21.6) in 2006–2015 ($p < 0.001$). In the Netherlands, 88.8% (71/80 evaluable patients) listed for LT could be classified as incomplete responders after one year of UDCA treatment according to the Paris-I criteria.
Conclusion: In our European-wide study on patterns in LT for PBC over 30 years, we show that despite a relative decrease, the absolute number of LTs for PBC patients has now reached a steady state. Still, more than 200 European patients with PBC undergo LT annually. Today, these patients are significantly older, have higher MELD scores, and are more likely to be males than 30 years ago.

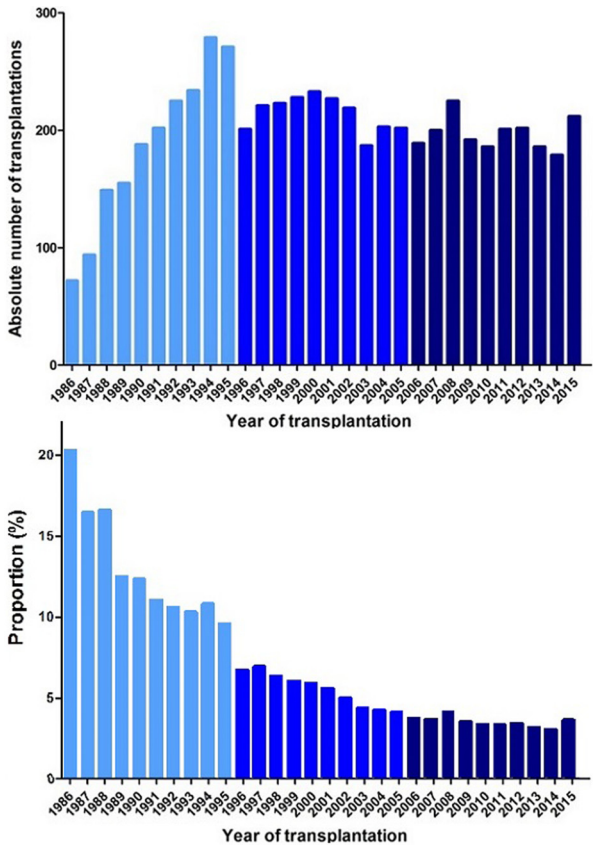


Figure: Annual absolute number of liver transplantations (LT) for PBC in Europe from 1986–2015 vs. annual proportional number of LT for PBC as compared to other aetiologies.

THU-195
The antidepressant mirtazapine improves survival in patients with primary biliary cholangitis
A.-A. Shaheen[1], G. Kaplan[2], W. Almishri[3], S. Patten[4], M.G. Swain[1]. *[1]University of Calgary, Cumming School of Medicine, Gastroenterology and Hepatology, Canada; [2]University of Calgary, Gastroenterology and Hepatology Division; [3]University of Calgary, Cumming School of Medicine, Calgary, Canada; [4]University of Calgary, Cumming School of Medicine*
Email: azshaheen@me.com

Background and Aims: Depressive symptoms are prevalent in primary biliary cholangitis (PBC) patients. However, the impact of depression and antidepressant use on PBC outcomes are unknown. Our aims were to examine the effects of depression and antidepressants on hepatic outcomes of PBC patients.
Method: We used the UK Health Improvement Network database to identify PBC patients between 1974 and 2007, and followed them to 2012. Our primary outcome was one of three clinical events: decompensated cirrhosis, liver transplantation and death. We assessed depression and each class of antidepressant medication in adjusted multivariate Cox proportional hazards models to identify independent predictors of outcomes. We included demographic, clinical, and coexisting liver conditions as covariates in our analysis. We carried out multiple sensitivity analysis to validate our findings by restricting our study population to PBC patients only using ursodeoxycholic acid (UDCA).
Results: We identified 1,177 PBC patients during our study period. In our cohort, 86 patients (7.3%) had a depression diagnosis prior to PBC diagnosis, while 79 patients (6.7%) had a depression diagnosis after PBC diagnosis. PBC patients with prior or current depression were younger than those without depression (median age 59 and 58 versus

63 years, P = 0.009), and were more commonly female (93% and 96% versus 87%, P = 0.02). Our cohort ten-year incidence of mortality, decompensated cirrhosis, and liver transplantation were 13.4%, 6.6%, and 2.0%, respectively. Approximately 70% of PBC patients were prescribed UDCA, which did not differ by depression status. Interestingly, among PBC patients without a diagnosis of depression, 24.6% were using antidepressants after their PBC diagnosis, while 11.1% used antidepressants prior to their PBC diagnosis. Mirtazapine was prescribed at a lower rate for patients with no history of depression (2.7%), or with a previous depression diagnosis (3.5%), compared to those with a current depression diagnosis (6.3%), P < 0.001. In our analysis, PBC patients with depression were less likely to die, compared to PBC patients without depression (P = 0.02). Our analyses demonstrated that depression was a confounder to the protective effect of the antidepressant mirtazapine. The effect of no other antidepressant was significant in our models. Using mirtazapine after PBC diagnosis was significantly protective (Adjusted HR 0.23: 95% CI 0.07–0.72) against poor outcomes (decompensation, liver transplant, mortality) in our adjusted models (Figure 1).

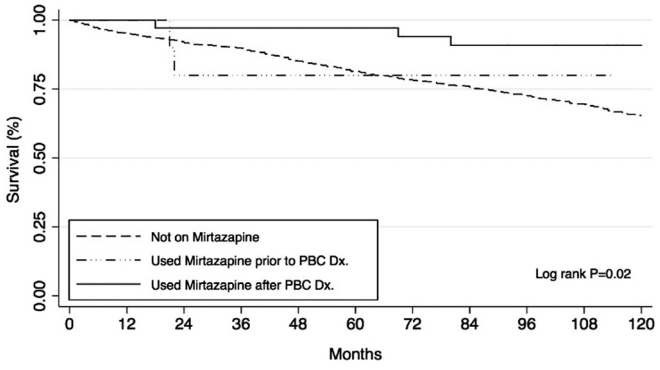


Figure 1: 10-year Kaplan-Meier Survival Curves among PBC patients according to Mirtazapine usage.

Conclusion: Mirtazapine reduced mortality, decompensated cirrhosis and liver transplantation in PBC patients. Future studies are needed to explore potential mechanisms underlying this beneficial impact of mirtazapine in PBC patients.

THU-196

Impact of access to specialized health care on the primary biliary cholangitis (PBC) patient outcomes: a Canadian experience

A.-A. Shaheen, S. Congly, K. Burak, M. Borman, M.G. Swain. *University of Calgary, Cumming School of Medicine, Gastroenterology and Hepatology, Canada*
Email: azshaheen@me.com

Background and Aims: Accessibility to health care service is a fundamental aspect of the health care system. The Canadian Health Care Act guarantees universal access to all Canadians. Access to specialized medical services in chronic diseases patients could affect disease outcome. Therefore, we assessed the impact of potential regional differences in access to specialized care on PBC patient clinical outcomes.
Method: We used the Discharge Administrative Database (DAD) to identify all PBC patients hospitalized in Alberta, Canada (2002–2017). An admission was considered a PBC-related hospitalization if PBC was the primary diagnostic code or a decompensated cirrhosis feature (ascites, variceal bleeding, hepatic encephalopathy or hepatorenal syndrome) was identified in any diagnostic field. Alberta is divided into five health regions serving 4.1 million people. Specialized health care facilities providing hepatology services are centralized in the Capital (Edmonton) and Calgary health regions, and liver transplants are only performed in Edmonton. In our analysis, we compared Albertans who live in these two health regions (direct access to specialist care) to the other three health care regions (remote access) with regards to demographics, comorbidities and cirrhosis decompensated features according to hepatology care access. We used appropriate statistical methods to compare clinical outcomes (in-hospital mortality, liver transplantation) between groups.
Results: We identified 374 PBC patients in Alberta who had PBC related hospitalizations. Among these patients, 237 (63.4%) resided in direct access health regions. PBC-related admissions were similar between groups (median, IQR; direct access: 1 (1–2), 1(1–3), P = 0.37). Both groups had similar demographics (median age: 61 vs. 60, P = 0.24; female %: 78.1% vs. 78.8%, P = 0.90; direct access vs. remote access, respectively). Both groups had similar comorbidities rates and decompensated cirrhosis features. Over 15 years of follow up, 109 patients (29.1%) died during one of their PBC-related hospitalizations. There was no difference in in-hospital mortality between direct access and remote access groups (31.2% vs. 25.5%, P = 0.29). Interestingly, PBC patients in remote access regions had higher rates of liver transplant (13.9% vs. 6.3%, P = 0.02). In our adjusted models for age, sex, comorbidities, and cirrhosis decompensation features living in a remote access area was an independent predictor of liver transplant (aOR, 95%CI: 2.27, 1.09–4.74).
Conclusion: In a single payer system with universal access, remote access to specialist care did not affect hospitalization rates, decompensated cirrhosis features, or in-hospital mortality in our large PBC cohort. Interestingly, we observed significantly higher liver transplant rates among patients with remote access.

THU-197

Biliary IL8 is a marker for disease progression and risk for biliary neoplasia in primary sclerosing cholangitis

M. Färkkilä[1,2], H. Mustonen[3], K. Jokelainen[2], S. Boyd[4], J. Arola[4], H. Alfthan[5]. *[1]Helsinki University, Helsinki, Finland; [2]Helsinki University Hospital, Gastroenterology, Helsinki, Finland; [3]Helsingin yliopisto, Biomedicum, Helsinki, Finland; [4]Helsinki University Hospital, Pathology, Helsinki, Finland; [5]Helsinki University Hospital, HusLab*
Email: harri.mustonen@helsinki.fi

Background: PSC is a chronic inflammatory disease of biliary epithelium leading to strictures of bile ducts. The chronic inflammation and increased proliferation of biliary epithelial cells are associated with development of biliary dysplasia and cholangiocarcinoma [CCA] with the lifetime risk around 10%. CCA is the most common reason for death among patients with PSC. Interleukin 8 (IL8) is a chemokine encoded by the CXCL8 gene, produced by eq. neutrophils and cholangiocytes as a response to microbial antigens and pro-inflammatory cytokines. Marked elevation of IL8 in has been demonstrated previously in PSC and it has shown to be a prognostic indicator in CCA.
Aims: To evaluate the role of biliary IL8 to predict (1) the disease progression based on changes in sequential ERC's examinations and for (2) the risk of biliary dysplasia detected by brush cytology or CCA.
Method: In total, 494 patients with PSC referred for ERC for dg or surveillance were included (295 males), mean age 40.5 ± 13.7 y. During ERC bile sample was aspirated using balloon catheter and immersed in liquid nitrogen (−196°C) and stored in −80°C. Brush cytology (BC) was collected from bile ducts for Papanicolau staining for grading dysplasia and inflammation. Neutrophilic inflammation was evaluated semi quantitatively (0 = neutrophils/epithelial cells <0.05, 1 = neutrophils /epithelial cells 0.05–0.4, 2 = neutrophils/epithelial cells >0.4). Bile concentrations of IL8 were analyzed using Human IL-8/CXCL8 DuoSet ELISA®. ERC findings were scored according to modified Amsterdam score. Based on sequential ERCs and scores an ERC-load/burden was calculated and likewise variables for biliary IL8 and neutrophils in BC in relation to time were determined.
Results: During the mean follow up of 6 years 20 patients were referred for liver transplantation, and biliary dysplasia or CCA was diagnosed in 35 patients. Biliary IL8 correlated with neutrophil load in BC. HR for IL8 load for predicting progression of PSC are presented

in Table 1. The risk ratios of IL8 load for development of biliary dysplasia and CCA are shown in Table 2.

Table 1: IL8 predicting risk for disease progression based on ERC-score >8

Variable	Value	HR	Lower	Upper	p-value
logIL8 Load	Continuous	2.06	1.68	2.52	0.000
IL8 Load	>=1.1	5.51	3.19	9.53	0.000
	>=3	4.37	2.76	6.90	0.000
	>=10	3.77	2.47	5.76	0.000

Table 2: IL8 predicting risk for development of dysplasia or CCA

Variable	Value	HR	Lower	Upper	p-value
logIL8 load	Continuous	2.27	1.52	3.37	0.000
IL8 load	>=1.1	25.67	3.47	190.02	0.001
	>=3	6.88	2.58	18.36	0.000
	>=10	3.87	1.75	8.53	0.001
	>=20	2.93	1.32	6.53	0.008

Conclusion: Biliary IL8 levels are reliable surrogate markers of bile duct inflammation, and can predict progression of the bile duct disease and the risk for development of biliary neoplasia.

THU-198

Pruritus strongly reduces quality of life in PBC patients – real life data from a large national survey

S. Hönig[1], B. Herder[2], A. Kautz[2], C. Trautwein[3], A. Kremer[1]. *[1]Friedrich-Alexander-University Erlangen-Nürnberg, Department of Medicine 1, Erlangen, Germany; [2]Leberhilfe Project, gUG, Köln, Germany; [3]RWTH-University Aachen, Department of Medicine III, Aachen, Germany*
Email: andreas.kremer@uk-erlangen.de

Background and Aims: Pruritus is a common and agonizing symptom in patients with primary biliary cholangitis (PBC). Epidemiological data is however scarce and validated questionnaires investigating quality of life (QoL) have not been performed in larger cohorts of PBC patients. We aimed to investigate this symptom, its effect on QoL, self-management as well as medical treatment in a large national survey in Germany.
Methods: We developed and validated a detailed questionnaire with a total of 89 questions. QoL in regard to pruritus was measured by the validated ItchyQoL questionnaire. Itch intensity was rated on a numeric rating scale (NRS). Data is given as mean ± SD.
Results: In total 577 PBC patients were included in this national survey. Sex ratio was 9:1 in favor of women (92% women, 8% men). The mean age was 53,2 (± 14,6) years with PBC being diagnosed in average 6,9 (0–37) years ago. More 60% of patients were well informed knowing the change name of the disease, the alkaline level, and stage of fibrosis. Reported symptoms included fatigue (82%), pruritus (56%), joint pain (62%) and abdominal pain (49%) while only 8% of patients stated to be asymptomatic. More than 70% of patients reported on a reduced QoL. Two third of patients with pruritus reported to suffer since many years of this symptom. The mean itch intensity during the last four week was rated 4.2 (49.3% moderate and 9.1% severe intensity), while the worst itch reached a level of 5.5 (51.4% moderate and 25.8% severe intensity) on a NRS. The QoL of affected patients quantified by the ItchyQoL closely correlated with mean (Spearman correlation coefficient: $r = 0,46$; $p < 0.001$) and worst itch intensity ($r = 0,42$; $p < 0.001$). Self-management of patients to improve pruritus consisted among others of topical treatment (55%), cold water (33%), rubbing (27%), use of scratch tools (24%), and cold/ice pads (13%). Medical treatment was performed only in 19% of patients with the majority receiving antihistamines (63%). Other treatments consisted of cholestyramine (29%), opioid antagonists (5%), rifampicin (3%) and fibrates (3%). Only 23 patients reported on a successful anti-pruritic treatment.
Conclusion: The prevalence of pruritus in the real life setting is high. Pruritus significantly reduces the QoL of affected patients with the majority of patients being not or only inadequately treated. Patients are forced to perform self-management. Pruritus represents a major unmet clinical need in PBC.

THU-199

Functional connectivity reveals altered activation of distinct brain areas in pruritus of cholestasis

A. Kremer[1], T. Buchwald[2], M. Vetter[1], A. Dörfler[3], C. Forster[2].
[1]Friedrich-Alexander University Erlangen-Nürnberg, Department of Medicine 1; [2]Friedrich-Alexander University Erlangen-Nürnberg, Institute of Physiology and Pathophysiology, Erlangen, Germany; [3]Friedrich-Alexander University Erlangen-Nürnberg, Department of Neuroradiology
Email: andreas.kremer@uk-erlangen.de

Background and Aims: Pruritus is a frequent symptom of hepato-biliary disorders particularly in those with cholestatic features. Various substances including bile salts and lysophosphatidic acid have been discussed as potential peripheral pruritogens in the peripheral nervous system. Our aim of this study was to investigate central mechanisms involved in itch sensation in patients suffering from cholestatic pruritus.
Methods: 23 patients with primary biliary cholangitis or primary sclerosing cholangitis. Patients were divided into two groups, those suffering from pruritus (N = 9) and those without pruritus (N = 14). Baseline itch intensity was quantified using a questionnaire and a visual analogue scale. Functional magnetic resonance imaging (fMRI) scans were using a classical connectivity fMRI-design with EPI sequences to BOLD signal changes. The first fMRI sequence was free from stimulation to detect the default mode (DM) network. During further fMRI sequences heat pain and itch stimuli were applied. Individual mean BOLD time courses were extracted from the seed regions thalamus for exploring an "input" network and the periaqueductal gray (PAG) for exploring the "output" network. Pearson's correlation coefficients were calculated between the seed regions and other regions in a whole brain study. In a 2nd level analysis contrasts were calculated between the connectivity within the DMN and that of the stimulations recordings to demonstrate stimulation related changes within the network.
Results: During the DM situation higher functional connectivity (FC) was seen within the group without pruritus in the "input" network of the thalamus to anterior parts of the insular cortex of both hemispheres and to the primary and secondary somatosensory cortex S1 and S2. In the group without pruritus the output network showed higher FC to frontal regions as compared to the group with pruritus. During both stimuli the activity within the DMN decreased in the group without chronic pruritus while in the group with chronic pruritus the FC either remained unchanged (thalamus with frontal regions, S1, S2) or increased (thalamus with Insular cortex). FC of the PAG and BA10 driving the descending control increased as compared to DM in the group without pruritus and showed no changes in patients with pruritus during an itch stimulus. Simultaneously changes of the FC from the PAG to other modulating areas (BA9, anterior insular cortex, anterior cingulate cortex) were contrary in the two groups.
Conclusion: The DM network is violated in patients with chronic pruritus probably due to the continuous pruritic input. Accordingly, changes within the networks due to an additional pruritic stimulus are less pronounced in the pruritus group as compared with subjects who are not suffering from spontaneous itching. This also affects the important descending control system.

THU-200

A stepwise algorithm for biliary brush cytology shows high diagnostic performance in primary sclerosing cholangitis

E. von Seth[1], H. Ouchterlony[1], S. Haas[1], K. Dobra[2], A. Hjerpe[2], A.M. Bergquist[1]. [1]*Karolinska Institutet, Department of Medicine, Huddinge, Stockholm, Sweden;* [2]*Karolinska Institutet, Department of Laboratory Medicine, Division of Pathology, Stockholm, Sweden*
Email: Erik.von.seth@ki.se

Background and Aims: Detection of early stage cholangiocarcinoma (CCA) in primary sclerosing cholangitis (PSC) remains a diagnostic challenge. Fluorescence in-situ hybridization (FISH) increases the sensitivity for the detection of biliary tract cancer but at the cost of decreased specificity. We analyzed the diagnostic accuracy of a multistep cytological approach to biliary brush cytology and FISH for the detection of biliary malignancy in PSC patients.
Method: We included patients with well-defined large duct PSC who underwent biliary brushings for clinical indications at Karolinska University Hospital during 2009–2015. Only results from the first sampling procedure during the study period were in the analysis. Brush cytology samples were categorized as; benign, atypical, atypical with suspicion of malignancy or positive for malignancy. Specimens categorized as atypical or atypical with suspicion of malignancy was further analysed with FISH (aneuploidy for chromosomes 3, 7 and 17, deletion of locus 9p21). Clinical outcomes were CCA, dysplasia from explanted livers or alive at follow up without signs of CCA. Patients were followed for 12 months or until endpoint.
Results: We included 208 PSC patients with at least one sampling procedure during the study period. During follow-up 15 patients were diagnosed with CCA, 3 with high-grade dysplasia and 5 with low-grade dysplasia, in explanted livers. Diagnostic accuracy for CCA, CCA and high-grade dysplasia and all dysplasia types is presented in Table 1.

Table 1: Diagnostic performance for detecting cholangiocarcinoma and dysplasia in first brushing of 208 PSC patients

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
CCA	80% (52–96%)	96% (92–98%)	60% (36–81%)	98% (95–100%)
CCA + HGD*	83% (59–96%)	82% (63–94%)	75% (51–91%)	89% (70–98%)
CCA + HGD + LGD*	78% (56–93%)	91% (72–99%)	90% (68–99%)	81% (61–93%)

*Only patients with follow up with liver transplantation, liver resection, biopsy or cancer related death included in analysis (n = 46).

Conclusion: In this stepwise approach to biliary brush cytology in PSC patients a positive FISH test seems to be highly predictive of CCA or biliary dysplasia.

THU-201

VCAM-1 and soluble CD-163 as novel non-invasive markers of liver fibrosis in patients with autoimmune hepatitis – a prospective study

M. Janik[1], B. Kruk[2], K. Kostrzewa[3], R.-W. Joanna[1], F. Lammert[4], M. Krawczyk[1,4], M. Milkiewicz[5], P. Milkiewicz[1]. [1]*Medical University of Warsaw, Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery, Warsaw;* [2]*Medical University of Warsaw, Laboratory of Metabolic Liver Diseases, Department of General, Transplant and Liver Surgery, Warsaw, Poland;* [3]*Warsaw School of Economics, Warsaw, Poland;* [4]*Saarland University Medical Center, Saarland University, Department of Medicine II, Homburg, Germany;* [5]*Pomeranian Medical University in Szczecin, Medical Biology Laboratory, Poland*
Email: mjanik24@gmail.com

Background and Aims: Novel, non-invasive markers of fibrosis in patients with autoimmune hepatitis (AIH) are urgently needed. The macrophage activation marker, soluble CD163 is associated with AIH activity, but its role in assessment of fibrosis has yet to be established. Vascular cell adhesion molecule-1 (VCAM-1) has recently been linked with fibrosis, but not investigated in patients with AIH so far. The aim of this study is to assess CD163/VCAM-1 as potential fibrosis markers in patients with AIH.
Method: Studied cohort compromised 120 patients with AIH (92 women, mean age 40.5 yrs, 46 cirrhotics) who prospectively underwent liver and spleen shear wave elastography (SWE, SuperSonic Imagine Aixplorer®). CD163 and VCAM-1 were quantified using ELISA. Fibrosis-4 (FIB-4), aspartate aminotransferase (AST)-to-platelet ratio index (APRI), AST-to-alanine aminotransferase (ALT) ratio (AAR) and FibroQ were applied as surrogate indices of fibrosis.
Results: Liver SWE showed a significant correlation with CD163, VCAM-1 ($p < 0.001$), it was also significant in fibrosis indices listed above. CD 163 correlated with fibrosis indices (all $p < 0.05$), markers of liver inflammation (all $p < 0.001$) and to a lesser extend with platelet ratio or spleen SWE. VCAM-1 showed significant (all $p < 0.001$) correlations with fibrosis indices and inflammatory markers (except ALT). In contrast to CD163, VCAM-1 significantly correlated with spleen SWE and platelets as signs of portal hypertension ($p < 0.001$). This may underline its role as a new marker of liver fibrosis and portal hypertension in AIH. VCAM-1 had AUROC 0.89 (95% CI 0.79–0.97), whilst AUROC of CD163 was 0.73 (95% CI 0.61–0.85) for detecting liver cirrhosis defined by SWE >13.0 kPa. Finally, liver SWE and VCAM-1, but not CD163, showed excellent correlation with esophageal varices (EV) and history of EV ligation (all $p < 0.001$). Spleen SWE showed the best correlation with all end points (all $p < 0.001$). There was a robust correlation ($r = 0.427$, $p < 0.001$) between liver and spleen SWEs.
Conclusion: Our study demonstrates that CD163 and VCAM-1 may help in assessment of liver fibrosis in patients with AIH. In line with the publication (Gronbaek et al., 2016), CD163 correlates with active inflammation in AIH, and VCAM-1 was related to portal hypertension. Future studies with these markers are required to establish their specific roles in clinical practice.

THU-202

Rituximab treatment experience in patients with complicated type 1 autoimmune hepatitis in Europe and North America

N.N. Than[1], D. Schmidt[1], J. Hodson[2], R. Wawman[1], K. Burak[3], M. Botter[1], R.L. Jones[4], A. Montano-Loza[5], N. Gautam[1], G. Appanna[6], A. Godkin[6], C. Schramm[7], F. Lammert[8], M.G. Swain[9], D. Adams[1], G. Hirschfield[1], Y.H. Oo[1]. [1]*University Hospital Birmingham NHS Trust, United Kingdom;* [2]*University of Birmingham, United Kingdom;* [3]*Division of Gastroenterology and Hepatology, University of Calgary, Department of Medicine, Calgary, Canada;* [4]*St James's University Hospital, Hepatology Department, Leeds, United Kingdom;* [5]*Division of Gastroenterology and Liver Unit, University of Alberta Hospital, Edmonton, Canada;* [6]*University Hospital of Wales, Gastroenterology and Hepatology, United Kingdom;* [7]*University Medical Centre Hamburg-Eppendorf, Department of Medicine, Hamburg, Germany;* [8]*Department of Medicine II, Saarland University Medical Center, Homburg, Germany;* [9]*Liver Unit, Division of Gastroenterology, Faculty of Medicine, University of Calgary, Canada*
Email: nwenithan@gmail.com

Background and Aims: Autoimmune hepatitis (AIH) is an immune mediated liver disease and due to its progressive nature necessitating transplantation in a subset of patients, alternative therapies are required in complicated cases of AIH.
The study aim was to determine the clinical response of patients with complicated AIH to Rituximab, an anti-B-cell depletion therapy.
Method: This was a multi-centre retrospective study of 22 patients with complicated type-1 AIH. Data were collected from the United Kingdom, Germany and Canada. The clinical response of Rituximab treatment was assessed by the changes in biochemical and immunological parameters, and prognostic scores of liver disease from the period before treatment to 24-months post-treatment. The

reduction in Prednisolone requirement after Rituximab treatment and the freedom from subsequent AIH flares were also assessed.

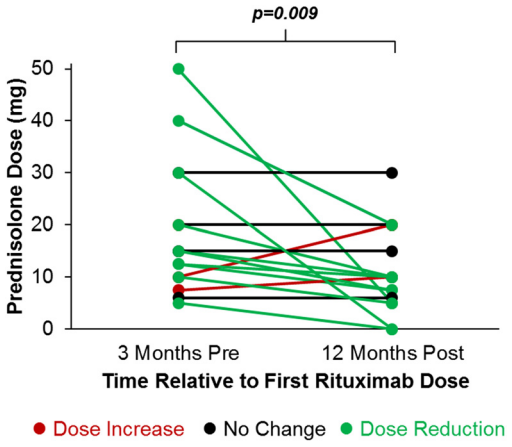


Figure 1: Changes in prednisolone doses following Rituximab therapy.

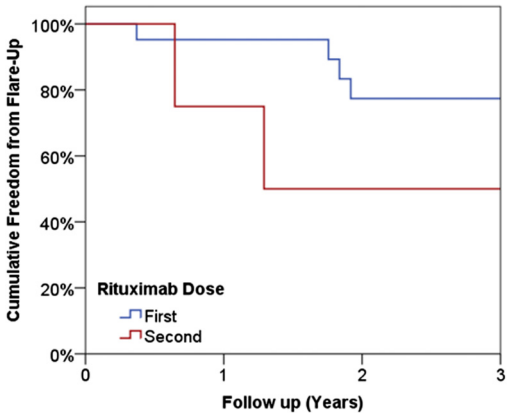


Figure 2: Kaplan-Meier curve of freedom from flare-up following Rituximab therapy.

Results: Among 22 patients, the majority were female (n = 15, 68%) and of Caucasian ethnicity (n = 18, 86%) with a median age at diagnosis of 44 years (range: 19, 79). Mean serum aminotransferase activities (ALT and AST) improved significantly following Rituximab therapy, with this improvement being sustained for the full 24 months of follow up ($p < 0.0010$). The mean ALT level improved from 167 IU/L pre-treatment to 32 IU/L at 24-months post treatment and mean AST level from 127 IU/L at pre-treatment to 29 IU/L at 24-months post treatment ($p < 0.001$). A trend toward improvement was detected in bilirubin ($p = 0.051$) and the international normalised ratio ($p = 0.068$) upon treatment. Immunoglobulin-G (Ig G) level also improved significantly from mean of 18.9 g/L pre-treatment to 13.2 g/L at 24 months ($p < 0.001$). Prednisolone requirement declined significantly by 12 months after treatment ($p = 0.009$) (Figure 1). The estimated rates of freedom from AIH flare were 95% and 77% at one and two years, respectively, following the first dose of Rituximab therapy (Figure 2).

Conclusion: Rituximab is effective in selected cases of complicated AIH patients, with improvement in biochemical liver enzymes and immunological parameters up to 24-months post-treatment.

THU-203

Primary biliary cholangitis in Spain: fewer symptoms and milder disease at presentation, but similar therapeutic response over the years

A. Reig[1], L.P. Llovet[1], M.R. Gomez[2], F. Sáez-Royuela[3], E. Fábrega[4], J. Salmerón[5], D. Horta[6], A. Castano-Garcia[7], A. Albillos[8], R.J. Andrade[9], M. Sala[10], J.A. Carrión[11], E.G. Domínguez[12], N. Chahri[13], I. Conde[14], A.G. Moya[15], M.H. Conde[16], M. Diago[17], Grupo del Registro Col-Hai Enfermedades Autoinmunes Y Colestásicas[18], A. Pares[1]. *[1]Hospital Clínic i provincial de Barcelona, Barcelona University, CIBERehd, IDIBAPS, Liver Unit, Spain; [2]Hospital Universitario Virgen del Rocío, CIBERehd, Sevilla, Spain; [3]Hospital Universitario de Burgos, Burgos, Spain; [4]Hospital Marqués de valdecilla Santander, Santander, Spain; [5]Hospital universitario San Cecilio Granada, Granada, Spain; [6]Hospital Mútua Terrassa, Terrassa, Spain; [7]Hospital Universitario Central de Asturias, Oviedo, Spain; [8]Hospital Ramón y Cajal Madrid, Madrid, Spain; [9]Hospital Universitario Virgen de la Victoria, Malaga, Spain; [10]Hospital Germans Trias i Pujol, CIBERehd, Badalona, Spain; [11]Hospital del Mar, IMIM UAB Barcelona, Barcelona, Spain; [12]Hospital Universitario Doce de Octubre, Madrid, Spain; [13]Hospital Universitario Sagrat Cor, Barcelona, Spain; [14]Hospital de la Fe Valencia, Valencia, Spain; [15]Hospital Santa Creu i Sant Pau, Barcelona, Spain; [16]Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [17]Consorcio Hospital General Valencia, Valencia, Spain; [18]AEEH. CIBERehd*
Email: anna.rg86@gmail.com

Background and Aims: Primary biliary cholangitis (PBC) affects mostly women. There are few data on the characteristics of this disease in Spain, so the objective of this study has been to evaluate the presentation, clinical, immunological and biochemical

Table: (abstract: THU-203)

Periods	06/1979 to 02/2000 n = 377	03/2000 to 02/2005 n = 377	03/2005 to 04/2012 n = 376	05/2012 to 07/2017 n = 378	p
Women %	93.9	92.9	92.5	87.3	= 0.007
Age years (IQR)	52(43–60)	54(45–63)	54(47–65)	56(47–66)	<0.001
Symptoms %	40.7	36.4	27	23.5	<0.001
Pruritus %	31.1	29.3	18.1	12.5	<0.001
Fatigue %	34.1	21.3	22	16	<0.001
Jaundice %	3.5	3.5	4.3	0,9	<0.001
Xanthelasma %	1.8	1.5	0.8	0	<0.001
Cirrhosis %	9.3	8.9	8.6	9.3	n.s.
AMA positive %	89.3	93.1	93.1	91	n.s.
ALT UNL	1.89 (1.26–2.89)	1.49 (0.95–2.34)	1.40 (0.82–2.22)	1.29 (0.83–1.98)	=0.012
GGT UNL	3.50 (2.32–9.54)	4.39 (1.93–9.05)	3.64 (2.09–7.08)	4.03 (2.13–7.45)	n.s
AP UNL	2.25 (1.31–4.61)	1.47 (1.07–2.53)	1.49 (1.00–2.36)	1.44 (1.01–2.34)	<0.001
Total Bilirubin mg/dL	0.70 (0.56–1.00)	0.60 (0.47–0.80)	0.53 (0.43–0.70)	0.55 (0.40–0.77)	n.s.
Platelets ui/mm^3	232 (183–274)	238 (205–286)	244 (202–301)	247 (198–289)	n.s
Global PBC < 0.30%	75.4	77.4	81.1	74.8	n.s

IQR: Interquarte range. ALT: alanine aminotransferase; GGT: gamma glutamyltransferase; AP: alkaline phosphatase; UNL: Upper normal levels.

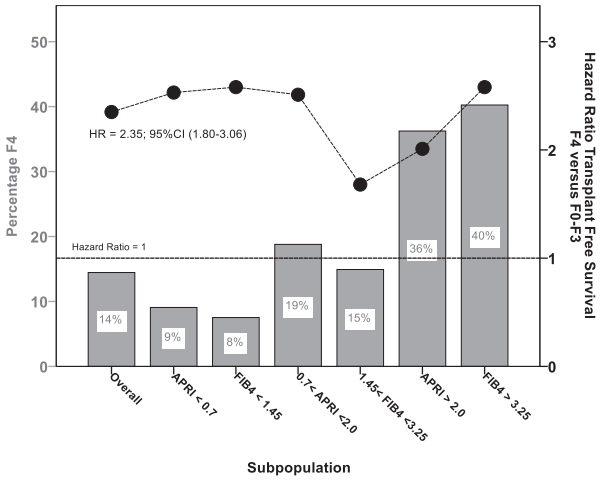
characteristics in an extensive sample of patients from different areas of the territory. Furthermore, presentation and response to treatment changes over the years have been analyzed.
Method: 1508 patients from 23 centers, diagnosed between June 1979 and July 2017, have been studied. According to the date of diagnosis, patients were divided into four periods. The demographic characteristics, symptoms and signs, biochemistry and immunology at diagnosis were evaluated, as well as presence of cirrhosis, treatment and biochemical response.
Results: There was a significant increase in the prevalence of males (from 6% to 13%) and age at diagnosis (from 52 to 56 years). A significant decrease of symptomatic patients was observed (from 40% to 23%), with lower prevalence of pruritus, asthenia, jaundice and xanthelasma. The biochemical cholestasis and hypertransaminasemia has also decreased. More than 96% of patients were treated with Ursodeoxycholic acid (UDCA). The number of patients receiving recommended adequate doses increased gradually. The prevalence of anti-mitochondrial antibodies, autoimmune (AI) comorbidities and cirrhosis at presentation were similar in all periods, as well as the response to UDCA according to Global PBC score and Barcelona criteria (table).
Conclusion: Presentation of primary biliary cholangitis has changed over the years, being diagnosed more frequently in men, in older patients, more asymptomatic and with less biochemical cholestasis. The suboptimal response to treatment remains important despite the milder presentation.

THU-204

Histologic stage is a stronger predictor of transplant free survival than APRI and FIB-4 in patients with primary biliary cholangitis

A. Gulamhusein[1], C.F.M. Perez[2], H. Van Buuren[3], C. Corpechot[4], P. Trivedi[5], M. Carbone[6], A. Pares[7], W.J. Lammers[3], M. Harms[3], A. Floreani[8], K. Lindor[9], C. Ponsioen[10], P. Invernizzi[11], M.J. Mayo[12], P.M. Battezzati[13], F. Nevens[14], T. Bruns[15], G. Dalekos[16], D. Thorburn[17], N. Larusso[18], K. Zachou[16], R. Poupon[4], V. Xavier[19], A.L. Mason[20], K.V. Kowdley[21], H. Janssen[1], G. Hirschfield[5], B. Hansen[1]. *[1]University Health Network; [2]University of Toronto; [3]Erasmus University Medical Center; [4]Hôpital Saint-Antoine; [5]University of Birmingham; [6]International Digestive Health Center; [7]Hospital Clinic I Provincial Barcelona; [8]University of Padova; [9]Arizona State University; [10]AMC; [11]University of Milan-Bicocca; [12]UT Southwestern; [13]Università degli Studi di Milano; [14]UZ Leuven; [15]Jena University Hospital; [16]University of Thessaly; [17]The Royal Free Hospital; [18]Mayo Clinic; [19]University Hospital; [20]University of Alberta; [21]Swedish Medical Center*
Email: a.gulamhusein@mail.utoronto.ca

Background and Aims: FIB-4 and the AST/Platelet Ratio Index (APRI) are indirect markers that predict fibrosis in patients with viral hepatitis. We sought to validate correlation with histology and clinical outcomes across a globally representative cohort of patietns with Primary Biliary Cholangitis (PBC).
Method: Patient data was retrieved from the Global PBC Study Group dataset. 1,952 patients with PBC and biopsy data were included. The diagnostic performance of FIB-4 and APRI was assessed and expressed as area under the ROC curve. Cox regression was performed to assess the association between histologic stage, APRI and FIB-4 and transplant free survival.
Results: The mean age of patients was 52.6 years, 90.2% were female and 91.5% were UDCA treated. There were 207 (10.6%) deaths and 156 (8%) liver transplants in the cohort. Neither APRI nor FIB-4 performed well in identifying or excluding significant degrees of fibrosis. The AUROC for APRI for ≥F2, ≥F3, =F4 was 0.62, 0.66 and 0.67, respectively. For FIB-4, the AUROC for ≥F2, ≥F3, =F4 was 0.61, 0.68 and 0.70, respectively.
Univariable Cox proprortional hazards models revealed that biopsy stage (HR 7.06 (4.9–10.2), p < 0.001), APRI (HR 6.2 (4.6–8.4), p < 0.001) and FIB-4 (HR 8.8 (6.3–12.3) p < 0.001) were significantly associated with worse transplant free survival. After adjusting for biopsy stage and non-invasive measures, histologic stage remained an independent predictor of outcome with a HR for F4 fibrosis 3.4 (2.3–5.1, p < 0.001) as did FIB-4 HR of 2.9 (1.1–7.4), p = 0.03 but APRI was no longer significant (p = 0.91).
When assessing thresholds with a high likelihood of cirrhosis (FIB-4 > 3.25 or APRI > 2), histologic cirrhosis remained a strong independent predictor of worse transplant free survival with a HR 2.4 (1.8–3.1, p < 0.001). Analysis of APRI and FIB-4 at different thresholds of fibrosis (APRI < 0.7 or FIB-4 < 1.45 and APRI >2.0 or FIB-4 > 3.25) revealed that 10–20% of patients with histologic cirrhosis were presumed to have lesser degrees of fibrosis by non-invasive testing, and these patients had worse transplant free survival (Figure 1), attesting to the suboptimal correlation between these parameters.



Conclusion: FIB-4 and APRI correlate poorly with histologic stage of fibrosis in patients with PBC and may underestimate risk for poor outcome. While they may have some predictive ability, histologic stage remains independently associated with transplant-free survival and continues to have a role in prognostication in this disease. This emphasizes the need to identify reliable non-invasive markers that strongly correlate with histology in patients with chronic cholestasis to allow non-invasive risk stratification in these patients.

THU-205

Morning bright light treatment for sleep-wake disturbances in Primary Biliary Cholangitis (PBC)

M. Turco[1], N. Cazzagon[2], I. Franceschet[2], G. Frighetto[1], F. Giordani[1], N. Cellini[3], G. Mazzotta[4], R. Costa[4], B. Middleton[5], D. Skene[5], S. Montagnese[1], A. Floreani[2]. *[1]University of Padova, Department of Medicine, Padova, Italy; [2]University of Padova, Department of Surgical, Oncological and Gastroenterological Sciences, Padova, Italy; [3]University of Padova, Department of General Psychology, Padova, Italy; [4]University of Padova, Department of Biology, Padova, Italy; [5]University of Surrey, Chronobiology, Faculty of Health and Medical Sciences, Guildford, United Kingdom*
Email: sara.montagnese@unipd.it

Background and Aims: Patients with PBC exhibit delayed sleep-wake habits, disturbed sleep and daytime sleepiness/fatigue. Such combination of symptoms is reminiscent of delayed sleep phase syndrome (DSPS), which benefits from morning light treatment.
Method: We therefore set out to test the effect of morning light in a group of 13 well-characterised patients with PBC (all females, 53 ± 10 yrs). Six healthy individuals (4 females, 57 ± 14 yrs) and 7 patients with cirrhosis (1 female, 57 ± 12 yrs) served as controls/disease controls. At baseline, all underwent an assessment of diurnal preference, sleep quality/timing (subjective plus actigraphy), daytime sleepiness, mood, quality of life and urinary 6-sulphatoxymelatonin (aMT6s) rhythmicity. Then they underwent a 15-day course of morning bright light treatment, immediately after getting

up (light box, 10,000 lux, 45 mins) whilst monitoring sleep-wake patterns (diaries plus actigraphy) and aMT6s.
Results: At baseline, both patients with PBC and patients with cirrhosis had significantly worse subjective sleep quality compared to controls (PSQI: 13.1 ± 4.0 and 11.3 ± 4.9 *vs.* 5.3 ± 2.0, p < 0.05, respectively); patients with PBC also had significantly more daytime somnolence. Post-treatment subjective sleep quality improved in all groups (group: F = 6.73, p = 0.007; treatment: F = 22.7, p < 0.0001; group*treatment: ns) as did daytime sleepiness (group: F = 5.7, p = 0.010; treatment: F = 7.6, p = 0.011; group*treatment: ns); the effect on daytime sleepiness was more pronounced in patients with PBC. The number of self-reported night awakenings decreased in all 3 groups. For actigraphy, a trend for an increase in sleep efficiency was observed in patients with cirrhosis. Post-treatment sleep onset/get-up time were advanced by approximately 30 minutes in PBC patients and healthy volunteers, while the change was less obvious in patients with cirrhosis (group: ns; treatment: F = 7.8, p = 0.010; group*-treatment: ns). Post-treatment, aMT6s rhythmicity was stronger with significantly improved cosinor fits in all three groups (group: ns; treatment: F = 5.8, p = 0.035; group*treatment: ns).
Conclusion: In conclusion, a brief course of morning bright light treatment had positive effects on sleep timing, sleep quality and circadian rhythmicity in patients with PBC and, to a lesser extent, also in patients with cirrhosis. Such unobtrusive and side-effect free, non-pharmacological treatment is worthy of further study.

THU-206

Novel protein biomarkers in serum extracellular vesicles for the diagnosis of primary sclerosing cholangitis (PSC) in patients with ulcerative colitis (UC)

A. Lapitz[1], A. Arbelaiz[1], M. Azkargorta[2,3], M. Krawczyk[4,5], A. Santos-Laso[1], M.J. Perugorria[1,3,6], R. Jimenez-Aguero[1], A. Lacasta[1], C. Ibarra[7], A. Sanchez-Campos[7], E. Gonzalez[8], F. Lammert[4], P. Milkiewicz[5,9], M. Marzioni[10], J. Marin[3,11], T.H. Karlsen[12,13], J. Falcon-Perez[3,6,8], M. Chaparro[3,14], J. Gisbert[3,14], F. Elortza[2,3], L. Bujanda[1,3], J. Banales[1,3,6]. *[1]Biodonostia Research Institute, Department of Gastrointestinal and Liver Diseases, San Sebastian, Spain; [2]CIC bioGUNE, Proteomics Platform, Derio, Spain; [3]Carlos III National Institute of Health, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas" (CIBERehd), Madrid, Spain; [4]Saarland University Medical Center, Department of Medicine II, Homburg, Germany; [5]Medical University of Warsaw, Department of General, Transplant and Liver Surgery, Warsaw, Poland; [6]IKERBASQUE, Basque Foundation for Science, Bilbao, Spain; [7]Hospital of Cruces, Bilbao, Spain; [8]CIC bioGUNE, Laboratory of Exosomes, Derio, Spain; [9]Pomeranian Medical University in Szczecin, Translational Medicine Group, Szczecin, Poland; [10]Università Politecnica delle Marche, Department of Gastroenterology, Ancona, Italy; [11]Biomedical Research Institute of Salamanca (IBSAL), Experimental Hepatology and Drug Targeting (HEVEFARM), Salamanca, Spain; [12]Norwegian PSC Research Center, Division of Cancer Medicine, Surgery and Transplantation, Oslo, Norway; [13]Research Institute of Internal Medicine, Oslo, Norway; [14]La Princesa University Hospital, Departament of Gastroenterology, Madrid, Spain*
Email: jesus.banales@biodonostia.org

Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic biliary disease of unknown etiology, which increases the risk of developing cholangiocarcinoma (CCA). In addition, PSC patients frequently (80%) present inflammatory bowel disease, mainly ulcerative colitis (UC) (PSC-UC). Currently, there are not available accurate non-invasive biomarkers for surveillance or early diagnosis of PSC in UC patients, which is warranted to monitor disease progression and to guide therapeutic strategies. We recently showed [Arbelaiz A. et al. HEPATOLOGY 2017] that serum extracellular vesicles (EVs) contain protein biomarkers for the differential diagnosis of PSC, CCA and hepatocellular carcinoma (HCC). The aim of this study was to investigate the usefulness of protein biomarkers in serum EVs for the differential diagnosis of PSC-UC and UC patients, which could help in the early diagnosis of PSC in UC patients.
Methods: Serum EVs were isolated from PSC-UC (n = 21), UC (n = 66; without PSC) and healthy individuals (n = 62) using ultracentrifugation/filtration methods. EVs characterization was performed by transmission electron microscopy (TEM), nanoparticle tracking analysis (NTA) and immunoblot. The proteome of EVs was analyzed by mass spectrometry-based proteomics.
Results: Serum EVs showed round morphology (by TEM), similar size (~180 nm diameter by NTA) and markers (CD9, CD63 and CD81 by immunoblotting) consistent with exosomes and small-size microvesicles. The proteomic profiles of serum EVs revealed 45 proteins to be differentially expressed in UC vs. controls, 66 in PSC-UC vs. controls, and 62 in PSC-UC vs. UC patients with high diagnostic performance (sensitivity and specificity). In particular, proteins such as Aminopeptidase N (AMPN), Polymeric immunoglobulin receptor (PIGR), G-protein coupled receptor family C group 5 member C (GPC5C) and Pantetheinase (VNN1)were exclusively upregulated ($p < 0.05$) in PSC-UC patients compared to UC and healthy controls. In contrast, proteins such as Complement factor I (CFAI), Ficolin-2 (FCN2) and Fibronectin (FINC) were downregulated ($p < 0.05$) in PSC-UC patients compared to UC and healthy controls.
Conclusion: Proteomic signatures found in serum EVs of PSC-UC and UC patients show potential as non-invasive tools for diagnosis and follow-up.

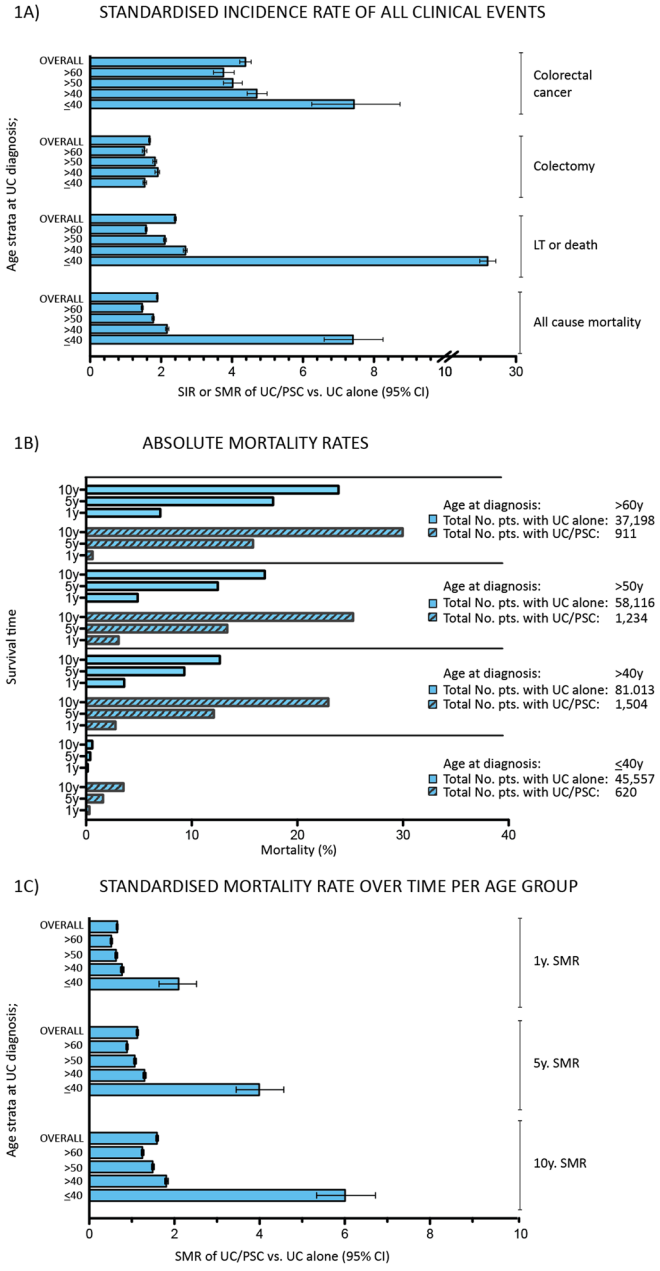
THU-208

A nationwide population-based evaluation of mortality and cancer-risk in patients with ulcerative colitis/primary sclerosing cholangitis – young age at diagnosis and the unmet need to reduce mortality

P. Trivedi[1,2,3,4], J. Mytton[5], F. Evison[5], S.K. Kamarajah[6], J. Reece[7], T. Iqbal[3], R. Cooney[8], F. Thompson[2], M. Walmsley[9], J. Ferguson[10,11], G. Hirschfield[10,11,12]. *[1]University of Birmingham, National Institute of Health Research (NIHR) Birmingham and Centre for Liver Research, Birmingham, United Kingdom; [2]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Liver Unit, Birmingham; [3]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Dept. of Gastroenterology, Birmingham; [4]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital Birmingham, Centre for Rare Diseases, Institute of Translational Medicine; [5]University Hospitals Birmingham NHS Foundation Trust, Department of Informatics, Birmingham; [6]University of Birmingham, National Institute of Health Research (NIHR) Birmingham and Centre for Liver Research, Birmingham; [7]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Dept. of Gastroenterology, Birmingham, United Kingdom; [8]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Dept. of Gastroenterology; [9]PSC Support (UK); [10]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Liver Unit; [11]University Hospitals Birmingham NHS Foundation Trust, Queen Elizabeth Hospital, Centre for Rare Diseases, Institute of Translational Medicine; [12]University of Birmingham, National Institute of Health Research (NIHR) Birmingham and Centre for Liver Research*
Email: p.j.trivedi@bham.ac.uk

Background: Advancing age is proposed as a risk factor for mortality in primary sclerosing cholangitis (PSC). However outcomes against a matched control population need evaluation.
Aim: Provide data-driven prioritisation of unmet need by comparing pts. with ulcerative colitis (UC) and coexisting primary sclerosing cholangitis (PSC) vs UC alone in a dedicated age-stratified outcomes' analysis.
Method: A population-based study was performed via linkage to the national Hospital Episode Statistics registry, which records every adult (>18 y of age) hospital attendance, admission or clinic event within England since 2006. Across the entire registry we captured all incident cases of UC alone (group I); and UC with an

established diagnosis of PSC, or UC diagnosed with PSC subsequently (group 2). Case finding/definition was as per Jess et al (Gastro 2012), by applying ICD10 codes for UC overall (inclusion K51), UC/PSC more specifically (inclusion K51 + K83.0) and excluding other causes of liver injury (K70-77, K80.3/4, B16-19). Cases were captured till 03/2015; follow-up ending 1 y thereafter. Event rates (colectomy, colorectal cancer [CRC], liver transplantation [LT]/death, and all-cause mortality) were stratified according to age strata at UC diagnosis.



Results: Over 10 years, 128,694 incident UC cases were identified (annualised incidence/100,000 population: 23.8 in 2006; rising to 25.1 in 2015). Of this group, 2,124 were diagnosed with PSC at some point (incidence in 2006 and 2015: 0.29 and 0.4, respectively). Observing the UC cohort in entirety, we observed 210 1st LT (206 in group I), 9,413 individuals who came to colectomy, 1,208 CRC cases, and 11,177 pt. deaths. The leading cause of mortality was coronary disease (1%) in group 1; whereas liver-related death (5.9%), cholangiocarcinoma (4.6%) and CRC (1%) predominated in group 2. The incidence rate ([IR] / 1000-pt.yrs.) was greater in the UC/PSC group for colectomy (17.3 vs 13.7), CRC (5.6 vs 1.5), LT/death (38.5 vs 15.1), and all cause mortality (26.4 vs 15.1); $p < 0.001$ for all. Time-dependent Cox regression validated the negative impact of PSC onset for each endpoint (adjusted hazard ratio: 1.62, 3.31, 2.47 and 1.62, respectively; $p < 0.001$ for all). Compared to UC alone, the standardised incidence ratio (SIR) for CRC was greatest in UC/PSC of young presenting age (<40 y.); a 7-fold increase (Figure 1A). This contrasted to pts. diagnosed above age 40 (SIR ~4). Although absolute mortality rate was elevated in older ages (Figure 1B) it was in young pts. with UC/PSC that the contrast vs UC alone was most evident at 5 y (1.6% vs 0.4%) at 10 y (3.6% vs 0.6%); a 4 and 6-fold increase, respectively. Indeed, standardised mortality (SMR) was the greatest across the ≤40 age group, plateauing with older diagnosis age (Figure 1C).

Conclusion: In pts. diagnosed aged ≤40 y with UC, development of PSC is associated with 6-fold increase in mortality and 7-fold increased risk of CRC.

THU-209

Differentiation of acute icteric autoimmune hepatitis from idiosyncratic drug-induced liver injury by histological and biochemical criteria

M. Sebode[1], U. Drebber[2], H.-P. Dienes[3], T. Krech[4], S.A. Weidemann[4], E. Vettorazzi[5], A. Lohse[1], C. Schramm[1]. *[1]University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; [2]University of Cologne, Institute for Pathology, Cologne, Germany; [3]Medical University of Vienna, Institute of Pathology, Vienna, Austria; [4]University Medical Center Hamburg-Eppendorf, Department of Pathology, Hamburg, Germany; [5]University Medical Center Hamburg-Eppendorf, Institute of Medical Biometry and Epidemiology, Hamburg, Germany*
Email: marcialsebode@web.de

Background and Aims: The clinical, biochemical, serological and histological presentation of acute icteric autoimmune hepatitis (AIH) and idiosyncratic drug induced liver injury (DILI) can be similar. The differentiation of the two entities is important as treatment differs: AIH requires long-term immunosuppression, whereas DILI does not. The aim of our study was to investigate biochemical, serological or histological criteria which could be used to differentiate acute AIH from DILI.

Method: 26 acute icteric cases of each entity who had received a liver biopsy at the time of presentation were analysed retrospectively. Final diagnosis was confirmed by clinical follow-up. To assure a comparable degree of liver damage between the two groups, AIH and DILI cases were matched for the value of total bilirubin at initial presentation. Patients with liver cirrhosis were excluded. Four independent liver pathologists extensively re-evaluated the liver histologies in a blinded manner.

Results: The most frequent drugs within this DILI cohort were phenprocoumon (23%) and antibiotics (15%). Serum levels of alanine aminotransferase (1311 U/l vs. 1149 U/l, p = 0,65), MELD scores (17 vs. 19,5, p = 0,59) at the time of initial presentation and bilirubin levels at the time of liver biopsy (12 vs. 11,5 mg/dl, p = 0,99) did not differ significantly between AIH and DILI. Including all biochemical, serological or histological criteria, a serum IgG-level above the upper limit of normal was the best predictor to differentiate AIH from DILI (ROC-AUC 0,866, 95%-CI 0,747–0,985) with a sensitivity of 68% and specificity of 90% (diagnostic odds ratio of 17,7). The predictive value of IgG could not be improved by any other biochemical, serological or histological criterion. The histological criteria that could best differentiate AIH from DILI were the grade of fibrosis and the presence of plasma cells. The accuracy of making the correct diagnosis differed significantly among the four pathologists (ROC-AUC 0,479–0,792).

Conclusion: Among histological criteria, the grade of fibrosis and the presence of plasma cells can differentiate acute icteric AIH from DILI

reasonably well. However, the best discriminator between the two entities is an elevation of serum IgG levels.

THU-210

Patients with primary biliary cholangitis exhibit reduced hippocampal volume and MRI evidence of neuroinflammation

V. Mosher, M.G. Swain, B. Goodyear. *University of Calgary, Calgary, Canada*
Email: mosher.v@gmail.com

Background and Aims: Primary biliary cholangitis (PBC) is associated with impaired cognition and altered mood – processes critically regulated by the hippocampus. Major depressive disorder (MDD) and a number of neuro-inflammatory diseases (e.g. MS, Alzheimer's Disease) are characterized by hippocampal alterations, including decreased volume and/or neuroinflammation. Neuroinflammation, characterized by iron deposition, can be non-invasively assessed via MRI and quantitative susceptibility mapping (QSM). Therefore, we used MRI to define how PBC impacts hippocampal volume and susceptibility.

Method: Seventeen female non-cirrhotic PBC patients and 17 age-matched healthy female controls underwent MRI. All patients were taking UDCA for ≥6 months prior to scanning. QSM and high-resolution hippocampal images (FreeSurfer v6.0) were collected to estimate susceptibility and hippocampal volume, respectively. QSM was analyzed using Cerebra-QSM to create brain susceptibility maps, and hippocampal regions from FreeSurfer applied to estimate hippocampal susceptibility. Hippocampal volume and susceptibility values were entered into a General Linear Model with age and intracranial volume as covariates. PBC patients completed the PBC-40 and HAM-D depression questionnaires prior to scanning, and impact of disease/symptom severity on hippocampal volume and QSM determined.

Results: The hippocampus was significantly smaller (5.3 ± 0.8% [SEM], $p = 0.023$), and exhibited significantly increased susceptibility ($p = 0.025$) in PBC patients as compared to healthy controls. These changes were not related to disease severity (liver stiffness, serum biochemistry), symptom severity (PBC-40 score), or biochemical response to UDCA treatment. No PBC patient was depressed based on history or HAM-D score.

Conclusion: PBC patients demonstrate significantly decreased hippocampal size (similar in magnitude to patients with MDD and MS) in association with increased neuroinflammatory changes. These hippocampal alterations were independent of disease/symptom severity, or UDCA response. Clearly PBC induces significant changes in the hippocampus. Although we did not find a link to symptoms in our patient cohort, these hippocampal changes are likely important and may represent an objective marker for assessing improvements in brain changes associated with response to therapeutic interventions in PBC.

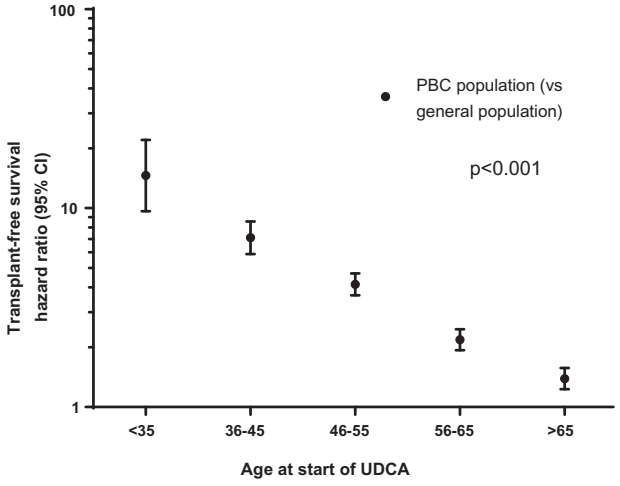
THU-211

Younger age is associated with lower transplant-free survival relative to a general population in patients with Primary Biliary Cholangitis

C.F.M. Perez[1,2], W.J. Lammers[3], H. Van Buuren[3], A. Gulamhusein[1], A. Cheung[4], C. Ponsioen[5], M. Carbone[6,7], A.L. Mason[8], C. Corpechot[9], M.J. Mayo[10], P. Invernizzi[11,12], P.M. Battezzati[13], A. Floreani[13], A. Pares[14], F. Nevens[15], K.V. Kowdley[16], T. Bruns[17], G. Dalekos[18], K. Zachou[18], D. Thorburn[19], N. Larusso[4], R. Poupon[9], P. Trivedi[20], V. Xavier[21], H. Janssen[1], G. Hirschfield[20], K. Lindor[22], B. Hansen[1,3,23].
[1]Toronto General Hospital- UHN, Toronto Centre for Liver Disease, Toronto, Canada; [2]University of Toronto, Institute of Medical Science, Toronto, Canada; [3]Erasmus University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; [4]Mayo Clinic, Division of Gastroenterology and Hepatology, Rochester, United States; [5]Academic Medical Center, Department of Gastroenterology and Hepatology, Amsterdam; [6]University of Milan-Bicocca, Department of Medicine and Surgery; [7]International Digestive Health Center, Division of Gastroenterology and Program for Autoimmune Liver Diseases; [8]University of Alberta, Division of Gastroenterology and Hepatology, Edmonton, Canada; [9]Hôpital Saint-Antoine, Centre de Référence des Maladies Inflammatoires des VoiesBiliaires, Paris, France; [10]UT Southwestern Medical Center, Digestive and Liver Diseases, Dallas; [11]International Digestive Health Centre, Division of Gastroenterology and Program for Autoimmune Liver Diseases, Milan, Italy; [12]Univereisty of Milan-Bicocca, Department of Medicine and Surgery, Milan, Italy; [13]University of Padua, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; [14]University of Barcelona, IDIBAPS, Barcelona, Spain; [15]KU Leuven, Department of Hepatology, Leuven, Belgium; [16]Swedish Medical Cener, Liver Care Network, Seattle, United States; [17]University of Jena, Department of Internal Medicine IV, Jena, Germany; [18]University of Thessaly, Department of Medicine and Research Laboratory of Internal Medicine, Larissa, Greece; [19]The Royal Free Hospital, The Sheila Sherlock Liver Centre, London, United Kingdom; [20]University of Birmingham, NIHR Biomedical Research Centre and Centre for Liver Research, Birmingham, United Kingdom; [21]Ghent University Hospital, Department of Gastroenterology and Hepatology, Ghent, Belgium; [22]Arizona State University, Phoenix, United States; [23]University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada
Email: bettina.hansen@utoronto.ca

Background and Aims: The prognostic impact of age on survival in Primary Biliary Cholangitis (PBC) patients is difficult to determine due to the relatively small proportion of young patients. Although asymptomatic patients over 55 years old have been shown to have the same mortality rate as a matched general population, the impact of age in a representative cohort of PBC patients remains unclear. The aim of this study was to identify whether presenting age at start of ursodeoxycholic acid (UDCA) therapy is associated with distinct transplant-free survival relative to the general population. It is important to assess survival relative to the general population because it is expected that older PBC patients have worse survival compared to younger patients.

Method: Patient data was retrieved from the Global PBC Study group database, which comprises data from 17 centers across Europe and North America. A total of 4355 UDCA-treated patients diagnosed between 1961 and 2014 were included in the analyses. The patients were grouped according to age at the start of UDCA treatment and transplant-free survival was compared. Furthermore, life table survival and Cox regression analyses within each age group compared transplant-free survival of PBC patients to an age-, gender-, and birth year-matched general Dutch population.



Results: Patients were grouped according to age at the start of treatment: ≤35 (n = 199), 36–45 (n = 727), 46–55 (n = 1305), 56–65 (n = 1234), >65 (n = 890). On Kaplan-Meier analysis, the 10-year transplant-free survival rate decreased with age in the corresponding age groups from youngest to oldest: 89.4%, 87.0%, 82.4%, 77.7%, and 64.1% (p < 0.001). In contrast, the transplant-free survival hazard ratio (HR) relative to the general population significantly decreased with age: ≤35 (HR 14.59, 95% CI 9.66–22.02), 36–45 (HR 7.10, 95% CI 5.87–8.58), 46–55 (HR 4.14, 95% CI 3.65–4.70), 56–65 (HR 2.18, 95% CI 1.93–2.46), and >65 (HR 1.39, 95% CI 1.23–1.57) (p < 0.001). Patients that were ≤35 years old had the highest hazard ratio and patients >65 years of age had the lowest (Figure).
Conclusion: Younger age in PBC is associated with lower transplant-free survival relative to a matched general population. This emphasizes the need for increased monitoring and additional therapies in younger patients.

THU-212

Risk factors for hepatocellular carcinoma in a large cohort of patients affected by primary sclerosing cholangitis

F. Saffioti[1,2], D. Roccarina[1], A. Marshall[1], M. Pinzani[1], D. Thorburn[1].
[1]UCL Institute for Liver and Digestive Health, The Royal Free Sheila Sherlock Centre, Royal Free Hospital, London; [2]University of Messina, Department of Clinical and Experimental Medicine, Division of Clinical and Molecular Hepatology, Messina, Italy
Email: fsaffioti.83@gmail.com

Background and Aims: Primary sclerosing cholangitis (PSC) patients are at risk of biliary tract cancer [cholangiocarcinoma (CCA) 5–10% of patients, gallbladder cancer (GBC) 2–4% of cases] and colorectal cancer (CRC). It has been suggested that the risk of developing hepatocellular carcinoma (HCC) may be lower in patients with PSC than in other causes of liver disease. There are no specific recommendations for HCC surveillance in this population. Our aim was to report the incidence of HCC in a large single centre cohort of PSC patients and consider the potential risk factors for HCC in this population.
Method: A retrospective analysis of the PSC database of our tertiary centre was performed, excluding patients with incomplete data. Demographics, type, location (intra/extrahepatic), duration and severity of PSC, IBD type and duration, prevalence of biliary tract cancers, HCC and CRC, pharmacological treatment, duration of follow-up (FUP) and outcome were recorded. FUP and patients-years at risk calculation started at time of PSC diagnosis. FUP was censored at occurrence of HCC, liver transplant (LT), death or last FUP. All the abovementioned variables were correlated with the incidence of HCC. Cox proportional hazard model was used for risk analysis.
Results: 281 patients followed-up between 1988 and 2016 were included. Patient's characteristics are summarized in Table 1. Eighty-two (29%) patients underwent LT/death. Eleven (3.9%) developed HCC (1 incidental on explant), 13 (4.6%) CCA, 2 (0.7%) GBC, 2 (0.7%) pancreatic cancer, 11 (3.9%) CRC. All HCC occurred in cirrhotic patients. The only variable significantly associated to the development of HCC at the univariate analysis was the presence of cirrhosis (p = 0.003). Statistical significance was not maintained on Cox regression (p = 0.161, HR 0.020). Incidence of HCC was 0.6% for the 1756 years FUP covering the entire cohort, 1.1% with regard to the 996 patient-years with cirrhosis.
Conclusion: In our cohort, incidence of HCC was low, as has been previously observed. Presence of cirrhosis was the only variable associated to HCC development, but risk proportion is unclear. Given the low incidence of HCC in this population, it further questions whether a strategy of surveillance for HCC in PSC patients with cirrhosis is justified.

Table 1: Characteristics of the study population

Patients, n (%)	281 (100)
Males, n (%)	181 (64)
Age, mean (SD)	48 (16)
Age at diagnosis, mean (SD)	41 (16)
Months from PSC diagnosis, median (range)	57 (6–413)
Large-duct/small duct/ overlap, n (%)	249 (88.6)/16(5.7)/16(5.7)
Cirrhosis, n (%)	158 (56.2)
Inflammatory bowel disease, n (%)	195 (69.3)
Ulcerative colitis, n (%)	167 (59.4)
Crohn's disease, n (%)	22 (7.8)
Indeterminate, n (%)	6 (2.1)
UDCA treatment, n (%)	146 (59.8)
Pre-LT azathioprine, n (%)	52 (18.5)
Pre-LT steroids, n (%)	51 (18.1)

SD, standard deviation; UDCA, ursodeoxycholic acid, LT, liver transplant.

THU-213

Optimal institution of azathioprine maintenance therapy in autoimmune hepatitis: a multicenter cohort study

S. Pape[1], T. Gevers[1], I. Mustafajev[1], F. van den Brand[2], K. van Nieuwkerk[2], G. Bouma[2], J.M. Vrolijk[3], B.V. Hoek[4], J. Hartl[5], A. Lohse[5], C. Schramm[5], G.W. Wong[6], M. Heneghan[6], J.P. Drenth[1].
[1]Radboud University Medical Center, Gastroenterology and Hepatology, Nijmegen, Netherlands; [2]VU University Medical Center, Gastroenterology and Hepatology, Amsterdam, Netherlands; [3]Rijnstate Hospital, Gastroenterology and Hepatology, Arnhem, Netherlands; [4]Leiden University Medical Center, Gastroenterology and Hepatology, Leiden, Netherlands; [5]University Medical Center Hamburg-Eppendorf, 1st Department of Medicine, Hamburg, Germany; [6]King's College Hospital, Institute of Liver Studies, London, United Kingdom
Email: Simon.Pape@radboudumc.nl

Background and Aims: Current treatment of autoimmune hepatitis (AIH) consists of induction therapy with prednisone followed by azathioprine (AZA) maintenance therapy. The EASL Clinical Practice Guideline on AIH advises on initiation of AZA after two weeks of prednisone treatment while the AASLD guideline advises on AZA initiation at onset of therapy. Delaying introduction of AZA at start of therapy discriminate between AZA-induced hepatotoxicity and primary non-response. However, the effect on remission is unknown. This study aims to compare both strategies in a cohort of patients with newly established AIH.
Method: We investigated the effect of early (<2 weeks) versus late (>2 weeks) initiation of AZA in AIH in an international multicenter cohort using chart review data from six centers. Eligible patients had an established AIH diagnosis, were ≥18 years old and initiated treatment with AZA. Primary outcome was biochemical remission, defined as a normal transaminases at 24 weeks of therapy. Secondary outcome was discontinuation of AZA before 24 weeks. We performed logistic regression to determine differences in primary outcome between the early and late groups, with correction for center, weight, baseline ALT, AST, bilirubin and AZA dose. Odds ratios (OR) with 95%-confidence intervals were calculated. We used chi-square testing for the secondary outcome.
Results: Primary analysis included 233 patients: the majority was female (78,1%) and mean age at diagnosis was 51,6 years (SD 17.5). The early AZA group consisted of 89 patients while 144 patients received AZA after >2 weeks of therapy. Early starters had significantly higher baseline transaminases (ALT, p < 0.01; AST p < 0.01), bilirubin (p < 0.01) and IgG (p < 0.01), while mean AZA dosage was lower (57.0 mg/day vs. 66.7 mg/day, p < 0.01). Biochemical remission at week 24 was higher in late starters when compared to early starters (72.9% vs. 64.0%), but this difference was not significant after correction for confounders (OR 0.76 (0.37–1.56, p = 0.45)). Patients in the late group discontinued AZA less frequently compared to the early group (2.1% vs. 9.0%, p = 0.02).

Conclusion: Delaying of azathioprine therapy does not decrease the likelihood of biochemical remission in AIH and might be associated with lower discontinuation rates of the drug.

THU-214

The risk predictive values of UK-PBC and GLOBE scoring system and performance of biochemical response criteria in Chinese patients with primary biliary cholangitis (PBC) on ursodeoeycholic acid

A. Huang[1], Y. Sun[1], Z. Zou[1], C. Wang[2,3], Y. Wang[2], J. Chen[2], T. Wu[2], V. Wu[2], G. Lau[4]. *[1]Centre of Non-Infectious Liver Diseases, Beijing 302 Hospital, Beijing, China; [2]Humanity and Health Research Centre, Hong Kong, Hong Kong; [3]State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Nanfang Hospital, Southern Medical University, Department of Infectious Diseases, Guangzhou, China; [4]Humanity and Health Research Centre, Unit 1505, Hong Kong, Hong Kong*
Email: gkklau@netvigator.com

Background and Aims: The biochemical response to ursodeoxycholic acid (UDCA) in primary biliary cholangitis (PBC) is a strong predictor of long-term outcome and thus facilitates the rapid identification of patients needing new therapeutic approaches. Numerous criteria for predicting outcome of treatment have been studied based on biochemical response to UDCA at 1 year. We sought to determine whether biochemical response based on these criteria could identify Chinese patients with PBC at risk of clinical adverse outcome, as defined by liver-related death, liver transplantation, and complications of cirrhosis.
Method: 119 consecutive patients (median age 46, female sex 83.2, median follow-up of 3.8 [range: 1.1–9.1]) all with biopsy-proved PBC treated with UDCA from one of the biggest tertiary hospitals in China (Beijing 302 hospital) were included. Clinical characteristics and liver biochemistry were collected at every 6-month interval. Death, liver transplantation (LT) and complications of cirrhosis were used as clinical adverse outcome. Cox proportional hazards regression analysis was used to identify the risk factors for progression after a year of UDCA treatment. The prognostic ability of UK-PBC score and GLOBE score were evaluated alongside those of the Barcelona, Paris-I, Rotterdam, and Paris-II criteria. The Area-Under-the-Receiver-Operating-Curve (AUROC) for survival analysis (c-statistics) was used to determine the performance of each prognostic method.
Results: The survival rates without adverse clinical outcome at 2, 5 and 8 years were 95.8% and 78.7% and 61.8% respectively. Under UDCA therapy, laboratory liver parameters experienced the most prominent improvement at 1st year (all $p < 0.05$). The Paris I and Paris II, but not the Rotterdam and Barcelona definition applied at 1st year after UDCA therapy significantly discriminated the patients in terms of long-term clinical outcome. Paris I was the most powerful predictor among four criteria (HR: 3.6, 95%CI: 1.5–8.3, AUROC 0.65) for non-responders versus responders. According to Paris I criteria 8-yrs survival was 79.6% for responders and 43.6% for non-responders. The AUROC was 0.78 for GLOBE scoring system (HR: 2.9, 95%CI: 1.9–4.4). Patients with a GLOBE score > 0.3 (non-responders) had a significantly diminished survival compared with those with a score <=0.3 (responders), and the 3-, 5- and 8-year clinical adverse outcome free survival rates were 95% vs. 74%, 91% vs. 64%, and 87% vs. 35%, respectively. The AUROC was 0.739, 0.738 and 0.738 for 3-, 5-, 8-year UK-PBC risk score.
Conclusion: This analysis confirms the prognostic value of previously proposed response criteria and scoring systems. Paris I was the most powerful predictor among all the criteria while GLOBE score predicted more accurate than UK-PBC score in Chinese cohort.

THU-215

Biochemical response to ursodeoxycholic acid predicts histologic primary biliary cholangitis progression

T. Namisaki[1], Y. Fujinaga[2], K. Moriya[1], M. Kitade[1], K. Kaji[1], H. Kawaratani[3], K. Seki[1], H. Takaya[1], S. Sato[1], Y. Sawada[1], T. Akahane[1], H. Yoshiji[1]. *[1]Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan; [2]Nara Medical University, Third Department of Internal Medicine; [3]Nara Medical University, Third Department of Internal Medicine*
Email: tadashin@naramed-u.ac.jp

Background and Aims: The prognosis and natural history of primary biliary cholangitis (PBC) have improved; its clinical endpoint needs to be discovered. We aimed to identify the surrogate markers for predicting histologic PBC progression.
Method: We enrolled the 99 patients to evaluate the potential correlation between biochemical response to ursodeoxycholic acid (UDCA) and histological stage at baseline according to both Scheuer (SC) and Nakanuma (NA) systems. We then conducted sequential biopsies in 35 patients with PBC treated with UDCA. They were divided into UDCA responders (R; n = 14) and non-responders (N; n = 21) based on reductions in γ-glutamyl transpeptidase levels at 1 year post UDCA therapy initiation (Nara criteria). We analyzed correlations between magnitude of biochemical response to UDCA and progression of histological changes of PBC. The Nakanuma system grades liver fibrosis (fibrosis score) and bile duct loss (BDL score).
Results: The proportion of R to N was significantly higher among patients in Scheuer and Nakanuma stages 1–3 and those with BDL scores of 0–2 compared with those in Scheuer and Nakanuma stages 4 and those with BDL score of 3, respectively ($P < 0.05$ for all). The number of stage 1, 2, 3, or 4 cases according to the SC was 6, 12, 17, and 0, respectively; according to the NA, it was 4, 18, 11, and 2, respectively. As per the SC, 1 patients had improved histological findings (I), 21 had stable histological findings (S), and 13 had histological progression (P); the NA categorized 4, 23, and 8 patients as I, S, and P, respectively. The fibrosis score progressed in 13 patients, while 1 showed improvement and 21 showed no progression; 4 patients exhibited improved BDL scores, while 23 showed no change and 8 showed worsening. In R (n = 14), proportions of patients with I, S, or P according to the SC were 0% (0/14), 78.5% (11/14), and 21.4% (3/14), respectively; this proportion per the NA was 14.3% (2/14), 57.1% (8/14), and 14.3% (4/14), respectively. Proportions of patients with improved, stable, or worsened fibrosis score were 0% (0/14), 64.3% (9/14), and 35.7% (5/14), respectively; as per BDL scores, it was 14.3% (2/14), 71.4% (10/14), and 14.3% (2/14), respectively. In N (n = 21), this proportion according to the SC was 4.8% (1/21), 47.6% (10/21), and 47.6% (10/21), respectively; per the NA, it was 9.5% (2/21), 71.4% (15/21), and 19.1% (4/21), respectively. The proportion for fibrosis score was 4.8% (1/21), 57.1% (12/21), and 38.1% (8/21), respectively; for the BDL score, it was 9.5% (2/21), 61.9% (13/21), and 28.6% (6/21), respectively. Histological progression rate per the SC and deterioration rate of BDL score was significantly higher in N than in R ($p < 0.01$ and $p < 0.05$, respectively).
Conclusion: The biochemical response to UDCA according to Nara criteria predicts the histological progression of PBC.

THU-216

Durable response in the markers of cholestasis through 36 months of open-label extension study of obeticholic acid in primary biliary cholangitis

M. Trauner[1], F. Nevens[2], M. Shiffman[3], J.P.H. Drenth[4], C. Bowlus[5], V.M.V. Blasco[6], P. Andreone[7], R. Pencek[8], E.S. Malecha[8], L. Macconell[8], D. Shapiro[8]. *[1]Medical University of Vienna, Wien, Austria; [2]UZ Leuven, Department of Hepatology, University Hospitals Leuven, Leuven, Belgium; [3]Liver Institute of Virginia, United States; [4]Radboud University Medical Center, Nijmegen, Netherlands; [5]University of California-Davis, Sacramento, United States; [6]Hospital Vall D'hebron, Universitat*

Autònoma Barcelona, Liver Unit; [7]Universitaria di Bologna, Bologna, Italy; [8]Intercept Pharmaceuticals, Inc., San Diego, United States
Email: michael.trauner@meduniwien.ac.at

Background and Aims: Obeticholic Acid (OCA) is a selective and potent farnesoid X receptor agonist indicated for treatment of primary biliary cholangitis (PBC). POISE is a 12-month double-blind (DB), placebo (PBO)-controlled, Phase 3 PBC study including an open-label extension (OLE). The purpose of the OLE is to assess safety and durability of the OCA effect on serum markers of cholestasis.
Method: Key POISE inclusion criteria: PBC diagnosis, ALP ≥1.67× ULN and/or total bilirubin (TB) >ULN to <2× ULN, stable UDCA dose or unable to tolerate UDCA. During the DB phase, 216 patients were randomized and dosed to: daily PBO, n = 73; OCA 5–10 mg (titration after 6 months based on response and tolerability), n = 70; or OCA 10 mg, n = 73. In the OLE, all patients were initially treated with OCA 5 mg regardless of DB treatment with the option to increase after 3 months based on response and tolerability.
Results: 193 of 198 (97%) patients completing the DB phase of the study enrolled in the OLE; 165 reached 36 months of the OLE: PBO, n = 49; OCA 5–10 mg, n = 59; OCA 10 mg, n = 57. At the end of the DB phase, patients on OCA had significant reductions in ALP and patients on PBO did not (Table 1). ALP reduction observed in OCA-treated patients was durable through 36 months OLE. PBO-treated patients experienced a significant reduction in ALP after switching to OCA, which was durable through 36 months OLE. Similar durable improvements were seen for GGT, ALT, and AST (data not shown). For OCA-treated patients, mean TB remained below BL through 36 months OLE. For PBO-treated patients, mean TB increased at 12 months DB, but trended back toward baseline (BL) with 36 months of OCA during OLE. During the OLE, 28 (15%) patients discontinued treatment, 7 (4%) patients for pruritus.

Table 1: ALP and TB mean change from BL through 36 month OLE

DB Phase Treatment Group	PBO	OCA 5–10 mg	OCA 10 mg
ALP (U/L)			
DB BL	327 (115)	326 (116)	316 (104)
Δ DB 12 mo†	−8 (88)	−104 (87)***	−118 (73)***
Δ OLE 24 mo‡	−101 (87)***	−121 (97)***	−103 (79)***
Δ OLE 36 mo‡	−113 (90)***	−101 (110)***	−85 (137)***
TB (μmol/L)			
DB BL	11.8 (7.2)	10.2 (5.5)	11.3 (6.6)
Δ DB 12 mo†	1.5 (4.1)	−0.5 (3.4)**	−1.2 (4.3)***
Δ OLE 24 mo‡	1.9 (7.6)	−0.4 (3.6)	−0.6 (4.8)
Δ OLE 36 mo‡	0.5 (3.6)	−0.5 (3.4)	−0.9 (4.1)

*p < 0.05, **p < 0.01, ***p < 0.0001. Values are Mean (SD).
†P-value for comparing active treatments to PBO is obtained using an ANCOVA model with Baseline value as a covariate and fixed effects for treatment and randomization strata factor.
‡P-value for the within treatment comparisons are obtained using the Student's t- test.

Conclusion: OCA treatment results in improvement in liver biochemistry; this improvement is shown to be durable in this analysis. For patients initially treated with PBO, switching to OCA is also associated with a durable biochemical response. Consistent with the DB phase, pruritus was the most common side effect of OCA, but discontinuation due to pruritus continues to be infrequent.

THU-217

Quantification of biliary phosphatidylcholine by non-invasive 31P magnetic resonance spectroscopy imaging suggests differences in cholangiopathies: A pilot study

E. Halilbasic[1], L. Pfleger[2,3], M. Gajdosik[3,4], M. Chmelik[2,5,6], S. Tratting[2,7], M. Krssak[2,3,8], M. Trauner[1]. *[1]Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; [2]Medical University of Vienna, Department of Biomedical Imaging and Image-guided Therapy, High-field MR Centre, Vienna, Austria; [3]Medical University of Vienna, Department of Internal Medicine III, Division of Endocrinology and Metabolism, Vienna, Austria; [4]New York University School of Medicine, Department of Radiology, Center for Biomedical Imaging, New York, United States; [5]University of Prešov, Faculty of Prešov, Prešov, Slovakia; [6]General Hospital of Levoča, Department of Radiology, Levoča, Slovakia; [7]Christian Doppler Laboratory for Clinical Molecular MR Imaging, Vianna, Austria; [8]Christian Doppler Laboratory for Clinical Molecular MR Imaging, Vienna, Austria*
Email: emina.halilbasic@meduniwien.ac.at

Background and Aims: Changes of bile composition play a role in the pathogenesis and progression of cholangiopathies. Phosphatidylcholine (PtdCh) is the major biliary phospholipid counteracting bile acid toxicity and may be targeted by novel therapeutic strategies. However studies on bile composition in patients are scarce due to invasive nature of bile sampling. PtdCh concentration can be assessed with ^{31}P MR spectroscopy (MRS) in human bile. Therefore, our aim was to investigate this non-invasive method for detection of the PtdCh concentration in the gall bladder of healthy controls in comparison with primary sclerosing cholangitis (PSC) and primary biliary cholangitis (PBC) patients.
Method: Biliary PC concentrations were studied in 4 healthy volunteers (3m/1f), 6 PBC (2m/4f) and 4 PSC (2m/2f) patients using ^{31}P MR spectroscopic imaging on a 7T Magnetom System (Siemens Healthineers, Erlangen, Germany) with a double-tuned ^{1}H/^{31}P surface coil. All PSC and PBC patient were treated with ursodeoxycholic acid. The signal quantification was based on a 3D sequence covering the liver and gall bladder of patients. The signal distribution of PtdC was then referenced to the corresponding localizer images and calibrated to mean γ-resonance of adenosine triphosphate concentration.
Results: Typical spectral from gall bladder region and homogeneous hepatic tissue was obtained in all included subjects. Calculated PtdCh concentration of the healthy volunteers was 11.77 ± 1.18 mmol/l (n = 4) comparable with previously published concentrations. In PSC patients, PtdCh content was much lower with 6.92 ± 0.80 mmol/l (n= 4) compared to controls (p < 0.001), whereas its concentration in PBC patients averaged at 12.81 ± 11.22 mmol/l (n = 6) and did not differ from control s. Interestingly, lowered PtdCh concentration (7.05 ± 1.76 mmol/l) was observed in all 4 female PBC patients (p < 0.01).
Conclusion: This pilot study confirmed that ^{31}P MRSI can be used to quantify the biliary PC concentration in non-invasive manner. Low biliary PtdCh concentration in PSC and female PBC patients strengthens the hypothesis that biliary composition may be an important pathogenetic factor. Further investigations are needed to validate ^{31}P MRS as a novel non-invasive method for addressing the role of PtdCh in cholangiopathies.

THU-218

Pre-treatment risk stratification in primary biliary cholangitis: a predictive model to guide first-line combination therapy

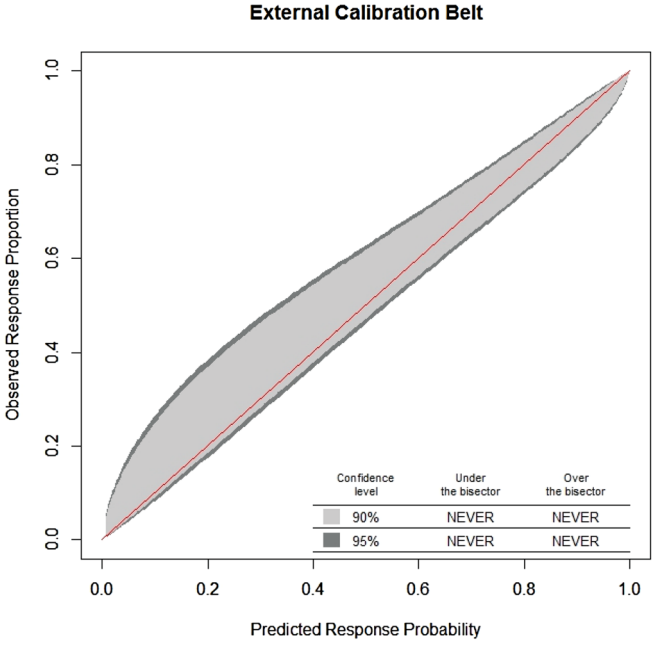
M. Carbone[1,2], A. Nardi[3], G. Carpino[4], M. Heneghan[5], D. Thorburn[6], S. Taylor-Robinson[7], A. Bathgate[8], M. Zuin[9], P.M. Battezzati[9], A. Floreani[10], E.G. Giannini[11], M.F. Donato[12], M. Marzioni[13], D. Alvaro[14], L. Miele[15], F. Marra[16], H. Ainsworth[17], L. Muratori[18], G. Bonato[2], V. Ronca[9], L. Cristoferi[2], D. Stocken[17], V. Cardinale[14], G. Hirschfield[19], G.J.M. Alexander[20], R. Sandford[21], D. Jones[22], P. Invernizzi[2], G. Mells[21]. *[1]University of Cambridge; [2]University of Milan Bicocca, Division of Gastroenterology, Milan, Italy; [3]Tor Vergata University, Department of Mathematics, Rome; [4]University of Rome "Foro Italico, Division of Health Sciences, Department of Movement, Human and Health Sciences, Rome, Italy; [5]King's College Hospital NHS Foundation Trust, Institute of Liver Studies, London, United Kingdom; [6]The Royal Free London NHS Foundation Trust, Sheila Sherlock Liver Center, London, United Kingdom; [7]Imperial College London, Liver Unit, Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, London; [8]Royal Infirmary of Edinburgh, Scottish Liver*

Transplant Unit, Edinburgh, United Kingdom; [9]Ospedale San Paolo, Division of Internal Medicine and Liver Unit, Milan, Italy; [10]University of Padova, Department of Surgery, Oncology and Gastroenterology, Padova, Italy; [11]IRCCS-Azienda Ospedaliera Universitaria San Martino-IST, Division of Gastroenterology, Department of Internal Medicine, Genova, Italy; [12]Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Gastroenterology and Hepatology Unit, Milan, Italy; [13]Ospedali Riuniti University Hospital, Clinic of Gastroenterology and Hepatology, Ancona, Italy; [14]Sapienza University of Rome, Department of Medico-Surgical Sciences and Biotechnologies, Polo Pontino, Rome, Italy; [15]Gemelli University Hospital, Department of Internal Medicine and Gastroenterology, Rome, Italy; [16]University of Florence, Department of Clinical and experimental Medicine, Florence, Italy; [17]Newcastle University, Institute of Health & Society, Newcastle, Italy; [18]Policlinico di Sant'Orsola-Malpighi, Liver Unit, Bologna, Italy; [19]University of Birmingham, Center for Liver Research and NIHR Biomedical Research Unit, Birmingham, United Kingdom; [20]University of Cambridge, Department of Medicine, Cambridge, United Kingdom; [21]University of Cambridge, Academic Department of Medical Genetics, Cambridge, United Kingdom; [22]Newcastle University, Institute of Cellular Medicine, Newcastle, United Kingdom
Email: mc767@medschl.cam.ac.uk

Background and Aims: PBC guidelines advocate risk-stratification after 12 months of treatment with UDCA to decide whether patients might benefit from addition of second-line agents (OCA or fibrate). In practice, this means that patients in greatest need of second-line therapy (i.e. those with active disease) must wait 12 months to start it. An alternative approach, albeit untested, is to treat high-risk patients with combination therapy from the outset. The aim of this study was to derive and validate a predictive model of UDCA response that will enable selection of patients at high risk of inadequate response to be directed to combination therapy from the outset.
Method: We analysed data on 2,703 patients from the UK-PBC Cohort treated with UDCA. We undertook logistic regression analysis of diverse explanatory variables to derive the best-fitting model. The endpoint was UDCA response, defined as alkaline phosphatase (ALP) <1.67× ULN after ≥12 months of UDCA therapy. The model underwent internal validation using boot-strapping as well as external validation in an independent PBC cohort from Italy (n = 460). We then explored the biological plausibility of the URS by looking at its correlation with several histological features in an independent cohort of patients (n = 20) for whom FFPE liver biopsies were available from the time of diagnosis.
Results: The following pre-treatment conditions were associated with greater probability of inadequate response to UDCA: higher ALP ($p < 0.0001$), higher bilirubin ($p = 0.0003$), lower transaminases (TA, $p = 0.0012$), younger age ($p < 0.0001$), larger interval from diagnosis to starting UDCA (time-lag, $p < 0.0001$) and worsening of ALP from diagnosis to starting UDCA (ΔALP, $p < 0.0001$). Based on these variables we derived a predictive score of UDCA response:

$$\text{UDCA response score (URS)}: 0.77 + 0.60 \times (\sqrt{TBdiag})^{-1} - 2.73 \times log(ALPdiag) + 0.35 \times log(TAdiag) + 0.03 \times age - 0.15 \times (time - lag) - 0.56 \times \Delta ALP$$

In external validation, the AUROC was 0.84 (0.80, 0.88) with a good calibration (Figure). In liver biopsies, the URS was inversely correlated with the extent of ductular reaction (DR) ($r = -0.777$, $p < 0.0001$) and extent of fibrosis ($r = -0.709$, $p < 0.0001$).
Conclusion: We derived and validated a model predicting future UDCA treatment response prior to initiation of therapy. Notably, delayed initiation of UDCA reduced the probability of response, emphasizing the importance of prompt initiation of therapy. Furthermore, the URS correlated with the extent of DR and fibrosis indicating that the score reflects the underlying pathologic process. A potential use for the URS is for pre-treatment selection of high-risk PBC patients for a clinical trial of primary vs sequential combination therapy. If primary combination therapy is shown to achieve higher rates of remission and faster times to remission, the model may then be used for pre-treatment risk stratification in clinical practice.



THU-219
Sustained biochemical response to oral antibiotics in pediatric PSC and ASC are correlated to changes in gut microbiota during therapy

P. Sambon[1,2], E. Amandine[2], V. Sharat[1], X. Stephenne[1,2], F. Smets[1,2], I. Scheers[1,2], M. Komuta[1,2], P. Cani[2], E. Sokal[1,2]. *[1]Cliniques Universitaires Saint-Luc, Woluwe-Saint-Lambert, Belgium; [2]Université catholique de Louvain, Louvain-la-Neuve, Belgium*
Email: etienne.sokal@uclouvain.be

Background and Aims: Concomitant presence of autoimmune hepatitis and primary sclerosing cholangitis (PSC) is labelled as autoimmune sclerosing cholangitis (ASC) in children. Based upon the possible implication of microbiota in the pathogenesis of PSC, oral antibiotics are increasingly being used as a novel therapeutic approach and shown to have benefit in PSC but their role in pediatric ASC is not well evaluated. We prospectively analysed the gut microflora before and after antibiotic therapy in children with ASC or PSC alone, and evaluated whether changes in gut microflora correlated with response to treatment.
Method: Patients diagnosed with ASC or PSC on basis of biochemical, liver biopsy and radiology findings were included. They prospectively received metronidazole (MTZ) for 14 days as induction or rescue therapy. Antibiotics were administrated in addition to the standard treatment of UDCA for PSC patients and azathioprine, UDCA and/or steroids for ASC patients. Stool samples were collected before and after antibiotic therapy. DNA isolation, amplification and Illumina sequencing to profile the microbiota composition were performed using the bacterial 16s rRNA. The beta-diversity measured the dissimilarity between each paired stool samples. The outcome parameters to assess the efficacy of antibiotics were reduction liver enzymes and subsequently achievement of sustained biochemical remission.
Results: Seven children (4 ASC, 3 PSC) were included, of which 5 have a concomitant ulcerative colitis (UC). All patients showed a significant decrease in their AST (–44%, $p < 0.025$), ALT (–56%, $p < 0.025$) and GGT (–41%, $p < 0.025$) under MTZ. Three children relapsed after stopping MTZ while the four others children showed a sustained

biochemical remission (liver enzymes below 1.5 times upper limit of normal) after a median follow-up of 375 days. Among these four patients, three exhibited a wide different microbial composition before and after MTZ as expressed by the beta-diversity variation. On the contrary, the microbiota of patients who relapsed remained unchanged pre- and post-MTZ.
Conclusion: Our study suggests that oral antibiotic could be an effective treatment of ASC and PSC, especially those with a concomitant UC, and that intestinal microflora play a major role in these diseases as sustained biochemical remission is associated with wide changes in gut microbiota communities after taking antibiotics.

THU-220

Primary biliary cholangitis specific T cell receptors on N-Ras high CD4+ T cells

R. Nakagawa[1,2], R. Muroyama[1], C. Saeki[2], M. Zeniya[3], N. Kato[4]. [1]*The Institute of Medical Science, The University of Tokyo, Division of Advanced Genome Medicine, Tokyo, Japan;* [2]*The Jikei University School of Medicine, Department of Gastroenterology and Hepatology, Tokyo, Japan;* [3]*International University of Health and Welfare, Clinical Research Center, Sanno Hospital, Tokyo, Japan;* [4]*Graduate School of Medicine, Chiba University, Department of Gastroenterology, Chiba, Japan*
Email: lake.vic30@gmail.com

Background and Aims: Primary biliary cholangitis (PBC) is an autoimmune liver disease with unknown pathogenesis. Recently, we have reported activated T cell receptor signaling pathway is associated with the production of inflammatory cytokines via N-Ras upregulation in PBC CD4+ T cells (J Hepatol 2017). Although TCR repertoires of CD4+ T cells are supposed to be concerned with PBC pathogenesis, those in PBC have never been analyzed. Moreover, next generation sequencer (NGS) enabled comprehensive expressional and structural analysis of TCR repertoires, thus we analyzed CD4+ T cell repertoires.
Method: In this study, 1 naïve PBC patient, 3 PBC patients receiving ursodeoxycholic acid (UDCA), and 3 healthy controls, who agreed to provide samples with written informed consent, were enrolled. N-Ras expression in CD4+ T cells from subjects was assessed by qRT-PCR. The repertoires of TCR α chain (TRA) and β chain (TRB) on CD4+ T cells were analysed by the NGS. Hierarchical analysis profiled the expression pattern of TCR repertoires. Motif analysis was performed to elucidate the structure of PBC specific TCR repertoires.
Results: N-Ras was upregulated in PBC CD4+ T cells compared to control ($P < 0.05$). Among 2,668 TRA repertoires, 6 TRA repertoires were significantly upregulated in PBC compared to control ($P < 0.05$, Fold change >1.8). Among 841 TRB repertoires, 8 TRB repertoires were significantly upregulated in PBC compared to control ($P < 0.05$, Fold change >1.8). No repertoire of TRA and TRB was downregulated in PBC compared to control. The expression of 6 TRA and 8 TRB was not significantly different between naïve and treated PBC. Among differentially expressed 6 TRA and 8 TRB, TRAV29/J22, TRBV6-5/J6-2, and TRBV10-1/J2-1 were expressed on PBC CD4+ T cells, however hardly expressed on CD4+ T cells of control. Moreover, the structure of TRAV29/J22, TRBV6-5/J6-2, and TRBV10-1/J2-1 was obviously different between PBC and control. In PBC, those structures were formed mature and longer compared to control.
Conclusion: The expression and structure of TCR repertories on N-Ras high CD4+ T cells of PBC were significantly different from those of control. Then TRAV29/J22, TRBV6-5/J6-2, and TRBV10-1/J2-1 was unique in PBC both expressionally and structurally. Thus, PBC specific TCR repertories might be associated with activating TCR signalling pathway via N-Ras expression.

THU-221

Validation of various prognostic models in primary biliary cholangitis in Korean patients

J.-J. Yoo[1], E.J. Cho[2], S.G. Kim[1], Y.S. Kim[1]. [1]*Soonchunhyang University Bucheon Hospital, Department of Internal Medicine, Bucheon, Republic of South Korea;* [2]*Seoul National University Hospital, Department of Internal Medicine, Seoul, Republic of South Korea*
Email: creatioex@gmail.com

Background and Aims: For primary biliary cholangitis (PBC), various prognostic models have shown good performance in predicting outcomes in Western countries, but have not been validated in Asian population. This study aimed to compare the prognostic performance of suggested models in an independent cohort of PBC patients.
Method: This retrospective study included consecutive 289 patients diagnosed as PBC from 2006 to 2016 by liver biopsy in a tertiary hospital, Korea. Decompensated PBC was defined as presence of ascites, variceal hemorrhage, or jaundice. Event-free survival (EFS) was defined as time until development of decompensation, liver transplantation or death during follow-up. Time-dependent ROC curve analysis was performed to compare the performance of each model.
Results: Mean age of the patients was 57.3 ± 11.9 years and 87.9% were female. Fifteen patients (5.2%) had decompensated PBC at initial diagnosis. During a median follow-up of 76.5 months (range, 4–212), 35 patients (12.1%) died, and 8 (2.8%) underwent liver transplantation. For the prediction of transplant or liver-related death, PARIS-II,

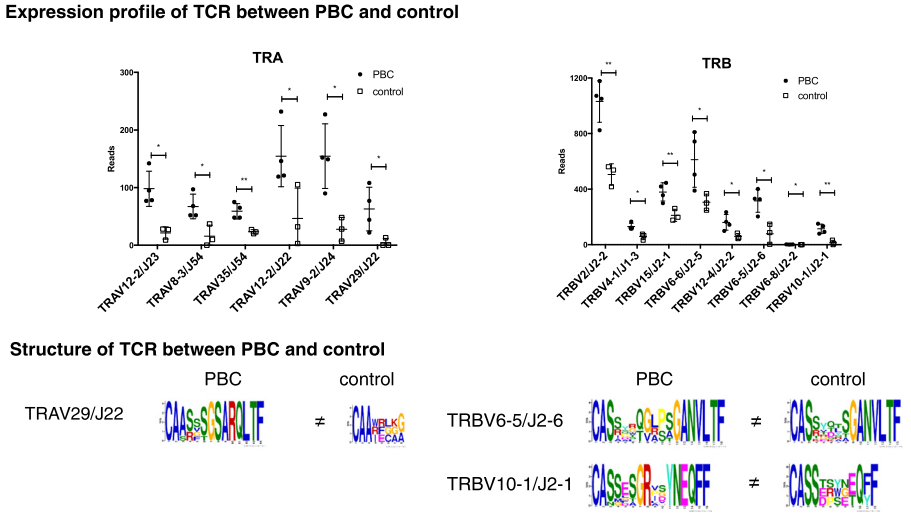


Figure: (abstract: THU-220)

PARIS-I and UK-PBC model showed moderate performance (area under the curves (AUCs), 0.74, 0.74 and 0.72, respectively), whereas GLOBE score and Barcelona model showed poor performance (AUCs, 0.6 and 0.57, respectively). When considering patients with compensated PBC, similar trends were observed. In addition, PARIS-II, PARIS-I and UK-PBC model showed moderate performance in the prediction of decompensation (AUCs, 0.71, 0.74 and 0.73, respectively), and the performance of GLOBE score and Barcelona model were poor (AUCs, 0.63 and 0.6, respectively). None of the models showed reliable performance in the prediction of EFS (all AUCs < 0.7).
Conclusion: Although most of the published prognostic models for PBC show moderate prediction, their prediction accuracies are relatively low in Korea. So it is necessary to develop new prediction model in PBC defined to Korean patients.

THU-222
Imaging features of macroregenerative nodules (MRN) in primary sclerosing cholangitis: MR imaging characteristics
A. Morgado[1], L. Pisani[2], C. Levy[1], B. Madrazo[1]. [1]*University of Miami, Department of Radiology, Miami, United States;* [2]*Pontifical Catholic University of Rio Grande do Sul, School of Medicine, Porto Alegre, Brazil*
Email: andres.morgado@jhsmiami.org

Background and Aims: Primary sclerosing cholangitis (PSC) is a rare cholestatic liver disease without available medical therapy. PSC is associated with increased risk of cholangiocarcinoma and imaging tests are frequently obtained for this patient population. Our aim was to delineate the spectrum of magnetic resonance (MR) imaging characteristics of macroregenerative nodules (MRN) of the liver in patients with PSC.
Method: We conducted a retrospective study of patients with PSC who had at least one hepatic MR imaging of the abdomen performed in a single institution between 2009 and 2017. The presence or absence of cirrhosis was determined by imaging findings. One abdominal radiologist retrospectively reviewed all images for the presence and imaging pattern of MRNs, specifically on diffusion weighted imaging. We used descriptive statistics to characterize study patients and MRI findings, and student t-test or chi-square test to evaluate for associations between patients' characteristics and the presence/absence of MRN on MRI.
Results: Forty-eight patients (26 male; mean age 48 years; age range, 77–20 years) with confirmed diagnosis of PSC underwent hepatic MR imaging. Of 48 patients, 20 (41%) had imaging findings of MRNs. MRNs were present in 11/13 patients with cirrhosis and 9/35 patients without cirrhosis (84.6% vs. 25.7%, $p < 0.001$), and in 14/26 males compared to 6/22 females (55% vs. 27%, $p = 0.06$). Age was not associated with presence of MRN's. These lesions showed absence of restricted diffusion on DWI/ADC imaging in all 20 (100%) cases, were not perceptible on T1 sequences, were low signal on T2 sequences, had no findings on opposed-phase imaging, did not enhance on post-gadolinium sequences and did not retained contrast on delayed images to suggest fibrosis. Another characteristic finding is that of a vascular bundle within the MRN's.
Conclusion: Macroregenerative Nodules (MRN) are lesions that have specific characteristic patterns on MRI imaging of the liver in patients with PSC and should not be confused with malignancy. These nodules are more frequent in males and in cirrhotic patients, although their presence cannot imply cirrhosis. Further studies are needed for better prognostic characterization of MRNs in PSC.

THU-223
Effect of nalfurafine hydrochloride for refractory pruritus in patients with primary biliary cholangitis: a multicenter, post-marketing, single-arm, prospective study
M. Yagi[1], A. Tanaka[1], T. Namisaki[2], M. Abe[3], A. Takahashi[4], A. Honda[5], Y. Matsuzaki[5], H. Ohira[4], H. Yoshiji[6], H. Takikawa[1]. [1]*Teikyo University School of Medicine, Department of Medicine;* [2]*Nara Medical University, The Third Department of Internal Medicine;* [3]*Ehime University Graduate School of Medicine, Department of Gastroenterology and Metabology;* [4]*Fukushima Medical University, Department of Gastroenterology;* [5]*Tokyo Medical University Ibaraki Medical Center, Department of Gastroenterology;* [6]*Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan*
Email: a-tanaka@med.teikyo-u.ac.jp

Background and Aims: Patients with primary biliary cholangitis (PBC) frequently suffer from pruritus, which could severely impair health-related quality of life (HrQOL). In 2015, nalfurafine hydrochloride (NH), a selective κ-opioid receptor agonist, was officially approved in Japan for refractory pruritus of patients with chronic liver diseases (Hepatol Res 2017:47:972), but it still remains unclear whether NH is effective for refractory pruritus in PBC. Herein, we conducted a multicentre, post-marketing, single-arm prospective study.
Method: As screening, we consecutively asked patients with PBC at out-patient clinic to fill out PBC-40, and also to evaluate their pruritus with the visual analogue scale (VAS). Then we administered NH at 2.5 μg daily for three months for patients who were assessed to have moderate to severe pruritus by PBC-40 itch score, and asked patients to fill the questionnaires at 3 months of NH treatment. Blood chemistries and serum autotaxin levels were also measured both at baseline and at 3 months.
Results: Four-hundred and ninety-six Japanese PBC patients (male/female = 52/444, 66.1 ± 9.9 yo) participated in the screening. Moderate to severe pruritus, defined as more than 4 out of 12 points in PBC-40 itch score, were present in 141 (29%) patients with PBC. The VAS was 1.94 ± 2.48, and strongly correlated with the itch score.
Among 141 patients with moderate-severe pruritus, 48 patients participated in this study. All patients completed 3 months' treatment with NH. The VAS was significantly decreased from 4.34 ± 2.23 at baseline to 2.89 ± 2.41 ($p = 0.001$) at 3 months of NH treatment. Overall PBC-40 itch score was declined from 5.56 ± 3.34 to 4.67 ± 2.89 ($p = 0.056$), and the score of #3 question of itch domain ("I felt embarrassed because of the itching") was significantly decreased from 5.56 ± 3.34 to 4.67 ± 2.89 ($p = 0.013$) at 3 months of NH treatment. The effect of NH change was not associated with age, sex, serum ALP and other biomarkers, and not observed in patients with advanced stage. No remarkable adverse effects of HN was observed. Serum autotaxin levels were not associated with the VAS and PBC-40 itch scores at baseline, and with effect of NH.
Conclusion: This study demonstrated that NH was safe and effective for moderate to severe pruritus in patients with PBC, while the effect of NH might be diminished in PBC patients with advanced stage.

THU-224
Primary biliary cholangitis (PBC) in the U.S.: real world effectiveness of obeticholic acid in TARGET-PBC
C. Bowlus[2], E. Carey[3], G. Demuth[4], K. Deane[5], M.J. Mayo[6], W. Ray Kim[7], B. Bacon[8], D. Bernstein[9], P.J. Thuluvath[10], L. Michael Weiss[11], U. Iloeje[12], M. Erickson[13], M. Strauss[13], M.W. Fried[14]. [1]*University of Miami, Miami, United States;* [2]*University of California Davis, Gastroenterology and Hepatology, Sacramento, United States;* [3]*Mayo Clinic, Phoenix, United States;* [4]*TARGET PharmaSolutions, Chapel Hill, United States;* [5]*TARGET PharmaSolutions, Clinical Operations, Chapel Hill, United States;* [6]*University of Texas Southwestern, Dallas, United States;* [7]*Stanford University Medical Center, Stanford, United States;* [8]*Saint Louis University, St. Louis, United States;* [9]*Northwell Health,*

Manhasset, United States; [10]Mercy Medical Center, Baltimore, United States; [11]Gastro Florida, Clearwater, United States; [12]Intercept Pharmacueticals, New York, United States; [13]Intercept Pharmacueticals, San Diego, United States; [14]University of North Carolina Chapel HIll, Chapel Hill, United States
Email: kdeane@targetpharmasolutions.com

Background and Aims: PBC is a rare cholestatic liver disease. Obeticholic acid (OCA) was FDA approved in 2016 for patients not responding or intolerant to ursodeoxycholic acid (UDCA). The aim is to evaluate safety and effectiveness of OCA as used in clinical practice.
Method: TARGET-PBC is a longitudinal observational study of PBC patients at 25 U.S. sites (19 academic/6 community). Enrollment after May 2017 was enriched to include only those with elevated alkaline phosphatase (ALP) despite UDCA therapy, those on OCA, or on fenofibrate. Data from consented patients is captured from redacted medical records within a database utilizing centralized data abstraction. Treatment of PBC and initiation of OCA is at the discretion of the treating physician.
Results: To date, 311 PBC patients have been enrolled. Among 32 (10%) OCA-treated patients, median age was 56 years, 94% were female, 91% Caucasian and 86% AMA positive. Cirrhosis was present in 56% and autoimmune hepatitis overlap in 16%. Mean Child Pugh score was 5.8 (range 5–8). Median duration of OCA treatment was 8 months (range 1 to 32). Current OCA dose was 5 mg/day in 57% and 10 mg/day in 18% of patients. All continued UDCA with a mean dose of 14.9 mg/kg/day. Last available pre-OCA lab values were compared to the last available values while on OCA. Reduction in ALP occurred in 19/23 (83%) patients (mean-25.6%, range –8.2% to –54.6%) compared to baseline. ALP decreased >15% in 16 patients (70%). Similarly, alanine aminotransferase decreased in 20/23 (87%) patients (mean –30.6%, range –4% to –70.5%). Most patients (19/23, 83%) had normal total bilirubin (TB) prior to OCA start and remained essentially unchanged during treatment. Four patients had elevated TB prior to OCA (range 2.0–10.6 mg/dL); 1 had progressive hepatic decompensation, with OCA dose reduction to twice weekly, and is undergoing transplant evaluation, while 3 remain stable on OCA without substantial TB change. Adverse events described during OCA therapy included pruritus (25%), fatigue (9.4%), gastroesophageal reflux (9.4%) and urinary tract infection (9.4%). Four patients (13%) discontinued OCA due to pruritus and 1 (3%) discontinued OCA after 3 weeks due to hepatic decompensation, concurrent with chemotherapy for colon cancer.
Conclusion: Consistent with data from the randomized trial, use of OCA has had a beneficial effect on liver biochemistries. Longitudinal follow-up of this expanding, real-world cohort will continue for 5 years.

THU-225
Primary biliary cholangitis (PBC) in the U.S.: clinical characteristics of patients enrolled in TARGET-PBC

C. Bowlus[2], E. Carey[3], G. Demuth[4], K. Deane[4], M.J. Mayo[5], W. Ray Kim[6], B. Bacon[7], D. Bernstein[8], P.J. Thuluvath[9], L. Michael Weiss[10], M.W. Fried[11]. *[1]University of Miami, Miami, United States; [2]University of California Davis, Sacramento, United States; [3]Mayo Clinic, Phoenix, United States; [4]TARGET PharmaSolutions, Chapel Hill, United States; [5]University of Texas Southwestern, Dallas, United States; [6]Stanford University Medical Center, Stanford, United States; [7]Saint Louis University, St. Louis, United States; [8]Northwell Health, Manhasset, United States; [9]Mercy Medical Center, Baltimore, United States; [10]Gastro Florida, Clearwater, United States; [11]University of North Carolina Chapel Hill, Chapel Hill*
Email: kdeane@targetpharmasolutions.com

Background and Aims: Primary biliary cholangitis (PBC) is an uncommon autoimmune cholestatic liver disease. The majority of PBC patients achieve a complete biochemical response with ursodeoxycholic acid (UDCA). Obeticholic acid (OCA) was approved by the FDA in 2016 for PBC patients not responding or intolerant to UDCA. The aim of this study is to determine the natural history of PBC and evaluate treatment regimens used in usual clinical practice.
Method: TARGET-PBC is a longitudinal observational study of PBC patients managed at 25 U.S. sites (19 academic and 6 community). Detailed information from consented patients is captured from redacted medical records within a common database utilizing centralized data abstraction. Optional biospecimens for biomarker and other translational studies are collected, along with patient reported outcomes.
Results: Total enrollment to date is 311 with evaluable data from 251 patients currently available. Enrollment after May 2017 was enriched to include only those with elevated serum alkaline phosphatase (ALP) despite UDCA therapy or those treated with OCA or fenofibrate (33% of current enrollment). Median age was 63 years, 89% were female, 85% Caucasian, 14% Hispanic and 84% were AMA positive. Mean duration of disease is 6 years (0–35 years). Cirrhosis (defined by biopsy and/or by clinical algorithm including non-invasive measures and clinical outcomes) was present in 34% of the cohort and autoimmune hepatitis overlap was identified in 16% of all patients. Other features included pruritus (39%), fatigue (41%), sicca syndrome (26%), hypothyroidism (25%) and hyperlipidaemia (21%). Sixty-one patients had a DEXA scan; 71% had osteopenia and 10% had osteoporosis. At the time of study entry, 63% had serum ALP above the site specific upper limit of normal (ULN): 30% (74/251) with ALP > 1.5× ULN and 22% (54/251) with ALP > 1.67× ULN. Total bilirubin was abnormal in 14% and albumin in 16%. Eighty-seven percent of patients were prescribed UDCA; 9% were prescribed OCA + UDCA and 4% were prescribed fenofibrate + UDCA.
Conclusion: Patients enrolled in TARGET-PBC include populations underrepresented in clinical trials and their characteristics are consistent with published data on PBC. More than half of patients still had abnormal ALP despite being on UDCA, with 30% having ALP >1.50× ULN. Increased awareness about the role of adjuvant therapies is needed. Longitudinal follow-up of this expanding, real-world cohort is ongoing.

THU-226
Stratification of hepatocellular carcinoma risk using the GLOBE score in patients with primary biliary cholangitis– the Global PBC Study Group

W.J. Lammers[1], P. Trivedi[2], G. Hirschfield[2], C. Corpechot[3], A. Floreani[4], F. Nevens[5], D. Thorburn[6], A. Pares[7], K.V. Kowdley[8], N. Larusso[9], P.M. Battezzati[10], C. Ponsioen[11], A.L. Mason[12], M.J. Mayo[13], P. Invernizzi[14], T. Bruns[15], G. Dalekos[16], V. Xavier[17], M. Harms[1], J. Goet[1], K. Lindor[18], H. Janssen[19], B. Hansen[1,20,21], H. Van Buuren[1]. *[1]Erasmus University Medical Center, Department of Gastroenterology and Hepatology; [2]University of Birmingham, NIHR Biomedical Research Unit and Centre for Liver Research; [3]Centre de Référence des Maladies Inflammatoires des VoiesBiliaires, Hôpital Saint-Antoine; [4]Department of Surgery, Oncology and Gastroenterology, University of Padua; [5]Department of Hepatology, University Hospitals Leuven, KU Leuven; [6]The Sheila Sherlock Liver Centre, The Royal Free Hospital; [7]Liver Unit, Hospital Clínic, CIBERehd, IDIBAPS, University of Barcelona; [8]Liver Care Network, Swedish Medical Center; [9]Mayo Clinic, Division of Gastroenterology and Hepatology; [10]Department of Health Sciences, Università degli Studi di Milano; [11]Academic Medical Center, Department of Gastroenterology and Hepatology; [12]University of Alberta, Divison of Gastroenterology and Hepatology; [13]UT Southwestern Medical Center, Digestive and Liver Diseases; [14]University of Milan-Bicocca, Division of Gastroenterology and Program for Autoimmune Liver Diseases, International Digestive Health Center, Department of Medicine and Surgery; [15]University of Jena, Department of Gastroenterology and Hepatology; [16]University of Thessaly, Department of Medicine and Research Laboratory of Internal Medicine; [17]Ghent*

University Hospital, Department of Gastroenterology and Hepatology; [18]Arizona State University; [19]University Health Network, Toronto, Canada; [20]Toronto Western&General Hospital, University Health Network, Liver Clinic; [21]University of Toronto, Institute of Health Policy, Management and Evaluation
Email: w.lammers@erasmusmc.nl

Background and Aims: Earlier studies indicate that 12-month biochemical non-response according to Paris-I, Rotterdam, Barcelona and Toronto criteria, confer an increased risk of hepatocellular carcinoma (HCC) development in primary biliary cholangitis (PBC). Recently, a new score was developed, the GLOBE score, that identifies ursodeoxycholic-acid (UDCA) treated patients with a diminished transplant-free survival. However, no data is available on its ability to stratify HCC risk in PBC.
Method: Patients were derived from the Global PBC Study Group database. Risk factor analyses were performed using univariate and multivariate cox regression models and Kaplan-Meier estimates. Response according to the GLOBE score was defined as a GLOBE score after one year of UDCA therapy below the following age-specific thresholds: <45 yr: −0.52, 45–52 yr: 0.01, 52–58 yr: 0.60, 58–66 yr: 1.01 and ≥66 yr: 1.69.
Results: 4851 PBC patients were included in this study. Within this cohort 155 patients developed HCC; and after excluding those with cancers that manifest early (<6 months from PBC diagnosis) 4820 patients and 124 HCC cases remained. The majority of female sex (n = 4317, 89.6%) with a mean age at diagnosis of 53.6 years (IQR 45.2–62.0) and most with an early histological stage of disease (1400/1917, 73.0%).
Of 4820 patients 85% (n = 4095) were UDCA treated of whom 28.5% (n = 1123 of 3938) had insufficient biochemical response after one year of treatment according to age-specific GLOBE thresholds. The incidence of HCC at 5- and 10-years for patients with an insufficient response versus those with adequate response was 32/705 (4.5%) versus 9/2010 (0.4%) and 43/376 (11.4%) versus 21/1119 (1.9%) respectively (P < 0.000).
On univariate analysis the earlier described factors late histological stage (HR 2.83, 95% CI 1.09–7.35, P < 0.0001), biochemical advanced stage (HR 2.57, 95% CI 1.32–4.98, P < 0.0001), male sex (HR 2.55, 95% CI 1.63–3.99, P < 0.0001) and thrombocytopenia (HR 7.14, 95% CI 4.35–12.5, P < 0.0001) retained association with HCC risk. Furthermore, higher GLOBE scores were associated with increased risk of HCC development, both as a continuous (HR 2.58, 95% CI 2.01–3.31, P <0.0001) and dichotomized variable according to age-specific thresholds (HR 7.72, 95% CI 2.75–21.71, P < 0.0001). When adjusting for aforementioned variables, elevated GLOBE scores retained association with increased risk of HCC (adjusted HR 1.96, 95% CI 1.46–2.62, P < 0.0001).
Conclusion: GLOBE scores after one year of UDCA treatment indicative of an insufficient response to treatment are associated with increased risk of HCC.

THU-227

A dose-response relationship in the association between ursodeoxycholic acid treatment and prolonged transplant-free survival in primary biliary cholangitis

A. Van der Meer[1], M. Harms[1], W.J. Lammers[1], C. Corpechot[2], D. Thorburn[3], P. Invernizzi[4], H. Janssen[5], P.M. Battezzati[6], F. Nevens[7], K. Lindor[8,9], A. Floreani[10], C. Ponsioen[11], M.J. Mayo[12], A. Pares[13], A.L. Mason[14], K.V. Kowdley[15], G. Hirschfield[16], H. Van Buuren[1], B. Hansen[1,5]. *[1]Erasmus University Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; [2]Hôpital Saint-Antoine, APHP, Centre de Référence des Maladies Inflammatoires des Voies Biliaires, Paris, France; [3]The Royal Free Hospital, The Sheila Sherlock Liver Centre, and UCL Institute of Liver and Digestive Health, London, United Kingdom; [4]University of Milan-Bicocca, Division of Gastroenterology and Program for Autoimmune Liver Diseases, International Center for Digestive Health, Department of Medicine and Surgery, Milan, Italy; [5]Toronto General Hospital, Toronto Centre for Liver disease, Francis Family Liver Clinic, Toronto, Canada; [6]Università degli Studi di Milano, Department of Health Sciences, Milan, Italy; [7]University Hospitals Leuven, KULeuven, Gastroenterology and Hepatology, Leuven, Belgium; [8]Mayo Clinic, Gastroenterology and Hepatology, Rochester, United States; [9]Arizona State University, College of Health Solutions, Phoenix, United States; [10]University of Padua, Department of Surgery, Oncology and Gastroenterology, Padua, Italy; [11]Academic Medical Center, Gastroenterology and Hepatology, Amsterdam, Netherlands; [12]UT Southwestern Medical Center, Digestive and Liver Diseases, Dallas, United States; [13]University of Barcelona, Liver Unit, Hospital Clínic, CIBERehd, IDIBAPS, Barcelona, Spain; [14]University of Alberta, Division of Gastroenterology and Program for Autoimmune Liver Diseases, International Center for Digestive Health, Department of Medicine and Surgery, Edmonton, Canada; [15]Swedish Medical Center, Liver Care Network and Organ Care Research, Seattle, United States; [16]University of Birmingham, NIHR Biomedical Research Unit and Centre for Liver Research, Birmingham, United Kingdom*
Email: m.h.harms@erasmusmc.nl

Background and Aims: Although the clinical efficacy of ursodeoxycholic acid (UDCA) in primary biliary cholangitis (PBC) has been questioned due to a lack of adequate RCTs, this treatment was recently shown to be independently associated with a prolonged liver transplantation (LT)-free survival among all patients with PBC. In this study, we aimed to assess the dose-response relationship between UDCA and both biochemical response and LT-free survival in PBC.
Method: In 10 Global PBC Study Group centers, data on the baseline dosages of UDCA in milligram (mg) per kilogram (kg) were collected. The associations between UDCA and biochemical response – classified by the GLOBE score- and LT-free survival were assessed with logistic regression and Cox survival analyses respectively, adjusting for sex, age, year of diagnosis, and baseline biochemistry including alkaline phosphatase, total bilirubin, albumin, platelet count, aspartate aminotransferase, and alanine aminotransferase.
Results: We included 2710 patients, who were followed for a median of 8.4 (IQR 4.7–13.1) years. Mean age was 54.4 (SD 11.9) years, 2363 (90.5%) were female and 2337 (86.2%) received UDCA. For 1585 out of 2337 UDCA-treated patients (67.8%), the baseline treatment dosage was available in mg/kg. In this group, treatment with UDCA was associated with an higher rate of biochemical response after 1 year (OR 3.55, 95%CI 1.89–6.67, p = 0.0006) as opposed to no treatment. In comparison to UDCA-untreated patients, those treated with an inadequate dosage of <13 mg/kg UDCA (n = 914, 57.7%) were more likely to have a biochemical response (OR 3.08, 95%CI 1.89–5.03, p = 0.0002). However, among those with an adequate dosage of ≥13 mg/kg UDCA (n = 671, 42.3%), the odds of a biochemical response were higher (OR 4.73, 95%CI 1.95–11.5, p = 0.0018). In the 1585 UDCA-treated patients with known dosages the risk of LT/death was lower than in untreated patients (HR 0.39, 95%CI 0.32–0.47, p < 0.0001). While this association was also significant in inadequately dosed patients (HR 0.40, 95%CI 0.34–0.47, p < 0.0001), it was stronger in those dosed with ≥13 mg/kg (HR 0.27, 95%CI 0.20–0.37).
Conclusion: Among patients with PBC, the association between UDCA treatment and both biochemical response and LT-free survival is dependent on the dosage of UDCA. These findings not only reinforce current guidelines recommending at least 13 mg/kg of UDCA for the treatment of PBC, but also support the causal relationship between UDCA and prolonged LT-free survival.

THU-228

Incidence of autoimmune hepatitis is increasing, while primary biliary cholangitis and primary sclerosing cholangitis have remain unchanged: a population-based study

M. Lamba[1], C. Stedman[1,2], J. Ngu[1]. [1]*Christchurch Hospital, Department of Gastroenterology, Christchurch, New Zealand;* [2]*University of Otaago, Christchurch, New Zealand*
Email: Mehullamba@gmail.com

Background and Aims: Autoimmune diseases arise from a complex interplay of environmental factors in genetically predisposed individuals, leading to a differential increase in the incidence of various autoimmune conditions. We aimed to investigate the incidence of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) in a population-based prospective study in Canterbury, New Zealand.
Method: All patients diagnosed with AIH, PBC and PSC in Canterbury were prospectively enrolled from 01/01/2008 until 31/12/2016. This included all paediatric and adult patients seen in out-patient clinic and in-patient admissions, in both public and private hospital. Diagnosis of AIH was based on score ≥6 on simplified criteria or score ≥10 on revised original criteria. PBC was diagnosed if at least 2 of the following were present: positive anti-mitochondrial antibody, raised alkaline phosphatase for > 6 months or compatible liver biopsy. PSC was diagnosed either radiologically or histologically. Change in incidence during the prospective study period was assessed by comparing the average incidence for predefined three 3-year blocks: 2008–2010, 2011–2013, 2014–2016.
Results: During 2008 to 2016, 99 patients were diagnosed with AIH, 25 patients with PBC and 44 patients with PSC. The annual incidence of AIH, PBC and PSC for the last year of study (2016) were 2.17 (95%CI 1.26–3.73), 0.67 (95%CI 0.25–1.78) and 0.33 (95%CI 0.08–1.33) cases per 100,000 respectively. The average annual incidence of AIH increased from 1.37 in 2008–2010 to 2.39 in 2014–2016 (p = 0.06). On the contrary, the average annual incidence of PBC and PSC remained unchanged during the same period. Point-prevalence of AIH on 31st December 2016 was 27.5 per 100,000 (95%CI 23.61–32.04), while that of PBC and PSC were 9.33 (95%CI 7.18–12.13) and 13.17 (95%CI 10.56–16.42) respectively.
Conclusion: In this population-based prospective study, we demonstrate that there is a trend towards an increase in the incidence of AIH, while the incidence of PBC and PSC have remain unchanged. As shown previously by our group, the incidence of PBC in Canterbury has remained lower than PSC or AIH. Since the population at-risk and the environmental factors have remained similar, the divergent trends in the incidence of autoimmune liver conditions suggests that these diseases likely have distinct etiopathogenesis rather than representing spectra of the same disease entity.

THU-229

Autoantibody-negative autoimmune hepatitis presents more commonly with advanced fibrosis or cirrhosis

M. Lamba[1], C. Stedman[1,2], J. Ngu[1]. [1]*Christchurch Hospital, Department of Gastroenterology, Christchurch, New Zealand;* [2]*University of Otago, Christchurch, New Zealand*
Email: Mehullamba@gmail.com

Background and Aims: Some patients with autoimmune hepatitis (AIH) do not have detectable typical autoantibodies. Clinical characteristics of this subgroup of AIH are not well-defined. We aimed to investigate the differences between phenotypes of autoantibody-negative AIH (Abneg-AIH) and autoantibody-positive AIH (Abpos-AIH) in a population-based prospective cohort study in Canterbury, New Zealand.
Method: All patients diagnosed with AIH based on either the simplified scoring system (score ≥ 6) or the revised original scoring system (score ≥ 10) were prospectively enrolled from 01/01/2008 to 31/12/2016. Typical autoantibodies were considered absent if all of following were negative: liver kidney microsomal antibody (LKM), anti-soluble liver antigen/liver-pancreas antibody (SLA/LP), anti-nuclear antibody (ANA) titre ≤ 1:20 and smooth muscle antibody (SMA) titre ≤1:20. Patients were followed-up till 31/07/2017.
Results: Ninety-nine patients were diagnosed with AIH based on the standardised criteria (62 definite AIH and 37 probable AIH). Liver biopsy was obtained in 98% of patients. Of the patients diagnosed with AIH, 15.15% met the inclusion criteria for Abneg-AIH. Only 40% of Abneg-AIH patients were diagnosed using the simplified scoring system, while the remaining patients met the diagnostic criteria when the revised original scoring system was applied. Immunoglobulin G was raised in only 60% of patients with Abneg-AIH compared to 86.9% in Abpos-AIH (p = 0.01). More patients with Abneg-AIH (73.33%) had advanced fibrosis or cirrhosis at the time of first biopsy compared to patients with Abpos-AIH (39.29%) (p = 0.01). During a median follow-up of 4 years, overall survival in Abneg-AIH was 91.67% (95%CI 53.9–98.78), which was not significantly different from Abpos-AIH – 87.45% (95%CI 76.78–93.42).
Conclusion: Fifteen percent of patients with AIH did not have detectable typical autoantibodies. Caution needs to be exercised when using simplified scoring system, as the diagnosis of Abneg-AIH can be missed. Most of the patients with Abneg-AIH had progressed to advanced fibrosis at the time of diagnosis. This may be due to a delay in diagnosis or may represent a more aggressive phenotype of the disease.

THU-230

Prognosis in patients with primary biliary cholangitis based on histological stage at diagnosis. A nationwide population-based study

L. Bossen[1], H. Grønbæk[1], P. Ott[1], P. Jepsen[1,2]. [1]*Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus C, Denmark;* [2]*Aarhus University Hospital, Department of Clinical Epidemiology, Aarhus N, Denmark*
Email: larsbossen@clin.au.dk

Background and Aims: Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease characterized by destruction of intrahepatic bile ducts, ultimately resulting in fibrosis and cirrhosis of the liver. Most patients are diagnosed with PBC before they develop cirrhosis. The aim of this study was to describe the prognosis of PBC patients diagnosed in the non-cirrhotic and cirrhotic stages, compared with age- and gender-matched controls without PBC.
Method: We included all Danish citizens 1997–2014 with a hospital discharge diagnosis of PBC and a histological diagnosis of PBC based on a liver biopsy. For every patient, we included five age- and gender-matched controls from the general Danish population. Patients and controls were followed until death, HCC, transplantation (LT), or 31 December 2014. We used the cumulative incidence function to calculate 10-year cumulative risk of death before requiring LT. Similarly we calculated the 10-year cumulative risk of HCC and LT before death or LT/HCC.
Results: 121 patients presented with PBC in the cirrhotic stage at diagnosis. Of those patients, 84.3% were women and their median age was 63 years (IQR 56.1–70.8). Their 10-year cumulative risk of death before requiring LT was 53.7% (95% CI 43.2–63.1%) compared with 23.7% (95% CI 19.6–28.0%) in age- and gender-matched controls (Figure 1). Of the 553 patients presenting with PBC in the non-cirrhotic stages at diagnosis, 87.7% were women who had a median age at PBC diagnosis of 58.5 years (IQR 48.9–66.4). Their 10-year cumulative risk of death before requiring LT was 28.7% (95% CI 23.9–33.7%) compared with 17.5% (95% CI 15.7–19.5%) in age- and gender-matched controls (Figure 1). Likewise, PBC patients with and without cirrhosis had a higher 10-year risk of HCC and LT compared with their matching controls.

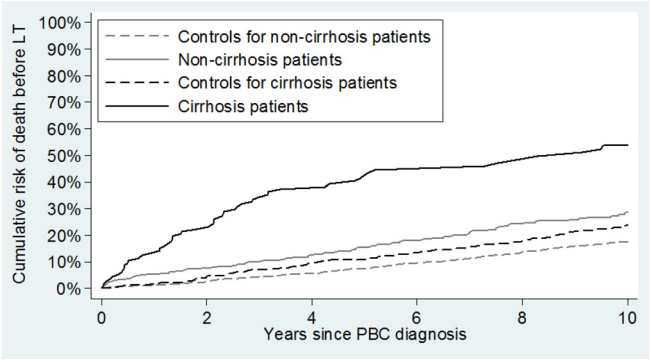


Figure 1: 10-year cumulative risk of death before requiring liver transplantation in PBC patients (solid) diagnosed with cirrhosis (black) and without cirrhosis (grey), and controls (dashed).

Conclusion: All patients with PBC were found to have worse prognosis than age- and gender-matched controls without PBC, and the prognosis was particularly poorer for those who were diagnosed after cirrhosis had developed.

THU-231

Change in bilirubin with obeticholic acid treatment in primary biliary cholangitis patients with high baseline bilirubin: a retrospective analysis of POISE, 201, and 202

G. Hirschfield[1], M. Shiffman[2], A. Pares[3], E.S. Malecha[4], R. Pencek[4], L. Macconell[4], D. Shapiro[4]. *[1]University of Birmingham, Centre for Liver Research, Birmingham, United Kingdom; [2]Liver Institute of Virginia, Newport News, United States; [3]University of Barcelona, Hospital Clinic, Barcelona, Spain; [4]Intercept Pharmaceuticals, Inc., San Diego, United States*
Email: g.hirschfield@bham.ac.uk

Background and Aims: In patients with primary biliary cholangitis (PBC), bilirubin (BILI) is a recognized marker of disease progression and a strong predictor of survival. Recently, the Global PBC Study Group reported the risk with elevated BILI extends into the normal range with a cutoff of 0.67× ULN identifying patients at risk. Obeticholic acid (OCA) is indicated for treatment of PBC in patients with an inadequate response or intolerability to ursodeoxycholic acid. The aim of this retrospective analysis was to evaluate the effect of OCA on BILI in this patient subpopulation.
Method: OCA has been evaluated in patients with PBC in one 12-month Phase 3 double-blind (DB) placebo (PBO)-controlled trial (POISE) and two 3-month Phase 2 PBO-controlled trials (201 and 202). Patients were eligible to continue treatment in open-label extensions (OLE) with all patients receiving OCA. Patients from the Phase 2 and 3 studies with baseline (BL) total BILI (TBILI) ≥0.67× ULN were evaluated for change in TBILI over 12 months in the following manner: 1) DB comparison of OCA vs PBO at 12 months in POISE and 2) DB + OLE OCA use totaling 1 year of treatment (POISE randomized to PBO, evaluated at 12 months OLE; Phase 2 randomized to OCA for 3 months, evaluated at 9 months OLE; and Phase 2 randomized to PBO, evaluated at 12 months OLE).
Results: The analysis included patients with TBILI ≥0.67x ULN at their OCA BL: POISE, n = 51; 201, n = 7; and 202, n = 7. In patients with BL TBILI ≥0.67x ULN, TBILI increased after 12 months of PBO treatment, and decreased after 12 months of OCA (Table 1). In the DB phase of POISE, of the 7 PBO-treated and 9 OCA-treated patients with abnormal TBILI at BL, 14% of PBO-treated and 78% of OCA-treated patients attained normal TBILI levels after 12 months. Further, of 10 PBO-treated and 20 OCA-treated patients with normal TBILI at BL, 60% of PBO-treated and 15% of OCA-treated patients worsened to abnormal TBILI after 12 months.

Table 1: Mean (SD) Change From BL in TBILI (μmol/L) in Patients with BL TBILI ≥0.67x ULN

12 Month Treatment	PBO	OCA				
Phase	DB			OLE		
Study	POISE			201	202	POISE
Dose (mg)	—	5–10	10	10 or 50	10, 25, or 50	5 to 10
n	17	15	14	7	7	17
Mean (SD) change from BL in TBILI	2.6 (6.5)	−3.3 (3.6)	−4.0 (7.8)	−8.1 (6.4)	−10.1 (8.1)	−1.6 (7.9)

OCA BL is defined as:

- OCA-randomized patients: if time from last visit in DB to first visit in OLE ≤30 days, mean of evaluations prior to first DB dose is used; if >30 days, last assessment prior to first dose in OLE is used; the initial OLE visit is included as a BL evaluation.
- PBO-randomized patients: last assessment prior to first dose in OLE is used; initial OLE visit is included as a baseline evaluation.

Conclusion: Patients treated with OCA had a trend toward reduction of TBILI compared with those treated with PBO. These data suggest that OCA may reduce progression of patients with more advanced liver disease.

THU-232

Chloroquine in monotherapy is safe and effective for induction of remission in anti-SLA/LP positive patients with autoimmune hepatitis

D. Terrabuio[1], A.S. Evangelista[2], A.L.V. Guedes[2], A.R. de Moreto Longo Galvão[3], F.J. Carrilho[3], E. Cancado[4]. *[1]Division of Gastroenterology and Hepatology, Gastroenterology, São Paulo, Brazil; [2]Division of Gastroenterology and Hepatology, Gastroenterology, Sao Paulo, Brazil; [3]Division of Gastroenterology and Hepatology, Gastroenterology, Sao Paulo, Brazil; [4]Division of Gastroenterology and Hepatology, Gastroenterology, Brazil*
Email: debora.terrabuio@hc.fm.usp.br

Background and Aims: The combination of azathioprine and prednisone (AZA/PD) is the standard treatment (ST) of autoimmune hepatitis (AIH); second-line treatment regimens are expensive, with few studies in literature, which justifies the search for new therapeutic options. In previous study antimalarials were effective in the maintenance of remission of AIH after treatment withdrawal. Our aim was to describe a series of 4 patients who relapsed AIH and achieved therapeutic response after the use of antimalarials in monotherapy.
Method: Four patients with AIH anti-SLA/LP (+) received chloroquine diphosphate (DFC) 250 mg/d or hydroxychloroquine (HCQ) 400–800 mg/d in monotherapy for induction of biochemical remission after relapse of the disease. Their treatment occurred as described next: histological remission with ST → ST withdrawal and antimalarial use for maintenance of remission for 1–3y → antimalarial withdrawal → relapse of AIH → re-introduction of antimalarial. Patients requested re-introduction of the drug in monotherapy instead of the ST, due to side effects related to corticosteroid use. Clinical and laboratory evaluations were made every 7–15 days until normalization of liver enzymes, thereafter every 2–3 months. 2/4 completed 18 months of biochemical remission and underwent liver biopsy to evaluate histological remission.
Results: Mean age at diagnosis of AIH was 30.5 ± 19.6 y. Anti-SLA/LP was the sole marker of disease in 2; 1 type 1 and 1 type 2 AIH. 2 had liver cirrhosis at diagnosis. Mean doses of AZA/PD in histological remission were, respectively, 93.7 ± 12.5 mg/d and 8.12 ± 2.4 mg/d. The mean interval between antimalarial withdrawal and relapse of AIH was 144.2 ± 54 days. The mean ALT at relapse was 118.5 ± 21 U/L. 2 patients took chloroquine DFC and 2 HCQ. During HCQ intake 1 patient needed further adjustment of drug to 800 mg/d for 15 days because of worsening of ALT from 130 to 246 U/L, which resulted in laboratory improvement, with subsequent reduction to the initial dose. 4/4 achieved biochemical remission, in a mean time of 88 ± 45.7

days. 2/4 patients had histological remission, the other 2 still do not have enough time of biochemical remission. The drug was well tolerated and there were no serious side effects.
Conclusion: Chloroquine monotherapy was safe and effective for induction of remission in a specific subgroup of AIH. This finding is unpublished and raises the possibility of including this drug as an option for initial treatment of AIH, not necessarily in monotherapy.

THU-233
Health-Related Quality of Life in patients with autoimmune hepatitis

A. Takahashi[1,2], K. Moriya[2,3], H. Ohira[1,2], T. Arinaga-Hino[2,4], T. Torimura[2,4], M. Zeniya[2,5], M. Abe[2,6], A. Takaki[2,7], J.-H. Kang[2,8], A. Inui[2,9], T. Fujisawa[2,9], K. Yoshizawa[2,10], Y. Suzuki[2,11], N. Nakamoto[2,12], K. Koike[2,13], H. Yoshiji[14], A. Goto[2,15], A. Tanaka[2,16], Z.M. Younossi[17], H. Takikawa[2,16]. *[1]Fukushima Medical University School of Medicine, Gastroenterology, Fukushima, Japan; [2]Japan AIH Study Group (JAIHSG), Japan; [3]Nara Medical University School of Medicine, Gastroenterology and Hepatology, Kashihara, Japan; [4]Kurume University School of Medicine, Medicine, Kurume-shi, Japan; [5]Sanno Medical Center, International University of Health and Welfare, Tokyo, Japan; [6]Ehime University Graduate School of Medicine, Gastroenterology and Metabology, To-on, Japan; [7]Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences, Gastroenterology and Hepatology, Okayama-city, Japan; [8]Teine Keijinkai Hospital, Center for Gastroenterology, Sapprro, Japan; [9]Saiseikai Yokohama Tobu Hospital, Pediatric Hepatology and Gastroenterology, Yokohama-City, Japan; [10]National Hospital Organization, Shinshu Ueda Medical Center, Gastroenterology, Ueda-City, Japan; [11]Toranomon Hospital, Hepatology, Tokyo, Japan; [12]Keio University School of Medicine, Internal Medicine, Tokyo, Japan; [13]The Third Hospital of Jikei University School of Medicine, Gastroenterology and Hepatology, Komae-shi, Japan; [14]Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan; [15]Fukushima Medical University School of Medicine, Center for Integrated Science and Humanities, Fukushima, Japan; [16]Teikyo University School of Medicine, Medicine, Tokyo, Japan; [17]Inova Health System, Betty and Guy Beatty Center for Integrated Research, Falls Church, United States*
Email: junior@fmu.ac.jp

Background and Aims: Health-Related Quality of Life (HrQoL) in patients with autoimmune hepatitis (AIH) is impaired, but has not been previously fully assessed, and the association between HrQoL and patient background remains unknown. We aimed to assess HrQoL in patients with AIH and identify factors associated with HrQoL impairment.
Method: We assessed HrQoL in patients with AIH, patients with chronic hepatitis C (CHC), and healthy subjects by using the Japanese version of the Chronic Liver Disease Questionnaire (CLDQ) and the 36-Item Short Form Survey (SF-36). We compared HrQoL in patients with AIH with that of patients with CHC and healthy subjects.
Results: Two-hundred sixty-five patients with AIH were enrolled in the study, of whom 88% were women, with a median age of 65 years. Of these patients, 10.6% and 57.0% had cirrhosis and complications, respectively. The overall CLDQ scores (5.5 vs. 6.2, $p < 0.001$) and physical (48.1 vs 54.2, $p < 0.001$) and mental (51.8 vs. 55.0, $p = 0.004$) component summaries of SF-36 were lower in the AIH patients than in the healthy subjects, but similar to those of the CHC patients. Having cirrhosis, complications, and treatment were associated with impaired HrQoL among patients with AIH. Particularly, prednisolone use was associated with lower scores in the worry domain in the CLDQ.
Conclusion: Patients with AIH showed HrQoL impairment, which was associated with not only disease progression, but also complications and treatment. Ways to improve HrQoL should be considered when disease outcome is not favorable and when using prednisolone.

THU-234
Pregnancy and autoimmune hepatitis: presentation and outcomes

L.P. Llovet[1], D. Horta[2], M.G. Eliz[3], M. Berenguer[3], E. Fábrega[4], F. Sáez-Royuela[5], M. García-Retortillo[6], Y.S. Torrijos[7], M.R. Gomez[8], C. Fernández-Rodríguez[9], E.G. Domínguez[10], A. Parés[1,11,11,12], M.C. Londoño[1,11,12]. *[1]Hospital Clínic Barcelona; [2]Hospital Mútua de Terrassa; [3]Hospital Universitario La Fe Valencia; [4]Hospital Universitario Marqués de Valdecilla; [5]Hospital Universitario de Burgos, Hepatology Department, Spain; [6]Hospital del Mar; [7]Hospital Universitario Virgen del Rocío; [8]Hospital Universitario Virgen del Rocio, Sevilla. Instituto de Biomedicina de Sevilla. CiberEHD, Hospital Universitario Virgen del Rocio, Sevilla, Spain; [9]Hospital Universitario Fundación Alcorconm; [10]Hospital Universitario Doce de Octubre; [11]CIBERehd; [12]IDIBAPS*
Email: llovet@clinic.cat

Background and Aims: There is a strong association between pregnancy and the outcome of autoimmune hepatitis (AIH). However, the information about this special situation is scarce. The outcome of the disease that has its onset in the postpartum period and the risk factors related to an adverse outcome or flares in pregnant patients who are already diagnosed of an AIH are currently unknown. Therefore, the aims of the study were: (1) To describe the outcomes of an AIH diagnosed in the postpartum period, and (2) To identify the risk factors associated to disease flares in pregnant patients with a previous diagnosis of AIH.
Method: This is a retrospective and multicentre cohort study. The clinical and laboratory characteristics of patients diagnosed of AIH in the postpartum and patients with AIH who presented at least a pregnancy during their follow-up were collected.
Results: Thirty-eight patients were included: 8 women diagnosed of AIH in the postpartum with a median age of 33 years-old (26–36), AST 648 UI/L (48–1815), ALT 814 UI/L (146–2398), bilirubin 9,3 mg/dL (0,9–12,7), INR 1,48 (1–1,7) and IgG 18 g/L (14–20). In all cases, the liver biopsy was compatible with the disease. After a median follow-up of 50 months (21–79), immunosuppression (IS) was successfully withdrawn in 4 patients (50%) and the rest maintained remission with monotherapy. Thirty patients with diagnosis of AIH (6 of whom had cirrhosis) and a median age of 34 years-old (27–35) had a total of 39 pregnancies. Nine (30%) had a postpartum flare. In these cases, the median time from AIH diagnosis and pregnancy was inferior (21 vs. 45 months; $p = 0.05$), and there was a tendency towards higher IgG levels (30 g/L vs. 24 g/L; $p = 0.43$). In addition, these patients had more flares unrelated to pregnancy (44% vs. 28%; $p = 0.03$), and required combined therapy (89% vs. 30%; $p = 0.03$) and second line therapies (33% vs. 3%; $p = 0.01$) to maintain remission more frequently. The success of immunosuppression withdrawal was inferior in patients who had a postpartum flare (22% vs. 43%; $p = 0.25$).
Conclusion: The acute onset of AIH in the postpartum is rare but the outcome of the disease seems to be excellent, requiring long-term minimal or non-immunosuppression. In patients with a previous diagnosis of AIH, postpartum flares are frequent, particularly in those patients with an inferior time after the diagnosis. The presence of postpartum flares appears to indicate a more aggressive form of the disease.

THU-235
Efficacy and safety of calcineurin inhibitors as salvage therapy in patients with autoimmune hepatitis

S. Strasser[1,2], R. Lim[3], J. Mitchell[4], A. Nicoll[5,6], K. Stuart[7], P. Gow[8], G. Macquillan[9], J. George[10,11], J. Mitchell[12], W. Kemp[4,6], G. Mccaughan[2,13], S. Roberts[4]. *[1]University of Sydney, Central Clinical School, Sydney, Australia; [2]Royal Prince Alfred Hospital, AV Morrow Gastroenterology and Liver Centre, Camperdown, Australia; [3]Royal Prince Alfred Hospital, AV Morrow Gastroenterology and Liver Centre, Sydney, Australia; [4]The Alfred, Gastroenterology, Melbourne, Australia;*

[5]Eastern Health, Gastroenterology, Box Hill, Australia; [6]Monash University, Medicine, Melbourne, Australia; [7]Princess Alexandra Hospital, Gastroenterology and Hepatology, Woolloongabba, Australia; [8]Austin Hospital, Liver Transplant Unit, Heidelberg, Australia; [9]Sir Charles Gairdner Hospital, Liver Transplant Unit, Perth, Australia; [10]Westmead Hospital, Storr Liver Unit, Sydney, Australia; [11]Westmead Institute for Medical Research, Sydney, Australia; [12]Sunshine Coast Hospital, Gastroenterology and Hepatology, Nambour, Australia; [13]Centenary Institute Cancer Medicine and Cell Biology Centre, Camperdown, Australia
Email: robertss@bigpond.net.au

Background and Aims: There is limited data on the outcomes of calcineurin inhibitors (CI) as salvage therapy in patients with autoimmune hepatitis (AIH) who fail to respond to standard therapy. This, we evaluated the efficacy and safety of cyclosporine A (CyA) and tacrolimus (TAC) in AIH patients who failed or were intolerant of corticosteroids with or without thiopurines.
Method: A retrospective study was performed of AIH patients who received either CyA or TAC after failure or intolerance of standard therapy. Patients were recruited from 7 major liver centres across Australia via the ALA Clinical Research Network. Records were reviewed for baseline demographics and liver disease characteristic, initial therapy, indications for CI initiation, treatment outcome and complications.
Results: A total of 28 patients with AIH (Type 1 96%, mean age 33 [range13–63 yrs], females 86%, Caucasian 96%, cirrhosis 54%) received CI therapy across the seven sites with 16 receiving CyA and 16 TAC, four of whom received TAC after failure/intolerance of CyA. The majority (89%) had received prior combination therapy with corticosteroids plus azathioprine/6-mercaptopurine; 17 (61%) had also received mycophenolate mofetil (MMF). The indication for CI was inefficacy of standard therapy with/without MMF in 22 (79%) and intolerance to treatment(s) in 6 (21%) patients. The median starting and maximal doses of CyA and TAC were 100 and 163, and 2 and 4 mg respectively. The overall biochemical remission rate on CI was 50% (16/32) including 10/23 (43%) patients receiving CI for treatment inefficacy and 6/9 (67%) with prior treatment intolerance. Treatment with CyA achieved remission in 10/16 (63%) patients including 6/11 (55%) in prior non-responders. In comparison TAC achieved remission in 6/16 (38%) patients (42% in CI naïve) including 4/12 (33%) in prior non-responders. Three patients experienced treatment failure on CI while one required liver transplantation. Eleven (73%) patients with cirrhosis achieved biochemical remission on CI therapy. 7 patients (TAC = 5) required dose-reduction due to side effects with 8 (50%) discontinuing CyA and 4 (33%) TAC mainly due to side-effects (50% for both) or treatment inefficacy. Fourteen patients (TAC = 9) reported significant side effects that mainly involved renal toxicity (n = 5), and neurologic (n = 10), dermatologic (n = 5), and musculoskeletal (n = 2) disorders. Three deaths occurred during follow up none of which were treatment related.
Conclusion: Salvage therapy with CyA and TAC in AIH patients who fail standard therapy is moderately effective achieving an overall remission rate of 50% including 43% in non-responders and 67% in those with prior treatment intolerance. Both CI appear relatively safe and reasonably well tolerated with the main side-effects being renal, neurologic and dermatologic in nature.

THU-236
Risk stratification using transient elastography and the new scoring systems for patients with primary biliary cholangitis

L. Perini[1], N. Cazzagon[1], F.P. Russo[2], G. Leardini[1], V. Baldo[3], M.F. Secchi[1], N. Perin[1], C. Mangini[1], A. Zago[1], A. Floreani[1]. [1]University of Padova, Dept of Surgery, Oncology and Gastroenterology, Padova, Italy; [2]University Hospital Padua, Gastroenterology, Padua, Italy; [3]University of Padova, Dept of Hygiene and Public Health, Padova, Italy
Email: annarosa.floreani@unipd.it

Background and Aims: The recent EASL guidelines recommend the use of transient elastography (TE) to monitor PBC progression and the risk scores to better define the individual risk of development of complications.
Method: 154 PBC patients prospectically seen between January 2009 and July 2017 were enrolled into the study. TE was performed at baseline and every 2 years thereafter (in the follow-up 111 pts had 2 measurements, and 52 pts 3 measurements). A cut-off of ≥9.6 kPa was chosen to determine the risk of decompensation. Globe score and UK-PBC scores were calculated at each interval. Risk factors were assessed using Cox proportional hazard models. Longitudinal variations of liver stiffness (LS) were assessed with the following formula: $\Delta LS/\delta t = (LS_2 - LS_1)/(t_2 - t_1)$.
Results: At baseline LS was positively correlated with the Globe score ($r = 0.395$, $p = 0.01$). UK-PBC score provided a survival outcome at 5, 10, and 15 years significantly correlated with the LS ($p < 0.001$). Survival at 15 years was 93.2 ± 5.4% in pts with LS ≤ 9.6 kPa, and 85.4 ± 11% in those with LS >9.6. The increase in LS/year was 0.15 ± 0.38 and 0.63 ± 1.6 kPa respectively ($p < 0.05$).
Conclusion: LS measurements and risk stratification scores are useful tools in the follow-up of PBC patients to establish prognosis and for decision-making for second line therapy.

THU-237
Independent predictors of primary biliary cholangitis (PBC) at high risk for progressive course in the United States: data from a large-real world database

Z. Younossi[1], M. Stepanova[2], R. Epstein[3], M. Strauss[4], P. Globai[5], F. Nader[2], A. Racila[5]. [1]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States; [2]Center for Outcomes Research in Liver Disease; [3]Epstein Health; [4]Intercept Pharmaceuticals; [5]Center for Liver Disease, Inova Fairfax Hospital
Email: zobair.younossi@inova.org

Background and Aims: Primary biliary cholangitis (PBC) is a chronic autoimmune liver disease that can lead to cirrhosis and its complications. Treatment options for PBC include ursodeoxycholic acid (UDCA, first line) and obeticholic acid (OCA). PBC patients with ALP levels ≥1.5×Upper Limit of Norm (ULN) tend to have high risk for a more progressive course. The real-world data regarding factors associated with biochemically uncontrolled/potentially progressive PBC is not available. The aim of the study was to use a large real-world electronic medical record/claims (EMR) database from the United States (US) to assess factors independently associated with high risk for progressive PBC.
Method: We used Owned Outcomes (O2) database containing comprehensive and continuous EMR/claims data from 500+ healthcare systems in the US. The database utilizes a proprietary computing platform to store HIPAA-compliant data. For this study, we selected patients ≥18 years old with an ICD-9/10 code for PBC who had continuous enrollment during 2014–2016 with a 1-year lookback period. Patients with ALP levels <1.5×ULN (regardless of treatment) were considered Low Risk (LR) and patients with ALP levels ≥1.5xULN who had received UDCA for at least 1 year were considered High Risk (HR). ALP levels came from the most current PBC-related visit during the enrollment period; duration of UDCA reflected cumulative exposure over entire enrollment history.
Results: Of 195 million patients comprising this real-world database, 36,317 adults had PBC. After applying inclusion and exclusion criteria, 13,843 patients comprised our final PBC cohort (n = 9,792 LR and n = 4,051 HR). The HR PBC patients were older, more female, more white, had more metabolic and autoimmune comorbidities, and had more compensated cirrhosis ($p < 0.05$). In multivariate analysis, older age, female gender, living in Midwest, presence of other autoimmune diseases and compensated cirrhosis were independently associated with HR PBC (Table).

Table: Independent predictors of uncontrolled PBC

Predictor	odds ratio (95% CI)	p
Age, per year	1.006 (1.003–1.009)	<0.0001
Male gender	0.48 (0.43–0.54)	<0.0001
Midwest region	2.86 (2.59–3.15)	<0.0001
West region	0.64 (0.58–0.70)	<0.0001
Medicaid payer	0.66 (0.54–0.80)	<0.0001
Autoimmune hepatitis	1.18 (1.03–1.35)	0.0173
Peripheral neuropathy	1.11 (1.01–1.23)	0.0359
Autoimmune dermatitis	1.17 (1.01–1.36)	0.0416
Sjogren's syndrome	1.38 (1.16–1.64)	0.0004
Compensated cirrhosis	1.46 (1.31–1.62)	<0.0001

Conclusion: Numerous clinical and sociodemographic factors predict high risk for potentially progressive PBC. These data should inform clinicians to implement strategies to optimize care of these patients.

THU-238

Pharmacokinetics and pharmacodynamics of seladelpar, a potent and selective PPAR-delta, in patients with primary biliary cholangitis

P. Boudes[1], G. Michael[2], C. Bowlus[3], G. Hirschfield[4], D. Jones[5], J. Odin[6], D. Sheridan[7], N. Gitlin[8], S. Harrison[9], T. Hassanein[10], C. Levy[11], M. Shiffman[12], D. Thorburn[13], P.J. Thuluvath[14], J. Vierling[15], Y.-J. Choi[1], M. Varga[1], A.(Sasha) Steinberg[1], C. Mcwherter[1], R. Martin[1]. *[1]CymaBay Therapeutics, Newark, United States; [2]Digestive Healthcare of Georgia, Atlanta, United States; [3]University of California Davis, Sacramento, United States; [4]University of Birmingham, Birmingham, United Kingdom; [5]University of Newcastle, Newcastle upon Tyne, United Kingdom; [6]Icahn School of Medicine at Mount Sinai, New York, United States; [7]Plymouth Hospitals NHS Trust & Plymouth University, Peninsula School of Medicine and Dentistry, Plymouth, United Kingdom; [8]Atlanta Gastoenterology Associates, Atlanta, United States; [9]Pinnacle Clinical Research, San Antonio, United States; [10]Southern California Research Center, Coronado, United States; [11]University Of Miami, University Of Miami, Miami, United States; [12]Institute of Virginia, Richmond, United States; [13]Royal Free London, London, United Kingdom; [14]The Institute for Digestive Health & Liver Diseases at Mercy, Baltimore, United States; [15]Advanced Liver Therapies, Baylor College of Medicine, Houston, United States*
Email: pboudes@cymabay.com

Background and Aims: Seladelpar, a selective agonist of the PPAR-δ receptor, is a potent anti-cholestatic agent that in rats is predominantly eliminated by the bile. We evaluated the plasma exposure of seladelpar in patients with primary biliary cholangitis (PBC) and compared it to healthy volunteers. We also explored the relationship between the exposure of seladelpar and its anti-cholestatic activity.
Method: Plasma drug profiles were obtained from a phase 2 study in PBC patients who were inadequate responders to or intolerant to ursodeoxycholic acid (UDCA) (EudraCT 2016-002996-91). Seladelpar was formulated in capsules and dosed at 2, 5, and 10 mg daily. Plasma concentration vs time profiles (seladelpar and its metabolites) were obtained on the first day of treatment and after 2 weeks of treatment. Markers of cholestasis, including serum alkaline phosphatase (AP), were collected at regular intervals up to 12 weeks. The relationship between seladelpar AUCs and alkaline phosphatase changes was analyzed with linear regression.
Results: Data from 3, 6, and 6 patients were available for the 2, 5, and 10 mg doses, respectively. The mean (SD) C_{max} at Day 1 were 19 (7), 59 (34), 169 (100) ng/mL and the mean (SD) $AUC_{(0-24)}$ were 175 (57), 606 (282), 1285 (406) ng·hr/mL for the 2, 5, and 10 mg, respectively. The mean (SD) C_{max} at Week 2 were 29 (12), 68 (21), 142 (53) ng/mL and the mean (SD) $AUC_{(0-24)}$ were 267 (120), 831 (246), 1387 (257) ng·hr/mL for the 2, 5, and 10 mg, respectively. There was no apparent difference in exposure to seladelpar between the first day of treatment and after two weeks of treatment and exposure appeared dose proportional. Seladelpar exposure after two weeks of treatment correlated with the anti-cholestatic activity (Figure).

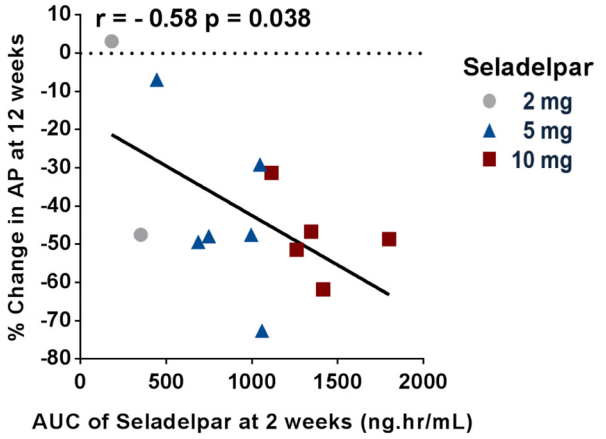


Figure: Correlation between seladelpar exposure and changes in AP.

Conclusion: Seladelpar anti-cholestatic activity correlates with plasma drug exposure after two weeks of treatment. The study is ongoing and has been modified to evaluate seladelpar exposure after 12 weeks of treatment, a time point when the anti-cholestatic activity is further established.

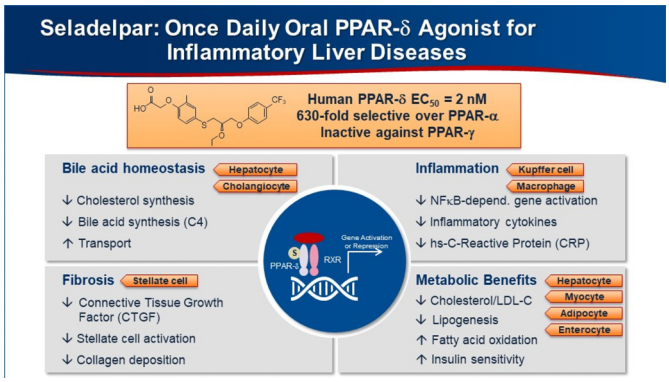
THU-239

Seladelpar's mechanism of action as a potential treatment for primary biliary cholangitis and non-alcoholic steato-hepatitis

P. Boudes[1], Y.-J. Choi[1], A.(Sasha) Steinberg[1], S. Bergheanu[2], C. Mcwherter[1]. *[1]CymaBay Therapeutics, Newark, United States; [2]Saberg Clinical Research, Rotterdam, Netherlands*
Email: pboudes@cymabay.com

Background and Aims: Seladelpar, a potent and selective agonist of the peroxisome-proliferator activated receptor (PPAR)-delta, is being developed for primary biliary cholangitis (PBC) and non-alcoholic steatohepatitis (NASH). PPARs are intra-nuclear receptors that form dimers with the retinoid X receptor (RXR) and regulate specific genes transcription. PPAR-delta is activated by lipids and controls metabolic and inflammatory pathways in the liver, inflammatory cells, muscle, and fat and intestinal tissues. It differs from PPAR-alpha and gamma because of its broad tissue distribution and its unique set of target genes. In the liver, the delta receptor differs from the other isotypes by its broad activity in hepatocytes, cholangiocytes, Kupffer cells and stellate cells. We present data supporting the mechanism of action of seladelpar for PBC and NASH.
Methods: Seladelpar was evaluated in a multiple dose ascending study in healthy volunteers; in two phase-2 studies in dyslipidemia (NCT00701883 and 02472535) and in two phase-2 studies in PBC (NCT02609048 and 02955602). Supportive data were obtained from preclinical in vivo models of metabolic diseases and from culture studies with hepatocytes, intestinal cells and macrophages.
Results: In hepatocytes, seladelpar suppressed CYP7A1, the key enzyme in bile acid (BA) synthesis, and decreased plasma C4, a marker of BA synthesis. It also decreased the synthesis and absorption of cholesterol, the substrate for BA synthesis. This results in potent anti-cholestatic activity. Seladelpar targets liver Kupffer cells, infiltrating macrophages, and stellate cells, responsible for liver fibrosis. The resulting anti-inflammatory effect is manifested clinically by decreases in transaminases and high-sensitivity C-reactive protein. In a mice model of NASH, this resulted in abrogation of hepatocyte ballooning, lymphocytic infiltrates and decreased fibrosis. Seladelpar inhibits lipogenesis and increases fatty acid oxidation which clinically is manifested by decreases in LDL-C, serum triglycerides and free fatty acids, and improved insulin sensitivity. Contrary to FXR agonists,

which also target PBC and NASH, seladelpar does not increase FGF19 or LDL-C and is not associated with drug-induced pruritus.



Conclusion: Seladelpar results in a profound anti-cholestatic and anti-inflammatory effects in PBC patients with no drug-induced pruritus. Seladelpar targets all mechanisms at play in NASH and may constitute a backbone therapy.

Cirrhosis: ACLF and Critical illness

THU-245

Class III (morbid) obesity is an independent risk factor for the development of acute on chronic liver failure in patients with decompensated cirrhosis

V. Sundaram[1], R. Jalan[2], J. Ahn[1], M. Charlton[3], D. Goldberg[4], C. Karvellas[5], M. Noureddin[1], R. Wong[6]. [1]*Cedars-Sinai Medical Center, Los Angeles, United States;* [2]*University College London Hospital, United Kingdom;* [3]*University Of Chicago Medical Center, Chicago, United States;* [4]*Perelman School of Medicine at the University of Pennsylvania, Philadelphia, United States;* [5]*University of Alberta Hospital, Edmonton, Canada;* [6]*Alameda Health System, Oakland, United States*
Email: vinaysundaram@yahoo.com

Background and Aims: Acute on chronic liver failure (ACLF) is a syndrome precipitated by systemic inflammation. Obesity, particularly class III (morbid) obesity, is a risk factor in cirrhosis for decompensation, infection, and mortality, possibly from a chronic inflammatory state. We aim to evaluate the association between obesity and ACLF, using two United States (US) registries.
Method: We first examined the United Network for Organ Sharing (UNOS) database, years 2005–2016, characterizing patients at wait-listing as non-obese (BMI < 30), obese class I-II (BMI 30–39.9) and obese class III (BMI >= 40). ACLF was determined based on the CANONIC study definition. We used Cox proportional hazards regression to assess the association between obesity and ACLF development at transplantation. We then validated our findings using the Nationwide Inpatient Sample (NIS), years 2009–2013, a database representing 20% of US hospital discharges. Obesity category, hepatic decompensation, and organ system failure was identified using validated diagnostic codes. Non-hepatic comorbidities were assessed using Deyo modification of the Charlson index. Logistic regression evaluated the association between obesity and ACLF development.
Results: Among 100,380 patients in the UNOS database, 63,712 (63.5%) were non-obese, 32,603 (32.5%) were obese class I-II, and 4,065 (4.0%) were obese class III. ACLF at time of transplantation was more prevalent among class III obesity patients (23.1%, $p < 0.001$), compared to non-obese (15.9%) and obesity class I-II (16.5%). In the NIS registry, 287,202 patient records with decompensated cirrhosis were studied, of which 258,402 (89.9%) were non-obese, 15,108 (5.3%) had class I-II obesity and 13,692 (4.7%) had class III obesity. ACLF was more prevalent among class III obesity patients (45.1%, $p < 0.001$), compared to non-obese (37.6%) and class I–II obesity (38.8%). Modeling from both databases revealed class III obesity to be independently associated with ACLF (Table 1). Furthermore, class III obesity patients had greater prevalence of renal failure in both analyses. Other organ failures and multi-organ system failure was similar among the three groups.

Table 1: Multivariable modeling regarding association with obesity category and ACLF

	Reference	Odds Ratio	95% CI
UNOS database*			
Obesity Class I–II	Non-obese	1.12	1.05–1.19
Obesity Class III		1.24	1.09–1.41
NIS database**			
Obesity Class I–II	Non-obese	0.987	0.95–1.03
Obesity Class III		1.28	1.23–1.32

*Adjusted for age, gender, ethnicity, etiology of liver disease, presence of ascites, presence of encephalopathy, diabetes, serum sodium, serum albumin, and MELD score at listing.
**Adjusted for age, gender, ethnicity, Charlson index category.

Conclusion: Class III obesity is a newly identified risk factor for ACLF. Development of renal failure is of particularly greater risk in this population.

THU-246

Regional variations in the development of acute-on-chronic liver failure (ACLF) in patients with cirrhosis and bacterial infections

F. Wong[1], V. Singh[2], P. Caraceni[3], R. Maiwall[4], S. Piano[5], S. Marciano[6], J. Fernandez[7], C. Alessandria[8], E. Soares[9], D.J. Kim[10], S.E. Kim[11], M. Marino[12], J. Vorobioff[13], R. de Cassia Ribeiro Barea[14], M. Merli[15], L. Elkrief[16], V. Manuel, V. Blasco[17], A. Krag[18], S. Singh[19], L.A. Lesmana[20], C. Toledo[21], V. Xavier[22], N. Intagliata[23], L. Rabinowich[24], T. Bruns[25], E.L. Yoon[26], M. Girala[27], N.T. Pyrsopoulos[28], T.H. Kim[29], S.Y. Yim[30], F. Durand[31], A. Gadano[6], P. Angeli[32]. [1]*University of Toronto, Toronto, Canada;* [2]*Postgraduate Institute of Medical Education and Research, Padova, Italy;* [3]*University of Bologna, Bologna, Italy;* [4]*Institute of Liver and Biliary Sciences (ILBS), New Delhi, India;* [5]*University of Padova, University and General Hospital of Padova, Padova, Italy;* [6]*Hospital Italiano de Buenos Aires, Buenos Aires, Argentina;* [7]*Hospital Clinic of Barcelona, Liver Unit, Barcelona, Spain;* [8]*University Hospital of Turin, Turin, Italy;* [9]*Gastrocenter-Unicamp, Campinas, Brazil;* [10]*Hallym University College of Medicine, Chuncheon,Republic of South Korea;* [11]*Hallym University Sacred Heart Hospital, Republic of South Korea;* [12]*Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina;* [13]*Universidad Nacional de Rosario, Rosario, Argentina;* [14]*Faculty of Medicine of Bahia, Campo Grande, Brazil;* [15]*Sapienza University of Rome, Rome, Italy;* [16]*University Hospital of Geneva, Geneva, Italy;* [17]*Hospital Vall d'Hebron, Liver Unit, Barcelona, Spain;* [18]*Odense University Hospital, Odense, Denmark;* [19]*Shri Ramachandra Bhanj Medical College, Orissa, India;* [20]*Digestive Disease and Oncology Centre (DDOC)-Medistra Hospital, Jakarta, Indonesia;* [21]*Hospital Valdivia, Universidad Australe de Chile, Valdivia, Chile;* [22]*Ghent University Hospital, Ghent, Belgium;* [23]*University of Virginia, Charlottesville, United States;* [24]*Tel-Aviv Medical Center, Tel-Aviv, Israel;* [25]*Jena University Hospital, Jena, Germany;* [26]*Sanggye Paik Hospital, Inje University Seoul, Seoul, Republic of South Korea;* [27]*Universidad Nacional de Asunciòn, Asunciòn, Paraguay;* [28]*Rutgers New Jersey Medical School, Newark, United States;* [29]*Ewha Womens University, Rep. of South Korea;* [30]*Anam Korea University Hospital, Seoul, Rep. of South Korea;* [31]*Hospital Beaujon, Clichy, France;* [32]*University of Padova, Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine, DIMED, Padova, Italy*
Email: pangeli@unipd.it

Background and Aims: Bacterial infections, by inducing an inflammatory state and by further perturbing the already abnormal hemodynamics of advanced cirrhosis, can potentially precipitate ACLF. Patterns of bacterial infections and antibiotic resistance vary in different regions of the world. These could possibly contribute to variations in the types of organ failure or severity of ACLF around the world. The aim was to evaluate the regional differences in the development of ACLF as a result of bacterial infections in cirrhosis.
Method: The International Club of Ascites (ICA) enrolled 1302 cirrhotic patients admitted for complications of cirrhosis with a concomitant bacterial infection worldwide from Oct 2015 to Sept 2016. All patients had baseline clinical, laboratory and microbiological data collected from the time of diagnosis of infection. Information on antibiotic given, antibiotic resistance, further complications, patient and infection outcomes were also collected. All patients were followed till liver transplant, or death, or discharge.
Results: Patients were divided into 6 regions worldwide (table). Patients were mostly middle aged (57 ± 13 years) men (69%) with alcoholic cirrhosis (52%). ACLF as defined by the EASL-Chronic Liver Failure (CLIF) Consortium was already present in 35% of patients at infection diagnosis, being significantly more prevalent (60%) and more severe in the Indian subcontinent (table) when compared to the rest of the world, possibly related to the high prevalence of multidrug resistant organisms in India (73% vs. 29%, p < 0.0001). Renal failure was the most common organ failure with ACLF across the world (17–34% of all organ failures). In patients without ACLF at infection diagnosis, further ACLF episodes occurred more frequently in Indian patients than in the other patients (44% vs. 25%, p = 0.0072). The severity of ACLF following treatment of infection was similar across the world (p = 0.078).

	South Europe (n= 428)	North Europe (n= 137)	South America (n = 252)	North America (n = 69)	Indian hospitals (n= 250)	Other Asian hospitals (n= 166)	P
ACLF – n (%)	111 (26)	39 (29)	93 (37)	24 (35)	151 (60)	42 (25)	<0.001
ACLF grade – n (%)							
Grade 1	53 (48)	24 (62)	44 (47)	9 (38)	41 (27)	19 (45)	<0.001
Grade 2	42 (38)	8 (21)	35 (38)	6 (25)	59 (39)	14 (33)	
Grade 3	16 (14)	7 (18)	14 (15)	9 (38)	51 (34)	9 (21)	

Conclusion: ACLF is common with bacterial infections in cirrhosis, and can occur even after infection is treated. Efforts should be made to prevent infection so to reduce the likelihood of ACLF.

THU-247

Number of organ failures is a better predictor of waitlist mortality in those who die within 30 days of listing for liver transplantation

P.J. Thuluvath[1], A. Thuluvath[2], Y. Savva[3]. [1]*Mercy Medical Center & University of Maryland School of Medicine, Medicine, Baltimore, United States;* [2]*Johns Hopkins University, Medicine, Baltimore, United States;* [3]*Mercy Medical Center, Institute of Digestive Health & Liver Diseases, Baltimore, United States*
Email: thuluvath@gmail.com

Background and Aims: It is possible that many patients with cirrhosis who died or transplanted within 30-days of listing have ACLF. The independent effect of organ failures (OF) on waitlist mortality is not well defined.
Method: We analyzed UNOS data from 2002 to 2016 of all adults who died within 30 days of listing for LT. We defined OF if patients had bilirubin ≥12 mg/dL, INR ≥2.5, serum creatinine ≥2 mg/dL or on dialysis, on ventilator, on life support or had stage 3 or 4 HE. Based on this, patients can have no OF or between 1 and 6 OF. The cumulative incidence of death based on the number of OF was estimated using a cumulative incidence competing risk (competing risk being liver transplantation) approach (CICR). For the models of the associations with risk factors, the Fine and Gray competing risk regressions were used and the goodness of fit was evaluated. We examined 3 models: Model 1 with age and organ failures, Model 2 with age and 6 MELD groups (see table), and Model 3 with age and MELD as a continuous variable.
Results: During the study period, 5,577 (5%; 1198 no OF, 2018 1-2 OF, 1430 3-4 OF, 679 5-6 OF) patients died and 21,580 (18%) patients were transplanted within 30 days of listing. For patients who died, mean MELD score was 31.1 ± 10.7, and 40.2% had MELD ≥35. 30-day mortality increased with increasing number of organ failures in those who were not transplanted (Figure); the incidence of mortality (%) was 1,8,16, 25, 33, 37 and 48 for the 7 groups respectively for OF 0 to OF 6. Additionally, the interval between listing and death or transplantation decreased with increase in organ failures. The median interval for death after listing was only 3–4 days for OF 4–6, 7–9 days for OF 2–3, and 14–18 days for OF 0-1. After adjusting for age, Model 1 using the number of organ failures fit 30-day mortality best (lowest AIC) compared to the other 2 models using MELD scores. Moreover, the likelihood ratio test confirmed that Model 1 fits the 30-day mortality better than the other 2 models (MELD categorical, Chi-square statistic 1441, P < 0.0001; MELD continuous Chi-square statistic 1712, P < 0.0001).

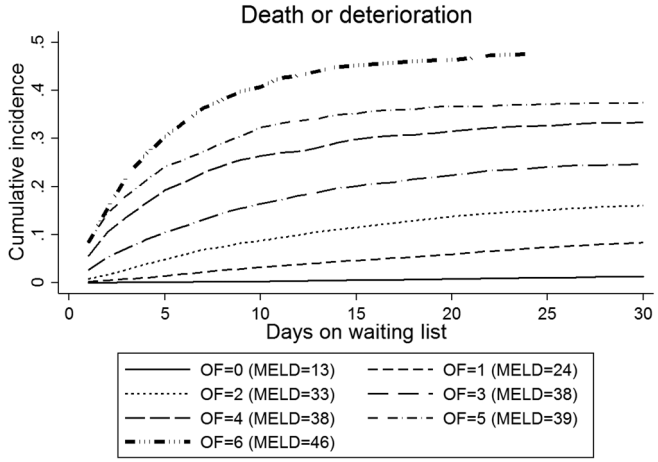


Table (abstract: THU-247).

Sub-distribution Hazard Ratio (HR) (*** = P <0.0001)

Model 1 (AIC = 118,242)		Model 2 (AIC = 119,680)		Model 3 (AIC = 119,943)	
Age	1.02 (1.02–1.02)***	Age	1.02 (1.01–1.02)***	Age	1.02 (1.02–1.02)***
OF		MELD		MELD score continuous	1.12 (1.12–1.12)***
0	1.00	≤20	1.00		
1	7.02 (6.47–7.61)***	21–25	5.85 (5.32–6.40)***		
2	15.16 (13.96–16.46)***	26–30	13.06 (11.94–14.27)***		
3	25.94 (23.71–28.39)***	31–35	19.15 (17.50–20.96)***		
4	41.65 (37.61–46.14)***	36–40	27.36 (24.98–29.96)***		
5	53.44 (47.79–59.75)***	≥41	43.25 (39.65–47.17)***		
6	65.41 (54.79–78.09)***				

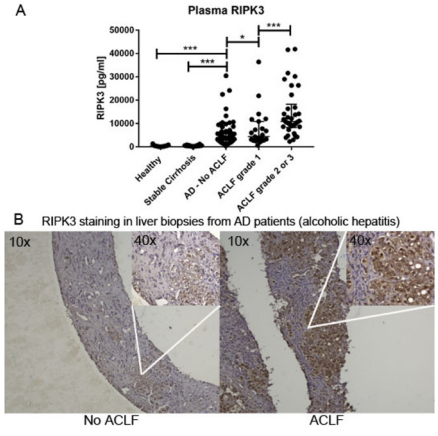
Conclusion: Waitlist mortality, within 30 days of listing, increases with an increase in the number of OF, and the median interval between listing and death is 3–7 days with 3 or more OF. Number of organ failures is a better predictor of mortality within 30 days of listing than MELD scores.

THU-248

Impact of receptor interacting protein kinase 3 levels on acute on chronic liver failure progression

T. Kondo, S. Macdonald, Y. Zheng, R. Mookerjee, F. Andreola, R. Jalan.
Institute for Liver and Digestive Health, University College London, London
Email: takakondonaika@yahoo.co.jp

Background and Aims: In cirrhotic patients with acute decompensation (AD), the occurrence of organ failures defines acute on chronic liver failure (ACLF); a condition characterized by liver cell death and high risk of short-term mortality. With progression from AD to ACLF the mode of cell death evolves from predominantly apoptotic to other non-apoptotic forms. Necroptosis is a newly described form of programmed cell death and results in a release of potentially pro-inflammatory cell contents that could drive further cell death, and organ failure. Receptor Interacting Protein Kinase 3 (RIPK3) is the key player in the necroptosis signaling pathway but its role in ACLF is unclear. We therefore, evaluated plasma and hepatic RIPK3 levels in patients with no ACLF and those with ACLF.
Method: One hundred forty cirrhotic patients from DASIMAR study cohort (NCT01071746) with AD were enrolled (83 with no ACLF, 23 with ACLF grade 1 and 34 with ACLF grade 2 or 3). Twenty-four of the no ACLF patients progressed to ACLF. Additional 42 patients with stable cirrhosis (SC) and 21 healthy volunteers (HV) were also studied. RIPK3 plasma levels and liver tissue expression were assessed by ELISA and immunohistochemistry, respectively.
Results: Plasma RIPK3 levels rose progressively with the severity of liver injury (HV: 322.1 pg/ml [51.18–1294], SC: 445.4 [28.83–1196], no ACLF: 3247 [371.9–30489], ACLF grade 1: 4383 [589.5–36383], ACLF grades 2 or 3: 10909 [2300–41878]) which demonstrated statistical significance between HV vs. AD ($p < 0.001$), SC vs. no ACLF ($p < 0.001$), no ACLF vs. ACLF grade1 ($p = 0.022$), ACLF grade1 vs. grade2 or 3 ($p < 0.001$) (Fig. 1A). Furthermore, plasma RIPK3 levels were a significant predictive factor for 90-day mortality ($p = 0.041$) (HR = 1.0001 [95%CI 1.0000–1.0001]).



Prediction of progression from AD to ACLF: Plasma RIPK3 levels were significantly higher in the patients who progressed from no ACLF to ACLF than those who did not (2658 [371.9–30489] vs. 4968 [1401–24159]) ($p = 0.002$) and significant predictive factor for progression from no ACLF to ACLF ($p = 0.023$).
Liver immunohistochemistry: Liver biopsies of ACLF patients showed a stronger RIPK3 staining compared to no ACLF patients (Fig. 1B).

Conclusion: These data demonstrate for the first time the importance of necroptosis, as measured by plasma and hepatic RIPK3 in ACLF and, its prognostic value in the risk of progression from no ACLF to ACLF and, mortality.

THU-249

NASH/NAFLD patients with end stage liver disease experienced high inpatient hospitalization costs and substantial disease progression: Results of a French national database on hospital care analysis

J. Boursier[1], C. Fabron[2], A. Lafuma[2], I. Bureau[2]. [1]*Angers Hospital University, France;* [2]*CEMKA, Bourg La Reine, France*
Email: jeboursier@chu-angers.fr

Background and Aims: Disease progression and inpatients costs have not been well characterized in NAFLD/NASH patients. This study examined mortality, healthcare resource utilization, and inpatient costs in NAFLD/NASH patients with end stage liver disease (ESLD) (decompensated cirrhosis, hepatocellular carcinoma or liver transplant) with and without type 2 diabetes mellitus (T2DM).
Method: Patients ≥18 years of age with NAFLD/NASH (ICD-10: K76.0, K75.8) were identified from the French National Database on hospital care (PMSI) between 2009 and 2015. Patients with other causes of liver disease were excluded. All hospital stays with ESLD were extracted. The index dates were first dates of ESLD diagnosis.
Results: 131,898 NAFLD/NASH patients were hospitalized during the study period, with 11.2% (n = 14,822) experiencing CC, ESLD, and/or death. The total percent of ESLD patients in the study population was 6.3% (n = 8,288) (2,810 progressed to ESLD and 5,478 diagnosed with ESLD at index). ESLD patients' mean age was 64.8 ± 16.1 years and 46.8% female. For the subset of patients (n = 2,559) who progressed directly from NAFLD/NASH at baseline study period to ESLD, mean time of progression was 21.4 months. 20% (n = 1,654) of ESLD patients progressed to death and mean time of progression was 14.4 months. ESLD patients had a high prevalence of comorbidities at ESLD index date: hypertension was 65%, hyperlipidemia was 34%, obesity was 42%, and T2DM was 46%. In subgroup analysis, the prevalence of comorbidities was significantly higher in T2DM than no T2DM patients. The mean number of hospitalizations and length of stay per hospitalization increased from 0.5 ± 1.2 to 2.8 ± 10.7 and from 2.2 ± 6.3 to 10.8 ± 13.2 days following ESLD diagnosis, respectively (both $P < 0.0001$). Additionally, following ESLD diagnosis, mean cost per stay increased from €1,119 ± 2,743 to €5,970 ± 6,318 and mean annual hospitalization costs increased from €3,474 ± 15,212 to €13,291 ± 27,225 (both $P < 0.0001$) (Figure).

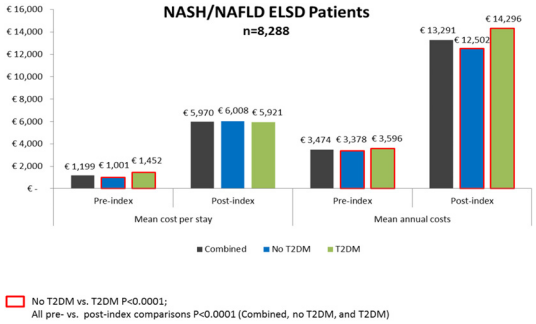


Figure: NASH/NAFLD ESLD patients mean cost per hospital stay and mean annual hospitalization costs pre- and post-index and stratified by T2DM and no T2DM patients.

Conclusion: NAFLD/NASH hospitalized ESLD patients had a high mortality rate. During the study period of 7 years, 20% of ESLD patients died in a mean time of 14.4 months. ESLD patients experienced an over 400% increase in mean annual number of hospitalizations, 400% increase in length of stay, and an almost 300% increase in annual hospitalization costs following ESLD diagnosis.

New treatments are urgently needed to prevent progression of NAFLD/NASH patients to ESLD and to reduce medical costs.

THU-250

Combinations of inflammatory markers, soluble (s)CD163, mannose receptor (sMR) and neutrophil gelatinase associated lipocalin (NGAL), predicts mortality in patients with acute-on-chronic liver failure

H. Grønbæk[1], H.J. Møller[2], D. Benten[3], R. Jalan[4], C. Moreno[5], A. Alex[6], P. Marco[6], P. Ginès[7], V. Arroyo[6]. [1]*Aarhus University Hospital, Department of Hepatology & Gastroenterology, Aarhus C, Denmark;* [2]*Aarhus University Hospital, Department of Clinical Biochemistry, Århus C;* [3]*University Hospital Hamburg-Eppendorf, Department of Gastroenterology and Hepatology, Hamburg, Germany;* [4]*University College London, Royal Free Hospital, Liver Failure Group, Institute for Liver Disease Health, London, United Kingdom;* [5]*Erasme Hospital, Universite Libre de Bruxelles, Department of Gastroenterology and Hepato-Pancreatology, Brussels, Belgium;* [6]*European Foundation for the study of Chronic Liver Failure (EF-CLIF), Barcelona, Spain;* [7]*University de Barcelona, Liver Unit, Hospital Clínic de Barcelona, Barcelona, Spain*
Email: henngroe@rm.dk

Background and Aims: Acute-on-chronic liver failure (ACLF) has a sinister prognosis and there is a need for precise biomarkers and scoring systems to better characterize ACLF patients and predict prognosis. Systemic inflammation and renal failure are hallmarks in ACLF disease development and progression. We hypothesized that the combination of specific inflammatory markers in combination with clinical scores are better predictors of survival than the originally developed CLIF-C acute decompensation (AD) and CLIF-C ACLF scores.
Method: We re-evaluated all measured inflammatory markers in 522 patients from the CANONIC study, 342 *without* and 180 *with* ACLF. We used the Harrell's C-index to determine the best marker alone or in combination with the original scores, and calculated new scores for prediction of mortality in the original CANONIC cohort.
Results: The best markers to predict 90-day mortality in patients *without* ACLF were macrophage activation markers soluble (s)CD163 and mannose receptor (sMR). Urinary neutrophil gelatinase associated lipocalin (UNGAL) and sCD163 were predictors for 28-day mortality in patients *with* ACLF. The new developed CLIF-C AD + sMR score in patients *without* ACLF improved 90-days mortality prediction compared to the original CLIF-C AD score (C-index 0.82(0.78–0.86) vs. 0.74(0.70–0.78, P = 0.004). Further, the new CLIF-C ACLF + UNGAL + sCD163 improved the original CLIF-C ACLF score for 28-days mortality (0.85(0.79–0.91) vs. 0.75(0.70–0.80), P = 0.039).
Conclusion: The capability of these inflammatory markers to improve the original prognostic scores in cirrhosis patienst *without* and *with* ACLF points to a key role of macrophage activation and inflammation in the development and progression of AD and ACLF.

THU-251

The outcome of acute-on-chronic liver failure in the intensive care is similar to a propensity matched ICU population without liver disease

S. van der Merwe[1], P. Meersseman[2], L. Langouche[3], H. Korf[4], J.D. Plessis[5], M. Mekeirele[2], D. Cassiman[6], W. Laleman[5,7], F. Nevens[5,7], A. Wilmer[2], G. Van den Berghe[2,3]. [1]*UZ Leuven, Department of Gastroenterology and Hepatology, Belgium;* [2]*UZ Leuven, Department of Internal Medicine, Leuven, Belgium;* [3]*KU Leuven, Clinical Division and Laboratory of Intensive Care Medicine, Department of Cellular and Molecular Medicine, Leuven, Belgium;* [4]*KULeuven, Laboratory of Hepatology, Leuven, Belgium;* [5]*KU Leuven, Laboratory of Hepatology, Leuven, Belgium;* [6]*University hospitals leuven, Gastroenterology and Hepatology, Leuven, Belgium;* [7]*UZ Leuven, Gastroenterology and Hepatology, Leuven, Belgium*
Email: hannelie.korf@kuleuven.be

Background and Aims: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of cirrhosis, development of organ failure and high short-term mortality. It is unclear whether the ICU outcome in ACLF is different from other ICU populations. We compared the clinical course and host response in critically ill ICU patients with or without ACLF matched for baseline severity of illness scores.
Method: A post-hoc analysis was performed of the large EPaNic ICU study (n = 4640): 133 patients were identified with cirrhosis of whom 71 patients fulfilled the Canonic criteria for ACLF. These patients were matched for type and severity of illness and demographics to 71 septic and 71 medical ICU patients without liver disease. The clinical, biochemical and outcome parameters were compared and, in a subset of 100 patients, day 1 serum cytokines were quantified.
Results: The outcome of ACLF when compared to septic or medical ICU patients, matched for baseline parameters of illness severity, was similar regarding length of ICU stay, development of new infections, organ failure and septic shock, ICU hospital and 90 day mortality. CRP and platelets levels were lower in ACLF patients throughout the first week in ICU. Baseline cytokines IL-10, IL-1β, IL-6, and IL-8 were similarly elevated in ACLF and septic ICU patients, whereas serum TNF-α was higher and CCL13 lower in ACLF.
Conclusion: ACLF patients admitted to the ICU showed comparable clinical and ICU outcomes compared to non-ACLF patients without liver disease with similar baseline severity of illness characteristics. This suggest that admission criteria to the ICU should not be different in ACLF compared to other populations. Furthermore, ACLF patients that are liver transplant candidates should be identified early in their ICU course.

THU-252

Early management of critically ill cirrhotic patients admitted in ICU for gastrointestinal bleeding: wait day 3 to avoid taking a bad decision

L. Meunier[1], A. De Jong[1], L. Caillo[2], J.U. Bedoya[1], S. Faure[1], S. Jaber[1], G.-P. Pageaux[3]. [1]*CHU St Eloi Montpellier;* [2]*CHU Caremeau Nimes;* [3]*CHU Montpellier, Montpellier, France*
Email: lucymeunier66@gmail.com

Background and Aims: Gastrointestinal bleeding is a serious complication of portal hypertension and a leading cause of death in cirrhotic patients. The main objective of this study was to determine the risk factors for hospital mortality of cirrhotic patients admitted to intensive care unit (ICU) for gastrointestinal bleeding related to portal hypertension.
Method: It was an observational retrospective study of prospectively collected data in the ICU at Montpellier University Hospital. Risk factors for hospital mortality were analyzed in univariate and multivariate analysis after logistic regression.
Results: Between November 1998 and March 2016, 200 cirrhotic patients with a gastrointestinal bleeding (219 admissions) admitted to the ICU were included. The median age was 55 ± 10.5 years, 78% were men and the cirrhosis was most frequently alcohol-related (64%) and advanced (78% of patients Child-Pugh B or C). Mortality rate in ICU was 29.5% and hospital mortality rate was 38.5%. On day 3 (D_3), AUROC for the prognosis scores were 0.73 (95% CI 0.64–0.82) for Chronic Liver Failure Sequential Organ Failure Assessment (CLIF SOFA) and 0.75 (95% CI 0.65–0.84) for grade of acute-on-chronic liver failure (ACLF). The independent risk factors for hospital mortality were, on D_3: Model for End-stage Liver Disease (MELD) score >20 on D_0 (OR: 2.78 (1.14–6.75), p = 0.0243), increase of bilirubin > 13% µmol/L between D_0 and D_3 (OR: 6.18 (2.33–16.38), p= 0.0003), mechanical ventilation until D_3 (OR: 3.51 (1.34–9.18), p = 0.0105), Extracorporeal Renal Replacement Therapy (ERRT) (OR: 5.06 (1.30–19.68), p = *0.0193)* and vasopressor therapy on D_3 (OR: 2.62 (1.05–6.59), p= 0.0401). AUROC curve obtained on D_3 from this risk factors was 0.86 (95% IC 0.78–0.91) (Figure).

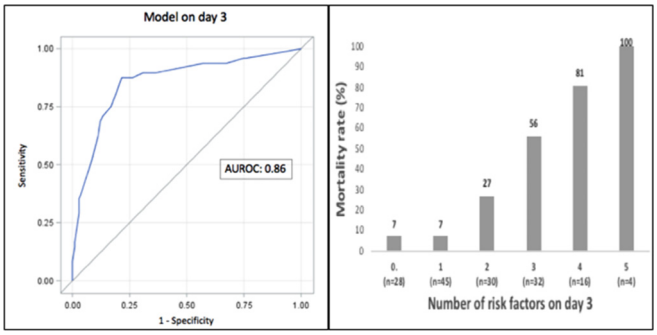


Figure: Model on D_3 obtained by multivariate analysis: AUROC curve and percentages of mortality according to number of items.

Conclusion: This is a large cohort specifically dedicated to cirrhotic patients admitted in ICU for gastrointestinal bleeding related to portal hypertension, in order to determine the risk factors for hospital mortality. On D3, we identified hepatic and non-hepatic risk factors that were independently associated with ICU mortality. The association of these risk factors on D_3 could help to discuss the futility or utility of the ICU management in these patients.

THU-253

Dynamic assessment is superior to baseline assessment in prognostication of patients with acute on chronic liver failure

S. Rathi[1], S. Taneja[1], A. Duseja[1], V. Gautam[2], Y. Chawla[1], R.K. Dhiman[1].
[1]PGIMER, Hepatology, Chandigarh, India; [2]PGIMER, Microbiology, Chandigarh
Email: rkpsdhiman@hotmail.com

Background and Aims: Acute on Chronic Liver Failure (ACLF) is a dynamic syndrome that leads to high risk of mortality in patients with cirrhosis. While the definitions of both acute events and underlying chronic liver disease are debated by different groups, the prognostic scoring models in all definitions are based on variables at presentation. We studied a dynamic model of prognosis assessment and compared it with the static models.

Method: We prospectively evaluated 160 patients who presented with acute decompensation of cirrhosis, which included development of ascites, hepatic encephalopathy, variceal bleeding or sepsis. These patients were assessed at baseline and at day 5–6 of admission in terms of prognostic scores like Model for End stage Liver Disease (MELD), Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF-SOFA), ACLF Grade, and Simple Organ Failure Count (SOFC), and followed up till 90 days or until death.

Results: Of the total, 126 patients were analysed. The mean age was 47.8 ± 12.4 yrs, and 104(82%) were males. Alcohol was the most common etiology of cirrhosis (52%), followed by non-alcoholic steatohepatitis/cryptogenic. Ascites was the most common acute decompensation (81%), and infections were the most common acute precipitating event. A total of 70 (55.6%) survived at 4 weeks, and 32 (25.4%) at 3 months. The prognostic scores at day 5–6 fared better than baseline scores in predicting 28-day mortality. SOFC and CLIF-SOFA score at day 5–6 were the best predictors of mortality with an AUROC of 0.88 and 0.87 respectively. For 90-day mortality, CLIF-C ACLF at day 5–6 fared the best (AUROC 0.79). Patients who showed worsening of organ failure were less likely to survive as compared to those who either remained stable or improved (28-day survival OR-0.36, 95% CI 0.16–0.79, P= 0.017; 90-day -day survival OR-0.34, 95% CI 0.13–0.87, P = 0.03). Moreover, patients with 3 or more organ failures

Table 1: (abstract: THU-253)

		Day 5-6 Grade							
Initial Grade		No ACLF		ACLF 1		ACLF 2		ACLF 3	
No ACLF	N	N	%	N	%	N	%	N	%
Prevalence	68	41		8		12		7	
28day mortality	19	5	12	3	38	5	42	6	86
90day mortality	37	17*	41	4	50	9	75	7	100
ACLF 1									
Prevalence	9	3		1		2		3	
28day mortality	6	1	33	1	100	1	50	3	100
90day mortality	7	1	33	1*	100	2	100	3	100
ACLF 2									
Prevalence	25	8		1		11		5	
28day mortality	15	3	38	0	0	7	64	5	100
90day mortality	20	5	62	0	0	10	91	5	100
ACLF 3									
Prevalence	24	5		2		2		15	
28day mortality	16	0	0	0	0	1	50	15	100
90day mortality	19	1	20	1	50	2	100	15	100

**one patient each in these groups underwent liver transplantation*

at day 5–6 had a uniformly poor survival irrespective of the severity at presentation.
Conclusion: ACLF is a dynamic process with a potential for reversibility. However, most prognostic models based on a single baseline assessment, which may not be adequate. A dynamic assessment at day 4–5 after initial stabilization in-hospital gives a much better measure of the severity of the disease and risk-stratification. Moreover, patients who fail to improve or deteriorate at day 4–5 have a uniformly poor prognosis, and an argument may be made for futility of care.

THU-254
Acute on chronic liver failure-comparison of patients identified by the European association for the study of the liver and the North American consortium for study of end-stage liver diseases
Z. Galvin, E.N.S. Fong, N. Selzner, F. Wong. *Universit Health Network, Toronto General Hospital, Toronto, Canada*
Email: zita.galvin@uhn.ca

Background and Aims: Acute-on-chronic liver failure (ACLF) is characterized by acute clinical deterioration, multiorgan failure and high-mortality in patients with established chronic liver disease. Current ACLF scoring systems have not been compared in liver transplant (LT) patients.
To compare the relevance of the NACSELD (North American Consortium for Study of End-Stage Liver Diseases) and the EASL-Chronic Liver Failure (CLIF) Consortium scoring systems for ACLF in determining post LT renal function and patient survival outcomes.
Method: This was a retrospective single center study of patients, excluding those who received MELD exception points, fulminant liver failure or evidence of intrinsic kidney disease, who received a LT between 2007 & 2014. Patients were screened for ACLF according to both sets of criteria during their last hospital admission prior to LT. Patient demographics, at time of listing and LT, and post LT renal outcome and overall survival were compared between groups.
Results: 581 (66% male, mean age at listing 51 years, 21% alcoholic) met the inclusion criteria. Of these, 175 (30%) met the EASL-CLIF criteria for ACLF, 61 of whom (11%) also met the NACSELD criteria. Both ACLF groups had significantly higher baseline serum creatinine (SCr), bilirubin, INR and MELD scores at listing compared with the no-ACLF group ($p < 0.01$). Significantly more patients with ACLF required renal replacement therapy post LT, had higher SCr during follow-up and significantly lower survival, especially in the NACSELD-group (Table 1).

Table 1: Listing, transplant and outcome data for LT recipients

	No ACLF	EASL-CLIF ACLF	NACSELD ACLF	P value
n	406	175	61	
Listing SCr (μmol/L)	75 (62–96)	108 (72–195)	117 (69–239)	<0.0001
MELD				
Listing	17 (14–20)	23 (17–34)	27 (18–36)	<0.0001
At LT	19 (14–23)	29 (23–36)	31 (24–38)	<0.0001
Post LT SCr (μmol/L)				
3M	92 (74–110)	96 (76–127)	96 (73–133)	0.114
6M	95 (78–115)	104 (88–135)	98 (82–134)	<0.0001
12M	95 (81–117)	108 (86–132)	111 (81–137)	0.001
Post LT RRT [n(%)]	6 (1.5)	19 (10.9)	14 (23.0)	<0.0001
Survival (%)				
6M	95.1	88.6	82.0	<0.0001
12M	93.6	86.9	80.3	<0.0001
24M	91.4	84.6	78.7	0.002

Conclusion: ACLF patients have worse post LT renal function and overall survival outcomes compared to non-ACLF. The NACSELD score identifies sicker patients and is easier to use in the LT setting since the presence of 2 organ failures is sufficient to meet the criteria.

THU-255
Liver transplantation in patients admitted to intensive care with acute-on-chronic liver failure
E. Theocharidou, T. Pirani, M. Heneghan, N. Heaton, W. Bernal, M. Mcphail. *King's College Hospital, Institute of Liver Studies, London, United Kingdom*
Email: eltheocharidou@hotmail.com

Background and Aims: Acute-on-chronic liver failure (ACLF) is characterized by acute decompensation of cirrhosis with organ failure(s) and is associated with high short-term mortality. Recent studies suggest a significant transplant benefit with liver transplantation (LT) in patients with ACLF-3 after admission to intensive care units (ICU) but with a high complication rate. This study assessed outcomes in patients with ACLF who underwent LT either from ICU (Group A), or after discharge from ICU to the ward (Group B), or shortly after discharge from hospital (group C).
Method: 736 patients with cirrhosis were admitted to a dedicated liver ICU at King's College Hospital between 2012–2016, 64 of which (8.7%) received LT within the year of ICU admission. Disease severity scores, outcomes, length of ICU and hospital stay were recorded.
Results: 18 patients were in group A, 24 in group B, and 18 in group C. Median time from ICU admission to LT was 9, 21 and 86 days, respectively. The admission MELD score (32, 29 and 25, $p = 0.023$), the CLIF-organ failure score (12, 11 and 10, $p = 0.018$) and the SOFA score (11, 9 and 8, $p = 0.023$) were significantly higher in group A compared to other groups. ACLF staging at admission to ICU was significantly different in the three groups ($p = 0.037$): group A – ACLF1 4 (22.2%), ACLF2 6 (33.3%), ACLF3 8 (44.4%); group B – ACLF0 4 (17.4%), ACLF1 2 (8.7%), ACLF2 10 (43.5%), ACLF3 8 (30.4%); group C – ACLF0 6 (40%), ACLF1 4 (26.7%), ACLF2 2 (13.3%), ACLF3 3 (20). Two patients in group B died (in-hospital mortality 8.3%) both with ACLF1 at ICU admission. All patients in group A and C survived. In-hospital mortality in the remaining 672 patients who did not receive LT was 42.7%. Length of ICU stay was significantly higher in group A (16, 4 and 2 days, $p < 0.0005$) compared with the other two groups. Length of hospital stay was significantly higher in groups A and B (50, 45 and 16 days, $p = 0.046$).
Conclusion: Survival rates with LT in patients with ACLF requiring ICU admission are high in those transplanted directly from ICU or shortly after transfer to the ward, although LT rates are lower than in other cohorts. These patients require a prolonged post-LT hospital stay. A significant number of patients with ACLF will survive ICU stay and can be transplanted from the ward and the optimal timing requires further investigation.

THU-256
Impact of the non-hepatic surgery on the survival of patients with viral cirrhosis: prospective study from the CirVir cohort
C. Zylberfajn[1], P. Nahon[2], L. Richard[3], C. Carole[4], R. Francoise[3], E. Audureau[3], R. Amathieu[1]. *[1]Hopital Jean Verdier, Intensive Care Unit, Bondy, France; [2]Hopital Jean Verdier, Hépatologie, Bondy, France; [3]Hopital Henri Mondor, Santé publique, Creteil, France; [4]Hopital Beaujon, Hépatologie, Clichy, France*
Email: cecile.zylberfajn@gmail.com

Background and Aims: Surgery in decompensated cirrhotic patient is associated with a high postoperative morbidity and mortality. Nevertheless, outcome after surgery in compensated cirrhotic patients are not well known.
The main objective of this study is to assess mortality and risk of death in compensated cirrhotic patients after surgery in the ANRS CO12 CirVIr cohort.
Method: Data were collected prospectively between 2006 and 2012 in 35 French centers from 1671 patients with histologically proven cirrhosis due to hepatitis B or C virus Patients were free of any decompensation episode before inclusion.
Patients with at least one surgical procedure during the follow-up were included in the study. Data were collected at the time of the

inclusion in the cohort for all patients and at the time of surgery for the patients who underwent surgery. The surgery was classified in hepatic or non-hepatic surgery, in minor and major surgery and in surgery for cancer or not.

Results: 1671 patients were included in the analysis. 19.4% (n = 324) underwent surgery, of witch 268 non-hepatic surgeries (82.7%), 137 minor surgeries (51.1%) and 130 major surgeries (48.5%).

Liver function tests were not statistically different in operated and non-operated patients: total bilirubin was 11.0 [8.0–16.0] vs 11.6 [8.0–16.0] μmol/l (p = 0.69), Prothrombin Time was 89% [80–98] vs 87.5% [78–97] (p = 0.056); and albuminemia was 42.0 [38.9–45.1] vs 41.8 [38.5–45.0] g/L (p = 0.17).

Patients with surgery during the follow-up, according to the type of surgery, had an increased risk of death compared to patients who did not require surgery (HR = 2.33 [1.74, 3.12], p < 0.001).

With the exception of cancer-related deaths, the causes of death were similar in both groups, including deaths from end-stage liver failure (13.6% vs. 12.7%).

However, patients with surgery had a greater risk of having decompensation of the cirrhosis than patients without surgery (HR = 2.35 [1.74; 3.17], p < 0.001).

In our model, in multivariate analysis, major non-digestive surgery had a significant mortality risk with a HR of 3.39 (1.79–6.44), p < 0.001

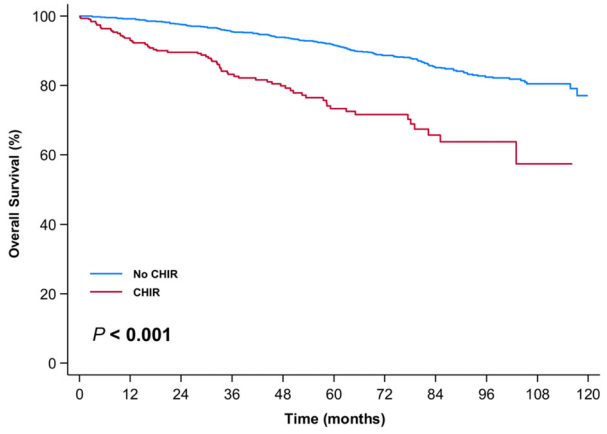


Figure: Survival curve according to the absence or the presence of a surgical act.

Conclusion: In patients with compensated viral cirrhosis, without prior decompensation history, surgery, seems to be an independent risk factor of mortality.

THU-257

Clinical phase 1b study results for safety, pharmacokinetics and efficacy of ND-L02-s0201, a novel targeted lipid nanoparticle delivering HSP47 SIRNA for the treatment of Japanese patients with advanced liver fibrosis

N. Sakamoto[1], K. Ogawa[1], G. Suda[1], K. Morikawa[1], T. Sho[1], M. Nakai[1], H. Suzuki[2], N. Yamagata[2], Y. Tanaka[2], W. Ying[3], Y. Tamura[4], Y. Niitsu[5], K. Maruyama[2]. *[1]Hokkaido University, Department of Gastroenterology and Hepatology, Graduate School of Medicine, Sapporo, Japan; [2]Nitto Denko, Tokyo, Japan; [3]Nitto BioPharma Inc., San Diego, United States; [4]Hokkaido University, Department of Molecular Therapeutics, Institute for the Business-Regional Collaboration, Center for Food & Medical Innovation, Sapporo, Japan; [5]Sapporo Medical University, Sapporo, Japan*

Email: sakamoto@med.hokudai.ac.jp

Background and Aims: ND-L02-s0201* is an injectable lipid nanoparticle that encapsulates a chemically-modified siRNA targeting HSP47, a collagen-specific chaperone, in hepatic stellate cells. In the US and European portion of a Phase 1b study, ND-L02-s0201, administered for 5 weeks, was associated with improvements in fibrosis, as assessed by biopsy, in subjects with advanced fibrosis due to nonalcoholic steatohepatitis (NASH) or hepatitis C virus (HCV) infection (The Liver Meeting 2017). Here we report results from the Japanese portion of the Phase 1b study.

Method: This study was an open label, multiple-dose escalation study to evaluate safety, pharmacokinetics (PK), and biological activity of ND-L02-s0201 in Japanese subjects with advanced fibrosis (METAVIR F3-4). ND-L02-s0201 was intravenously infused once weekly for 5 weeks to 3 cohorts (0.2, 0.4, and 0.6 mg/kg). Subjects had a baseline biopsy within 6 weeks. In Cohort 1, subject who had biopsy within 12 months before screening was eligible. A post-therapy biopsy was done at Week 6. Open biopsy reading was performed by pathologist at the site.

Results: The study included 10 subjects across 3 cohorts, previously diagnosed with NASH (n = 5), HCV-SVR (n = 3), hepatitis B virus (n = 1; sAg (-)) or alcoholic hepatitis (AH) (n = 1). 8 subjects completed 5-week dosing. 5 out of 10 subjects had adverse events (AEs), possibly related to the study drug. 1 subject had a serious AE of *Staphylococcus aureus* infection in the right shoulder and lumbus. Other AEs were observed during infusion and were all mild and transient. The HSP47 siRNA had a linear PK profile. Improvement in Ishak and METAVIR scores were observed in 3 out of 8 evaluable subjects (Table), including 1 subject showing reduction of METAVIR score from F4 to F2 (Cohort 1), and 2 subjects (1 each in Cohort 2 and 3) from F3 to F2. An increase in Ishak score was noted in 1 subject, but no increase in METAVIR score. The subjects who showed improvement in Ishak and METAVIR scores were diagnosed with NASH- (n = 2) and AH-related fibrosis (n = 1).

Table Fibrosis Change at Week 6 (Compared to Baseline)

	Improved	No Change	Worsened
Ishak	3/8 (37.5%)	4/8 (50%)	1/8 (12.5%)
METAVIR	3/8 (37.5%)	5/8 (62.5%)	0/8 (0%)

Conclusion: ND-L02-s0201 was well tolerated in Japanese subjects with advanced liver fibrosis, with no dose-limiting toxicities up to 0.6 mg/kg for 5 weeks, and an acceptable PK profile. Histological improvement was observed at all tested doses. Given the unmet medical need for advanced liver fibrosis, these results support further evaluation of the efficacy and safety of ND-L02-s0201.

*Further clinical development as BMS-986263

THU-258

Acute kidney injury in patients with hepatitis B virus related acute-on-chronic liver failure is different from in decompensated cirrhosis

Q. Jiang, M. Han, K. Ma, G. Chen, W. Wu, Y. Wang, J. You, W. Yan, D. Xi, Q. Ning. *Tongji Hospital Tongji Medical College, University of Science and Technology*

Email: qning@vip.sina.com

Background and Aims: Acute kidney injury (AKI) is a common complication of acute-on-chronic liver failure (ACLF) and decompensated cirrhosis(DC). However, the differences of AKI between these two diseases are little known. To clarify it, we evaluated the biomarkers levels of tubular damage including neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), kidney injury molecule-1 (KIM-1),liver-type fatty acid binding protein (L-FABP), and cystatin C (cysC), clinical response to terlipressin and prognosis in patients of AKI with ACLF or DC in chronic hepatitis B (CHB) patients.

Methods: Total 280 patients with HBV-ACLF and 132 with HBV-DC consecutively admitted to Tongji hospital between December 2015 and July 2017 were enrolled in a prospective study, and 24 patients with chronic hepatitis B(CHB) and 20 healthy controls(HC) at the

same period were also investigated. Patients' plasma and/or urine specimens from these patients were collected. The correlation between the levels of biomarkers of AKI representing kidney injury and clinical features of AKI in CHB patients with ACLF and DC were analyzed.

Results: 71(25.4%) and 28(21.2%) patients developed AKI in CHB patients with ACLF and DC, named ACLF-AKI group and DC-AKI, respectively (p = 0.358). Compared with DC-AKI patients, the rate of AKI progression was higher [39(54.9%) vs 5(17.9%), p = 0.002] and clinical response rate to terlipressin was lower in ACLF-AKI patients [14(32.6%) vs 11(57.9%), p = 0.018]. Most of the biomarkers (NGAL,L-FABP,CysC, and IL-18) levels representing kidney tubular injury in urine were significantly higher in ACLF-AKI patients than in DC-AKI patients as well as CHB patients and healthy control. While there were no significant difference between DC-AKI patients and CHB patients as well as healthy control. Two plasma biomarkers levels (NGAL,CysC) were higher in patients with AKI than patients without AKI, but there was no significant difference between ACLF-AKI group and DC-AKI group. Moreover, the survival rates at 28-day and 90-day were markedly decreased in ACLF-AKI group than DC-AKI group (both p < 0.001).

Conclusions: The degrees of structural kidney injury in ACLF-AKI group were severer than that in DC-AKI group. ACLF-AKI group displayed greater possibility to progression, less response to terlipressin treatment as well as with poorer prognosis compare with DC-AKI group.

THU-259

Invasive fungal infections in Acute on chronic liver failure – An Asia Pacific experience from the AARC consortium

S. Taneja[1], S. Rathi[2], R.K. Dhiman[1], A. Duseja[1], A. Choudhury[3], P. Jain[4], I. Paulson[4], H. Deverbhavi[5], S.-S. Tan[6], C. Eapen[7], A. Goel[7], S. Shah[8], C. Kalal[8], A. Kadir Dokmeci[9], A. Shukla[10], D.J. Kim[11], J.-D. Jia[12], D. Amarapurkar[13], G.H. Lee[14], S.G. Lim[14], N.R. Padaki[15], S.S. Hamid[16], W. Jafri[17], Z. Abbas[18], S.K. Sarin[3]. *[1]Postgraduate Institute of Medical Education and Researchch, Hepatology, Chandigarh, India; [2]Postgraduate Institute of Medical Education & Research, Hepatology; [3]ILBS, New Delhi, Hepatology; [4]ILBS, Hepatology, India; [5]St Johns Medical College, Banglore, India; [6]Hospital Selayang, Bata Caves, Hepatology, Selangor; [7]CMC Vellore, Hepatology; [8]Global Hospital, Hepatology, Mumbai, India; [9]Ankara University School of Medicine, Hepatology, Turkey; [10]KEM Hospital, Hepatology, India; [11]Hallym University College of Medicine, Hepatology, Rep. of South Korea; [12]Beijing Friendship Hospital, Capital University, Hepatology; [13]Bombay Hospital, Hepatology; [14]Yong Loo Lin School of Medicine, Hepatology; [15]Asian Institute of Gastroenterology, Hepatology, India; [16]Aga Khan University, Hepatology; [17]Aga Khan University Hospital., Hepatology; [18]Ziauddin University Hospital, Karachi*
Email: drsuniltaneja@hotmail.com

Background & Aims: Invasive fungal infections (IFI) have been associated with higher morbidity and mortality in critically ill cirrhosis patients. Emerging evidence suggests similar trends in patients with acute on chronic liver failure (ACLF).

Aims: To compare the clinical and laboratory profiles of ACLF patients with bacterial and fungal infections and their impact on outcome.

Methods: All patients with proven IFI (culture positive) as per EORTC/MSG guidelines from the APASL-ACLF research consortium prospectively collected database were analysed. Age, gender, and etiology-matched patients of ACLF with bacterial infections were taken as controls. Baseline clinical and laboratory variables, prognostic scores and length of hospital stay were compared in both groups.

Results: A total of 74 patients with ACLF had evidence of IFI. 101 matched ACLF controls with bacterial infections were randomly selected from the database with bacterial infections. There were no differences in the demographic parameters, acute precipitating events and etiology of chronic liver disease between the groups. The baseline Child-Pugh (Mean ± SD- 12.2 ± 1.7 vs 12.1 ± 1.4; p = 0.75), MELD (32.1 ± 7.9 vs 30.4 ± 7.8; p = 0.16), APACHE II (20.0 ± 6.2 vs 17.9 ± 6.4; p = 0.18) and CLIF-SOFA (12.3 ± 3.1 vs 12.5 ± 2.9; p = 0.7) scores were similar in both groups.

Duration of hospital stay (16.7 ± 14.3 vs 13.9 ± 10; p = 0.2) and ICU stay (7.1 ± 7.8 vs 5.8 ± 5.3; p = 0.33) were similar for both groups. The 30-day mortality too was similar in both groups (OR 1.3, 95% CI 0.7–2.4; p = 0.43), however, in the 90-day mortality; there was a trend towards higher mortality in the bacterial infection group (OR 1.9, 95%CI 1.0–3.8, p = 0.07).

Among the patients with IFI, urinary tract involvement was the most common (n = 54, 73%), followed by pulmonary (n = 15, 20%) and fungemia (n = 8, 11%). There was no difference in the duration of hospital stay or ICU stay between patients with different foci of fungal infection.

		FUNGAL N = 74		BACTERIAL N = 101		p-value
		MEAN	SD	MEAN	SD	
Age		44.6	11.0	45.9	12.2	0.47
Gender (Males, %)		74 (89%)		88 (87%)		0.68
Acute	Alcohol	40		47		0.9
	HBV reactivation	10		15		
	Other Hepatotropic viruses	8		12		
	DILI	8		13		
	Others	8		14		
Chronic	Alcohol	41		56		0.65
	Viral	13		22		
	NASH	9		9		
	Others	10		20		
CTP		12.2	1.7	12.1	1.4	0.75
MELD		32.1	7.9	30.4	7.8	0.16
CLIF-SOFA		12.3	3.1	12.5	2.9	0.7
APACHE II		20.0	6.2	17.9	6.4	0.18
Organ Failures		2.1	1.2	2.0	1.3	0.69
Hospital Stay		16.7	14.3	13.9	10	0.2
ICU stay		7.1	7.8	5.8	5.3	0.33
30-d mortality		43, (58%)		48, (65%)		0.43
90-d mortality		65, (64%)		79, (78%)		0.07

Conclusion: Patients with Acute on Chronic Liver Failure with IFIs have similar poor outcomes as those with bacterial infections. The diagnosis and treatment of IFI at baseline in most patients in this study may be responsible for the attenuation of the outcome difference between bacterial and fungal infections. Thus, a high index of suspicion and early diagnosis and treatment may improve the outcome in this group.

THU-260

Albumin function in acute-on-chronic liver failure (ACLF): Effect of plasma exchange with albumin 5% (PE-A5%)

M. Torres[1], R. Horrillo[2], N. Afonso[1], L. Núñez[1], A.M. Ortiz[2], A. Pérez[2], M. Costa[2], V. Arroyo[3], J. Fernández[3], S. Grancha[2], A. Páez[1]. *[1]Grifols, Clinical, Barcelona, Spain; [2]Grifols, R+D, Barcelona, Spain; [3]Hospital Clinic, Hepatology, Barcelona, Spain*
Email: mireia.torres@grifols.com

Background and Aims: Non-oncotic albumin function relays on its capacity to bind and transport endogenous and exogenous biologically active free molecules, including fatty acid and aminoacid-derived inflammatory mediators as well as reactive oxygen species (due to albumin antioxidant scavenger capacity), thus modulating their biological effects. Since severe systemic inflammation and organ failure are the main differential characteristics of ACLF, it is suggested that PE-A 5% may be an effective treatment for ACLF patients. In this study we assessed the effect of PE-A 5% on albumin functional

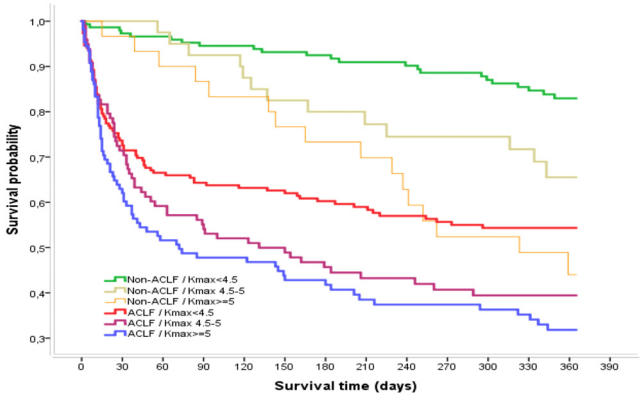
capacity in ACLF patients (*study 1*) and we characterized the albumin functionality in ACLF patients at baseline compared to healthy controls (*study 2*).
Method: *Study 1* was a phase II, open-label, single arm, pilot clinical trial (EudraCT: 2010-021360-15) in 10 patients with ACLF treated with 6 PE-A 5% sessions of 1.1 plasma volumes for 11 days. Albumin functional capacity was assessed. *Study 2* used plasma samples of ACLF patients at baseline from study 1 and age-matched healthy controls (n = 19). Albumin binding capacity of fatty acid and aminoacid derivatives were measured by Electronic Paramagnetic Resonance and by specific fluorescence with dansylsarcosine, respectively. The albumin Cys34 thiol antioxidant capacity was analyzed by anionic-exchange chromatography and expressed as total amount of the reduced albumin (HMA). Results are expressed as lsmean ± SEM.
Results: *Study 1:* 10 ACLF patients were enrolled (12 screened): age 55.0 ± 9.3 years old. PE-A 5% increased serum albumin concentration (29.5 ± 1.3 to 32.5 ± 1.3 g/l, $p < 0.01$), albumin binding capacity to fatty acids (Kd: 8.2 ± 1.4 to 3.1 ± 1.5 μM; $p < 0.005$) and to dansylsarcosine (15.3 ± 1.6 to 18.9 ± 1.7 vs. normalized ABiC/mL; $p < 0.005$), and antioxidant capacity (9.5 ± 1.5 vs. 14.6 ± 1.6 HMA mg/dl; $p < 0.005$). *Study 2:* The albumin function in ACLF patients was significantly lower than in age-matched controls: fatty acids Kd increased 6.8-fold ($p < 0.001$), binding to dansylsarcosine was 2.1-fold lower ($p < 0.001$) and antioxidant capacity decreased 2.5-fold ($p < 0.001$).
Conclusion: Albumin binding capacity to fatty acids and aminoacid derivatives as well as albumin antioxidant capacity are markedly decreased in advanced cirrhosis, which may contribute to the pathogenesis of systemic inflammation and ACLF. PE-A 5% improved non-oncotic albumin functions in ACLF patients.

THU-261

Hyperkalemia influences the outcome of patients with cirrhosis with acute decompensation (AD) and acute on chronic liver failure (ACLF)

G. Mezzano[1], A. Cardenas[1,2], F. Aguilar[3], M. Pavesi[3], C. Sole[1], E. Solà[1], L. Napoleone[1], I. Graupera[1], A. Juanola[1], M. Carol[1], G. De Prada[1], N. Fabrellas[1], J. Martinez[4], F. Saliba[5], T. Welzel[6], V. Arroyo[3], P. Ginès[7].
[1]Hospital Clinic, Liver Unit, Barcelona, Spain; [2]Institut d'Investigacions Biomediques August Pi i Sunyer y Centro de Investigaciones en Red Hepaticas y Digestivas (CIBERehd), Barcelona, Spain; [3]EASL CLIF Consortium, European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain; [4]Hospital Universitario Ramón y Cajal, Department of Gastroenterology and Hepatology, Spain; [5]Hôpital Paul Brousse, Hepatology, Spain; [6]JW Goethe Universität, Hepatology, Germany; [7]Liver Unit, Barcelona, Spain
Email: acardena@clinic.cat

Background and Aims: Hyperkalemia is considered a risk factor of mortality in different clinical scenarios such as heart failure, chronic kidney disease and diabetes mellitus. The aim of this study was to investigate whether hyperkalemia is a risk factor for mortality in patients with cirrhosis and acute decompensation (AD) with and without ACLF
Method: We performed an analysis of the Chronic Liver Failure Consortium CANONIC database in 1,314 consecutive patients admitted to 29 European centers with AD both with and without associated ACLF (294 and 1,020 respectively). Hyperkalemia was defined as serum potassium above 5.0 mEq/L. For the analysis, we considered all patients with presence of at least one valid measure of serum potassium from admission through hospitalization.
Results: Of the 1314 patients admitted with AD, 294 presented ACLF at admission. Prevalence of hyperkalemia in the whole cohort was 11.7% with a mean serum potassium of 5.47 mEq/L. The prevalence of hyperkalemia was significantly higher in patients with ACLF versus those with AD (22.4% and 8.6% respectively, $p < 0.001$). Presence of hyperkalemia was associated with an increased 90, 180 and 360-day mortality risk with higher hazard ratio (HR) in ACLF than in acute decompensation (10 vs 2.3 at 90-day $p < 0.001$, 8.9 vs 3.1 at 180-day, $p < 0.001$ and 5.8 vs 3.8 at 360-day, $p < 0.001$). In a multivariate analysis development of hyperkalemia during admission was independently associated with 90-day mortality [HR 2.4 (1.7–3.4)]. To assess further the prognostic value in the whole cohort, we compared the ROC curves of the MELD score with and without hyperkalemia during admission; this showed an increase of the AUC for MELD score from 0.74 to 0.76 $p < 0.001$. This MELD-K model resulted in a higher diagnostic accuracy to predict 90-day mortality on the whole cohort.



Conclusion: The presence of hyperkalemia is an independent predictive factor of survival in patients with cirrhosis AD and ACLF. The addition of hyperkalemia to the MELD score improves the diagnostic accuracy to predict 90-day mortality in patients with AD and ACLF.

THU-262

Impact of organ failure in patients with acute on chronic liver failure (ACLF) and the newly defined AARC liver failure score in predicting 90 days survival-results from APASAL-ACLF research consortium (AARC)

A. Pande[1], A. Choudhury[1], M. Kumar[1], S. Rahman[2], H. Deverbhavi[3], Z. Duan[4], D.J. Kim[5], C. Eapen[6], Q. Ning[7], Y. Chawla[8], W. Jafri[9], S.-S. Tan[10], H.L. Ghazinyan[11], D. Amarapurkar[12], S. Treeprasertsuk[13], G.H. Lee[14], J.H. Hu[15], L.A. Lesmana[16], A. Shukla[17], S. Shah[18], C. Kalal[18], M. Sahoo[19], Z. Abbas[20], S. Joyes[21], F. Karim[22], G. Lau[23], N.R. Padaki[24], D. Payawal[25], A. Kadir Dokmeci[26], V. Saraswat[27], M.-F. Yuen[28], V. Gm[29], O. Yokosuka[30], A. Shrestha[31], I. Paulson[32], P. Jain[32], G. Kumar[32], S.K. Sarin[1]. *[1]Institute of liver and Biliary Sciences, Hepatology, New Delhi, India; [2]Bangabandhu Sheikh Mujib Medical university, Dhaka, Bangladesh, Dhaka; [3]St John Medical College, Bangalore, India; [4]Beijing You'an Hospital/Translational Hepatology Institute Capital Medical University, China; [5]Hallym University College of Medicine, South Korea/ Beijing Friendship Hospital, Capital University, Beijing, China; [6]CMC; [7]Tongji Medical College; [8]PGI; [9]Aga Khan University Hospital; [10]Hospital Selayang, Bata Caves, Selangor; [11]Nork Clinical Hospital of Infectious Disease Armenia; [12]Mumbai; [13]Chulalongkorn University, Bangkok; [14]Yong Loo Lin School of Medicine, National University of Singapore; [15]302 Millitary Hospital Beijing, China; [16]Medistra Hospital, Jakarta, Indonesia; [17]KEM Hospital and Seth GSMC; [18]Global Hospital, Mumbai, India; [19]IMS &SUM hospital, Odisa; [20]Ziauddin University Hospital, Karachi; [21]University of Santo Tomas, Manila, Philippines; [22]Sir Salimullah Medical College, Mitford Hospital Bangladesh; [23]Humanity and Health Medical Group, China; [24]Asian Institute of Gastroenterology Hyderabad, India; [25]Cardinal Santos Medical Center10 Wilson St. Greenhills West San Juan City, Metro Manila; [26]Ankara University School of Medicine; [27]Sanjay Gandhi Postgraduate Institute, Gastroenterology, Lucknow, India; [28]Queen Mary Hospital Hong Kong, China; [29]VGM Hospital; [30]Chiba University Japan; [31]Foundation Nepal Sitapaila Height, Kathmandu; [32]ILBS*
Email: pandeap@gmail.com

Background and Aims: Acute hepatic insult leading to liver failure with or without extra-hepatic organ failure leads to a high short-term mortality. However, the impact of organ failure(s) on long- term, i.e. beyond 90 days survival is unknown. We studied the impact of organ failures and on survival beyond 90 days in ACLF patients.
Method: The patients diagnosed to have ACLF (APASL definition) were recruited from 52 centres across Asia Pacific. The data was prospectively collected in this observational study cohort on a predefined format in the database from October 2012 to September 2017. Clinical and laboratory parameters, severity score, organ failures were analysed at baseline and their dynamic changes at D4 and D7 to predict the survival beyond 90 days. Liver failure (serum bilirubin 12.0 mg/dl or more), Kidney failure (2.0 mg/dl or more, or on renal replacement therapy), Cerebral failure (Grade III or IV hepatic encephalopathy), Coagulation failure (INR >2.5 and/or platelet <20.000/cc).
Results: A total of 3037 prospectively enrolled patients, 2553 (84%) males and 484 (15.4%) females with a mean age of 45 ± 12.7 years were analyzed. Baseline characteristics in all the groups were comparable. The most common acute insult was alcohol (43%) reflecting a change akin to the West, and followed by viral etiologies (23.3%). The mean baseline MELD score was 28 ± 7.6; SOFA score was 8.9 ± 3.2; CLIF-SOFA-11.47 ± 2.74 and AARC score was 9.89 ± 2.15. There were 395 (15.8%), 984(39.5%) and 1115 (44.7%) patients with no; one and two organ failures respectively. Mortality at the end of 1 year and 5 year was 955/1855 (51.5%) and 982/1855 (52.5%) respectively. Presence of organ failure increased short-term mortality [HR = 1.99 (95CI 1.53–2.26); HR = 4.41(95 CI 3.38–5.75) and 10.33(95 CI 7.64–13.18)] for 1.2 and >2 organ failures respectively. AARC Score was better than other scores in predicting the 90 day survival outcome.

	AUC	p value	95%CI	Cut off	Sensitivity	Specificity
ARRC Score	0.721	<0.002	0.68–0.78	10	69.6	61
MELD	0.708	<0.002	0.672–0.72	30	67.1	65
CTP	0.646	<0.002	0.608–0.76	30	70	50
Organ failure ≥2	0.698	<0.002	0.68–0.72	30	70.4	61

Conclusion: The organ failure has an impact in predicting the short-term outcome i.e. 3 months in patients of ACLF. Recently defined AARC Score i.e. a liver failure better predict the outcome than the existing disease severity score.

THU-263

Tenofovir is more potent over entecavir in reducing the viral load in patients of hepatitis B reactivation presenting as Acute on Chronic Liver Failure (ACLF)-Results of multination study from APASL-ACLF Research Consortium (AARC)

J. Ahmad[*,1], A. Choudhury[1], M. Kumar[1], M. Al-Mahtab[2], S. Rahman[2], Q. Ning[3], K. Ma[3], Z. Duan[4], Y. Chen[4], J.H. Hu[5], J. Hu[4], S.-S. Tan[6], S.S. Hamid[7], A. Subhan[7], W. Jafri[7], L.A. Lesmana[8], R. Lesmana[8], H.L. Ghazinyan[9], J.-D. Jia[10], G.H. Lee[11], S.G. Lim[11], S. Taneja[12], Y. Chawla[12], G. Lau[13], M. Sahoo[14], A. Shukla[15], H. Deverbhavi[16], M.-F. Yuen[17], Z. Abbas[18], D. Amarapurkar[19], F. Karim[20], S. Treeprasertsuk[21], A.K. Dokmeci[22], A. Goel[23], C. Eapen[23], D. Payawal[24], S. Shah[25], C. Kalal[25], A. Kulkarni[26], S. Chaudhury[26], I. Paulson[26], P. Jain[26], G. Kumar[26], S.K. Sarin[27]. *[1]ILBS, Hepatology, New Delhi, India; [2]Bangabandhu Sheikh Mujib Medical university, Dhaka, Bangladesh; [3]Tongji Hospital, Tongji Medical College; [4]Beijing You'an Hospital/Translational Hepatology Institute Capital Medical University; [5]302 Millitary Hospital Beijing, China; [6]Hospital Selayang, Bata Caves, Selangor; [7]Aga Khan University Hospital, Karachi; [8]Medistra Hospital, Jakarta, Indonesia; [9]Nork Clinical Hospital of Infectious Disease Armenia; [10]Hallym University College of Medicine, South Korea/Beijing Friendship Hospital, Capital University, Beijing, China; [11]Yong Loo Lin School of Medicine, National University of Singapore; [12]PGIMER, Chandigarh, India; [13]Humanity and Health Medical Group, China; [14]IMS &SUM Hospital, Odisa; [15]KEM Hospital and Seth GSMC; [16]St John Medical College, Bangalore, India; [17]Queen Mary Hospital Hong Kong, China; [18]Ziauddin University Hospital, Karachi; [19]Bombay Hospital & Medical Research Center, Mumbai, India; [20]Sir Salimullah Medical College, Mitford Hospital Bangladesh; [21]Chulalongkorn University, Bangkok; [22]Ankara University School of Medicine; [23]CMC, Vellore, India; [24]Cardinal Santos Medical Center 10 Wilson St. Greenhills West San Juan City, Metro Manila, Philippines; [25]Global Hospital, Mumbai, India; [26]ILBS; [27]ILBS, Hepatology*
Email: ahmadjuned43.jk@gmail.com

Background and Aims: Reactivation of hepatitis B is a well-characterized syndrome marked by abrupt reappearance or rise of HBV DNA in the serum of a patient with previously inactive or resolved HBV infection. A significant number of patients of spontaneous acute exacerbation of CHB may present with, high HBV DNA, jaundice, liver failure (bilirubin >5 mg/dl), INR >1.5). The presentation, response to therapy and outcome were analyzed.
Method: The patients diagnosed to have ACLF (APASL definition) were recruited from 52 centres across Asia Pacific. The data was prospectively collected in this observational study cohort on a predefined format in the database from October 2012 to September 2017. A total of 560 patients of ACLF (ACLF-HBVr), predominantly male (361, 64.5%) with mean age 40.6 ± 10.4 yr those receiving Nucs i. e. tenofovir(Group-A) or enetcavir(Group-B) or combination (Group-C) were analyzed in relation to viral load at presentation, at 90 days and its impact on 90 days survival.
Results: 312 patients received Tenofovir (Gr. A) and 203 patients received entecavir (Gr. B) and 35 patients received combination of tenofovir and entecavir (Gr.C). Baseline characteristics in all the groups were comparable. All had high MELD (Gr. A-23.4 ± 3.1; Gr.B-25.2 ± 2.3; Gr. C-24.1 ± 3.1; p = 0.51),CTP score (Gr.A-11.5 ± 2.3;Gr.B-11.2 ± 1.9 Gr.C-12.4 ± 1.9;p = 0.32) and AARC score (Gr.A-11.6 ± 2.5,Gr. B-11.9 ± 2.1,Gr.C-12.3 ± 2.1) were comparable. Cirrhosis was seen on biopsy in 73% (408/560) of patients. HBsAg inclusion bodies were seen in 67% (375/560). Fever was seen in 91% (509/560) and features of serum sickness in 57/560 (9.8%). Most common cause of reactivation was spontaneous in 88.6% (496 /560) followed by chemotherapy in 7.67% (43/560), HCV therapy (21/560). Baseline DNA-Gr.A-$1.2 \times 10^5 \pm 0.8 \times 10^3$ IU/ml,Gr.B-$2.3 \times 10^5 \pm 1.1 \times 10^3$ IU/ml, Gr.C $4.3 \times 10^7 \pm 2.1 \times 10^3$ IU/ml(p = NS),quantitative HBsAg{Gr.A-5.6×10^3,Gr.B-7.8×10^3, Gr.C-8.1×10^3 (p = NS)}. Tenofovir lead to significant decline in HBV DNA at 3 months i.e., log 3.1 ± 0.8 decline in Gr. A compared to log 1.7 ± 0.9 in Gr. B and 3.2 ± 1.02 log in Gr.C.(p = 0.03). There was comparable decline in HBsAg levels in all the groups {Gr.A-log 1.1 ± 0.4; Gr.B log 1.1 ± 0.7; Gr. C – 1.5 ± 0.9(p = 0.2). Mortality at 3 months was comparable among all groups {Gr.A-36.7%; Gr.B-41.5% and Gr.C-38.3%p = NS}. Baseline DNA, HBsAg (q), bilirubin and INR, cirrhosis on biopsy were significant predictors of mortality on univariate analysis whereas bilirubin and INR were predicators of mortality in multivariate as well. Mean MELD/CTP/SOFA/AARC score were predictors of outcome.
Conclusion: Tenofovir is more potent than entecavir in Asian patients with ACLF-HBVr in reducing viral load, though there is no mortality benefit.

THU-264

Serum caspase-1 level as a diagnostic and prognostic biomarker for HBV-related acute-on-chronic liver failure

X. Zhang, H. Shi, Y. Chen, Z. Duan, F. Ren. *Beijing YouAn Hospital, Beijing, China*
Email: renfeng7512@hotmail.com

Background and Aims: Liver inflammation is crucial in the pathogenesis of HBV-related acute-on-chronic liver failure (ACLF). The aim of this study is to investigate the role of Caspase-1 as biomarker of disease progression and prognosis in HBV-related ACLF.

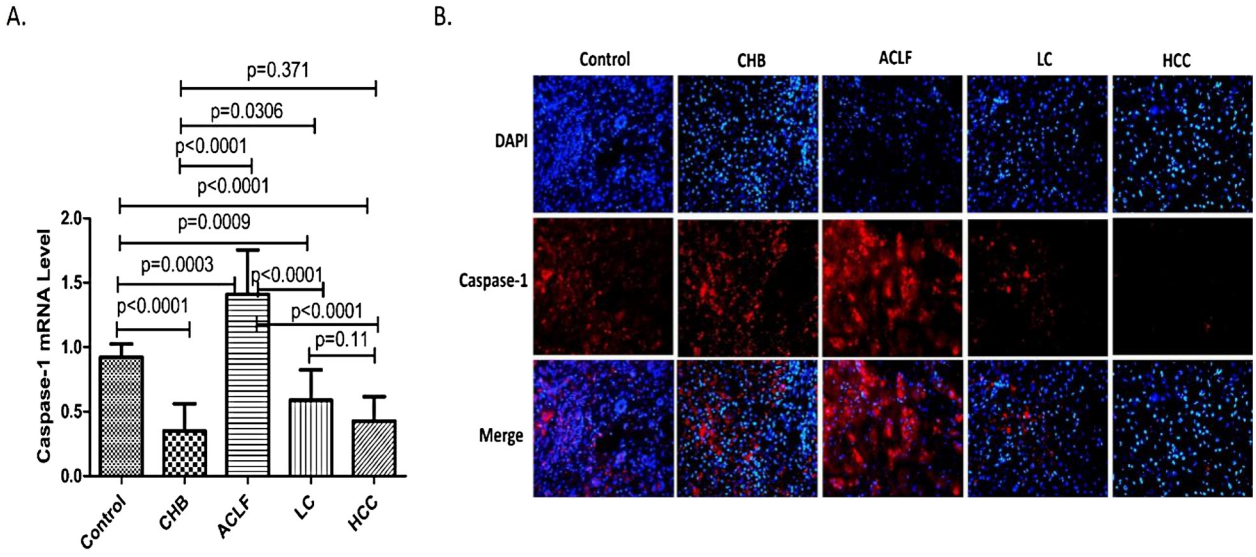


Figure 1: (abstract: THU-264): Altered hepatic mRNA and protein expression of Caspase-1 in the HBV-related liver disease.

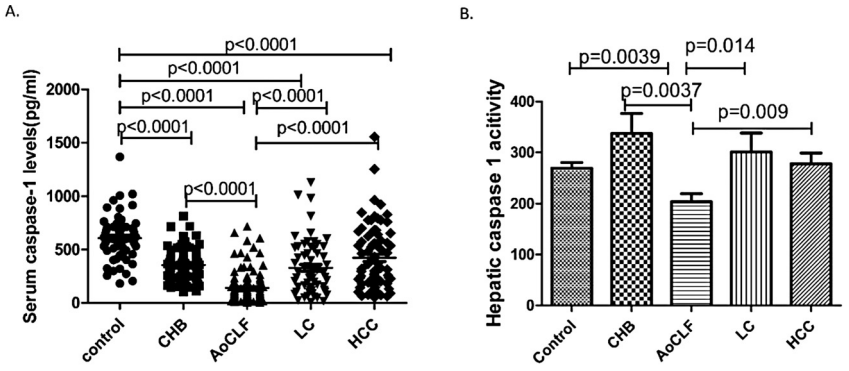


Figure 2: (abstract: THU-264): Altered serum Caspase-1 levels and hepatic Caspase-1 activity in the HBV-related liver disease.

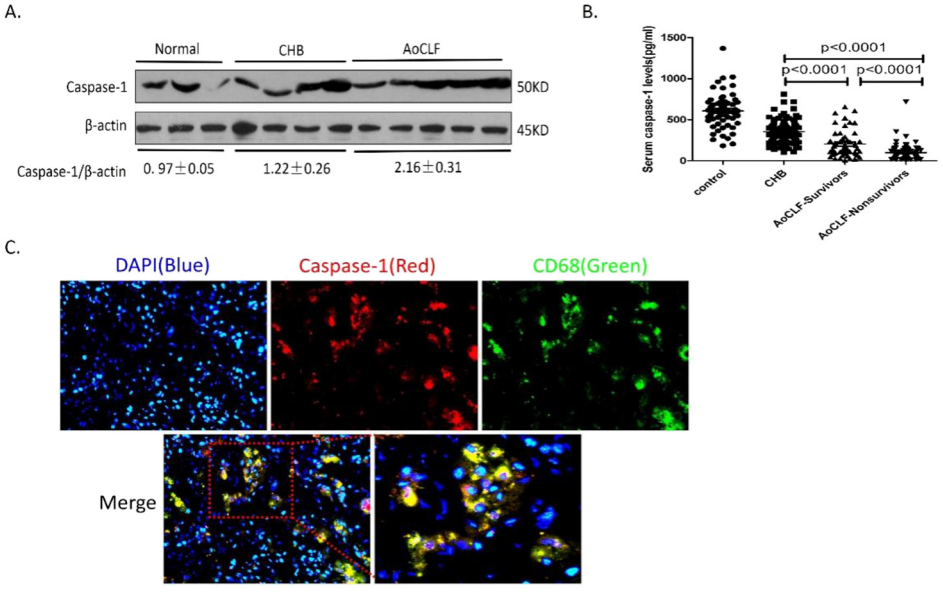


Figure 3: (abstract: THU-264): Expression of serum and hepatic Caspase-1 in ACLF patients.

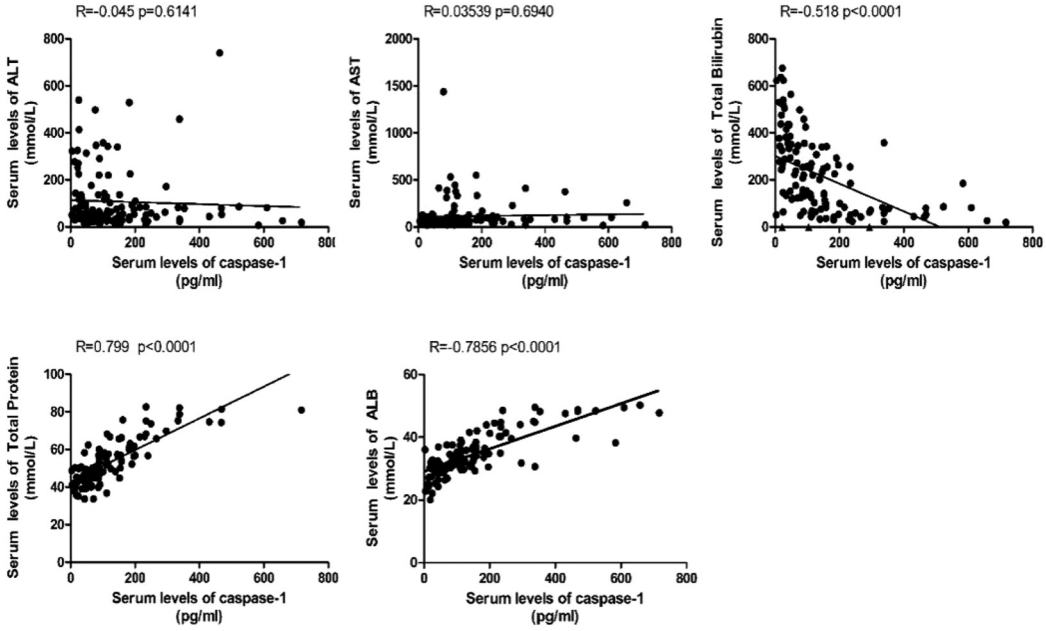


Figure 4: (abstract: THU-264): Association of serum Caspase-1 levels with liver injury in ACLF.

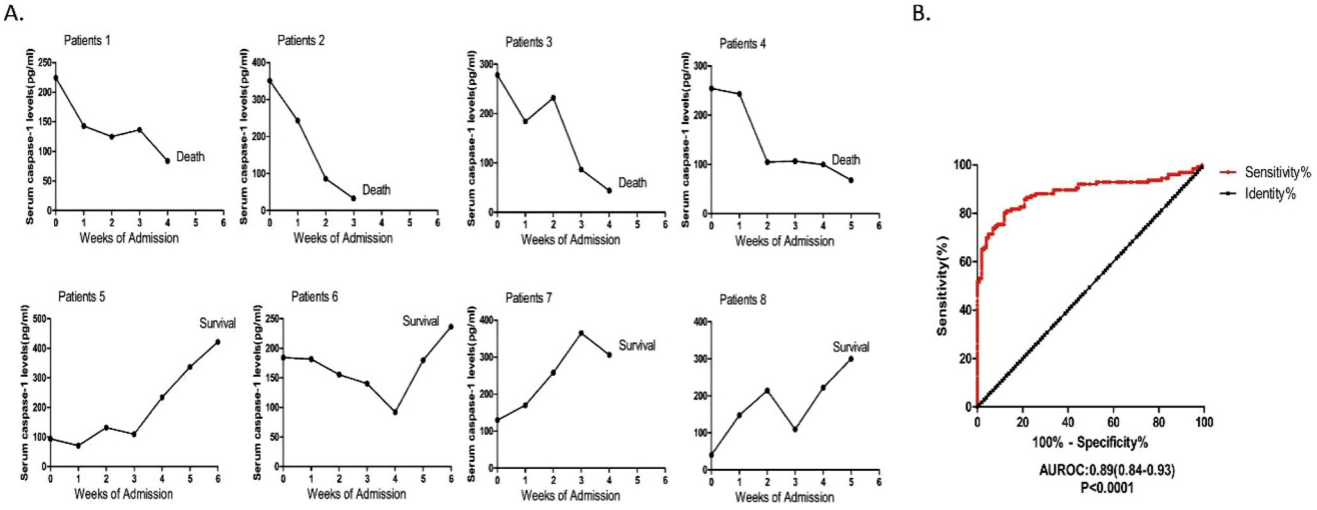


Figure 5: (abstract: THU-264): Diagnostic potential of Caspase-1 for predicting ACLF.

Method: The subjects with HBV-related hepatocellular cancer (HCC, n = 80), subjects with HBV-related liver cirrhosis (LC, n = 62) and subjects HBV-related ACLF (n = 126), to those of chronic hepatitis B (CHB) subjects (n = 101) were selected. The expression of Caspase-1 were measured using liver tissues from normal control subjects (n = 10), CHB patients (n = 12) and HBV-related ACLF patients (n = 19).

Results: Compared with CHB patients, the ACLF patients had distinctly decreased serum levels of Caspase-1, however, the HCC patients and LC patients showed no significant difference; the serum levels of Caspase-1 was showed a negative correlation with serum TBIL and a positive correlation with the serum total protein (TB) and albumin (ALB), although there are no correlation with ALT and AST. The intrahepatic mRNA and protein expressions of Caspase-1 were decreased in CHB subjects compared to healthy individuals and were increased in ACLF subjects compared to CHB subjects; however, the activity of Caspase-1 were gradually decreased in ACLF subjects compared to healthy individuals and CHB subjects. Importantly, the serum Caspase-1 levels in the survival group with ACLF was more significant higher than those of in the dead group patients and analyses of area under the receiver operating characteristic curve (ROC-AUC) indicated that Caspase-1 (0.84) may be useful for independently predicting ACLF patients.

Conclusion: We demonstrate for the first time that Caspase-1 plays a pivotal role in the pathogenesis of in ACLF patients caused by acute exacerbation of CHB, and Caspase-1 maybe a potential non-invasive diagnostic and prognostic biomarker for ACLF patients.

THU-265

Outcome of bacterial infections complicated or not by acute-on-chronic liver failure in patients with cirrhosis admitted to hospital for acute decompensation

M. Bartoletti[1], M. Baldassarre[2], M. Domenicali[2], M. Rinaldi[1], M. Giannella[1], R. Lewis[1], M. Tufoni[3], G. Zaccherini[3], M. Tamé[4], L. Napoli[5], R.M. Pavarin[6], S. Berardi[7], G. Ballardini[8], M. Bernardi[9], P. Viale[10], P. Caraceni[2]. *[1]S.Orsola-Malpighi Hospital, Infectious Diseases Unit - Department of Medical and Surgical Sciences, Bologna, Italy; [2]University of Bologna, Department of Medical and Surgical Sciences Center for Applied Biomedical Research (C.R.B.A.), Bologna, Italy; [3]University of Bologna, Department of Medical and Surgical Sciences, Bologna; [4]S. Orsola-Malpighi Hospital, University of Bologna, Department of Digestive Diseases and Internal Medicine, Bologna, Italy; [5]University of Bologna, Unit of Internal Medicine, Department of Medical and Surgical Sciences, Bologna; [6]Mental Health DSM DP, Local Heath Unit, Epidemiological Monitoring Center on Addiction, Bologna, Italy; [7] Sant'Orsola-Malpighi Hospital, University of Bologna, End-stage liver disease Unit, Bologna, Italy; [8]Infermi Hospital, Internal Medicine and Hepatology Division, Rimini, Italy; [9]University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; [10]S. Orsola-Malpighi Hospital, Department of Clinical Medicine and Surgery, Section of Infectious Diseases, Bologna, Italy*
Email: michele.bartoletti4@unibo.it

Background and Aims: Bacterial infections (BIs) are a frequent complication in patients with cirrhosis and often trigger the onset of acute-on-chronic liver failure (ACLF). This prospective observational study aims to describe the clinical and microbiological characteristics, risk factors and 1-year survival of patients admitted to hospital for acute decompensation (AD) with or without BIs and the relationship with the onset and outcome of ACLF.

Method: From January 2014 to March 2016 patients with cirrhosis admitted for AD at the S. Orsola-Malpighi University Hospital, Bologna, and at the "Infermi" Hospital, Rimini, were consecutively enrolled. Data were recorded at admission and during hospitalization. Survival was recorded up to 1-year. The diagnosis of BIs was confirmed by an Infectious Disease specialist according the current international guidelines.

Results: Among the 516 patients enrolled, 108 (21%) presented an infection at admission, while additional 61 (12%) developed a nosocomial infection. Overall, 1-year survival was lower in patients with nosocomial (43%) and community acquired/healthcare related (52%) infections as compared to non-infected patients (65%) ($p < 0.001$). ACLF was diagnosed more frequently in infected (either at the time or after the diagnosis of infection) than in non-infected patients (36 vs 26%; $p = 0.002$). Multivariate logistic regression showed that higher MELD-Na score ($p = 0.001$), QuickSOFA score ≥2 points ($p = 0.004$), bacteremic ($p = 0.004$) and multidrug-resistant (MDR) infections ($p = 0.048$) were independent predictors of ACLF.

Kaplan-Meyers curves showed that 1-year survival was similar in infected and non-infected patients without ACLF (71 vs 67%, $p = 0.337$). As expected, 1-year survival was worsened by the presence of ACLF. Interestingly, ACLF related to BIs was associated to a significantly lower survival rate than ACLF precipitated by other events (23 vs 47%, $p = 0.010$). Finally, multivariate Cox regression showed that only BIs complicated by ACLF are associated to an increased risk of death ($p < 0.001$) independently from MELD-Na and Charlson comorbidity index.

Conclusion: This large prospective study indicated that the adverse impact of BIs on long-term survival in decompensated cirrhosis is not universal, but limited to those patients who also develop ACLF. Both disease severity and microbiological factors predispose infected decompensated patients to ACLF.

THU-266

Typing acute-on-chronic liver failure according to World Gastroenterology Organization working party definition in HBV-related patients

X. Tang, T. Qi, B. Li, C. Zhu, J. Gao, G. Lu, M. Xiong, Q. He, Y. Chen, F. Zhou, J. Chen, J. Hou. *Nanfang Hospital, Southern Medical University, Hepatology Unit, Department of Infections Diseases, Guangzhou, China*
Email: chjj@smu.edu.cn

Background and Aims: Acute-on-chronic liver failure (ACLF) can be divided into 3 categories depending on whether or not there is underlying cirrhosis, and in patients with cirrhosis, whether or not there is a history of previous hepatic decompensation. For now, this criterion hasn't been validated and described in HBV-related ACLF patients. Therefore, we aimed to investigate the characteristics and prognosis of the three types of ACLF in patients with hepatitis B virus infection.

Method: Hospitalized patients infected with hepatitis B virus who met European Association for the Study of the Liver (EASL) defined ACLF from January 2012 to June 2016 in hepatology unit, Nanfang hospital were included in this retrospective study, which were subsequently grouped according to WGO criterion: ACLF on non-cirrhotic as type A, on well compensated cirrhosis as type B and on

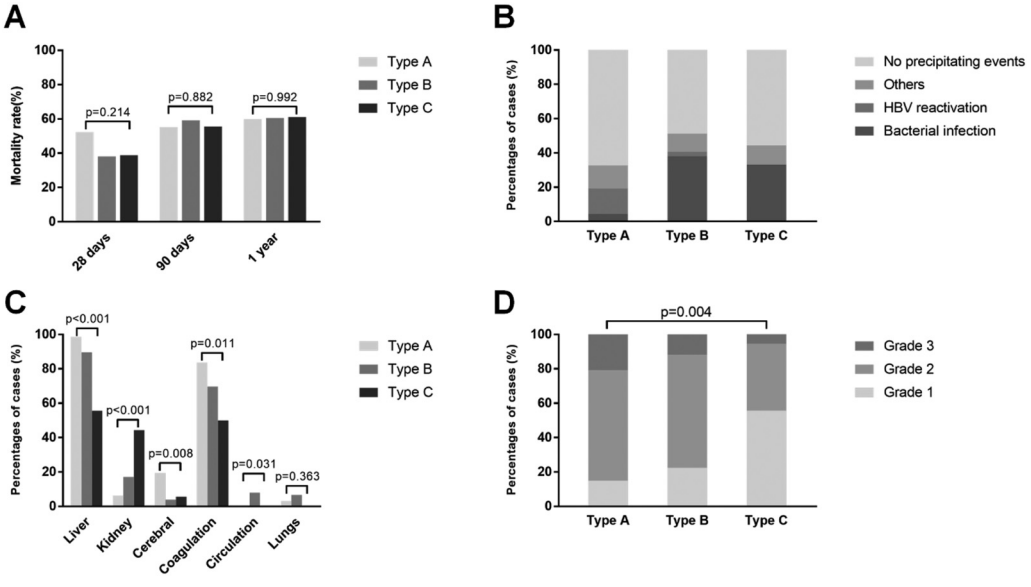


Figure: (abstract: THU-266)

previous hepatic decompensation as type C. The precipitating events, organ failures, laboratory tests and outcomes were compared among these three types of ACLF.

Results: Of the 161 subjects enrolled, 67 (41.6%), 76(47.2%) and 18 (11.2%) had type A, B and C ACLF at enrollment, respectively. Subjects with type A ACLF were the youngest, which had highest leukocytes counts, bilirubin levels, highest Model for End-stage Liver Disease (MELD) score, but lowest C-reactive protein and serum creatinine among the three types (Table). The 28-day, 90-day and 1 -year mortality rates were all comparable among these types (28-day: 52.2% vs. 38.1% vs. 38.9%, p = 0.214; 90-day: 55.2% vs. 59.2% vs. 55.6%, p = 0.882; 1-year: 59.7% vs. 60.5% vs. 61.1%, p = 0.992, Figure A). However, there were several distinct characteristics among the three ACLF types. For precipitating event, HBV reactivation was more common among type A subjects (14.9% vs. 2.6% vs. 0%, p = 0.014), while bacterial infection contributed more among type B and type C subjects (4.5 vs. 38.2% vs. 33.3%, p < 0.001, Figure B). Liver, coagulation and cerebral failure were more frequently seen type A ACLF compared with type B and C (Liver: 98.5% vs. 89.5 vs. 55.6%, p < .001; Coagulation: 83.6% vs. 69.7% vs. 50.0%, p = 0.011, Cerebral: 19.4% vs. 3.9% vs. 5.6%, p = 0.008). On the contrary, the proportion of kidney failure was highest in type C, followed by type B ACLF (44.4% vs. 17.1% vs. 6.0, p < 0.001, Figure C). Furthermore, the distribution of ACLF grades were significantly different among the three types (p = 0.004). Grade 2 ACLF was the most frequent in both type A (65.2%) and B (65.8%) subjects, while 55.6% subjects with type C were grade 1 ACLF (Figure D).

Conclusion: EASL defined HBV-ACLF can be further classified into three types according to WGO criterion, which have similar short and long-term prognosis, but distinct characteristics in precipitating event, organ failures and ACLF grades.

THU-267

Analyzing the Duration Between Acute Insult and ACLF in a Chinese 14 centers, prospective study for natural course of ACLF

G. Wenyi[1,2], B.-Y. Xu[3], X. Zheng[4], J. Chen[5], X.-B. Wang[6], Y. Huang[7], Y. Gao[8], Z.-J. Meng[9], Z.-P. Qian[10], F. Liu[11], X.-B. Lu[12], J. Shang[13], H. Li[14], S. Wang[15], H. Li[2,16]. *[1]Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, Department of Gastroenterology, Shanghai, China; [2]Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Department of Gastroenterology, Shanghai, China; [3]Southwest Hospital, Third Military Medical University, Department of Infectious Diseases, Chongqing, China; [4]Institute of Infection and Immunology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Infectious Diseases, Wuhan, China; [5]Nanfang Hospital, Southern Medical University, Department of Infectious Diseases, Guangzhou, China; [6]Beijing Ditan Hospital, Capital Medical University, Department of Infectious Diseases, Beijing, China; [7]Xiangya Hospital, Central South University, Department of Infectious Diseases, Hunan, China; [8]The First Hospital of Jilin University, Department of Infectious Diseases, Jilin, China; [9]Taihe Hospital, Hubei University of Medicine, Department of Infectious Diseases, Hubei, China; [10]Shanghai Public Health Clinical Centre, Fudan University, Department of Infectious Diseases, Shanghai, China; [11]The Second Hospital of Shandong University, Department of Infectious Diseases, Shandong, China; [12]The first Affiliated Hospital of Xinjiang Medical University, Department of Infectious Diseases, Xinjiang, China; [13]Henan Provincial People's Hospital, Department of Infectious Diseases, Henan, China; [14]Affiliated Hospital of Logistics University of People's Armed Police Force, Department of Infectious Diseases, Tianjin, China; [15]Fuzhou General Hospital of Nanjing Military Command, Department of Infectious Diseases, Fujian, China; [16]Shanghai Jiao Tong University, Shanghai Institute of Digestive Disease, Key Laboratory of Gastroenterology & Hepatology, Chinese Ministry of Health, Shanghai, China*
Email: haili_17@126.com

Background and Aims: Patients with chronic liver disease who are at high Acute-on-Chronic liver failure (ACLF) risk are characterized by precipitating events (PE), intra- and extrahepatic organ failure(OF) and rapid deterioration to death. Although the time interval between PE and single liver failure(LF) as four weeks has been defined in APASL consensus, however studies on such interval and clinical course of ACLF are scarce. Whether intra- and extrahepatic PE lead to distinct durations remains uncertain. Hereby we analyzed the intervals of PE-to-single LF and PE-to-ACLF in Chinese CANONIC study patients.

Method: A Chinese nationally 14 liver centers representative cohort comprising 2600 chronic liver disease patients (including 70% cirrhotic and 30% non-cirrhotic) with acute decompensation or acute liver injury(defined as ALT > 3NL or TB > 2NL) was recruited. single LF (TB > 12 mg/dl) and ACLF were diagnosed using CLIF-OF score. We evaluated PE-to-single LF interval among cirrhotic patients who developed single LF at admission or within 28-days hospitalization after admission. Next, PE-to-ACLF interval was studied among patients who had defined PE and developed ACLF during hospitalization. The two intervals were then compared in patients with isolated defined intrahepatic PEs (including HBV reactivation, active alcohol intaking, superimposed hepatic virus and drug-induced hepatic injury)and those with infections as only existing extrahepatic PE.

Results: Among 1833 cirrhotic patients, 1070(58.4%) had explicit PE. Among those PE defined patients, 205 patients had single LF, and 76% patients develop single within 4 weeks when PE occurred. 71.5% etiology are HBV related and 20.6% developed ACLF. PE-to-single LF intervals for patients with intra-(n = 94) and extrahepatic PE (n = 111) were 19(7–42) (median and interquartile range) and 4(1–11) days, respectively (p < 0.0001). There was a significant PE-to-ACLF interval difference between intra- (n = 41) and extrahepatic (n = 55) PE(21(8–44) vs 15(9–24) days, p = 0.02). Comparing with bacterial infection as an only existing extrahepatic PE (n = 84), those with intrahepatic PEs (n = 51) had significant longer PE-to-single LF interval (intra:16(7–35) vs extra: 2(1–7) days, p < 0.0001), when PE-to-ACLF interval reached borderline significance(intra:16.5(7–44) days, n = 16 vs extra 15(9–24) days, n = 36; p = 0.05).

Conclusion: Our multicenter, prospective study showed both single LF and extrahepatic OF were most likely to occur within less than 4 weeks after PE presence among eastern type cirrhotic patients. Additionally, Both single LF and ACLF developed more rapidly with the presence of extrahepatic insult, especially in patients with bacterial infection. Exploring the interval from both PE-to-single LF and PE-to-ACLF interval will help to understand the natural course evolution about HBV dominated Eastern type ACLF.

THU-268

Relative adrenal insufficiency in acute-on chronic liver failure – a new futility marker?

S. Chiriac[1], A. Trifan[1,2], A.-M. Singeap[1,2], C. Cojocariu[1,2], I. Girleanu[1,2], O. Stoica[1], T. Cuciureanu[1,2], L. Huiban[1,2], C.-M. Muzica[1,2], C. Alexandru[1,2], C. Stanciu[2]. *[1]"Grigore T. Popa" University of Medicine and Pharmacy, Gastroenterology, Iasi, Romania; [2]"St. Spiridon" Emergency Hospital, Institute of Gastroenterology and Hepatology, Iasi, Romania*
Email: ancatrifan@yahoo.com

Background and Aims: Acute-on Chronic Liver Failure (ACLF) is a condition characterized by organ failure in the setting of decompensated liver cirrhosis and associating high short-term mortality. Urgent liver transplantation could represent a life-saving intervention but only in selected patients, before the progression to multiple organ failure. Relative adrenal insufficiency (RAI) is frequently diagnosed in patients with severe sepsis, severe burns, after major surgery, and in the case of hemodynamically unstable cirrhotic patients with and without sepsis. Moreover, RAI has been considered another organ failure in the setting of decompensated cirrhosis, further worsening the prognosis of critically-ill patients. We aimed to evaluate the prognosis significance of RAI in patients with ACLF and to

assess the association of RAI as a possible marker of futility in ACLF patients.
Method: We conducted a prospective study of patients with decompensated liver cirrhosis who were hospitalized between March 2015 and September 2016 in the Hepato-Gastroenterology unit of the Clinical Emergency Hospital "St. Spiridon" Iasi, Romania. 153 patients were included. ACLF was defined according to the CANONIC study criteria. The concentration of serum cortisol (SC) was measured at 08:00 hours (baseline cortisol) and 30 minutes after intravenous administration of 250 μg of synacthen (tetracosactide) (peak cortisol). RAI was defined as a baseline cortisol value <5 μg/dl or as a delta cortisol value (the difference between baseline cortisol and peak cortisol) <9 μg/dl.
Results: RAI was diagnosed in 72 patients (47%). 113 patients (74.3%) were diagnosed with ACLF, out of which 62 (55%) had RAI. 30 patients had ACLF grade 1, 32 ACLF grade 2, and 51 ACLF grade 3. Short-term mortality rates were high in ACLF patients (58.44%) and varied progressively according to ACLF grade (7.6% grade 1, 22.7% grade 2, and 69.7% grade 3). The mortality rates were higher among patients with ACLF grade 3 and RAI (39 patients, 81.2%) compared to 7 patients (38.9%) in ACLF grade 3 without RAI. In patients with ACLF, RAI was associated with an increased risk for 28-days mortality [OR = 2.6, CI (1.705–4.059), P < 0.001]. Deceased patients with RAI had a lower median survival time 7 days (5–12), compared to patients without RAI, of 19.5 days (9.75–65.5), P = 0.001. In the ACLF group, univariate analysis identified RAI, alcoholic hepatitis, liver failure, renal failure, coagulation failure, respiratory failure, and cerebral failure as independent risk factors for death.
Conclusion: Patients with ACLF have high short-term mortality rates, which vary according to ACLF grade. The association of RAI represents another risk factor for death and in the case of grade 3 ACLF with RAI the mortality rates are the highest. The association of RAI may thus represent a futility marker for transplantation, particularly in ACLF grade 3 patients.

THU-269
The combination of acute-on-chronic liver failure (ACLF) as defined by EASL-CLIF consortium definition and MELD can predict post-transplant survival in patients with ACLF

U. Agbim[1], A. Sharma[2], S. Karri[2], J. Vanatta[1], H. Gonzalez[1], S. Nair[1], J. Eason[1], B. Maliakkal[1], S. Satapathy[1]. *[1]University of Tennessee Health Science Center, Department of Surgery; [2]University of Tennessee Health Science Center, Department of Medicine*
Email: uagbim@uthsc.edu

Background and Aims: Acute-on-chronic liver failure (ACLF) is an increasingly recognized entity that was recently redefined by European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium. The aim of this study was to characterize post-transplant early survival outcomes based on pre-transplant ACLF severity as defined by the EASL-CLIF consortium definition and Model for End Stage Liver Disease (MELD).
Method: This was a retrospective review of 833 consecutive liver transplant (LT) recipients between April 2006 and March 2013 at Methodist University Hospital Transplant Institute. Patients with no evidence of chronic liver disease, dual-organ transplant, acute liver failure, and re-transplants were excluded. We defined "ACLF" and "no ACLF" using the EASL-CLIF Consortium definition and categorized those with ACLF into Grades 1–3. Further, ACLF Grade 2 and 3 was considered high ACLF and a MELD score ≥30 was considered a high MELD. To analyse the combined effect of MELD and ACLF we divided patients into the following categories: high MELD with high ACLF, high MELD with low ACLF, low MELD with high ACLF, and low MELD with low ACLF. Demographic and clinical variables were collected and patient outcomes were analysed using Kaplan-Meier survival analysis.

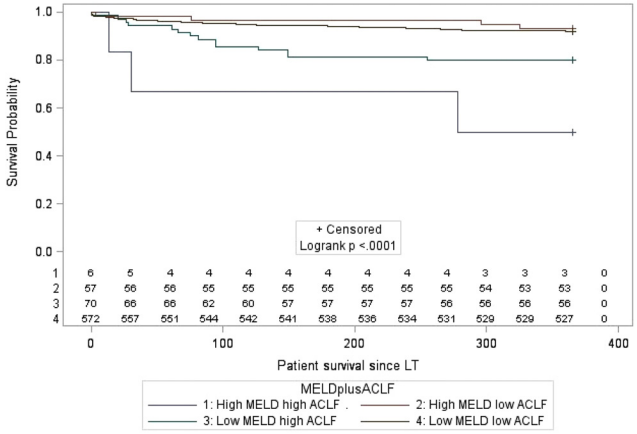


Figure 1: Kaplan-Meier Survival in Days of LT Recipients Stratified by MELD and ACLF.

Results: 582 LT recipients were found to have no ACLF, whereas 123 patients had ACLF. This was further subdivided into ACLF Grade 1 [47 (38.2%)], ACLF Grade 2 [47(38.2%)], and ACLF Grade 3 [29(23.6%)]. The median MELD was 17 (IQR 17–22). There were 6 LT recipients with high MELD with high ACLF, 57 with high MELD with low ACLF, 70 with low MELD with high ACLF, and 572 with low MELD with low ACLF. Using the low MELD with low ACLF group as control we noted an inferior patient survival in the high MELD with high ACLF (P = 0.003) and the low MELD with high ACLF group (P = 0.005) Figure 1.
Conclusion: Using the combined effect of MELD and ACLF, the patient survival of LT recipients with high MELD with high ACLF as well as the low MELD with high ACLF group was markedly inferior do the other groups. This suggests that the presence of extra hepatic organ failures not included in the MELD, but encompassed by ACLF, strongly influences morbidity and mortality in this critically ill group.

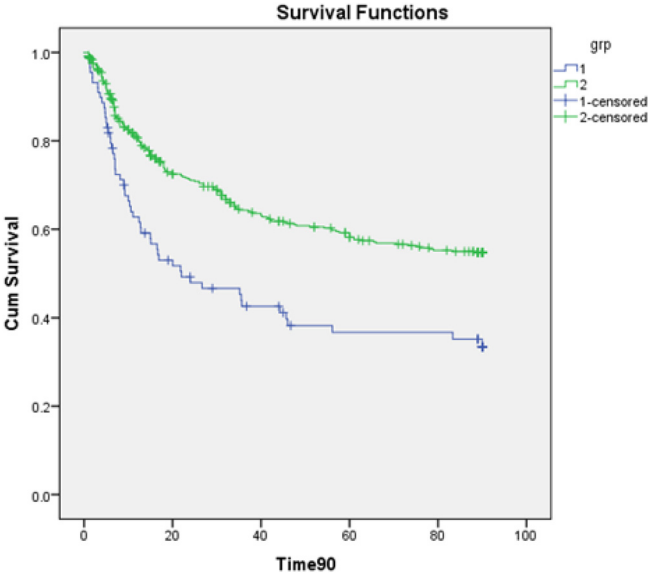
THU-270
Hemophagocytic Lymphohistiocytosis (HLH) in patients of acute on chronic liver failure-Results of multination study from APASL-ACLF research consortium (AARC)

H.V. Tevethia[1], A. Choudhury[2], H.L. Ghazinyan[3], C. Eapen[4], A. Goel[4], Z. Duan[5], Y. Chen[5], D.J. Kim[6], J.-D. Jia[6], D. Amarapurkar[7], S.S. Hamid[8], W. Jafri[8], S.-S. Tan[9], Z. Abbas[10], G.H. Lee[11], S.G. Lim[11], J.H. Hu[12], Y. Chawla[13], S. Taneja[13], S. Shah[14], C. Kalal[14], H. Deverbhavi[15], O. Yokosuka[16], P. Jain[17], I. Paulson[17], G. Kumar[17], S.K. Sarin[2]. *[1]ILBS, Hepatology, New Delhi, India; [2]ILBS, Hepatology; [3]Nork Clinical Hospital of Infectious Disease Armenia, Hepatology; [4]CMC, Hepatology, Vellore, India; [5]Beijing You'an Hospital/Translational Hepatology Institute Capital Medical University; [6]Hallym University College of Medicine, South Korea/Beijing Friendship Hospital, Capital University, Beijing, China; [7]Bombay Hospital & Medical Research Center, Mumbai, India; [8]Aga Khan University Hospital, Karachi; [9]Hospital Selayang, Bata Caves, Selangor; [10]Ziauddin University Hospital, Karachi; [11]Yong Loo Lin School of Medicine, National University of Singapore; [12]302 Millitary Hospital Beijing, China; [13]PGIMER, Chandigarh, India; [14]Global Hospital, Mumbai, India; [15]St John Medical College, Bangalore, India; [16]Chiba University; [17]ILBS*
Email: hershey4686@gmail.com

Background and Aims: Activation of macrophages in response to acute hepatic insult in patients with pre-existing chronic liver disease presenting as ACLF is a new entity, HLH. Considered to be result of a cytokine storm, uncontrolled inflammatory response, HLH has a poor survival. We studied patients of ACLF to investigate the spectrum, presentation and influence of HLH syndrome on organ failure, disease severity and short-term survival.
Method: The patients diagnosed to have ACLF (APASL definition) were recruited from 52 centres across Asia Pacific. The data was prospectively collected in this observational study cohort on a

predefined format in the database from October 2012 to September 2017. A total of 615 patients of ACLF with ferritin >500 µg/l, were analyzed among those fulfilling the HLH criteria [5 of 8 criteria i.e. fever, splenomegaly, bicytopenia,hypofibrinogenemia & ferritin >500 µg/l, irrespective of the bone marrow examination).

Results: Out of 615 patients with ferritin above >500 µg/l, the HLH was seen in 90 (14.6%) cases i.e. full-filling 5 criteria. Males were 84.1% and with mean age of 43.31 ± 11.69 yrs. Alcohol was the most common acute and chronic etiology followed by Hepatitis B reactivation. The most common presentation was Jaundice (98.5%), hypofibrinogenemia (93.3%), Spleenomegaly (73.1%) and Fever (61%). Organ failures more than 2, Creatinine >1.49 mg/dl, albumin <2.3 gm/l, INR >2.4, Total Bilirubin >22.3 mg/dl and HE at baseline independently predicted 90 day mortality. Presence of HLH increased mortality ($p < 0.001$) even though various disease severity scores MELD Na [31.49 ± 7.56 vs 28.05 ± 7.38,* p = 0.27], SOFA [10.69 ± 3.20 vs 8.78 ± 3.09, p = 0.84], AARC Score [10.37 ± 2.15 vs 9.85 ± 2.19, p = 0.79] were not different between those dying versus surviving.



Conclusion: Presence of HLH even in absence of bone marrow confirmation is a poor predictor of outcome in patients of ACLF. Diagnosis of HLH predicts worse prognosis. Newer definition and criteria for HLH and its inclusion in liver severity scores is required in ACLF patients.

THU-271

Human beta-defensin-1 is a highly predictive marker of mortality in patients with acute-on-chronic liver failure

I. Mani, L. Vasilieva, A. Alexopoulou, E. Hadziyannis, D. Agiasotelli, T. Alexopoulos, D. Zampetas, S. Ntourakis. *2nd Department of Internal Medicine and Research Laboratory, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece*
Email: alexopou@ath.forthnet.gr

Background and Aims: Human beta-defensin-1 (hBD-1) is a natural antimicrobial peptide expressed in the epithelia of multiple tissues including the digestive tract. Acute-on-chronic-liver-failure (ACLF) is defined as an acute deterioration of liver disease with high mortality in patients with cirrhosis. In the current study, hBD-1 levels were determined in different subsets of patients with decompensated cirrhosis including ACLF. In addition, the association of both hBD-1 and C-reactive protein (CRP) values with mortality was assessed.

Method: 125 patients were divided into 3 groups: 39 with ACLF, 46 with acute-decompensation without ACLF (AD) and 40 with decompensated cirrhosis without an acute event (DC). The hBD-1 was evaluated in serum by enzyme-linked-immunosorbent-assay. 15 healthy individuals were used as control group.

Results: Serum hBD-1 levels were higher in ACLF compared to AD ($P < 0.001$) and more elevated in AD compared to DC-group ($P < 0.001$). In contrast, CRP values showed a blunt association with severity of liver disease. Controls demonstrated lower values compared to cirrhotics ($P < 0.001$). Serum hBD-1 levels were not correlated with CRP ($r = 0.224$). In ROC curve, the value of 30.635 ng/ml was associated with the best prediction of 60-day mortality in ACLF-group (c-statistic 0.931, sensitivity 87.5%, specificity 100%). CRP was less accurate in predicting mortality (c-statistic 0.792, sensitivity 87.5%, specificity 66.7%). In AD-group neither serum hBD-1 nor CRP seemed to be associated with poor survival (c-statistics 0.500 and 0.596, respectively). In DC-group serum hBD-1 and CRP were equally accurate markers in predicting mortality (c-statistics 0.800 and 0.808, respectively). In ACLF-group, patients with high hBD-1 (>30.635) had a poor prognosis compared to those with low values (log-rank P = 0.001). In Cox univariate analysis, variables that had at least a trend ($P < 0.10$) for association with survival included age, gender, CLIF-C OF ACLF, MELD, sodium and CRP. In multivariate cox regression analysis only serum hBD-1 [hazard ratio (HR) 13.088, 95% confidence interval (CI) 1.475–116.101, P = 0.021] and liver function as assessed by MELD score (HR 1.106 95%CI 1.012–1.120, P = 0.027) emerged as independent predictors of death in ACLF group.

Conclusion: High serum hBD-1 was detected at presentation in patients with ACLF who died during the 60-day-follow-up period. Serum hBD-1 is an accurate predictor of short-term mortality in patients with ACLF.

THU-272

Thromboelastography parameters in acute on chronic liver failure

S. Goyal[1], Shalimar[1], S.S. Jadaun[1], S. Kedia[1], S.K. Acharya[1], S. Verma[2], B. Nayak[1], B. Thakur[1]. *[1]All India Institute of Medical Sciences, Gastroenterology, New Delhi, India; [2]Max Hospital, Department of Pediatric Hepatology and Gastroenterology, New Delhi, India*
Email: drshalimar@yahoo.com

Background and Aims: Patients with acute on chronic liver failure (ACLF) are assumed to have coagulation abnormalities on the basis of conventional tests (CCTs) – prolonged international normalized ratio (INR) and activated partial thromboplastin time (aPTT) and decreased platelet counts. Thromboelastography (TEG) assesses the global coagulation cascade. We aimed to evaluate TEG parameters in patients with acute on chronic liver failure (ACLF), and their ability to predict complications.

Method: Consecutive patients diagnosed with ACLF were included. We also included patients with chronic liver disease having acute decompensation and no ACLF (AD), and healthy subjects (HC) as controls. CCTs and TEG parameters were assessed within 24 hours of admission, and compared between the 3 groups. Cox-proportional hazard analysis was used to assess predictors of outcome.

Results: In this prospective study (June 2015 to June 2016), 68 ACLF (17-grade1, 20-grade 2, 31-grade 3), 53 AD patients and 58 HC were included. Alcohol consumption was the most common etiology. CCTs were significantly prolonged in patients with ACLF and AD as compared to HC. The mean values of INR in ACLF, AD and HC groups were 2.9 ± 1.4, 1.6 ± 0.4 and 1.1 ± 0.2; $P < 0.001$. Among TEG parameters- maximum amplitude (MA) was low in ACLF and AD patients as compared with HC (52.4 ± 14.3, 58.3 ± 13.7 mm and 66.9 ± 13.3 mm, respectively; $P < 0.001$). Lysis at 30 (LY30) min was high in ACLF patients as compared to AD and HC (8.6 ± 14.1%, 5.0 ± 9.5% and 4.9 ± 9.8%, respectively; P = 0.060). Among ACLF and AD patients, abnormal LY30 (>15 min) was seen in 23.5% and 15.1% patients, respectively. There were no differences in r time, k time, and alpha angle between the 3 groups. There was no difference in TEG parameters between different ACLF grades, whereas CCTs were more deranged with increasing grades. In the ACLF group, on multivariate analysis, MA was an independent predictor of outcome

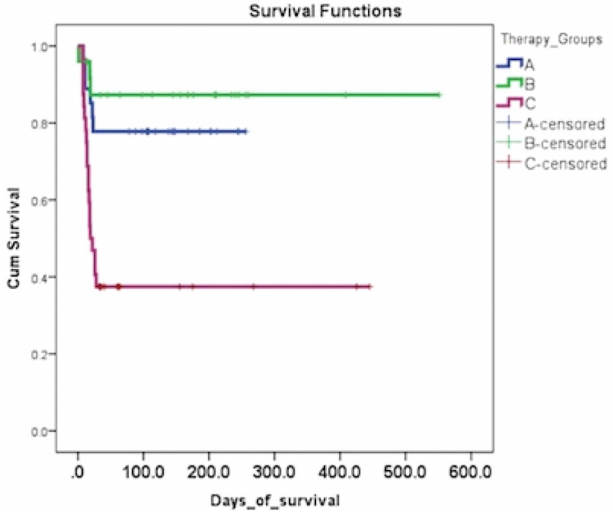
(HR 0.973 (95% CI, 0.948–0.998, P = 0.036) after adjusting for sex, total leucocyte count, hepatic encephalopathy, mean arterial blood pressure, creatinine, INR and LY30.
Conclusion: TEG parameters are abnormal in ACLF. MA may be of benefit in predicting outcome.

THU-273
Features of levels of neurospecific proteins in patients with hepatic encephalopathy
N. Dynnyk[1], E. Manzhalii[2], O. Baka[3], M. Lysianyi[4]. [1]*Bogomolets National Medical University, Internal Medicine, Kyiv, Ukraine;* [2]*Bogomolets National Medical University, Propedeutics of Internal Medicine;* [3]*Hospital for Scientists, Gastroenterology, Kyiv, Ukraine;* [4]*The State Institution Romodanov Neurosurgery Institute National Academy of Medical Sciences of Ukraine*
Email: dynka@ukr.net

Background and Aims: Today role of autoimmune processes in the pathogenesis of hepatic encephalopathy (HE) is not fully established. Many studies concerning damages of the nervous system showed the change of the content of some marker proteins, including myelin basic protein (MBP), cerebral antigen (CA), neuron specific enolase (NSE) and S100 proteins and the increasing of the titer of antibodies to these antigens. These phenomena are underlying the development of autoimmune processes in the conditions of the nervous tissue injury. However, there are no enough data on these proteins changes in the conditions of HE.
The aim was to establish the level of autoantibodies to neuron specific antigens: MBP, CA, NSE and S100 proteins in patients with HE.
Method: The study involved 51 patients aged 34–69 years (average age 49,4 ± 5,8 years) dominated by men (80%) with cirrhosis and hepatitis with the transition to cirrhosis with two or more documented episodes of HE over the last 6 months who were hospitalized and then under nursing. The levels of autoantibodies to MBP, S100, NSE and CA were measured by ELISA using specific antibodies (Sigma) in the serum of patients with HE. We studied the correlation between these autoantibodies and the level of general indicator of neurological status of patients in points. This figure included the assessment of the presence of oral automatism, anisoreflexia, statico-locomotory ataxia, violation of the sensitivity in patients. Each of the symptoms measured in the categorical values: there is either no violation. Accordingly, the overall rate of neurological.
Results: It was found a significant increase in the level of antibodies to CA, protein S100, NSE and MBP in patients with HE. In blood serum of patients CA increased by 33.4% ($p < 0.001$), S100 protein – by 81.1% ($p < 0.001$), NSE – by 39.6% ($p < 0.001$), MBP – by 55.1% ($p < 0.001$) compared with normal level.
Conclusion: The positive correlation between these proteins and the degree of neurological disorders in patients was revealed. Therefore, these indicators can be considered as markers of the degree of severity of HE. Determination of the levels of autoantibodies in patients with HE has a high diagnostic value. This gives us a reason to associate increase in these parameters with the process of destruction of brain tissue, which allows to predict the course of the disease and develop treatment tactics.

THU-274
Non inferiority of combination of slow continuous albumin, furosemide with low dose Terlipressin with Noradrenaaline infusion in ACLF patients in comparison to slow continuous albumin, furosemide and Terlipressin
G. Pandey[1], A. Kumar[2], M. Durgappa[2], A. Singh[2], A. Nehra[2], K. Vp[2], P. Sharma[2], P. Mishra[2], S. Mohindra[2], V. Saraswat[3]. [1]*Sanjay Gandhi Institute of Medical S, Hepatology and Gastroenterology, Lucknow, India;* [2]*Sanjay Gandhi Institute of Medical S, Gastroenterology, Lucknow, India;* [3]*Sanjay Gandhi Postgraduate Institute, Gastroenterology, Lucknow, India*
Email: drgauravpandey@yahoo.com

Background and Aims: Slow continuous albumin,furosemide ± terlipressin(SAFI ± T) infusion mobilizes ascites and significantly improves systemic hemodynamics and intestinal permeability in acute on chronic liver failure (ACLF) patients. Due to potential adverse effects of terlipressin at high doses a combination approach of low doses of 2 vasocosntrictors – Terlipressin and Noradrenaline in-effect causing splanchnic and systemic vasoconstriction synergistically with potentially lower side effects in ACLF patients was studied to look at the side effects and efficacy of the 2 regimen,comparing 28 day mortality with Standard medical treatment(SMT) arm.
Method: A case control prospective study with 3 groups of ACLF. Arm I SAFI ± T, Arm II SAFIT + Noradrenalin (SAFIT ± NA),ArmIII- SMT. In Arm I- Furosemide at 2 mg/ hour and albumin 2 gm/hour (20 g/d) was started(40 g/d). Blood and urine(electrolytes) done 12 hourly and corrected as required. Graded increase of furosemide was done by 1 mg (max 6 mg/hr) if UNa < 80 mmol/d. At 48 hours UNa <80 mmol/d then terlipressin infusion @2 mg/12 hours was started after correcting anemia and response guided increase (1 mg/12th hourly) was done (maximum 6 mg/24 hours). Arm II -the same protocol was followed but Terlipressin at 2 mg/24 hrs low dose was supplemented with Noradrenalin at 0.5 mcg/kg/min and titrated to max 1.5 mcg/kg/min if UNa < 80 mmol/day. Patients were shifted to oral diuretics at discharge maintaining UNa > 80 mmol/24 hours. Arm III received SMT including Albumin, and Terlipressin wherever indicated with oral diuretics.
Results: 84 ACLF patients-27(32%), 25 (30%) and 32(38%) in Arms I, II, III were enrolled. Overall age 47.3 ± 12 yrs and etiology were not significantly different. Baseline characteristics of Arm I, II and III including MELD 31.3 ± 6.7 vs 29.3 ± 4.6 vs 29.7 ± 5.6, Number of Organ failure 1.9 ± 0.8 vs 1.6 ± 0.7 vs 1.4 ± 0.8, Serum Creatinine 1.7 ± 0.8 vs 1.6 ± 0.7 vs 1.3 ± 0.9 mg/dl and CLIF-C-ACLF –49.9 ± 8 vs 47 ± 8 vs 52 ± 8 were not significantly different. Baseline urine sodium in Arm I (37.9 ± 27) and II (31 ± 11.5) increased to 235.8 ± 159 and 246 ± 146 mmol/24 hrs at discharge. 28 day survival in Arm I, II and III were 77% vs 88% vs 37.5% with p = 0.002 and 0.001 between Arm I-III and Arm II-III and p = 0.396 between Arm I and II. There was also significant improvement in systemic hemodynamics and intestinal permeability (NMR based Lactulose Mannitol ratio) in Arm I and II. No major adverse events were noted in Arm II.



Conclusion: Non inferiority of SAFIT ± NA over SAFI ± T in ACLF with no major adverse effects was seen.

THU-275

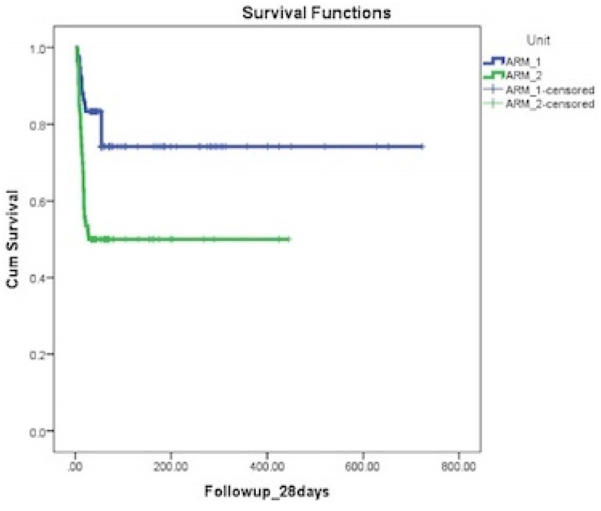
Impact of response guided aggressive pharmacological therapy with slow continuous albumin, furosemide and terlipressin infusion in chronic liver failure consortium acute on chronic liver failure score

G. Pandey, A. Kumar, M. Durgappa, S. Mohindra, A. Singh, V. Saraswat, K. Vp. *SGPGIMS, Gastroenterology, Lucknow, India*
Email: drgauravpandey@yahoo.com

Background and Aims: In Acute on chronic liver failure (ACLF) patients, chronic liver failure-consortium-acute-on-chronic liver failure score (CLIF-C ACLF) 35–65 identifies the sub-group of patients with good response to intervention. This is a prospective case-control study to assess the prognostic performance of ACLF patients with large ascites admitted with CLIF-C ACLF score between 35–65 treated with slow continuous albumin, furosemide ± terlipressin(SAFI ± T) infusion or standard medical therapy(SMT) and compare their 28-d mortality.

Method: Arm I Furosemide infusion at 2 mg/hour and albumin 2 gm/hour (20 g/d) was started. Blood and urine (electrolytes) samples were collected every 12 hours for UNa,UK and graded increase of furosemide was done by 1 mg (max 6 mg/hr) if UNa < 80 mmol/l. Aggressive potassium supplementation (oral/iv) was done in all patients. If after 48 hours UNa was still <80 mmol/l then terlipressin infusion @2 mg/12 hours was started after correcting anemia and baseline ECG (repeated 12th hourly) and response guided increase (1 mg/12th hourly) was done (maximum 6 mg/24 hours). Patients were shifted to oral diuretics at discharge maintaining UNa > 80 mmol/24 hours. Arm II received SMT including Albumin, and Terlipressin wherever indicated with oral dirutics. Central line wasplaced in oliguric/anuric patients.

Results: 211 patients Overall etiology: alcohol (49.5%) cryptogenic (23%), HCV (12.2%), HBV (6%), NASH (5.3%) and autoimmune (4%) was not significantly different. Baseline characteristics of Arm I(80) vs Arm II(14 patients) including mean age 46.7 ± 11.7 years, CTP 11.5 ± 2.7 vs12 ± 0.9, MELD 23 ± 5.7 vs24.3 ± 5.6, CLIF-SOFA-9.8 ± 1.8 vs 10.2 ± 2.1, Number of Organ failure2 ± 1.1 vs 1.6 ± 1, Serum Creatinine 1.52 ± 1.15 vs 1.4 ± 0.9 mg/dland CLIF-C-ACLF –2 ± 12.6 vs 49.6 ± 10.8 (p > 0.05)was not significantly different. Baseline urine sodium in Arm I increased from 32.6 ± 23 to 155 ± 143.8 mmol/24 hrs at discharge. 28 day mortality in Arm I was 75% vs 50% (p < 0.01). There was also significant improvement in systemic hemodynamics and intestinal permeability(NMR based Lactulose Mannitol ratio) in Arm I.



Conclusion: CLIF-C ACLF score ≤ 65 offers a window of opportunity for aggressive therapy in these extremely sick patients having beneficial impact on hemodynamics, intestinal permeability and survival.

THU-276

Impact of Clostridium difficile 027 ribotype in decompensated cirrhotic patients

A. Fernandez, L. Carrion, L. Dieguez, C. Villaseca, A. Conthe, M. Valerio, L. Ibañez, R. García, R. Bañares. *Hospital Gregorio Marañon, Liver Unit, Madrid, Spain*
Email: afyunquera@gmail.com

Background and Aims: Clostridium difficile (CD) constitutes an important cause of morbidity and mortality in hospitalized patients, especially with the emergence of a virulent strain known as BI/NAP1/027. The aim of the study was identify factors predisposing to CD disease and evaluate the impact on outocomes in decompensated cirrhotic patients hospitalized during a CD-027 ribotype outbreak in a terciary center.

Method: A retrospective analysis of cirrhotic patients hospitalized with decompensation and all CD 027 episodes at a terciary center, from November 2014 to January 2016 (CD027 outbreak) was made. Etiology of cirrhosis, decompensation data, comorbid condition, infection data, type of contact and history of hospitalization, use of antibiotics (including norfloxacin or rifaximin) and proton-pump inhibitor were collected. Mortality, length of stay, determinant for CD disease, and outcomes of cirrhosis were analyzed with a logistic regression and Cox model. Patients with CD ribotype 027 were intensified early treated with vancomicina.

Results: Cirrhosis was the most frequent disease associated with CD027 in the hospital (18.5%). 173 cirrothic patients were admitted with complete data in 121 cases. Patients with CD disease were 24% (CI 95% 16.7–32.6) and CD 027 14% (CI 95% 8.36–21.48). No differences in severity and hospital mortality were found (serious disease: CD027 26.7% no CD027 36.4%; p = 0.61; hospital mortality: CD027 17.6% no CD027 8.3%; p = 0.62). Diabetes mellitus, antibiotic in the previous six weeks, rifaximin or norfloxacin use, history of hospitalization in the previous three months, Child B-C were associated with CD in univariate analysis. Child B-C (OR 11.9), rifaximin/norfloxacin (OR 3.72) and antibiotic in the previous six weeks (OR 22.33) were associated with CD and also in CD027 in multivariate analysis. Length of stay was higher in CD than no CD [56.39 days (17.40) Vs 17.10 (11.34) P < 0.001] especially in CD027 [76.64 (27.70) Vs 17.99 (9.86) P < 0.001]. Diabetes mellitus (HR 1.78), female sex (HR 2.28) and CLIF-AD score (HR 1.05) were associated to survival.

Conclusion: Although cirrhosis constitutes a risk factor for CD027 disease, it is not associated with a higher risk of serious disease and mortality if intensified early treatment is applied.

THU-277

Albumin administration in the prevention of hepatorenal syndrome (HRS) and death in patients with advanced cirrhosis and non-SBP infections

J. Fernandez, P. Angeli, J. Trebicka, M. Merli, T. Gustot, C. Alessandria, N.K. Aagaard, A. De Gottardi, S. Zeuzem, A. Gerbes, G. Soriano, V. Vargas, A. Albillos, F. Salerno, F. Durand, R. Bañares, R.E. Stauber, V. Prado, M. Arteaga, F. Morando, C. Jansen, B. Lattanzi, C. Moreno, A. Risso, H. Grønbæk, R. Garcia, M. Pavesi, V. Arroyo. *Hospital Clinic, Liver Unit, Spain*
Email: jfdez@clinic.ub.es

Background: Albumin administration prevents HRS and death in SBP. Previous studies failed to demonstrate a clinically relevant beneficial effect of this treatment in non-SBP infections.

Aims and Method: Open-label, multicenter European RCT aimed to evaluate if albumin administration improves short-term survival in patients with non-SBP infections and advanced cirrhosis (serum creatinine ≥1.2 mg/dl, serum sodium ≤130 mEq/l and/or serum bilirubin ≥ 4 mg/dl). Initial sample size was estimated in 512 patients, 256 per treatment arm.

Results: 119 patients were finally included. The study was prematurely stopped due to low recruitment rate and expiration of the

study drug. Sixty subjects were randomized to receive antibiotics + albumin within the first 72 h after infection diagnosis (1.5 g/kg at inclusion, 1 g/kg on day 3) and 59 to receive antibiotics. Baseline clinical and analytical characteristics were similar between groups with no differences in Child-Pugh, MELD score, type of infection (pneumonia: 28% vs. 37%, UTI: 27% vs. 20%, bacteremia: 23% vs. 19% in the albumin and non-albumin groups, respectively) or severity (nosocomial: 30% vs. 32%; ACLF: 25% vs. 18%). Hospital mortality rate, the main aim of the study, was similar between groups: 13% in patients receiving albumin compared to 10% in the non-albumin group. Seven patients were lost to follow-up after hospital discharge (2 in each group at 28-d and 5 and 2 in the albumin and non-albumin group at 90-d). Twenty-eight day (13% vs. 8.5%) and 90-d (28% vs. 22%) mortality rates were also similar between groups. Two patients in the albumin group and 6 in the non-albumin group were transplanted during follow-up (3% vs. 10%; p = NS). Transplantation was performed within 28 days after inclusion in 1 and 5 patients in the albumin and non-albumin groups, respectively. Four patients receiving albumin (7%) developed pulmonary edema during hospitalization (2 pneumonia, 1 bacteremia, 1 suspected infection) compared to none in the non-albumin group.

Conclusion: Albumin administration does not improve short-term survival in cirrhotic patients with non-SBP infections and liver and/or renal dysfunction.

Viral hepatitis C: Therapy and resistance

THU-281

Emergence and long-term persistence of NS3, NS5A, and NS5B resistance associated substitutions after treatment with direct-acting antivirals

D. Wyles[1], E. Lawitz[2], B. Mcnabb[3], J. Lu[3], S. Chang[3], A. Osinusi[3], E.S. Svarovskaia[3], D. Brainard[4], S. Pianko[5], J. Feld[6], H. Mo[3], H. Dvory-Sobol[3]. *[1]Denver Health Medical Center, Denver, CO, United States; [2]Texas Liver Institute, The University of Texas Health San Antonio, San Antonio, United States; [3]Gilead Sciences, Foster City, United States; [4]Gilead Sciences, Foster City, CA, United States; [5]Monash Health and Monash University, Melbourne, Australia; [6]Toronto Centre for Liver Disease, Toronto, Canada*
Email: hadas.dvory-sobol@gilead.com

Background and Aims: Limited data on the long-term persistence of NS5A and NS3 HCV resistance associated substitutions (RASs) are available after treatment with clinically relevant HCV regimens. The aim of this study was to evaluate the persistence of NS3, NS5A and NS5B nucleotide inhibitor (NI) RASs in patients not achieving SVR in Gilead-sponsored treatment studies who were enrolled in a follow-up Sequence Registry.

Method: Patients who did not achieve SVR following treatment with a DAA-containing regimen in a Gilead treatment protocol were eligible for enrollment into the Sequence Registry where they were followed for up to an additional 144 weeks. Patients had NS5A, NS3 and/or NS5B regions sequenced if they were exposed to an NSS5A inhibitor (ledipasvir [LDV] or velpatasvir [VEL]), an NS3 inhibitor (vedroprevir [VDV] or voxilaprevir [VOX]), and/or an NS5B NI (sofosbuvir [SOF]), respectively. Patients were discontinued if they received HCV treatment or once RASs were no longer detectable. Results are reported using a 15% cutoff.

Results: Treatment-emergent NS5A and NS3 RASs were observed at the time of virologic failure (VF) in 95% and 93% of registry enrolled patients treated with non-SOF based regimens, respectively. NS5A and NS3 RASs were present at Week 144 in 63% and 25% of non-SOF treated patients, respectively. Treatment-emergent NS5A resistance was observed in 48% of registry enrolled patients at the time of VF with a SOF-based regimen. No treatment-emergent NS3 RASs were detected among the SOF/VEL/VOX failures enrolled in the study (Table). More than 1 NS5A RAS was detected in 47% and 7% of patients treated with non-SOF and SOF-based regimens, respectively. Treatment-emergent NS5B NI RASs were observed in 13/227 (6%) patients treated with a SOF-based regimens at the time of VF. No S282T was observed in any patient.

	Emergent RASs n/N (%)					
		Registry Study				
	Virologic Failure	Baseline	FU 12	FU 48	FU 96	FU 144
	NS5A RASs					
Non SOF-based[1]	138/145 (95)	137/145 (94)	107/115 (93)	92/107 (86)	64/86 (74)	27/43 (63)
SOF-based[2]	32/67 (48)	32/67 (48)	14/31 (45)	5/11 (45)	0/3	–
SOF/VEL/VOX	1/10 (10)	1/10 (10)	1/6 (17)	1/5 (20)	–	–
	NS3 RASs					
Non SOF-based[1]	105/113 (93)	102/113 (90)	68/82 (83)	37/81 (46)	16/63 (25)	8/32 (25)
SOF/VEL/VOX	0/10	0/10	0/6	–	–	–

[1]LDV + VDV + tegobuvir ± ribavirin (RBV) ± pegylated-interferon.
[2]LDV/SOF ± RBV, SOF/VEL ± RBV, SOF/VEL/VOX.

Conclusion: Among patients enrolled in this follow up registry, treatment-emergent RASs at the time of VF as well as long-term persistence of NS5A and NS3 RASs were more common among patients receiving regimens without SOF. NS5A RASs were more likely to persist than NS3 RASs, and NS5B RASs were uncommon. RASs were infrequent among patients failing treatment with SOF/VEL/VOX.

THU-282

Behavioral and clinical factors and Direct Acting Antiviral effectiveness in HCV/HIV co-infection; clinical experience from the TRIO network

G. Huhn[1], D. Jayaweera[2], K. Althoff[3], J. Eron[4], S. Milligan[5], A. Mills[6], G. Moyle[7], S. Santiago[8], P. Sax[9], G. Voskuhl[10], D. Wyles[11], R. Elion[12]. *[1]The Ruth M. Rothstein CORE Center – Rush University Medical Center, Chicago, United States; [2]Miller School of Medicine – University of Miami, Division of Infectious Disease, Miami, United States; [3]Johns Hopkins, United States; [4]Division of Infectious Diseases – UNC Chapel Hill; [5]Trio Health, La Jolla, United States; [6]Southern California Men's Medical Group, United States; [7]Chelsea and Westminster Hospital; [8]Care Resource, Miami, United States; [9]Brigham and Women's Hospital and Harvard Medical School; [10]Prism Health, Baylor University Medical Center, United States; [11]Division of Infection Diseases, Denver Health Medical Center, United States; [12]George Washington University School of Medicine*
Email: ghuhn@cookcountyhhs.org

Background and Aims: Clinical studies of Direct Acting Antivirals (DAA) in patients co-infected with HIV and hepatitis C virus (HCV) have demonstrated comparable efficacy and tolerability to studies with HCV mono-infected individuals. However, many co-infected patients in clinical care have psychosocial issues (e.g. active drug or alcohol use) excluded or not well represented in clinical trials. This study assesses DAA effectiveness in HIV/HCV co-infected patients.

Method: Data were extracted from the electronic medical records of 450 HIV/HCV co-infected patients who initiated DAAs between Jan 2014 and Mar 2017 and were in care at 5 US-based HIV treatment centers. The primary outcome was sustained virologic HCV response at ≥12 weeks (SVR12) from the end of DAA therapy.

Results: 6 regimens accounted for 96% (430/450) of treatment: 68% (304/450) ledipasvir-sofosbuvir (LDV-SOF) +/– ribavirin (RBV), 9% (39/450) SOF + RBV, 8% (34/450) simeprevir (SMV) + SOF +/– RBV, 4% (18/450) elbasvir-grazoprevir (EBR-GZR) +/– RBV, 4% (18/450) ombitasvir-paritaprevir-ritonavir and dasabuvir (PrOD) +/– RBV, and 4% (17/450) daclatasvir (DCV) + SOF +/– RBV. Outcomes in the intent to treat (ITT) population were 90% (404/450) achieved SVR12,

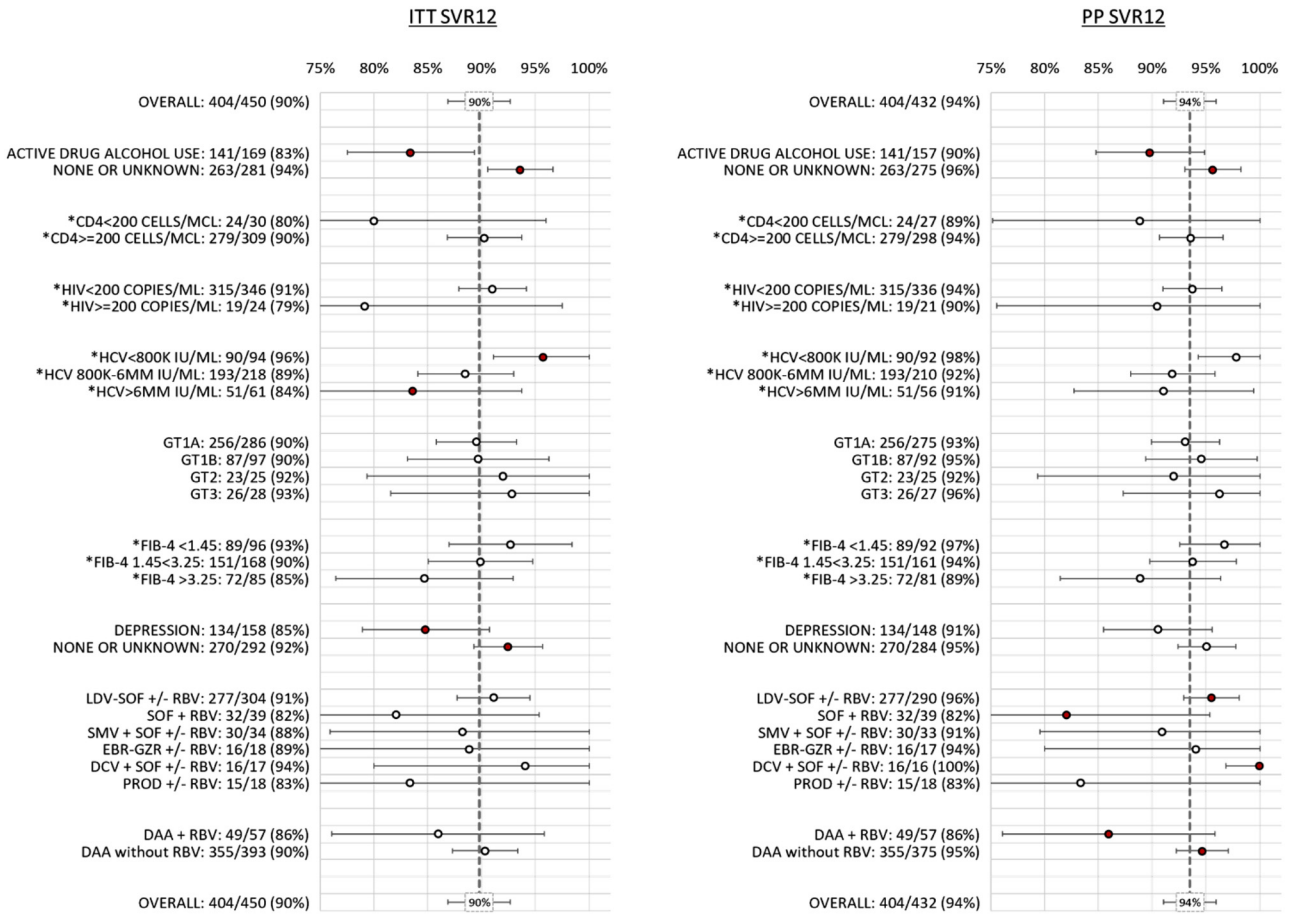


Figure: (abstract: THU-282): Univariate analyses of variable association with ITT SVR12 (left) or PP SVR12 (right). Filled circles indicate subgroups that are significantly different for rates ($p<=0.05$) based on chi-square or z-tests for population proportions. * indicates measures at baseline relative to DAA treatment. @ denotes that PP SVR12 rates were significantly different between SOF + RBV and LDV-SOF +/– RBV or DCV + SOF +/– RBV but not between LDV-SOF +/– RBV and DCV + SOF +/– RBV.

6% (28/450) completed therapy but did not achieve SVR12, 2% (8/450) completed but were lost to follow up, 1% (4/450) discontinued, and 1% (6/450) died. The per protocol (PP) SVR12 rate, limited to patients who completed therapy and an SVR assessment, was 94% (404/432). By regimen, SVR12 rates were highest for LDV-SOF +/– RBV (ITT 91%, 277/304; PP 96%, 277/290) and DCV + SOF +/– RBV (ITT 94%, 16/17; PP 100%, 16/16) and lowest for SOF + RBV (ITT 82%, 32/39; PP 82%, 32/39) and PrOD +/– RBV (ITT 83%, 15/18; PP 83%, 15/18). Characteristics significantly associated with failure to achieve HCV SVR12 were active drug or alcohol use, HCV > 6MM IU/ml, depression, use of SOF + RBV, and use of DAA containing RBV (Figure).

Conclusion: In this analysis of co-infected patients in US clinical care, effectiveness of anti-HCV regimens was 90% (ITT SVR12) with 6% having virologic failure. Discontinuation and lost to follow up rates were low compared to HCV mono-infection in TRIO real-life studies. Variables significantly associated with failure to achieve SVR primarily include those likely to predict poor medication adherence and follow-up, highlighting a need for improved patient engagement in conjunction with highly effective DAAs.

THU-283

HCV-FiS (HEpatitis C Virus Finger-stick Study): HCV RNA point-of-care testing by GeneXpert in the setting of DAA therapy

V. Calvaruso[1], F. Bronte[1], D. Ferraro[2], M.G. Bavetta[1], S. Petta[1], V.D. Marco[1], A. Craxi[1]. [1]*University of Palermo, Gastroenterology and Hepatology Unit, DIBIMIS, Palermo;* [2]*University of Palermo, Virologia Dip.PRO.SA.M.I., Palermo*
Email: vincenza.calvaruso@unipa.it

Background and Aims: DAA regimens have simplified HCV patient care and provide the opportunity to cure patients of the disease, but HCV RNA assessment at baseline, during and after therapy still relies on assays requiring blood collection and transport to a specialized laboratory, all of which compromise linkage to care. GeneXpert HCV Viral Load (GXHVL, Cepheid, Sunnyvale, CA, USA) is a plasma-based assay and results are available within 2 hours of sampling. In HCV-FiS we evaluated the performance of GXHVL with a modified protocol for point-of-care testing using finger-stick capillary whole-blood samples in the setting of a hospital-based outpatient clinic caring for HCV patients (1).

Methods: 59 consecutive chronic HCV patients (F3 24:40.7%; F4 35:59.3%) were enrolled in HCV-FiS. HCV genotype was 1a in 7 patients, 1b in 41, 2 in 8, 3 in 1, and 4 in 2. Capillary blood collected by finger-stick was processed on site by a trained nurse on the GeneXpert platform. HCV viral load (VL) was tested on a simultaneous venous blood sample by the Hospital's Virology Lab using a standardized Real Time (RT) PCR (Roche TaqMan). DAA regimens were prescribed according to the current EASL recommendations. The performance of the GXHVL and of the TaqMan assay were compared at baseline (BL), at week 4 (W4) and at end of therapy (EOT) and at week 12 of follow up to evaluate the sustained virological response (SVR12).

Results: 57 patients (mean age 65.8 ± 12.1 years; 54% males) were tested with both assays, while 2 were excluded due to mishandling of the GXHVL specimen at BL. At BL 56/57 (98.2%) patients were HCV RNA positive. In one patient HCV RNA was undetectable by both methods but had tested positive by TaqMan two months earlier.

Linear regression analysis confirmed the high concordance in HCV RNA quantification between GXHVL test and the RT-PCR HCV VL assay (R = 0.809; R2: 0.654 p < 0.001) at BL (median VL:778,400 vs 123,0000 IU/ml respectively). At W4, 39/56 (69.6%) and 42/56 (75%) patients had undetectable HCV-RNA by GXHVL and RT-PCR test, respectively. Six patients had undetectable HCV RNA by RT-PCR but levels <10 IU/ml by GXHVL test; 5 patients had undetectable HCV RNA by GXHVL but <15 IU/ml by RT-PCR. Both assays demonstrated undetectable HCV-RNA in all 56 patients (100%) at EOT. At SVR12 both assays identified the single case of HCV relapse in the cohort (HCV-RNA: 248,600 vs 822,000 IU/ml by GXHVL and RT-PCR respectively) with a concordance rate, a sensitivity and specificity of 100%.

Conclusion: GeneXpert as a point-of-care assay used in the outpatient setting, provides results fully comparable to the laboratory-based test. Its excellent performance characteristics and ease of use suggest its adoption in non-specialist settings where simplicity of care is paramount to implement HCV eradication campaigns.

Reference

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THU-284

Therapy with DAAs in patients with chronic hepatitis C and advanced chronic kidney disease: Real-world experience from the German Hepatitis C-Registry (DHC-R)

J. Wiegand[1], P. Buggisch[2], S. Mauss[3], K. Boeker[4], H. Klinker[5], T. Müller[6], R. Guenther[7], Y. Serfert[8], M.P. Manns[9], S. Zeuzem[10], T. Berg[1], H. Hinrichsen[11], D.H. C-Register[8]. *[1]University Hospital Leipzig, Leipzig, Germany; [2]IFI-Institute for Interdisciplinary Medicine, Hamburg, Germany; [3]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; [4]Center of Hepatology, Hannover, Germany; [5]University Hospital Würzburg, Würzburg, Germany; [6]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [7]Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Germany; [8]Leberstiftungs-GmbH Deutschland, Hannover, Germany; [9]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [10]University of Frankfurt, Department of Medicine, Frankfurt, Germany; [11]Gastroenterology-Hepatology Center Kiel, Kiel, Germany*
Email: johannes.wiegand@medizin.uni-leipzig.de

Background and Aims: Real-world experience with direct antiviral agents (DAA) in patients with chronic hepatitis C virus (HCV) infection and a glomerular filtration rate (GFR) < 30 ml/min is limited to case series so far. The German Hepatitis C-Registry (DHC-R) is a prospective, multicenter real-world registry study for patients with chronic hepatitis C. We investigated the safety and effectiveness of novel DAAs in patients with impaired kidney function.

Method: The DHC-R comprises approximately 11,000 patients recruited by more than 250 centres. Patients are treated at the discretion of the physician. The present analysis is based on 5,833 patients with treatment initiation between February 2014 and September 2015.

Results: Overall, antiviral therapy was associated with a GFR improvement in 330/4,527 (7.3%) individuals, a deterioration to GFR < 30 ml/min occurred in in 9/4483 (0.2%) patients (Table 1). Only 46/5,833 (0.8%) patients initiated antiviral therapy with a baseline GFR of <30 ml/min (87%/9%/4% HCV-genotype 1/3/4; 26% cirrhosis; 54% treatment-naïve, 43% interferon-experienced). They suffered significantly more frequently from hypertension, coronary heart disease and chronic heart failure than individuals with GFR > 30 ml/min. Treatment regimens were based on sofosbuvir (+ ribavirin n = 2, +simeprevir n = 3, +daclatasvir n = 5, +ledipasvir n = 18; each ± ribavirin) or paritaprevir/r, ombitasvir ± dasabuvir ± ribavirin (n = 18). Adverse events did not occur more often in patients with GFR < 30 vs. >30 ml/min (treatment without ribavirin: 58% vs. 50%; treatment with ribavirin 67% vs. 72%), however, serious adverse events were significantly more frequently in individuals with GFR < 30 ml/min (treatment without ribavirin: 13% vs. 3%, p = 0.02; treatment with ribavirin 33% vs. 5%, p < 0.001). Treatment discontinuation due to (serious) adverse events occurred more often in patients with GFR < 30 ml/min (6.5% vs. 1.1%; p = 0.02) and were associated with the use of ribavirin. Overall sustained virologic response rates (SVR12) did not differ significantly between cases with GFR < 30 vs. >30 ml/min (91% vs. 97%).

Table 1: Comparison of GFR (ml/min/1.73 m^2) between baseline and end of treatment

	End of treatment GFR				
Baseline GFR	**0-15**	**>15-30**	**>30-60**	**>60-90**	**>90**
0-15 (n=26)	92.6% (n=25)	0	0	0.1% (n=1)	0
>15-30 (n=18)	0	58.8% (n=10)	2.6% (n=7)	0.1% (n=1)	0
>30-60 (n=232)	0	29.4% (n=5)	56.8% (n=154)	3.8% (n=61)	0.5% (n=12)
>60-90 (n=1,396)	3.7% (n=1)	0	38.7% (n=105)	65.2% (n=1,042)	9.5% (n=248)
>90 (n=2,855)	3.7% (n=1)	11.8% (n=2)	1.8% (n=5)	30.9% (n=494)	90.0% (n=2,353)

Conclusion: Adherence to treatment guidelines were very high in this large real world cohort as only few patients started sofosbuvir-based therapy with a baseline GFR of <30 ml/min. However, safety and efficacy was good in selected patients with impaired kidney function but RBV was a main cause of treatment discontinuations. RBV-free treatment options like grazoprevir/elbasvir or glecaprevir/pibrentasvir will therefore be of major importance for these patients.

THU-285

Uniform addition of ribavirin to sofosbuvir/velpatasvir for genotype 3 patients with cirrhosis: real world outcomes

A. Boyle[1,2], F. Marra[1,2], E. Reilly[1], C. Fleming[1], M. Heydtmann[3], R. Fox[4], M. Priest[5], J. Morris[6], S. Barclay[7]. *[1]NHS Greater Glasgow and Clyde, Pharmacy Department, United Kingdom; [2]University of Liverpool, Department of Molecular and Clinical Pharmacology; [3]NHS Greater Glasgow and Clyde, Royal Alexandra Hospital, United Kingdom; [4]NHS Greater Glasgow and Clyde, Brownlee Centre for Infectious Diseases; [5]NHS Greater Glasgow and Clyde, Gartnavel General Hospital, United Kingdom; [6]NHS Greater Glasgow and Clyde, Queen Elizabeth University Hospital; [7]NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary, United Kingdom*
Email: alisonboyle2@nhs.net

Background and Aims: In registration trials sofosbuvir/velpatasvir (SOF/VEL) for 12 weeks achieved an SVR rate of 93% in untreated patients with genotype 3 (GT3) HCV and cirrhosis. Treatment-experienced patients, and those with baseline NS5a resistance-associated substitutions, achieved suboptimal SVR rates of <90%. In patients with decompensated cirrhosis, the addition of ribavirin (RBV) to SOF/VEL led to an increased SVR rate. EASL recommends that, where baseline resistance is not performed, RBV be added to SOF/VEL for patients with compensated cirrhosis, however evidence of increased efficacy is lacking. In line with EASL guidance we elected to treat all GT3 cirrhotic patients with SOF/VEL/RBV with a view to maximising SVR. Child's Pugh (CP) A/B patients were treated with weight based RBV, CPC patients received 600 mg with escalation if tolerated. We report initial results.

Method: Patients with cirrhosis and GT3 infection commencing treatment with SOF/VEL/RBV prior to 01/10/2017, in Glasgow treatment centres were identified from the Scottish HCV database. Baseline data on age, gender, liver stiffness (LSM), CP score, end of treatment response (EOTR) and SVR were collected. Significant anaemia (Hb < 10 g/l) and RBV dose reductions were recorded from chart review.

Results: Eighty patients (62 male, mean age 49.3 (± 6.8) years, 2 HIV co-infected, 46 on Methadone) commenced treatment. Eighteen patients were decompensated (12 CPB, 6 CPC). Amongst the CPA patients, median liver stiffness was 21.5 kPa (IQR 14.2). Thirteen

patients (8 CPA, 4 CPB, 1 CPC) were treatment-experienced including 6 interferon/RBV/sofosbuvir failures. To date, 57 patients have completed treatment, 1 (CPC) prematurely due to nausea/vomiting, all achieving an EOTR. Eight (10%) patients developed significant anaemia and 18 (22.5%) required RBV dose reduction (12/62 (19.3%) CPA, 5/12 (41.7%) CPB, 1/6 (16.7%) CPC). Amongst CPA patients reaching SVR12 time point, SVR was achieved by 12/13 (92.3%) of treatment-naïve patients and 5/6 (83%) of treatment-experienced patients. To date, 6/6 (100%) of decompensated patients achieved SVR.

Conclusion: SOF/VEL/RBV was well tolerated in a real-world cohort of patients with compensated and decompensated cirrhosis. RBV frequently required dose reduction, particularly in CPB patients. Despite addition of RBV, early SVR results in compensated patients are not higher than those obtained without RBV in clinical trials. Full SVR12 data will be presented.

THU-286

Direct Antiviral Agents are safe and efficacious in paediatric patients with chronic hepatitis C; Real world data from the public health perspective

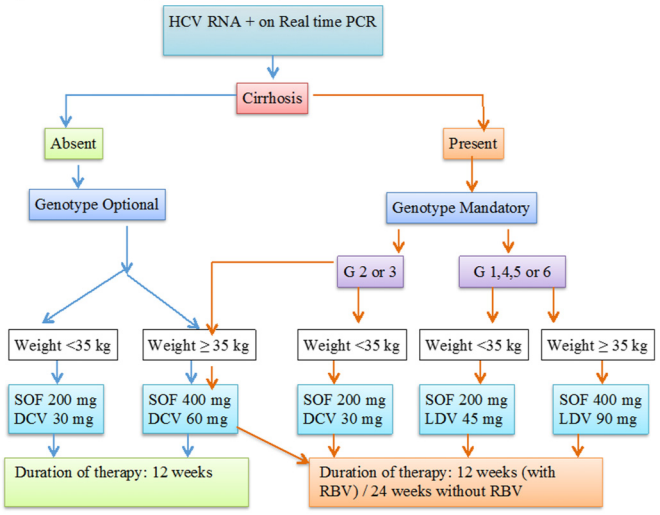
M. Premkumar[1], G. Grover[2], S. Rathi[1], S. Taneja[1], A. Duseja[3], R.K. Dhiman[1]. [1]*PGIMER, Hepatology, Chandigarh, India;* [2]*Program Officer, Hepatitis C Treatment Programme, Chandigarh, India;* [3]*PGIMER, Chandigarh, India*
Email: rkpsdhiman@hotmail.com

Background and Aims: The Mukh-Mantri Punjab Hepatitis C Relief Fund (MMPHCRF) is a public health initiative for prevention and control of hepatitis C (HCV) in Punjab, India. We assessed the efficacy of decentralized public health services and safety of 12 or 24 weeks of sofosbuvir (SOF) + ledipasvir (LDV) or SOF + daclatasvir (DCV) with or without ribavirin (RBV) in the treatment of pediatric HCV patients (aged 12 to <18 years).

Methods: Consecutive chronic HCV infected children [age: 12 to <18 years; both treatment-naïve (TN) and treatment-experienced, (TE)] were enrolled. As per the devised algorithm (see Figure), genotyping was not recommended for patients without cirrhosis of liver/ TN and were treated with SOF + DCV for 12-weeks, while genotyping was recommended for patients with cirrhosis of liver/TE. Patients with liver cirrhosis/TE and genotype (G)3 were treated with SOF + DCV for 24 weeks, while non-G3 patients were treated with SOF + LDV for 24-weeks. SVR-12 was mandatory in all patients.

Results: In the first 16 months (18 June 2016 to 31st October 2017) of the MMPHCRF program, 78 pediatric patients [74.3% male, mean age 15.8 ± 1.86 years, (range 12–17)] were enrolled. Fifty-six (72.3%) were from a rural background. The mean age was 15.8 years (range 12–17 years), mean weight 42 ± 3.8 kg, 74.3% were male, mean baseline HCV RNA $\log_{10}$ IU/ml was 6.0 (range, 4.2–7.5 $\log_{10}$ IU/ml), with 45.6% having HCV RNA >6.0×10^6 IU/ml, 65.5% with G3, 73 (93.5%) as TN, and 2 (2.5%) with cirrhosis. Of the 57 who have completed treatment, SVR-12 was achieved in 56 (96.9%), except one non-cirrhotic G3 patient with poor drug compliance. Unsafe medical practice 30 (48.5%), prior surgery-10 (15.5%), and IV drug abuse-5 (8%) were the main modes of transmission. Genotype was not done in 54 (69.2%) patients as they were non-cirrhotic, and received SOF/DCV therapy for 12 weeks with SVR-12 of 100%. The treated genotypes were G1, 9 (10.2%); G3, 22 (25%); G4, 2 (2.3%), and G5,1 (1.1%). Comparable results were noted in cirrhotic patients (SVR-12, 100%) versus non-cirrhotic (SVR-12, 97%; p = 0.672), and G3 (SVR-12, 94.3%) versus non-G3 (SVR-12, 100%; p = 0.073). No serious adverse effects like anemia, decompensation of liver disease, headache, diarrhea, and fatigue were reported. Transient nausea was noted in 4 (5.1%) patients, which resolved.

Figure 1: Treatment algorithm for pediatric patients in the MMPHCRF



Abbreviations: PCR,polymerase chain reaction; SOF, sofosbuvir; DCV, daclatasvir; LDV, ledipasvir; RBV, ribavirin
Cirrhosis treatment path:
Non cirrhotic treatment path:

Conclusion: This study has demonstrated that our decentralized algorithm based public health HCV elimination programme can ensure high efficacy (SVR 12, 96.9%), safe, and low-cost generic direct acting antiviral based treatment of pediatric HCV.

THU-287

Treatment of chronic hepatitis C with direct acting antivirals and its effect on body mass index and hepatic steatosis as measured by controlled attenuation parameter

H. Shousha[1], R. Abdelaziz[1], S. Musa[1], M. Khairy[1], S. Afifi[2], M. Mehrez[2], A. Yosry[1]. [1]*Faculty of Medicine, Cairo University, Endemic Medicine Department, Cairo, Egypt;* [2]*NHTMRI, Endemic Medicine Department, Cairo*
Email: hendshousha@yahoo.com

Background and Aims: Direct Acting Agents (DAAs) have high cure rate but still lack the knowledge of their effect on hepatic steatosis in chronic hepatitis C (CHC). Controlled Attenuation Parameter (CAP), evaluated with transient elastography, could help in assessment of steatosis grades. Aim: to evaluate the effect of DAAs on body mass index and steatosis in CHC using CAP.

Method: This cohort study included 155 CHC patients, divided into 3 groups according to the DAAs regimen. All patients were subjected to pre-treatment and 3-months post-treatment BMI, laboratory workup and liver stiffness measurement and CAP using the FibroScan® M probe. Cut off values for steatosis: S0: <238 dB/m = Grade 0, S1: 238–258 dB/m and S2: 259–291 dB/m = Grade 1 (mild-moderate steatosis) and S3: ≥292 dB/m = Grade 2 (severe steatosis). Changes in steatosis grades were defined as improvement or worsening (one grade or more change).

Results: Patients mean age was 45.78 ± 11.6 years, mean BMI 26.63 ± 2.75 and 18.1% were cirrhotic. Baseline assessment revealed no steatosis in 43.9%, 32.9% had mild-moderate steatosis and 23.2% had severe steatosis. The overall sustained virological response 12 was 93.6%. Follow up revealed stationary steatosis in 56.7% and regression in 21.3%. Mean pre-treatment CAP were significantly lower in responders 244.9 ± 62.4 dB/m vs non-responders; 300 ± 28.4 dB/m (p = 0.04). ROC curve delineated 273 dB/m as best cut-off for detection of responders with an AUC of 0.801, sensitivity 68.2%, and specificity 100%. BMI significantly increased after treatment (p = 0.004) particularly in patients with worsened steatosis (p = 0.001). On the other hand, a decrease in BMI was found in 55% of patients

Table: (abstract: THU-287)

N (%)	Total (Number (N) = 155)		Group 1 (n = 82) Sofosbuvir + daclatasvir ± ribavirin		Group 2 (n = 42) Sof + simeprevir		Group 3 (n = 31) sof + RBV + weekly Peg IFN	
Improved	33 (21.3%)		20 (24.4%)		6 (14.3%)		7 (22.6%)	
Stationary	88 (56.7%)		42 (51.2%)		27 (64.3%)		19 (61.3%)	
Worsened	34 (22%)		20 (24.4%0		9 (21.4%)		5 (16.1%)	
P value	<0.001		<0.001		0.006		0.002	
CAP value mean ± SD	Pre TTT	Post TTT	Pre TTT	Post TTT	Pre TTT	Post TTT	Pre TTT	Post TTT
	246.39 ± 62.34	248.03 ± 53.78	246.99 ± 55.22	249.98 ± 54.39	248.64 ± 67.51	249.52 ± 54.13	241.74 ± 73.9	240.84 ± 52.78
P value	0.726		0.533		0.846		0.651	

Steatosis							
Total (N = 155)	Improved (N = 33)		Stationary (N = 88)		Worsened (N = 34)		P value
	N	%	N	%	N	%	<0.001
BMI Decreased (N = 59)	18	55.0%	37	42%	4	12.2%	
Stationary (N = 3)	0	0%	2	2.4%	1	2.4%	
Increased (N = 93)	15	45.0%	49	55.6%	29	85.4%	

with improved steatosis grade. Steatosis significantly correlated with BMI (r = 0.3, p < 0.001).

Conclusion: DAAs cause a significant change in steatosis grade in a subset of treated patients. Pretreatment CAP was significantly lower in responders. BMI significantly increases following treatment particularly in patients with worsened steatosis.

THU-288

Factors associated with nonresponse in a cohort of 10655 chronic hepatitis C patients treated with direct acting antivirals

H. Shousha[1], M. Said[1], D. Saleh[1], Y. Saad[1], H. Dabees[2], M. El-Serafy[1], K. Elsaees[3], Y. Elshazly[3]. *[1]Faculty of Medicine, Cairo University, Endemic Medicine Department, Cairo, Egypt; [2]National Medical Institute of Damanhour, Hepatology; Egypte, [3]Ain Shams University, Internal Medicine Department, Egypte*
Email: hendshousha@yahoo.com

Background and Aims: Hepatitis C virus (HCV) is a worldwide aetiology of chronic hepatitis and cirrhosis particularly in Egypt where genotype 4 is responsible for >90% of cases, and the remaining is due to genotype-1. The introduction of interferon-free direct acting antivirals has resulted in very high sustained virological response rates. On the other hand, there are still a minority who fails to achieve SVR.

Aim: to study the factors associated with nonresponse and relapse using routine pretreatment workup.

Method: A retrospective study included 10,655 Egyptian chronic HCV patients who were candidates for anti-viral therapy according to the international and the National Committee for Control of Viral Hepatitis (NCCVH) guidelines. Pretreatment demographics, routine laboratory data, ultrasonography, FIB-4, Pretreatment, 16 and 24 weeks quantitative HCV PCR were collected.

Results: At week 16, 10,495 patients (98.5%) had negative HCV PCR and 160 (1.5%) were non responders. 50.6% of non-responders were males vs 39.7% responders, p 0.005, 61.3% were cirrhotic. They had significantly higher baseline BMI (Mean ± SD): 30.6 ± 5.6 vs 28.8 ± 5.5, p 0.005), higher liver enzymes (ALT: 63.6 ± 38.9 vs 54.6 ± 36.6, p < 0.01 and AST: 72.0 ± 42.3 vs. 57.5 ± 38.2), higher AFP: 18.4 ± 23.6 vs 10.2 ± 27.1. Significantly lower albumin level, platelet count: 141.3 ± 57.3 vs. 177.4 ± 77.7) $\times 10^3/mm^3$, p < 0.001 and FIB-4: 4.1 ± 3.2 vs 4.8 ± 25.9 p < 0.001. AST, AFP > 10, albumin, platelet count, hemoglobin, FIB-4 and having an abnormal liver echopattern on ultrasonography were the independent factors associated with nonresponse by multivariate regression model.

At week 24, HCV PCR results were available only for 7259 patients and 7049 (97.1%) were responders and 210 (2.9%) were relapsers. 54.8% were cirrhotic and 51.4% were males vs 38.8% responders, p < 0.001, significantly higher AST: 66.1 ± 40.6) vs. 58.5 ± 39.5, higher AFP: 14.3 ± 20.4 vs 9.5 ± 25.2. Significantly lower albumin level, prolonged INR, platelet count: 152 ± 62.3 vs. 175.9 ± 76.2) x103/mm3, p < 0.001 and FIB-4: 3.6 ± 2.7 vs 4.6 ± 21.7 p < 0.001. An abnormal liver echopattern on ultrasound, AST, AFP > 10, platelet count and FIB-4 were the independent factors associated with relapse.

Regression model at week 16	95% C.I.			
	P value.	Odds ratio	Lower	Upper
AST	0.014	0.981	0.967	0.996
AFP (>10 vs ≤10)	0.001	0.362	0.197	0.664
Albumin	0.044	1.854	1.017	3.380
Hb	0.045	0.861	0.744	0.997
platelets	<0.001	1.021	1.010	1.031
Fib4	0.002	1.561	0.687	2.408
Liver (abnormal echopattern)	0.021	3.016	0.934	1.021
Regression model at week 24	Sig.	OR	95% CI: Lower	95% CI: Upper
Liver abnormal echo pattern	0.005	3.622	1.467	8.942
AST	0.011	0.980	0.965	0.995
AFP (>10 vs ≤10)	0.003	0.399	0.219	0.728
platelets	0.000	1.021	1.010	1.031
Fib4	0.004	1.546	1.151	2.075

Conclusion: Routine pre-treatment workup can help in prediction of the minority of non-SVR patients.

THU-289

Incidence and outcome of portal vein thrombosis in HCV cirrhotic patients treated with direct-acting antivirals: a single-center prospective 3-year study

E. Degasperi[1], G. Tosetti[1], R. D'ambrosio[1], A. Aghemo[2], M. Borghi[1], R. Soffredini[1], M. Primignani[1], P. Lampertico[1]. *[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Humanitas University, Department of Biomedical Sciences, Rozzano, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: Treatment of hepatitis C virus (HCV) with direct-acting antivirals (DAAs) is associated with improved outcomes in cirrhotic patients, however the risk of portal vein thrombosis (PVT) is still undefined. We evaluated incidence and predictors of PVT in HCV cirrhotics treated with DAAs.

Method: HCV Child (CPT) A-B cirrhotic patients consecutively treated with DAAs between November 2014 and December 2016 at a single center and without PVT were enrolled. Patients underwent blood tests, 6-month abdominal imaging and regular esophageal varices (EV) screening. PVT was graded according to Yerdel classification.
Results: 557 HCV cirrhotics were enrolled: age was 64 (28–87) years, 60% males, 49% HCV genotype 1b, 83% CPT score A, platelet count (PLT) was 118 (26–753) × 10^3/mL, spleen size 13 (7–24) cm, LSM 17.0 (12.1–75.0) kPa, 32% patients had baseline EV. 465 (96%) achieved a sustained virologic response. During 22 (1–36) months of follow-up, 9 (1.6%) patients developed PVT, with a 3-year cumulative probability of 2%, 7 (78%) PVT occurring during the first 12 months from DAA start. PVT patients were CPT B (56%), all had EV at baseline (small varices CRS- in 2, primary prophylaxis in 4, secondary in 3). PVT were Yerdel grade 1 in 4 patients, grade 2 in 3, grade 3 and 4 in 1 patient. No PVT was related to tumor vascular invasion. PVT was associated with de novo or worsening of ascites in 4 (44%) patients, while it was asymptomatic and detected on routine imaging in the remaining 5 (56%). At PVT diagnosis, EV worsened compared to baseline in 3 (33%) patients but no GI bleeding occurred. Thrombophilic conditions were detected in 3/7 (43%) patients with available screening: hyperhomocysteinemia in 2 and G20210A prothrombin gene mutation in one patient. The most important baseline predictors of PVT reflected the degree of disease severity (CPT score, MELD score, bilirubin, albumin) and portal hypertension (EV and PLT count). The 3-year cumulative probability of PVT was 5.2% vs 0% in patients with or without baseline EV, respectively (p = 0.002). PVT was treated by anticoagulation in 8 (LMWH in 5 and oral anticoagulation in 3) patients, leading to partial or complete PVT recanalization in 6 (5 and 1, respectively) patients after 4 (3–7) months from anticoagulation start.
Conclusion: Among HCV cirrhotics treated with DAA, non neoplastic PVT is a rare complication that however may cause clinical decompensation.

THU-290

Diagnosis and treatment of hepatitis C virus in a Spanish jail

J.J. Urquijo, C. Albert-Antequera, M. Latorre, G.A. Castillo, P. Marqués, C. Alventosa, M. Diago. *Hospital General Universitario Valencia, Hepatology, Valencia, Spain*
Email: juanjo.urquijo@gmail.com

Background and Aims: HCV infection in prisoners is considered a special care group in the National Hepatitis C Plan in Spain with high risk of transmission.
Our aim is to assess the efficacy and safety of new DAA in VHC patients of the Picassent'S Penitentiary Center (PPC) –2,200 inmates- whose referral hospital is the University General Hospital of Valencia (CHGUV).
Method: All incoming inmates are screened for anti-HCV antibody and those with HCV viremia are remitted to CHGUV to undergo a full diagnostic study, including transient elastography (Fibroscan®), before being treated according to current guidelines.
197 patients have been treated with DAA, 182(92.4%) were males, the median age was 46 years (23–68). 77 (39%) had a history of drug addiction, 77(39%) were HIV co-infected. 32 (16.2%) had received prior treatment. According to degree of fibrosis, 51 were F0-F1 (25.9%), 60 F2 (30.5%), 42 F3 (21.3%) and 44 F4 (22.3%). The most common HCV genotypes (G) were G1a (89 patients, 45.2%), followed by G3 (43 patients, 21.8%), G4 (36 patients, 18.3%), G1b (20 patients, 10.2%), G1 (5 patients, 2.5%), G2 (1 patient, 0.5%) and 3 coinfections (1.5%): 1 + 3, 1a + 4 and 1b + 4.
The prescription and follow-up until viral response has been done by hepatologists and infectologists, and the clinical evolution by a physician of the CPP with controlled administration of the pills. Patients have been treated with different combinations of DAA according to current guidelines, taking into account comorbidities, interactions, and avoiding the use of RBV: 126 patients with SOF + LDV (63.95%, 2 to 24w, 94 to 12w, 21 to 8w); 34 with SOF + DAC (17.2%), 10 with SOF + VEL (5.1%); 9 with EBV + GZV (4.6%); 8 with SOF + SMV (4%); 10 with 3D or 2D regime (5%).
Results: 135 of 197 (68.5%) treated patients have reached 12w after treatment, showing an overall SVR of 97.8% (132 patients), and 3 relapses (2.2%), 1 to 12w SOF + DAC and 2 to 12w SOF + LDV, one of them retreated with 24w SOF + EBV + GZV + RBV.
There hasn't been any serious adverse drug event nor death, although a chronic myeloid leukemia and a laryngeal neoplasm were diagnosed, both with SVR. Follow-up was more difficult due to frequent transfers of inmates from one prison to another and prisoners released during treatment and lost in follow-up.
Conclusion: Most of our inmates were men, naïve to treatment and infected with 1a, 3 and 4 genotypes. The most used treatment has been SOF + LDV. DAA show a high efficacy (97.8%) and good security profile, similar to general population.

THU-291

Sofosbuvir + Glecaprevir/Pibrentasvir in patients with difficult to treat HCV infection. Final results of the French compassionate use

V.D. Ledinghen[1], V. Anne[2], U.-B. Jose[3], P. Lucia[4], H. Jean-Baptiste[1], S. Giovanna[2], M. Wassil[1], G.-P. Pageaux[5], F. Helene[4], L. Alric[6], C. Hezode[2]. *[1]CHU Bordeaux, Hepatology Unit, Bordeaux, France; [2]APHP Henri Mondor, Hepatology Unit; [3]CHU Montpellier, Hepatology Unit, Montpellier, France; [4]APHP Cochin, Hepatology Unit, France, [5]CHU Montpellier, Montpellier, France; [6]CHU Toulouse, Internal Medicine Unit, Toulouse*
Email: victor.deledinghen@chu-bordeaux.fr

Background and Aims: Glecaprevir/Pibrentasvir (G/P) has been poorly evaluated in difficult to treat patients including DAA failure patients. Moreover, the efficacy and tolerance, and the usefulness of adding Sofosbuvir (SOF) to G/P are unknown in these patients. The aim of this open-label study was to evaluate safety and efficacy of G/P ± SOF in HCV difficult to treat, including DAA failure, patients.
Method: A total of 60 patients (47 males; mean age 60 years) were treated with SOF + G/P (n = 26) or G/P alone (n = 34) for 12 or 16 weeks. Patients were chronically infected with HCV genotype 1 (n = 26), 2 (n = 9), 3 (n = 15), 4 (n = 9) and had advanced fibrosis or compensated cirrhosis (FibroScan > 9.5 kPa) in 39% of cases. Among the 60 patients, 5 had liver transplant recipient, 13 had end stage renal disease (ESRD), and 43 patients were DAA experienced. Previous treatment was SOF/LDV (n = 17), SOF/DCV (n = 16), 3D (n = 4), GZR/EBR (n = 2), SOF/VEL (n = 2), and SOF/DCV/SMV (n = 2). Baseline resistance testing was performed in 56 patients and NS5A, NS3, and NS5B RASs were present in 35, 5, and 3 patients, respectively.
Results: Among 21 patients with available result at SVR4, SVR4 was observed in 19/21 (90.5%). SVR12 will be available for all patients in April 2018. Two SVR4 failures were observed in two DAA experienced patients with cirrhosis treated without SOFG/P without SOF. To date, no serious adverse events (SAE) occurred. No study treatment was discontinued due to SAEs.
Conclusion: We show that G/P is a good option for difficult to treat patients, especially DAA failure patients. The role of adjunction of SOF to G/P will be evaluated in this largest cohort ever published of 26 patients.

THU-292

Sustained virologic response (SVR) to direct-acting antiviral (DAA) therapy in patients with chronic hepatitis C virus (HCV) infection and hepatocellular carcinoma (HCC): a systematic review and meta-analysis

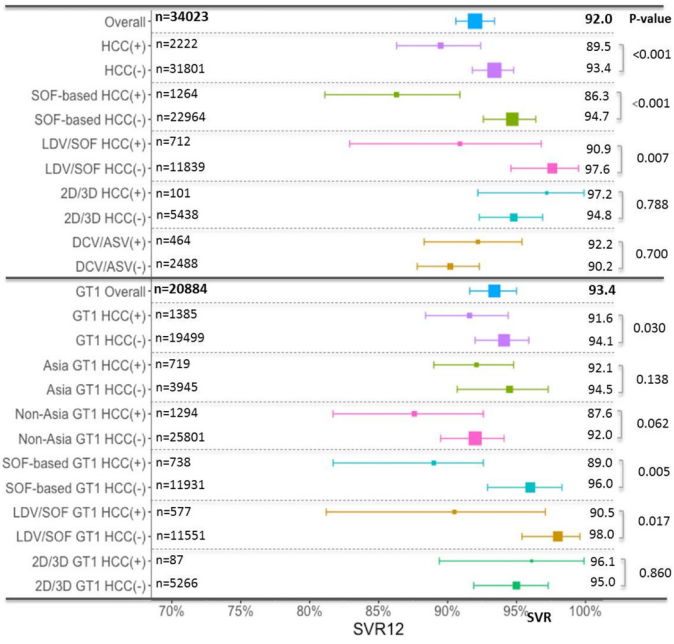
F. Ji[1,2,3], M.T. Wei[4], Y.H. Yeo[4], B. Wei[4], E. Ogawa[4,5], D.H. Lee[4,6], M. Enomoto[7], H. Toyoda[8], M.B. Bass[9], J. Lubel[10,11], T. Ide[12], C.M. Preda[13], E. Iio[14], F. Conti[15], T. Minami[16], R. Bielen[17], H. Sezaki[18], M. Barone[19], P.-S. Chu[20], V. Virlogeux[21], D. Eurich[22], T. Kanai[23], S. Dang[24], Z. Li[2,25], N. Furusyo[26], F. Zoulim[21], P. Andreone[15], R.C. Cheung[4,27], Y. Tanaka[28], A. Tamori[7], M. Nguyen[4]. *[1]Stanford University Medical Center, Division of*

Gastroenterology and Hepatology, Palo Alto, CA, United States; [2]The Second Affiliated Hospital of Xi'an Jiaotong University, Shaanxi Provincial Clinical Research Center for Hepatic & Splenic Diseases, Xi'an, China; [3]the Second Affiliated Hospital of Xi'an Jiaotong University, Department of Infectious Diseases, Xi'an, China; [4]Stanford University Medical Center, Division of Gastroenterology and Hepatology, Palo Alto, United States; [5]Kyushu University Hospital, Department of General Internal Medicine, Fukuoka, Japan; [6]Good Gang-An Hospital, Division of Gastroenterology, Department of Internal Medicine, Busan, Korea, Rep. of South; [7]Osaka City University Graduate School of Medicine, Department of Hepatology, Osaka, Japan; [8]Ogaki Municipal Hospital, Department of Gastroenterology, Ogaki, Japan; [9]Stanford University; [10]Eastern Health, Department of Gastroenterology, Melbourne, Victoria, Australia; [11]Monash University, Eastern Health Clinical School, Melbourne, Victoria, Australia; [12]Kurume University School of Medicine, Division of Gastroenterology, Department of Medicine, Fukuoka, Japan; [13]Institutul Clinic Fundeni-Gastroenterologie si Hepatologie, Gastroenterology and Hepatology, Bucuresti, Romania; [14]Nagoya City University, Graduate School of Medical Sciences, Department of Gastroenterology and Metabolism, Nagoya, Japan; [15]University of Bologna, Center for Study and Research on Hepatitis, Department of Medical and Surgical Sciences, Bologna, Italy; [16]Graduate School of Medicine, The University of Tokyo, Department of Gastroenterology, Tokyo, Japan; [17]Faculty of Medicine and Life Sciences, Hasselt University, Department of Gastroenterology and Hepatology, Genk, Belgium; [18]Toranomon Hospital, Department of Hepatology, Tokyo, Japan; [19]Azienda Universitario-Ospedaliera Policlinico, University of Bari, Gastroenterology Unit, Department of Emergency and Organ Transplantation, Bari, Italy; [20]Keio University School of Medicine, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokyo, Japan; [21]Groupement Hospitalier Nord, Hospices Civils de Lyon, Department of Hepatology, Lyon, France; [22]Charité Campus Virchow, Department of General, Visceral and Transplant Surgery, Germany; [23]Keio University School of Medicine, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokyo, Japan; [24]the Second Affiliated Hospital of Xi' an Jiaotong University, Department of Infectious Diseases, Xi'an, China; [25]the Second Affiliated Hospital of Xi'an Jiaotong University, National & Local Joint Engineering Research Center of Biodiagnosis and Biotherapy, Xi'an, China; [26]Kyushu University Hospital, Department of General Internal Medicine, Fukuoka, Japan; [27]Veterans Affairs Palo Alto Health Care System, Division of Gastroenterology and Hepatology, Palo Alto, United States; [28]Nagoya City University, Graduate School of Medical Sciences, Department of Virology & Liver Unit, Nagoya, Japan
Email: mindiehn@stanford.edu

Background and Aims: Outcome data concerning DAA therapy for chronic HCV infection in HCC patients are currently limited in individual studies. Our goal was to perform a systematic review and meta-analysis to evaluate the effect of HCC on SVR 12 or 24 weeks after the end of DAA treatment.

Method: PubMed, EMBASE, Web of Science and Cochrane databases up to August 31, 2017 were searched for studies that included HCC ($n \geq 10$) and with or without non-HCC HCV mono-infected patients treated with any DAA with available SVR. All data searches and extractions were independently performed by 2 reviewers with discrepancies resolved by consensus with a third reviewer. Random-effects model was used to estimate pooled SVR. Meta-regression was performed to determine how HCC affects SVR.

Results: A total of 34 studies with 2,222 HCC and 31,801 non-HCC treated patients were included. The overall SVR12 rate in HCC patients was lower than in those without HCC (89.5 vs. 93.4%, p = 0.0004) (Fig. 1, top panel). On meta-regression analysis, HCC patients had 5.07% (95%CI 0–8.01) reduction in SVR rate compared to non-HCC patients overall. However, patients at the time of treatment with active HCC (viable tumor on imaging) (n = 217) had a 20.6% (95%CI 8.33–35.4) reduction in SVR rate compared to patients with inactive HCC (absence of residual tumor/complete necrosis) (n = 940) (71.5 vs 93.8%, p < 0.0001). HCC patients treated with sofosbuvir (SOF)-based regimens overall (I^2=76.8%, p < 0.01) or ledipasvir (LDV)/SOF (I^2=82.7%, p < 0.01) had lower SVR12 than those without HCC (I^2=95.6% and I^2 = 95.8%, both p < 0.01); however, heterogeneity was high. Heterogeneity for subanalysis of patients treated with daclatasvir/asunaprevir (DCV/ASV) (all from Japan) was lower and showed similar SVR12 between HCC (I^2 = 34.6%, p = 0.14) and non-HCC patients (I^2 = 66.4%, p < 0.01). SVR12 was similar in HCC and non-HCC patients treated with the 2D/3D ± RBV (all from non-Asia centers) though there were only 101 HCC patients in this analysis. For GT1 patients (Fig. 1, bottom panel), there was no statistically significant differences in SVR12 between HCC and non-HCC patients within Asia or within US/Europe/Australia.



SVR: Sustained virological response; HCC: Hepatocellular carcinoma; DAA, direct-acting antiviral; SOF, Sofosbuvir; LDV, Ledipasvir; 2D/3D, paritaprevir/ritonavir, ombitasvir ± dasabuvir DCV, Daclatasvir; ASV, Asunaprevir; GT1, genotype 1.

Conclusion: Overall, SVR was lower in HCC compared to non-HCC patients especially in those with active HCC. HCC treatment should be considered prior to DAA therapy. Additional large cohort studies or individual participant data meta-analysis are also needed to identify predictors for treatment failure in DAA-treated HCC patients.
The SVR12 rate of all HCC and non-HCC patients by DAA regimens (top panel) and for genotype 1 patients by study location and DAA regimens (bottom panel).

THU-293

Management of patients with chronic kidney disease in the setting of interferon-free treatment for chronic HCV hepatitis

E.L. Iliescu, S. Ioanitescu, L. Toma, M.B. Ureche, A. Mercan-Stanciu, C. Iancu, M. Dodot. *Fundeni Clinical Institute, Internal Medicine, Bucharest, Romania*
Email: laura_ate@yahoo.com

Background and Aims: Renal disease, manifest either by decreased clearance or proteinuria can appear in a variety of situations associated with chronic HCV hepatitis. Frequent situations are: chronic kidney disease, renal transplant recipients or patients under hemodialysis with HCV infection, or proteinuria due to autoimmune conditions associated with HCV. This study aims to describe the types and management of renal disease in patients undergoing treatment with ombistavir/ paritaprevir/ ritonavir (OMB/PTV/r), dasabuvir (DSV) with or without ribavirin (RBV).

Method: We included 368 patients (57% females; mean age 57 +/−21.5 years) with F2 to F4 liver fibrosis (evaluated by liver biopsy or Fibromax®) undergoing treatment with OMB/PTV/r + DSV +/− RBV during December 2015 – October 2017. Evaluations were performed at the initiation of the treatment, monthly during treatment, at the end of treatment and 12 weeks after treatment and consisted of serum urea, creatinine, uric acid, C3 and C4 fractions of the complement, rheumatoid factor, erythrocyte sedimentation rate, C reactive protein, serum cryoglobulins, proteinuria measured in 24 hours.
Results: In our study, there were 49 patients with renal lesions as previously described. According to the type of injury, 28 patients had proteinuria caused by cryoglobulinemia (23 of them with nephrotic syndrome), 6 patients had undergone renal transplantation- 2 of them had graft reject and were undergoing hemodialysis. 2 patients had stage V chronic kidney disease due to type 1 diabetes. 10 patients had stage 2 to stage 4 chronic kidney disease due to diabetes and hypertension and one patient had class 4 lupus nephritis with severe proteinuria. During antiviral treatment none of the patients experienced worsening of kidney function. However, anemia due to ribavirin was more pronounced and required discontinuation of ribavirin and administration of erythropoietin. Immunosuppressive therapies in patients with autoimmune disorders had to be discontinued because of interactions with the direct antiviral. Despite this, lower levels of proteinuria have been observed even after one month of therapy, especially in patients who had previously answered mildly to immunosuppression (p = 0.03). Serum markers of inflammation also decreased significantly (p = 0.002) In patients with renal transplant, treatment with tacrolimus had to be reduced to 5 mg/week and closely monitored. Hemodialysis was programmed before treatment hours, to minimize elimination. Notably, all patients achieved sustained virologic response.
Conclusion: All oral antiviral treatment with OMB/PTV/r + DSV +/− RBV is safe in patients with renal disease. Caution must be taken in regard to potentially severe anemia. Antivirals have proven to be more effective in decreasing proteinuria in autoimmune disorders than immunosuppressive therapy.

THU-294
Untreated HCV in HIV/HCV co-infection: Data from the TRIO network

D. Jayaweera[1], K. Althoff[2], J. Eron[3], G. Huhn[4], S. Milligan[5], A. Mills[6], G. Moyle[7], S. Santiago[8], P. Sax[9], G. Voskuhl[10], D. Wyles[11], R. Elion[12].
[1]Miller School of Medicine – University of Miami, Division of Infectious Disease, United States; [2]Johns Hopkins, United States; [3]Division of Infectious Diseases, UNC Chapel Hill, United States; [4]The Ruth M. Rothstein CORE Center, Rush University Medical Center, United States; [5]Trio Health, La Jolla, United States; [6]Southern California Men's Medical Group, United States; [7]Chelsea and Westminster Hospital; [8]Care Resource, United States; [9]Brigham and Women's Hospital and Harvard Medical School, United States; [10]Prism Health – Baylor University Medical Center, United States; [11]Division of Infection Diseases, Denver Health Medical Center – United States; [12]George Washington University School of Medicine, United States
Email: djayawee@med.miami.edu

Background and Aims: Per AASLD-IDSA guidelines, treatment of hepatitis C should be prioritized in patients co-infected with HIV and hepatitis C virus (HCV). This recommendation is based on a higher rate of HCV disease progression in this population, along with reported treatment responses comparable to HCV mono-infected patients. However, in clinical practice many patients with HIV/HCV co-infection do not receive HCV treatment. In this study, we characterize HIV/HCV co-infected populations who were not treated for HCV.
Method: Data were extracted from the electronic medical records of 1303 HIV/HCV co-infected patients who were in care between Jan 2014 and Sep 2017 at 5 large US-based HIV treatment centers. Co-infection was confirmed by antibody-based test or RNA detection for HIV and detection of HCV RNA (HCV viremia). The primary outcome was initiation of DAA treatment. However, in a subgroup analysis we evaluated all participants who were not prescribed DAA or did not start their regimen over a minimum of 90 days follow up from the last HCV measure. Bivariate analysis was performed to assess demographic and clinical factors associated with DAA prescription and initiation. Baseline measures were relative to DAA treatment or to the last detected HCV viral measurement.
Results: Of 1,303 co-infected patients with detectable HCV, 648 (50%) were not prescribed DAA. Of the 655 (50%) patients who were prescribed DAA, 86 (13%) did not initiate treatment. Baseline characteristics of these groups are provided in the Table. Measures appropriate for DAA selection, such as Fibrosis staging and HCV genotype, were sparsely recorded in patients who were not prescribed or prescribed but did not start therapy. Variables significantly associated with not being prescribed DAA include younger age, non-Hispanic, active drug or alcohol drug use, lower baseline ALT, lower baseline CD4 counts, and baseline HIV > 200 copies/ml. Variables associated with non-starts after prescription include younger age, white, lower baseline HCV viral load, lower baseline ALT and AST, and patients with FIB-4 < 3.25.

Figure: Patient Disposition.

Conclusion: In this large US database, 56% of co-infected patients remain untreated for HCV and those with uncontrolled HIV (high HIV RNA and/or low CD4 cell count) or active alcohol or drug use were less likely to be prescribed HCV therapy. In contrast to prior TRIO studies, payer type was not associated with non-start of therapy.

THU-295
Changing landscape of HCV treatment in Germany: Data from a large real-world cohort 2014–2017

J. Petersen, K. Olah, T. Lorenzen, U. Stefan, C. Harder, K. Wursthorn, A. Plettenberg, B. Andre, M. Kathrin, A. Stoehr, P. Buggisch. *IFI Institute Hamburg, Liver Center, Hamburg, Germany*
Email: petersen@ifi-medizin.de

Background and Aims: DAA therapies have yielded SVR12 rates of more than 90% in randomized clinical trials and in real-world cohorts. Understanding factors and trends in changes of patient populations and treatment failures may help in guidance of therapies towards elimination of HCV in a certain geographical region like Germany where access of drugs is not limited. We have recently reported small failure rates, equally distributed to viral and non-viral factors (Petersen et al., EASL 2017). Here we report about changes in baseline demographics over time in a large number of patients from a high volume treatment center of ID physicians and hepatologists selecting patients conjointly for HCV treatment. We assessed the characteristics of patients over time who cured HCV and who failed available DAA therapies since licensing of these all oral drugs in Germany in mid 2014.
Method: Data were collected retrospectively from patients from a single treatment center using a centralized electronic data base. All HCV patients with available data that started DAA treatment after May 2014 and finished treatment (fu12) until November 10, 2017 were included in this analysis (n = 1488).
Results: Overall, treatment initiation rate was highest in 2015 and continued to decrease until the last quarter of 2017. There was a trend towards a shift in the most common genotype, from 1b towards 1a.

Moreover, there was a significant change towards patients with low fibrosis grading starting HCV treatment, qualifying for simplified treatment or for shorter treatment duration, adding to an overall trend for less virological failures. Contrary, patients with more complicated PWID or OST history were started on DAA treatment, leading to a higher number of cases with lower adherence and more non-virological failures over time. Overall, SVR rate of this very heterogeneous patient population remained very high at 92%. Of the patients that did not achieve SVR, 4.5% lacked adherence, discontinued treatment, or were lost to follow-up. 3.5% were virologic failures, mostly relapsers, viral breakthrough only n = 3. SVR rates of retreatment of DAA virological failure patients with triple-therapy will be reported at the meeting.

Conclusion: With the reported changes in baseline demographics, patient selection and education seems to be of more importance to reduce non-virological failures compared to the development of further optimized treatment regimen. Furthermore, without more appropriate screening methods it seems unlikely to move forward towards elimination of HCV within a certain time frame, even when HCV drug access does not play a role.

THU-296

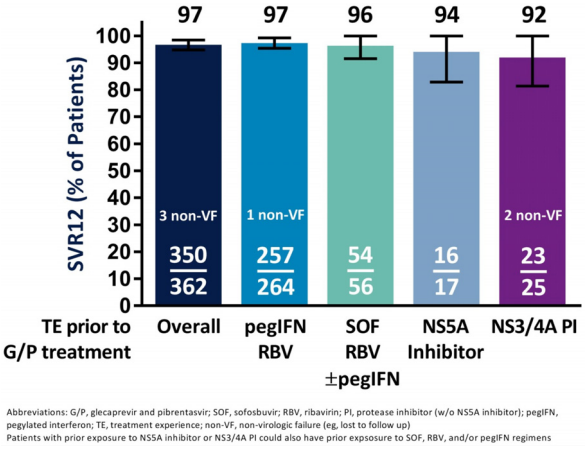
Glecaprevir/pibrentasvir in patients with hepatitis C and prior treatment experience: an integrated phase II/III analysis

F. Poordad[1], S. Zeuzem[2], A. Asatryan[3], G. Foster[4], E. Gane[5], D. Wyles[6], P. Stanislas[7], M.B. Ferret[8], P. Kwo[9], T. Asselah[10], K.V. Kowdley[11], C. Hezode[12], K. Agarwal[13], S. Wang[3], N. Zadeikis[3], I.C. Ng[3], T. Pilot-Matias[3], Y. Lei[3], J. Kort[3], C.-W. Lin[3], F. Mensa[3]. *[1]The Texas Liver Institute, San Antonio, TX, United States; [2]University of Frankfurt, Department of Medicine, Frankfurt, Germany; [3]AbbVie, North Chicago, IL, United States; [4]Queen Mary University of London, London, United Kingdom; [5]Auckland City Hospital, Liver Unit, Auckland, New Zealand; [6]Denver Health Medical Center, Denver, CO, United States; [7]AP-HP Cochin University Hospital, Paris, France; [8]Vall d'Hebron University Hospital and CiBERHED del Instituto Carlos III, Barcelona, Spain; [9]Stanford University, Division of Gastroenterology and Hepatology, Palo Alto, CA, United States; [10]Centre de Recherche sur l'Inflammation, Inserm UMR 1149, Université Paris Diderot, Service d'hépatologie, AP-HP Hôpital Beaujon, Clichy, France; [11]Swedish Medical Center, Seattle, WA, United States; [12]Hôpital Henri Mondor, Université Paris-Est, Créteil, France; [13]Kings College Hospital, Institute of Liver Studies, London, United Kingdom*
Email: poordad@txliver.com

Background and Aims: Patients with hepatitis C virus (HCV) infection who failed prior HCV therapy generally have decreased response to subsequent therapy. Glecaprevir/pibrentasvir (G/P; glecaprevir identified by AbbVie and Enanta) has demonstrated high rates of sustained virologic response at posttreatment week 12 (SVR12) across all six major HCV genotypes, including patients with prior treatment experience.

Method: This integrated analysis included efficacy and safety data from nine phase II and III clinical trials. Patients had chronic HCV genotype 1–6 infection and prior HCV treatment experience with at least one of the following treatments: interferon or pegylated interferon (pegIFN) plus ribavirin (RBV), sofosbuvir (SOF) plus RBV (with or without pegIFN), or a regimen that contained either an NS3/4A protease inhibitor (PI) or an NS5A inhibitor, but not both. Patients were included in the analysis if they received the European EMA and/or US FDA label-recommended duration of G/P treatment (8, 12, or 16 weeks) based on genotype, prior treatment history, and cirrhosis status. Safety was assessed in all patients that received at least one dose of G/P and the primary efficacy endpoint was the percentage of patients with SVR12.

Results: Overall, 362 patients with prior treatment experience were treated with G/P for an EMA/FDA approved duration. A majority of patients was male (65%), white race (81%), and was experienced with pegIFN plus RBV (73%); 31% of patients had compensated cirrhosis. HCV genotypes 1, 2, 3, and 4–6 were represented by 64%, 9%, 20%, and 6% of patients, respectively. Across all patients who received at least one prior treatment regimen, <2% and 13% of patients had key baseline substitutions in NS3 and NS5A, respectively. Overall, 97% (350/362) of patients had SVR12; 2% (9/362) of patients had virologic failure. Additional efficacy data are shown in the Figure. Presence of NS3 and NS5A baseline substitutions was not predictive of virologic failure. Adverse events occurring in ≥10% of patients were headache and fatigue. There were no serious adverse events considered related to study drug administration, there was a low rate of grade ≥3 increases in total bilirubin (<1%), and no patient had grade ≥3 increases in alanine aminotransferase.



Conclusion: HCV retreatment with G/P demonstrated a high overall rate of SVR12 (97%), including in patients with prior NS3/4A PI or NS5A inhibitor experience, and was well tolerated.

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Comparison of resistance profiles among DAA-naive and DAA-experienced patients infected with HCV non-1 genotype in Italy

V.C.D. Maio[1], S. Barbaliscia[1], E. Teti[2], I. Lenci[3], M. Aragri[1], E. Polilli[4], G. Fiorentino[5], V.P. Palitti[6], B. Bruzzone[7], S. Paolucci[8], C. Nicola[9], T. Ruggiero[10], T. Pollicino[11], F. Niero[12], V. Micheli[13], L.A. Nicolini[14], S. Marenco[15], A. Bertoli[1], I.R. Maida[16], S. Francioso[3], L. Foroghi[2], V. Calvaruso[17], F. Morisco[18], A. Lleo[19], V. Boccaccio[19], A. Ciancio[20], R. Maserati[21], M. Puoti[22], M. Zazzi[23], B. Rossetti[24], V. Vullo[25], R. D'ambrosio[26], L. Boglione[27], S. Bonora[27], S. Babudieri[16], G.A. Gubertini[12], M.G. Rendina[28], A. Pellicelli[29], V. Sangiovanni[30], A. Ciaccio[31], G. Taliani[32], G. Raimondo[11], G.B. Gaeta[9], A. Craxi[17], C. Pasquazzi[5], L. Sarmati[2], G. Parruti[4], M. Angelico[3], M. Andreoni[2], V. Cento[1], C.F. Perno[33], F.C. Silberstein[1]. *[1]University of Rome Tor Vergata, Department of Experimental Medicine and Surgery, Rome, Italy; [2]University Hospital of Rome Tor Vergata, Infectious Diseases, Rome, Italy; [3]University Hospital of Rome Tor Vergata, Hepatology Unit, Rome, Italy; [4]Pescara General Hospital, Infectious Disease Unit, Pescara, Italy; [5]Sant'Andrea Hospital – "La Sapienza" University, Infectious Diseases, Rome, Italy; [6]Pescara General Hospital, Hepatology Unit, Pescara, Italy; [7]IRCCS AOU San Martino-IST, Hygiene Unit, Genoa, Italy; [8]IRCCS Policlinic Foundation San Matteo, Molecular Virology, Pavia, Italy; [9]Second University of Naples, Infectious Diseases and Viral Hepatitis Unit, Naples, Italy; [10]Amedeo di Savoia Hospital, ASL Città di Torino, Laboratory of Microbiology and Virology, Turin, Italy; [11]University Hospital of Messina, Department of Internal Medicine, Messina, Italy; [12]ASST Fatebenefratelli Sacco, Division of Infectious Disease, Milan, Italy; [13]ASST Fatebenefratelli Sacco, Clinical Microbiology, Virology and Bioemergencies, Milan, Italy; [14]IRCCS AOU San Martino-IST, Infectious Diseases, Genoa, Italy; [15]IRCCS AOU San Martino-IST, Hepatology, Genoa, Italy; [16]University of Sassari, Infectious Disease Unit, Sassari, Italy; [17]"P. Giaccone" University Hospital, Gastroenterology, Palermo, Italy; [18]University "Federico II" of Naples, Department of Clinical Medicine and*

Surgery, Naples, Italy; [19]Humanitas University, Department of Biomedical Sciences and Humanitas Clinical and Research Center, Rozzano, Milan, Italy; [20]University of Turin, Department of Medical Sciences, City of Health and Science of Molinette Turin Hospital, Unit of Gastroenterology, Turin, Italy; [21]University of Pavia, Institute of Infectious Diseases, Pavia, Italy; [22]Hospital Niguarda Ca'Granda, Department of Infectious Diseases, Milan, Italy; [23]Siena University Hospital, Virology, Siena, Italy; [24]Siena University Hospital, Infectious Diseases, Siena, Italy; [25]Sapienza University of Rome, Department of Public Health and Infectious Diseases, Rome, Italy; [26]IRCCS Foundation "Ca' Granda-Ospedale Maggiore Policlinico", Unit of Gastroenterology and Hepatology, Milan, Italy; [27]Amedeo di Savoia Hospital, University of Turin, Unit of Infectious Diseases, Department of Medical Sciences, Turin, Italy; [28]University Hospital, Department of Emergency and Organ Transplantation, Section of Gastroenterology, Bari, Italy; [29]San Camillo Forlanini Hospital, Hepatology Unit, Rome, Italy; [30]Hospital Cotugno, Naples, Italy; [31]University of Milan-Bicocca, Department of Medicine and Surgery, Milan, Italy; [32]"La Sapienza" University of Rome, Infectious and Tropical Diseases Unit, Department of Clinical Medicine, Rome, Italy; [33]University of Milan, Milan, Italy
Email: Di.Maio@med.uniroma2.it

Background and Aims: Pan-genotypic direct acting antivirals (DAA) will be the most used anti-HCV regimens against all genotypes (GTs). However, their use in short, ribavirin (RBV)-free regimens may be affected by the presence of resistance-associated substitutions (RASs), whose prevalence is variable within the different GTs. This study aimed to investigate the resistance profile in HCV 2-3-4 infected, DAA-naïve and DAA-experienced, patients (pts) in Italy.
Method: Pts with GT2-3-4 (n = 109/289/121) infection, either naïve (n = 419) or DAA-experienced to a recommended regimen according to European 2017 guidelines (n = 116, including 16 with also baseline sample available) were included. Sanger sequencing of NS3 ± NS5A ± NS5B was performed by home-made protocols.
Results: Phylogenetic analysis identified the following HCV subtypes: GT2c (100%), GT3a/h (99.3%/0.7%), GT4a/d (11.6%/88.4%). Overall, 67/419 (16.0%) DAA-naïve and 97/116 (83.6%) DAA-failures had at least 1 RAS (p < 0.001). Notably, 11.2% of pts were treated with a suboptimal DAA-regimen due to a previous incorrect GT assignment and harbored RASs in 92.3% of cases.
The NS3-Q80K was mainly detected in GT3a paritaprevir-failures (25%, vs 1% in DAA-naïves, p = 0.007). The NS3-D168V was detected in 66.7% GT2c and 100% GT4d paritaprevir-failures, and in 45.4% GT4d simeprevir failures, while was rarely observed in naïve GT2c and GT4d pts (0.0% and 2.6%, respectively). The Y93H NS5A RAS was highly prevalent in NS5A-experienced GT3a (78.9%), GT4a (25%) and GT4d (14.3%) pts, while it was rarely detected in DAA-naïves (3.9% prevalence in GT3a, and <2% in GT4a/d). No pts with GT2c infection ever showed the Y93H RAS, while the F28C was detected in 71.4% GT2c NS5A-failures and in 27.8% GT2c DAA-naïves (p = 0.03). The S282T sofosbuvir RAS was found only in pts failing a sofosbuvir-containing regimen, rarely in GT4d (3.3%) and GT3a (4.4%), while was frequently detected (75%) in GT4a (p = 0.001).
Notably, of the 75 GT3 DAA-naïve pts treated with daclatasvir + sofosbuvir ± ribavirin for 12-24w, 67 (89.3%) reached a sustained virological response (SVR). 2/4 (50.0%) pts with baseline Y93H RAS reached SVR *vs* 63/68 (92.6%) without NS5A-RAS (p = 0.04).
Conclusion: HCV sequencing allows correct GT assignment and evaluation of resistance in all GTs. Failure is frequently associated with RASs, particularly Y93H-NS5A in GT3a, F28C-NS5A in GT2c and S282T-NS5B in GT4a, with potential impact on retreatment efficacy.

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Impact of direct acting antiviral treatment in hospital admission rates in patients with cirrhosis and hepatitis C virus infection

Á.H. Romero, L.C. del Campo, E.G. Domínguez, M.B. Valbuena, M.L.M. Alonso, R.M. Gómez, G.C. Tortajada, I.F. Vázquez. *Hospital Universitario Doce de Octubre, Gastroenterology and Hepatology, Madrid, Spain*
Email: lccampo06@gmail.com

Background and Aims: Wide availability of direct acting antivirals (DAA) agents has led to a substantial improvement in hepatitis C virus (HCV) infection treatment and might change the natural history of the disease. To evaluate the impact of DAA treatment in hospital admission rates and causes in cirrhotic hepatitis C patients, as subrogated markers of morbidity and mortality.
Method: Retrospective and observational study, which analyzes the frequency and causes of hospital admission in hepatitis C patients due to hepatic decompensation in the Hepatology department of a reference hospital. We compared two equal periods of time (group 1: 2013–2014 and group 2: 2016–2017) taking as reference the beginning of DAA treatment in 2015. We considered HCV infection as etiology whether it was associated to other hepatic diseases or not. We performed the statistical analysis using Epidat 4.2 program.
Results: A total of 496 patients with cirrhosis were included (170 hepatitis C; 224 alcoholic cirrhosis, 57 idiopathic or criptogenetic, 8 autoimmune hepatitis, 20 non-alcoholic fatty liver disease, 7 cardial cirrhosis and 10 hepatitis B), 315 of whom were admitted at the hospital in the first period (group 1) and 181 in the second (group 2). The hospital admission rates of hepatitis C patients decreased since DAA introduction from 39.7% (125/315) in the first period to 24.8% (45/181) in the second (p = 0.001). Regarding causes of hospitalization of hepatitis C cirrhotic patients, ascites was the main cause (55 [44%] vs 27 [60%], p = 0.06), followed by hepatic encephalopathy (29% vs 31%, p = 0.8) and hemorrhage due to variceal bleeding (16% vs 8%, p = 0.2), respectively. Other less frequent causes of admission were acute or chronic liver failure (8.8% vs 0%) and hepatocarcinoma (1.6% vs 0%). On the other hand, the rate of hospital admission of patients with alcoholic cirrhosis significantly increased in the 2nd period compared with the 1st one (129 [41%] vs 95 [52.5%] p = 0.01).
Conclusion: These results demonstrate that introduction of DAA therapy was associated with a progressive decrease on admission rates in HCV-associated cirrhotic patients. However, the causes that motivated admission did not change significantly.

THU-299

A national study of risk for non-liver cancer in people with hepatitis C treated with direct acting antivirals or an interferon-based regimen

C. Lybeck[1], D. Bruce[2], S. Montgomery[3], S. Aleman[4], A.-S. Duberg[1]. *[1]Örebro University, faculty of medicine and health., Department of Infectous diseases, Örebro, Sweden; [2]Scandinavian Development Services, Department of Statistics, Danderyd, Sweden; [3]Örebro University, Faculty of Medicine and Health., Department of Clinical Epidemiology and Biostatistics, Örebro, Sweden; [4]Karolinska Institutet, Department of Infectious Diseases, Stockholm, Sweden*
Email: lybecklotta@gmail.com

Background and Aims: Direct acting antivirals (DAA) against hepatitis C virus (HCV) have been shown to have an immune modulatory effect, with a possibly decreased tumour specific CD8 T cell response. Reports indicative of a high risk for hepatocellular carcinoma or advanced tumours early after DAA treatment, have raised concerns about whether the risk for non-liver cancer could be increased. Therefore, our aim was to study the early incidence of non-liver cancer after initiation of DAA or interferon (IFN-based) therapy in a national HCV cohort.
Method: All diagnosed HCV-infected persons in Sweden, their antiviral treatments, non-liver cancer or death/emigration were identified retrospectively, using the national HCV-surveillance

register and other national registers. Cox regression was used to compare persons treated with DAAs (n = 1,920), IFN-based therapy (n = 2,586) or no HCV therapy (n = 13,872) between 2009 and 2015. Persons with a previous cancer diagnosis (5.7%) were studied separately. Age was used as the time-scale, and the analyses were stratified by sex and adjusted for the Charlson comorbidity index.

Results: In total 492 non-liver cancers were diagnosed, with 222 among persons with no previous cancer and 270 new cancer diagnoses among those with previous cancer. Among persons with no previous cancer, 21, 24 and 177 developed non-liver cancer following DAA, IFN-based and no treatment, respectively. The corresponding numbers for those with previous cancer were 25, 20 and 225, respectively. The hazard ratios (and 95% confidence intervals) for non-liver cancer in the no previous cancer group are 1.35 (0.66–2.76; p = 0.41) for men and 1.75 (0.59–5.18; p = 0.31) for women with DAA treatment, compared with IFN treatment. For those with previous cancer, the corresponding hazard ratios are 1.03 (0.41–2.57; p = 0.95) for men and 0.86 (0.35–2.13; p = 0.75) for women with DAA treatment.

Conclusion: This study did not demonstrate any significantly increased risk for non-liver cancer early after DAA therapy initiation. The hazard ratio was slightly increased among those without previous cancer, but the cancers were few and the results were not statistically significant. Further studies with higher numbers of DAA treated patients and longer follow-up are needed to fully explore this issue.

THU-300

Sofosbuvir plus ribavirin and sofosbuvir plus daclatasvir-based regimens are suboptimal in genotype 2 patients: real-life experience

C. Hezode[1], V. De Ledinghen[2], G. Haour[3], J.-P. Bronowicki[4], F. Zoulim[5], D. Larrey[6], M. Sophie[7], T. Albert[8], M. Patrick[9], D. Samuel[10], O. Chazouillères[11], C. Stephane[1], D. Celine[3], F. Helene[12], J.-M. Pawlotsky[1], C. Fabrice[3], P. Stanislas[12]. *[1]Hopital Henri Mondor, Creteil, France; [2]Hopital haut leveque, Pessac; [3]INSERM, UMR-S 1136, Paris, France; [4]CHU Nancy, Nancy; [5]CHU Lyon, Lyon, France; [6]Hopital Saint Eloi, Montpellier, France; [7]CHU Toulouse, Toulouse, France; [8]CHU NIce, Nice, France; [9]Hopital Beaujon, Clichy, France; [10]Hopital Paul Brousse, Villejuif, France; [11]Hopital Saint Antoine, Paris, France; [12]Hopital Cochin, Paris, France*

Email: christophe.hezode@hmn.aphp.fr

Background and Aims: Data on real-life use of direct acting antivirals (DAAs) in patients with HCV genotype 2 chronic infection are limited. We report the real-life efficacy and safety data of SOF + RBV and SOF + DCV ± RBV in HCV genotype 2

Method: ANRS CO22 HEPATHER "Therapeutic options for hepatitis B and C: a French cohort" is a large multicenter observational cohort (ClinicalTrials.gov, NCT01953458). Between August 6 2012 and October 31rst 2016, Among 12,101 HCV chronically infected patients included, 278 with a HCV genotype 2 infection who initiated a combination of SOF/RBV (n = 233) for 12 or 24 weeks or SOF/DCV ± RBV (n = 45) for 12 or 24 weeks. The mean age was 62 years, cirrhosis (F4) was present in 103 (37.1%) patients. The main endpoint criteria was sustained virological response (SVR12) defined by the undetectability of HCV RNA 12 weeks after the last treatment intake.

Results: The total SVR12 was 87.8% (244/278); 87.5% (204/233) and 88.9% (40/45) for SOF/RBV and SOF/DCV ± RBV groups, respectively. AEs were more frequently observed in patients receiving RBV (p = 0.01) and SAEs were reported in only 21 (7.5%) patients.

Conclusion: In the real life setting, the combinations SOF/RBV and SOF/DCV ± RBV are suboptimal in genotype 2 patients, especially in cirrhotic and/or PR treatment experienced patients. Analysis of NS5A and NS5B RASs at baseline and at the time of failure is ongoing and will be presented in patients treated with DCV regimens for explaining these unsatisfactory and unexpected results.

SVR12	SOF + RBV 12 weeks n = 188	SOF + RBV 24 weeks n = 45	SOF/DCV ± RBV 12 weeks n = 34	SOF/DCV ± RBV 24 weeks n = 11
Total, n (%)	165/188 (88)	39/45 (87)	30/34 (88)	10/11 (91)
No cirrhosis, n/n (%)	116/130 (89)	18/20 (90)	15/16 (94)	4/4 (100)
Cirrhosis, n/n (%)	47/56 (84)	21/25 (84)	12/15 (80)	6/7 (86)
Naïve, n/n (%)	103/112 (92)	15/16 (94)	15/18 (83)	4/4 (100)
PR treatment-experienced, zn/n (%)	62/76 (82)	24/29 (83)	15/16 (94)	6/7 (86)

THU-301

Efficacy and safety of Elbasvir/Grazoprevir in women infected with hepatitis C virus genotype 1 or 4 and co-administered oral contraceptives or hormone replacement therapy

C. Hezode[1], P. Kwo[2], J. Sperl[3], G. Dore[4], P. Hwang[5], J. Long[6], R. Talwani[7], M. Robertson[6], B. Haber[8]. *[1]Hopital Henri Mondor, Paris, France; [2]Stanford University, Stanford, United States; [3]Institute for Clinical and Experimental Medicine, Prague, Czech Republic; [4]The Kirby Institute, University of New South Wales; [5]Merck & Co., Inc., UG1C-46, North Wales, PA, United States; [6]Merck & Co., Inc.; [7]Merck & Co., Inc., Kenilworth, NJ, United States; [8]Merck and Co, Merck, North Wales, United States*

Email: barbara.haber@merck.com

Background and Aims: The prevalence of HCV infection has increased among women of child-bearing potential, in part due to the opioid epidemic. Some direct-acting antiviral regimens have safety or efficacy concerns if co-administered with oral contraceptives that contain ethinyl estradiol (OCPs) or hormone replacement therapy (HRT). The aim of this study was to determine if co-administration of OCPs or HRT impacted the efficacy or safety of elbasvir 50 mg (EBR)/grazoprevir 100 mg (GZR) in women chronically infected with HCV genotype (GT) 1 or 4.

Methods: Efficacy and safety data from 12 clinical trials of EBR/GZR were pooled. A total of 1022 female participants (pts) received 12 weeks of daily EBR/GZR. 81 pts (7.9%) received and 941 pts (92.1%) did not receive concomitant OCPs or HRT. The primary efficacy endpoint was sustained virologic response 12 weeks after the end of therapy (SVR12) in the full analysis set (all patients who received at least one dose).

Subgroup	SVR12 in women not on concomitant OCP/HRT n/N (%)	SVR12 in women on concomitant OCP/HRT n/N (%)
Overall	906/941 (96.3%)	77/81 (95.1%)
18 to 35 years of age	87/89 (97.8%)	21/23 (91.3%)
>35 years of age	819/852 (96.1%)	56/58 (96.6%)
GT1a	229/245 (93.5%)	35/38 (92.1%)
GT1b/1-other	647/665 (97.3%)	39/39 (100.0%)
GT4	30/31 (96.8%)	3/4 (75.0%)
Baseline HCV RNA ≤800000 IU/mL	290/299 (97.0%)	34/35 (97.1%)
Baseline HCV RNA >800000 IU/mL	616/642 (96.0%)	43/46 (93.5%)
HCV Mono-infected	862/897 (96.1%)	75/79 (94.9%)
HCV/HIV Co-infected	44/44 (100.0%)	2/2 (100.0%)
Treatment-naive	755/785 (96.2%)	62/64 (96.9%)
Previously treated	151/156 (96.8%)	15/17 (88.2%)
Non-cirrhotic	748/778 (96.1%)	68/71 (95.8%)
Cirrhotic	146/151 (96.7%)	6/7 (85.7%)
Unknown cirrhosis status	12/12 (100.0%)	3/3 (100.0%)
IL28B CC genotype	392/409 (95.8%)	22/24 (91.7%)
IL28B non-CC genotype	507/525 (96.6%)	55/56 (98.2%)
IL28B genotype unknown	7/7 (100.0%)	0/1 (0.0%)

Results: SVR12 was similar in women on OCP/HRT (77/81 [95.1%]) compared to women not on OCP/HRT (906/941 [96.3%]). The efficacy of EBR/GZR in women on or not on OCP/HRT was similar among subgroups including HCV GT1a, GT1b/1-other, GT4, and cirrhosis/no cirrhosis (Table). Safety was similar among women on OCP/HRT or not on OCP/HRT; serious drug-related adverse event (AE) occurred in

0/81 (0%) compared to 3/941 (0.3%) in women on vs. not on OCP/HRT. One of 81 women (1.2%) on OCP/HRT discontinued due to an AE compared to 7/941 (0.7%) not on OCP/HRT. Of the discontinuations, 1 woman on OCP/HRT and 4 not on OCP/HRT discontinued due to an AE of ALT/AST increase. ALT values >5 times baseline were observed in 2/81 (2.5%) women on OCP/HRT compared to 14/940 (1.5%) not on OCP/HRT. Three-quarters of the OCP/HRT regimens taken by participants contained estradiol, estrogen, synthetic estrogen or a selective estrogen receptor modulator (69/92 [75%]), and one-quarter of the regimens contained progestin or a synthetic progesterone hormone (24/92 [26%]).

Conclusion: The efficacy and safety of 12 weeks of EBR/GZR was similar in female participants on concomitant OCP/HRT compared to those not on concomitant OCP/HRT.

THU-302

Outcomes of direct-acting antiviral therapy for chronic hepatitis C following unrestricted access in Australia: Real-world outcomes from the state of South Australia

J. Haridy[1,2], A. Wigg[3], K. Muller[3], J. Ramachandran[3], E. Tilley[3], V. Waddell[4], D. Gordon[4,5], D. Shaw[6,7], D. Huynh[8], J. Stewart[8,9], R. Nelson[7,9], M. Warner[7,9], M. Boyd[7,10], A. Chinnaratha[11], D. Harding[11], L. Ralton[10,11], A. Colman[12], G. Iyngkaran[2], E. Tse[12]. *[1]University of Melbourne, Melbourne; [2]Royal Melbourne Hospital, Department of Gastroenterology, Melbourne, Australia; [3]Flinders Medical Centre, Hepatology and Liver Transplantation Unit, Adelaide, Australia; [4]Flinders Medical Centre, Department of Infectious Diseases, Adelaide, Australia; [5]Flinders University, Bedford Park, Australia; [6]Royal Adelaide Hospital, Department of Infectious Diseases, Adelaide, Australia; [7]University of Adelaide, Faculty of Health and Medical Sciences, Adelaide, Australia; [8]The Queen Elizabeth Hospital, Department of Gastroenterology, Adelaide, Australia; [9]The Queen Elizabeth Hospital, Department of Infectious Diseases, Adelaide, Australia; [10]Lyell-McEwin Hospital, Department of Infectious Diseases, Adelaide, Australia; [11]Lyell-McEwin Hospital, Department of Gastroenterology, Adelaide, Australia; [12]Royal Adelaide Hospital, Department of Gastroenterology, Adelaide, Australia*
Email: jamesharidy@gmail.com

Background and Aims: In March 2016, the Australian Government offered unrestricted access to Hepatitis C (HCV) directly-acting antiviral (DAA) therapy, including prescription by any medical practitioner. The primary aim of this study was to determine the outcomes of DAA therapy in this setting over the first 12 months for an entire state health region, South Australia (SA).

Method: Prospective outcome data (SVR12; sustained virological response 12 weeks after treatment) was collected on all patients initiating DAA therapy for HCV at or in consultation with four tertiary hospitals in Adelaide, SA, between March 2016 and Feb 2017. Biochemistry and Fibroscan® score was collected retrospectively. Analysis was by Intention to Treat (ITT) and per-protocol (PP, including only those completing prescribed treatment and follow-up).

Results: 1921 patients were included representing an estimated 90% of patients treated in SA over the first 12-months of unrestricted DAA access.; Demographics were: mean age 52 years (range 18–92), 67% male, 2% Aboriginal or Torres Strait Islander (ATSI), 77% history of injecting drug use, 6% currently injecting, 5% incarcerated, 1% HIV co-infection, 12% diabetes, <1% hepatitis B co-infection and 19% had prior HCV treatment experience. Of the 26% of subjects with cirrhosis, 67% were Child-Pugh A. 20% of treatment initiations were through remote consultation and 25% resided in a regional or remote area.

SVR12 by ITT and PP was 80% and 96% respectively. 14% were lost to follow-up, 4% failed therapy; <1% either discontinued treatment due to adverse effects or poor adherence and <1% (13 patients) died. Factors associated with lower SVR12 on ITT analysis included ATSI (68% v 81%, p = 0.05), older age (mean 55 v 52y, p = 0.02), remote consultation (72% v 82%, p < 0.001); and incarceration (71% v 81%, p = 0.03). Factors associated with virological failure on PP analysis included cirrhosis (93% v 97%, p < 0.001) and prior HCV treatment history (92% v 96%, p = 0.03). 92% subjects achieving SVR12 experienced normalization of ALT compared to 61% who failed DAA therapy.

A marked decline in treatment initiations occurred in the latter 6 months of the study period (1251 v 668 patients) combined with a shift from hospital-based to community-based treatment via remote consultation (from 12% in first six-months to 33% in latter).

Conclusion: PP results were consistent with the high responses in clinical trials but a significant gap exists between SVR12 on ITT analysis in our real-world cohort, primarily due to loss to follow-up. A shift to community-based management highlights a need to develop and support additional models of care including GP and nurse-led treatment. The declining treatment initiation rate observed emphasizes the importance of exploring additional strategies to identify and recall the large number of remaining patients in Australia in order to achieve elimination targets.

THU-303

Risk and outcome of hepatitis B virus reactivation during chronic hepatitis C treatment with direct-acting antivirals in patients with HCV-related advanced fibrosis: a single-center experience

R. D'ambrosio[1], E. Degasperi[1], A. Aghemo[2], M. Borghi[1], R. Perbellini[1], S.D. Nicola[3], G. Lunghi[4], P. Lampertico[1]. *[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Humanitas University, Department of Biomedical Sciences, Rozzano, Italy; [3]ASST Grande Ospedale Metropolitano Niguarda, Hepatology and Gastroenterology Unit, Milan, Italy; [4]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Microbiology and Virology Unit, Milan, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: Reactivation of hepatitis B virus (HBV) following treatment of hepatitis C virus (HCV) infection with direct-acting antivirals (DAAs) has been described in patients with HBV coinfection (HBV/HCV) or resolved HBV infection, however studies in patients with advanced fibrosis are lacking. Therefore, we investigated the prevalence and outcome of HBV reactivation in a large cohort of HCV patients with advanced fibrosis treated with DAAs.

Method: All consecutive patients treated with DAAs for advanced HCV-related fibrosis were prospectively enrolled. HBV/HCV coinfection was defined by the presence of both detectable HCV-RNA and HBsAg positivity; resolved HBV infection was defined as HBsAg negativity and anti-HBc positivity (± anti-HBs). Fibrosis stage was defined clinically, histologically (METAVIR F3 or F4) or according to liver stiffness measurement (LSM: 10 kPa for F3, 11.9 kPa for F4). Treatment monitoring was performed monthly. HBV reactivation was defined as an increase of HBV-DNA > 1 Log in HBV/HCV patients, and as HBsAg seroreversion ± detectable HBV-DNA in anti-HBc positive patients.

Results: Between January 2015 and December 2016, 692 patients with F3-F4 fibrosis started DAAs. They were males (60%), with a median age of 63 (23–89). HCV genotype was 1a in 16%, 1b in 46%, 2 in 14%, 3 in 11%, 4 in 12% and 5 in 1%; median HCV-RNA was 581,270 (764–13,333,872)IU/ml. Baseline LSM was 14 (9–75)kPa, and cirrhosis was present in 526 (76%) patients. Patients with HBV/HCV coinfection were 10 (1.4%), while 301 (43%) were anti-HBc positive (54% anti-HBs positive). HBV/HCV patients were males (60%), aged 67 (45–79), mainly cirrhotics (70%). Median LSM was 21 (9–43.5)kPa. They were all HBeAg negative, with baseline HBV-DNA values undetectable in 5 (50%); anti-HBV nucleot(s)ides (NUCs) had been previously started in 4 (40%). After 2 weeks of DAAs treatment, HBV reactivated in 3 (50%) patients who were left untreated for HBV. At reactivation, ALT was 21 (18–52)U/l, HBV-DNA was 330 (248–6,915) IU/ml, HBsAg was 62 (1.1–1,329)UI/ml and HCV-RNA was 148 (18–389)IU/ml. No episodes of clinical decompensation were recorded and NUC was started in all of them. HBV-DNA became undetectable

after 8 (6–39) weeks, whilst HBsAg was lost in one patient, only. None of the 301 anti-HBc positive patients experienced any clinical or virological reactivation. Overall SVR rates to HCV treatment were 96%, without differences according to HBV status (p = 0.71).
Conclusion: HBV reactivation is frequently observed among HBV/HCV coinfected patients but not among HCV patients with resolved HBV infection.

THU-304
Generic sofosbuvir-based interferon-free direct acting antiviral agents for patients with chronic hepatitis C virus infection: a real-world multicenter observational study

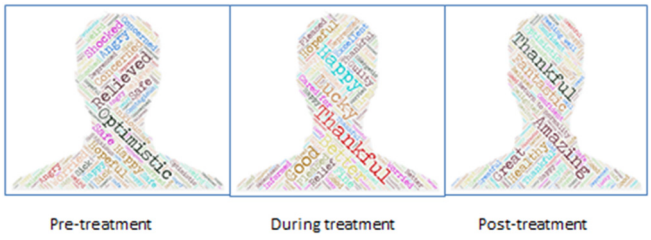
C.-H. Liu[1], S.-S. Yang[2], S.-S. Yang[3], H.-Y. Sun[4], C.-J. Liu[5], W.-C. Liu[4], T.-H. Su[6], H.-C. Yang[7], C.-M. Hong[4], T.-C. Tseng[4], P.-J. Chen[8], D.-S. Chen[9], C.-C. Hung[4], J.-H. Kao[10]. *[1]National Taiwan University Hospital, Internal Medicine, Taipei, Taiwan; [2]Taichung Wing total (Taiwan Avenue), Taiwan; [3]Cathay General Hospital , Taiwan; [4]National Taiwan University Hospital, Taiwan; [5]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [6]National Taiwan University Hospital, Department of Internal Medicine, Taipei, Taiwan; [7]National Taiwan University Hospital, Department of Internal Medicine, Taiwan; [8]Department of Medical Research, National Taiwan University, Taiwan; [9]National Taiwan University Hospital, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan; [10]National Taiwan University Hospital, Zhongzheng District, Taiwan*
Email: jacque_liu@mail2000.com.tw

Background and Aims: Data regarding to the effectiveness of generic sofosbuvir (SOF)-based interferon-free direct acting antiviral agents (DAAs) for patients with chronic hepatitis C virus (HCV) infection are limited.
Method: Five hundred seventeen chronic HCV-infected patients receiving 12 or 24 weeks of SOF-based therapies were retrospectively enrolled in 4 academic centers in Taiwan. The rate of sustained virologic response, defined as HCV RNA level < lower limit of detection (LLOD, 15 IU/ml) at week 12 off-therapy (SVR_{12}), was assessed for each regimen. The baseline characteristics and on-treatment HCV viral decline potentially related to SVR_{12} were analyzed.
Results: The SVR_{12} was achieved in 29 of 34 patients (85.3%, 95% confidence interval [CI]: 69.6%–93.6%), 130 of 139 patients (93.5%, 95% CI: 88.2%–96.6%), 119 of 124 patients (96.0%, 95% CI: 90.9% –98.3%) and 215 of 220 patients (97.7%, 95% CI: 94.8%–99.9%) who received SOF in combination with ribavirin (RBV), ledipasvir (LDV), daclatasvir (DCV) and velpatasvir (VEL), respectively. All 15 patients with virologic failures were relapsers. Two patients with decompensated cirrhosis had on-treatment deaths which were not related to DAAs. All the 7 patients who were lost to follow-up had HCV RNA level < LLOD at the last visit. The SVR_{12} rates were comparable in terms of baseline patient demographics, HCV viral load/genotype, treatment regimen, or viral decline at week 4 of treatment.
Conclusion: Generic SOF-based therapies provide high SVR_{12} rates for patients with chronic HCV infection.

THU-305
"How do you feel about your diagnosis of Hepatitis C today?": The emotional benefits of direct-acting antiviral therapy

S. Montague, C. Mazzarelli, T. Ow, K. Childs, L. Smith, G. Dusheiko, K. Agarwal, M.D. Cannon. *Institute of Liver Studies, King's College Hospital, London, United Kingdom*
Email: sarah.montague@nhs.net

Background and Aims: Direct-acting antiviral (DAA) therapy for hepatitis C (HCV) and virologic "cure" is associated with improvements in quality of life. This has been demonstrated in numerous studies which demonstrated improvement in patient-reported outcome measures. The literature is lacking with regard to qualitative data of patients' emotions about the diagnosis of HCV, and how this changes in parallel with DAA treatment for HCV. Inspired by the work of Feighan et al.,[1] we explored the feelings and emotions of patients with HCV before, during and after treatment with DAAs.
Method: Over a five-week period (September-October 2017), patients with HCV attending the viral hepatitis outpatient clinic at King's College Hospital were invited to participate in this study. All participants were either about to start DAA treatment, currently on treatment, or attending for post-treatment follow-up. A single question was posed in writing: "How do you feel about your diagnosis of Hepatitis C today?". 52 patients of a target enrolment of 250 patients consented verbally to participate. Data collection is ongoing and complete data will be presented at the meeting. We replicated the method of analysis of Feighan et al.[1] by transcribing patient responses verbatim and manually coding by theme. Results were visualised using Wordle and WordArt software.
Results: As suggested by the images, a patients' perception of the impact of HCV on their lives evolves during the course of DAA treatment. In fact, it is clear that patients feel much better about their diagnosis of HCV once they initiate DAA therapy, with further improvements following treatment completion. Pre-treatment responses were predominantly negative, although some patients expressed hope and optimism regarding the commencement of an effective treatment in the foreseeable future. Negative emotions appeared to subside once treatment had been initiated. Although reasons for expressed emotions were not always given, we can perhaps deduce that the information given to patients at their clinic appointments enabled them to feel more informed and less worried about their future. Limitations of our data included not being able to further explore unexpected responses, for example, why some patients continue to experience depression after treatment completion.



How do you feel about your diagnosis of Hepatitis C today?

Conclusion: In summary, our study demonstrates that treatment of HCV not only brings about physical health advantages. A cure has far reaching benefits such as improved mental health, and can also promote a more positive outlook on life. Responses, on the whole, although not unexpected will help to further remind us that for some patients HCV also confers an emotional burden, and a broader view should be taken with regard to DAA treatment benefits.

Reference

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THU-306
Rapid virological response, as a predictor of sustained virological response of Sofosbuvir and Ribavirin in Korean patients with genotype 2 chronic hepatitis C virus infection

H.Y. Woo, J. Heo, S.Y. Han, Y.J. Park, D.H. Baek, D.U. Kim, G.H. Kim, G.A. Song. *Pusan National University Hospital, Department of Internal Medicine, Busan, Republic of South Korea*
Email: jheo@pusan.ac.kr

Background and Aims: Recent advances in testing instruments have enabled the measurement of HCV RNA levels below 50 IU/ml, even 15 IU/ml and its utility for predicting sustained virological response (SVR) has not been investigated. The aim of this study is to investigate

real-world data with sofosbuvir/ribavirin (SOF/RBV) in Korean patients with genotype 2 hepatitis C virus (HCV) infection and to investigate predicting factor of SVR 12.
Method: 140 patients with genotype 2 chronic HCV infection treated with SOF/RBV were investigated prospectively. 400 mg of SOF combined with weight adjusted RBV was administered for 12 weeks in patients without cirrhosis and for 16 weeks with cirrhosis. HCV RNA level was examined in pre-treatment, 4 weeks, end of treatment, and 12 weeks after end of treatment by RT-PCR method (COBAS® TaqMan® Analyzer, low detection limit, 15 IU/ml; non-detection and below 15 IU/ml reported separately). The definition of rapid virological response (RVR) was defined as non-detection of HCV RNA at 4 weeks only.
Results: A total of 136 completed the treatment. 55 was male (40.4%) with a mean age of 61.6 ± 11.1 years. 99 (72.8%) were treatment naïve, 6 (4.4%) had a history of HCC, 23 (16.9%) had diabetes, and 33 (24.3%) had cirrhosis, of which had decompensation in 6. RVR was 77.9% (106/136), end of treatment response was 100% (136/136) and SVR12 was 96.0% (122/127). Of 5 with relapse, 4 were received 12 weeks of treatment and three of them did not reach RVR. Clinical factors associated with SVR12 were RVR status in multivariable analysis (p = 0.031). Contributing factors of RVR, cirrhosis, estimates glomerular filtration rate, and pre-treatment HCV RNA level were found to be significant. According to treatment duration, in 16 weeks treatment, SVR12 was not significantly different in RVR (−) and RVR (+) (94.7% vs. 100%, p = 0.483). However, in 12 weeks treatment, SVR12 was significantly higher in RVR (+) than RVR (−) (98.7% vs. 83.3%, p = 0.003). During treatment, 51/136 (37.5%) showed mild to moderate adverse events (urticaria, anemia, fatigue, insomnia, headache). 26 (19.1%) were reduced RBV dose due to anemia.
Conclusion: SOF/RBV treatment in genotype 2 HCV was effective, tolerable and RVR is an important predictor of SVR12. 16 weeks of treatment would be better for patients without RVR.

THU-307

Ledipasvir 90 mg/sofosbuvir 400 mg for treatment of children with CHC genotype 4: Single Centre experience

G. Sheha[1,2], R. Elsayed[1,3], M. Elbasiony[1,2], N. Mikhail[4]. *[1]Egyptian Liver Research Institute and Hospital (ELRIAH), Mansoura, Egypt; [2]Mansoura University, Internal Medicine Dept, Mansoura, Egypt; [3]Port Said University, Tropical Medicine, Mansoura, Egypt; [4]Egyptian Liver Research Institute and Hospital (ELRIAH)*
Email: g_shiha@hotmail.com

Background and Aims: A considerable number of children have chronic HCV infection and are at risk for complications. Approximately 11 out of 115 million of the infected persons in the world are younger than 15 years. Newly developed DAAs provide powerful tool in treatment of chronic HCV patients with good safety profiles. Food and Drug Administration (FDA) in April 2017 approved supplemental applications of sofosbuvir and ledipasvir in treatment of HCV in children aged 12 to 17 years.
Blood transfusion and some surgical interventions (circumcision) are the main risk factors of HCV infection in young in the developing countries.
Our aim is to evaluate the safety and efficacy of single daily dose of Ledipasvir 90 mg/sofosbuvir 400 mg in treatment of HCV infected children (12–17 years) either treatment-naïve or experienced to INF therapy, with or without history of blood disease (leukemia, lymphoma, thalassemia).
Method: Seventy three child with positive HCV antibodies examined at outpatient clinic of ELRIAH from the period of May 2017 till now, 53 (72.6%) were positive for HCV RNA, 15 (28.3%) patients were treatment experienced, 12 (22.6%) patients had history of blood diseases: acute lymphocytic leukemia (n = 3), non-Hodgkin lymphoma (n = 4), β thalassemia (n = 2) and hemophilia A (n = 3). 45 children (54.9%) are males. All children are not cirrhotic (fibroscan < 10 Kpa) and received treatment in the form of Ledipasvir 90 mg/sofosbuvir 400 mg for 12 weeks.
Results: Log10 HCV RNA level was 5.41 ± 0.85 IU (By cobas Taqman). All patients achieved early virological response (PCR < 15 IU at week 4 of treatment). Twenty patients reached PTW12, all of them achieved SVR12.BY time of the conference all patients will reach PTW12 and complete results will be presented. No serious adverse events reported till now.
Conclusion: Ledipasvir 90 mg/sofosbuvir 400 mg for 12 weeks was well tolerated and promising in treatment of children with CHC genotype 4.

Clinical trial number: ClinicalTrials.gov # NCT03343444.

THU-308

Safety and effectiveness of DAA treatment and clinical outcomes of HCV liver transplanted patients with recurrent hepatitis C infection: a single center 3-year study from Italy

F. Invernizzi[1], M.F. Donato[1], S. Monico[1], M. Borghi[1], D. Dondossola[2], B. Antonelli[2], G. Lunghi[3], R. Perbellini[1], F. Fabrizi[4], G. Rossi[2], P. Lampertico[1]. *[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, HBP Surgery and Liver Transplantation Unit, Milan, Italy; [3]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Microbiology and Virology Unit, Milan, Italy; [4]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Division of Nephrology and Dialysis, Milan, Italy*
Email: pietro.lampertico@unimi.it

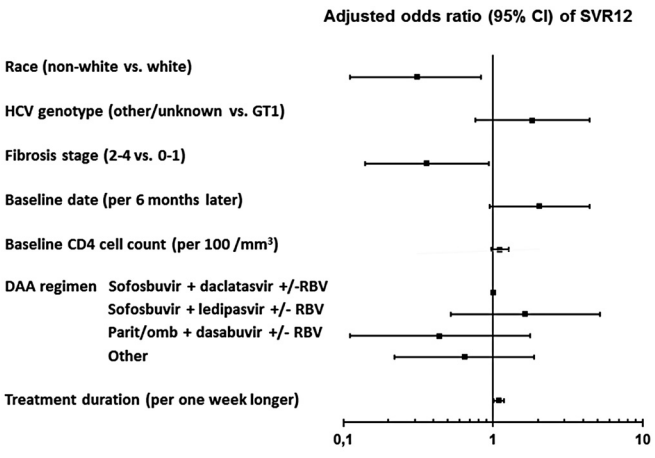
Background and Aims: Hepatitis C virus (HCV) recurrence after liver transplantation (LT) was associated with a poor clinical outcome until the new introduction of direct-acting antiviral agents (DAAs). This study was aimed to report the clinical outcome of DAA treated recipients with recurrent hepatitis C after LT.
Method: from May 2012 to January 2016, 125 HCV-RNA positive LT patients received DAA-treatment (with/without IFN) 46 (0–268) months from LT: 78% of the patients received a SOF-based regimen plus ribavirin (RBV), 6% patients SIM/DCV/RBV or 3D-regimen and 17% received PEG-IFN/RBV plus Telaprevir or Sofosbuvir. At DAA start, age was 61 years, 76% males, 71% HCV-1 infected, 69% treatment naïve, 48% transplanted for HCC, 58% on dual immunosuppression (CNI plus MMF), 75% had arterial hypertension, 52% diabetes, 23% cirrhosis/FCH, 5 patients portal vein thrombosis, 42% eGFR < 60 ml/min. The median HCV-RNA level was 1.890.231 UI/ml (14.588–51.491.894).
Results: A virological response was achieved in all patients (in 97% of them after the first course of therapy). DAA treatment was well tolerated and side effects were anaemia (erythropoietin support = 57 and blood transfusion = 15), asthenia and mild gastrointestinal disorders. After a median time of 10 months (3–18) from DAA start, 10 (8%) patients showed a liver graft dysfunction successfully treated by increasing immunosuppression. After a median follow-up of 26 months, liver stiffness declined from 11 to 7 kPa (p < 0.05), while 4% of patients developed a de-novo portal thrombosis 30 months after starting DAA; HCC recurred in 2 out of 60 HCC transplant recipients (at month 2 and 13). Extra-hepatic cancer (renal, bladder) occurred in 2 patients (month 26 and 12). eGFR values did not significantly change (65 vs 63 ml/min) but 5 patients ultimately worsened kidney function (one required haemodialysis 8 months post-DAA; 3 had a nephrotic syndrome 9 to 20 months post-DAA). Overall, the 3-year cumulative incidence of hepatic and extrahepatic complications was 24% and the 3-year survival was 99%, as only one patient died after 19 months post-DAA due to sepsis-related multi-organ failure.
Conclusion: DAA-treatment for HCV recurrence after LT is highly effective and safe. The 3-year survival was excellent but a quarter patients experienced hepatic or extrahepatic complications.

THU-309

Efficacy and safety of IFN-free DAA therapy in HIV/HCV co-infected patients: Results from a pan-European study

L. Peters[1], J.D. Lundgren[1], J. Rockstroh[2], A. Mocroft[3]. [1]*Rigshospitalet, CHIP, Department of Infectious Diseases, Copenhagen, Denmark;* [2]*University of Bonn, Medizinische Universitätsklinik I;* [3]*Institute for Global Health, UCL, Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME)*
Email: Lars.peters@regionh.dk

Background and Aims: Real-life data on efficacy and safety of direct-acting antiviral (DAA) therapy in HIV/HCV co-infected patients from Europe, especially Eastern Europe, are scarce. We aimed to investigate the efficacy of DAAs and the prevalence and reasons for premature discontinuation of DAAs.
Method: We included all HIV/HCV coinfected from the EuroSIDA study who started IFN-free DAAs after June 1 2014 and had ≥12 weeks of follow up after completing treatment. Sustained virological response (SVR) was defined as undetectable HCV-RNA ≥ 12 weeks after treatment completion. Logistic regression was used to examine factors associated with SVR.
Results: Among 632 persons starting DAA, the median age was 51 years, 79% were males, 58% with a history of injecting drug use and 19% MSM; 98.6% had HIV-RNA < 500 cp/ml and median CD4 cell count was 600/mm^3; 32.4% had cirrhosis.164 persons had unknown SVR status, 82 (50%) of whom were HCV-RNA negative at end of treatment and 82 (50%) with unknown treatment response. Ribavirin was used in 272/632 (43%) DAA regimens. Patients with unknown SVR status were generally similar to those with known SVR status, but more likely to be from Central East and Eastern Europe, p = 0.059). In an intention to treat analysis, 433/632 (68.5%; 95% CI 64.9–72.1) achieved SVR. In a per protocol analysis, 433/468 (92.5%; 95% CI 90.1–94.9%) achieved SVR. The SVR rate was 95.8% in Western Europe and 92.0%, 89.6%, 88.9% in South, North and Central East/East Europe, respectively, p = 0.27. In adjusted analysis, only white race vs. non-white race, fibrosis stage 0–1 vs. 2–4 and treatment duration per one week longer were associated with higher odds of SVR (figure). Thirty-one (4.9%; 95% CI 3.2–6.6%) out of 632 patients stopped one or more HCV drugs earlier than scheduled. The reasons included toxicity (n = 11), viral failure (n = 1), physician choice (n = 3), drug out of stock (n = 1), substance abuse (n = 1), other (n = 7) and unknown (n = 7). In nine out of 11 treatment stops due to toxicity, ribavirin was the only drug in the regimen that was stopped due to well-known adverse effects.



Model adjusted for factors shown. Gender, age, region of Europe, HIV risk, HCV viral load, prior HCV treatment, HBsAg, nadir CD4 cell count and treatment duration ≤ 12 vs. >12 weeks all had p>0.1 in univariate analysis

Conclusion: In a diverse population of HIV/HCV co-infected patients from all regions of Europe, DAA therapy was generally well tolerated and resulted in high SVR rates in all regions. Further data is required from Central East and Eastern Europe as we found a non-significant trend towards missing SVR12 results which could reflect loss to follow-up.

THU-310

Emergence of hepatitis C virus resistance associated variants in patients failing direct acting antivirals by ultra-deep sequencing

T. Nguyen[1,2], S. Akhavan[3], F. Caby[4], L. Bonyhay[5], L. Larrouy[6], A. Gervais[7], P. Lebray[5], T. Poynard[8], Y. Calmus[9], A. Simon[10], M.-A. Valantin[4], V. Calvez[2,11], A.-G. Marcelin[2,11], E. Todesco[1,2]. [1]*Institut Pierre-Louis Epidémiologie, Paris, France;* [2]*Sorbonne Universités, UPMC Univ Paris 06;* [3]*Department of Virology, Hôpital Pitié-Salpêtrière, APHP, Paris, France;* [4]*Infectious Diseases Department, Hôpital Pitié-Salpêtrière, APHP, Paris, France;* [5]*Service d'Hépato-Gastroentérologie, Hôpital Pitié-Salpêtrière, Paris, France;* [6]*IAME, UMR 1137, INSERM, Université Paris Diderot, Sorbonne Paris Cité, Laboratoire de Virologie, Hôpital Bichat, AP-HP, Paris, France;* [7]*Service des maladies infectieuses et tropicales, AP-HP, Hôpital Bichat Claude Bernard;* [8]*Groupe Hospitalier Pitié Salpêtrière APHP, Paris, France Sorbonne Universités, UPMC Univ Paris 06, UMR_S 938, Institute of Cardiometabolism and Nutrition (ICAN), INSERM, Paris, France;* [9]*APHP, Hôpital Pitié-Salpêtrière, Unité Médicale de Transplantation Hépatique, Hépato-Gastro-Entérologie. Hôpital Pitié-Salpêtrière UPMC Paris VI, Boulevard de l'Hôpital, Paris, France;* [10]*Assistance Publique des Hôpitaux de Paris, Hôpital Pitié-Salpêtrière, Département de Médecine Interne et Immunologie Clinique, Paris, France;* [11]*Institut Pierre-Louis Epidémiologie, France*
Email: thithu-thuy.nguyen@aphp.fr

Background and Aims: Resistance-Associated Variants (RAVs) are one of the main reasons for failure to Direct-Acting Antiviral (DAA) therapies in HCV infected patients. Studies realised by population (Sanger) sequencing about the impact of RAVs at baseline to treatment outcome by inhibitors of NS5A, NS3, and NS5B possibly underestimated their prevalence and their clinical significance. Moreover, these studies focused largely on HCV of genotype 1 (1a and 1b). In this study, we investigated presence of RAVs prior and post-treatment, their emergence under DAA pressure, and the possible impact of baseline RAVs on treatment outcome in patients infected by HCV of various genotypes and failing DAA therapies by ultra-deep sequencing technique (UDS).
Method: Sanger and UDS were performed for plasma samples prior and post-treatment of 23 patients failing DAAs [3 genotypes (GT)1a, 3 GT1b, 2 GT1not-a not-b, 5 GT3a, 3 GT4a, 5 GT4d, 1 GT4r, 1 GT2q]. The SmartGene IDNS ASP service was used to analyze UDS data. We analyzed amino acid positions considered to be implicated in resistance to DAAs which were mentioned in *geno2pheno* rules (updated February 2017) and EASL guidelines 2016.
Results: At baseline**,** pre-existing RAVs and natural polymorphisms including minority RAVs were detected by UDS in viruses of 10 patients (1 on NS3 and 9 on NS5A) among whom 4 were treatment-naïve. At failure, 1/23 patients developed S282T on NS5B which was not detected at baseline even by UDS. Presence of RAVs or polymorphisms on NS3 and NS5A genes was detected at relapse by Sanger and UDS in viruses of 1/1 and 14/18 patients, respectively. Emergence of substitutions from minority at baseline to majority at failure was detected on NS5B for viruses of 2/23 and on NS5A for 7/18 patients especially L28M/F for 3 GT4, L31M for 1 GT1e, and Y93H for 1 GT3a virus. Furthermore, these minority substitutions were accompanied by polymorphisms detected at 100% at baseline and at failure such as L28F accompanied by T58P in 1 GT4d, L28M by L30R in 1 GT4a and 1 GT4d, and L31M by K24R and S58P in 1 GT1e virus.
Conclusion: Viruses of a large part of patients failing NS5A inhibitors carried pre-existing RAVs and natural polymorphisms at baseline and developed majority RAVs at failure. The emergence at failure of pre-existing substitutions on NS5A and NS5B genes especially in little explored GT3 and GT4 virus is undoubtedly important and needs to be further investigated.

THU-311

HCV clearance and pro-thrombotic shift in advanced liver disease

E. Biliotti[1], D. Palazzo[1], R. Cangemi[2], R. Carnevale[3], R. Esvan[1], P. Maida[1], C. Nocella[3], P. Perinelli[1], M. Santori[1], M. Spaziante[1], L. Sulekova[1], F. Tamburini[1], F. Violi[2], G. Taliani[1]. [1]*Sapienza University of Rome, Clinical Medicine, Rome, Italy;* [2]*Sapienza University of Rome, Department of Internal Medicine and Medical Specialties, Rome, Italy;* [3]*Sapienza University of Rome, Department of Medical-Surgical Sciences and Biotechnologies, Rome, Italy*
Email: elisabiliotti@yahoo.it

Background and Aims: Hepatitis C virus (HCV) infection is associated to an increased risk of cardiovascular disease (CVD) and thromboembolic events. Direct acting antiviral (DAA) agents have an excellent safety profile and induce HCV viral clearance in almost all treated patients, but their impact on CVD risk remains unclear. Platelet activation and oxidative stress play a crucial role on the onset of thrombosis and CVD. We investigated the levels of urinary thromboxane B2 (TxB2), a marker of platelet activation, and 8-iso-prostaglandin F2α (8-iso-PGF2α), a marker of oxidative stress, during and after DAA treatment in HCV patients with advanced liver disease.
Method: We enrolled 90 consecutive HCV patients with advanced fibrosis (Metavir F3-F4) who achieved SVR after DAA treatment (65.6% with ribavirin, 77.8% with sofosbuvir). Urinary levels of TxB2 and 8-iso-PGF2α were measured at baseline (T0), end-of-treatment (EOT) and after 12-weeks of follow-up (FU) by ELISA commercial kits. Statistical analysis was performed by IBM SPSS version 21.0.
Results: The characteristics of enrolled patients were: age 59.3 ± 10.8 years, 58.9% males, BMI 25.0 ± 3.6, 75.6% HCV Gt-1, HCV viral load 6.1 ± 0.8 Log 10 IU/ml, platelet 156.0 × 10^6/mm^3, liver stiffness 19.7 ± 12.7 KPa. Urinary TxB2 levels increased sharply and significantly during antiviral treatment (161.5 [150.0–188.5] vs 230.0 [185.0–265.0]ng/mg creatinine, $p < 0.001$) with a small further increase during FU (242.5 [179.7–298.5]ng/mg creatinine, $p = 0.057$). Conversely, urinary 8-iso-PGF2α levels increased steadily during therapy (150.0 [136.5–161.0] vs 165.0 [151.5–210.0]pg/mg creatinine, $p < 0.001$) and FU (210.0 [167.5–255.0] pg/mg creatinine, $p < 0.001$). A significant correlation between the increase of TxB2 and 8-iso-PGF2α levels was observed during the study period ($r = 0.421$, $p < 0.001$). Modifications of platelet levels did not correlate neither with TxB2 ($r = -0.043$, $p = 0.48$) nor with 8-iso-PGF2α increase ($r = -0.027$, $p = 0.66$) and no clinical, biochemical, virological or treatment factors were found to correlate with TxB2 and 8-iso-PGF2α level changes.
Conclusion: The fast and significant increase of TxB2 and 8-iso-PGF2α levels observed in patients with advanced fibrosis successfully treated with DAA might indicate a shift toward a pro-thrombotic profile concomitant with viral clearance. These findings support the potential need of an antithrombotic prophylaxis administration early on treatment with DAA therapy.

THU-312

Identification of novel resistance associated substitutions for sofosbuvir in HCV genotype 3a

D. Smith[1], A. Ansari[1,2], A. Magri[1], D. Bonsall[1,2], C. Ip[1,2], A. Trebes[2], A. Brown[1], P. Cicconi[2], R. Bowden[2], P. Simmonds[1], E. Barnes[1]. [1]*University of Oxford, Peter Medawar Building for Pathogen Research, Nuffield Department of Medicine, Oxford, United Kingdom;* [2]*University of Oxford, Oxford Genomics Centre, Wellcome Centre for Human Genetics, Oxford, United Kingdom*
Email: david.smith@ndm.ox.ac.uk

Background and Aims: Sofosbuvir is a key component in the treatment of genotype 3 (gt3) HCV infected patients, with a higher barrier to resistance than other direct acting anti-viral compounds. However, resistance associated substitutions (RASs), like NS5B S282T, have been documented. Here, we report novel amino acid substitutions associated with treatment failure identified from a large cohort of gt3a-infected patients treated with sofosbuvir, ribavirin, +/– PEG-interferon (Boson study).

Method: Viral RNA was extracted from 428 baseline (BL) and 68 non-SVR 12-week post treatment (12WPT) viraemic samples, then sequenced with the Illumina MiSeq. To account for host and viral population structure, we only used samples from gt3a infected patients with self-reported "White" ethnicity. BL consensus sequences were scanned for known sofosbuvir RASs in the NS5B protein (L159F, S282T, C316H/N, L320F and V321A). The BL sequences were used to perform a systematic and unbiased viral genome wide association study (GWAS) to investigate the effect of individual amino acid substitutions on SVR. Finally, we compared the BL sequences to the 12WPT sequences and investigated enrichment of previously reported and putative RASs.
Results: No previously reported sofosbuvir RASs were present at BL, however the NS5B RAS L159F was significantly enriched in the 12WPT sequences in comparison to the BL sequences ($p = 6 \times 10^{-4}$). In our viral GWAS of BL sequences for SVR, the only site significantly associated with treatment outcome (at a 10% false discovery rate (FDR)) was I129V in the NS2 protein (Figure), this site was also enriched in our 12WPT samples ($p = 0.01$). Within the NS5B protein, there were no significant associations with SVR at baseline (at 10% FDR), however from the top two strongest associations with SVR, site A150V was significantly enriched in the 12WPT samples ($p = 9 \times 10^{-4}$).

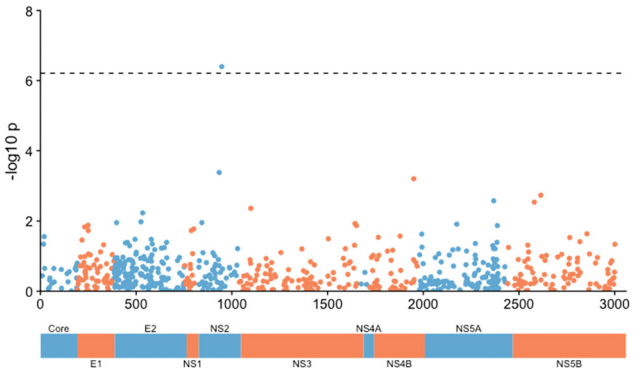


Figure: Manhattan plot of sites in HCV proteome association with SVR. Y-axis shows amino acid position in HCV proteome, X-axis shows the –log10(p) of the association test between the amino acid and SVR. Only the most significant association is shown per position. The dashed line indicates a 10% FDR.

Conclusion: In addition to known sofosbuvir RAS L159F, we identify novel amino acid substitutions in NS2 I129V and NS5B A150V associated with sofosbuvir treatment failure in HCV gt3 infection. Interestingly, A150V has been previously reported as being significantly associated with host IFNL4 genotype in this cohort (Ansari MA, et al., Nat Genet. 2017).

THU-313

Utilization and outcomes of elbasvir/grazoprevir in genotype 1B chronic hepatitis C: updated retrospective data analyses from the Trio network

N. Tsai[1], B. Bacon[2], M. Curry[3], S. Flamm[4], S. Milligan[5], C. Nwankwo[6], N. Wick[5], Z. Younossi[7], N. Afdhal[3]. [1]*Queens Medical Center, University of Hawaii, Honolulu, United States;* [2]*Saint Louis University School of Medicine, St. Louis, United States;* [3]*Beth Israel Deaconess Medical Center, Boston, United States;* [4]*Northwestern University Feinberg School of Medicine, Chicago, United States;* [5]*Trio Health, La Jolla, United States;* [6]*Merck & Co., Inc., Kenilworth, United States;* [7]*Inova Fairfax Hospital, Department of Medicine, Falls Church, United States*
Email: naoky@hawaii.edu

Background and Aims: Genotype 1B (GT1B) is the most prevalent genotype in many European countries. This study examines utilization of and outcomes with elbasvir/grazoprevir (EBR/GZR)-

containing regimens in an updated cohort of GT1B Chronic Hepatitis C (HCV) patients treated as part of the TRIO network in the US.

Method: Data were collected from providers and specialty pharmacies through Trio Health's disease management program. Patients (n = 319) with GT1B HCV who initiated EBR/GZR therapy between Jan 28, 2016 (FDA approval) to Jun 2017 were included. The primary outcome was per protocol sustained virologic response at 12 weeks post treatment (SVR12).

Results: 307 (96%) patients received 12-week EBR/GZR, 6 (2%) 12-week EBR/GZR + RBV, 1 (<1%) 16-week EBR/GZR, and 5 (2%) 16-week EBR/GZR + RBV. Of the patients that received 12-week EBR/GZR, 68/269 (22%) had eGFR < 30 ml/min, 81/267 (26%) had FIB-4 > 3.25 and 55/307 (18%) were treatment experienced. Of the patients that received EBR/GZR with RBV and/or 16 weeks of therapy, 2/10 (20%) had eGFR < 30 ml/min, 3/10 (30%) had FIB-4 > 3.25 and 7/12 (58%) were treatment experienced. At time of data extraction, outcomes were available for 204/319 patients and were: 2% (4/204) died, 6% (12/204) discontinued, 3% (7/204) completed but were lost to follow up, 1% (3/204) completed therapy and had virologic failure, and 87% (178/204) achieved SVR12. The resultant per protocol (PP) SVR12 rate (limited to patients who completed therapy and had an SVR assessment) was 98% (178/181). By regimen, the PPSVR12 was 171/173 (99%) for 12-week EBR/GZR, 4/4 (100%) for 12-week EBR/GZR + RBV, 1/1 (100%) for 16-week EBR/GZR, and 2/3 (67%) for 16-week EBR/GZR + RBV.

Conclusion: The majority of patients with GT1B HCV were treated with 12-week EBR/GZR without RBV in clinical practice with 99% PPSVR. 12-week EBR/GZR is highly effective in this population. Complete SVR results will be available for the conference.

THU-314

Effectiveness and utilization of Grazoprevir and Elbasvir in HCV genotype 1 and 4 infection in the veterans affairs healthcare system in the US

A. Puenpatom[1], J. Kramer[2], Y. Cao[2], D. Smith[2], H. El-Serag[2], F. Kanwal[2].
[1]*Merck Sharp & Dohme Corp;* [2]*Michael E DeBakey VA Medical Center, United States*
Email: puenpatom.amy@merck.com

Background and Aims: Elbasvir/grazoprevir (EBR/GZR), which is indicated for the treatment of chronic Hepatitis C genotype (GT)1 and GT4 infection, has demonstrated high efficacy across clinical studies. We evaluated the real-world effectiveness and utilization among HCV GT1 and GT4 infected patients treated with EBR/GZR regimens in clinical settings within the US Department of Veterans Affairs (VA) healthcare system.

Method: This was a retrospective database analysis of HCV-infected patients treated with EBR/GZR ± RBV in VA clinics. The nationwide VA Corporate Data Warehouse includes laboratory, pharmacy, hospitalizations, and clinical diagnoses data. We included patients with positive HCV RNA who received EBR/GZR ± RBV from January-December 2016 who received treatment for at least 11 weeks. SVR rates were examined overall and by clinical characteristics and comorbidities. We calculated 95% confidence intervals (CIs) for SVR rates using the binomial distribution.

Results: After applying inclusion and exclusion criteria, we identified 4,755 HCV-infected veterans treated with EBR/GZR regimens. Mean age (± SD) was 63.5 ± 6.1 years, 97.0% were male, and 66.3% had viral load higher than 800,000 IU/ml. There were 30.5 percent with cirrhosis, 32.1% with chronic kidney disease (CKD) stage 3–5, and 52.8% diagnosed with diabetes. More than half had history of drug and alcohol abuse (54.2% and 62.9%, respectively). 92.3% of those with GT1 and GT4 were treated with EBR/GZR, 5.8% with EBR/GZR + RBV, and 1.9% with EBR/GZR + SOF ± RBV.

Overall, 96.3% (4579/4755, 95%CI: 95.7%-96.8%) achieved SVR. Of the 4,660 GT1 or GT4 patients, 96.3% (4489/4660, 95%CI: 95.8%-96.9%) achieved SVR. By genotype, 94.8% (1863/1966) of patients with GT1a reached SVR compared to 97.4% (2430/2494) with GT1b, and 97.9% (95/97) with GT4. SVR rates were high across patient subgroups, including for cirrhosis (95.4%, 1356/1421), CKD stage 3–5 (96.5%, 1456/1509), African American (96.6%, 2548/2639), and viral load > 800 k IU/ml (95.5%, 2960/3101).

Conclusion: In this large VA cohort, EBR/GZR was highly effective in GT1 and GT4. HCV-infected veterans in this real-world cohort were older and had high prevalence of health and mental comorbidities. High SVR was achieved across patient subgroups regardless of gender, race/ethnicity, presence of cirrhosis, or level of viral load.

THU-315

Efficacy, safety and clinical outcomes of Paritaprevir/Ombitasvir/r + Dasabuvir 8 weeks: results from a Spanish real world cohort (Hepa-C)

M. Puigvehí[1], B.D. Cuenca[2], D. Giménez[1], F. Gea[3], M. Diago[4], S. Lens[5], E. Badia-Aranda[6], J. Turnés[7], A.O. Martin[8], J. Salmerón[9], J.M. Pascasio[10], J.L.C. Urda[11], J.L.C. Panero[12], J. Cabezas[13], X. Torras[14], E. Molina[15], J.M. Moreno[16], J. Sánchez-Ruano[17], J. De la Vega[18], S. Montoliu[19], P. Cordero[20], J.J. Moreno[21], J.A. Carrión[1]. [1]*Hospital del Mar, Barcelona, Spain;* [2]*Hospital Universitario de Getafe, Getafe, Spain;* [3]*Hospital Universitario Ramón y Cajal, Madrid, Spain;* [4]*Hospital General de Valencia, Valencia, Spain;* [5]*Hospital Clínic de Barcelona, Barcelona, Spain;* [6]*Hospital Universitario de Burgos, Burgos, Spain;* [7]*Complejo Hospitalario de Pontevedra, Pontevedra, Spain;* [8]*Hospital Carlos III / La Paz, Madrid, Spain;* [9]*Hospital Universitario San Cecilio, Granada, Spain;* [10]*Hospital Universitario Virgen del Rocío, Sevilla, Spain;* [11]*Hospital Severo Ochoa, Leganés, Spain;* [12]*Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain;* [13]*Hospital Marqués de Valdecilla, Santander, Spain;* [14]*Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [15]*Centro Hospitalario de Santiago de Compostela, Santiago de Compostela, Spain;* [16]*Centro Hospitalario Universitario de Albacete, Albacete, Spain;* [17]*Centro Hospitalario de Toledo, Toledo, Spain;* [18]*Hospital San Agustín, Avilés, Spain;* [19]*Hospital Universitari Joan XXIII, Tarragona, Spain;* [20]*Hospital Virgen de la Macarena, Sevilla, Spain;* [21]*Hospital General de Segovia, Segovia, Spain*
Email: 95565@parcdesalutmar.cat

Background and Aims: The interferon-free 3D regimen (OBV/PTV/r + DSV) has shown high efficacy in patients with hepatitis C virus (HCV) genotype 1b infection. The 3D regimen can achieve sustained virological response (SVR) in 100% of genotype 1b infected patients with or without cirrhosis when administered during 12 weeks [*Andreone et al, Gastroenterology 2014; Feld et al, JHepat 2016*]. Recently, the 8 week administration of the 3D regimen (3D8) has shown 98% SVR rates in treatment-naive non-cirrhotic patients infected by genotype 1b [*Welzel et al, Hepat Int 2017*]. The aim of our study was to assess the efficacy and safety of 3D8 in a real-world cohort of genotype 1b infected treatment-naive patients with mild-moderate liver fibrosis (F0-2).

Method: Multicenter observational study from a Spanish real-life cohort. Treatment-naive patients infected by genotype 1b receiving 3D during 8 weeks (October'16–July'17) and registered in Hepa-C were included. Patients with advanced fibrosis (liver stiffness measurement, LSM > 9.6 kPa [*Ziol et al, Hepatology 2005*]) were excluded. Clinicaltrials.gov: NCT03122132.

Results: A total of 155 patients were registered from 21 Spanish centers. Six patients were excluded (LSM > 9.6 kPa). Preliminary results are presented. Baseline characteristics: 41.6% (n = 62) male, median (range) age was 56.5 (23–86), ALT 48 (22–494)IU/ml, viral load 6.1 (3.3–8.2) $\log^{10}$ IU/ml, 74.5% mild (F0-1) and 25.5% moderate (F2) liver fibrosis. Among patients with available data, viral load was undetectable (<15 IU/ml) at week 4 after treatment initiation in 107 out of 119 (89.9%) patients, at end of treatment (EOT) in 126 out of 126 (100%) and at week 12 after EOT (SVR12) in 93 out of 96 (96.9%). No virological failures occurred during antiviral treatment. After EOT, a relapse in viral load was observed in 3 patients. Regarding treatment safety, one patient showed anemia (Hb < 10 g/dl) not related to 3D regimen (basal Hb level of 9.6 g/dl), and 2 patients developed an

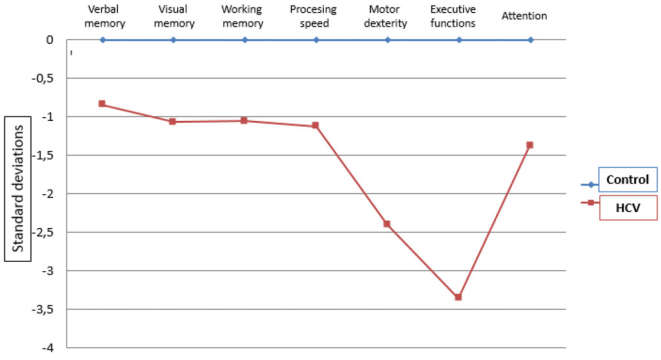
increasement of ALT > 5xULN. No patients had to be discontinued due to adverse events.
Conclusion: Preliminary results of eight weeks of OBV/PTV/r + DSV (3D8) in genotype 1b infected treatment-naive patients with mild-moderate fibrosis show excellent efficacy in a real-life cohort similarly to clinical trials. Moreover, treatment safety of 3D8 is excellent, without treatment discontinuations due to adverse events. Final results will be presented in International Liver Congress®.

THU-316
Multidisciplinary Support Program for patients with addictions and suspected chronic hepatitis C (MSP ADIC-C) to improve their evaluation and access to antiviral treatment
M. Puigvehí[1], F. Fonseca[2], E. González-Colominas[3], D. Giménez[1], A. Viu[1], R. Fernández[1], J. Tirado[2], L. Badenas[2], P. Samos[2], S. Jornalé[2], G. Vallecillo[2], C. Castillo[2], N. Cañete[1], T. Broquetas[1], M.G. Retortillo[1], S. Coll[1], R.S. Lamoglia[1], M. Torrens[2], J.A. Carrión[1]. *[1]Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), Liver Section, Gastroenterology Department, Barcelona, Spain; [2]Institut de Neuropsiquiatria i Addicions, Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain; [3]Hospital del Mar, Pharmacy Department, Barcelona, Spain*
Email: 95565@parcdesalutmar.cat

Background and Aims: Patients with addictions (illicit drugs or heavy alcohol intake) have high chronic hepatitis C (CHC) prevalence (32% in our area) (Roncero et al. EJGH, 2017). Alcohol intake and HIV coinfection accelerate the progression to cirrhosis and hepatocellular carcinoma in patients with CHC. Thus, it is a priority to create Multidisciplinary Support Programs (MSP) to identify, evaluate and treat these patients with direct acting antivirals (DAAs). The aim of our study was to create a MSP including primary care physicians and specialists in Mental Health, Internal Medicine, Pharmacy and Hepatology, for the screening, diagnosis, evaluation, treatment and follow-up of patients with addictions and suspected CHC (MSP ADIC-C).
Method: Open prospective study since January 2016, including patients with addictions and suspected CHC (HCV + antibodies) from our hospital. Patients dependent in basic activities of daily living (DBADL), deceased or in jail during the study period were excluded. CHC was confirmed using a PCR test with 15 IU/ml sensitivity. Fibrosis stage was evaluated using transient elastography (TE).
Results: 110 patients with HCV+ antibodies and addictions have been evaluated. Nine patients were excluded. Among 101 included patients, 78 (77.2%) were male, with median (range) age of 45.6 (25.6–64.4), 19 (18.8%) consumed some illicit drug, 17 (16.8%) alcohol intake, 57 (56.4%) under opioid replacement therapy and 8 (7.9%) were abstinent. Forty-seven (46.5%) had a severe mental disorder. Only 6 (5.9%) had received previous antiviral treatment. HIV antibodies were determined in 100 (99%) patients, being positive in 42 (42%), HCV-RNA in 91 (90%) confirming CHC in 90 (98.9%), and HCV genotype in 60 (59.4%). Liver fibrosis was evaluated in 55 (54.5%) patients, showing advance fibrosis or cirrhosis (TE > 9 kPa) in 23 (41.8%). Treatment with DAAs was started in 22 (21.8%): 7 are in treatment, 2 lost during follow-up and 13 are in week 12 after end of treatment; 12 of them (92.3%) have achieved SVR12.
Conclusion: A Multidisciplinary Support Program for patients with addictions and suspected HCV infection (MSP ADIC-C) has allowed to identify and to diagnose practically all patients. Liver fibrosis has been evaluated in more than a half of them, identifying advanced fibrosis or cirrhosis in 41.8%. Preliminary SVR rate is high (92.3%).

THU-318
Direct acting antiviral treatment improves hepatitis C-related neurocognitive impaiment
J.C. Gonzalez[1], R. Ayesa[2], E. Setién[2], P. Iruzubieta[1], Á. Estébanez[1], B. Crespo-Facorro[2], J. Crespo[1]. *[1]Marqués de Valdecilla University Hospital. IDIVAL. CIBERehd., Department of Gastroenterology and Hepatology; [2]Marqués de Valdecilla University Hospital. IDIVAL., Department of Psychiatry*
Email: joweycabezas@gmail.com

Background and Aims: Hepatitis C-related extra-hepatic manifestations include those affecting central nervous system that could drive to neurocognitive impairment. Our aim is to investigate relationship between chronic hepatitis C and neuropsychological derangements.
Method: We have included two cohorts: 1. Inmates from a penitentiary centre (n = 41), we evaluated them at baseline and post-treatment, after receiving an IFN-free DAA (direct acting antiviral) regimen; 2. Patients attended in our regular out-patient clinic (non-cirrhotic, n = 55). And a control group of 15 subjects, matched by age, gender and educational level. Inmates' post-treatment results were compared to their baseline data.
Results: Inmates (Mean 45.5 ± 6.5 years-old) showed a significant cognitive impairment in visual memory ($p < 0.05$), working memory ($p < 0.05$), processing speed ($p < 0.05$), executive function ($p < 0.05$), attention ($p < 0.05$) and motor dexterity ($p < 0.05$). Executive function and motor dexterity domains showed an intense impairment (Figure). After DAA treatment (all patients achieved sustained virological response), patients showed a significant improvement in: initial verbal learning ($p < 0.05$), speed processing ($p < 0.05$) and attention ($p < 0.05$). Patients at the out-patient clinics showed slight changes, we found a trend in motor dexterity domain ($F = 3.7$, $p = 0.056$), HCV infected patients got the lowest punctuations.



Conclusion: Our preliminary results suggest that HCV infected patients develop motor dexterity impairment; this dysfunction can be recovered after a successful DAA treatment.

THU-319
Effectiveness of 8 vs. 12 week ledipasvir-sofosbuvir (LDV/SOF) in black, treatment naïve patients with non-cirrhotic, genotype 1 HCV and baseline viral load
M. Curry[1], B. Bacon[2], S. Flamm[3], A. Landen[4], S. Milligan[4], N. Tsai[5], Z. Younossi[6], N. Afdhal[1]. *[1]Beth Israel Deaconess Medical Center, Boston, United States; [2]Saint Louis University School of Medicine, St. Louis, United States; [3]Northwestern University Feinberg School of Medicine, Chicago, United States; [4]Trio Health, La Jolla, United States; [5]Queens Medical Center – University of Hawaii, Honolulu, United States; [6]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States*
Email: mcurry@bidmc.harvard.edu

Background and Aims: AASLD/IDSA guidance does not recommend shortening ledipasvir-sofosbuvir (LDV/SOF) to less than 12 weeks for treatment-naïve black patients with non-cirrhotic genotype 1 (GT1) HCV. In the ION-3 trial, black patients who were treatment naïve, F0-3

with GT1 HCV treated with LDV/SOF had SVR rates of 96% (26/27) with 8 weeks and 96% (22/23) with 12 weeks which was similar to that observed in non-black patients (97% and 96% for 8 and 12 weeks, respectively). This updated analysis of TRIO health examines the efficacy of LDV/SOF for 8 or 12 weeks in a larger sample of black, treatment naïve patients with non-cirrhotic genotype 1 HCV and baseline viral load <6 mm IU/ml.

Method: Data were collected from providers and specialty pharmacies through Trio Health's disease management program. Exclusion criteria included baseline platelets <150 K/mcl, baseline FIB-4 > 3.25, HIV or HBV coinfection, unknown genotype 1 subtype, and prior treatment experience. Patients not removed by the exclusion criteria, self-identified as black, and who initiated 8 (n = 114) or 12 (n = 98) week LDV-SOF therapy between Oct 2015 to Mar 2017 were included.

Results: The 8 and 12-week treatment groups were similar for baseline characteristics of genotype subtype, viral load, eGFR, ALT, AST, BMI, and FIB-4. Also similar were mean age, percent male gender, and rates of anxiety, depression, diabetes, and hypertension. Significant differences between the groups were limited to payer type; a greater percentage of patients treated for 8 weeks had commercial or Medicaid coverage. Patient disposition is shown in the Figure. The per protocol (PP) SVR12 rates, limited to patients who completed therapy and an SVR assessment, were 97% (93/96) for the 8-week treatment group and 99% (86/87) for the 12-week group; rates not statistically different (Z = –0.91; p = 0.36).

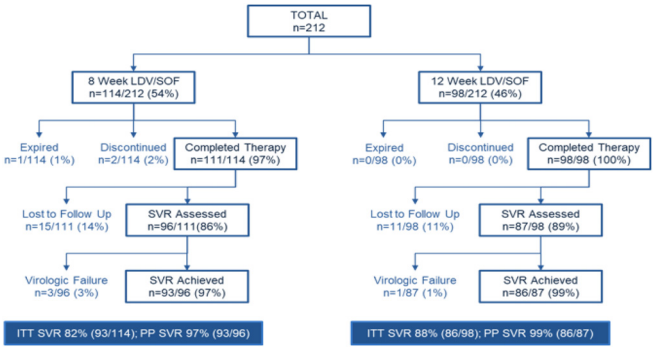


Figure: Patient Disposition.

Conclusion: Clinical efficacy as measured by PP SVR12 is high with both 8 and 12 week LDV/SOF in black, treatment naïve patients with non-cirrhotic genotype 1 HCV and baseline viral load <6 mm IU/ml, demonstrating that this population does not benefit from extended duration of treatment.

THU-320

Effectiveness of elbasvir/grazoprevir in patients with cirrhotic genotype 1 or 4 chronic hepatitis C: updated retrospective data analyses from the Trio network

M. Curry[1], S. Flamm[2], B. Bacon[3], S. Milligan[4], C. Nwankwo[5], N. Tsai[6], N. Wick[4], Z. Younossi[7], N. Afdhal[1]. [1]*Beth Israel Deaconess Medical Center, Boston, United States;* [2]*Northwestern University Feinberg School of Medicine, Chicago, United States;* [3]*Saint Louis University School of Medicine, St. Louis, United States;* [4]*Trio Health, La Jolla, United States;* [5]*Merck & Co., Inc., Kenilworth, United States;* [6]*Queens Medical Center-University of Hawaii, Honolulu, United States;* [7]*Inova Fairfax Hospital, Department of Medicine, Falls Church, United States*
Email: mcurry@bidmc.harvard.edu

Background and Aims: Historically, HCV treatment has been less effective in patients with cirrhotic disease. This study examines utilization of and outcomes with elbasvir/grazoprevir (EBR/GZR)-containing therapies in patients with cirrhosis and genotype (GT) 1 or 4 Chronic Hepatitis C (HCV).

Method: Data on patients who initiated EBR/GZR therapy between Jan 28, 2016 (FDA approval) to Jun 2017 for GT1 or 4 were collected from providers and specialty pharmacies in the US through Trio Health's disease management program. To ensure the correct identification of cirrhosis, patients were required to have both a baseline FIB-4 > 3.25 and practice-reported fibrosis score 4 for inclusion in the analysis. The primary outcome assessed was per protocol (PP) sustained virologic response at 12 weeks post treatment (SVR12).

Results: 115 patients met the study inclusion criteria. 3/115 (3%) patients had GT4 HCV. 2/3 of GT4 patients received 12 week EBR/GZR; 1 completed therapy and was lost to follow up and 1 achieved SVR. The resultant per protocol (PP) SVR12 rate (limited to patients who completed therapy and had an SVR assessment), was 1/1 (100%). 1/3 GT4 patients received 12 week EBR/GZR + RBV and achieved SVR (PPSVR12 1/1, 100%). 112/115 (97%) patients had GT1 HCV; 103/112 (92%) received 12-week EBR/GZR and 9/112 (8%) received EBR/GZR with RBV and/or for 16 weeks duration. At time of data extraction, outcomes were available for 85/112 GT1 patients and were: 5/85 (6%) died, 3/85 (4%) discontinued, 2/85 (2%) completed therapy but were lost to follow up and 75/85 (88%) had an SVR12 assessment. The PPSVR12 rate for GT1 was 72/75 (96%); by regimen, the PPSVR12 rates were 66/67 (99%) and 6/8 (75%) for 12-week EBR/GZR and EBR/GZR with RBV and/or for 16 weeks duration, respectively.

Conclusion: In this study of cirrhotic, EBR/GZR-treated patients in US clinical care, most patients were with GT1 HCV and treated with 12-week EBR/GZR without RBV. 12-week EBR/GZR was highly effective with an overall PPSVR12 rate of 67/68 (99%). Complete SVR results will be available for the conference.

THU-321

Utilization of elbasvir/grazoprevir (EBR/GZR) and adoption of resistance associated substitutions (RAS) testing in real-world treatment of HCV genotype 1 (GT1) infection: results from the German Hepatitis C Registry (DHC-R)

H. Hinrichsen[1], H. Klinker[2], A. Stoehr[3], C. John[4], R. Heyne[5], G. Klausen[6], K.-G. Simon[7], M. Cornberg[8], M. Kuhn[9], U. Naumann[10], M. Bilzer[11], K. Bayer[12], V. Witte[12], S. Zeuzem[13]. [1]*Gastroenterology-Hepatology Center, Kiel, Germany;* [2]*University Hospital Wuerzburg, Wuerzburg, Germany;* [3]*IFI – Institute for Interdisciplinary Medicine, Hamburg, Germany;* [4]*Private Practice of Internal Medicine, Berlin, Germany;* [5]*Leberzentrum am Checkpoint, Berlin, Germany;* [6]*Schwerpunktpraxis Berlin-Mitte, Berlin, Germany;* [7]*MVZ Dres. Eisenbach, Simon, Schwarz GbR, Leverkusen, Germany;* [8]*Hannover Medical School, Hannover, Germany;* [9]*Practice of Gastroenterology, Kassel, Germany;* [10]*Praxiszentrum Kaiserdamm, Berlin, Germany;* [11]*Bilzer Consulting, Munich, Germany;* [12]*MSD Sharp & Dohme GmbH, Haar, Germany;* [13]*University of Frankfurt, Department of Medicine, Frankfurt, Germany*
Email: vanessa.witte@msd.de

Background and Aims: HCV GT1b infection independent of baseline viral load (BVL) as well as GT1a infection with BVL < 800,000 IU/ml can be successfully treated with EBR/GZR for 12 weeks. In contrast, for GT1a infection with BVL > 800,000 IU/ml European guidelines recommend baseline NS5A RAS-testing and lengthening of EBR/GZR to 16 weeks together with RBV in the presence of NS5A RAS or when RAS-testing is not available. Therefore, the present analysis investigated the real-world utilization of this recommendations and the possible impact on EBR/GZR effectiveness in a large GT1 cohort of the German Hepatitis C Registry.

Method: From September 2016 until August 2017, 535 patients (pts) with genotype 1 infection were treated with EBR/GZR +/– RBV for 12 to 16 weeks in 110 medical practices and hospital outpatient departments. The present interim analysis was restricted to 531 pts with documented GT1 subtypes.

Results: In total, 180 pts with GT1a infection (33.9%) and 351 pts with GT1b infection (66.1%) received EBR/GZR-based treatment and showed the following characteristics (GT1a vs. GT1b): mean age 48 vs. 56 years, female gender 27 vs. 44%, BVL > 800.000 IU/ml 52 vs. 58%, liver cirrhosis 18 vs. 18%, opioid substitution 27 vs. 4%, HIV co-infection 9 vs. 2%, renal dysfunction 8 vs. 12% and treatment-naïve 75 vs. 77%. RAS at baseline were tested in 39 of 92 GT1a pts (42%) with BVL > 800.000 IU/ml. 4 pts (10%) had NS5A RAS of which 3 were treated with EBR/GZR + RBV and 1 with EBR/GZR. Furthermore, 3 pts without RAS and 29 pts without RAS testing received RBV. In total, 35/92 of GT1a pts (38%) with high BVL were treated with EBR/GZR + RBV. Although not recommended by the European guidelines, NS5A RAS were tested in 35 of 86 GT1a pts (41%) with low BVL and in 23 of 351 pts (7%) with GT1b infection while 7 of 86 pts (8%) with GT1a and low BVL and 1 of 351 pts (0.3%) with GT1b infection received RBV. By now SVR12 results were available from 63/531 pts. Overall per protocol SVR12 was 98% (61/62) with comparable SVR12 rates for GT1a (100%, 18/18) and GT1b (98%, 43/44).

Conclusion: In German real-world practice, 92% of pts with GT1 receiving EBR/GZR are treated without RBV. Addition of RBV is mainly restricted to pts with high BVL > 800,000 IU/ml of which more than 40% are tested for NS5A RAS at baseline. The current treatment with EBR/GZR seems to be highly effective. Full SVR12 data by GT1 subtypes and BVL will be presented at the conference.

THU-322

High efficacy of IFN-free DAA therapy for acute HCV infection in HIV patients

D. Chromy[1], M. Mandorfer[1], T. Bucsics[1], P. Schwabl[1], B. Scheiner[1], C. Schmidbauer[1], M. Aichelburg[2], P. Ferenci[1], M. Trauner[1], M. Peck[1], T. Reiberger[1]. *[1]Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; [2]Medical University of Vienna, Dermatology, Immunology, Allergy and Infectious Diseases, Vienna, Austria*
Email: n1142399@students.meduniwien.ac.at

Background and Aims: In a recent study treatment of acute hepatitis C (AHC) with direct-acting antivirals (DAA) for 6 weeks was highly effective in AHC mono infection. However, same treatment duration resulted in suboptimal sustained virologic response rates twelve weeks after treatment (SVR12) in AHC/HIV coinfection. Thus, we evaluated the virological response to IFN-free DAA regimens in HIV+ patients with AHC.

Method: All patients diagnosed with AHC at our HIV/Liver outpatient clinic since the availability of DAAs were retrospectively analyzed. Diagnosis of AHC was established in accordance with the criteria defined by the European AIDS treatment network (NEAT) consensus conference. Two patients with chronification prior to treatment uptake and diagnosis of plasma cell myeloma, respectively, were excluded from analysis.

Results: n = 28 HIV+ male patients with AHC with high-risk MSM practices under recreational drug influence as the main suspected route of transmission (86%, 24/28) were started on IFN-free DAA regimens. The mean age was 44.5 ± 9.85 years, HCV Genotype (GT) was predominately GT-1a in 71% (20/28) followed by GT-1b 11% (3/28), GT-3 11% (3/28) and GT-4 7% (2/28). Alanine transaminase (ALT) was significantly elevated at AHC diagnosis (280 ± 260 IU/mL) and 64% (18/28) presented with a median liver stiffness (LS) of 7.70 kPa (5.00).

Most patients (57%; 16/28) received ombitasvir/paritaprevir/ritonavir/dasabuvir, while ombitasvir/paritaprevir/ritonavir, sofosbuvir/ledipasvir, grazoprevir/elbasvir and glecaprevir/pibrentasvir were initiated in 7% (2/28), 18% (5/28), 7% (2/28) and 11% (3/28), respectively.

All patients were on antiretroviral therapy (ART), mostly on nucleosidic reverse transcriptase inhibitors (96%; 27/28) plus integrase inhibitors (79%; 15/28), prescribed concomitantly. In 25% (7/28) was an ART switch required prior to treatment initiation to avoid drug-drug interactions. Suppression of HIV-RNA under antiretroviral therapy (<50 copies/ml) was observed in 89% (25/28).

Patients received HCV treatment for at least 12 weeks following recommendations for chronic HCV. At the time of data collection, information on SVR12 was available in 64% (18/28) of patients with all (100%) achieving SVR12. Furthermore, all patients had ALT levels within the upper limit of normal at SVR12 while median LS declined (6.50 kPa (3.80) vs. baseline; p = 0.334).

Conclusion: In our cohort, treatment with IFN-free DAA regimens achieves 100% SVR12 rates in HIV+ patients with AHC. SVR12 resulted in significant decreases in transaminases and a trend towards LS reduction. Future studies should evaluate shorter treatment durations with IFN-free DAA regimens in AHC/HIV coinfection.

THU-323

High SVR rates in patients with and without cirrhosis treated in real life with Sofosbuvir/Velpatasvir (SOF/VEL) combination for 12 weeks without Ribavirin (RBV)

A. Mangia[1], V. Piazzolla[1], R. Losappio[2], M. Mazzola[2], E. Visaggi[3], D. Bacca[4], F. Sogari[5], D. Potenza[6], R. Santoro[1], I. Carraturo[7], V. Tagarielli[8], G. Lauletta[9], A. Giannelli[2], A. Gesualdo[10], N. Minerva[11]. *[1]Liver Unit IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo, Italy; [2]Infectious Diseases, Bisceglie, Italy; [3]Infectious Diseases, Terlizzi, Italy; [4]Gastroenterology, Casarano, Italy; [5]Internal Medicine, Tranto, Italy; [6]Infectious Diseases, Brindisi; [7]Infectious Diseases, Lecce; [8]Infectious Diseases, Acquaviva delle Fonti; [9]Internal Medicine Baccelli Policlinico, Bari; [10]Internal Medicine Murri Policlinico, BAri; [11]Internal Medicine, Canosa*
Email: a.mangia@tin.it

Background and Aims: Pangenotypic regimens are now available for treatment of patients with chronic HCV infection. However, for some of them, treatment duration needs to be adjusted depending on cirrhosis and/or genotype. To confirm in real life usefulness of "one size fits all" strategy using SOF/VEL for 12 weeks regardless of baseline features, we analysed data on treatments performed in Puglia (Italy) in patients with and without cirrhosis regardless of HCV genotype.

Method: From the Regional register, 1,099 patients were started on treatment from May 15th to November 1st 2017. Patients were treated at physician discretion and data collected within a collaborative group. Diagnosis of advanced fibrosis/cirrhosis was based on transient elastography and APRI score according to the standard thresholds. This analysis refers to 513 HCV mono-infected patients who completed SVR4 by November 1st.

Results: The majority of patients were male (55%), of mean age 63.2 (18–90). High proportion of patients (38.9%) was older than 70 yrs. 223 (43.5%) had cirrhosis/advanced fibrosis as compared to 27.8% with stage 0-1; the remaining had fibrosis stage 2. The proportion of naïve was 75.3%. Diabetes was present in 20.5%, history of IVDA in 19.5%% and active IVDA in 8.8%. GT1 was represented in 36.2% of cases; however, as a consequence of high GT2 prevalence in our region, GT2 was the most frequent (46.8%). Of the remaining, 17.2% had GT3 and 9.8% GT4. All but 4 patients received 12 weeks of therapy without RBV. 4 patients prematurely discontinued treatment; in 2 of 4 HCV RNA is currently undetectable.

Overall, SVR was 98.6% at ITT analysis and 99% at PP analysis. Rates were 97.9% in patients with advanced fibrosis/cirrhosis and 98% in those with mild fibrosis. Among fibrosis stage 2, 100% of patients achieved SVR. No differences in SVR rates were observed across HCV genotypes: SVR was 100% in GT1b, 98% in GT1a, 97.9% in GT2 and 100% in GT3 and GT4. SVR was 99.2% and 98.6% in naïve and experienced respectively. No difference in SVR rates was observed between diabetic and non-diabetics (100% vs 98.6%). Among IVDA, 100% achieved SVR.

Conclusion: Pangenotypic SOF/VEL combination is associated with 98.6% SVR4 in patients with all HCV genotypes, with or without cirrhosis treated for 12 weeks. RBV is not needed in patients with compensated cirrhosis treated with this combination. SOF/VEL is a suitable treatment for HCV infected patients regardless of baseline characteristics.

THU-324

The evolution of treatment for HCV Genotype 3 (GT3) infected patients with advanced fibrosis/cirrhosis over time

A. Mangia[1], G. Cenderrello[2], M. Copetti[3], R. Santoro[1], F. Sogari[4], V. Piazzolla[1], N. Minerva[5], M. Mazzola[6], R. Losappio[6], P. Vincenzo[7], G. Spinzi[8], D. Potenza[9], G.D. Stefano[10]. *[1]Liver Unit IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo; [2]Galliera Hospital, Infectious Diseases, Genova; [3]Biostatistic Unit IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo; [4]Internal medicine, SS Annunziata Hospital, Taranto; [5]Internal Medicine, Ospedale Caduti in Guerra, Canosa; [6]Infectious Disease, Vittorio Emanuele II Hospital, Bisceglie; [7]Internal Medicine, Padiglione Murri Policlinico, Bari; [8]Gastroenterology, Valduce Hospital, Como; [9]Infectious Disease, Perrino Hospital, Brindisi; [10]Infectious Disease, Ospedale Santa Maria delle Grazie, Matera*
Email: a.mangia@tin.it

Background and Aims: Treatment of GT3 remains challenging. To identify, in a large cohort of Italian patients with cirrhosis/advanced fibrosis, the impact of viral predictors of virological failure, across recently used Interferon-(IFN) free regimens.
Method: Patients were treated following the Italian guidelines within a protocol implemented by 9 centers from South and 2 from North of Italy working together on genetic projects.
Results: Between March 2015 and September 2017, the combinations of sofosbuvir (SOF) plus ribavirin (RBV), SOF plus daclatasvir (DCV) and SOF plus velpatasvir (VEL) were implemented. Of 355 patients with available SVR, 39.2% were Peg/IFN-experienced. SOF/RBV was used in 19.5%, SOF/DCV in 62.0%, SOF/VEL in 18.5%. Overall SVR was 87.5% ranging from 78.6% after SOF/RBV to 87.2% after SOF/DCV or 98.4% after SOF/VEL (p = 0.003). 169 patients (47.6%) had cirrhosis. SVR was 83.2% for cirrhotics and 91.4% for non cirrhotics (p = 0.024). Baseline NS5A associated RASs were present in 9.2%, PNPLA3GG genotypes in 8.2%, IL28BCC in 33.7%. No association between favorable genetics and SVR was observed. Independent predictors of relapse were prior Peg/IFN/RBV failure (OR = 3.82, 95%CI 1.70–8.58), baseline NS5ARASs (OR = 3.73 95%CI 1.32–10.51), cirrhosis (OR = 2.41, 95%CI 1.10–5.31) and treatment regimen (OR = 2.88 95% CI 1.56–5.33).

	Overall n = 355	SOF/RBV n = 70	SOF/DCV n = 219	SOF/VEL n = 66	P value
Male (n, %)	289 (81.5)	60 (85.7)	173 (79.0)	56 (89.1)	0.28
	66 (18.5)	10 (14.3)	46 (21.0)	10 (14.2)	
Age (mean, range)	50.5	50.9	50.7	49.2	0.45
	18–87	37–66	26–87	18–69	
Treatment history					
Naive	216 (60.8)	33 (47.1)	136 (62.1)	46 (69.8)	0.06
Relapser	52 (14.8)	12 (17.1)	34 (15.5)	6 (9.5)	
Prior Non responders	87 (24.4)	25 (35.7)	49 (22.4)	14 (20.6)	
Cirrhosis	169 (47.6)	37 (52.9)	100 (45.7)	32 (48.4)	0.57

Conclusion: Our real-world results validate the efficacy of past and current GT3 IFN-free regimens suggesting that, among patients with severe disease, Peg/IFN/RBV experience and NS5A associated RASs resulted till recently predictors of relapse. Their relevance can be expected to decline with the use of SOF/VEL.

THU-325

Impact of acid-reducing agents on effectiveness of Elbasvir/Grazoprevir in treating US veterans affairs population with hepatitis C virus

J. Kramer[1], A. Puenpatom[2], Y. Cao[1], D. Smith[1], H. El-Serag[1], F. Kanwal[1]. *[1]Michael E DeBakey VA Medical Center, Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Houston, United States; [2]Merck Sharp & Dohme Corp, Whitehouse Station, United States*
Email: jkramer@bcm.edu

Background and Aims: Acid-reducing agents (ARAs) including proton pump inhibitor (PPI) and histamine H2-receptor antagonist (H2RA) use may decrease bioavailability of some direct acting antiviral agents (DAAs), leading to treatment failures of hepatitis C (HCV) infection treatment. Clinical trials showed that no drug-drug interaction is expected when elbasvir/grazoprevir (EBR/GRZ) is co-administered with ARAs. This study assessed the effect of ARAs use on SVR among HCV-infected patients treated with EBR/GRZ in a large real-world clinical setting.
Method: We conducted a nationwide retrospective observational cohort study of HCV patients seen at the US Department of Veterans Affairs (VA) using the VA Corporate Data Warehouse (includes laboratory, pharmacy, hospitalizations, and clinical diagnoses). The study population included patients with positive HCV RNA who had filled prescriptions for at least 11 weeks of EBR/GRZ with or without ribavirin (RBV) during January–December 2016. Concomitant PPI or H2RA use was defined as ≥1 filled prescription <30 days prior to EBR/GRZ initiation date through the end of treatment. We examined SVR rates overall and stratified by PPI and H2RA use.
Results: We evaluated 4,755 HCV-infected patients treated with EBR/GRZ regimens. Most were male (97.0%), African American (56.3%), with mean age of 63.5 (SD = 6.1), and 96% infected with genotype (GT)1. Overall, 32.8% of patients had concomitant PPI use, of these 41.5% had twice daily and 58.5% had once daily. Other comorbidities included diabetes (52.8%), depression (57.5%), cirrhosis (30.5%), and HIV (2.8%). Among those treated with EBR/GZR regimens with GT1 and GT4, 96.3% (n = 4,489/4,660; 95%CI: 95.8%-96.9%) achieved SVR. In patients with concomitant PPI use, 96.5% (N = 1481/1535) achieved SVR compared with 96.3% (n = 3,008/3,125) in patients without PPI use (p = 0.70). There was no significant difference in SVR in patients with twice daily or once daily PPI (96.4%, n = 616/639 vs. 96.5%, n= 865/896; p = 0.92). There was no significant difference of SVR rates were found in patients with H2RA use (95.9% vs. 96.4% without H2RA; p = 0.72).
Conclusion: EBR/GRZ achieved high effectiveness in treating HCV in the VA population. These results demonstrate that PPI and H2RA concomitant use with EBR/GZR had no clinically significant effect on SVR rates in genotype 1 or 4-infected patients.

THU-326

HCV treatment responses among people who use drugs: an evaluation of patients on and off opiate agonist therapy in a real-life setting

J. Holeksa, A. Bassi, A. Alimohammadi, A. Thiam, B. Conway. *Vancouver Infectious Diseases Centre*
Email: julie.holeksa@vidc.ca

Background and Aims: Current guidelines identify people who use drug (PWUD) as a "priority population" to receive HCV treatment within a multidisciplinary system of care. Clinical trials have shown such an approach to be successful within the context of individuals integrated in opiate agonist therapy (OAT) care (C-EDGE CO-STAR). Other trials (D3FEAT, SIMPLIFY) have evaluated HCV-infected PWUD receiving health care many of whom were not on OAT. SVR12 rates > 90% were obtained in both studies, and participation in OAT did not

appear to affect the likelihood of achieving this outcome. There is a need to confirm these data in real life with a view to evaluating whether enrollment in an OAT program is necessary prior to initiating HCV therapy.

Method: Patients receiving all oral HCV therapy at the Vancouver Infectious Diseases Centre (VIDC) between 06/15 and 09/17 were enrolled in this observational study. All participants were active PWUD (positive urine drug screen for recreational drugs within the previous month) and enrolled in our multidisciplinary program (delivery of medical, social, psychiatric, and addiction-related services) for at least one month. HCV therapy was initiated according to the contemporary standard of care. At baseline, participants were considered according to enrollment on OAT (methadone or suboxone) or not, as clinically indicated. The outcome of interest was achievement of SVR12, as a function of receipt of OAT therapy, while accounting for other variables potentially correlated with successful HCV therapy.

Results: A total of 101 subjects were enrolled (64/37 on and off OAT respectively). Key baseline characteristics were: median age 52 years; 75% male; 71/6/15/8% GT 1a, 1b, 3, other; 20% F4; 77/42/41% using opiates/cocaine/amphetamines. In comparing the OAT and non-OAT patients there were no marked differences in any of these baseline parameters. Of 37 subjects not on OAT, 34 achieved SVR, 1 discontinued, and 2 were lost to follow up (ITT SVR12 92%, mITT 97%). Of 64 subjects on OAT, 55 achieved SVR, 5 were lost to follow up, and 4 experienced virologic relapse (ITT SVR 12 86%, mITT 93%). Due to sample size, significance analysis could not be performed to compare SVR rates between the two groups. The 4 virologic relapses were all male, GT 1a, 3/4 reported active drug use during treatment in addition to receiving OAT, and 2/4 are co-infected with HIV.

Conclusion: These real-life data confirm the results of clinical trials of HCV treatment among PWUD. They further suggest that prior enrollment in OAT is not a pre-condition of considering HCV therapy in this group. The variable of interest to consider HCV therapy may be enrollment in a multidisciplinary program such as ours. This information is essential to the development of programs among PWUD to achieve the World Health Organization goals for the control of HCV infection by 2030.

THU-327

VIEKIRA PAK (ritonavir-boosted paritavir/ombitasvir and dasabuvir) associated drug-induced interstitial lung disease: Case series with systematic review

Y.J. Wong[1], S.Y. Chew[2], P.H. Thurairajah[3], R. Kumar[1], J.H. Chen[1], R.S. Gokhle[2], I.M. Noor[2], J. Tan[1]. *[1]Changi General Hospital, Gastroenteorlogy and Hepatology, Singapore, Singapore; [2]Changi General Hospital, Respiratory Medicine and Critical Care, Singapore, Singapore; [3]Changi General Hospital, 2 Simei Street 3, Singapore, Singapore*
Email: eugene.wong@mohh.com.sg

Chronic hepatitis C virus (HCV) infection is a serious cause of liver-related morbidity and mortality worldwide, affecting more than 170 million patients globally. Oral direct-acting antivirals (DAA) have since replaced conventional interferon and ribavirin as first line HCV therapy due to a better tolerability profile and high efficacy in achieving sustained virological response. VIEKIRA PAK (ritonavir-boosted paritavir/ombitasvir and dasabuvir), a combination of potent DAA, is an effective initial treatment for HCV genotype 1 infection in patients with or without cirrhosis and in patients who may or may not have received interferon-ribavirin therapy before. We describe two patients who developed severe DILD requiring mechanical ventilation for respiratory failure on day 8 and day 40 of VIEKIRA PAK therapy who recovered after supportive management with systemic corticosteroids and systemically reviewed the literature on VIEKIRA PAK associated DILD. Although the incidence of pulmonary toxicity is low in Phase 3 clinical studies, there have been emerging case reports of VIEKIRA PAK associated drug-induced interstitial lung disease (DILD). Although recovery is reported with supportive care in all cases, VIEKIRA PAK associated DILD is often life-threatening and VIEKIRA PAK may have to be discontinued permanently. In summary, VIEKIRA PAK associated DILD is a rare yet potentially near-fatal complication that should be recognized early by physicians.

THU-328

HCV genetic diversity by geographic region within genotype 1–6 subtypes among patients treated with Glecaprevir and Pibrentasvir

G. Schnell, R. Tripathi, P. Krishnan, J. Beyer, T. Reisch, M. Irvin, T. Dekhtyar, L. Lu, I.C. Ng, W. Xie, T. Pilot-Matias, C. Collins. *AbbVie Inc., Research & Development, North Chicago, United States*
Email: gretja.schnell@abbvie.com

Background and Aims: The regimen containing glecaprevir (GLE, NS3/4A protease inhibitor, identified by AbbVie and Enanta) and pibrentasvir (PIB, NS5A inhibitor) is highly efficacious for the treatment of HCV genotype (GT) 1–6 infection. We analyzed a large dataset of NS3/4A and NS5A sequences generated from HCV GT1–6-infected patient samples to assess genetic diversity within HCV subtypes by geographic region, and determined the activity of GLE or PIB against NS3 or NS5A GT1–6 clinical isolates.

Methods: The full-length HCV NS3/4A and NS5A genes from 2416 available baseline samples in studies SURVEYOR-1, -2, ENDURANCE-1, -2, -3, -4, -5/6, and EXPEDITION-1, -4 were sequenced by next-generation sequencing using Illumina MiSeq. NS3/4A and NS5A sequences were grouped by genotype and subtype, and included in phylogenetic analyses to assess genetic relationships within GT1–6 subtypes and prevalence of baseline polymorphisms by country. The activity of GLE or PIB was assessed against HCV transient replicons containing NS3 or NS5A from a panel of GT1–6 clinical samples.

Results: Among 2416 baseline samples, 47 subtypes were identified, including 3 GT1 (n = 861), 9 GT2 (n = 537), 3 GT3 (n = 635), 15 GT4 (n = 170), 1 GT5 (n = 49), and 16 GT6 (n = 77) subtypes. Phylogenetic analyses of GT1 sequences confirmed the presence of 2 clades in subtype 1a, and in subtype 1b clustering by country was most notable for sequences from Poland and Taiwan. In GT2a, sequences from Europe (especially Lithuania) and North America sorted away from Asian countries of Korea and Taiwan, while sequences from New Zealand clustered in both subtypes 2a and 2b. Minimal clustering was seen by country in GT3. In GT5a, clustering was most notable for sequences from Belgium. Two distinct phylogenetic groups were detected in both GT4a and GT6e, representing 2 putative clades in these subtypes. Among GT1–6 clinical isolates, GLE or PIB retained activity against NS3 or NS5A with or without polymorphisms at positions important for the inhibitor class.

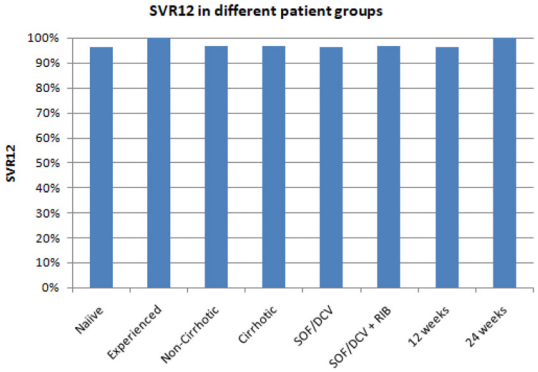
Conclusions: Phylogenetic clustering by country was detected in HCV subtypes 1b, 2a, 2b, and 5a, suggesting that genetically similar virus lineages are circulating in some countries. Two putative clades were detected in GT4a and GT6e, which did not segregate by country of enrollment. Regardless of the phylogenetic diversity within each subtype, high virologic response rates were observed among GT1–6-infected patients treated with the regimen of GLE/PIB.

THU-329

Is treatment of hepatitis C with controlled generic direct acting antiviral drugs effective? An Egyptian experience

G. Soliman[1], M.S. Negm[1], M. Elzalabany[2], A.A. Malik[1], A. Khattab[3], M. Elshair[1], M.G. Abdel-Hamid[4], M.Y. Soliman[5], D. Miller[6], T. Hassanein[7]. *[1]Faculty of Medicine, Al-Azhar University, Tropical Medicine, Gastroenterology and Hepatology Department, Cairo, Egypt; [2]Ahmed Maher Teaching Hospital, Internal Medicine Department, Cairo, Egypt; [3]Agoza Police Hospital, Tropical Medicine, Gastroenterology and Hepatology Department, Cairo, Egypt; [4]Aswan University Hospitals, Tropical Medicine Department, Aswan, Egypt; [5]Tanta Fever Hospital, Hepatology and Endoscopy Department, Tanta, Egypt; [6]John A. Burns School of Medicine, University of Hawaii, Department of Tropical Medicine, Medical Microbiology and Pharmacology, Honolulu, Hawaii, United States; [7]Southern California Liver Centers, Coronado, CA, United States*
Email: dr_msf@hotmail.com

Background and Aims: Oral DAAs have revolutionized the treatment of HCV with shorter treatment duration and higher rates of SVR, albeit being very expensive. Egypt has very high HCV prevalence and the cost of treatment is prohibitive. Here, we report real life treatment outcomes using affordable generic sofosbuvir (SOF) and daclatasvir (DCV) at Tahya Misr HCV Treatment Center in Luxor, Egypt.
Method: Patients aged 18–75 years and positive for HCV RNA were enrolled into the treatment program, while patients with advanced cirrhosis (CTP B&C), hepatocellular carcinoma, extrahepatic malignancy, uncontrolled diabetes and pregnancy were excluded. Eligible patients were classified into two groups; Easy to treat (ET) (treatment naive, albumin ≥3.5 gm/dl, bilirubin ≤1.2 mg/dl, platelet count ≥150,000 cell/mm^3, INR ≤ 1.2) and difficult to treat (DT) (interferon experienced, albumin <3.5 gm/dl, bilirubin >1.2 mg/dl, platelet count <150,000 cell/mm^3, or INR > 1.2). ET patients were treated with SOF 400 mg plus DCV 60 mg once daily for 12 weeks. Ribavirin (RBV) 600 mg daily was added for DT patients. Patients who previously failed SOF-based regimens were treated with SOF/DCV/RBV for 24 weeks. We analyzed the data of 522 patients treated at the center from June to September 2016. 12 patients (2.3%) did not complete treatment due to lack of adherence and 86 patients (16.5%) were lost to follow-up after finishing therapy.
Results: Of the 424 patients included, 251 were males (59.2%). The mean age was 55.5 ± 9.8 years. 389 patients (91.8%) were treatment naive, 15 patients (3.5%) were experienced to interferon and 20 patients (4.7%) to SOF-based regimens. 21.2% of the patients were cirrhotic. Six patients were positive for HBsAg with low HBV viral load. 262 patients (61.8%) were treated with SOF/DCV and 162 patients (38.2%) with SOF/DCV/RBV. 405 patients (95.5%) were treated for 12 weeks and 19 patients for 24 weeks. SVR12 was achieved in 410 patients (96.7%), while 14 patients (3.3%) failed therapy. SVR was not affected by the different variables (Figure). SVR was similar in both ET & DT groups. Side effects were reported in less than 10% and were mainly headaches, fatigue and nausea.



Conclusion: (1) The combination of SOF/DCV is highly effective in curing HCV GT4; (2) Applying standard protocols, SVR rate in real life is similar to clinical trials; (3) Generic SOF/DCV is safe and as effective in treating HCV GT4 as brand DAAs. In summary, guaranteeing the quality of generic DAAs will impact HCV therapy in low income countries.

THU-330

Real-life experience of ritonavir-boosted paritaprevir, ombitasvir plus ribavirin for treatment of HCV-GT4 in Egyptian patients with severe renal impairment

H. Omar[1], M. Said[1], Z. Abdellatif[1], Y. Saad[1], H. Dabes[2], S. Hamed[2], M. El-Serafy[1], K. Elsaeed[3], Y. Elshazly[3]. *[1]Faculty of Medicine, Cairo University, Endemic Medicine and Hepatology Department, Egypte; [2]National Medical Institute of Damanhour; Egypte; [3]Faculty of Medicine. Ain Shams University, General Medicine, Hepatology and Gastroenterology Department, Egypte*
Email: hebaomar1202@hotmail.com

Background and Aims: Management of HCV in adults with significant kidney disease (estimated glomerular filtration rate (eGFR) < 30 ml/min per 1.73 m^2) has been markedly revolutionized with the availability of new direct-acting antiviral agents. However, little is known about the efficacy and safety of these agents in the treatment of this historically difficult-to-treat population. The current study aimed at evaluation of the efficacy and safety of 12 weeks therapy with ritonavir-boosted paritaprevir, ombitasvir plus ribavirin for chronic HCV patients with severe renal impairment.
Method: 171 patients with HCV genotype 4 infection and severe chronic kidney disease (eGFR < 30 ml/min/1.73 m^2 +/– requiring hemodialysis) were prospectively included and treated with ritonavir-boosted paritaprevir, ombitasvir and ribavirin for 12 weeks at Damanhur specialized HCV treatment center affiliated to the Egyptian NCCVH from 4/2016 to 10/2017. The most common etiology of CKD was diabetes and/or hypertension (n = 67). The primary end point was sustained virologic response (serum HCV RNA <15 IU/ml) 12 weeks after treatment ended (SVR12). Data on on-treatment adverse events (AEs), serious AEs, laboratory abnormalities, treatment discontinuation were collected.
Results: 171 patients were included (females 35%, mean age 53 years). 29 patients had liver cirrhosis. All included patient reached the end of treatment (EOT) with no treatment discontinuations. The overall EOT response was 100%. 122/122 (100%) patients who reached 4 weeks post-treatment have achieved SVR4, and 80/80 (100%) have achieved SVR12. To date, no reported SAEs. Ribavirin therapy was interrupted in 25% (43/171) of patients due to anaemia; 16 patients required blood transfusions. The median eGFR increased from 33.5 (15) ml/min/1.73 m^2 at baseline to 35 (36)ml/min/1.73 m^2 at SVR8 (p = 0.0003).
Conclusion: In real-life, the use of ombitasvir, paritaprevir, and ritonavir in the treatment of HCV infected patients with advanced renal disease was safe and effective, Moreover, it was associated with significant improved eGFR.

THU-331

The efficacy of paritaprevir/ritonavir/ombitasvir + dasabuvir and ledipasvir/sofosbuvir is similar in patients who failed interferon-based treatment with first generation protease inhibitors

E. Janczewska[1], R. Flisiak[2], D. Zarębska-Michaluk[3], P. Arkadiusz[1], A. Staniaszek[4], A. Gietka[4], W. Mazur[5], M. Tudrujek[6], K. Tomasiewicz[6], T. Belica-Wdowik[7], B. Baka-Ćwierz[7], D. Dybowska[8], W. Halota[8], B. Lorenc[9], M. Sitko[10], A. Garlicki[10], H. Berak[11], H. Andrzej[11], I. Orłowska[12], S. Krzysztof[12], Ł. Socha[13], M. Wawrzynowicz-Syczewska[13], J. Jaroszewicz[14], D. Zbigniew[15], A. Czauż-Andrzejuk[2], J. Citko[16], R. Krygier[17], A. Piekarska[18], Ł. Laurans[19,20], B. Dobracka[21], J. Bialkowska-Warzecha[22], T. Olga[23], M. Pawłowska[24]. *[1]ID Clinic, Hepatology Outpatient Clinic, Myslowice, Poland; [2]Medical University of Bialystok, Department of Infectious Diseases and Hepatology, Bialystok, Poland; [3]Voivodship Hospital and Jan Kochanowski University, Department of Infectious Diseases, Kielce, Poland; [4]Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Department of Internal Medicine and Hepatology, Warszawa, Poland; [5]Specialist Hospital in Chorzów, Medical University of Silesia, Clinical Department of Infectious Diseases, Chorzow, Poland; [6]Medical University of Lublin, Department of Infectious Diseases and Hepatology, Lublin, Poland; [7]Regional Center for Diagnosis and Treatment of Viral Hepatitis and Hepatology, Krakow, Poland; [8]Faculty of Medicine, Collegium Medicum Bydgoszcz, Nicolaus Copernicus University Toruń, Department of Infectious Diseases and Hepatology, Bydgoszcz, Poland; [9]Pomeranian Center of Infectious Diseases, Medical University of Gdańsk, Department of Infectious Diseases and Hepatology, Gdansk, Poland; [10]Jagiellonian University Collegium Medicum, Department of Infectious and Tropical Diseases, Krakow, Poland; [11]Hospital for Infectious Diseases in Warsaw, Warsaw, Poland; [12]Wroclaw Medical University, Department of Infectious Diseases and Hepatology, Wroclaw, Poland; [13]Pomeranian Medical University, Department of Infectious Diseases, Hepatology and Liver Transplantation, Szczecin; [14]Medical University of Silesia in Katowice, Department of Infectious Diseases, Hepatology and Liver Transplantation, Bytom, Poland; [15]Biegański Regional Specialist Hospital, Ward of Infectious Diseases and Hepatology, Lodz, Poland; [16]Regional Hospital, Medical Practice of Infections, Olsztyn; [17]NZOZ "Gemini", Infectious Diseases and Hepatology Outpatient Clinic, Żychlin, Poland; [18]Medical University of Łódź, Department of Infectious Diseases and Hepatology, Lodz, Poland; [19]Pomeranian Medical University, Department of Infectious Diseases, Hepatology and Liver Transplantation, Szczecin, Poland; [20]Multidisciplinary Regional Hospital in Gorzów Wielkopolski, Gorzow Wielkopolski, Poland; [21]MED-FIX Medical Center, Wrocław, Poland; [22]Medical University of Łodz, Department of Infectious and Liver Diseases, Lodz, Poland; [23]Medical University of Warsaw, Department of Transplantation Medicine, Nephrology, and Internal Diseases, Warsaw, Poland; [24]Collegium Medicum Bydgoszcz, Nicolaus Copernicus University Toruń, Department of Infectious Diseases and Hepatology, Faculty of Medicine, Bydgoszcz, Poland*
Email: e.janczewska@poczta.fm

Background and Aims: According to the EASL guidelines, recommended treatment for patients (pts) who failed to achieve an SVR on prior interferon-based triple therapy with protease inhibitors (PI) are combinations of sofosbuvir and NS5A inhibitors. Our national recommendations, supported by results of the early-access studies (AMBER) also allow the use of paritaprevir/ritonavir/ombitasvir + dasasbuvir +/–RBV (PrODR) in this group of patients. The aim of the study was to evaluate the efficacy and safety of PrODR vs. ledipasvir/sofosbuvir +/– RBV (LSR) in PI-experienced patients in real-life setting.

Method: Our analysis included patients treated with IFN-free regimens in the year 2016, voluntarily registered by treating physicians in the nationwide, multicenter EpiTer-2 database.

Results: Among 2879 pts registered in total, 313 subject with genotype 1 (95% 1b) were previously treated with IFN-based regimens with PIs: 108 with boceprevir (BOC), 180 with telaprevir (TVR) and 25 with simeprevir (SVR). Sex, age and BMI distribution were similar in all groups. Pts with advanced fibrosis (F3/F4) were significantly predominant (BOC 26%/60%, TVR 18%/65%, SMV 27%/42%, respectively). Majority of patients (303) met criteria of Child-Pugh class A, 9 pts class B and 1 subject class C.
Assignment of subjects to IFN-free retreatment was as follows:

BOC group: 55 pts (51%) PrODR and 51 (48%) LSR
TVR group: 90 pts (50%) PrODR and 85 (47%) LSR
SMV group:19 pts (73%) PrODR and 7 (27%) LSR

Pts classified as Child-Pugh B or C were treated with LSR.
SVR12/24 rates in all pts were 97% in ITT and 99% in mITT analyses.
SVR12/24 rates in particular groups were as follows:

BOC: PrODR- ITT/mITT 100%; LSR – ITT 98%, mITT 100%
TVR: PrODR- ITT 97%, mITT 99%; LSR – ITT 96%, mITT 98%
SMV: PrODR- ITT 90%, mITT 94%; LSR – ITT/ mITT 100%.

Both treatment regimens had favorable safety profile. The reported adverse events (AEs) were generally mild or moderate in severity. Two deaths were reported (not treatment-related). The treatment was stopped due to AEs in 5 pts (3 treated with PrODR and 2 with LSR).

Conclusion: Efficacy of the treatment with PrODR and LSR was similar in BOC or TVR-experienced pts. The results of treatment with PrOD in SMV group were less satisfactory than with LSR, but low number of subjects and disproportion between the patients assigned to both regimens didn't allow us to draw reliable statistical conclusions. Our findings will be verified after collecting more data in EpiTer-2 registry.

THU-332

Characteristics and retreatment of HCV DAA failure patients: Real-life experience

I. Ruiz, S. Fourati, A. Varaut, S. Giovanna, M. François, M. Wlassow, L. Poiteau, F. Donati, A. Soulier, C. Stephane, A. Mallat, J.-M. Pawlotsky, C. Hezode. *CHU Henri Mondor, APHP*
Email: isaac.ruiz@me.com

Background and Aims: In the era of DAA treatment 5 to 10% of patients fail to achieve a SVR. Baseline characteristics and retreatment data are poorly documented in these patients. The aim of this study was to report the baseline characteristics of HCV patients who failed with DAA strategy recommended by EASL guidelines and results of retreatment of these patients.

Method: 75 patients with chronic HCV infection who previously failed a DAA treatment according to EASL guidelines were studied. Clinical and virological baseline characteristics, including genotype and subtype, and RASs by population sequencing (15%) before starting the first and second course of DAA, were collected. Regarding, retreatment, the rescue-therapy was chosen during a multidisciplinary meeting, according to EASL guidelines. Patients received sofosbuvir-based regimen plus 1 or 2 DAA, with or without ribavirin, for 12, 16, or 24 weeks or were included in clinical trials or early access program. Efficacy was defined by SVR12.

Results: 75 patients, (males 63.0%, median age 59.3 years) were enrolled. Ethnicity distribution was: Caucasian (51%), black (40%), and other (9%). Concerning genotype distribution of 30 blacks: GT1, 9/30 (30%); and GT4, 15/30 (50%); of them 9/30 (30%) were GT4r. Median FibroScan score was 19.4 kPa (range 4.0–67.8), 30 (40%) of patients had a cirrhosis (FibroScan > 12.5 kPa), 5/30 (16.7%) were Child-Pugh B; 2/30 (6.7%) had MELD score >15. Genotype distribution is shown in Table 1. Median HCV RNA level before retreatment was 5.87 Log^{10} IU/ml (range 4.39–7.04). Resistance test before the retreatment has

shown NS3/4 RASs, NS5A RASs, and NS5B RASs in 20(32.9%), 54 (82.2%), and 10(27.4%) patients, respectively. Of the 9 GT4r patients, 6 were previously treated with SOF/LDV ± RBV 12/24weeks, 1 with SOF/SMV, and 1 with 2D/RBV. Résistance analysis showed that 8/9 had L28V NS5A RASs, and 3/8 had S282C/T NS5B RASs. Among the 41 patients who reached week 12 follow-up, 39 patients (95.1%) achieved a SVR12.

Table 1: Genotype distribution

HCV genotype	All patient		Blacks	
	n = 75	%	n = 30	%
Overall				
Common	37	49.3	7	23.3
Uncommon	38	50.7	23	76.7
By Genotypes				
1 a/b	19	25.3	4	13.3
1 d/e/l	6	8.0	5	16.7
2 a	1	1.3	0	0
2 (other than 2a)	6	8.0	4	13.3
3 a	16	21.3	2	6.7
3 (other than 3a)	3	4.0	0	0
4 b	1	1.3	1	3.3
4 g/h/r	20	26.7	14	46.7
5/6 c	3	4.0	0	0

Conclusion: Uncommon genotypes and black patients were over represented in patients who failed after DAA regimens according to EASL guidelines. These genotypes and patients should benefit from second generation pangenotypic regimens. In addition, retreatment according to 2016 EASL guidelines seems to be an effective strategy in these patients.

THU-333

Concomitant drug use in patients with chronic hepatitis C and change over time: A nationwide population-based register study from 2005 to 2013

J. Söderholm[1,2], O. Weiland[3], A. Brolund[1], J. Kövamees[1], M. Baartz[4], A. Nystedt[5], K. Buesch[2,6]. *[1]AbbVie, Medical Affairs, Solna, Sweden; [2]Karolinska Institutet, Department of Laboratory Medicine, Stockholm, Sweden; [3]Karolinska Institutet, Department of Medicine, Stockholm, Sweden; [4]AbbVie, Market Access, Sydney; [5]Sunderby Hospital, Center for Communicable Disease Control, Luleå, Sweden; [6]AbbVie, HEOR, Solna, Sweden*
Email: jonas.soderholm@abbvie.com

Background and Aims: Chronic hepatitis C (CHC) infection carries an increased risk of comorbidities with an overall higher use of medical drugs. The aim of the present study was to evaluate the use of co-medications and to evaluate the potential risk for Drug-Drug Interactions (DDIs) for each Direct-Acting Antivirals (DAAs) currently used for treating hepatitis C.
Method: The analysis of potential DDIs during one calendar year included all expedited drugs during 2013 for all diagnosed CHC patients in Sweden alive as of December 31st 2013 (n = 34,633). The CHC patients were identified using B18.2 according to the International Classification of Diseases (ICD)-10 diagnosis code in the inpatient care, day surgery (1997–2013) and the non-primary outpatient care (2001–2013) registries in the nationwide Swedish Patient Register. Information on expedited drugs was obtained using ATC codes in the prescribed drug register (June 2005–2013), which covers all dispensed prescriptions in Sweden. For the longitudinal analysis of drug use, only the CHC patients diagnosed as of June 2005 through 2013 were included (n = 21,954) in the analysis. Follow-up started at the diagnosis of CHC until death, emigration or 2013-Dec-31 whichever came first. The DDI profiles for the DAAs were evaluated using the HEP Drug iChart (University of Liverpool, UK, [accessed 2017-Aug-29]).
Results: A median of 4 drugs were used during the year after CHC diagnosis. During the second year, 45% of the patients used a decreased number of drugs (median 3 fewer drugs) and 37% used an increased number of drugs (median 2 extra drugs) ($P < 0.0001$ paired T-test). During 2013, a total of 974 different drugs were expedited. In a theoretical analysis, the number of drugs considered as "Do not co-administer" were 19 (2.0%) for EBR/GZR, 11 (1.1%) for LDV/SOF, 20 (2.1%) for GLE/PIB, 48 (4.9%) for OBV/PTV/r + DSV, 15 (1.5%) for SOF/VEL, and 28 (2.9%) for SOF/VEL/VOX. Carbamazepine (n = 705) was the most common "Do not co-administer" drug for EBR/GZR, LDV/SOF, and SOF/VEL, comprising of 39%, 71%, and 71% respectively of the "Do not co-administer" drugs per DAAs. Simvastatin (n = 1,695) was the most common "Do no co-administer" for GLE/PIB, OBV/PTV/r + DSV, and SOF/VEL/VOX, comprising of 45%, 15%, and 45% respectively of the "Do not co-administer" drugs per DAAs.
Conclusion: The use of co-medications significantly decreased the year after CHC was diagnosed, possibly due to a more adequate care of the patients' co-morbidities. In addition, few co-medications (1–5%) expedited to CHC patients during 2013 were considered to be in the category "Do not co-administer" (HEP Drug iChart).

THU-334

Unexpected findings from a large Asian HCV real life study

S.G. Lim[1], W.W. Phyo[1], S. Shah[2], K.M. Win[3], S.S. Hamid[4], T. Piratvisuth[5], S.S. Tan[6], Y.Y. Dan[1], Y.M. Lee[1], T. Ahmed[7], W.L. Yang[8], K.P. Chen[8], M. Kamat[9], M. Wadhawan[10], K. Madan[11], R. Mehta[12], A. Shukla[13], P. Dhore[13], C.E. Eapen[14], P. Abraham[15], S. Tyagi[16], A. Koshy[17], H.B. Aung[3], W. Jafri[4], S. Abid[4], F.A.Q. Arisar[4], T. Tanwandee[18], T.P. Yin[19], H.P. Tee[20], R.B.H.M. Said[21], K.L. Goh[22], S.H. Ho[22], R. Mohamed[22], N.A. Bakar[23]. *[1]National University Health System, Gastroenterology and Hepatology, Singapore, Singapore; [2]Global Hospital – Super Speciality and Transplant Center, Hepatology, Mumbai, India; [3]Yangon GI & Liver Centre, Yangon, Myanmar; [4]Aga Khan University, Medicine, Karachi, Pakistan; [5]NKC Institute of Gastroenterology and Hepatology, Medicine, Hat Yai, Thailand; [6]Selayang Hospital, Medicine, Batu Caves, Malaysia; [7]Khoo Teck Phuat Hospital, Medicine, Singapore, Singapore; [8]Tan Tock Seng Hospital, Gastroenterology and Hepatology, Singapore, Singapore; [9]Global Hospital – Super Speciality and Transplant Center, Department of Hepatology, Mumbai, India; [10]Liver & Digestive Diseases Institute (FELDI), Hepatology & Liver Transplant (Medicine), New Delhi, India; [11]Artemis Health Institute, Artemis Centre of Excellence for Digestive and Liver Diseases, Gurgaon, India; [12]Surat Institute of Digestive Sciences, SIDS, Gastroenterology, Surat, India; [13]Seth GSMC & KEM Hospital, Department of Gastroenterology, Mumbai, India; [14]Christian Medical College, Dept of Hepatology, Vellore, India; [15]Christian Medical College, Department of Clinical Virology, Vellore, India; [16]Kailashi Superspeciality Hospital, Department of Gastroenterology, Meerut, India; [17]Lakeshore Hospital, Research & Hepatology, Kochi, India; [18]Siriraj Hospital, Faculty of Medicine, Bangkok, Thailand; [19]Sime Darby Medical Centre, Subang Jaya, Malaysia; [20]Hospital Tengku Ampuan Afzan, Kuantan, Malaysia; [21]Hospital Ampang, Kuala Lumpur, Malaysia; [22]University of Malaya Medical Centre, Kuala Lumpur, Malaysia; [23]Hospital Raja Perempuan Zainab II, Kota Bharu, Malaysia*
Email: mdclimsg@nus.edu.sg

Background and Aims: There is a paucity of information on direct antiviral agents (DAA) HCV therapy in Asia, hence we evaluated such patients from prospectively collected databases in Asian countries with approved DAA regimens.
Method: Asia-Pacific physicians were invited to participate and the following data were collated from their database of patients enrolled for therapy of HCV. Treatment with DAA included: sofosbuvir + ribavirin (SR), sofosbuvir, pegylated interferon + ribavirin (SPR),

sofosbuvir, ledispasvir ± ribavirin (SL ± R), sofosbuvir, daclatasvir ± ribavirin (SD ± R), ombatisvir, parateprevir, dasubuvir ± ribavirin (3D ± R). Baseline clinical, virological and biochemical characteristics, sustained virological response at week 12 (SVR12), and virologic failure were collected. SVR12 outcome was based on intention-to-treat. Multivariate analysis was used to assess independent risk factors for SVR12 using SPSS version 20.

Results: A total of 2,171 patients were evaluated from India (n = 977), Myanmar (n = 552), Pakistan (n = 406), Thailand (n = 139), Singapore (n = 72) and Malaysia (n = 25). Baseline features were a mean age of 49 years, 50% were male and 41.8% had cirrhosis. Overall SVR12 was 89.5% and based on genotype (GT) was 91% for GT1, 100% GT2, 91% GT3, 64% GT4, 87% GT6, and 79% in those not tested. Virologic failure based on GT was 4% GT1, 0% GT2, 3% GT3, 4% GT4, 13% GT6 and 8% in GT not tested. Patients with cirrhosis had lower SVR12 than non-cirrhotics (85% vs 93%, $p < 0.001$). Patients with GT1 and 3 treated with sofosbuvir/ribavirin (SR) had 88% and 89% SVR12 respectively but those GT6 treated with sofosbuvir/ledipasvir (SL) had only 77.6% SVR12. Multivariate analysis showed that absence of cirrhosis was associated with higher SVR12.

Conclusion: Patients with GT1 and 3 with and without cirrhosis had surprisingly high efficacy using SR which is not recommended suggesting that Asians may respond better to some DAAs. However, poor GT6 response to SL suggests this regimen may be suboptimal for this genotype.

THU-335

A comparison of elbasvir/grazoprevir, ledispasvir/sofosbuvir and velpatisvir/sofosbuvir therapy among people who use drugs (PWUD): real world experience

A. Alimohammadi, J. Holeksa, Y. Bhutani, A. Thiam, A. Bassi, B. Conway
. *Vancouver Infectious Diases Centre, Vancouver, Canada*
Email: arshia.alimohammadi@vidc.ca

Background and Aim: Up to 70 million people are infected with Hepatitis C virus (HCV) worldwide, including more than 240,000 Canadians, over 50% of whom are PWUD. To meet the World Health Organization (WHO) goals for the elimination of HCV as a public health concern by 2030, specific outreach programs will be needed to engage vulnerable populations with a high prevalence of HCV infection, such as PWUD. The most prescribed regimens in Canada include elbasvir/grazoprevir (E/G), ledipasvir/sofosbuvir (L/S) and velpatasvir/sofosbuvir (V/S). While clinical trials have highlighted the efficacy of these regimens, real world data is required to confirm these results, especially among PWUD.

Methods: A retrospective analysis was performed on all HCV-infected PWUD (positive urine drug screen in previous month) initiating HCV treatment (rx) at our centre between 06/15–10/17. All subjects were enrolled in a multidisciplinary model of care, addressing medical, psychologic, social and addiction-related needs. The primary outcome was achievement of SVR12 (undetectable HCV RNA 12 or more weeks after the completion of HCV therapy). A secondary outcome was maintenance of SVR in long-term follow-up in subjects with ongoing risk behaviors for recurrent viremia.

Results: A total of 148 eligible individuals (all active PWUD, 66% heroin/58% cocaine) have initiated therapy with one of E/G, L/S, or V/S. The E/G cohort (n = 39) includes 6 HIV+, 18 on opiate substitution therapy (OST), 31 Rx naïve, 21 GT1a, 7 GT3a, 4 cirrhotic. To date, 29/31 achieved SVR12, with no virologic failures (2 LTFU). One LTFU individual took E/G for 2 weeks, reintegrated care and achieved SVR12. The L/S cohort (n = 64) includes 7 HIV+, 6 on OST, 36 Rx naïve, 43 GT1a, 19 cirrhotic. To date, 49/55 achieved SVR12, with 2 virologic relapses, 4 LTFU, one unrelated opioid overdose death. The V/S cohort (n = 45) includes 6 HIV+, 13 on OST, 30 Rx naïve, 9 GT1a, 23 GT3a, 10 cirrhotic. To date, 12/12 achieved SVR12. Of the 50 individuals not having reached the SVR12 time point, all remain in follow-up at our centre.

Conclusion: Currently prescribed all-oral HCV treatment regimens appear to be highly and equally effective in a real world PWUD cohort. This provides support for expanded access to HCV treatment, even in the setting of active drug use. Pending complete and ongoing follow-up in this important cohort, health care providers have three excellent options to provide HCV treatment to PWUD engaged in care, in support of the WHO's global elimination targets.

THU-336

Real world experience of retreatment of chronic hepatitis C patients who failed IFN-free DAA therapy

K. Kozbial[1], R. Al-Zoairy[2], B. Schaefer[2], M. Gschwantler[3], R.E. Stauber[4], S. Hametner[5], A. Maieron[6,7], H. Laferl[8], M. Strasser[9], A. Hayat-Khayyati[10], C. Datz[11], L. Kramer[12], I. Graziadei[13], A. Stättermayer[1], S. Beinhardt[1], P. Munda[1], H. Zoller[14], M. Trauner[1], H. Hofer[1,15], P. Ferenci[1]. *[1]Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; [2]Medical University Innsbruck, Dept. of Internal Medicine I, Innsbruck, Austria; [3]Wilhelminenspital, Department of Internal Medicine IV, Vienna, Austria; [4]Institute of Pathology, Graz, Austria; [5]Ordensklinikum Linz, Internal Medicine IV, Linz, Austria; [6]University Clinics St. Pölten, Department of Internal Medicine II; [7]Ordensklinikum Linz, Department of Internal Medicine IV; [8]Kaiser-Franz-Josef-Spital, Department of Internal Medicine, Vienna, Austria; [9]Paracelsus Medical University, Department of Internal Medicine I; [10]Kepler University Clinics, Department of Internal Medicine II, Linz, Austria; [11]Krankenhaus Oberndorf, Department of Internal Medicine, Austria; [12]Krankenhaus Hietzing, Department of Gastroenterology; Austria, [13]Landeskrankenhaus Hall, Department of Internal Medicine, Austria; [14]Medical University Innsbruck, Dept. of Internal Medicine I; Austria, [15]Klinikum Wels-Grieskirchen, Department of Internal Medicine I, Austria*
Email: karin.kozbial@meduniwien.ac.at

Background and Aims: Only few chronic hepatitis C patients treated with interferon-free DAA combinations fail to clear the virus. In this study we summarize our "real world" experience of retreating these patients in Austria.

Method: One hundred and one HCV monoinfected patients (80 male; GT1a:28, GT1b:36; GT1:5, GT2:3, GT3:26, GT4:3; IL28 non-C/C:34/41; therapy experienced:31/58; cirrhosis:57) failed IFN-free DAA therapy (98 relapsers, 3 nonresponders). These account for about 3% of DAA-treated patients in the participating centers. Drugs for the first treatment were prescribed according to availability and funding: ombitasvir/paritaprevir/dasabuvir (3D) ± ribavirin(RBV):24; ombitasvir/paritaprevir (2D):1; sofosbuvir(SOF)/daclatasvir(DCV) ± RBV:14; SOF/Ledipasvir(LDV) ± RBV:29; SOF/Velpatasvir(VEL):2; SOF/Simeprevir(SMV):10; SOF/RBV:18; Elbasvir/Grazoprevir(EG):3. Treatment duration and addition of RBV were at the discretion of the treating physician. For retreatment patients who had failed a SOF-free regimen received a SOF-containing regimen, those without a NS5A-inhibitor a NS5A containing regimen, and those after SOF/NS5A received SOF/protease inhibitor ± other NS5A-inhibitor ± RBV.

Results: Currently 73 patients have finished a DAA-retherapy and 59 (81%) achieved SVR (3D ± RBV:15, 3D/SOF/RBV:2; 2D + RBV:1; SOF/DCV ± RBV:6; SOF/LDV ± RBV:14; SOF/SMV ± RBV:2; SOF/VEL ± RBV:13, EG ± RBV:6); 14 patients relapsed (GT1a:5,GT1b:3,GT3a:5; GT4:1; 10 cirrhotics; positive NS5A-, NS5B-, or NS3 RAS in 8/11; 3D ± RBV:4; SOF/DCV ± RBV:3; SOF/LDV ± RBV:3; SOF/VEL:2; SOF/SMV:2). Further 14 are on retreatment. In two nonresponders to the first DAA-therapy retesting of the genotype revealed a different genotype: GT3a instead of GT1a and a yet unclassified subtype close to 1c instead of GT1b, respectively. Resistance-associated substitutions (RAS) analyses were available in 51 patients. Overall 42/50 had RAS; 16 in NS3, 36 in NS5A, and 15 in NS5B.

Seven of the 14 relapsers have finished a 3rd treatment yet, 3 of them relapsed again (SOF/VEL/RBV:GT3a; SOF/LDV/RBV:GT1a; EG/SOF/RBV:GT1b; 2 cirrhotics; all had NS5A RAS). One of the relapsers to the 3rd therapy achieved SVR after 24 weeks of 3D/SOF/RBV (GT1a).
Conclusion: Most DAA failures retreated with a different regimen achieved SVR, however, few patients failed multiple treatment attempts. Their treatment will require combination of existing DAAs with new antivirals. Presence of cirrhosis and IL28-T allele appear to be associated with primary DAA-failure.

THU-337

Safety and effectiveness comparing generic and original sofosbuvir-based treatment regimens in patients with hepatitis C: A prospective multicenter study from Argentina

E. Ridruejo[1,2], M. Mendizabal[3], F. Piñero[3], C. Alonso[3], A. Palazzo[4], M. Sixto[5], S. Ceballos[6], C. Gadea[4], D. Perez[4], M.V. Reggiardo[7], V. Moreno[6], S.E. Mengarelli[6], A. Bruno[8], C. Mendoza[9], J. Vila[10], F. Barreyro[11], M.G.V. Zuain[12], N. Ratusnu[13], M. Silva[3]. *[1]Hospital Universitario Austral, Hepatology and Liver Transplant Unit; [2]Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC"., Hepatology Section, Department of Medicine; [3]Hospital Universitario Austral, Hepatology and Liver Transplant Unit, Pilar; [4]Hospital Padilla, Tucuman, Argentina; [5]Hospital Santa Fe, Santa Fe, Argentina; [6]Hospital San Roque, Argentina; [7]Hospital Centenario, Rosario, Argentina; [8]Hospital Dr Cosme Argerich, Buenos Aires; [9]Hospital Rio Cuarto, Rio Cuarto, Argentina; [10]Hospital Corrientes, Corrientes, Argentina; [11]Hospital Posadas, Posadas, Argentina; [12]OSECAC, Buenos Aires, Argentina; [13]Hospital Tierra del Fuego, Usuahia, Argentina*
Email: fpinerof@cas.austral.edu.ar

Background and Aims: A major limitation to the wide use of HCV direct acting antivirals (DAAs) in developing countries is its high cost. Generic versions of sofosbuvir are available in Argentina since 2016. Our aim was to evaluate effectiveness, safety, and post-treatment decompensation episodes in patients treated in real-life setting with generic sofosbuvir (G-SOF) or original SOF (O-SOF).
Method: A prospective multicenter cohort from the Latin American Liver Research Educational and Awareness Network (LALREAN) was analyzed. We included patients from Argentina who received either O-SOF or G-SOF in combination with daclatasvir for 12 or 24 weeks with or without ribavirin (RBV) according to international guidelines. SOF type was assigned by payers and not by physicians.
Results: From a total of 378 patients treated with DAAs, 191 patients received SOF-DCV regimen. Baseline characteristics and outcomes are in Table 1. Only 3 (1.6%) patients presented treatment failure, all of them received G-SOF. Median follow-up since the end of treatment was 10.6 weeks and 13.1 weeks in the G-SOF and in the O-SOF, respectively (p = 0.01). During post-SVR12 follow-up 1 patient developed ascites, 2 patients encephalopathy and 1 patient variceal bleeding in the G-SOF group, while in the O-SOF group only 1 patient presented ascites (p = NS). One out of 11 and 2 out of 5 patients were delisted in the G-SOF and the O-SOF groups, respectively (p = NS). One patient in the G-SOF group and 2 patients in the O-SOF group developed de-novo HCC. No major adverse events occurred requiring treatment discontinuation.

Table 1:

	Original-SOF (n = 101)	Generic-SOF (90)	P
Male sex (%)	59	48	0.13
Age (mean, yrs)	53	58	0.02
Cirrhosis (%)	70	61	0.34
GT1, 2, 3 (%)	57/8/14	62/19/9	0.4
SVR12, (%)	100	96	0.240
With RBV (%)	42	37	0.14
Any adverse event (%)	16	23	0.22

Conclusion: Although generic and original SOF presented similar safety and effectiveness, SVR12 was slightly superior in the O-SOF group. Post-treatment decompensation events were more frequent among those treated with G-SOF despite the fact they were followed for a shorter period of time. To confirm our results, larger cohorts and longer pharmacovigilance studies are need.

THU-338

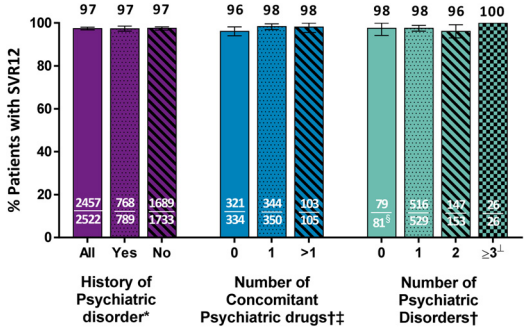
Integrated efficacy and safety of glecaprevir/pibrentasvir in patients with psychiatric disorders

D. Back[1], P. Belperio[2], M. Bondin[3], F. Negro[4], A. Talal[5], C. Park[3], Y. Lei[3], E. Crown[3], F. Mensa[3], F. Marra[1]. *[1]University of Liverpool, Liverpool, United Kingdom; [2]U.S. Department of Veterans Affairs, VA Palo Alto Healthcare System, Palo Alto, United States; [3]AbbVie, Inc., North Chicago, United States; [4]University of Geneva, Geneva, Switzerland; [5]University of Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, United States*
Email: d.j.back@liverpool.ac.uk

Background and Aims: The once daily combination of glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor; coformulated as G/P) demonstrated sustained virologic response rate at post-treatment week 12 (SVR12) of ≥97% across HCV genotypes 1 through 6 and a favourable safety profile in clinical studies. The prevalence rates of psychiatric illness in patients with HCV infection are higher than those rates in the general US population. Herein we report the integrated efficacy and safety of G/P from ten Phase 2 and 3 studies in patients with psychiatric disorders.
Method: Data were pooled from SURVEYOR-I and -II, MAGELLAN-I, ENDURANCE-1, -2, -3, and -4, and EXPEDITION-1, -2 and -4 studies. Treatment-naive and -experienced patients were classified as having a psychiatric disorder if they were taking a psychiatric medication at the time of G/P initiation or had a medical history of a psychiatric disorder. Efficacy was assessed as the percent of patients achieving SVR12 (HCV RNA <lower limit of quantification) using an intent-to-treat analysis. Safety was assessed in all patients.
Results: Of the 2,522 HCV-infected patients included, 789 (31%) had a psychiatric disorder. Baseline characteristics are outlined in Table 1. SVR12 by history of psychiatric disorder and number of concomitant CNS medications/psychiatric disorders are reported in Figure 1. Overall, G/P was well-tolerated in patients with psychiatric disorders with no DAA-related serious adverse events (0/789) and <1% (5/789) adverse events leading to discontinuation of G/P.

Table 1: Baseline Characteristics

Characteristic, n (%)	Psychiatric disorder N = 789	No Psychiatric disorder N = 1,733
Male	403 (51)	1,043 (60)
White	685 (87)	1,344 (77)
Age < 65	703 (89)	1,489 (86)
Treatment naïve	568 (72)	1,197 (69)
Baseline HCV RNA ≥ 1 million	489 (62)	1010 (58)
Compensated Cirrhosis	124 (16)	200 (12)
Diagnosed Psychiatric Disorders ≥5% of patients, n (%)		
Depression	506 (64)	N/A
Anxiety	216 (27)	N/A
Bipolar Disorder	57 (7)	N/A
Concomitant CNS drug use in ≥10% of patients by class, n (%)		
Antidepressants	396 (50)	N/A
Opioids	272 (34)	221 (13)
Anxiolytics	244 (31)	74 (4)
Antiepileptic	217 (28)	69 (4)
Hypnotics and sedatives	159 (20)	98 (6)
Antipsychotics	117 (15)	N/A
Drugs used in addictive disorders	116 (15)	98 (6)



*Patients treated for or diagnosed with a CNS psychiatric disorder

†Only includes patients with History of Psychiatric Disorders

‡Concomitant psychiatric drug were allowed in studies except for carbamazepine, phenytoin, pentobarbital, phenobarbital, and primidone

§Patients did not have a clinical diagnosis of a psychiatric disorder, but were taking at least one concomitant psychiatric drug

⊥Includes n = 25 patients with 3 diagnoses and n = 1 patient with 4

Conclusion: Use of G/P in chronic HCV genotype 1–6 infected patients who were either receiving concomitant CNS drugs or had a history of a psychiatric disorder was well-tolerated and achieved high SVR12 rates.

THU-339

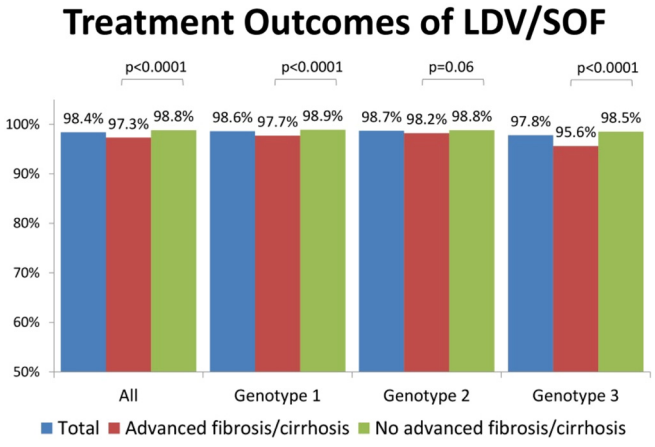
Real world effectiveness of Ledipasvir/Sofosbuvir based regimens in hepatitis C virus genotype 1,2 and 3 infection within national hepatitis C elimination program in the country of Georgia

T. Tsertsvadze[1,2], N. Chkhartishvili[1], A. Abutidze[1], L. Sharvadze[3,4], V. Kerashvili[1], M. Butsashvili[5], J. Zarkua[6], B. Skaggs[7], L. Gvinjilia[8], S. Shadaker[9], M. Nasrullah[10], A. Gamkrelidze[11], V. Kvaratskhelia[12], N. Afdhal[13], S. Zeuzem[14], S. Arora[15], K. Thornton[15], F. Averhoff[10]. *[1]Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia; [2]Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia; [3]Ivane Javakhishvili Tbilisi State University, Tbilisi; [4]Hepatology clinic HEPA, Tbilisi, Georgia; [5]Health Research Union, Tbilisi, Georgia; [6]Medical Center Mrcheveli, Tbilisi, Georgia; [7]South Caucasus Office of the U.S. Centers for Disease Control (CDC), Tbilisi, Georgia; [8]CDC Foundation, Tbilisi, Georgia; [9]CDC Foundation, Atlanta, Georgia; [10]Centers for Disease Control and Prevention, Atlanta, United States; [11]National Center for Disease Control and Public Health, Tbilisi, Georgia; [12]Ministry of labour, health and social affairs of Georgia, Tbilisi, Georgia; [13]Beth Israel Deaconess Medical Center Liver Center, Boston, United States; [14]University of Frankfurt, Department of Medicine, Frankfurt, Germany; [15]University of New Mexico, Albuquerque, United States*
Email: tengizt@gol.ge

Background and Aims: Ledipasvir/sofosbuvir (LDV/SOF) is currently approved for the treatment of HCV genotypes 1 and 4. However data on its effectiveness in genotype 2 and 3 infection are limited. In April 2015, the country of Georgia, with the support of U.S. CDC and Gilead Sciences, launched a national hepatitis C elimination program. LDV/SOF was recommended for HCV genotypes 2 and 3 as well within the program. We report on real-world effectiveness of LDV/SOF-based regimens for various genotypes in Georgia.

Method: Data for analysis were extracted from the hepatitis C elimination program treatment database. The study included 20,066 treatment-naïve and treatment-experienced patients with HCV genotypes 1, 2 and 3, who completed treatment and were assessed for sustained virologic response (SVR) by April 30, 2017. Genotype 1 patients received LDV/SOF alone or in combination with ribavirin (RBV) based on condition of a patient, while all genotype 2 and 3 patients received LDV/SOF in combination with RBV. Advanced fibrosis/cirrhosis was defined as F ≥ 3 by Metavir score based on elastography and/or Fib-4 score >3.25.

Results: Among 20,066 patients included in the analysis, 9,468 (47.2%) patients had genotype 1, 4,580 (22.8%) had genotype 2, and 6,018 (30.0%) had genotype 3. Of 20,066 patients 5,073 (25.3%) persons had advanced fibrosis/cirrhosis. Overall SVR rate was 98.4% (19742/20066), including 98.6% (9,335/9,468) in genotype 1, 98.7% (4,519/4,580) in genotype 2 and 97.8% (5,888/6,018) in genotype 3. Overall, 97.3% (4,935/5,073) of patients with advanced fibrosis/cirrhosis achieved SVR vs. 98.8% (14,635/14,816) of patients without advanced fibrosis/cirrhosis ($p < 0.0001$). Difference in SVR by advanced fibrosis/cirrhosis status was statistically significant in genotype 1 ($p < 0.0001$) and genotype 3 ($p < 0.0001$). In genotype 2 patients 98.2% of patients with advanced fibrosis/cirrhosis achieved SVR compared to 98.8% among patients with no advanced fibrosis/cirrhosis ($p = 0.06$). SVR rate among patients who failed prior SOF-based regimens was 93.7% (443/473).



Conclusion: LDV/SOF-based treatment was highly effective in this real-world cohort, including among patients with advanced disease and in whom previous SOF-based therapy failed. High cure rates were observed in all genotypes. Combination of LDV/SOF/RBV appears to be an effective treatment option for genotype 2 and 3 infections at least in Georgian settings.

THU-340

Effectiveness of sofosbuvir and ledipasvir/sofosbuvir based regimens in hepatitis C virus genotype 3 infection: real-world data from Georgian hepatitis C elimination program

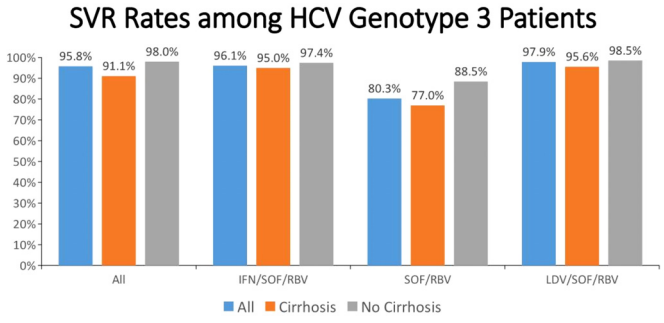
T. Tsertsvadze[1,2], N. Chkhartishvili[1], A. Abutidze[1], L. Sharvadze[2,3], V. Kerashvili[1], G. Kamkamidze[4], M. Zakalashvili[5], B. Skaggs[6], L. Gvinjilia[7], S. Shadaker[7], M. Nasrullah[8], A. Gamkrelidze[9], V. Kvaratskhelia[10], S. Zeuzem[11], N. Afdhal[12], S. Arora[13], K. Thornton[13], F. Averhoff[14]. *[1]Infectious Diseases, AIDS and Clinical Immunology Research Center, Tbilisi, Georgia; [2]Ivane Javakhishvili Tbilisi State University, Tbilisi, Georgia; [3]Hepatology clinic HEPA, Tbilisi, Georgia; [4]Health Research Union, Tbilisi, Georgia; [5]Medical Center Mrcheveli, Tbilisi, Georgia; [6]South Caucasus Office of the U.S. Centers for Disease Control (CDC), Tbilisi, Georgia; [7]CDC Foundation, Tbilisi, Georgia; [8]Centers for Disease Control and Prevention, Atlanta, United States; [9]National Center for Disease Control and Public Health, Tbilisi, Georgia; [10]Ministry of labour, health and social affairs of Georgia, Tbilisi, Georgia; [11]Goethe University Hospital, Frankfurt am Main, Germany; [12]Beth Israel Deaconess Medical Center Liver Center, Boston, United States; [13]University of New Mexico, Albuquerque, United States; [14]Centers for Disease Control and Prevention, Atlanta, United States*
Email: tengizt@gol.ge

Background and Aims: HCV genotype 3, which is considered as the most difficult to treat, accounts for 34% of all HCV infections in the country of Georgia. In April 2015 in collaboration with US CDC and commitment from Gilead Sciences to donate direct acting antivirals (DAAs) Georgia launched the world first national hepatitis C elimination program. The aim of this study was to evaluate the effectiveness of sofosbuvir (SOF)-based and ledipasvir/sofosbuvir

(LDV/SOF)-based regimens among HCV genotype 3 patients treated within the Georgian elimination program.

Method: Data were obtained from the Georgia's hepatitis C elimination program treatment database. SOF was prescribed either in combination with pegylated interferon (IFN) and ribavirin (RBV), or only with RBV. LDV/SOF plus RBV became recommended regimen for HCV Genotype 3 in Georgia. Analysis included 7,857 HCV genotype 3 patients who completed treatment and were assessed for sustained virologic response (SVR) by April 30, 2017. Advanced fibrosis/cirrhosis was defined as F ≥ 3 by METAVIR score based on elastography and/or FIB-4 score >3.25.

Results: Of 7,857 patients included 2,428 (30.9%) had advanced fibrosis/cirrhosis, 1143 (14.5%) received IFN/SOF/RBV for 12 weeks, 807 (10.3%) received SOF/RBV for 24 weeks and 5907 (75.2%) received LDV/SOF/RBV for either 12 or 24 weeks. The IFN/SOF/RBV arm had an overall SVR rate of 96.1% (1099/1143) and this regimen was more effective in patients with no advanced fibrosis/cirrhosis versus patients with advanced fibrosis/cirrhosis (97.4% vs. 95.0%, p = 0.04). SOF/RBV achieved SVR in 80.3% (648/807) of patients, with higher rates also observed in patients without advanced fibrosis/cirrhosis (88.5% vs.77.0%, p < 0.0001). Patients receiving LDV/SOF/RBV achieved SVR rate of 97.9% (5783/5907) with higher cure rate among patients without advanced fibrosis/cirrhosis vs. patients with advanced fibrosis/cirrhosis (98.5% vs. 95.6%, p < 0.0001). IFN and LDV/SOF based regimens were more effective than SOF/RBV in both patients with or without advanced fibrosis/cirrhosis (p < 0.001). LDV/SOF/RBV arm achieved higher cure rate compared to patients receiving IFN/SOF/RBV (p = 0.0004).



Conclusion: Overall SVR in genotype 3 patients was up to 98% in LDV/SOF/RBV regimens, which was more effective than SOF/RBV (80% SVR) and IFN/SOF/RBV (96% SVR) in Georgia. LDV/SOF and RBV may be considered as effective treatment option for HCV genotype 3 infection even in patients with advanced disease.

THU-341

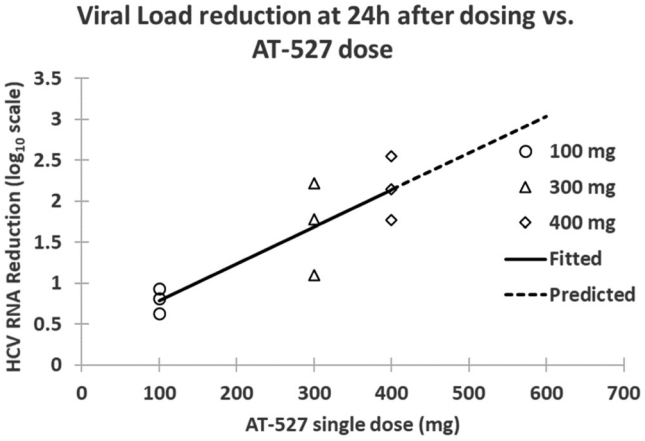
AT-527, a pan-genotypic purine nucleotideprodrug, exhibits potent antiviral activity in subjects with chronic hepatitis C

X.-J. Zhou[1], E. Berliba[2], F. Vanhoutte[3], M. Bogus[2], P.-J. Berghmans[3], K. Pietropaolo[1], S. Good[1], A. Moussa[1], R. Murphy[4], J.-P. Sommadossi[1]. [1]*Atea Pharmaceuticals, Inc., Boston, United States;* [2]*ARENSIA Exploratory Medicine, Chisinau, Moldova;* [3]*SGS Life Sciences, Antwerpen, Belgium;* [4]*North Western University, Department of Infectious Diseases, Chicago, United States*

Email: zhou.xj@ateapharma.com

Background and Aims: AT-527 is a novel purine nucleotide NS5B polymerase inhibitor currently in clinical development for treatment of chronic hepatitis C virus (HCV) infection. AT-527 possesses a favourable and highly differentiated antiviral profile compared to sofosbuvir (SOF). AT-511, the free base of AT-527, showed potent pan-genotypic antiviral activity *in vitro* against wild-type clinical isolates with EC_{95} <80 nM, which is 4- to 14-fold more potent than SOF. Moreover, AT-511 maintained antiviral activity against SOF-resistant S282T single and S282T/L159F double variants with approximately 50-fold greater potency than SOF.

Method: This is an ongoing multiple part study evaluating AT-527 in single ascending doses up to 400 mg in healthy subjects with embedded food effect at 200 mg (Part A), escalating single doses up to 600 mg in HCV-infected subjects (Part B), and escalating multiple doses up to 150, 300 and 600 mg/day (QD) for 7 days in HCV-infected subjects (Part C). Safety is assessed via adverse events (AEs), vital signs, electrocardiograms (ECGs) and standard safety laboratory tests. Plasma levels of AT-511 and its nucleoside metabolite AT-273 are measured using LC-MS/MS. HCV RNA is quantified using COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 with a LLQ of 15 IU/ml.



Results: At abstract submission, Part A was complete, Part B was complete through 400 mg, and dosing of 150 mg QD × 7 days in Part C was initiated. AT-527 exhibited comparable pharmacokinetics between healthy and HCV-infected subjects. Food had no major impact on plasma exposure of AT-273, the nucleoside metabolite representative of intracellular active triphosphate. After a single dose in GT 1b HCV-infected subjects, potent and dose-related antiviral activity was obtained: mean maximum plasma viral load reduction was 0.8, 1.7 and 2.2 $\log_{10}$ IU/ml for 100, 300 and 400 mg, respectively. Dose-response analysis suggests that viral load reduction ≥ 2.5 $\log_{10}$ IU/mL is achievable with a single dose up to 600 mg (Fig. 1). No SAEs or discontinuations were reported. The most common AE has been mild or moderate headache. No dose-related trends for laboratory parameters, vital signs or ECGs were observed.

Conclusion: AT-527 has been well-tolerated after single doses in healthy and HCV-infected subjects. Single doses resulted in potent dose-related antiviral activity, implying even greater viral suppression in the ongoing 7-day dosing cohorts.

THU-342

Impact of treatment with Elbasvir and Grazoprevir on chronic hepatitis C virus disease specific health related quality of life outcomes in HCV/HIV coinfected patients

D. Serrano[1], C. Nwankwo[2], H.L. Platt[2], S. Klopfer[2], M. Shaughnessy[2], J.M. Arduino[2]. [1]*Pharmerit International;* [2]*Merck & Co., Inc., United States*

Email: chizoba.nwankwo@merck.com

Background and Aims: Hepatitis C progresses more quickly in patients with HIV infection than in patients without HIV. In addition, HRQoL is diminished in HCV/HIV coinfected patients compared to HIV mono-infected patients. The aim of this study was to investigate the relationship between treatment of coinfected HCV/HIV patients with Elbasvir and Grazoprevir (EBR/GZR) and time-dependent mean change in Health Related Quality of Life (HRQoL).

Methods: The analysis was conducted using data from the C-EDGE Coinfection study, a Phase III, single-arm, multi-center, open-label clinical trial which evaluated the efficacy and safety of EBR/GZR

therapy, among treatment-naïve chronic HCV GT1, GT4, or GT6 patients coinfected with HIV. All subjects received the fixed-dose combination of EBR/GZR for 12 weeks. Chronic HCV disease specific HRQoL was measured by the Chronic Liver Disease Questionnaire-Hepatitis C Virus (CLDQ-HCV) which was completed at baseline, during the treatment period at Treatment Week (TW)4, and TW12, and in post-treatment follow-up at Follow-up Week (FW)12, and FW24. The full analysis set (FAS) population was the primary population within which efficacy, safety, and HRQoL outcomes were assessed.

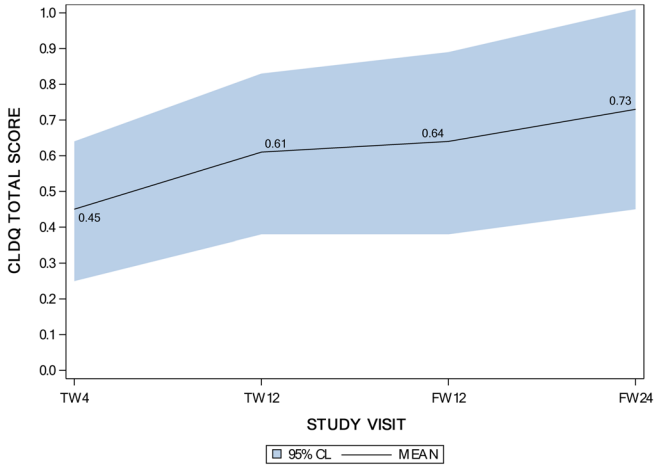


Figure 1: Mean change from baseline in CLDQ total score over time.

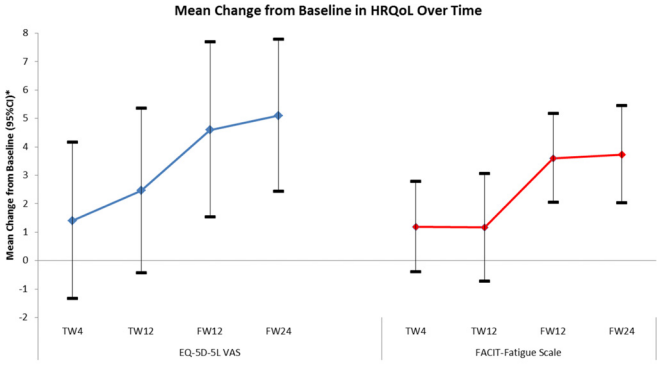
Results: 218 subjects were enrolled into the FAS, and 216 subjects completed the study. Among the FAS population, treatment efficacy for the SVR12 endpoint was 95% (207/218). Change from baseline for the CLDQ-HCV total score demonstrated significant 15% improvement ($p < 0.05$) for all follow-up periods (Figure 1). This was also true for all CLDQ-HCV sub scores. Improvement from baseline to 24-week follow-up was 14% for the Activity/Energy domain, 13% of the Emotion domain, 18.5% for the Worry domain, and 13% for the Systemic domain.
Conclusion: EBR/GZR combination therapy significantly improves HRQoL among treatment naïve coinfected HCV/HIV patients.

THU-343

C-EDGE treatment experienced: Effect of 12 week oral regimens of Elbasvir and Grazoprevir on health related quality of life in prior treatment experienced patients with chronic hepatitis C infection

C. Nwankwo[1], D. Serrano[2], B. Haber[1], P. Hwang[1], W. Li[1], L. Lin[1], J.M. Arduino[1]. [1]*Merck & Co., Inc., United States;* [2]*Pharmerit International, United States*
Email: chizoba.nwankwo@merck.com

Background and Aims: Chronic HCV infection is a major health burden and decreases quality of life HRQoL among those affected with the disease. The aim of this study was to describe the changes in HRQoL amongst prior TE patients with Chronic HCV.
Method: The analysis was conducted using patient reported outcomes (PRO) data collected from participants treated with Elbasvir and Grazoprevir (EBR/GZR) for 12 weeks with/without ribavirin (RBV) as part of the C-EDGE treatment experienced (TE) study which was a Phase III, randomized, parallel-group, multi-site, open-label trial of EBR (50 mg)/GZR (100 mg) with/without RBV in participants with chronic HCV genotypes 1, 4, or 6, who had previously failed treatment with Pegylated interferon and RBV. Participants were randomized 1:1:1:1 to 12 or 16 weeks of EBR/GZR with or without RBV. Changes in fatigue and overall general health were measured by the FACIT-Fatigue Scale and EQ-5D-5L VAS with PRO data collected at baseline, Treatment Week (TW) 4, TW12, Follow-up Week (FW) 12 and FW24.
Results: 209 participants were treated for 12 weeks: 105 with EBR/GZR only and 104 with EBR/GZR + RBV. SVR12 was achieved in greater than 90% of participants, in each cohort. At FW24 there was a 9% and 3% improvement from baseline FACIT-Fatigue scores amongst participants receiving EBR/GZR and EBR/GZR + RBV respectively. On average a 6% and 4% improvement in general health as measured by the EQ-5D-5L VAS was also observed amongst participants receiving EBR/GZR and EBR/GZR + RBV respectively between baseline and FW24. These improvements in HRQoL were also observed during treatment in participants treated with EBR/GZR (Figure) but not in participants treated with EBR/GZR + RBV, although in this cohort HRQoL improved to above baseline by FW12 and FW24.



*<0: worst health status, ≥0: same or better health status.

Conclusion: Overall, EBR/GZR regimens had a favourable impact on the HRQoL of participants after 12 weeks of treatment as demonstrated by higher PRO scores at FW24 relative to baseline.

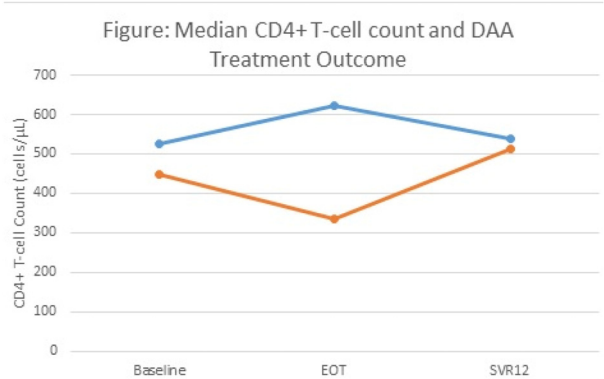
THU-344

Impact of CD4+ T-cell count on sustained virologic response to direct-acting antivirals in HIV-negative cancer patients with chronic hepatitis C

H. Pritchard[1,2], G. Angelidakis[2], Y. Jiang[2], H. Torres[2,3]. [1]*Baylor College of Medicine, Department of Medicine, Division of Infectious Diseases, Houston, United States;* [2]*University of Texas MD Anderson Cancer Center, Department of Infectious Disease, Infection Control, and Employee Health;* [3]*University of Texas MD Anderson Cancer Center, Department of Gastroenterology, Hepatology, and Nutrition*
Email: htorres@mdanderson.org

Background and Aims: Factors associated with failure of direct-acting antivirals (DAAs) for treatment of hepatitis C (HCV) include cirrhosis, hepatocellular carcinoma (HCC), and HCV genotype 3 (HCV3) infection. Clinical trials using DAAs in HCV-HIV co-infected patients typically exclude patients with CD4+ T-cell count <100 cells/µl. We have previously shown that DAAs have equivalent safety and efficacy in cancer patients with chronic HCV compared to non-cancer patients; however to identify new risk factors for DAA failure, we evaluated the impact of CD4+ T-cell count on treatment outcomes in HCV-monoinfected cancer patients.
Method: HCV-infected cancer patients treated with DAAs between January 2014 and August 2017 were enrolled in an ongoing prospective observational study. CD4+ T-cell count was measured by flow cytometry at baseline, end of treatment (EOT), and at 12 weeks after EOT (sustained virologic response or SVR12). We evaluated demographics, HCV genotype, type of malignancy, presence of cirrhosis, and type of treatment (ribavirin-containing vs. non ribavirin-containing treatment regimens). Univariate and multivariate analyses were performed to determine impact of CD4+ T-cell count on SVR.

Results: 138 patients were included in the analysis. All were treated with DAAs either with (35/138, 25.4%) or without ribavirin (103/138, 74.6%). Most (121/138, 88%) of patients achieved SVR12. Univariate analysis showed that cirrhosis ($p < 0.001$), HCC ($p < 0.0001$), HCV3 ($p = 0.027$), and history of prior HCV treatment with an interferon-based regimen or a DAA-based regimen ($p = 0.004$) were risk factors for treatment failure with a trend toward significance by African-American race ($p = 0.073$). A multivariate logistic regression model found that the odds ratio for failure was 15.4 for HCC ($p < 0.0001$), 5.4 for HCV3 ($p = 0.027$), and 6.5 for treatment-experienced patients ($p = 0.004$). There was no statistically significant difference in median CD4+ T-cell count at baseline, EOT, or SVR12 between the responder and treatment failure groups (Figure). There was a numeric difference in median CD4+ T-cell count at EOT, but it did not achieve significance ($p = 0.11$). Only 3 patients (2.2%) had a CD4 + T-cell count less than 100 cells/μl at baseline.



	Median CD4+ T-cell count (range)		
	Baseline[a]	EOT[b]	SVR12[c]
SVR12	525 (84-1557)	621 (55-1870)	539 (83-1925)
Failure	449 (78-1293)	335 (230-1147)	512 (83-774)

[a]p= 0.89, [b]p= 0.62, [c]p=0.52

Conclusion: CD4 T-cell count appears not to impact rates of SVR12 in HCV-monoinfected cancer patients receiving DAAs. Further studies with larger sample sizes are needed to characterize novel risk factors for DAA treatment failure in the immunocompromised population.

THU-345

The real-world safety and efficacy of sofosbuvir plus ribavirin for eldery patients over 75 years of age

H. Tamai[1], N. Shingaki[1], Y. Ida[2], R. Shimizu[2], S. Maeshima[2], J. Okamura[3], A. Kawashima[3], T. Nakao[3], T. Hara[4]. *[1]Wakayama Rosai Hospital, Department of Hepatology, Wakayama, Japan; [2]Wakayama Medical University, Second Department of Internal Medicine, Wakayama; [3]Naga Municipal Hospital, Department of Internal Medicine, Kinokawa, Japan; [4]Wakayama Rosai Hospital, Department of Gastroenterology, Wakayama, Japan*
Email: hdy-tamai@wakayamah.johas.go.jp

Background and Aims: In May 2015, the clinical use of combination therapy using sofosbuvir and ribavirin was first approved in Japan for patients infected with genotype 2 hepatitis C virus. This therapy was well tolerated and achieved a high SVR rate (96%) in a Japanese Phase III trial. However, patients aged older than 75 years old were excluded in the phase III trial. The present study aimed to evaluate the safety and efficacy of sofosbuvir plus ribavirin for elderly patients over 75 years old of age and to clarify whether extremely high sustained virological response (SVR) rate can be achieved even in a real-world setting.
Method: This was a multicenter prospective cohort study. Exclusion criteria were any of followings: (1) being infected with other genotypes other than genotype 2, (2) hemoglobin level <10 g/dl, (3) estimated glomerular filtration rate (eGFR) ml/min/1.73 m^2 < 30, (4) decompensated cirrhosis, (5) any form of cancer. Between June 2015 and May 2017, 225 patients were treated by standard doses of sofosbuvir (400 mg/day) plus ribavirin (1,000 mg/day for patients weighing more than 80 kg, 800 mg/day for patients weighing between 80 and 60 kg, and 600 mg/day for patients weighing less than 60 kg) for 12 weeks. The negativity of HCV-RNA at week 12 after the end of therapy was defined as SVR.
Results: Median age was 68 (17–86) years old. There were 128 male and 97 female patients. The SVR rates of overall, patients <65 years, patients ≥65 and <75 years, and patients ≥75 years were 97% (219/225), 99% (78/79), 96% (75/78), and 97% (66/68), respectively. The SVR rates of male, female, ineligible patients to interferon, cirrhotic patients, patients with anemia (hemoglobin level <12 g/dL), patients with moderate chronic kidney disease (eGFR < 60), patients with treatment failure of ribavirin and interferon, and patients with history of HCC treatment were 97% (124/128), 98% (95/97), 97% (174/180), 95% (81/85), 93% (28/30), 96% (44/46), 97% (32/33), and 89% (25/28), respectively. The SVR rate of patients with history of HCC treatment was significantly lower than that of other patients ($p < 0.05$). One patient (0.4%) discontinued treatment due to drug-induced pneumonia. Dose reduction or interruption of ribavirin was required in 29 (13%) patients because of anemia, and that appeared in 4% (3/79) of patients <65 years, in 13% (10/78) of patients ≥65 and < 75 years, and in 24% (16/68) of patients ≥75 years.
Conclusion: In a real-world setting, although ribavirin dose reduction or interruption was required along with advanced age, extremely high SVR rate was achieved even in elderly patients older than 75 years of age. When patients without severe anemia or renal failure are selected, sofosbuvir plus ribavirin would be safe and highly effective treatment irrespective of age. However, patients with history of HCC treatment may not be good candidates for this treatment.

THU-346

Sustained virologic response rates (SVR-12) for chronic hepatitis C genotype 6 patients treated with Ledipasvir/Sofosbuvir or Sofosbuvir/Velpatasvir

E. Nguyen[1], S. Trinh[2], H. Trinh[1], H. Nguyen[1], K. Nguyen[1], B. Levitt[1], M. Nguyen[1], T. Purohit[1], E. Shieh[1], M. Nguyen[2]. *[1]San Jose Gastroenterology, San Jose, United States; [2]Stanford University Medical Center, Division of Gastroenterology and Hepatology, Palo Alto, United States*
Email: mindiehn@stanford.edu

Background and Aims: Genotype 6 (GT 6) is a rare sub-type of hepatitis c (HCV). As such, GT 6 has been underrepresented in clinical trials using the new interferon and ribavirin free all oral acting agents (DAA's) to treat and cure HCV, limiting the generalization of the results. A newer DAA combination of sofosbuvir (SOF) and velpatasvir (VEL) was recently approved for treatment of HCV GT 6. The study aim was to compare sustained virologic response (SVR-12) rates between the first approved DAA ledipasvir (LDV)/SOF and SOF/VEL for treatment naive, cirrhotic, and non-cirrhotic GT6 patients.
Method: This was a retrospective study of consecutive adult patients with HCV GT 6 (n = 114) who were treated with LDV/SOF (n = 81) or SOF/VEL (n = 33) for 8–24 weeks from 2014–2017 in the United States. These patients were not in any previous clinical trials. One patient treated with LDV/SOF/RBV was included in the LDV/SOF group. After exclusion for patients with hepatocellular carcinoma (HCC) (n = 5) and/or prior treatment (n = 9), the LDV/SOF group had 58 patients and the SOF/VEL group had 28 patients. Among the HCC patients, all had cirrhosis with 4 patients in the LDV/SOF group.
Results: Overall, the mean age was 63.5 ± 9.9 years, with 47% male, 96% Vietnamese and 96.5% GT 6 and 3.5% GT 6c (all in the LDV/SOF group). The adverse events reported were headache (3.5%), fatigue (2.6%), insomnia (4.9%), or other (2.6%) (all in LDV/SOF group besides 1 patient who experienced fatigue in the SOF/VEL group). There was a higher percentage of cirrhotic patients (49.4%) in the LDV/SOF cohort

than the SOF/VEL cohort (15.2%, p < .001). Overall, 94.8% of LDV/SOF cohort obtained SVR-12 compared to 100% of the SOF/VEL cohort. Among the non-cirrhotic patients, 96.9% of LDV/SOF cohort achieved SVR-12 compared to 100% of the SOF/VEL cohort. Among patients with cirrhosis, 92.3% of the LDV/SOF achieved SVR-12 compared to 100% of the SOF/VEL cohort (Table).

	LDV/SOF	SOF/VEL
SVR12 for genotype 6 patients		
Treatment naïve overall	55/58 (94.8%)	28/28 (100.0%)
Treatment naïve & non cirrhotic	31/32 (96.9%)	25/25 (100.0%)
Treatment naïve & cirrhotic	24/26 (92.3%)	3/3 (100.0%)
Treatment experienced overall	4/5 (80.0%)	—

Conclusion: SOF/VEL achieved a SVR 12 rate of 100% for GT 6 patients though those treated with LDV/SOF also experienced >90% SVR-12 rate. Further research is needed to determine if the difference in SVR-12 outcomes was due to the higher number of cirrhotic patients in the LDV/SOF group, the presence of GT6c or other variables. Regardless, HCV GT 6 patients have excellent treatment options.

THU-347

Clinical and virological characteristics of DAA-experienced patients with chronic HCV infection treated with sofosbuvir/velpatasvir/voxilaprevir: results from the Frankfurt Resistance Database

J. Vermehren[1], J. Dietz[1], K.-H. Peiffer[1], S. Susser[1], S. Zeuzem[2], C. Sarrazin[1]. [1]*Universitätsklinikum Frankfurt, Frankfurt am Main, Germany;* [2]*University of Frankfurt, Department of Medicine, Frankfurt, Germany*
Email: johannes.vermehren@kgu.de

Background and Aims: Patients with chronic hepatitis C virus (HCV) infection who do not achieve a sustained virologic response following treatments with direct-acting antiviral agents (DAAs) have limited retreatment options. Combination therapy with sofosbuvir, velpatasvir, and voxilaprevir (SOF/VEL/VOX) is now approved for retreatment of patients in whom prior DAA therapy has failed. Our aim was to investigate the clinical and virological characteristics of patients retreated with SOF/VEL/VOX in a real-world setting.
Method: The Frankfurt Resistance Database was retrospectively searched for all patients with prior DAA treatment failure who were retreated with SOF/VEL/VOX as rescue therapy. Resistance testing was performed in all patients prior to starting rescue therapy. Resistance associated substitutions (RASs) were determined by means of population sequencing of the NS3, NS5A, and NS5B coding regions.
Results: A total of 27 patients (81% males; mean age, 57 years; 48% cirrhosis) with previous failure to direct-acting antiviral agents (DAAs) were started on SOF/VEL/VOX rescue therapy. Patients were infected with genotypes (GTs) 1a (n = 8), 1b (n = 5), 3 (n = 11), and 4 (n = 3). The majority of patients had previously received NS5A-based (n = 18) and NS5A plus NS3-based regimens (n = 8). Five patients had failed at least two different DAA regimens. Prior to starting VOX/VEL/SOF rescue therapy, 40% of GT1 patients had resistance-associated substitutions (RASs) in NS5A and 60% had RASs in at least two DAA targets. Ninety-one percent of GT3 patients had NS5A RASs (Y93H in all but one). End-of-treatment response was achieved in 9/9 GT1 patients (n = 4 with SVR4). SVR12 data will be presented at the meeting.
Conclusion: Our preliminary real-world data confirm that SOF/VEL/VOX is an effective rescue therapy in patients with prior DAA treatment failure despite the presence of high-level RASs and/or multiple previous DAA therapies.

THU-348

Are patients treated with direct antiviral agents for HCV infection at greater risk for extrahepatic malignancies?

T. Saadi, R. Kramskay, H. Sholy, A. Yaccob, V. Ben-Hakoun, E. Veitsman, J. Khoury. *Rambam Health Care Campus, Liver Unit, Haifa, Israel*
Email: t_saadi@rambam.health.gov.il

Background and Aims: Direct antiviral agents (DAAs) have become the treatment of choice for chronic hepatitis C virus (HCV). A safety concern was raised about a possible relationship between DDAs and hepatocellular carcinoma (HCC) development. It appears that development of de-novo HCC is unrelated; however, the recurrence of HCC is controversial. We report on seven patients who developed extra hepatic malignancies after treatment with DAAs.
Method: 292 patients were treated with DAAs in our unit between January 2015 and October 2017. 246 patients finished treatment. The most common regimen used was the combination of paritaprevir/ritonavir/ombitasvir with/without dasabuvir (PrOD). The most common genotype was G1b. Two patients had viral relapse, one had a breakthrough vermia, and one patient stopped treatment because of side effects. All were treated with a second treatment regimen. All patients achieved sustained viral response (SVR). Adverse events were recorded during treatment and after finishing treatment. Efficacy was determined by assessment of serum HCV RNA.
Results: We observed unexpected development of extrahepatic malignancies in seven patients (2.4%): Three patients developed lymphoma, two developed laryngeal carcinoma, one developed pancreatic adenocarcinoma and one developed recurrent aggressive transitional cell carcinoma of the urinary bladder. Four patients were treated with PrOD, and the rest with simeprevir and sofosbuvir, daclatasvir and sofosbuvir or daclatasvir with peginterferon. The occurrence of the malignancies was three months to four years after the end of the treatment. The incidence of these malignancies in the cohort was 1.2%, 0.8%, 0.4% and 0.4% respectively, while the incidence in the general population is 7, 20, 8.8 and 142 to 100,000, respectively. Besides, 7 patients (2.4%) developed de novo or recurrent HCC.
Conclusion: This report raises a question about a possible relationship between treatment with DAAs and development of extrahepatic malignancies in addition to the reports regarding hepatic malignancied. Thus, data collection from larger cohorts is critical to determine the relationship possibility.

THU-349

Real world adherence to Direct-Acting Antivirals in a cohort of drug users in Rome, Italy

E. Teti[1], L. Foroghi[1], V. Malagnino[1], V. Cento[2], C. Stingone[1], M. Compagno[1], G. Malerba[1], A. Gentile[1], R.A. Cavasio[1], L. Coppola[1], E. Rossi[3], D. Masci[3], P. Sammarco[3], B. Coladarce[3], G. Rodoquino[3], M. Patti[3], C. Sarrecchia[4], C.F. Perno[2], F.C. Silberstein[2], M. Barra[3], L. Sarmati[1], M. Andreoni[1]. [1]*Tor Vergata University, Clinical Infectious Diseases, Rome, Italy;* [2]*Tor Vergata University, Virology Unit, Rome, Italy;* [3]*Villa Maraini Foundation, Rome, Italy;* [4]*Tor Vergata University, Clinical Infectious Diseases, Italy*
Email: elisabetta.teti@gmail.com

Background and Aims: For a long time, drug-addiction strongly limited anti-HCV treatment. Since newer direct-acting antivirals (DAAs) significantly improved tolerability and manageability, we evaluated adherence and efficacy of DAA-regimens in a drug-users cohort.
Method: Drug users with chronic hepatitis C were enrolled from June 2015 to October 2017. Adherence was calculated as percentage of control-visits attended among those scheduled (monthly during treatment and at 4, 12 and 24 weeks of follow-up). Regularity of medication uptake was investigated by questionnaires.
Results: Patients' cohort was so represented: active drug users (group A, n = 22/93, 23.7%), opioid substitution treatment patients (group B, n = 15/93, 16.1%) and rehab patients (group C, n = 19/93, 20.4%); 37/93 patients (39.8%) fell into the A/B group. Drug users (n = 93, male 82%)

with complex viral, clinical and social features received at least one DAA-dose. Genotype-1a and genotype-3 infections were the most common (54.3% and 31.5%); 47.2% of patients had cirrhosis () and 28.2% and resistance-associated variants. Overall, median [IQR] liver stiffness was 12.2 (10.4–23.4) kPa); 9.8% of patients was HIV-coinfected; 60.2% was unemployed, and 38.7% had psychiatric comorbidities. Overall treatment adherence was 91%, in particular: adherence to visit-schedule was higher among those with more stability and support (groups B [96.2%] and C [96.4%]), and lower in active drug users (group A [90.7%]; group A/B [87.4%]) (p = 0.04). The A/B group of patients was that with significant lesser adherence (60% of fully-adherent patients; p = 0.015). Full adherence was associated with shorter regimens (83% vs. 63% in 24-weeks regimens; p = 0.059), while no differences were observed according to HIV-coinfection, psychiatric comorbidities, imprisonment and unemployment. Detention resulted as a factor significantly associated with non-adherence in the whole treatment period and follow up (p = 0.01). *Per protocol* SVR_{12} rate in 64/93 patients who completed treatment at the time of the analysis was 98.4% (one relapse); four patients discontinued prematurely (three of these because of advanced liver clinical conditions).

Conclusion: Although drug users still face several clinical and social issues, our data indicate that even active drug-users can be highly adherent to DAA treatment, achieving optimal HCV cure-rates, especially with shorter DAA-regimens.

THU-350

Efficacy and safety of direct-acting antivirals for 1,961 Japanese chronic hepatitis C patients – Real Word Data from a multicenter cohort

N. Furusyo[1], E. Ogawa[1], N. Hideyuki[2], K. Dohmen[3], N. Higashi[4], K. Takahashi[5], A. Kawano[6], K. Azuma[7], T. Satoh[8], M. Nakamuta[9], T. Koyanagi[10], M. Kato[11], S. Shimoda[12], E. Kajiwara[13], J. Hayashi[14].
[1]Kyushu University Hospital, Department of General Internal Medicine; [2]Shin-Kokura Hospital, The Center for Liver Disease; [3]Chihaya Hospital, Department of Internal Medicine; [4]Steel Memorial Yawata Hospital, Department of Hepatology; [5]Hamanomachi Hospital, Department of Medicine; [6]Kitakyushu Municipal Medical Center, Department of Medicine; [7]Kyushu Central Hospital, Department of Medicine; [8]National Hospital Organization Kokura Medical Center, Center for Liver Disease; [9]Kyushu Medical Center, National Hospital Organization, Department of Gastroenterology; [10]Fukuoka City Hospital, Department of Medicine; [11]Kyushu University, Department of Medicine and Bioregulatory Science; [12]Kyushu University, Department of Medicine and Biosystemic Science; [13]Kajiwara Clinic, Department of Medicine; [14]Haradoi Hospital, Kyushu General Internal Medicine Center, Japan
Email: furusyo@gim.med.kyushu-u.ac.jp

Background and Aims: Little real-world data has been reported for Asians who have received interferon-free regimen with direct-acting antivirals for chronic hepatitis C. Our large, multicenter, real-world cohort study of Japanese chronic hepatitis C patients was done to assess the effectiveness of Japan-approved direct-acting antiviral (DAA) treatment for patients who were both treatment-naïve and -experienced with or without compensated cirrhosis.

Method: This multicenter cohort consisted of 1,961 (GT1: 1,312, GT2: 649) consecutive Japanese patients who initiated a 12-week course of the following DAA treatment. Patients with under aged 20 years, decompensated cirrhosis, or co-infection with HBV/HIV were excluded: GT1: Sofosbuvir (SOF)/Ledipasvir (LDV) (n = 1,101), Ombitasvir (OBV)/Paritaprevir (PTV)/Ritonavir (r) (n = 106), Elbasvir (EBR)+Grazoprevir (GZR) (n = 105), GT2: Sofosbuvir (SOF)+Ribavirin (RBV) (n = 649), For GT1 patients, NS5A gene amino acid positions 31 (L31I/F/M/V) and 93 (Y93C/F/H/N/S) were measured by direct-sequencing. These resistance associated variants (RAVs) were examined at baseline and at the time of relapse.

Results: The sustained virological response (SVR) rates of the GT1 patients who underwent SOF/LDV was 98.7%, only 14 relapsers (1.3%) were found, by intention-to-treat analysis. SVR rate of those with cirrhosis plus RAVs was 87.5%; ratio among all was just 6% (n = 53). The 14 relapsers included 5 with failure of DCV + ASV. The SVR rates of the GT1 patients who underwent OBT/PTV/r and EBZ + GZR were 98.1% and 100%, respectively, by intention-to-treat analysis. The SVR rate of the GT2 patients who underwent SOF + RBV was 96.1%, 25 non-SVR (3.9%) were found, by intention-to-treat analysis. SVR rate of those with cirrhosis plus treatment-experience was 85.4%; ratio among all was just 7.4% (n = 48).

Conclusion: Japan-approved DAA treatment for both HCV GT 1 and GT2 was exceptionally effective. However, NS5A RAVs undermined the virological effect for cirrhosis GT1 patients, and RBV-experience did the effect for cirrhosis GT2 patients.

THU-351

Adverse reactions of direct-acting antiviral agents in HCV patients: Our experience

D. Padovani[1], S. Colla[2], F. Masutti[1], C. Abazia[1], K. Parenzan[2], R. Patti[1,3], M.R. Buonocore[1,3], D. Macor[1,3], V. Lanzillotti[1], S. Paolo[2], S.L. Croce[1,3,4].
[1]ASUITS Cattinara Hospital, Liver Disease Unit, Trieste, Italy; [2]ASUITS Cattinara Hospital, Pharmacy, Trieste, Italy; [3]University of Trieste, Medical Science Department, Trieste, Italy; [4]Fondazione Italiana Fegato, Trieste, Italy
Email: padovanidiana@gmail.com

Background and Aims: Direct-acting Antiviral Agents (DAAs) have shown a high rate of Sustained Virologic Response (SVR) in the treatment of hepatitis C, with few and mild adverse reactions. The aim of this study was to evaluate: (1) The efficacy of DAAs; (2) The incidence of adverse reactions; (3) The interactions with other drugs in our centre.

Method: We performed an observational study of all HCV patients treated with DAAs in our centre from 01/01/2015 to 01/08/2017. We recorded: patient demographic information, grade of fibrosis by point-Shear Wave Elastography on Philips IU22 before and 12 months after treatment, HCV genotype, DAAs adverse reactions and therapeutic scheme, and concomitant drugs.

Results: We treated 142 HCV consecutive patients with second generation DAAs. We obtained a Sustained Virologic Response at 12 weeks (SVR12) in 93.5% of patients, 9 failures and 3 treatment interruptions due to adverse effects. Only 3 patients did not show any adverse reaction. In almost half of the cases fatigue and a reduction of at least 2 g/dL of haemoglobin levels were observed. Another frequent adverse effect was hyperglycemia (31.7%), observed in around 70% of the patients with type 2 diabetes treated with insulin or oral hypoglicemic agents and only in 25% of the non-diabetic patients. Hyperglycemia was more frequent in patients taking Daclatasvir + Sofosbuvir (45.7% vs 31.7% – p < 0.001) without a correlation with a specific antidiabetic drugs. Moreover, higher degrees of fibrosis were associated with a higher number of adverse reactions (p < 0.001). Patients who take Ribavirin display a high rate of anaemia also present with only DAA, even if less severe (67% vs 28% – p < 0.001).

Conclusion: In this real life study, DAAs confirmed the excellent therapeutic success already known in literature. However, we found a higher rate of adverse effects especially in more advanced liver disease. In particular we have noticed a relevant rate of hyperglycemia, an adverse effect that has not been reported in literature and that appears to be related to the drug's class or the hepatic effect of HCV clearance rather than drug-drug interactions.

THU-352

A comparison of renal function before and after treatment in chronic hepatitis C patients who achieved sustained viral response with direct acting antivirals

P. Fitzmorris[1], O. Sims[1], Y. Guo[1], M. Shoreibah[1], J. Romano[2], V. Kommineni[2], M. Massoud[3], T. Matin[2], O. Massoud[1]. [1]*University of Alabama at Birmingham, Department of Gastroenterology and Hepatology;* [2]*University of Alabama at Birmingham, Department of Internal Medicine;* [3]*University of Tennessee Health Science Center at Chattanooga, Department of Internal Medicine*
Email: omassoud@uabmc.edu

Background and Aims: There is limited data with regard to the effect of direct acting antivirals (DAA) on renal function. The purpose of this study was to examine differences in renal function before and after treatment in HCV patients who achieved SVR with all-oral DAAs.
Method: This is a single-center, retrospective analysis of patients with chronic HCV who were treated with DAAs between December 2014 and December 2015. Patients were excluded if they did not achieve SVR or if they did not have glomerular filtration rate (GFR) and serum creatinine data before and 3–6 months after achieving SVR. Measures of central tendency and frequency distributions were used for univariate analysis. The paired-samples t-test was used to compare before and after treatment serum creatinine levels.
Results: 306 patients were included. The majority of patients were male (53%), non-Hispanic white (70%), and insured (98%). The mean age was 57 years and nearly one-third of patients were active smokers (29%). Eight-four percent of patients were genotype 1, 49% were cirrhotic, 14% were decompensated, and 5% had hepatocellular carcinoma. The majority of patients were treatment naïve (70%) and received ledipasvir/sofobuvir (83%). At baseline, the mean creatinine level was 0.96, and 90% had normal renal functioning and 10% had renal impairment. Of those with normal renal functioning at baseline, GFR stayed the same in 97% of patients and worsened in 3%. Of those with renal impairment at baseline, GFR improved in 23% of patients, stayed the same in 68%, and worsened in 10%. Altogether, GFR improved or stayed the same in 96% of patients and worsened in 4% of patients. There were no differences of statistical significance between creatinine levels before and after treatment insert here (0.96 vs. 1.00, t (305) = 1.44, p = 0.15).

Table: Proportion of HCV Patients with Renal Improvement, No Change, or Worsening 3–6 Months Post-SVR

Renal Function Before Treatment	GFR Improved at Follow Up (3–6 months)	GFR Stayed the same at Follow Up (3–6 months)	GFR Worsened at Follow Up (3–6 months)
Normal (GFR > 60): 275 (90%)	0 (0%)	266 (97%)	9 (3%)
Impaired (GFR < 60): 31(10%)	7 (23%)	21 (68%)	3 (10%)
Grand Total: 306 (100%)	306 (100%)	287 (94%)	12 (4%)

Conclusion: In this study, DAAs were well tolerated from a renal function standpoint. Nearly one-fourth of patients with baseline renal impairment had improvements in renal function achieving SVR. DAA treatment may improve renal function in some patients. Larger, prospective studies are needed to further investigate our findings.

THU-353

Fast-track HCV check-up enhances possibility of sustained virologicalresponse in HCV infected patients

T. Antonini[1], M.G. Tateo[2], P. Attali[2], E. De Martin[2], A. Coilly[2], B. Roche[2], R. Sobesky[2], D. Samuel[3], A.M. Roque-Afonso[2], J.-C. Duclos-Vallée[4]. [1]*Hôpital universitaire Paul Brousse, Centre hépato-biliaire, Villejuif, France;* [2]*AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, France;* [3]*AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, F-94800, France, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France;* [4]*Hôpital universitaire Paul Brousse, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France*
Email: teresa.antonini05@aphp.fr

Background and Aims: New direct acting antiviral (DAA) against chronic hepatitis C virus (HCV) have drastically changed and shortened duration of treatments. However, the "HCV care course" (from diagnosis to sustained virological response (SVR)), represents an important challenge.
Aims: To evaluate the impact of a new fast-track HCV check-up in terms of retention in care and SVR. In order to assess the efficacy we provide a comparison between the first 50 pts of the FT-HCV (Fast track HCV check-up) in 2016 to 50 pts followed in our "standard" out clinic practice (control group (CG)) in 2015.
Method: FT-HCV is a new assessment unit of our center. In the same half-day, pts benefit of a complete assessment of liver function: blood test with HCV-Ab and HCV viral load, genotype (G) determination, Fibrotest® and transient elastography. Three hours after admission, we were able to confirm HCV and to discuss the eligibility to an HCV treatment in accord to regulatory framework.
Results: Groups were comparable for age and sex**:** 50 pts of each group were analysed (FT-HCV: Male n = 34 (68%), mean age: 49 ± 14 years; CG: Male n = 35 (66.6%), mean age: 53 ± 13 years). In FT-HCV and CG fibrosis (F) was: mild F0-F1 n = 15 (30%), F2 n = 12 (24%), F3 n = 10 (20%), F4 n = 13 (26%), and F0-F1 n = 18 (36%), F2 n = 12 (24%), F3 n = 9 (18%), F4 n = 10 (20%), unknown n = 1 (2%) respectively. All cirrhotic pts had compensated cirrhosis (Child A/MELD 8–10). Six pts (12%) in the FT-HCV group were excluded because HCV viral load was negative. G distribution in the FT-HCV and in CG was: G1 n = 25(50%), G3 n = 8 (16%), G4 n = 11 (22%), and G1 n = 29 (58%), G2 n = 5 (10%), G3 n = 7 (14%), G4 n = 7 (14%), G6 n = 6 (4%) respectively. Thirty (69%) and 26 (52%) pts received DAA in FT-HCV and CG.
Mean delay and numbers of out-clinic visits in FT-HCV and CG for treatment were 108 days (± 84) *versus* 260 days (± 85) p = 0.009 and 2 (2–5) vs 4 (2–9) p = 0.0003, respectively.
To date in FT-HCV pts: SVR was achieved in 22 pts (74%), waiting for SVR12 in 7 pts (23%) and 1 pt was not responder (3%). Complete results SVR 12 for all pts will be presented. In CG SVR was achieved in 23 pts (88%), 1 pt was non-responder (3%) and 2 pts (6%) were lost of follow-up.
Conclusion: FT-HCV is a performing assessment of HCV infected patients and improves retention in care, management and rates of SVR.

THU-354

Grazoprevir/elbasvir dosing according to viral load and NS5A resistance: real world confirmation of the efficacy of EASL guidance

F. Marra[1,2], A. Boyle[1,2], R. Gunson[3], A. Bradley[3], E. Thomson[4,5], S. Barclay[6]. [1]*NHS Greater Glasgow and Clyde, Pharmacy Department;* [2]*University of Liverpool, Department of Molecular and Clinical Pharmacology;* [3]*NHS Greater Glasgow and Clyde, West of Scotland Specialist Virology Centre;* [4]*NHS Greater Glasgow and Clyde, Brownlee Centre for Infectious Diseases;* [5]*MRC Centre for Virus Research;* [6]*NHS Greater Glasgow and Clyde, Glasgow Royal Infirmary*
Email: fiona.marra@liverpool.ac.uk

Background and Aims: Twelve weeks of grazoprevir/elbasvir (GRZ/ELB) is highly effective against genotype 1a infection. The presence of elbasvir specific NS5a resistance-associated substitutions (RASs) in patients with a high baseline viral load may have a suboptimal response, which may be overcome by extending treatment duration to 16 weeks and adding ribavirin. As per EASL guidelines, our local

protocol is to treat patients with a baseline viral load <800,000 IU/ml for 12 weeks, and to conduct resistance testing for those >800,000. Those with elbasvir RASs are treated for 16 weeks with RBV, those without with 12 weeks GRZ/ELB. We report the initial outcomes of this approach.

Method: Patients with GT1a commencing treatment with GRZ/ELB in Glasgow treatment centres, prior to 01/09/2017 were identified from the Scottish HCV database. Baseline data on age, gender, cirrhosis status, and virological response were collected. RAS testing for mutations at positions M28, Q30, L31, H58 and Y93 was conducted using Sanger sequencing by the West of Scotland Specialist Virus laboratory.

Results: Of 176 patients who met the inclusion criteria, 125 (71.0%) were male with a mean age 45.7 years (± 9.0) and 94 (53.4%) were on opiate substitution therapy. There were 39 (22.2%) patients with a diagnosis of cirrhosis. Ninety-eight patients (55.6%) with a high viral load underwent RAS testing, of whom 5 (5.1%) had elbasvir specific RASs, and were treated with 16 weeks in combination with ribavirin. All other patients were treated with 12 weeks of GRZ/ELB. To date, 126 patients have completed treatment, 5 (3.9%) prematurely. To date, 45 patients have attended for SVR12 bloods (1 treated for 16 weeks plus ribavirin, 12 with cirrhosis). 44/45 (97.8%) have achieved SVR, including all with cirrhosis.

Conclusion: Early results confirm the efficacy of 12 weeks of GRZ/ELB for patients with a low viral load, or a high viral load in the absence of elbasvir specific RASs, with 16 weeks plus RBV reserved for those with a high viral load and RASs. Further SVR12 data will be presented.

THU-355

Impact of HCV viral load on elbasvir/grazoprevir effectiveness in Chronic Hepatitis C: Updated retrospective data analyses from the Trio network

S. Flamm[1], B. Bacon[2], M. Curry[3], S. Milligan[4], C. Nwankwo[5], N. Tsai[6], N. Wick[4], Z. Younossi[7], N. Afdhal[3]. *[1]Northwestern University Feinberg School of Medicine, Chicago, United States; [2]Saint Louis University School of Medicine, St. Louis, United States; [3]Beth Israel Deaconess Medical Center, Boston, United States; [4]Trio Health, La Jolla, United States; [5]Merck & Co., Inc., Kenilworth, United States; [6]Queens Medical Center- University of Hawaii, Honolulu, United States; [7]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States*
Email: s-flamm@northwestern.edu

Background and Aims: Lengthening elbasvir/grazoprevir (EBR/GZR) treatment to 16 weeks and adding ribavirin (RBV) is recommended by the EMA for patients with Genotype (GT) 1A or 4 Chronic Hepatitis C (HCV) and baseline viral load >800 K IU/ml. This study examines the association of viral load and observed SVR12 outcomes in patients treated with EBR/GZR.

Method: Data were collected from providers and specialty pharmacies in the US through Trio Health's disease management program. Patients (n = 1032) who initiated EBR/GZR therapy between Jan 28, 2016 (FDA approval) to Jun 2017 were included. The primary outcome assessed was per protocol sustained virologic response at 12 weeks post treatment (SVR12).

Results: 381/1032 (37%) patients had baseline viral load ≤800 K IU/ml and 651/1032 (63%) >800 K IU/ml. 12-week EBR/GZR without RBV was the predominant therapy regardless of baseline viral load, used in 347/381 (91%) of ≤800 K IU/ml group and 605/651 (93%) of >800 K IU/ml group. At time of data extraction, outcomes were available for 694/1032 patients and were: 10/694 (1%) died, 42/694 (6%) discontinued, 28/694 (4%) completed but were lost to follow up, 11/694 (2%) completed therapy and had virologic failure, and 603/694 (87%) achieved SVR12. The per protocol (PP) SVR12 rate (limited to patients who completed therapy and had an SVR assessment), was 603/614 (98%). Outcomes were similar between groups stratified by baseline viral load: PPSVR12 rates of 230/232 (99%) for ≤800 K IU/ml and 373/382 (98%) for >800 K IU/ml. For patients with GT1A HCV and baseline viral load >800 K IU/ml, 12-week EBR/GZR resulted in PPSVR12 of 228/231 (99%). For patients with GT4 HCV and baseline viral load >800 K IU/ml, 12-week EBR/GZR resulted in PPSVR12 of 6/6 (100%).

Conclusion: In clinical practice in the US, no obvious impact from baseline viral load >800 K IU/ml on PPSVR12 was observed as patients in the ≤800 and >800 K IU/ml groups had similar PPSVR12. Full SVR12 data across sub populations will be presented at the conference.

THU-356

Therapeutic Drug Monitoring of DAAs overcomes contra-indications against anti-epileptics in HCV treatment (HepNed003)

M. van Seyen[1], S.J. Elise[2], V.W. Peter[3], J.P.H. Drenth[4], M. Wouthuyzen-Bakker[5], R. de Knegt[6], H. Pieter[7], O. El Sherif[8], D. Back[9], D. Burger[1]. *[1]Radboud University Medical Center, Dept of Pharmacy, Nijmegen, Netherlands; [2]Isala Hospital, Dept of Pharmacy, Zwolle, Netherlands; [3]Amphia Hospital, Dept of Internal Medicine, Breda, Netherlands; [4]Radboud University Medical Center, Dept of Gastroenterology & Hepatology, Nijmegen, Netherlands; [5]University Medical Center Groningen, Medical Microbiology and Infection Prevention, Groningen, Netherlands; [6]Erasmus MC, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [7]Albert Schweitzer Hospital, Dept of Gastroenterology & Hepatology, Dordrecht, Netherlands; [8]St James's Hospital, Dept of Hepatology, Dublin, Ireland; [9]University of Liverpool, Dept of Molecular and Clinical Pharmacology, Liverpool, United Kingdom*
Email: minou.vanseyen@radboudumc.nl

Background and Aims: Drug-drug interactions between direct-acting antivirals (DAAs) and co-medication occur frequently. They may have clinical consequences necessitating dose modification, intensified monitoring and/or drug substitution. The anti-epileptic drugs carbamazepine, phenytoin and phenobarbital, which are strong inducers of CYP450 enzymes and membrane transporters, are contra-indicated with all available DAA combinations, and therefore should be replaced. In rare cases, patients and/or neurologists are unable to substitute the anti-epileptic drug. As separate sofosbuvir (SOF) and daclatasvir (DAC) formulations are available, dose adjustment of individual agents is possible. We hypothesize that increased dosage of DAC with PK monitoring against a backbone of SOF could be an effective approach in these difficult to treat patients.

Method: We established a cohort of HCV patients on anti-epileptics who were unable stopping treatment. Patients were treated with an increased dose of DAC and underwent intensive PK monitoring followed by further dose-adaptation if needed. Patients were treated with a standard dose of SOF as this is a P-gp substrate and expected to be less vulnerable to the inducing effects of anti-epileptics. Addition of ribavirin and treatment duration was according to treatment guidelines. Here we report on six patients (n = 4 male) with a median age of 55.4 (48.5–66.5) years using the anti-epileptic drugs carbamazepine 400–1200 mg/day (n = 4), phenytoin 225 mg/day (n = 1) or phenobarbital 100 mg/day (n = 1). Most patients were infected with genotype 1 (n = 5) and treatment-naïve (n = 4). METAVIR scores were F0 (n = 3), F3 (n = 1) and F4 (n = 2).

Results: The standard dose of DAC 60 mg QD was adjusted to 60 mg BID (n = 2) and 60 mg TID (n = 4). After PK evaluation, one of the patients receiving 60 mg DAC BID, had the DAC dose increased to

60 mg TID because of suboptimal levels. The median C_{last}, C_{max} and AUC_{0-24h} of DAC were 0.097 (0.086–0.45)mg/l, 0.42 (0.34–0.94) mg/l and 4.75 (4.03–14.93)mg*h/l, respectively. These values were 58.2%, 72.8% and 66.3% lower for C_{min}, C_{max} and AUC_{0-24h} respectively, when compared to reference values for DAC. No serious adverse events were reported. So far, three patients reached SVR12, another patient had SVR4, and for the two other patients SVR data are pending.
Conclusion: This cohort study using an adaptive dosing strategy demonstrates the feasibility of studying DAA combinations with the contra-indicated anti-epileptic drugs. Despite lower exposure to DAC, all patients with sufficient follow-up have achieved SVR.

THU-357

What impact do the new direct acting antiviral drugs have on the patients' quality of life?

M. Gentili[1], C.F. Magni[2], C. Carnovale[1], E. Cesari[1], D. Cattaneo[1], M. Schiavini[2], S. Landonio[2], F. Niero[2], V. Scalzi[3], S. Vimercati[3], S. Radice[1], E. Clementi[1], G. Rizzardini[2]. [1]*"Luigi Sacco" University Hospital, Unit of Clinical Pharmacology, Department of Biomedical and Clinical Sciences, Milan, Italy;* [2]*"Luigi Sacco" University Hospital, Units of Infectious Diseases, Milan, Italy;* [3]*"Luigi Sacco" University Hospital, Unit of Pharmacy, Milan, Italy*
Email: marta.gentili77@gmail.com

Background and Aims: The non-specific symptomatology of hepatitis C (HCV) as well as the side effects of its therapy can significantly influence patients' quality of life. To date, the number of real life studies investigating this aspect are still limited. For this reason, a retrospective observational study was performed using a questionnaire to understand the impact of new direct acting antiviral drugs (DAAs) on the patients' quality of life.
Method: The survey consists of 19 open and multiple choices questions divided into 5 sections. The questionnaires were administered to all patients from the Infectious Diseases Department of our hospital, who had completed the anti-HCV therapy with DAAs. The collected responses were matched against clinical data.
Results: 201 patients who had completed therapy with DAAs were interviewed: 111 (55.2%) were naive and 90 (44.8%) had been treated with previous HCV therapies. 90% of this latter group said they prefer the new therapy. All patients showed significant improvement in symptomatology. However, calculating the incidence of symptomatology related to the period before and during DAA therapy, there were 322 adverse drug reactions (ADR), which led to the discontinuation of therapy in two cases (one case of hepatocellular carcinoma and one of skin cancer). As shown in Figure 1, only 10.5% of ADRs were reported by the attending physicians' worthy of mention, 50,3% of all ADRs were unknown, as they are not reported previously on the clinical data sheet of suspected drug. The most frequent ADRs were insomnia, altered mood, loss of appetite, anxiety and irritability whereas the most clinically relevant were herpes zoster, optic ischemia, amaurosis and breast hypertrophy.
Conclusion: Despite the good safety profile shown by DAAs during registration trials, the patients' point of view has provided important, new information on their safety profile, helping us to identify novel drug-related adverse reactions. Nevertheless, physicians are still mandatory for a correct and appropriate differential diagnosis of iatrogenic pathology, eventually working in team with pharmacologists, which have the tools, skills and expertise to check and prevent drug-to-drug interaction-related ADRs, identifying them before the introduction of DAAs. Lastly, the identification of ADRs not known and the search for a possible mechanism of action that may have exacerbated them is certainly one of the strengths of our work.

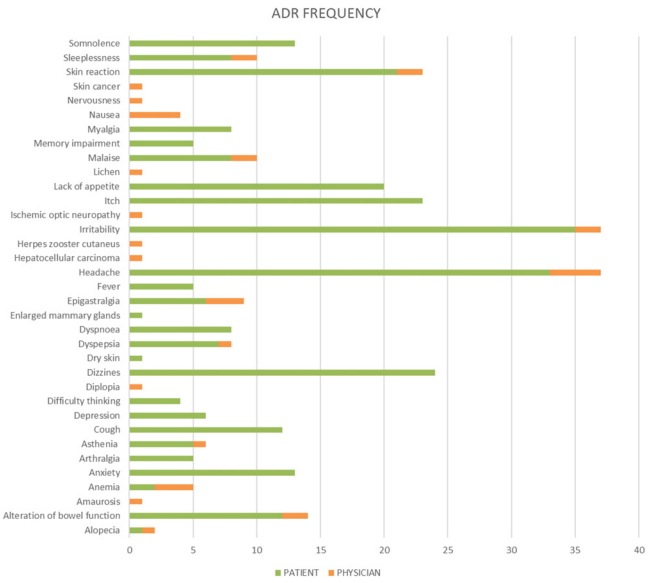


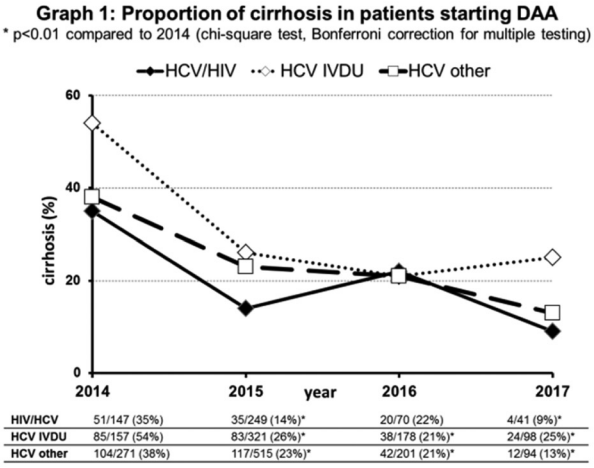
Figure 1: Frequency of Adverse drug reactions recorded in our real life survey.

THU-358

Significant changes of HCV patient characteristics over time in the era of direct antiviral agent therapy – are all HCV subpopulations treated similarly? – Results from the German hepatitis C Cohort

S. Christensen[1], P. Ingiliz[2], J. Schulze Zur Wiesch[3], K. Schewe[4], C. Boesecke[5], D. Hüppe[6], A. Baumgarten[7], L. Thomas[8], G. Schmutz[9], S.K. Georg[10], B. Florian[11], B. Heiner[12], S. Mauss[11]. [1]*Center for Interdisciplinary Medicine (CIM), Infectious Diseases, Muenster, Germany;* [2]*Center for Infectiology Berlin (CIB), Infectious Diseases, Berlin, Germany;* [3]*Heinrich Pette Institute – Leibniz Institute for Experimental Virology, Infectious Diseases, Hamburg, Germany;* [4]*ICH Hamburg, Infectious Diseases, Hamburg, Germany;* [5]*Universitätsklinik Bonn, Mediznische Klinik 1, Bonn;* [6]*Practice for Gastroenterology, Hepatology, Herne, Germany;* [7]*Center for Infectiology, Infectious Diseases, Berlin, Germany;* [8]*Infektiologikum, Infectious Diseases, Frankfurt, Germany;* [9]*Center for HIV and Hepatogastroenterology, Infectious Diseases, Duesseldorf, Germany;* [10]*Practice for Gastroenterology, Leverkusen, Germany;* [11]*Center for HIV and Hepatogastroenterology, Duesseldorf, Germany;* [12]*Center for Interdisciplinary Medicine, Infectious Diseases, Muenster, Germany*
Email: christensen@cim-ms.de

Background and Aims: The German healthcare system provides access to all approved direct antiviral agent (DAA) regimen allowing pangenotypic therapy and retreatment of patients with relapse and reinfection. However, access to care and therapy may differ between patient populations at risk in the real life setting, which could potentially result in differences in the proportion of patients presenting with advanced liver disease.
Method: The German hepatitis C Cohort (GECCO) cohort is a prospective multicenter cohort from 9 sites in Germany. For this analysis all chronically HCV infected patients started on a DAA based therapy between 2/2014 and 9/2017 were included. Baseline demographics and treatment outcome according to the calendar year DAA treatment was initiated are reported.
Results: Until September 2017 n = 2,367 patients, 64% GT1 and 25% GT3 infected, initiated DAA based therapy, mostly with sofosbuvir/



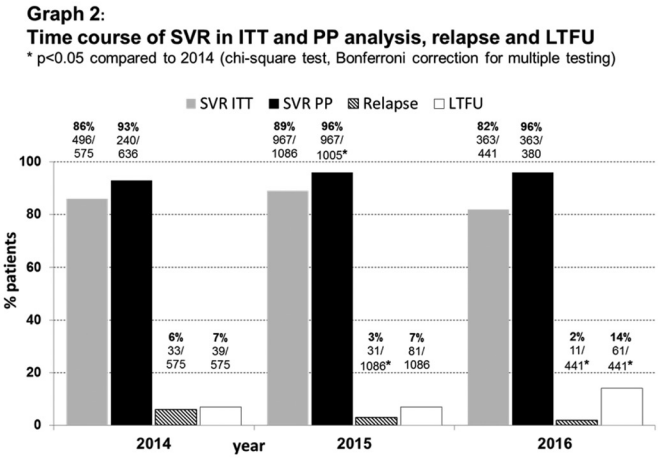


Figure: (abstract: THU-358)

ledipasvir ± ribavirin (45%). There has been a continuous decrease in (a) the proportion of previously treated HCV patients (2014:83%, 2017:24%, p < 0.0001), and (b) patients with liver cirrhosis defined by FibroScan® >12,5 kPa or APRI >2 (2014:42%, 2017:17%, p < 0.0001). More importantly, the decrease in the proportion of patients with liver cirrhosis was comparable in patients with HCV-monoinfection and history of intravenous drug use (IVDU), HIV/HCV coinfection or neither of those (Graph 1). The proportion of HIV/HCV coinfection decreased (2014 26%, 2017 19%, p < 0.01), whereas the number of patients with history of IVDU increased from 33% 2014 to 50% 2017 (p < 0.001). Mean age dropped from 52 years in 2014 to 48 years in 2017 (p < 0.01). Neither in the intention to treat analysis (ITT) (2014: 86%, 2016: 82%, p = 0.096) nor in the per protocol analysis (PP) (2014: 93%, 2016: 96%, p = 0.072) SVR12 significantly changed over time. In fact, relapse rates decreased from 6% 2014 to 2% 2016 (p < 0.05) but lost to follow (LTFU) doubled between 2014 (7%) and 2016 (14%) (Graph 2).

Conclusion: In this real life cohort the decrease in the proportion of patients initiating therapy with liver cirrhosis was comparable in different risk groups including IVDU. A shift to younger, treatment naïve and patients with IVDU as transmission risk occurred. Antiviral effectiveness increased over time as indicated by the very low relapse rates in the last two years of analysis. However, lost to follow up after end of therapy increased substantially indicating lower adherence to structured monitoring in more recently treated patients.

THU-359

National quality control and validation of hepatitis C NS3, NS5A and NS5B genotypic resistance testing

T. Ruggiero[1], V. Cento[2], M. Aragri[2], M. Arosio[3], F. Baldanti[4], M. Brunetto[5], B. Bruzzone[6], E. Boeri[7], D. Cavallone[5], C. Nicola[8], M.A.D. Stefano[9], V. Ghisetti[1], M.P. Callegaro[3], M.R. Capobianchi[10], C. Caudai[11], N. Cuomo[12], S. Galli[13], E. Galmozzi[14], A. Garbuglia[10], W. Gennari[15], A. Lai[16], S. Menzo[17], V. Micheli[18], C. Minosse[10], L. Monno[19], S. Paolucci[4], T. Pollicino[20], A. Raddi[12], G. Raffa[20], G. Raimondo[20], M. Sanguinetti[21], R. Santangelo[21], T. Santantonio[9], S. Soldini[21], M. Starace[8], M.L. Vatteroni[22], A. Craxi[23], C.F. Perno[24], F.C. Silberstein[25], M. Zazzi[11]. *[1]Microbiology and Virology Laboratory, Amedeo di Savoia Hospital ASL Città di Torino, Torino; [2]Department of Experimental Medicine and Surgery, University of Rome Tor Vergata, Rome, Italy; [3]Microbiology and Virology, ASST Papa Giovanni XXIII, Bergamo; [4]Molecular Virology, IRCCS Policlinic Foundation San Matteo, Pavia; [5]Hepatology Unit, Azienda Ospedaliero-Universitaria Pisana; [6]Hygiene Unit, Ospedale Policlinico San Martino, Genova; [7]Microbiology e Virology Unit, Ospedale San Raffaele, Milano; [8]Infectious Disease Department, University of Campania"Luigi Vanvitelli", Napoli; [9]Infectious Disease Department, Polo Biomedico "E. Altomare", Foggia; [10]Virology Laboratory, INMI Lazzaro Spallanzani, Roma; [11]Department of Medical Biotechnology, University of Siena, Policlinico S. Maria alle Scotte, Siena; [12]Microbiology and Virology Laboratory, Azienda Ospedaliera dei Colli, Cotugno, Napoli; [13]Microbiology Unit, Ospedale S. Orsola-Malpighi, Bologna; [14]Division of Gastroenterology and Hepatology, Fondazione IRCCS Ca" Granda, Ospedale Maggiore Policlinico, University of Milan, Milano; [15]Microbiology and Virology Unit, University Hospital Policlinico of Modena, Modena; [16]ASST Fatebenefratelli Sacco Hospital, Milano; [17]Virology Laboratory, Ospedali riuniti di Ancona, Ancona; [18]Clinical Microbiology, Virology and Bioemergencies, ASST Fatebenefratelli Sacco, Milano; [19]Infectious Disease Department, Azienda Ospedaliera Policlinico di Bari, Bari; [20]Department of Internal Medicine, Azienda Ospedaliera Universitaria Policlinico "G Martino", Messina; [21]Institute of Microbiology, Policlinico Universitario Agostino Gemelli, Roma; [22]Virology Laboratory, Azienda Ospedaliero-Universitaria Pisana; [23]Gastroenterology, "P. Giaccone" University Hospital, Palermo, Italy; [24]University of Milan, Milan, Italy; [25]University of Rome Tor Vergata, Department of Experimental Medicine and Surgery, Rome, Italy*
Email: tinarugg@gmail.com

Background and Aims: International guidelines currently recommend HCV genotypic resistance testing (GRT) in selected cases. However, GRT application is limited in many countries by the lack of a commercial assay. Within the Italian VIRONET C activity, we conducted a multicentre HCV Sanger GRT quality control study, with the aim of providing a standardized GRT at National level.

Method: A panel of 10 blinded clinical samples with HCV genotypes (GT)1a-1b-2c-3a-4a-4d, with a median (IQR) HCV-RNA of 5.8 (5.6–5.9) logIU/ml, was provided to 23 laboratories (lab)of VIRONET C. NS3, NS5A and NS5B GRT was performed by using different Sanger sequencing protocols at 22 labs, while Illumina next-generation sequencing (NGS) was performed at 1 lab, and used as comparator with 15% detection cut-off. The Geno2pheno (G2P) tool was used for detection of resistance associated substitutions (RASs).

Results: Fourteen labs generated all the 30 expected sequences, while the remaining 8 generated a mean ± SD of 24.3 ± 3.6 sequences. Fourteen labs used the same Sanger protocol while all the others used a unique system. G2P identified a total of 7 RASs in the 30 sequences generated by NGS. Comparing the NGS sequences to the Sanger consensus sequences derived from all the available results revealed four major RASs discordances, including a NS5A Y93H and a NS3 Q168QK detected by 100% and 35% Sanger reactions, respectively, but not by NGS, and a NS5B S556G detected by NGS (98%) in 2 samples

(GT 3a and 2c) but not by any Sanger reaction. When excluding these method discrepancies, the overall Sanger accuracy with respect to the consensus sequence was 85%, and particularly 81% for NS3, 85% for NS5A and 90% for NS5B. The disagreement was more common for particular GT/subtypes (2c and 3a for NS3, 1b and 4a for NS5A). The rate of sequencing success and RAS disagreement were almost equal among the labs using the same assay *vs* the others (86% *vs* 85% and 14% *vs*15%, respectively). The overall RAS detection disagreement among laboratories was 9% in NS3, 7% in NS5A, 0% in NS5B.
Conclusion: Most of the 22 labs participating to the Italian VIRONET C network provided HCV GRT results for all circulating HCV GTs and all clinically relevant genes. Accuracy and inter-laboratory precision were affected by the use of different methods, highlighting the challenge of HCV variability. Quality control programs for HCV GRT should be promoted to allow its fruitful use in optimizing HCV treatment.

THU-360

Genetic diversity of genotype 6 HCV infections in France: epidemiology and consequences for treatment strategy

C. Pronier[1], F. Helene[2], D. Celine[3], P. Stanislas[2], F. Carrat[3], V. Thibault[1], On Behalf of the Afef/Anrs Hepather Sutdy Group Afef-Anrs[4].
[1]INSERM U1085-IRSET University Rennes 1, Virology, Rennes, France; [2]APHP Cochin, Hepatology, PARIS, France; [3]Institut Pierre Louis d'Epidémiologie et de Santé Publique, Epidemiology, PARIS, France; [4]ANRS-AFEF, PARIS, France
Email: vincent.thibault@chu-rennes.fr

Background and Aims: With 26 described subtypes, genotype 6 (Gt6) exhibits the highest genetic diversity among the 7 HCV genotypes. The aim of this study was to document Gt6 diversity among 14,603 HCV mono-infected patients recruited between 08/06/12 and 10/09/17 in the French ANRS-CO22 Hepather cohort (NCT01953458) and to analyze treatment efficacy within each subtype.
Method: For all Gt6 HCV infections identified in the database, HCV subtype was determined on a plasma sample drawn at inclusion. After HCV RNA extraction, NS3, NS5A and NS5B regions were RT-PCR amplified and sequenced by the Sanger method. Phylogenetic analyses were performed by comparing obtained and reference Gt6 sequences. Resistance polymorphisms were also studied.
Results: Gt6 infections were identified in 38 patients. Two were excluded as NS5B analysis revealed misclassified Gt1 and Gt3 infections. Gt6e was the most prevalent (27.8%), followed by 6a (22.2%), 6q (13.9%) and 6o (11.1%). Each subtype p and xc were found in 2 patients (5.6%) and subtypes f, h, k, r and t were each detected in only one patient. Concordant phylogenetic analyses whatever the studied HCV fragment eliminated any recombination event in this part of the genome. All but 3 patients were born in an Asian country, Cambodia (44%), Vietnam (42%) or Laos (8%). Subtype 6a and 6e were found in 17% of patients born in Vietnam and Cambodia, respectively. Subtype 6q was mostly found in patients from Cambodia (80%). Among the 3 patients born in Europe, 2 were contaminated with subtype 6o, also found in 2 Vietnamese. Phylogenetic analyses indicated a harmonious distribution reflecting genetic heterogeneity from different countries and no specific clustering. Twenty-six patients received sofosbuvir based DAA combinations and 3 received glecaprevir/pibrentasvir. For the 23 patients with a documented follow-up, 14 with advanced fibrosis (≥F3), SVR12 was reached. Several polymorphisms potentially impacting sensitivity to each DAA classes were identified in baseline sequences. Resistance associated substitutions were unevenly distributed according to each subtype but did not seem to impact treatment efficacy.
Conclusion: Genotype 6 infections are not common in France and show a large genetic diversity, likely reflecting contamination within the country of origin rather than locally acquired infections. Despite the presence of genetic polymorphisms potentially affecting DAA efficacy, all treated patients were successfully treated using recommended DAA associations.

THU-361

Hepatitis C direct-acting antiviral failures: clinical characteristics and resistance testing from a real-world setting

R. Mitchell[1], G. Ou[1], A. Leung[2], J. Feizi[2], A. Howe[3], O. Cerocchi[4], H. Kuriry[4], J. Feld[4], H.H. Ko[1], A. Ramji[1]. *[1]University of British Columbia, Vancouver, Canada; [2]St. Paul's Hospital, Gastrointestinal Research Institute, Vancouver, Canada; [3]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, Canada; [4]University of Toronto, Toronto, Canada*
Email: rmitch86@gmail.com

Background and Aims: A small proportion of patients fail Hepatitis C (HCV) treatment with direct-acting antivirals (DAAs) for various reasons. Real-world data on DAA failures and the development of resistance associated substitutions (RAS) are limited. This study aims to characterize clinical parameters and RAS patterns in patients who failed DAA regimens.
Method: Retrospective chart review at two tertiary hepatology clinics between 01/2015 and 11/2017. Patients treated with DAAs who did not achieve SVR12 were included. Baseline clinical characteristics and RAS testing at SVR12 were collected. HCV sequence data were obtained from Next Generation Sequencing. Mutations >5% of viral population were reported. Resistance phenotype was predicted based on EC_{50} fold-shift in mutant vs. wild-type replicons.
Results: Sixty-three patients were included: mean age 59.7 years (range 43–84) and mostly male (82.5%). Genotypes (GT) included GT1a (n = 28; 44.4%), GT1b (n = 8; 12.7%), GT2 (n = 5; 7.9%), GT3 (n = 19; 30.2%), GT4 (2; 3.2%), GT6 (n = 1; 1.6%). DAA regimen durations were 8 weeks (n = 6; 9.7%), 10 weeks (n = 1; 1.6%), 12 weeks (n = 38; 61.3%), 16 weeks (n = 2; 3.2%) or 24 weeks (n = 15; 24.2%). Pre-treatment fibrosis by transient elastography (n = 41) revealed F0–2 (39.0%), F3 (12.2%) and F4 (48.8%).
Post-DAA RAS testing was available for 59 patients. In 21 GT1a patients treated with SOF/LDV, 16 had a NS5A RAS, 8 of which were 93 position variant. All 6 GT1b patients who failed SOF/LDV had a NS5A RAS, with 5 being at position 93. 17 of 21 GT1a patients had an NS3 RAS, 10 were Q80K. Two GT1a EBR/GZR failures had both a NS5A and a non-Q80K NS3 RAS. Of 2 GT1a patients who failed OBV/PTV/r + DSV/RBV, 1 had NS5A.
In 17 of 19 GT3 patients RAS testing was available. DAA regimes included SOF/RBV (n = 11), SOF/VEL (n = 2), SOF/VEL/RBV (n = 2), SOF/RBV/Interferon (n = 2) and SOF/LDV/RBV (n = 2). Three patients had NS5B RAS, conferring possible SOF resistance (159wt/F, 321wt/A, 142S). There were no S282T RAS. All 4 GT3 patients failing SOF/VEL +/-RBV had NS5A RAS, 3 were Y93H. Of 11 GT3 patients with SOF/RBV +/-IFN treatment and RAS testing, 2 had NS5A RAS (S62L, A30K).
Conclusion: Distinct RAS patterns are present depending on genotype and DAA regimen failed. Virologic failure with a NS5A based regimen confers a high risk of developing a NS5A RAS, which may have implications on future treatments in these patients. Additional analysis to explore baseline patient characteristics associated with RAS is pending.

THU-362

Prevalence of baseline NS5A resistance associated substitutions in treatment naive patients with genotype 1a or 3

A. Ramji[1,2], E. Tam[3], J. Feld[4], C. Cooper[5], A. Wong[6]. *[1]University of British Columbia, Gastroenterology, Vancouver, Canada; [2]University of British Columbia, Vancouver, Canada; [3]LAIR Center, Vancouver, Canada; [4]Toronto, Canada; [5]University of Ottawa, Ottawa, Canada; [6]Regina Qu'Appelle Health Region, Regina, Canada*
Email: ramji_a@hotmail.com

Background and Aims: HCV DAA treatment achieves high SVR in almost all populations. However, a small proportion of patients fail. The primary virologic reason for failure is the presence of baseline resistance-associated sequences (RAS). International Guidelines

(EASL & AASLD) recommend assessment of baseline NS5A RAS testing in persons with GT1a and GT3, dependent on the DAA regimen and fibrosis stage. Uptake and impact of these recommendations are unclear.

Aim: To evaluate the prevalence and impact of baseline NS5A RAS in NS5A treatment naïve (TN) persons with GT1a and GT3 in clinical practice.

Method: A retrospective chart review from 5 centres in Canada between January 2016 to November 2017. Patients evaluated included NS5A TN with GT 1a or GT 3, with baseline RAS testing. Patient demographics and fibrosis stage were collected. HCV sequence data by Next Generation Sequencing from the BC Centre for Excellence in HIV. Mutations >5% of viral population were reported. Resistance phenotype was determined on EC_{50} fold-shift in mutant vs. wild-type replicons. Only RAS that confer high level resistance to elbasvir or ledipsavir for GT1a and velpatasvir for GT3, as suggested by EASL/AASLD guidelines and the reference laboratory were evaluated.

Results: A total of 366 patients were included (264 GT1a and 98 GT3). Mean age was 52 years, 59% were male. Fibrosis data were available in 326 patients, with F0-2 in 197 (53.8%), F3 in 25 (7.6%) and F4 in 104 (32%) patients. Baseline NS5A RAS were present in 13 GT1a (4.9%) and 16 with GT3 (16.3%) patients tested. Of the 29 patients with baseline RAS 14 (48%) were F3-F4. In GT1a patients, 7 of 13 had a Y93H RAS, and 6 persons had 2 or more RAS. In GT3 patients 7 of 16 had a Y93H RAS, 12 had an A30 RAS, and 10 had 2 or more baseline RASs. No baseline S282T RAS were detected. In patients with treatment data available, ribavirin was added in 7 of 13 persons with a baseline RAS. SVR data in persons with a baseline RAS is pending. Overall SVR is 93% (70/75). Relapse occurred in 5 persons, none had a high potency baseline RAS. However, 1 GT1a patient had H54Y baseline RAS and a GT3 patient failed SOF/RBV had a S62 baseline RAS.

Conclusion: The prevalence of baseline NS5A RAS in this Canadian cohort is low in GT1a at <5%, and high in GT3 is higher at 16%. Half of the baseline NS5A RAS conferring high level resistance are of the Y93 type. Testing is preferentially conducted in those with advanced fibrosis.

THU-363

Efficacy and safety of glecaprevir/pibrentasvir in renally-impaired patients with chronic hepatitis C virus genotype 1–6 infection

M. Persico[1], R. Flisiak[2], M. Abunimeh[3], M. Sise[4], J.Y. Park[5], M. Kaskas[6], A. Bruchfeld[7], M.-A. Wörns[8], A. Aglitti[1], Z. Xue[3], J. Rullman[3], A. Pocalla[3], E. Lawitz[9]. [1]*University of Salerno, Internal Medicine and Hepatology Unit, Salerno, Italy;* [2]*Medical University of Bialystok, Department of Infectious Diseases and Hepatology, Bialystok, Poland;* [3]*AbbVie, Inc, North Chicago, United States;* [4]*Massachusetts General Hospital, Department of Medicine, Boston, United States;* [5]*Yonsei University College of Medicine, Department of Internal Medicine, Seuol, Korea, Rep. of South;* [6]*Northwest Louisiana Nephrology, Shreveport, United States;* [7]*Karolinska Institutet, Department of Renal Medicine, Karolinska University Hospital, Stockholm, Sweden;* [8]*University Medical Center of the Johannes Gutenberg-University Mainz, Department of Internal Medicine, Mainz, Germany;* [9]*University of Texas Health San Antonio, The Texas Liver Institute, San Antonio, United States*
Email: mpersico@unisa.it

Background and Aims: The direct acting-antivirals (DAA) glecaprevir (NS3/4A protease inhibitor; developed by AbbVie and Enanta) and pibrentasvir (NS5A inhibitor), coformulated as G/P, are a once-daily, all-oral treatment regimen with high rates of sustained virologic response at 12 weeks post-treatment (SVR12) and a favourable safety profile indicated for use in patients at any stage of chronic kidney disease (CKD). Here we report preliminary data from a Phase 3b study assessing the efficacy and safety of 8, 12, and 16 weeks of G/P treatment in patients with chronic hepatitis C virus (HCV) genotype (GT) 1–6 infection and CKD Stage 3b, 4, or 5, including those on dialysis. This study aims to provide further evidence supporting G/P's labeled regimen among patients with moderate or severe CKD, including efficacy of an 8-week G/P treatment duration for patients who are treatment naïve and non-cirrhotic.

Method: EXPEDITION-5 (NCT03069365) is an ongoing, Phase 3b, multicenter study evaluating the efficacy and safety of G/P in patients without cirrhosis or with compensated cirrhosis and with CKD. Patients were either treatment-naïve or -experienced with interferon (IFN), pegIFN ± ribavirin (RBV), or sofosbuvir (SOF) + RBV ± pegIFN. Prior treatment with a DAA other than SOF was not permitted. Patients had an estimated glomerular filtration rate (eGFR) < 45 ml/min/1.73 m^2 without a history of acute renal failure within 3 months prior to screening. Patients were treated with label (U.S. and E.U.) indicated treatment duration. Efficacy was evaluated by the percent of patients achieving SVR12 (HCV RNA < lower limit of quantification). Safety was assessed in all patients.

Results: In total, 101 patients were enrolled with 84, 13, and 4 patients receiving G/P for 8, 12, and 16 weeks, respectively. Demographics for the first 99 patients are as follows: 41 (41%) were female, 72 (73%) were white and 13 (13%) had compensated cirrhosis. At screening, 7 (7%), 17 (17%), and 75 (76%) patients had CKD stage 3b, 4, and 5, respectively; 73 (74%) patients required dialysis. Preliminary safety information identified pruritus, occurring in 14%, as the only adverse events (AEs) reported in ≥5% of patients. Grade ≥3 serious and non-serious treatment-emergent AEs were reported in 5% of patients; none of which were related to G/P or led to treatment discontinuation. To date, 5/5 patients treated with G/P for 8 weeks have achieved SVR12.

Conclusion: Preliminary safety data suggest that G/P was safe and well-tolerated. Complete SVR12 results will be presented at the congress.

THU-364

Multicenter study on outcome of HCV elimination using LDV/SOF combination in Mongolians

L. Nemekhbaatar[1,2], B. Oidov[2], D. Radnaa[2], S. Ulziibayar[2], M. Sarandavaa[2], J. Palam[2], T. Davaadorj[2], E. Damba[2], B. Dorjgotov[3], N. Dulmaa[4], A. Jenskhan[2], C. Nagir[2], S. Batmunkh[2], G. Uugantsetseg[5], M. Batmunkh[1], A. Jazag[2,6]. [1]*Institute of Medical Sciences, Mongolia, Central Scientific Research Laboratory, Ulaanbaatar, Mongolia;* [2]*Mongolian Association for the Study of Liver Diseases (MASLD);* [3]*Third Generel Hospital of Mongolia;* [4]*Darkhan-Uul Province Central Hospital;* [5]*National Center of Communicable Diseases;* [6]*Happy Veritas Diagnostic Center*
Email: lkhaasuren.ims@mnums.edu.mn

Background and Aims: The incident of liver cancer in Mongolia generally caused by HBV and HCV, and it is 7 times higher than that of world average. HCV, the most prevalent cause of HCC in Mongolia, is number one public health issue. Mongolia is one of the first countries that registered Ledipasvir/Sofosbuvir (LDV/SOF) regimen from developing countries. By the support of Access program run by Gilead Sciences, USA, we started HCV treatment program from January 2016.

Method: We followed and evaluated treatment outcome of patients with HCV infection using combination of 90 mg ledispavir/400 mg sofosbuvir (manufactured by Gilead Science) in 937 treatment naïve and 83 treatment experienced patients. All patients were treated with LDV/SOF for 12 weeks and, their treatment was evaluated by quantitative HCV-RNA assays prior and W (week) 4 and W12 of treatment. Sustained virological response (SVR) after 12 weeks treatment was assessed. Virus genotype analysis using cDNA microarray, liver enzymes, CBC and drug related adverse events were assessed in every patient. The laboratory tests were conducted at National Center of Communicable Diseases, Happy Veritas Laboratories and other provinces' health care center.

Results: We conducted largest ever (415/1020) HCV genotype (GT) distribution study in Mongolian chronic HCV patients. 96.6% (n = 401) of assessed patients were GT1b; 0.7% (n = 3) were GT2; 0,2% (n = 1) were GT1a and b; 0.9% (n = 4) were GT1b and 2; 0.5% (n = 2) were

GT1b and 6;0.2% (n = 1) were GT5 and 0.2% (n = 1) were GT1b and 80 k mutants respectively.
992/1020 (97.3%) patients achieved SVR12W, 28 (2.7%) patients who did not achieve SVR12W were all genotype 1b. Median ALT level significantly dropped during treatment from 95.5 ± 84,1 IU/l to 27.2 ± 18.6 IU/l and slightly increased by the end of treatment 42.9 ± 17.4 IU/l. Total of 39 adverse events were observed in 595/1,020 patients (58,3%). Single adverse events were observed in 401/1,020 (39.3%) whereas 2 and more events were observed in 194 (19%) patients respectively. Unreported adverse events such as partial facial palsy, AFP (alpha-fetoprotein) increase, melasma were observed.
Conclusion: We achieved 97.3% SVR12W for 3 months treatment with LDV/SOF this time. But viral relapse has to be determined repeatedly at weeks 24 and 48 post treatment. All viral relapses (n = 14) and non-responders (n = 14) were GT1 in our study. According to HCV genotype assessment, there was no difference in treatment outcomes between patients who had different genotypes. Genotype distribution of Mongolian patients confirmed the results of other smaller studies. HCV RNA clearance during treatment was no different than clinical trials, but the slight increase of ALT by the end of treatment was commonly observed. It might have happened due to rebound of immune reaction after clearance of HCV or a drug induced effect.

THU-365

Salvage treatment of HCV patients by Sofosbuvir, Daclatasvir, Simeprevir and Ribavirin after repeated treatment failures is associated with SVR and reduced risk of hepatocellular carcinoma

A. Hanafy[1], S. Abd-Elsalam[2], S. Soliman[3]. [1]*Zagazig University, Faculty of Medicine, Internal Medicine, Hepatology and Endoscopy Division, Zagazig, Egypt;* [2]*Tanta University, Tropical Medicine, Egypt;* [3]*Menoufyia University, Public Health, Egypt*
Email: dr_amr_hanafy@yahoo.com

Background and Aims: Although the response rates are enhanced after direct acting antiviral agents (DAAs), re-treatment of patients who failed prior DAAs remains challenging. No current FDA-approved regimen for prior DAA treatment failures. The aim was to evaluate the impact of repeated treatment failures to combined antiviral therapy on fibrosis progression, development of HCC and the efficacy of treatment of those patients with Sofosbuvir, Daclatasvir, Simeprevir and Ribavirin on the rate of SVR.
Method: The study included 100 patients with previous repeated treatment failures due to relapse, breakthrough or null response more than once to weight based ribavirin and pegylated interferon, ribavirin and sofosbuvir, or sofosbuvir, daclatasvir and weight based ribavirin. They were assigned as a study group (n = 50) who were given salvage treatment composed of Sofosbuvir 400 mg, Daclatasvir 60 mg, Simeprevir 150 mg and weight based Ribavirin for 3 months or a control group (n = 50) who were matched for age and gender and received placebo. Both groups were followed up for 2 years starting from the last non-respnse. All underwent routine investigations preliminary to combined anti viral therapy. Quantitative

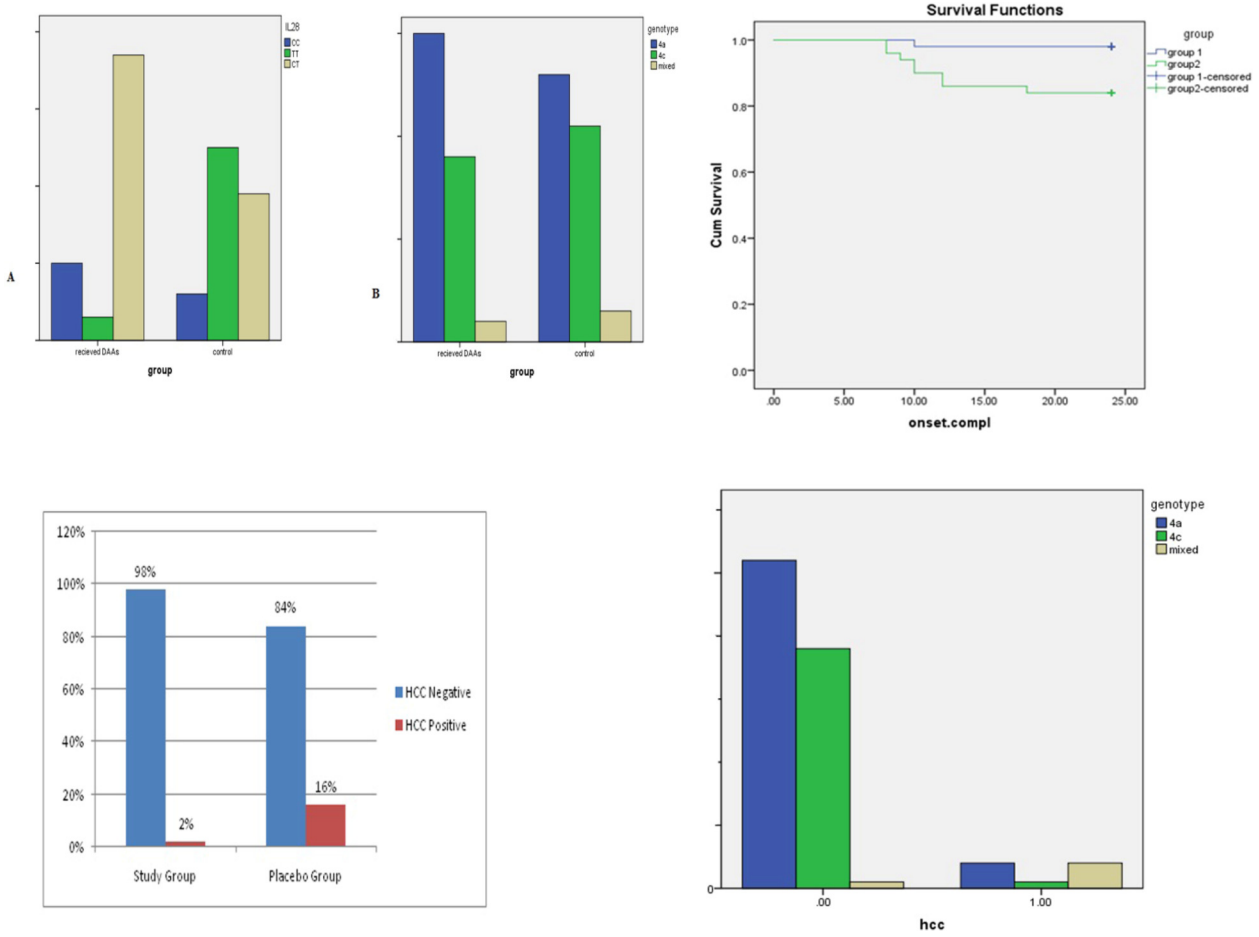


Figure: (abstract: THU-365)

measurement of HCV load by real time Quantitative PCR. Baseline Genotyping for the IL-28B polymorphism by PCR-based restriction fragment length polymorphism. Genotyping for HCV using INNO-LiPA II.

Results: IL-28 polymorphism CT was predominant (74%) followed by CC (20%) in the study group (p = 0.001). TT (50%) and CT (38%) were prominent in the control group (p = 0.000). Patients who received salvage treatment achieved SVR (100%) which was safe and well tolerated. one case (2%) in the study group developed HCC, while 8 cases (16%) in the placebo group developed HCC (p = 0.03) with risk ratio of 4.85 folds more in developing HCC than the study group. 3 cases (6%) in the HCC subgroup experienced hypoalbuminemia and ascites. The study group had significantly longer mean time to develop HCC than placebo group. A logistic regression analysis was performed to ascertain the effects of the drug, on the likelihood of having HCC and showed that Patients who did not have the assumed treatment were 9.33 times more likely to develop HCC. Variables independently associated with the occurrence of HCC if salvage therapy was not given were diabetes, BMI, and HCV genotype with a likelihood ratio (69.4, 15.4 and 29.8 respectively). The whole HCC patients were diabetics (n = 9, 100%), 4 patients were genotype 4a (44.4%), 4 patients were mixed 4,1b (44.4%). Although salvage therapy was protective from HCC, however SVR was not associated with improvement of liver stiffness by fibroscan.

Conclusion: Salvage Treatment of HCV by Sofosbuvir, Daclatasvir, Simeprevir and Ribavirin is highly effective in HCV patients with repeated treatment failures and is associated with 100% SVR and much lower risk of HCC in these patients.

THU-366

Sofosbuvir/Ledipasvir: Efficacy and tolerance in HCV positive patients naïve or pre-treated in Cameroun

S. Tchamgoue[1], H. Leundji[2], M. Tagny-Sartre[3], C. Tzeuton[4], G. Esmat[5].
[1]*Polyclinique Bordeaux Douala, Infectious Disease, Douala, Cameroon;* [2]*SOS Hepatites, Viral Department, Douala, Cameroon;* [3]*Cabinet medical la Cathedrale, Viral Hepatitis, Yaounde, Cameroon;* [4]*Cameroun Hepatogastroenterologic Society, Viral Hepatitis, Douala, Cameroon;* [5]*Cairo University, Faculty of Medicine, Cairo, Egypt*
Email: stchamgoue@yahoo.fr

Background and Aims: In Cameroun, HCV sero prevalence is around 2–7%. HCV is characterized in Cameroun by its high genetic diversity with the circulation of three genotypes HCV-1, HCV-2 and HCV-4 and more than 10 HCV subtypes. Health authorities have decided to import and prescribe Direct Acting Antivirals (DAA) in generic form from 29/07/2016. Decentralization of DAA prescriptions in five of the ten regions followed, under the operational responsibility of the Regional Therapeutic Committees. This was the genesis of this observational study, approved by Cameroon's National Committee of Ethics, whose purpose was to check the efficiency of these new generic antiviral treatment on local VHC viral strains characterized by their phylogenetic diversity, under normal conditions of use in the regions.

Objective: To assess the safety and efficacy of fixed-dose combination SOF/LED (Sofosbuvir 400 mg/Ledipasvir 90 mg) in HCV G1 & 4 patients.

Method: Observational study. **Inclusion criteria:** Age ≥ 18, HCV G 1 or 4, HCV naïve or pre-treated, consent to treatment. **Exclusion criteria:** Pregnant woman, HBV co-infection, Liver decompensation, malignancy, Impaired clinic disorder, Creatinine Clairance MDRD <70 ml/mn**,** drugs: Amiodarone, Digoxin, Amlodipine, Diltiazem, Rosuvastatin, Rifampicine, Carbamazepim, Ongoing Local Traditional Drugs.

Intervention: Drug1: SOF/LDV, ***Mpiviropack Plus****(*Marcyl pharmaceutical-Le Caire, Egypt*): one tablet per day during 12W. Drug 2: Ribavirine 200 mg (<75 kg = 1000 mg and ≥75 kg = 1200 mg). If previous Peg IFN.

Endpoint: % of patients with SVR 12.

Results: Socio-demographic: Female Sex: n = 38/65 (58%), Alcohol Consumption n = 16/59 (27%), Age > 63 ans n = 32/64 (50%), BMI > 27 n = 23/45 (50%), HIV positive n = 2/55 (3.6%), Tobacco n = 2/64 (3.1%), Cannabis n = 0, Diabetes n = 10/63 (16%), HTA n = 25/64 (39%). **Clinic** : Pre treated Peg IFN n = 9/64 (14%), Pre treated (Telap/Bocep/Sofosbuvir) n = 0, Fibrosis : Fibroscan F0 (0–1 kpa) n = 5/61 (8.2%), F1 (2–5 kpa) n = 16/61 (26.2%), F2 (6–9 kpa) n = 18/61 (29.5%), F3 (10–13 kpa) n = 7/61 (11.4%), F4 (≥14 kpa) n = 15/61 (24.5%), Cirrhosis n = 15/61 CHILD A n = 15/15, Ascite n = 0, Digestive Bleeding n = 0, Encephalopathy n = 0. **Virology**: VHC genotype 1 n = 33/65 (50.7%), Genotype 4 n = 32/65. Subtypes G1 (n = 33): a= 6 b = 19 ab = 1 h = 1 l = 1 nc = 2 undetermined n = 3. Subtypes G4 (n = 32): abc = 1 acd = 2 e = 1 f = 18 nc = 1 r = 1 t = 1 undetermined n = 7.

Outcome August 31, 2017: HCV VL < 15 UI at **SVR12 n = 30/33 (90.91%).** HCV VL < 15 UI at W12 n = 45/46 (97.8%). HCV VL < 15 UI at S4 n = 16/22 (72.7%). **Tolerance at W4**: headache n = 2/43 (4.7%), Insomnia n = 1/43 (2.3%), Asthenia n = 3/43 (6.9%).

Conclusion: In this local regional Camerounian context, the efficiency (90% of patients cured) and tolerance of this Sofosbuvir/Lédipasvir generic form was similar to the data previously published in developed country.

THU-367

Hepatitis B virus reactivation during direct-acting antiviral therapy in hepatitis B/C co-infected patients on hemodialysis

C. Hu[1], J. Wang[2], J. Liu[2], T. Yan[2], Y. Yang[2], T. Chen[2], Y. Zhao[2], Y. He[2].
[1]*School of Medicine, Xi'an Jiaotong University, Department of Infectious Diseases, Xi'an, China;* [2]*First Affiliated Teaching Hospital, School of Medicine, Xi'an Jiaotong University, Department of Infectious Diseases, Xi'an, China*
Email: xjtuhuchunhua@163.com

Background and Aims: There are increased reports of hepatitis B virus (HBV) reactivation during direct-acting antivirals (DAAs) treatment in HBV and hepatitis C virus (HCV) co-infected patients. The potential risk of HBV reactivation in the patients with end-stage renal disease who are undergoing hemodialysis has been also noted. Whereas, there are a lack of data pertaining to the reactivation risk during DAAs treatment in those co-infected patients undergoing hemodialysis.

Method: HBV/HCV co-infected patients were screened from 178 persons in the two blood purification centers of Zhen'An County, Shaanxi province, China and received sofosbuvir (200 mg) combined with daclatasvir (60 mg) daily. The risk of HBV reactivation during DAAs treatment in those co-infected patients undergoing hemodialysis was retrospectively analyzed.

Results: HBV reactivation occurred in 5 of 11 (45.45%) HBV/HCV co-infected patients with hemodialysis during DAAs treatment, which was much higher than the reported rate (approximately 12%) in co-infected patients without hemodialysis. Among the 11 co-infected patients, 7 were HBsAg(+) before DAAs treatment, 5 of the 7 subjects had significant increase of HBV DNA load (5.04 ± 3.41 Log_{10} IU/ml) after the treatment; 4 patients were negative for HBsAg and positive for anti-HBc or HBV DNA at baseline, all of the 4 subjects were persistent HBsAg(−) and had no elevated HBV DNA levels during the whole DAAs treatment. None of the 11 patients had severe hepatitis, hepatic failure or icteric hepatitis due to HBV reactivation, 3 in 5 (60%) patients with HBV reactivation had mild hepatitis (peak ALT levels were 45.92, 54.00 and 63.74 U/l, respectively), whereas none of the 6 patients without HBV reactivation developed hepatitis.

Conclusion: A significant proportion of HBV/HCV co-infected patients undergoing hemodialysis developed HBV reactivation after DAAs therapy. The risk of HBV reactivation was more significant in the HBsAg(+) patients compared to those patients with HBsAg(−) and anti-HBc(+) or HBV DNA(+).

THU-368

High efficacy of resistance guided retreatment of Genotype 3 in real life

A.B.P. Jimenez[1], A. Sánchez[1], F.T. Pérez[2], M. Jiménez[3], J. Salmerón[4], J.M.R. Zabal[5], J.C.A. Arboledas[6], M. Casado[7], D. Merino[8], A.D.L.I. Salgado[9], A.R.C. Romacho[10], M.J. Álvarez-Ossorio[11], J. Hernández-Quero[12], J.M. Pascasio[13], N. Espinosa[14], C. Delgado[15], F.G.D.A. Clotilde[16], J. De Juan[17], A. Poyato[18], F.M. Jimenez[19], B.B. Carral[20], F.G. Garcia[21]. *[1]Hospital Campus de la Salud, Clinical Microbiology, Granada, Spain; [2]Hospital de la Línea de la Concepción, Infectious Diseases Unit, La Línea de la Concepción, Spain; [3]Hospital Regional de Málaga, Digestology Unit, Málaga, Spain; [4]Hospital Universitario San Cecilio, Digestology Unit, Granada, Spain; [5]Hospital Costa del Sol, Infectious Diseases Unit, Marbella, Spain; [6]Hospital Jerez de la Frontera, Clinical Microbiology, Jerez de la Frontera, Spain; [7]Hospital General Torrecárdenas, Digestology Unit, Almería, Spain; [8]Hospital Infanta Elena, Infectious Diseases Unit, Huelva, Spain; [9]Hospital Infanta Elena, Clinical Microbiology, Huelva, Spain; [10]Hospital General Torrecárdenas, Infectious Diseases Unit, Almería, Spain; [11]Hospital Nuestra Señora de Valme, Infectious Diseases Unit, Sevilla, Spain; [12]Hospital Campus de la Salud, Infectious Diseases Unit, Granada, Spain; [13]Hospital Universitario Virgen del Rocío, Digestology Unit, Sevilla, Spain; [14]Hospital Universitario Virgen del Rocío, Infectious Diseases Unit, Sevilla, Spain; [15]Hospital Alto Guadalquivir, Infectious Diseases Unit, Andújar, Spain; [16]Hospital Universitario Puerta del Mar, Clinical Microbiology, Cádiz, Spain; [17]Centro Penitenciario de Córdoba, Penitenciary Institution Physician, Córdoba, Spain; [18]Hospital Universitario Reina Sofía, Digestology Unit, Córdoba, Spain; [19]Hospital Juan Ramón Jiménez, Digestology Unit, Huelva, Spain; [20]Hospital Punta de Europa, Clinical Microbiology, Algeciras, Spain; [21]Hospital Universitario San Cecilio-Campus de la Salud. Instituto de Investigación Biosanitaria Iba, Clinical Microbiology, Spain*
Email: fegarcia@ugr.es

Background and Aims: Hepatitis C Virus Genotype 3 treatment with conventional regimens results in higher rates of virological non-response than in other genotypes. Here we describe the characteristics of genotype 3 infected patients that have failed to first line direct acting antiviral (DAA) treatment, how they have been retreated and what was the efficacy when the new regimen was resistance guided.

Method: Genotype 3 patients from the GEHEP004 cohort were selected. After virological failure, population sequencing of NS5B & NS5A HCV genes was performed, and a comprehensive resistance report was given to the treating physician. After follow up, SVR12 of the retreatment regimen was evaluated.

Results: GEHEP-004 includes 86 patients infected by GT3a that have failed a first line treatment with DAA [93.0% male, median age 53 (IQR 49–56), median log Viral Load 5.90 (IQR 5.32–6.56), 70.6% cirrhotic, 28.2% HIV coinfected, 40.6% treatment experienced-TE]. Patients had failed SOF/DCV ± RBV (59.3%), SOF/LDV ± RBV (28.0%) and SOF/RBV (8.1%). Six patients were GT3a at failure but GT1 (2 GT1a, 4 GT1b) at baseline; 4.7% of the patients failed PrO ± DSV ± RBV. At failure, Y93H was detected in 47 patients (54.7%), and was significantly more prevalent in PrOD ± RBV (100.0%; 4/4) and SOF/DCV ± RBV (70.6%; 36/51) than SOF/LDV ± RBV (25.0%; 6/24) failures [$p < 0.01$]. Almost two thirds of the patients (53) have not been retreated. Cirrhosis (23 vs 25, $p = 0.55$), HIV coinfection (11 vs 9, $p = 0.29$), TE (14 vs 12, $p = 0.75$) and RASs (25 vs 23, $p = 0.13$) were not significantly related to the decision of starting retreatment. Of the 33 patients that have been retreated, 24 have completed treatment evaluation, and 21 have reached SVR12: 12/14 (85.7%) with SOF/DCV ± RBV for retreatment, 1/1 SOF/VEL, 3/3 SOF/LDV ± RBV, 2/2 SOF/GRZ/EBV/RBV, 2/2 PegINF/SOF/RBV and 1/2 with SOF/RBV. Three additional patients have reached EOT response with SOF/VEL/RBV and 1 with SOF/GRZ/EBV/RBV.

Conclusion: More than half of the GT3a infected patients that have failed a first line treatment with DAAS are on hold for retreatment. Waiting for new regimens was not related to cirrhosis, HIV coinfection, TE or RASs detection at failure. Resistance guided retreatment of GT3a resulted in high SVR12 rates, close to 90%.

THU-369

Z-PROFILE: Real-world utilization and effectiveness of elbasvir/grazoprevir in adult patients with chronic hepatitis C in Canada

B. Conway[1], E. Tam[2], J. Tremblay[3], C. Fraser[4], A. Ramji[5], S. Borgia[6], K. Tsoi[7], E. Yoshida[8], B. Rajendran[9], K. Stewart[10], G. Macphail[11], B. Trottier[12], P. Ghali[13], J. Halsey-Brandt[14], J. Trepanier[14]. *[1]Vancouver Infectious Diseases Centre, Vancouver, Canada; [2]LAIR Centre, Vancouver, Canada; [3]Centre Sida Amitié, Canada; [4]The Cool Aid Community Health Centre, Victoria, Canada; [5]GI Research Institute (GIRI), Gastroenterology Division, Vancouver, Canada; [6]William Osler Health System, Canada; [7]St. Joseph's Healthcare Hamilton, Hamilton, Canada; [8]Vancouver General Hospital, Vancouver, Canada; [9]The Peterborough Clinic, Canada; [10]Saskatchewan Infectious Disease Care Network, Saskatoon, Canada; [11]Calgary Urban Project Society (CUPS), Canada; [12]Clinique Médicale du Quartier Latin, Canada; [13]McGill University Health Center, Canada; [14]Merck Canada Inc., Canada*
Email: brian.conway@vidc.ca

Background and Aims: Elbasvir/grazoprevir (EBR/GZR) is approved in Canada for the treatment of chronic HCV infection: genotypes (GT) 1 and 4, with/without ribavirin, and GT3 with sofosbuvir (SOF). The aim of this study is to describe the effectiveness of EBR/GZR and the profile of patients selected for treatment in a Canadian real-world setting.

Method: A multicenter retrospective chart review of HCV-infected patients treated with EBR/GZR among selected Canadian health care providers was undertaken.

Results: In this interim analysis, a total of 267 patients from 13 sites who initiated treatment between 01/2016 and 10/2017 were included. The mean age was 53.5 years, 61.0% were male, 76.8% Caucasian and 7.9% Aboriginal. Genotype distribution included GT1a (n = 153, 57.3%), GT1b (n = 47, 17.6%), GT3 (n = 34, 12.7%), GT4 (n = 13, 4.9%), and other (n = 20, 7.5%). Pre-treatment fibrosis evaluation (by FibroScan in 84% of cases) included F0-1 (n = 144, 53.9%), F2 (n = 44, 16.5%), F3 (n = 23, 8.6%), F4 (n = 51, 19.1%) and 5 (1.9%) not assessed for fibrosis. In this cohort, 8.6% had CKD stages 3–5 and 18.4% had documented injection of illicit drugs within 12 months of EBR/GZR treatment initiation. There were 36 patients tested for baseline resistance-associated substitutions (RAS). Baseline NS5A RAS of potential clinical relevance (ie. 28, 30, 31 or 93) were detected in 2 patients at position 28 and in 1 patient at position 30. Prescribed regimens included: EBR/GZR × 8 weeks (n = 1, 0.4%); EBR/GZR × 12 weeks (n = 245, 91.7%); EBR/GZR +/− RBV × 16 weeks (n = 21, 7.9%). Patients receiving longer courses of treatment were most often infected by GT1a (n = 14) and/or treatment experienced (n = 17, including 3 who previously failed all-oral DAAs). Sofosbuvir was prescribed with EBR/GZR for all 35 patients with GT3, including the 2 with mixed genotypes. Among patients who had SVR data available at the time of data collection, the per protocol SVR12 rate was 96.6% (140/145).

Conclusions: The combination of EBR/GZR is highly effective in a variety of patient populations in real life, including a broad range of genotypes, disease stages, with or without RAS testing and in special populations (CKD, PWUD). Its use in clinical practice will play an important role in achieving the World Health Organization goals of eliminating HCV infection as a public health concern by 2030. Final results of the full cohort (n = 400) will be presented.

THU-370

Efficacy of Elbasvir-Grazoprevir/Sofosbuvir and Ribavirin in direct acting antiviral therapy failures in pre and post liver transplant patients: A single center experience

H. Elbeshbeshy[1], H. Hasan[2], I. Salih[2], H. Elsiesy[2], W. Alhamoudi[2], F.A. Alkhail[2]. *[1]King Faisal Specialist Hospital & Research Center, Liver Transplant; [2], Saudi Arabia*
Email: hany.elbeshbeshy@yahoo.com

Background and Aims: Hepatitis C Virus (HCV) is the leading cause of liver cirrhosis and hepatocellular carcinoma (HCC). It is also so far still the most common indication of liver transplantation. Treatment of HCV will lead to reduction of progression to advanced liver disease, decrease the incidence of HCC and increase overall survival both patient & graft, patients who achieve Sustained Virologic Response (SVR) have better graft outcome.
Significant advances in treatment of HCV have been achieved with the use of Direct Acting Antivirals (DAA's). Treatment of HCV in DAA failures is a new challenge with limited data available. There has been new data supporting treatment of HCV DAA failures with fixed dose Elbasvir-Grazoprevir/Sofosbuvir with Ribavirin.
To determine the efficacy of fixed dose Elbasvir-Grazoprevir/Sofosbuvir with Ribavirin, in the treatment of HCV DAA failures, pre & post liver transplant.
Method: This is a single arm retrospective observational study of patients with HCV DAA failures pre & post liver transplant. Patients received fixed dose Elbasvir-Grazoprevir/Sofosbuvir with Ribavirin for 16 weeks, with weeks 4 & 16 HCV-PCR & SVR 12 reported.
Data was collected from the liver transplant Clinic over 16 months from June 2016 to October 2017 for adult patients (>18 years) before & after liver transplant with HCV who previously failed prior DAA regimens. Only patients who completed 16 weeks of therapy were enrolled. Follow up every 2–4 weeks during treatment & every 3 months after treatment or as clinically indicated.
Results: 22 patients have been identified & included in this study, 14 males & 8 females, with age range between 39–75 years old. With 2 patients had genotype 1a, 2 patients had genotype 1b, 1 patient had genotype 3, 7 patients had mixed genotypes 1 & 4, & 10 patients had genotype 4. From the study cohort, 8 (36.4%) were treated preLiver transplant, & 14 (63.6%) were treated post liver transplant. 19 patients were relapsers to prior treatment with one DAA regimen & 3 patients relapsed to treatment with two DAA regimens. The baseline HCV-PCR before starting re-treatment ranged from 89,473 to 18,212,025 IU/ml. HCV-PCR was undetectable at week 4 in 9 patients (45.5%), and at week 16 HCV-PCR was undetectable in 20 patients with 2 patients have no results as they missed their week 16 HCV-PCR testing.
At the time of reporting this data, SVR12 was achieved in 100% of 19 patients (86.4%) with 3 patients (13.6%) still awaiting SVR12 results.
Conclusion: Fixed dose Elbasvir-Grazoprevir/Sofosbuvir with Ribavirin is highly effective in patients who are DAA relapsers with intention to treat SVR12 of 100%.

THU-371

Real world experience with twelve weeks of therapy without ribavirin in genotype 1 HCV infected compensated cirrhotics

D. Zarębska-Michaluk[1], R. Flisiak[2], E. Janczewska[3], H. Berak[4], H. Andrzej[5], J. Jaroszewicz[6], A. Garlicki[7], M. Sitko[7], B. Dobracka[8], A. Czauż-Andrzejuk[2], D. Dybowska[9], W. Halota[9], M. Włodzimierz[10], K. Tomasiewicz[11], M. Tudrujek[11], D. Zbigniew[12], B. Baka-Ćwierz[13], T. Belica-Wdowik[13], I. Orłowska[14], S. Krzysztof[14], J. Bialkowska-Warzecha[15], B. Lorenc[16], R. Krygier[17], A. Piekarska[18], J. Citko[19], A. Gietka[20], A. Staniaszek[20], M. Wawrzynowicz-Syczewska[21], Ł. Laurans[21], Ł. Socha[21], M. Pawłowska[9]. *[1]Voivodship Hospital Kielce, Department of Infectious Diseases, Kielce, Poland; [2]Medical University of Białystok, Department of Infectious Diseases and Hepatology, Białystok, Poland; [3]ID Clinic, Mysłowice, Poland; [4]Hospital for Infectious Diseases, Warszawa, Poland; [5]Hospital for Infectious Diseases, Warsaw, Poland; [6]Medical University Katowice, Department of Infectious Diseases, Bytom, Poland; [7]Collegium Medicum Jagiellonian University, Department of Infectious and Tropical Diseases, Kraków, Poland; [8]MED-FIX, Wrocław, Poland; [9]Faculty of Medicine, Collegium Medicum Bydgoszcz, Nicolaus Copernicus University Toruń, Department of Infectious Diseases and Hepatology, Bydgoszcz, Poland; [10]Specialist Hospital in Chorzów, Clinical Department of Infectious Diseases, Chorzów, Poland; [11]Medical University of Lublin, Department of Infectious Diseases and Hepatology, Lublin, Poland; [12]Biegański Regional Specialist Hospital, Ward of Infectious Diseases and Hepatology, Łódź, Poland; [13]John Paul II Hospital, Regional Center for Diagnosis and Treatment of Viral Hepatitis and Hepatology, Kraków, Poland; [14]Wrocław Medical University, Department of Infectious Diseases and Hepatology, Wrocław, Poland; [15]Medical University of Łódź, Department of Infectious and Liver Diseases, Łódź, Poland; [16]Medical University of Gdańsk, Pomeranian Center of Infectious Diseases, Department of Infectious Diseases, Gdańsk, Poland; [17]NZOZ "Gemini", Infectious Diseases and Hepatology Outpatient Clinic, Żychlin, Poland; [18]Medical University of Łódź, Department of Infectious Diseases and Hepatology, Łódź, Poland; [19]Regional Hospital, Medical Practice of Infections, Olsztyn, Poland; [20]Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Department of Internal Medicine and Hepatology, Warszawa, Poland; [21]Pomeranian Medical University, Department of Infectious Diseases, Hepatology and Liver Transplantation, Szczecin, Poland*
Email: dorota1010@tlen.pl

Background and Aims: Large majority of cirrhotic patients were up to now treated with addition of ribavirin, which was associated with enhanced risk of adverse events. We evaluated efficacy of 12 weeks interferon-free regimens without ribavirin in cirrhotic patients in real-world experience.
Method: Data of HCV infected patients with compensated liver cirrhosis from 22 centers were analysed. Patients were assigned to treatment schedule based on physician decision, then treated according to recommendations. Data were collected retrospectively using the online questionnaire.
Results: A total of 1105 cirrhotic patients infected with genotype 1 (97% genotype 1b) HCV treated with any regimen were included into analysis. Among them 240 were treated for 12 weeks without ribavirin, that included: 44% treatment-experienced (mostly PegIFN + RBV), 78% patients with comorbidities (mostly hypertension and diabetes), 70% with concomitant medications. They were assigned to OBV/PTV/r + DSV regimen (90%), LDV/SOF (9%) or SOF + SMV (1%) and were treated for 12 weeks. Overall, SVR rate was 96% in ITT analysis and 98% in modified ITT analysis that excluded patients lost to efficacy follow-up. SVR rate for LDV/SOF and SOF + SMV regimens reached 100%, and for OBV/PTV/r + DSV 98%. Adverse events were documented in 38% with the most common weakness/fatique. Serious adverse events were observed in 5% patients and one death not related to medication was reported.
Conclusion: In this real-world study we confirmed no need of ribavirin addition and treatment lenght exceeding 12 weeks in genotype 1 HCV infected compensated cirrhotics.

THU-372

Sofosbuvir-based treatment of viral hepatitis C genotype 3 infection – A Polish real-world study

D. Zarębska-Michaluk[1], R. Flisiak[2], J. Jaroszewicz[3], E. Janczewska[4], A. Czauż-Andrzejuk[5], H. Berak[6], H. Andrzej[7], A. Staniaszek[8], A. Gietka[9], M. Tudrujek[10], K. Tomasiewicz[10], D. Dybowska[11], W. Halota[11], A. Piekarska[12], M. Sitko[13], A. Garlicki[13], I. Orłowska[14], S. Krzysztof[15], T. Belica-Wdowik[16], B. Baka-Ćwierz[16], M. Włodzimierz[17], J. Bialkowska-Warzecha[18], Ł. Socha[19], M. Wawrzynowicz-Syczewska[19], Ł. Laurans[19], D. Zbigniew[20], B. Lorenc[21], B. Dobracka[22], T. Olga[23], M. Pawłowska[11]. *[1]Voivodship Hospital, Department of Infectious Disease, Kielce, Poland; [2]Medical University of Bialystok, Department of Infectious Disease, Bialystok, Poland; [3]Department of Infectious Diseases and He, Medical University of Silesia in Katowice, Bytom, Poland; [4]ID Clinic, Hepatology Outpatient Clinic, Myslowice, Poland; [5]Department of Infectious Diseases and Hepatology, Medical University of Białystok, Białystok, Poland; [6]Hospital for Infectious Diseases, Warsaw, Warsaw, Poland; [7]Warsaw Medical University, Department of Adults' Infectious Diseases, Warsaw, Poland; [8]Department of Internal Medicine and Hepatology, Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Poland; [9]Central Clinical Hospital of the Ministry of Internal Affairs and Administration, Department of Internal Medicine and Hepatology,*

Poland; [10]Medical University of Lublin, Department of Infectious Diseases and Hepatology, Poland; [11]Nicolaus Copernicus University, Faculty of Medicine, Collegium Medicum, Department of Infectious Diseases and Hepatology, Bydgoszcz, Poland; [12]Medical University of Łódź, Department of Infectious Diseases and Hepatology, Poland; [13]Jagiellonian University Collegium Medicum, Department of Infectious and Tropical Diseases, Poland; [14]Wrocław Medical University, Department of Infectious Diseases and Hepatology, Poland; [15]Wrocław Medical University, Department of Infectious Diseases and Hepatology, Wroclaw, Poland; [16]John Paul II Hospital, Regional Center for Diagnosis and Treatment of Viral Hepatitis and Hepatology, Poland; [17]Szpital Specjalistyczny, Clinical Department of Infectious Diseases, Chorzów, Poland; [18].Medical University of Łódź, Department of Infectious and Liver Diseases, Lodz, Poland; [19]Pomeranian Medical University, Department of Infectious Diseases, Hepatology and Liver Transplantation, Poland; [20]WSSz im. Wł. Biegańskiego, Ward of Infectious Diseases and Hepatology, Łódź, Poland; [21]Medical University of Gdańsk, Pomeranian Center of Infectious Diseases, Department of Infectious Diseases, Poland; [22]MED-FIX, Medical Center, Wroclaw, Poland; [23]Medical University of Warsaw, Department of Transplantation Medicine, Nephrology, and Internal Diseases, Warszawa, Poland
Email: dorota1010@tlen.pl

Background and Aims: Currently available therapeutic options for patients infected with genotype 3 HCV are based on sofosbuvir. Aim of the study is analysis of treatment available for those patients in Poland at the beginning of interferon-free era and evaluation of efficacy and safety of different therapeutic options administered in real world setting.
Method: We analysed data of HCV genotype 3 infected patients who started antiviral therapy after 1 July 2015 and completed before 31 December 2016. Patients were assigned to treatment regimen based on the physician discretion.
Results: A total of 198 patients were enrolled to the analysis. 57.6% of them had liver cirrhosis and 46% were treatment-experienced. 60.8% of study cohort presented comorbidities and 61.3% were treated with concomitant medications. 50% of patients were assigned to SOF + PegIFNa + RBV, 9% to PegIFNa + RBV, 36% received SOF + RBV and 5% SOF + DCV ± RBV. Cirrhotic patients were assigned more frequently to IFN-free regimens. Overall, the sustained virological response achieved 84% patients in intent-to-treat analysis (ITT) and 87% in modified ITT. For SOF + PegIFNa + RBV or SOF + DCV ± RBV regimens SVR rate reached 94% and 100% respectively, whereas two other therapeutic options demonstrated efficacy below 80%. SVR rate in non-cirrhotics was higher compared to cirrhotics irrespective of regimen. There was no difference of adverse events prevalence in respect to interferon administration (51% vs 54%) with the most common weakness/fatique and anemia related to RBV.
Conclusion: We confirmed effectiveness and safety of the sofosbuvir-based treatment in real-world cohort of patients with chronic HCV genotype 3 infection. Most notably we demonstrate good tolerability and high efficacy of SOF + PegIFNa + RBV regimen which are comparable to DCV + SOF ± RBV.

THU-373

Naturally occurring drug resitance substitutions in the NS5A and NS5B regions in Hepatitis C virus genotype 2 and response to sofosbuvir plus ribavirin therapy

K. Hayashi, M. Ishigami, Y. Ishizu, T. Kazuya, T. Honda, Y. Hirooka, H. Goto. *Nagoya University, Gastroenterology and Hepatology, Nagoya, Japan*
Email: kazuh@med.nagoya-u.ac.jp

Background and Aims: Interferon (IFN) free therapy has improved sustained virological response (SVR) and decreased adverse events compared than IFN based therapy. However, IFN free therapy has resistance associated amino acid substitution (RAS) in the target regions and preexisting these RAS reduces the SVR rate. Majority of these reports about association between RAS and SVR were investigated among patients infected with HCV genotype 1. However, little was known about association between RAS and effect on response to Sofosbuvir (SOF) plus ribavirin (RBV) therapy in patients with genotype 2. Although SOF plus RBV combination therapy has been recently replaced by the new regimen as SOF plus velpatasvir combination in Europe and USA, SOF and RBV combination therapy was still standard care for patients with HCV genotype 2 in Japan. The aim of this study was to investigate the prevalence of RAS in NS5A and NS5B regions and association between RAS and SVR to SOF and RBV combination therapy in patients with genotype 2.
Method: One hundred sixty five patients with chronic hepatitis C genotype 2 were enrolled. Patients received SOF once day plus weight dose RBV for 12 weeks. HCV was genotyped by direct sequencing of the 5'-untranslated region and/or NS5B region. Identification of RAS in the NS5A and NS5B regions was detected by direct sequencing at pretreatment.
Results: NS5A RAS T24A (n = 8), L31M (n = 100), and C92S/Y (n = 2) in genotype 2a and T24A (n = 1), L31M (n = 38), and C92S/Y (n = 24) in genotype 2b were detected at pretreatment. NS5B RAS M298V/I (n = 3) in genotype 2a and M298V/I (n = 10) in genotype 2b and were detected. NS5A Y93H and NS5B S282T which are lead to a high level resistance to NS5A and NS5B inhibitors respectively were not found. One hundred thirty of 136 (95.6%) patients showed a SVR. RAS at baseline was not related to SVR on univariate analysis. There were no significant differences in other factors related to SVR, including age, sex, aspartate aminotransferase, alanine aminotransferase, platelet count, HCV genotype, and HCV viral load. We compared the alignment of the amino acid sequence of NS5A and NS5B region at baseline and at the time of relapse in patient with non-SVR but RAS did not emerged after failure to treatment.
Conclusion: The naturally occurring RAS such as T24A (5%), L31M (83.6%), C92S/Y (3.6%) in NS5A and M298V/I (7.9%) in NS5B were found in patients with HCV genotype 2. The presence of RAS in NS5A and NS5B region at pretreatment was not associated with response to SOF plus RBV combination in patients with HCV genotype 2. No RAS in NS5A and NS5B region emerged in patients who fail to SOF plus RBV combination therapy.

THU-374

Effectiveness and safety of direct-acting antiviral therapies in chronic hepatitis C infections patients with cirrhosis in Turkey

F. Tabak[1], N.O. Cuvalci[2], B. Kurtaran[3], Y. Onlen[4], N.D. Sari[5], S. Kaya[6], N. Ince[7], S. Esen[8], I. Dokmetas[9], M. Namiduru[10], A. Batirel[11], T. Yamazhan[12] and Hepatit C Study Group[13]. *[1]Istanbul University School of Medicine, Department of Infectious Diseases; [2]Antalya Research and Training Hospital, Department of Infectious Diseases; [3]Cukurova University Medical School, Department of Infectious Diseases; [4]Mustafa Kemal University School of Medicine, Department of Infectious Diseases; [5]Istanbul Research and Training Hospital, Department of Infectious Diseases; [6]Istanbul University School of Medicine, Department of Gastroenterology; [7]Duzce University School of Medicine, Department of Infectious Diseases; [8]On Dokuz University School of Medicine, Department of Infectious Diseases; [9]Sisli Research and Training Hospital, Department of Infectious Diseases; [10]Gaziantep University School of Medicine, Department of Infectious Diseases; [11]Kartal Research and Training Hospital, Department of Infectious Diseases; [12]Ege University School of Medicine, Department of Infectious Diseases; [13]Turkey*
Email: fehmitabak@yahoo.com

Background and Aims: Turkish Viral Hepatitis Society (VHSD) and Infectious Diseases and Clinical Microbiology Specialty Society (EKMUD) created an online database and collect data of patients with chronic hepatitis C (CHC) patients using direct-acting antiviral therapies (DAA) in Turkey. This abstract aims to evaluate effectiveness and safety of DAA in chronic hepatitis C infection patients with cirrhosis in Turkey.

Method: Between April 2017 and October 2017, 36 centres from Turkey recorded 1500 patients to the database. Patients >18 years with CHC under direct-acting antiviral therapies were enrolled in this non-interventional observational study. Efficacy and safety results are only given for the patients with SVR12 data. The study was approved by ethics committee and registered to clinicaltrials.gov (NCT03145844)

Results: Of the 1500 patients; 13.7% (205/1500) were cirrhotic. Of those, 51.2% (105/205) were female and mean age was 64.2 (SD:10.9) years. The most common HCV genotype was GT1 (90.7%, 186/205; of those 86.6% GT1b, 7.0% GT1a). 87.3% (179/205) had compensated cirrhosis whereas 11.2% (23/205) had decompensated cirrhosis (Child-Pugh B-C).

Of the patients 51.2% (105/205) were treatment experienced and 86.7% (91/105) had used peginterferon/ribavirin, 6.7% (7/105) peginterferon/ribavirin plus boceprevir and 2.9% (3/105) peginterferon/ribavirin plus telaprevir. Current treatments were ledipasvir/sofosbuvir ± ribavirin (60.5%, 124/205), paritaprevir/ritonavir/ombitasvir ± dasabuvir ± ribavirin (27.8%, 57/205) and sofosbuvir + ribavirin (3.9%,8/205).

Of the 205 cirrhotic patients; 48.8% (100/205) had an SVR12 evaluation. Before DAA and at SVR12; median AST was 52.0 and 22.4 U/l, median ALT was 49.0 and 19.0 U/l, median INR was 1.10 and 1.10, median platelet was 119,000 count/mL and 122,500 count/mL, respectively. Before DAA, median HCV RNA was 1.49×10^6 copies/mL. At month 1, treatment end and 12 weeks after treatment end (SVR12); 92.1% (70/76), 100% (99/99) and 97% (97/100) had HCV viral load <12 IU/ml, respectively (Figure). After DAA had been started; 25% (25/100) patients experienced 44 adverse events, reported adverse events were pruritus (10%, 10/100), asthenia (7%, 7/100), headache (4%, 4/100), nausea (4%, 4/100), insomnia (3%, 3/100), and others (14%, 14/100).

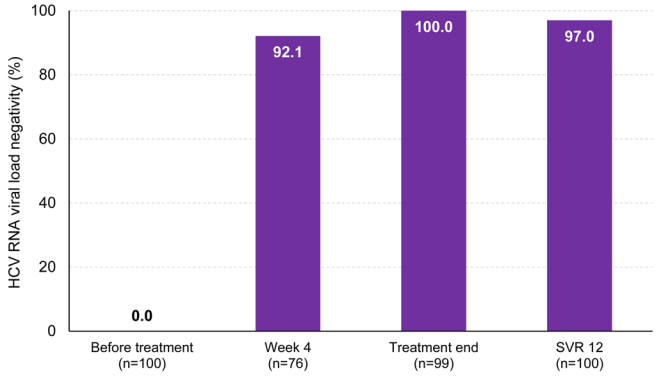


Figure: HCV RNA viral load negativity (cut-off point <12 IU/mL) over time.

Conclusion: DAA are effective and safe treatment for HCV infection among cirrhotic patients. The results from a real-life setting in Turkey are similar to those from real-life settings in other countries and previous clinical trials.

*Hep-C Study Group

Yıldız İE, İnan D, Zerdali E, Güner R, Barut Ş, Karaosmanoğlu H, Günal Ö, Tosun S, Karsen H, Köksal İ, Bodur H, Hızel K, Gül HC, Sırmatel F, Türker K, Duygu F, Sünnetcioğlu M, Özgüneş İ, Karabay O, Şener A, Şenateş E, Çelebi G, Akbulut A, Baykam N

THU-375

Prevalence of baseline NS5A resistance associated substitutions in a real world cohort of veterans with chronic genotype 1 HCV infection

N. Oliver[1], S. Levy[2], E.J. Cartwright[1]. *[1]Atlanta Veterans Affairs Medical Center, Infectious Diseases, Decatur, United States; [2]Atlanta VA Medical Center, Internal Medicine, Decatur, United States*

Email: oliver.nora@gmail.com

Background and Aims: Data examining prevalence of Hepatitis C virus (HCV) NS5A resistance-associated substitutions (RAS) are limited to clinical trial cohorts. The aim of this study is to characterize the prevalence of baseline and pre-treatment NS5A RAS in a real world veterans cohort.

Method: This retrospective chart review examined 793 veterans with chronic HCV from the Atlanta Veterans Affairs Medical Center from March 16, 2016 to present. A convenience sample of 415 patients with HCV genotypes 1a, 1b, or 3 was analyzed. These patients underwent baseline/pre-treatment NS5A RAS testing at the Public Health Reference laboratory (PHRL) in Palo Alto, CA. PHRL uses RT-PCR and population-based sequencing to determine the HCV NS5A gene amino acid sequence. Mixtures are scored at positions where the minority population is 20% or more. Demographic information included sex, age, and race. Other clinical information included HIV status, pre-treatment HCV viral load, any prior HCV treatment, and pre-treatment fibrosis-4 (FIB-4) score. Cirrhosis (including F3, F4 stages) designation was based on clinical information, radiology, FIB-4 score, and/or transient elastography results. NS5A RAS testing detailed the presence of signature NS5A mutations at the Y93, L31, M28, and Q30 codon positions. Descriptive analysis was performed with Microsoft Excel (2010, version 14.6.5).

Results: The cohort included 415 veterans (Table). The average age was 63 years, and the majority was men (99%), African American (79.5%), and HIV negative (92%). Most patients were infected with HCV genotype 1a (87.4%), and cirrhosis was present in 33% of patients. Most patients were HCV treatment naïve (84%), and of those with prior therapy, interferon-based therapy was the main regimen (9%). Baseline NS5A signature RAS were found 21.4% (89) of the total cohort. In patients with genotype 1a infections, NS5A signature RAS were found in 80 (22%) patients. The most common NS5A RAS in the total cohort and in genotype 1a patients was at the M28 codon (7.4% and 8.2%, respectively). In the genotype 1b group, RAS were mostly at the L31 position (10%). In treatment naïve patients, NS5A RAS were found at the Y93 (10, 2.8%), M28 (25, 7%), Q30 (10, 2.8%), and L31 (9, 2.5%) positions. Of the patients with prior treatment, NS5A RAS were at positions Q30 (12, 18.4%), Y93 (10, 15.4%), L31 (7, 10.7%), and M28 (6, 9%). In 137 patients with cirrhosis, NS5A RAS were at positions Y93 (10, 7%), Q30 (12, 9%), L31 (6, 4%), and M28 (8, 6%). 74% of patients with cirrhosis were treatment naïve.

Conclusion: In this real world cohort, veterans with chronic HCV commonly had NS5A RAS on baseline testing. Our study found signature NS5A RAS that often confer significant resistances to standard, first-line DAA therapy in 20% of patients tested at baseline, which could impact treatment success. Limitations include single center location and homogenous study population.

THU-376

Efficacy and safety of sofosbuvir-containing regimen for Korean patients with chronic hepatitis C virus infection: A retrospective, nationwide, real-world study

S.-H. Jeong[1], E.S. Jang[1], K.-A. Kim[2], I.H. Kim[3], W.J. Chung[4]. *[1]Seoul National University Bundang Hospital; [2]Inje University Ilsan Paik Hospital; [3]Chonbuk National University Hopital; [4]Keimyung University Hospital*

Email: jsh@snubh.org

Background and Aims: Sofosbuvir-based therapy (SOF-regimen) had been widely used for chronic hepatitis C virus (HCV) infected patients since Jan 2016 in Korea. This study aimed to describe a real-world efficacy and safety of SOF-regimen in South Korea.

Method: A total of 541 patients with chronic HCV infection who started SOF-regimen were consecutively enrolled from 7 tertiary hospitals during Jan 2016 ~ Dec 2016. Retrospective analysis on the end-of-treatment response (ETR), sustained virological response (SVR), and adverse events was performed.

Results: Mean age of enrolled patients was 61.2 (SD 11.3) y.o., 222 (41.6%) were males. The patients with genotype (GT) 1, 2, and 3 were

72 (13.3%), 435 (80.4%) and 8 (1.5%), respectively. Treatment-experienced patients were 37 (51.4%), 77 (10.1%) and 2 (25%) in genotype 1, 2, and 3, respectively. Follow-up was lost in 63 patients during (n = 19) and after (n = 44) treatment. Per-protocol ETR and SVR rates in treatment-naïve patients were 100% (29/29) and 100% (29/29) in genotype 1, respectively. Those of genotype 2 were 100% (317/317) and 96.2% (305/317) respectively. In genotype 3 patients, all the 3 obtained ETR, but one of them did not show SVR. Among treatment-experienced patients, SVR rates were 90.9% (30/33), 97.2% (69/71), and 100% (2/2) in genotype 1, 2, and 3, respectively. Among139 (25.7%) liver cirrhosis (LC) patients, 10 of 11 decompensated LC had completed scheduled antiviral therapy without serious adverse events and showed SVR (90.9%). Antiviral therapy had been withdrawn in 24 (4.6%) due to high cost (n = 4), viral breakthrough (n = 1), and follow-up loss (n = 19). Any grade of adverse events had been reported in 177 (33.2%) of treated patients, but none discontinued the antiviral therapy due to adverse event.

Table: Per-protocol sustained virologic response rates according to treatment regimens in genotype 1, 2, and 3

	Sofosbuvir + ribavirin	Sofosbuvir/ ledipasvir	Sofosbuvir + daclatasvir
Genotype 1 (n = 62)		49/50 (98%)	10/12 (83.3%)
Naïve (n = 29)		24/24 (100%)	5/5 (100%)
Experienced (n = 33)		25/26 (96.2%)	5/7 (71.4%)
Genotype 2 (n = 388)	369/383 (96.3%)		5/5 (100%)
Naïve (n = 317)	302/314 (96.2%)		3/3 (100%)
Experienced (n = 71)	67/69 (97.1%)		2/2 (100%)
Genotype 3 (n = 5)	1/1 (100%)		3/4 (75%)
Naïve (n = 3)			2/3 (66.7%)
Experienced (n = 2)	1/1 (100%)		1/1 (100%)

Conclusion: Sofosbuvir-containing antiviral therapy showed very high real-life efficacy and safety in Korean patients with chronic HCV infection regardless of previous antiviral treatment experience. Moreover, SOF-regimen could be an effective and safe antiviral therapy to treat decompensated HCV related LC patients.

THU-377

Real-life efficacy and safety of daclatasvir and asunaprevir therapy for genotype 1b chronic hepatitis C patients without NS5A resistance-associated substitution: A nationwide study in South Korea

S.-H. Jeong. *Seoul National University Bundang Hospital*
Email: jsh@snubh.org

Background/Aim: Daclatasvir (DCV) and asunaprevir (ASV) combination therapy have been widely used for Korean patients with chronic hepatitis C virus (HCV) genotype 1b infection since May 2015. This study aimed to investigate the real-life effectiveness and safety of dual all-oral therapy with DCV and ASV in Korean patients.
Methods: A total of 533 patients with genotype 1b HCV infection, who were treated with at least one dose of DCV plus ASV therapy during May 2015 ~ Oct 2016 were consecutively enrolled in the 7 tertiary hospitals located in different major regions in South Korea. Retrospective review of medical record and data analysis was performed.
Results: Mean age of enrolled patients was 58.9 ± 12.4 years old, and 247 (46.3%) were males. The diagnosis of liver disease was chronic hepatitis in 380 (71.3%) patients, liver cirrhosis (LC) in 117 (22.0%), and hepatocellular carcinoma in 36 (6.8%). Of 369 treatment naïve patients, end-of treatment response (ETR) rates were 91.3% (337/369) in intention-to-treat analysis and 95.7% (331/346) in per-protocol analysis. Sustained virological response (SVR) rate was 88.9% (328/369) and 93.6% (324/346), respectively. Of 164 treatment-experienced patients, ETR rates were 92.7% (152/164, ITT) and 94.4% (151/164, PP), and SVR rates were 92.1% (151/164, ITT) and 93.8% (151/161, PP), respectively. DCV plus ASV therapy was withdrawn in 46 (8.6%) due to no early virologic response or breakthrough (11), adverse event (9), high cost (4) and lost to follow-up (18). Any grade of adverse events was reported in 186 (34.9%), but 9 (4.8%) of them discontinued DCV plus ASV therapy due to transaminase elevation (6), ascites (1), seizure (1) and headache (1). Transaminase elevation more than 2 times of upper normal limit during treatment had developed in 42 (7.9%) and resulted in discontinuation of the treatment in 6 (1.1%).
Conclusions: Dual all-oral therapy with DCV and ASV showed high efficacy with tolerable safety in genotype 1b compensated HCV infected patients with pretreatment RAV negativity. Discontinuation of DCV and ASV combined therapy due to adverse event was observed in 4.8%, and adequate monitoring for transaminase elevation is warranted.

THU-378

Genotype 3 Infection in HIV/HCV co-infected subjects in the DAA era: Real life data from the ICONA/HepaICONA Foundation cohorts

R. Rossotti[1], P. Lorenzini[2], M. Merli[1], A. Castagna[3], A. De Luca[4], A. Antinori[2], M. Chiamenti[5], I. Mastrorosa[2], G. Verucchi[6], F. Maggiolo[7], A.D. Monforte[5], M. Puoti[1]. *[1]ASST Grande Ospedale Metropolitano Niguarda, Infectious Diseases, Milan, Italy; [2]National Istitute for Infectious Diseases "Lazzaro Spallanzani" IRCCS, Rome, Italy; [3]San Raffaele Scientific Institute, University Vita-Salute San Raffaele, Department of Infectious Diseases, Milan, Italy; [4]Infectious Diseases Unit, Azienda Ospedaliera Universitaria Senese, University of Siena, Department of Medical Biotechnologies, Siena, Italy; [5]ASST Santi Paolo and Carlo, Department of Health Sciences, University of Milan, Clinic of Infectious and Tropical Diseases, Milan, Italy; [6]Infectious Diseases Unit, Sant'Orsola-Malpighi Hospital, University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; [7]ASST Papa Giovanni XXIII, Infectious Diseases Unit, Bergamo, Italy*
Email: roberto.rossotti@ospedaleniguarda.it

Background and Aims: Genotype (GT) 3 has emerged as a difficult-to-treat viral strain, achieving Sustained Virologic Response (SVR) rates lower than other genotypes. Data about GT3-infected HIV patients are scarce either from clinical trials or real life.
Aims: describe the outcome of GT3 co-infected individuals treated with DAA; explore factors associated with virological failure.
Method: Retrospective analysis included all GT3 patients starting DAA and with a 12-week follow up enrolled in the ICONA/HepaICONA cohorts up to October 2017. SVR rates were assessed and univariable/multivariable models evaluating predictors of viral response were developed.
Results: 176 patients were included: 132 males (75%), mainly intravenous drug users (80.7%); 27 individuals had a diagnosis of AIDS (15.3%). 96 subjects were cirrhotic (54.6%), 29 were anti-HCV treatment experienced (16.5%); few individuals were HBV co-infected (1.1%). Median HCV RNA was 5.8 $\log_{10}$ UI/mL (IQR 5.0–6.3). The combination sofosbuvir plus daclatasvir was used in 132 individuals (75.0%), mainly for 24 weeks of treatment (70.5%) and with ribavirin (66.5%). Cumulatively, SVR rate was 90.9%; univariable/multivariable analyses are shown in Table 1.
Conclusion: The rate of SVR was high and similar to what reported in the main trials for GT3 in mono-infected subjects. Traditional predictors of viral response (except BMI) failed to foretell SVR achievement while AIDS status and sub-optimal DAA regimens were strong predictors of virological failure.

Table 1: Predictors of virological failure

Factor	Univariable			Multivariable		
	OR	95%CI	p	AOR	95%CI	p
Gender						
Males	1					
Females	0.40	0.09–1.84	0.240			
Age						
≤50						
>50	0.90	0.27–2.97	0.866			
FIB-4 at baseline						
<1.45	0.64	0.07–5.76	0.692	0.34	0.03–4.50	0.414
1.45–3.25	2.43	0.77–7.65	0.128	1.77	0.47–6.64	0.395
>3.25	1			1		
Missing	7.70	0.59–100.13	0.119	14.32	0.78–262.06	0.073
HCV Tx History						
Naïve	1					
Experienced	0.70	0.15–3.28	0.654			
HCV Tx						
SOF + DCV ± RBV	1			1		
SOF + RBV ± IFN	1.53	0.45–5.18	0.499	1.78	0.45–7.01	0.41
Other*	4.07	0.72–22.83	0.111	11.88	1.36–104.21	0.025
Length of Tx						
8 weeks	6.85	1.03–45.48	0.046	5.34	0.53–53.76	0.155
12 weeks	0.70	0.19–2.63	0.598	0.51	0.11–2.28	0.377
24 weeks	1			1		
Ribavirin use						
No	1					
Yes	1.57	0.48–5.10	0.452			
Diabetes						
No	1					
Yes	0.60	0.07–4.85	0.632			
BMI						
<18.5	3.15	0.29–33.80	0.343	7.98	0.40–157.65	0.173
18.5–24.9	1			1		
25–29.9	2.92	0.73–11.71	0.131	5.99	1.12–32.16	0.037
≥30	1.75	0.18–17.45	0.633	3.22	0.26–40.05	0.363
Missing	1.41	0.36–5.50	0.624	2.03	0.41–10.00	0.382
AIDS diagnosis						
No	1			1		
Yes	3.97	1.31–12.07	0.015	5.55	1.53–20.17	0.009
CD4 at baseline, cell/mmc						
0–350	1					
350–500	0.28	0.03–2.49	0.251			
<500	0.93	0.30–2.90	0.901			

*Included SOF + DCV + IFN/RBV and ledipasvir/sofosbuvir + RBV.

THU-379

Safety and efficacy of Daclatasvir at doses other than 60 mg daily in HIV/HCV co-infected subjects: Data from the ICONA/HepaICONA Foundation cohorts

R. Rossotti[1], A. Tavelli[2], S. Bonora[3], A. Cingolani[4], S.L. Caputo[5], A. Saracino[5], G. Lapadula[6], L. Marinaro[3], C. Uberti-Foppa[7], C. Mussini[8], M. Puoti[1], A.D. Monforte[9]. [1]*ASST Grande Ospedale Metropolitano Niguarda, Department of Infectious Diseases, Milan, Italy;* [2]*Icona Foundation, Italy;* [3]*Amedeo di Savoia Hospital, University of Torino, Torino, Italy., Unit of Infectious Diseases, Department of Medical Sciences, Turin, Italy;* [4]*Fondazione Policlinico Universitario A. Gemelli -Università Cattolica del Sacro Cuore, Infectious Diseases Unit, Rome, Italy;* [5]*University of Bari, Clinic of Infectious Diseases, Bari, Italy;* [6]*ASST Monza, San Gerardo Hospital, Clinic of Infectious Diseases, Monza, Italy;* [7]*San Raffaele Scientific Institute, University Vita-Salute San Raffaele, Department of Infectious Diseases, Milan, Italy;* [8]*University of Modena and Reggio Emilia, Infectious Disease Clinic, Department of Medical and Surgical Sciences for Children & Adults, Modena, Italy;* [9]*ASST Santi Paolo and Carlo, University of Milan, Clinic of Infectious and Tropical Diseases, Department of Health Sciences, Milan, Italy*
Email: roberto.rossotti@ospedaleniguarda.it

Background and Aims: Daclatasvir (DCV) is a pan-genotypic NS5A inhibitor. In HIV co-infected subjects standard 60 mg daily dose should be adjusted to 30/90 mg depending on concomitant anti-retroviral regimen according to SmPC.
Aims: describe the use of different DCV dosages in the ICONA cohort; assess if dose prescription complies with SmPC; evaluate safety and efficacy of 60 *versus* 30/90 mg and adequate (i.e. concordant with SmPC) *versus* incorrect (not concordant with SmPC) prescriptions.
Method: Retrospective analysis included all patients starting DCV with sofosbuvir up to October 2017: demographic, clinical and laboratory data were collected. Sustained Virological Response (SVR) achievement and liver adverse events (LAE) development were assessed. Incidence rates of LAE were calculated and Poisson regression model was used to identify factors associated with the incidence of LAE.
Results: 290 patients were included: 221 males (76.2%), mainly infected by genotype 3 HCV (70.4%). 141 subjects were cirrhotic, 33 had decompensated disease. DCV 60 mg was prescribed in 230 subjects; an inadequate dosage was used in 32 individuals (10.7%): 8.3% had a lower and 2.7% a higher dose than what recommended by SmPC. No difference in terms of SVR was observed (92.9% with 60 and 90.9% with 30/90 mg, p = 0.658; 92.1% with adequate and 95.2% with incorrect dosage, p = 0.610). There were 28 LAE with an incidence rate of 3.06 per 100 patients/months of follow up (95%CI 2.11–4.43) with no differences in the two-paired groups. Relative risk assessment for LAE is shown in Table 1.

Table 1: Relative Risk of developing LAE

Factor	Unadjusted Model			Adjusted* Model		
	RR	95%CI	p	RR	95%CI	p
DCV dose						
60 mg	1					
30/90 mg	0.92	0.35–2.41	0.859			
Appropriate DCV dose	0.83	0.28–2.40	0.737			
HCV Genotype						
3	1					
Non-3	2.14	1.02–4.49	0.045	1.97	0.84–4.62	0.116
Ribavirin Use	0.56	0.27–1.18	0.127			
FIB-4						
<1.45	1					
1.45–3.25	0.79	0.21–2.91	0.722			
>3.25	0.84	0.24–2.88	0.781			
Decompensated Cirrhosis	2.57	1.13–5.83	0.024	2.33	0.89–6.08	0.084
Baseline HIV RNA <50 cps/mL	0.29	0.10–0.83	0.021	0.13	0.03–0.45	0.001
Baseline GGT per 10 increase	0.94	0.88–0.99	0.050	0.93	0.88–0.99	0.029
Baseline total bilirubin per 10 increase	0.45	0.01–27.80	0.705			
Baseline ALT per 10 increase	0.98	0.93–1.04	0.527			

*Adjusted for GTT, HIV RNA, Decompensated Cirrhosis, HCV Genotype.

Conclusion: DCV led to high SVR rate regardless of dosage and adequate prescription. Baseline GGT and HIV RNA < 50 copies/mL resulted to be protective for LAE. A not negligible number of incorrect regimens were prescribed but it did not affect SVR or LAE rate. Potency and safety of DCV have been confirmed, but wrong prescriptions could have led to a cost increase.

THU-380

Cost-effectiveness analysis of baseline testing for resistance-associated polymorphisms to optimise treatment duration in genotype 1 non-cirrhotic treatment-naive patients with chronic hepatitis C virus

C. Fawsitt[1], P. Vickerman[1], G. Cooke[2], N.J Welton[1]. [1]*University of Bristol;* [2]*Imperial College London, United Kingdom*
Email: c.fawsitt@bristol.ac.uk

Background and Aims: Sustained virologic response (SVR – effective cure) to direct-acting antiviral regimens containing non-structural protein 5A (NS5A) inhibitor over UK standard eight weeks treatment duration is 95% in genotype 1 (GT1) non-cirrhotic treatment-naïve

(TN) patients with chronic hepatitis C virus (HCV). However, patients with resistance to the NS5A inhibitor have lower SVR (<85%), and there is evidence that higher SVR (>95%) can be achieved with 12 weeks treatment. We compare the lifetime cost-effectiveness of testing for NS5A resistance at baseline and optimising treatment duration based on the presence of NS5A polymorphisms, using a UK National Health Service perspective.

Method: A decision tree and Markov model is used to simulate treatment outcomes and natural disease progression for HCV GT1 non-cirrhotic TN patients in the UK. We compare baseline testing with "no testing". Under "no testing", patients receive eight weeks treatment with ledipasvir/sofosbuvir (LDV/SOF). Under "testing", patients with (15%) and without (85%) NS5A polymorphisms are given LDV/SOF for 12 and eight weeks, respectively. We model retreatment with the same regimen for 12 weeks in patients that fail initial treatment and consider a range of SVR thresholds. Evidence on model parameters are taken from a review of the literature.

Results: Baseline testing for NS5A polymorphisms generates marginally higher lifetime costs (£32,593.78) and quality-adjusted life years (QALYs) (15.29) per 1,000 patients over "no testing" (£31,207.36; 15.27), assuming 80% SVR to retreatment in each arm, and produces an incremental cost-effectiveness ratio (ICER) of £75,618.55. If the SVR rate for retreatment is 100% in those without NS5A polymorphisms, against 80% in other patients, the ICER is £30,797.79; if the SVR rate is reduced to 70% in NS5A-resistant patients, the ICER is £33,289.90.

Conclusion: Optimising treatment duration with LDV/SOF for HCV GT1 non-cirrhotic TN patients based on NS5A resistance is not cost-effective, unless high levels of SVR to retreatment are observed in patients with and without NS5A polymorphisms. Results are also sensitive to the prevalence of NS5A polymorphisms and baseline test-costs.

THU-381

Recurrence and occurrence of hepatocellular carcinoma following ledipasvir and sofosbuvir treatment for chronic hepatitis C in patients with advanced liver disease: Turkish multicenter early access program

R. Idilman[1], M. Demir[2], M. Aladag[3], S. Kaymakoglu[4], C. Erol[1], B. Cavus[4], R. Iliaz[4], U.S. Akarca[5], S. Koklu[6], Y. Cakaloglu[7], M. Sahin[8], I. Koksal[9], M. Ozgenel[10], B. Toka[11], Z. Karasu[5], G. Ersoz[5], M. Kiyici[12], M. Akdogan[13], E.A.P. Turkey[14]. *[1]Ankara University School of Medicine, Department of Gastroenterology; [2]Mustafa Kemal University School of Medicine, Department of Gastroenterology; [3]Inonu University School of Medicine, Department of Gastroenterology; [4]Istanbul University School of Medicine, Department of Gastroenterology; [5]Ege University School of Medicine, Department of Gastroenterology; [6]Hacettepe University School of Medicine, Department of Gastroenterology; [7]Sisli Memorial Hospital, Department of Gastroenterology; [8]Mersin State Hospital, Department of Gastroenterology; [9]Karadeniz Technical University Farabi Medical Faculty, Department of Infectious Diseases; [10]Osmangazi University School of Medicine, Department of Gastroenterology; [11]Sakarya University School of Medicine, Department of Gastroenterology; [12]Uludağ University School of Medicine, Department of Gastroenterology; [13]Turkiye Yuksek Ihtisas Hospital, Department of Gastroenterology; [14]Turkey*
Email: ramazan.idilman@medicine.ankara.edu.tr

Background and Aims: The aim of the present study was to investigate the efficacy and safety of ledipasvir (LDV)/sofosbuvir (SOF) ± ribavirin (RBV) in chronic hepatitis C (CHC) patients with advanced liver disease and in patients with liver transplantation (LT) in a Turkish multicentre early access program. The natural course of HCC after LDV/SOF treatment was also assessed.

Method: Patients received LDV 90 mg and SOF 400 mg in a fixed dose combination tablet once daily plus RBV (800–1200 mg/day) according to the physician's discretion. Recommended treatment duration was 24 weeks.

Results: Between Apr2015-Jan2016, a total of 200 patients were enrolled; 8 patients were lost to follow-up, 16 patients died during the study; 11 during the treatment, 5 after discontinuing the treatment. All patients were Caucasian, 53% were female and the median age was 62 years. Median serum HCVRNA level was 5.14 $\log^{10}$ IU/ml and ALT was 55 U/l, 81% of the patients had GT1b HCV infection. 58% of patients had previously received interferon-based treatment. Median CTP and MELD scores were 8 and 16, respectively. 7 patients had HBV co-infection. 37 patients had the previous HCC treated by surgical resection, LT, ablation, trans-arterial chemo/radioembolization or medical treatment. 48 (24%) had liver transplantation. The median interval between transplantation and LDV/SOF treatment start was 29.4 months.

With ITT analysis, SVR12 was 86.0% (172/200), whereas SVR12 was 98.3% (172/175) with per protocol analysis. Three patients with GT1b experienced a virologic failure (relapse). From baseline to SVR12, serum ALT level and MELD score were significantly improved ($p < 0.001$).

Most common adverse events (AE) were headache (5%), nausea (1%), anaemia (1%), constipation (1%), pruritus (1%) and rash (1%) 3 patients had serious AE, one patient had to prematurely discontinue therapy. No HBV reactivation was observed. No clinically relevant drug-drug interactions were noted. None of the deaths was related to LDV/SOF.

37 patients (M/F: 21/15, 85% GT1b) had previous HCC. During the follow-up period; the median time between HCC treatment and the start of LDV/SOF treatment was 4 months. Twelve (12/200, 6.0%) (M/F: 7/5, median age: 68 years) of them had HCC recurrence or progression after treatment. Median time from LDV/SOF treatment start to recurrence was 7 months. Among these 12 patients, 10 had GT1b, 2 had radical HCC treatment (surgical resection, LT). De novo HCC was detected only in one patient without previous HCC. Four patients died due to liver function deterioration and HCC progression.

Conclusion: Based on the results of this study, LDV/SOF ± RBV treatment is an effective treatment for HCV genotype 1,4 infected patients with the advanced liver disease. LDV/SOF treatment was well tolerated. Virologic suppression is associated with an improvement of hepatic function but does not seem to reduce HCC recurrence.

THU-382

Resistance analysis of hepatitis C virus NS5A gene in Brazilian patients infected with genotypes 1 and 3 treated with Daclatasvir

V. Costa[1], C. Brandão-Mello[2], M.M.A. Pires[3], F.C.D.A. Mello[1], P.G.C.S. Silva[1], E.P. Nunes[4], L.L. Lewis-Ximenez[1], E. Lampe[1]. *[1]Oswaldo Cruz Institute, Viral Hepatitis Laboratory, Rio de Janeiro, Brazil; [2]University of Rio de janeiro, Internal Medicine Department, Rio de Janeiro, Brazil; [3]Gaffrée e Guinle University Hospital, Gastroenterology & Hepatology Division, Rio de Janeiro, Brazil; [4]Oswaldo Cruz Institute, Evandro Chagas Institute, Rio de Janeiro, Brazil*
Email: cedubrandao@gmail.com

Background and Aims: In Brazil, hepatitis C virus (HCV) seroprevalence is about 1.3% and approximately 10,000 cases are notified each year. The most prevalent subtypes are 1a and 1b, followed by 3a. Daclatasvir, a NS5A protein inhibitor, is a direct-acting antiviral (DAA) approved for combined IFN-free therapies for both genotypes and is characterized by a low genetic barrier to resistance. Several amino acid changes at positions M28, Q30, L31 and Y93 for HCV-1 and A30, L31, S62 and Y93 for HCV-3 have been associated with daclatasvir resistance. The aim of this study was to investigate the presence of resistance-associated variants (RAVs) in HCV NS5A gene in responders and non-responders patients infected with HCV genotypes 1 and 3 treated with daclatasvir.

Method: A total of 119 serum samples (HCV-1a: n = 54; HCV-1b: n = 46; HCV-3: n = 19) was collected at baseline along with 13 serum samples from non-responders patients (HCV-1a: n = 7; HCV-1b: n = 1; HCV-3: n = 5) after 12-week of treatment with daclastavir. Methodology included viral RNA extraction, RT-PCR reactions with

specific primers for each genotype and purification followed by nucleotide sequencing reaction.
Results: Considering HCV-1a responders, RAVs L31M (1/47; 2.1%) and Q30L (1/47; 2.1%) were identified at baseline. NS5A mutation L31M has been potentially associated with reduced response rates to daclatasvir in HCV-1a patients, however, here, treatment outcome was not influenced by this particular mutation. Substitutions M28T and Q30R, characteristic of RAVs for NS5A DAAs daclatasvir, ledipasvir and ombitasvir, were identified in HCV sequence from one (1/7; 14.2%) non-responder patient infected with HCV-1a after 12-week treatment with daclatasvir. For HCV-3 responders, amino acid residues at position 31 and 93 were conserved in all sequences analyzed. RAVs at position 62, S62T and S62L, were observed in 4/14 (28.5%) and 1/14 (7.1%) baseline sequences, respectively. Among five non-responders patients infected with HCV-3, RAVs A30S (1/5; 20%) and A30K (1/5; 20%) were identified in baseline and after therapy, respectively. A30K is highly associated with resistance to daclatasvir.
Conclusion: Viral factors, such as the infecting genotype, alongside drug resistance mutations, represents negative predictive factors to achieve sustained virologic response for Brazilian patients. This study highlights the importance of identifying baseline RAVs for HCV-3 prior to treatment prescription, as conventional combined therapy using daclatasvir might not be effective when primary resistance mutations are present in the infecting viral variants.

THU-383

Variables associated with persistence of elevated ALT after SVR in patients with chronic hepatitis C: Data from the German Hepatitis C-Registry (DHC-R)

S. Mauss[1], P. Buggisch[2], K. Boeker[3], H. Klinker[4], T. Müller[5], R. Guenther[6], J. Wiegand[7], M. Cornberg[8], C. Lange[9], T. Berg[7], S. Zeuzem[10], F. Tacke[11] and Deutsches Hepatitis C-Register[12]. *[1]Center for HIV and Hepatogastroenterology, Düsseldorf, Germany; [2]ifi-Institute for Interdisciplinary Medicine, Hamburg, Germany; [3]Center of Hepatology, Hannover, Germany; [4]University Hospital Würzburg, Würzburg, Germany; [5]Charité Campus Virchow-Klinikum (CVK), Berlin, Germany; [6]Universitätsklinikum Schleswig-Holstein (UKSH), Campus Kiel, Kiel, Kiel, Germany; [7]Universiyt Hospital Leipzig, Leipzig, Germany; [8]Hannover Medical School, Hannover, Germany; [9]University Hospital Frankfurt, Frankfurt am Main, Germany; [10]University of Frankfurt, Department of Medicine, Frankfurt, Germany; [11]Universiyt Hospital Aachen, Aachen, Germany; [12]Leberstiftungs-GmbH Deutschland, Hannover, Germany*
Email: stefan.mauss@center-duesseldorf.de

Background and Aims: Patients with hepatitis C achieving SVR that do not normalize ALT levels might have confounding hepatic and extrahepatic comorbidities. We therefore analyzed variables associated with persistent elevations of SVR after successful HCV therapy in a large nationwide real-life cohort.
Method: The German Hepatitis C registry is a national multicentre cohort that includes a high fraction of no to early fibrotic (F0-1, 28.4%) patients treated with direct antiviral agents. Patients were treated at the discretion of the physician. Data were collected by a web-based data system and confirmed by plausibility checks and on site monitoring. Normal ALT activity was defined as <35 U/l (at 37°C) regardless of sex. Variables assessed were HCV genotype, sex, HIV-coinfection, BMI, alcohol consumption, opioid substitution, age, liver cirrhosis, treatment response (EOT, SVR), treatment regimen, cardiovascular disease, psychiatric disorders, diabetes mellitus, thyroid disorders, statin use, hypertension, ethnicity, country of origin. Statistical analyses were performed using univariate and multivariate regression analysis.
Results: 3,440 patients had data available for ALT at baseline, all variables and 12 weeks after therapy. At week 12 after end of therapy 18.1% of the patients remained ≥35 U/l. By multivariate analysis, ALT ≥35 U/l at week 12 after therapy was independently associated with male sex ($p < 0.0001$), higher BMI ($p < 0.0001$), liver cirrhosis ($p < 0.0001$) and no SVR ($p < 0.0001$). On the contrary, ALT <35 U/l was associated with female sex ($p < 0.0001$), lower BMI ($p < 0.0001$), no liver cirrhosis ($p < 0.0001$) and SVR12 ($p < 0.0001$).
Conclusion: ALT levels may remain persistently elevated in a substantial fraction of HCV-infected patients despite completion of DAA therapy. Risk factors associated with increased ALT at week 12 after end of therapy apart from virologic non-response were primarily related to metabolic risk factors and liver cirrhosis.

THU-384

Time to viral suppression does not impact SVR in patients treated with Glecaprevir/Pibrentasvir for 8 weeks

C. Sarrazin[1,2], T. Tran[3], D. Dylla[4], J. Feld[5], S. Arora[6], D. Victor[7], Y. Hu[4], S. Wang[4], F. Mensa[4], D. Wyles[8]. *[1]JW Goethe University Hospital, Frankfurt, Germany; [2]St. Josefs-Hospital, Wiesbaden, Germany; [3]Cedars Sinai Medical Center, Los Angeles, United States; [4]AbbVie, Inc., North Chicago, United States; [5]University of Toronto, Toronto Centre for Liver Disease, Toronto, Canada; [6]University of New Mexico, Albuquerque, United States; [7]Houston Methodist Hospital, Houston, United States; [8]Denver Health Medical Center, Denver, United States*
Email: sarrazin@em.uni-frankfurt.de

Background and Aims: The pangenotypic direct-acting antivirals (DAAs) glecaprevir (developed by AbbVie and Enanta) coformulated with pibrentasvir (G/P) are approved as an 8-week regimen to treat chronic HCV infection for all six major genotypes (GT). Historically, an on-treatment predictor of HCV cure with interferon (IFN)-containing regimens has been viral suppression at treatment week 4. However, the relevance of viral kinetics as predictors of cure in the era of shortened, 8-week DAA regimens is unclear, and concerns remain that failure to suppress HCV RNA quickly may lead to relapse. An integrated analysis of patients treated with G/P for 8 weeks was performed to investigate factors impacting time to viral suppression, and whether lack of viral suppression by treatment week 4 was predictive of relapse.
Method: Data were pooled from five phase 2 or 3 clinical studies, and included patients with HCV GT 1–6 infection without cirrhosis who were either treatment naïve or experienced with IFN or pegIFN with or without ribavirin (RBV) or sofosbuvir and RBV with or without pegIFN. G/P (300 mg/120 mg) was orally dosed once-daily for 8 weeks. Patients lost to follow up or with missing SVR12 data (n = 13) were excluded from the analysis since the impact of viral suppression (HCV RNA below lower limit of quantification [LLOQ]) on response cannot be assessed in these patients. Two patients with on-treatment virologic failure were excluded since we sought to determine whether detectable HCV RNA at treatment week 4 was predictive of relapse.

Table 1. HCV RNA Suppression at Treatment Week 4 and Achievement of SVR12

	Patients with HCV RNA < LLOQ at Treatment Week 4, n/N (%)	Patients with SVR12, n/N (%)
Total	906/942* (96)	943/950 (99)
Subgroup		
HCV RNA <6,000,000 IU/mL†	695/716 (97)	720/724 (99)
HCV RNA ≥6,000,000 IU/mL†	211/226 (93)	223/226 (99)
BMI <30 kg/m^2	737/772 (96)	774/779 (99)
BMI ≥30 kg/m^2	169/170 (99)	169/171 (99)
Black race	63/63 (100)	63/63 (100)
Non-black race	843/879 (96)	880/887 (99)
HCV genotype 3	184/198 (93)	198/203 (98)
Treatment-compliant‡	805/835 (96)	832/839 (99)
Treatment non-compliant‡	101/107 (94)	111/111 (100)

*8 patients missing data at treatment week 4
† For phase 2 studies, HCV RNA levels quantified by COBAS Ampliprep/TaqMan® RT-PCR assay v. 2.0; LLOQ = 15 IU/mL. For phase 3 studies, HCV RNA levels were manually processed using the High Pure System and quantified by COBAS TaqMan® RT-PCR assay v. 2.0; LLOQ = 25 IU/mL.
‡Treatment compliance measured by pill count; values <80% and/or >120% were considered non-compliant.

Results: The analysis included 950 patients; 63 (7%) were black, 171 (18%) had BMI ≥ 30, and 24% had baseline HCV RNA ≥ 6 million. The majority of patients were white, male, and HCV treatment-naïve. Among 942 patients with data, 906 (96%) had HCV RNA < LLOQ at treatment week 4, and of those, 899/906 (99%; 95% CI 98.4–99.6) achieved SVR12; additional results by subgroups are in Table 1. There was no common baseline factor more frequently observed among the 7 seven patients who relapsed other than male sex (5/7; 71%). Of the 36 patients with HCV RNA > LLOQ at treatment week 4 (median baseline HCV RNA 6.7 $\log_{10}$ IU/ml; range 5.2–7.6 $\log_{10}$ IU/ml), 100% (95% CI 90.4–100.0) achieved SVR12.
Conclusion: In patients treated with G/P for 8 weeks, failure to suppress HCV RNA by treatment week 4 was not predictive of treatment outcome, suggesting that treatment extension in patients eligible for 8-week regimens based on this milestone is not warranted.

THU-385

Identification, by Cold-PCR, of treatment-resistant HCV mutations in baseline samples of patients treated with DAAs

A. Madejón[1,2,3], I. Francisco-Recuero[1,2,3], M. Romero[1,2,3], A. García-Sánchez[1], A.O. Martin[1,3], J.C. Erdozaín[1], P. Castillo[1], R. Mena[4,5], F.J.G.-S. Rey[1,3,5]. *[1]Hospital Universitario La Paz, Hepatology Unit, Madrid, Spain; [2]IdiPAZ, m; [3]CIBERehd, Madrid, Spain; [4]Instituto de Genética Médica y Molecular (INGEMM), Madrid, Spain; [5]IdiPAZ, Madrid, Spain*
Email: javiersamaniego@telefonica.net

Background and Aims: Baseline testing of HCV resistant mutants is not routinely indicated –especially using ultradeep sequencing techniques-due to the high response rates observed with DAAs. In this setting, the use of techniques for the selective amplification of minor variants in complex mixtures of nucleic acids, such as Cold-PCR, could be a useful tool. For this reason, the aim of this work was to analyze the usefulness of the Cold-PCR for the rapid identification of minor treatment resistant variants in patients with chronic hepatitis C at risk of therapeutic failure.
Method: We included 8 non-responder patients (without SVR): 5 Gt 1 (4 Gt 1a and 1 Gt 1b) treated with SOF/LDV and 3 Gt 3a with SOF/DCV. A control group of 22 cured patients was also included: 17 treated with SOF/LDV and 5 with SOF/DCV. The baseline samples of all patients and the end of follow-up samples of non-responders were analyzed by both conventional and COLD-PCR, and subsequent analysis by bulk sequencing. In addition, 5 samples of non-responders were analyzed by ultradeep sequencing.
Results: Analysis of baseline samples: Sixteen (53%) of the 30 baseline samples were positive by Cold-PCR (presence of minority variants), including 7/8 (87%) non-responder patients. In 5 of the non-responder patients, treatment resistant variants were detected by bulk sequencing: among the 4 patients treated with SOF/LDV, the L31M mutation was identified in one, Y93H in another one, and both mutations simultaneously in the remaining 2 patients. In a patient treated with SOF/DCV the Y93H mutation was identified. By contrast, the analysis of the baseline samples with conventional PCR did not detect any resistant mutants in none patient. **Analysis of follow-up samples:** The final samples of the 8 non-responder patients gave a positive result using both conventional and Cold-PCR techniques. The bulk sequence analysis showed resistant variants in the 8 patients by conventional PCR and in only 7/8 with Cold-PCR. The high throughput sequencing of 5 of these samples demonstrated a 100% correlation with the results of the other techniques.
Conclusion: These results show that it is possible to identify resistance mutations in baseline samples in up to 62% (5/8) of non-responders, coupling a Cold-PCR reaction and population sequencing. This strategy, which uses technology implanted in most hospitals, is considerably faster and cheaper than the universal analysis by massive sequencing.

THU-386

Persistence and risk of transmission of the hepatitis C virus NS5B S282T substitution in a HIV-positive man who has sex with men

A. Newsum[1], J.T.M. Van Der Meer[2], R. Molenkamp[2], S.P.H. Rebers[2], M. Prins[1], M. van der Valk[2], J. Schinkel[2]. *[1]Public Health Service of Amsterdam, Amsterdam, Netherlands; [2]Academic Medical Center, Amsterdam, Netherlands*
Email: anewsum@ggd.amsterdam.nl

Background and Aims: The hepatitis C virus (HCV) nonstructural protein 5B (NS5B) S282T is a resistance-associated substitution (RAS) which confers major resistance to sofosbuvir in vitro. This substitution has never been found in treatment-naïve patients because it is associated with a severe fitness loss and therefore usually not persists after cessation of treatment. Here, we report a case of a HIV/HCV coinfected patient with persistence of S282T upon treatment failure.
Method: Clinical and laboratory data were extracted from patient records. For resistance analysis, PCR and Sanger sequencing of NS5B and NS5A was performed.

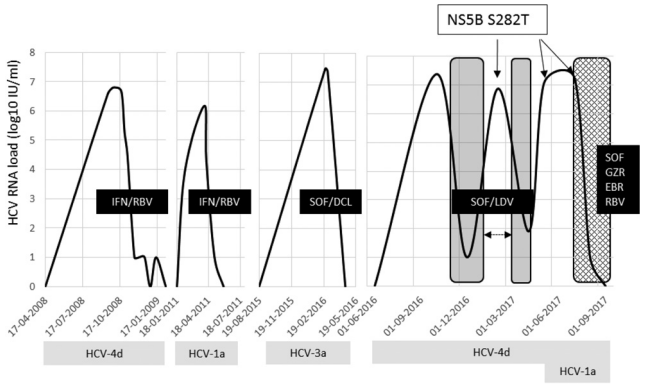


Figure: HCV RNA dynamics during and following several HCV infections in a HIV/HCV coinfected patient: Grey and square-patterned boxes indicate period of treatment. Black boxes contain treatment regimens (IFN = (pegylated)-interferon-alpha; RBV = ribavirin; SOF = sofosbuvir; DCL = daclatasvir; LDV = ledipasvir; GZR = grazoprevir; EBR = elbasvir).

Results: A 66-year-old HIV-infected man who has sex with men (MSM) acquired his fourth HCV infection with genotype 4d in September 2016. He reported an active sex life with multiple male partners at different locations across Europe and the USA. All previous HCV infections were successfully treated with diverse antiviral regimens (Figure). He initiated treatment with SOF/LDV in November 2016, for a planned duration of 12 weeks. At treatment initiation, sequence analysis showed no RAS in NS5B, but P/T58L in NS5A. Twelve weeks after treatment initiation, presumably during treatment discontinuation, HCV RNA load was 7,570,000 IU/mL. Sequence analysis showed the S282T substitution in NS5B (Figure). In NS5A, 58L was still present. Hereafter, HCV RNA load levels fluctuated but increased again over time (Figure). At treatment failure the patient reported that he stopped taking SOF/LDV at week 8 and restarted 2–4 weeks afterwards. The latter might have explained the HCV RNA rise and decrease in February 2017 (Figure). Remarkably, the S282T substitution persisted over time, even when HCV RNA levels were rising (Figure). Surprisingly, after this rise a superinfection with genotype 1a was found. This genotype was not detectable in earlier samples, using a subtype specific PCR. Sequence analysis did not show any RAS in genotype 1a. In July 2017, the patient initiated treatment consisting of sofosbuvir, elbasvir/grazoprevir and ribavirin, after which HCV RNA decreased quickly. Final treatment outcome is pending.
Conclusion: In this HIV-infected MSM the NS5B S282T substitution remained detectable for >5 months after treatment for his 4th HCV infection, indicating that viral fitness was not compromised. Given the very high HCV RNA load at HCV superinfection combined with

high-risk sexual behavior, onward transmission of a S282T strain, associated with sofosbuvir resistance, cannot be excluded.

THU-387

On treatment HCV-RNA evaluation in real-life: Still a role in the era of direct acting antiviral agents?

V.C. Di Maio[1], V. Cento[1], V. Micheli[2], C. Masetti[3], C.F. Magni[4], E. Teti[5], I. Lenci[3], S. Passerini[4], S. Francioso[3], M. Milana[3], A. Bertoli[1], M. Ciotti[6], M. Aragri[1], L. Sarmati[7], M. Schiavini[4], G. Gubertini[4], M. Andreoni[5], A. Mario[3], C.F. Perno[8], G. Rizzardini[4], F.C. Silberstein[1]. *[1]University of Rome Tor Vergata, Department of Experimental Medicine and Surgery, Rome, Italy; [2]ASST Fatebenefratelli Sacco, Clinical Microbiology, Virology and Bioemergencies, Milan, Italy; [3]University Hospital of Rome Tor Vergata, Hepatology Unit, Rome, Italy; [4]ASST Fatebenefratelli Sacco, Division of Infectious Disease, Milan, Italy; [5]University Hospital of Rome Tor Vergata, Infectious Diseases, Rome, Italy; [6]Polyclinic Tor Vergata Foundation, Laboratory of Molecular Virology, Rome, Italy; [7]University Hospital of Rome Tor Vergata, Infectious Disease Unit, Rome, Italy; [8]University of Milan, Milan, Italy*
Email: ceccherini@med.uniroma2.it

Background and Aims: Guidelines recommend HCV-RNA measurements at specific time-points during direct acting antivirals (DAA)-therapy. However, it remains unclear, how these results should be interpreted today and how can be helpful for treatment management.
Method: This retrospective study includes 571 HCV patients (pts) treated in 2 Italian hospitals receiving recommended DAA-regimens by 2017 guidelines: sofosbuvir + ledipasvir ± ribavirin (RBV) (n = 203), sofosbuvir + daclatasvir ± RBV (n = 125), paritaprevir/r + ombitasvir ± dasabuvir ± RBV (n = 197/46). All pts had baseline and 4w HCV-RNA values, and at least one early assessment of HCV-RNA at 1w [n = 466] and/or 2w [n = 375]. Serum HCV-RNA was quantified by Abbott Real*Time* HCV (lower limit of detection: 12 IU/ml). RBV use (n = 348) and treatment-duration (12w n = 212, 16w n = 1, 24w n = 358) were at the investigator's discretion.
Results: Pts were infected with HCV-genotype (GT) 1a/1b/1g (n = 135/233/2), GT2 (n = 34), GT3 (n = 77) and GT4 (n = 77). Overall, median [IQR] liver stiffness was 14.0 [10.3–21.3]kPa; 55.7% of pts were cirrhotic. In addition, 16.5% were HIV-coinfected, and 37.1% had a previous treatment-experience (including 5.2% with DAAs). Median (IQR) baseline HCV-RNA was 5.9 (5.2–6.2) log IU/ml, and 47.1% of pts had values ≥800,000 IU/ml. Sustained virological response (SVR) at 12w of follow-up was 98.1%: 2 pts were non-responders (NRs), 1 was re-infected and 8 pts relapsed.
After DAA therapy initiation, an increased number of pts with HCV-RNA ≤ 12 IU/ml was observed over time: 66 at 1w (50.0% cirrhotic), 112 at 2w (43.7% cirrhotic), 354 at 4w (52.2% cirrhotic). Interestingly, few pts showed detectable HCV-RNA at the end of therapy (EOT): 15.3% at 12wEOT and 6.8% at 24wEOT. However, all achieved SVR with the exception of the 2 NRs treated for 12w.
Due to the high rate of SVR, HCV-RNA levels during early treatment were not significantly related to failure, neither with cirrhosis, HIV coinfection, or RBV use. However, early HCV-RNA ≤ 12 IU/ml at 1w was associated with GT2, HCV-RNA < 800,000 IU/ml and no-treatment experience, while at 2w only with HCV-RNA < 800,000 IU/ml.
Conclusion: Given the high efficacy of the current DAA regimens, and a considerable number of pts with early HCV-RNA ≤ 12 IU/ml, beyond baseline HCV-RNA, also on-treatment HCV-RNA could be interesting for guiding shorter treatment durations with the aim of reducing treatment costs and increasing the number of pts to be treated. This hypothesis requires further investigation.

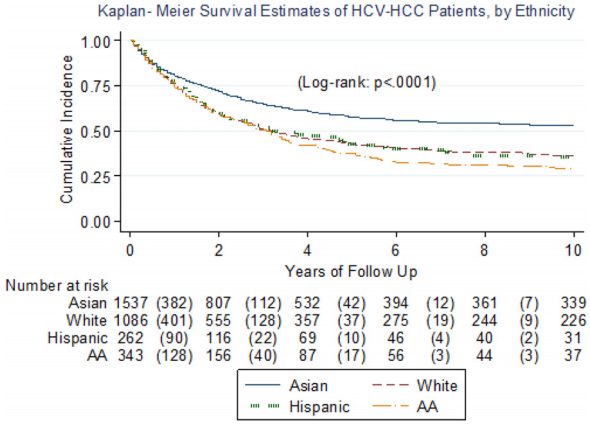
Viral hepatitis C: Clinical aspects except therapy

THU-389

Ethnic differences in HCV-related HCC outcomes: Report from the Real-world Evidence by the Asia Pacific Rim Liver Consortium for HCC (REAL-HCC)

D. Prasad[1], P. Nguyen[2], J. Guy[3], M.-L. Yeh[4], J. Leong[5], J. Yang[6], W. Saeed[7], Y.-C. Hsu[8], P.-C. Tsai[4], C.-Y. Dai[4], J.-F. Huang[4], Y.-L. Chen[9], D.W. Jun[7], L. Roberts[6], M. Schwartz[5], M.-L. Yu[4], E. Gane[1], M. Nguyen[2]. *[1]Auckland City Hospital, New Zealand Liver Transplant Unit, Auckland, New Zealand; [2]Stanford University, School of Medicine, Palo Alto, United States; [3]California Pacific Medical Center, Division of Hepatology, San Francisco, United States; [4]Kaohsiung Medical University Hospital, Hepatobiliary Division, Kaohsiung, Taiwan; [5]Mt. Sinai Hospital, Recanati/Miller Transplantation Institute, New York City, United States; [6]Mayo Clinic, Division of Gastroenterology and Hepatology, Rochester, United States; [7]Hanyang University Medical Center, Division of Gastroenterology, Seoul, Korea, Dem. People's Rep. of; [8]E-Da Hospital, Department of Gastroenterology and Hepatology, Kaohsiung, Taiwan; [9]Changhua Christian Hospital, Division of General Surgery, Changhua, Taiwan*
Email: mindiehn@stanford.edu

Background and Aims: HCV is one of the leading causes of HCC globally. The impact of ethnicity on the clinical presentation and subsequent outcome of HCV-related HCC (HCV-HCC) is unknown.
Method: In a retrospective study, HCV-HCC patients enrolled at 4 U.S. centers and 5 Asia Pacific (AP) centers were analyzed to identify ethnic differences in their presentation and outcome.



Results: Of 3339 patients identified with HCV-HCC, 1601 (48%) were Asian (330 US, 1271 AP), 1119 (34%) Caucasian, 272 (8%) Hispanic and 347 (10%) African American (AA). Asian patients were more likely to be female (41.8% vs. 25.9% for non-Asians) and older (mean age 65.9 vs. 60.1) (p < 0.0001 for both). The proportion of patients with decompensated cirrhosis (CTP Class B/C) was highest in Hispanic (64.4% vs. 44.4% non-Hispanics, p < 0.0001). Among cases of HCC where screening history was documented, AA had a much lower proportion of screen-detected HCC (42.5% vs 75% in non-AA, p < 0.0001). Screening was documented for 66.7% of US Asians and highest at 84.9% for AP Asians. HCC was diagnosed at an early or intermediate stage (BCLC stage 0/A/B) in 83.5% Asian (80.1% US, 84.5% AP), 75.3% Caucasians, 74.1% Hispanics, and 76.0% AA (p < 0.0001). Rate of OLT listing was lowest at 16.6% for Asian (20.7% US, 1.3% AP) and 25% for AA compared with White 42.9% and Hispanic 42.9% (p < 0.0001). Actual OLT rates were even lower for Asian at 4.1% overall (9.0% US, 2.7% AP) followed by AA 16.9%, Hispanic 21.5%, and highest in White 24.5% (p < 0.0001). However, curative treatment rate overall

(OLT, resection, RFA) were highest for AA 27.6%, followed by Asian 18.0%, White 17.3% and lowest for Hispanic 14.0%. On Kaplan-Meier survival estimates (see Figure), respective 5 and 10-year overall survival was lowest for African Americans (37.6% and 29.0%), followed by Whites (42.8% and 36.5%) and Hispanics (42.7% and 34.4%) and highest for Asians (57.8% and 53.2%)($p < 0.0001$), with AP Asians having higher 5- (40.7% US and 61.6% AP) and 10-year survival (26.7% US and 58.7% AP) than US Asians ($p < 0.0001$).

Conclusion: In this large international collaborative study, ethnicity was an important determinant of HCV-HCC presentation, treatment, and long-term survival. African Americans with HCC have poor outcomes, likely reflecting both poor screening uptake and poor access to OLT. In contrast, despite lower OLT rates and overall curative treatment rate, Asians had the highest HCC screening rates and better long-term outcomes.

THU-390

Changes in the characteristics of hospital admissions due to complications of cirrhosis in the era of direct-acting antivirals against HCV

M. Fraile, L. Franco, A. Gomez, M. Torner, A. Castano-Garcia, P.F. Díez, V.J. Beltrán, N.R. Ferreiro, M. Varela, M. Luisa, G. Dieguez , V. Cadahía-Rodrigo, C. Álvarez-Navascués, M. Rodríguez. *Hospital Universitario Central de Asturias, Liver Unit. Division of Gastroenterology & Hepatology, Oviedo, Spain*
Email: miguelfrailelopez@gmail.com

Background and Aims: To determine if there have been changes in the characteristics of patients admitted to a general hospital due to liver cirrhosis (LC) complications in the era of direct-acting antivirals (DAAs).

Method: Hospital admissions were prospectively analyzed in a hepatology unit of a general hospital in two periods of time: P-I: Nov/12-Sep/14 and P-II:Jul/16-Oct/17. Clinical and demographic variables were collected and the usual statistical methods were used. LC and its complications were diagnosed according to the universally accepted criteria.

Results: 622 admissions were collected in 382 patients; 348 admissions in 198 patients in the P-I and 275 in 184 patients in the P-II. The number of incomes was 15.1/month in P-I and 17.1/month in P-II. Comparing both periods, no differences were observed in sex, prevalence of hepatocellular carcinoma (HCC) or in the proportion of patients with previously unknown LC (12% vs. 11%; p = 0,69). Patients were younger in P-I (61 ± 11 vs. 64 ± 11 years; p = 0.005). Regarding the etiology of LC, there was no difference between P-I and P-II in the proportion of admissions for LC due to alcohol (71.4% vs. 71.2%, p = 0.69), HBV (2.8% vs. 3.2%, p = 0.77) or autoimmunity (1.7% vs. 2.1%, p = 0.68). Admissions for HCV cirrhosis were more frequent in P-I (21.9% vs. 15.2%, p = 0.036), while admissions for cirrhosis due to NASH (11.2% vs. 4.3%; p = 0.001) and CBP (6.1% vs. 2.0%, p = 0.007) were more frequent in P-II. The number of admissions for HCV cirrhosis was 3.3/month in P-I and 2.6/month in P-II. There were no differences between the two periods in the reasons for admission: encephalopathy (30.2% vs. 29.1%), variceal hemorrhage (21.6% vs. 19.6%), ascites (16.4% vs. 19.6%) or SBP (7.8% vs. 7.6%). Comparing patients with HCV cirrhosis in both periods, no differences were observed in sex, age, proportion of unknown LC, prevalence of HCC or reason for admission. Patients in P-II were less frequently viremic (59.5% vs. 98.6%, p < 0.001) and had more frequently coexistence of another cause of cirrhosis (52.3% vs. 30.2%, p = 0.018).

Conclusion: The proportion of hospital admissions due to complications of cirrhosis attributable to HCV has decreased by 30% in the era of DAAs; in addition, the characteristics of patients with HCV cirrhosis have changed. On the contrary, the proportion of incomes related to cirrhosis due to NASH has increased. Approximately one in 10 patients admitted for a complication was not previously diagnosed of cirrhosis and this rate has not changed during the study period.

THU-391

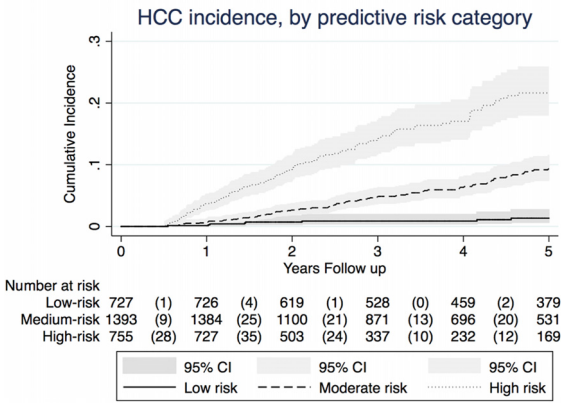
Validation of a clinical scoring system to predict risk of hepatocellular carcinoma in an ethnically diverse cohort of patients with chronic hepatitis C virus infection

M.T. Wei[1], M.H. Le[2], A. Le[2], H.N. Trinh[3], G. Wong[4], C. Landis[5], J. Zhang[6], P. Nguyen[2], M.-H. Lee[7,8], F. Ji[2,9], D.H. Lee[2,10], E. Ogawa[2,11], M. Chang[2], M. Nguyen[2]. *[1]Stanford University, Department of Medicine, Palo Alto, United States; [2]Stanford University, Division of Gastroenterology and Hepatology, Palo Alto, United States; [3]San Jose Gastroenterology, San Jose, United States; [4]The Chinese University of Hong Kong, Institute of Digestive Disease, Hong Kong, China; [5]University of Washington, Division of Gastroenterology and Hepatology, Seattle, United States; [6]Chinese Hospital, San Francisco, United States; [7]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan; [8]Academia Sinica, Genomics Research Center, Taipei, Taiwan; [9]The Second Affiliated Hospital of Xi' an Jiaotong University, Department of Infectious Diseases, Xi'an, China; [10]Good Gang-An Hospital, Division of Gastroenterology, Busan, Republic of South Korea; [11]Kyushu University Hospital, Department of General Internal Medicine, Fukuoka, Japan*
Email: mindiehn@stanford.edu

Background and Aims: Hepatitis C virus (HCV) is one of the leading causes of hepatocellular carcinoma (HCC). However, currently there is no well-established algorithm to predict high-risk HCV patients for HCC development. Our goal was to validate an algorithm inclusive of age, aspartate transaminase (AST), alanine transaminase (ALT), HCV RNA, HCV genotype, and cirrhosis developed by the REVEAL-HCV study.

Method: This is a retrospective study of 2,875 patients aged 30 to 65 with chronic HCV without HBV or HIV co-infection and without HCC at baseline or within 6 months of presentation at 4 U.S. centres and 1 Hong Kong centre from 11/1994–10/2017. We stratified patients as low-, medium-, and high-risk using the REVEAL-HCV risk scores described above and used the area under receiver operating curve (AUROC) to assess model performance.

Figure 1. HCC incidence in total cohort, by predictive risk category (log rank p<0.0001)



Results: Our cohort consisted of 53.2% White, 18.9% Hispanic, 12.4% Asian, and 6.8% African-American patients. The Hispanic cohort had a higher proportion of male (65.1%) and patients with cirrhosis (80.9%), as well as the highest percentage of patients in the high-risk category (31.6%) relative to other racial groups. Asian patients had the lowest percentage of patients in the medium-risk (36.5%) but had the highest percentage of patients in the low-risk category (43.8%).

HCC incidence were 1.34, 9.35, and 21.6 per 1,000 person-years for low, medium and high-risk patients, respectively ($p < 0.0001$) (Figure 1). Compared to treated patients, untreated patients had a much higher HCC incidence (13.4 vs. 2.9 per 1,000 person-years, $p < 0.0001$). As shown in Table 1, AUROC was high for untreated patients overall and for most ethnic groups except Hispanic patients.

Table 1: (abstract: THU-391)

Table 1. The 1-, 3-, and 5- year predicted risk for hepatocellular carcinoma among untreated patients with HCV, by ethnicity

Year	Overall AUROC (95% CI) N= 2,875	Caucasian AUROC (95% CI) N= 1102	Hispanic AUROC (95% CI) N= 407	African American AUROC (95% CI) N= 161	Asian AUROC (95% CI) N= 185
1	0.806 (0.734-0.853)	0.798 (0.701-0.895)	0.728 (0.609-0.844)	0.900 (0.857-0.943)	0.814 (0.694-0.935)
3	0.771 (0.734-0.812)	0.776 (0.732-0.838)	0.700 (0.640-0.816)	0.804 (0.616-0.975)	0.770 (0.662-0.875)
5	0.773 (0.745-0.819)	0.784 (0.729-0.836)	0.676 (0.624-0.797)	0.813 (0.674-0.946)	0.811 (0.724-0.919)

Conclusion: The REVEAL-HCV risk score has good validity and discrimination for most untreated patients except Hispanic patients. Further studies are needed to develop a risk prediction model for untreated Hispanic patients and for patients treated with DAA.

THU-392

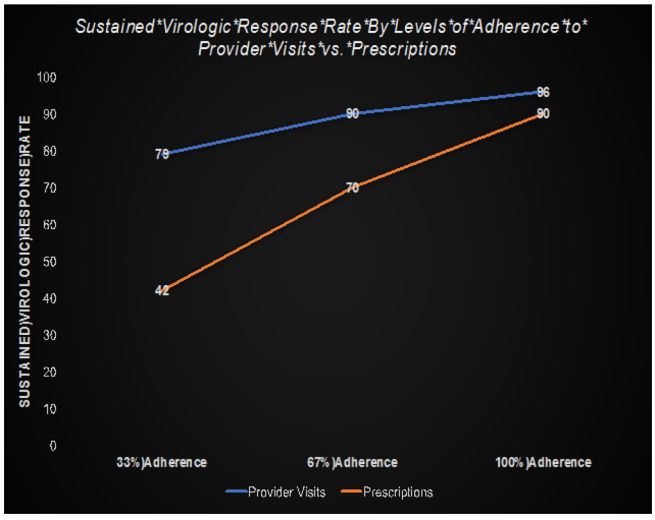
Minimal monitoring of direct-acting antiviral therapy within a real world, urban population

B. Emmanuel[1], S. Kottilil[1], H. Masur[2], S. Kattakuzhy[1]. [1]*Institute of Human Virology at the University of Maryland School of Medicine Baltimore, Baltimore, United States;* [2]*National Institutes of Health, Critical Care Medicine, Bethesda, United States*
Email: skattakuzhy@ihv.umaryland.edu

Background and Aims: The treatment of hepatitis C (HCV) utilizing direct-acting antiviral therapy (DAA) has traditionally been monitored with monthly treatment visits, laboratory evaluation, and prescriptions, followed by assessment of sustained virologic response (SVR) 12 weeks after medication completion. However, limited evidence exists on the minimal monitoring necessary to retain high rates of cure. We investigated different monitoring measures of patients who underwent DAA therapy within a real-world, urban population.

Method: Chronic HCV-infected patients received treatment with ledipasvir/sofosbuvir under the phase IV clinical trial ASCEND, and underwent three measures of monitoring: provider visits, prescription receipt, and SVR testing. Adherence to provider visits was defined as attendance ± 14 days from the scheduled on-treatment visit date. Adherence to prescriptions was defined as picking up of prescribed number of pill bottles. A composite monitoring score used both provider visits and prescription receipt. Adherence to SVR testing was defined as lab testing completed 12-weeks ± 14 days from the end date of DAA therapy.

Results: 551 patients were predominately male (69%), black (96%), genotype 1a (72%), treatment-naïve (82%) with 21% cirrhotic and 20% HIV/HCV-coinfected. 134 patients (24%) had 100% adherence to provider visits, while 417 (76%) did not, which was associated with SVR (96% vs. 83%, p < 0.0001). SVR decreased to 90% in patients with 67% adherence to provider visits (n = 230), to 79% in patients with 33% adherence (n = 108), and to 55% in patients with no provider visits (n = 44). For prescription adherence, 477 (87%) picked up all prescription bottles, while 74 (13%) did not, with a significant difference in SVR (90% vs. 62%, p < 0.0001). SVR decreased to 70% in patients with 67% adherence to prescriptions (n = 46), and further to 42% in patients with 33% adherence (n = 19). With a composite monitoring score, 128 patients had 100% adherence to provider visits and prescriptions, while 68 did neither, with a siginificant difference in SVR (SVR 96% vs. 58%, p < 0.0001). 349 patients had both 100% prescription adherence but <100% provider visit adherence, while 6 patients had 100% provider visits but <100% prescription adherence (SVR 87% vs. 100%, p = 1.0). After DAA therapy, 213 (39%) came within the SVR testing window and 338 (61%) did not, which was not associated with SVR (95% vs. 93%, p = 0.21).



Conclusion: In the era of safe and efficacious DAA therapy, SVR can likely be achieved with a minimalistic approach which includes adherence to most prescriptions and some provider visits. Further studies with validation of provider visit and prescription adherence is needed to design the optimal monitoring approach.

THU-393

Improving detection and management of HCV infection in prisons

N. Ekeke[1], S. Francis-Graham[2], T. King[3], S. Demma[1], W. Rosenberg[1]. [1]*UCL Institute for Liver and Digestive Health, Royal Free London NHS Foundation Trust, London, United Kingdom;* [2]*UCL NIHR Health Protection Research Unit, Royal Free London NHS Foundation Trust, London, United Kingdom;* [3]*HMP Pentonville, London, United Kingdom*
Email: w.rosenberg@ucl.ac.uk

Background and Aims: Prisons have a high prevalence of hepatitis C virus (HCV) infection where diagnosis and treatment can be offered. In the UK HCV has been reported to infect 20% of prisoners compared to 1% of the general population. Highly effective and safe oral treatments have led to the introduction of blood bourn virus (BBV) opt-out testing in UK prisons in 2016. Diagnosis of infection mandates linkage to care including treatment so we developed a linked pathway of care for HCV positive prisoners. We have evaluated the initial introduction of BBV opt-out testing and linkage to care for HCV infected prisoners in a London remand prison with the aim of identifying opportunities to improve effectiveness.

Method: Quantitative data relating to opt-out testing and linkage to care were collected from December 2015 to February 2017. Data were extracted from prison and hospital electronic patient records and analysed using Microsoft Excel 2016.

Results: 6,767 prisoners entered Pentonville prison between December 2015 and February 2017. 6,450 (95%) were offered BBV opt-out testing and health promotion. 1,324 (21%) accepted testing. HCV infection was confirmed in 96 cases (7%). Investigations were complete for 79 (82%) cases.
22 (23%) HCV infected prisoners were referred to the hepatology nurse specialist; 11 patients (50%) were seen and all were discussed at the Operational Delivery Network (ODN) multi-disciplinary team (MDT) meeting. 6 (54%) either started treatment after MDT approval (3) or were referred to another ODN for ongoing care (3).
Overall 1.4% of prisoners were diagnosed with HCV infection and 6% of these cases were managed in accordance with ODN policy. 3% were cured.
Reasons for failure of BBV testing included communication of the offer, access to testing and test acceptance. Reasons for failure of linkage to care included completion of investigations, provision of results and failure to refer to the ODN MDT.
Low prioritisation scores and NHSE treatment quotas resulted in prisoners not accessing treatment during custody.
Conclusion: This initial evaluation revealed that neither BBV opt-out testing nor the planned linkage to care was effective. The reasons behind the failure of this pathway have been identified and are being addressed through better training of staff, the use of mandatory scripts for opt-out testing and strategies to ensure investigation and referral occur within one week. ODN prioritisation and NHSE quotas will continue to limit the number of prisoners who can be cured.

THU-394

Full analysis of comorbidities in chronic hepatitis Cpatients compared with matched comparators: A nationwide population-basedregister study from 2001 to 2013

J. Söderholm[1,2], K. Buesch[2,3], L. Frelin[2], A. Brolund[1], J. Kövamees[1], M. Sällberg[2], M. Lagging[4]. [1]*AbbVie, Medical Affairs, Stockholm, Sweden;* [2]*Karolinska Institutet, Department of Laboratory Medicine, Stockholm, Sweden;* [3]*AbbVie, HEOR, Stockholm, Sweden;* [4]*University of Gothenburg, Institute of Biomedicine, Gothenburg, Sweden*
Email: jonas.soderholm@abbvie.com

Background and Aims: Patients with Chronic hepatitis C (CHC) have shown an increased risk of comorbidities. However, in order to make the analysis of comorbidities more easily manageable and more relevant to capture extra-hepatic manifestations of hepatitis C, most previous studies have grouped morbidity diagnoses into larger groups often using comorbidity indexes like the Charlson Comorbidity Index. In the present study we analyzed the risk of comorbidities in CHC patients for all ICD-10 diagnoses.
Method: CHC patients were identified using B18.2 according to ICD-10 from 2001 through 2013 in the inpatient care, day surgery, and non-primary outpatient care in the nationwide Swedish Patient Register (n = 42,522). For each patient up to 5 non-CHC diagnosed age/sex/place of residency-matched comparators were drawn from the general population at time of diagnosis (n = 202,694). Follow-up started at date of CHC diagnosis and patients accrued person-time until death, emigration or 31st December 2013, whichever came first. Risk of disease was calculated as Standardized Incidence Ratio (SIR) with 95% confidence interval (CI). Diseases were grouped depending on blocks according to WHO (n = 264) or individual ICD-10 codes (n = 2213). Poisson probability distribution with Bonferroni correction for multiple analyses was used to calculate the P-value (significance $p < 0.0002$ for block analysis and $p < 0.00002$ for individual ICD-10 code analysis).
Results: CHC were at higher risk for 194 blocks of ICD-10 diagnoses (73%) with Viral Hepatitis (B15–B19 excluding B18.2 [SIR 86.1, 83.9–88.3 95% CI]), Disease of liver (K70–K77 [SIR 23.6, 23.0–24.3 95% CI]), and HIV (B20–B24 [SIR 21.6, 20.2–23.1 95% CI]) being the three groups the CHC patients had the highest increased risk. The CHC patients had a lower risk for three blocks of diagnoses (1%); Demyelinating diseases of the central nervous system (G35–G37 [SIR 0.43, 0.31–0.57 95% CI]), Glaucoma (H40–H42 [SIR 0.74, 0.67–0.80 95% CI]), and Malignant neoplasms of male genital organs (C60–C63 [SIR 0.81, 0.73–0.90 95% CI]). In addition, the CHC patients were at higher risk for 878 (40%) ICD-10 diagnoses and lower risk for 12 (5%) ICD-10 diagnoses.
Conclusion: CHC patients were at higher risk of being diagnosed with between 40% to 73% of the diseases captured by the ICD-10 classification either alone or in group after comparing with the matched comparator from the general population. Also the CHC patients were at lower risk 1%–5% of the diagnoses.

THU-395

Lower risk of multiple sclerosis in patients with chronic hepatitis C: A nationwide population-based register study 2001–2013

J. Söderholm[1,2], A. Yilmaz[3], K. Buesch[2,4], R. Wejstål[3], A. Brolund[1], J. Kövamees[1], M. Sällberg[2], M. Lagging[3], M. Gisslén[3]. [1]*AbbVie, Medical Affairs, Stockholm, Sweden;* [2]*Karolinska Institutet, Department of Laboratory Medicine, Stockholm, Sweden;* [3]*University of Gothenburg, Institute of Biomedicine, Gothenburg, Sweden;* [4]*AbbVie, HEOR, Stockholm, Sweden*
Email: jonas.soderholm@abbvie.com

Background and Aims: Patients with a previous infection with some neurotropic viruses such as Epstein-Barr, measles, rubella, and varicella zoster have been shown to be at higher risk of developing multiple sclerosis (MS). In contrast, people living with HIV, which is also a neurotropic virus, have been demonstrated to have a lower risk of developing MS. The aim of the present study was to investigate the risk for MS in chronic hepatitis C (CHC) patients by using the Swedish patient registries.
Method: CHC patients were identified using diagnose code B18.2 and MS using G35 according to International Classification of Diseases (ICD)-10 in the inpatient care, day surgery (1997–2013), and non-primary outpatient care (2001–2013) in the nationwide Swedish Patient Register. For each patient up to five non-CHC diagnosed age/sex/place of residency-matched comparators were drawn from the general population at time of diagnosis. Follow-up time was calculated from date of CHC diagnosis until death, emigration, or 31st December 2013, whichever came first. Risk of disease was calculated as Standardized Incidence Ratio (SIR) with 95% confidence interval (CI).
Results: CHC were at lower risk of developing MS (SIR 0.36, 0.26–0.50 95% CI). The prevalence of MS in the CHC cohort was 0.087% (37/42,522) compared with 0.27% (544/202,694) in the matched comparator cohort. The mean age at onset of MS was 46 years in the CHC cohort and 49 in the comparator cohort. The proportion men in the full cohorts were 64%, with the proportion men with MS in the CHC cohort was 57% and 44% in the comparator cohort.
Conclusion: Patients with CHC patients were at a lower risk of developing MS compared with the comparators. Life-style associated factors, or possibly that the altered immune milieu during the chronic infection could have some impact.

THU-396

A universal offer of blood borne virus testing substantially increases diagnosis and treatment of hepatitis C in prisons

S. Morey[1,2], A. Hamoodi[3], M. Valappil[1], D. Jones[4], C. Thompson[4], J. Dhuny[5], M. Hewett[1], E. Buchanan[1], C. Miller[1], T. Young[1], E. Hunter[1], S. Mcpherson[1,6]. [1]*The Newcastle upon Tyne Hospitals NHS Foundation Trust, Viral Hepatitis Service, Newcastle upon Tyne, United Kingdom;* [2]*Northumbria University, United Kingdom;* [3]*Public Health England North East, United Kingdom;* [4]*G4S Health Services, United Kingdom;* [5]*NHS England North East and Cumbria, United Kingdom;* [6]*Newcastle University, Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom*
Email: stuart.mcpherson@nuth.nhs.uk

Background and Aims: Chronic hepatitis C virus infection (HCV) is a major cause of end stage liver disease. With recent advances in anti-viral therapy there is an opportunity to "eliminate" HCV from the UK.

It is known that HCV is common in incarcerated individuals, with previous estimates suggesting ~7% of the UK prison population is anti-HCV antibody positive. Increasing diagnosis and treatment of HCV in prison is therefore a priority in order to achieve "elimination". HCV testing rates in UK prisons are, however low (4%) and largely opportunistic. In order to increase diagnosis and treatment of HCV in prisons in the North East of England (NEE) we have implemented: 1. A universal offer of blood borne virus testing (UBBVT) using dry blood spot testing for prisoners at reception to increase diagnosis; 2. Prison Telemedicine clinics within NEE Prisons to increase HCV treatment rates.

Method: We present the results of the 1 year pilot of UBBVT in Durham Prison (DP) and the pilot of Telemedicine HCV treatment clinics in Northumberland Prison (NP).

Results: UBBVT was implemented at DP, the major remand prison in NEE, in Mar 2016. From Mar 2016 to Feb 2017 2,831 of the 4280 (66%) new receptions were offered BBV testing, compared with 164 of the 7,000 new receptions (2.3%) in 2013–14. A total of 1,495 (53% of offered) of new receptions accepted BBV testing, of whom 95 (6.4%) were anti HCV antibody positive. Of these 47 (49.5%) were HCV RNA positive confirming active infection (3.1% of all tested). 7 (0.5%) individuals were HBsAg positive and 2 (0.1%) were HIV positive. Common reasons for non-acceptance of the test were "doesn't want it" (54%) and "already had test" (37%). In parallel, a Consultant-led Telemedicine clinic (TC) with Specialist Nurse in-reach was implemented in NP. This prison houses longer stay prisoners that are frequently transferred from DP. Between August 2015 and October 2017 80 individuals were seen in the TC. Prior to implementation of the TC, in 2015 only 6 patients/year received HCV treatment. Of those seen in the TC, 57 (71%) commenced anti-HCV treatment. Overall, satisfaction with the TC among the prisoners was very high (80% good or excellent). Moreover, this is very cost effective with reduced cost of prisoner movement (Est £500/hospital visit). SVR and adherence data will also be presented.

Conclusion: A universal offer of BBV testing to prisoners at reception to prison can substantially increase testing rates and lead to many new diagnoses of HCV. Non-acceptance rates still remain high so it is important that there are other opportunities for testing within the prison. Telemedicine clinics with Nurse-led Prison in-reach offer a cost effective and efficient method of treating HCV in the prison environment. These services have now been implemented in all but one NEE Prisons.

THU-397

Multifactor risk evaluation in patients who have eradicated HCV infection: an interim analysis in the PITER cohort

L. Kondili[1], M.G. Quaranta[1], S. Rosato[1], M. Monti[2], B. Coco[3], R. Filomia[4], E. Biliotti[5], A. Iannone[6], A. Zanetto[7], S. Bruno[8], A. Giorgini[9], M. Loi[10], F. Baragli[11], C. Baiguera[12], M. Vinci[13], C. Eleonora[14], A. Ciaccio[15], R. Corsini[16], R. D'ambrosio[17], S. Labanca[18], M. Dallio[19], A. Orlandini[20], A. Ciancio[21], A.R. Buonomo[22], V. Guarnieri[23], V. Cossiga[24], M. Masarone[25], D. Ieluzzi[26], M. Cannizzaro[27], A. Soria[28], M. Siciliano[29], D.C. Amoruso[30], G. Brancaccio[31], L.E. Weimer[1], L. Ferrigno[1], M.E. Tosti[1], C. Estes[32], H. Razavi[32], V. Calvaruso[33]. *[1]Istituto Superiore di Sanità, Center for Global Health, Rome, Italy; [2]Interdepartmental Centre MASVE, University of Florence, Department of Experimental and Clinical Medicine, Florence, Italy; [3]University Hospital Pisa, Hepatology, Pisa, Italy; [4]University Hospital of Messina, Internal Medicine, Messina, Italy; [5]Umberto I Hospital-"Sapienza" University, Infectious and Tropical Diseases Unit, Rome, Italy; [6]University Hospital of Bari, Gastroenterology, Bari, Italy; [7]Padova University Hospital, Department of Surgery, Oncology and Gastroenterology, Padova, Italy; [8]Ospedali Riuniti Foggia, Infectiuos Disease, Foggia, Italy; [9]ASST Santi Paolo e Carlo, Liver and Gastrenterology Unit, Milan, Italy; [10]University of Cagliari, Liver Unit, Cagliari, Italy; [11]S.M. Annunziata Hospital, Infectious Disease, Florence, Italy; [12]Niguarda Cà Granda Hospital, Infectious Disease, Milan, Italy; [13]Niguarda Cà Granda Hospital, Hepatitis Center, Milan, Italy; [14]University Hospital of Padua, Infectious Disease, Padua, Italy; [15]San Gerardo Hospital, Hepatology, Monza, Italy; [16]Arcispedale Santa Maria Nuova, Infectious Disease, Reggio Emilia, Italy; [17]IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Gastroenterology and Hepatology, Milan, Italy; [18]San Giuseppe Hospital, Gastroenterology and Hepatology, Milan, Italy; [19]Università degli Studi della Campania Luigi Vanvitelli, Gastroenterology and Hepatology, Naples, Italy; [20]University of Parma, Infectious Disease and Hepatology, Parma, Italy; [21]Città della Salute e della Scienza-Ospedale Molinette, Gastroenterology Unit, Torino, Italy; [22]Federico II University, Infectious Disease, Naples, Italy; [23]University of Bologna, Hepatology, Bologna, Italy; [24]Federico II University, Gastroenterology Unit, Naples, Italy; [25]Salerno University, Internal Medicine and Hepatology, Salerno, Italy; [26]University Hospital Verona, Liver Unit, Verona, Italy; [27]Villa Sofia-Cervello Hospital, Internal Medicine, Palermo, Italy; [28]San Gerardo Hospital, Infectious Disease, Monza, Italy; [29]Catholic University of Rome, Internal Medicine and Gastroenterology, Rome, Italy; [30]Gragnano Hospital, Hepatology, Naples, Italy; [31]Università della Campania, Infectious Diseases, Università della Campania, Infectious Diseases, Napoli, Italy; [32]Center for Disease Analysis Foundation, Polaris Observatory, Lafayette, United States; [33]University of Palermo, Gastroenterolgy and Liver Unit, DiBiMIS, Palermo, Italy*
Email: loreta.kondili@iss.it

Background and Aims: High SVR rates are reported in patients treated with DAAs in the real life. However, other than HCV, several factors are involved in the progression of liver damage. We aimed to evaluate the prevalence of cofactors involved in liver disease progression in HCV-treated patients who achieved the SVR12 following a DAA therapy in the PITER cohort.

Method: Data of HCV-infected patients, consecutively enrolled in PITER, who were treated and achieved the SVR12, were evaluated. In patients for whom at least 6 months follow-up post-SVR12 was available, the liver function tests and Child Pugh score changes according to the presence of these cofactors were evaluated.

Results: Of 3,485 patients who achieved the SVR12, 1,965 (56%) had liver cirrhosis, 1,164 (33%) reported actual alcohol use, 693 (20%) reported non-virus-non-alcohol-related fatty liver, 567 (16%) were diabetics, 1,781 (51%) had BMI > 25 of whom 60% had hypertension and 30% had BMI ≥ 30, 43 (1%) were HBsAg positive and 185 (5%) were HIV-infected. Of the overall treated patients: none of the above concurrent risk factors for liver disease progression was recorded in 523 (15%) patients of whom 46% had cirrhosis; one cofactor was recorded in 1093 (31%) patients of whom 57% had cirrhosis; two or more cofactors were present in the remaining 1869 (54%) patients of whom 59% had cirrhosis. Age, male sex, actual alcohol use, BMI > 25, previous IFN treatment, diabetes and HCV genotype 3 were independent factors associated to cirrhosis by logistic regression analysis (see table below). After a median follow-up of 12 months (range 9–18 months) following the SVR12, no differences regarding liver function tests according to the cofactors analyzed were observed. Improvement (median 1 point: range 1–4 points) in the Child Pugh score was observed in 72% of 324 patients with a Child Pugh score equal or higher than A6, without significant differences (chi-square test: p > 0.5) according to the different cofactors analyzed.

Factors independently associated with liver cirrhosis by Logistic Regression Analysis in patients who achieved the SVR12 in the PITER cohort

Parameters	Adjusted OR	95% Confidence Limits	
Age	1.03	1.02	1.04
Male sex	1.19	1.09	1.29
BMI>25	1.29	1.02	1.63
Actual alcohol use	1.21	1.10	1.33
HCV Genotype3	1.22	1.07	1.39
HIV positivity	1.08	0.91	1.29
HBV positivity	1.02	0.81	1.70
Previous IFN Therapy	1.22	1.13	1.31
Diabetes	1.53	1.37	1.71

Conclusion: Concurrent risk factors for liver disease progression are present in a significant proportion of patients who successfully eradicated HCV infection. Although no further liver disease progression was associated to the presence of such cofactors in a short term evaluation, their role in the overall morbidity and mortality is a health issue that need to be addressed. In the lack of longer prospective studies, a modelling of liver disease progression after HCV eradication, using these real life data, is ongoing.

THU-398

DNA methylation and immune cell markers demonstrate associations of accelerated aging with chronic HCV/HIV co-infection and liver fibrosis

S. Kottilil[1], Y. Gindin[2], B. Emmanuel[1], A. Ghosh[1], B. Poonia[1], J.G. Mchutchison[2], A. Gaggar[2], M. Subramanian[2]. *[1]University of Maryland School of Medicine, Institute of Human Virology; [2]Gilead Sciences Inc.*
Email: anuj.gaggar@gilead.com

Background and Aims: DNA methylation (DNAm) levels in whole blood have been previously shown to indicate age acceleration (AA) in HIV-infected patients (Horvath & Levine, 2015). Here, we evaluated blood DNAm to explore biological AA in patients with chronic HCV infection, with or without HIV infection. We also developed an immune cell marker panel that is associated with DNAm, and explored the impact of treatment on changes in AA.

Method: DNA, extracted from PBMCs, was assayed for DNAm on the Illumina 450k methylation array for HCV (n = 32) and HCV/HIV co-infected patients (n = 31) who underwent DAA therapy as well as publically available healthy control samples, selected to match the age range of HCV/HIV patients (n = 253). A regression model was derived relating chronological and DNAm-based age in controls. AA was calculated as the difference between an individual's DNAm age and one calculated from a linear model derived using the control samples. Blood immune marker data were collected for HCV and HCV/HIV patients who achieved SVR (n = 269) using flow cytometry, including the 63 patients assayed for DNAm. A model to infer AA from immune cell marker data was built using a regularized regression method (elastic net) using baseline data from the 63 patients for whom both immune marker and DNAm data were available. The elastic net model identified a set of 16 derivative immune markers, along with their coefficients as optimal predictors, which was then used to predict AA independently of DNAm.

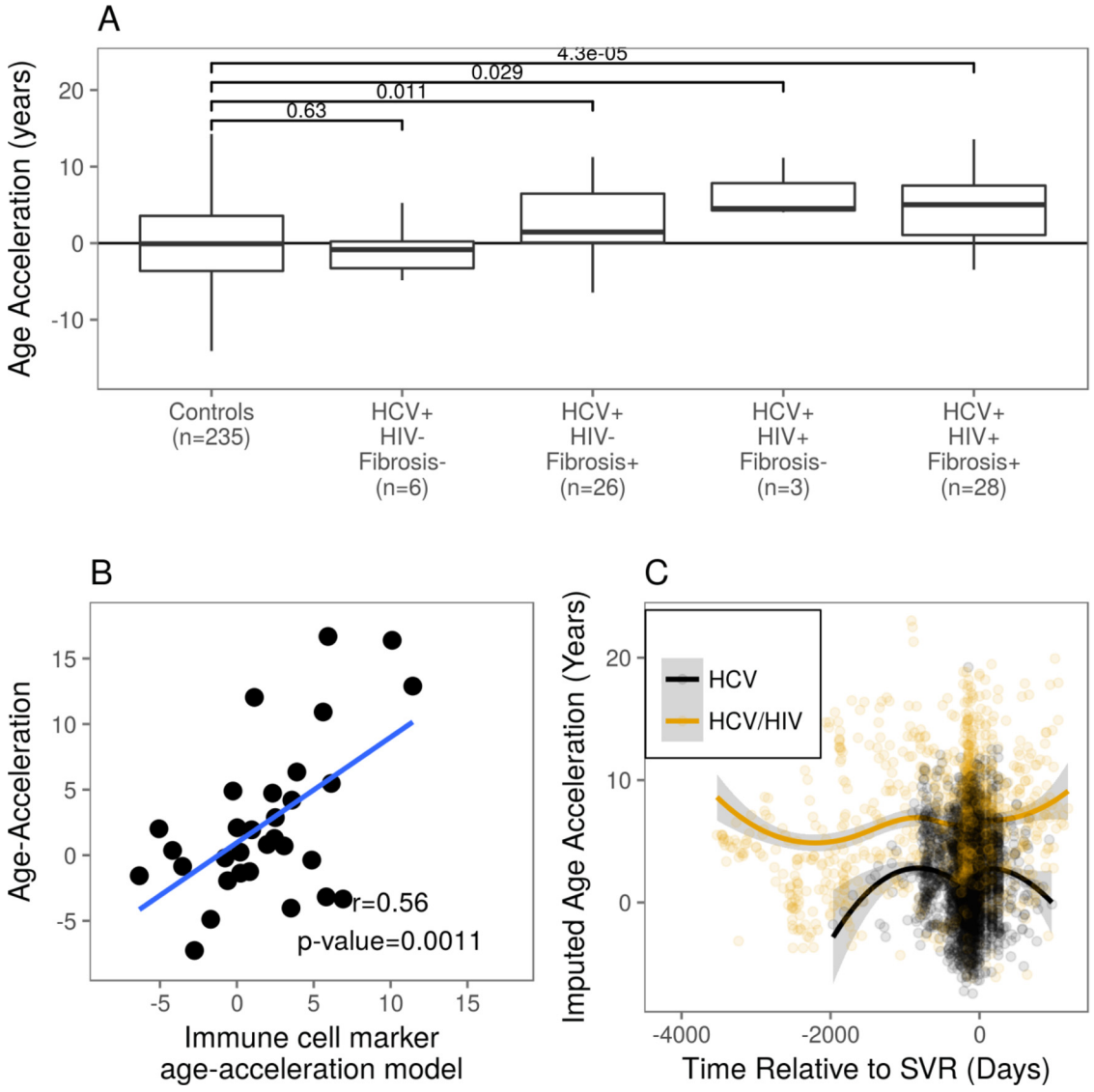


Figure: (abstract: THU-398)

Results: HCV patients co-infected with HIV were observed to have greater AA compared to controls regardless of the presence of liver fibrosis (liver fibrosis: 5.02 years; $p = 4.3 \times 10^{-5}$; no liver fibrosis: 4.51 years; $p = 0.029$). HCV mono-infected patients with liver fibrosis are more age accelerated (1.84 years; $p = 0.011$) whereas HCV mono-infected patients without liver fibrosis are not age accelerated (−0.84 years; $p = 0.63$) compared to controls (Figure 1A). We developed and validated an AA model based on immune cell marker data. AA inferred from post-treatment blood marker data (validation dataset) is concordant with DNAm-based measure ($r = 0.65$; $p = 0.00022$) (Figure 1B). Longitudinal immune marker-inferred AA data shows distinct patterns of AA relative to SVR depending on the patient's infection status: greater AA in HCV/HIV dual-infected patients prior to DAA therapy and a trend of AA reversal in HCV patients post SVR ($p = 0.021$; Figure 1C).

Conclusion: Liver fibrosis and HIV infection are associated with AA in chronic HCV patients. AA can be inferred from a novel set of peripheral cell activation markers. While SVR is associated with reversal of AA in chronic HCV, patients with HIV/HCV co- infection have persistent AA despite SVR, likely suggestive of persistent HIV-induced immune activation.

THU-399
Incidence and prevalence of extrahepatic manifestations of HCV

H. El-Serag[1], I. Christie[1], A. Puenpatom[2], D. Castillo[1], F. Kanwal[1], J. Kramer[1]. [1]*Michael E. DeBakey VA Medical Center, Center for Innovations in Quality, Effectiveness and Safety (IQuESt), Houston, United States;* [2]*Merck Sharp & Dohme Corp, Whitehouse Station, United States*
Email: hasheme@bcm.edu

Background and Aims: Chronic hepatitis C virus (HCV) infection has been associated with several extrahepatic manifestations (EHMs). Direct acting antiviral (DAA) therapy has revolutionized the treatment of HCV, and may have a beneficial role in EHMs. However, contemporary DAA era data on the prevalence and incidence of EHM in patients with active HCV are limited.
Methods: We conducted a retrospective matched cohort study of patients with and without HCV in the national U.S. Veterans Affairs Corporate Data Warehouse. The HCV positive cohort included individuals with positive HCV RNA between 10/1999 and 10/2016, age 20 to 85 years at earliest positive HCV date (index date), and with more than one year of follow-up after index date. The HCV negative cohort was defined using the same criteria but with absence of a positive HCV RNA and their index date was a clinic visit date in the same year. Cases and controls were matched using 1:1 ratio on DOB (±5 years), first visit date in VA system (± 1 year), HCV/visit index date (±1 year), and gender. Prevalence, incidence rates (IR), and incidence rate ratios (IRR) were estimated for EHMs, including mixed cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, lichen planus, non-Hodgkin's lymphoma, and diabetes. EHMs were identified by the presence of at least one inpatient or outpatient ICD-9/10 diagnoses between 10/1999–10/2017. Prevalence was defined as diagnosis either prior to or up to one year following index date. Incidence rates were calculated by dividing new diagnoses by total person-years from index date through either the patients' diagnosis or last clinic visit in the VA system; all prevalent cases were excluded for the purpose of incidence rate calculation.
Results: We identified 244,655 patients (mean age = 54.6 years, 96.3% men, and 32.5% African American, 55.1% white) with active HCV, and 244,655 matched controls without HCV. The prevalence, IRs and IRRs of EHM in HCV– and HCV+ cohorts are shown in the Table. Baseline prevalence and IRRs were higher in patients with HCV compared with no HCV for mixed cryoglobulemia, glomerulonephritis, porphyria cutanea tarda, and lichen planus but not for non-Hodgkin's lymphoma and diabetes. For example, patients with HCV were 4 times more likely to develop mixed cryoglobulemia than patients without HCV. In the DAA era (post 9/2014), the prevalence of one or more of these 4 EHM conditions was 5.78% (12,183 of 210,564) of HCV+ cases.
Conclusion: Both the prevalence and risk of several EHMs of HCV infection is elevated among HCV positive patients. Extrahepatic benefits of SVR attainment should be examined so it can be included in the cost-benefit analyses of new antiviral drugs for HCV infection.

THU-400
Changes in hepatic steatosis measured by CAP-fibroscan in patients with chronic hepatitis C treated with direct action antivirals

P. Linares[1], R. Quiñones[1], B. Álvarez-Cuenllas[1], F. Jorquera[2], N. Reyes[1], C. Villar[1], G. Molina[1], R.P. Fernandez[1], L. Vaquero[1]. [1]*Complejo Asistencial Universitario de León, Servicio de Digestivo, Unidad de Hepatología, León, Spain;* [2]*Complejo Asistencial Universitario de Léon, Servicio Aparato Digestivo, Spain*
Email: plinares68@gmail.com

Background and Aims: The relationship between the hepatitis C virus (HCV) and the development of hepatic steatosis is well known, due to different mechanisms that include a direct cytopathic effect, interaction in the liver turnover of triglycerides, etc. Likewise, liver steatosis next to HCV can contribute to the progression of hepatic fibrosis. At present, the CAP (Controlled Attenuation Parameter) allows the quantification of hepatic steatosis in a non-invasive way at the same moment of the realization of fibroscan. Our aim is to analyze what happens with steatosis measured by CAP after treatment of hepatitis C with direct action antivirals (DAA) and its relationship with anthropometric variables, lipid profile, viral variables, elastometry and type of treatment used.
Method: retrospective study from January 2015 to March 2017 of the cases treated with DAA in which a baseline and 24 weeks post-treatment determination of a CAP-fibroscan was made.
Results: 364 patients were collected (40% women), mean age 57 years (20 to 88), 53% naive, 26% with hypertension, 12.4% diabetes,

Table 1: (abstract: THU-399)

Table: Prevalence and crude incidence rates of extrahepatic outcomes of hepatitis C virus infection (HCV+ vs HCV-).

	HCV+			HCV-			
Outcome	**Prevalence**	**Events**	**IR/1000 PY**	**Prevalence**	**Events**	**IR/1000 PY**	**IRR (95% CI)**
Mixed cryoglobulinemia	0.27%	1,689	0.76	0.08%	391	0.19	4.03 (3.61-4.49)
Glomerulonephritis	1.50%	6,139	2.82	1.20%	4,224	2.07	1.36 (1.31-1.41)
Porphyria cutanea tarda	0.61%	903	0.41	0.05%	105	0.05	8.04 (6.57-9.84)
Lichen planus	0.33%	1,573	0.71	0.22%	690	0.33	2.12 (1.94-2.32)
Non-Hodgkin lymphomas	0.72%	2,258	1.02	0.65%	2,091	1.02	1.00 (0.95-1.06)
Diabetes mellitus	20.50%	36,322	22.5	24.40%	38,098	26.3	0.86 (0.84-0.87)

Abbreviations: CI, confidence intervals; IR, incidence rate; IRR, incidence rate ratio; PYs, person-years

12.8% with dyslipidemia and 28.2% cirrhosis, which reached the sustained viral response (SVR). The predominant genotype was 1b (48.6%) and genotype 3 was 11.6%. The mean basal fibroscan was 12.4 KPa and post-treatment was 9.19 KPa ($p < 0.05$). The mean baseline CAP was 239.1 ± 50 and after treatment was 246.27 ± 56 dB/m ($p < 0.05$). 38.66% of the patients had basal liver steatosis moderate-severe (CAP ≥ 248 dB/m) and this percentage increased to 44.63% after treatment ($p = 0.004$). A direct relationship was found between the basal quantification of steatosis and the degree of liver fibrosis ($p < 0.05$): F0 (216.5 dB/m), F1 (222.1 dB/m), F2 (239.2 dB/m), F3 (254 dB/m) and F4 (247 dB/m). 20% of patients with fibrosis F < 2 had steatosis grade 2–3 (CAP > 250 dB/m) vs 42.23% of patients with F ≥ 2, ($p = 0.003$). The same occurred in the post-treatment CAP (17.9% in F < 2 vs 52% in F ≥ 2, $p = 0.009$). 66.7% of patients with genotype 3 had basal steatosis grade 2–3 vs 34.5% of the rest of genotypes, ($p = 0.023$) and this difference decreased after treatment (55.9% vs 43.5%). In the multivariable analysis, the increase in basal CAP was significantly related to weight gain, high viral load, genotype 3, high HOMA, atherogenic index (HDL/total cholesterol), coronary risk (HDL/LDL) and degree of hepatic fibrosis. No association was found with age, sex, type of treatment used and other comorbidities.
Conclusion: In our cohort, 40% of the patients with hepatitis C had a moderate-severe steatosis measured by CAP, which was more evident in patients with genotype 3, high viral load and greater degree of fibrosis. The cure of hepatitis C was associated with an increase in liver steatosis, which was directly related to changes in lipid profile, insulin resistance, weight gain and increased atherogenic and coronary risk.

THU-401

Influence of statines in the modifications of lipid and hydrocarboned metabolism in patients with chronic hepatitis C treated with direct-acting antivirals

P. Linares[1], B. Álvarez-Cuenllas[1], F. Jorquera[1,2,3], R. Quiñones[1], N. Reyes[1], G. Molina[1], C. Villar[1], M. Guerra-González[4], E. Fernández-Moran[4], E. Gutiérrez-Gutiérrez[4], D. Fierro-González[5].
[1]Complejo Asistencial Universitario de León, Servicio de Digestivo, Unidad de Hepatología, Spain; [2]IBIOMED; [3]CIBERhep; [4]Complejo Asistencial Universitario de León, Servicio de Farmacia, Spain; [5]Centro de Salud Astorga 2, Medicina Familiar y Comunitaria, Spain
Email: plinares68@gmail.com

Background and Aims: The hepatitis C virus (HCV) modifies the lipid and hydrocarbon metabolism of the host. Statins interact with direct-acting antivirals (DAA) and are stopped before the start of ADAs and reintroduced at the end. Objective: To compare the variations of the lipid profile and insulin resistance in HCV patients treated with DAA after obtaining the sustained viral response in week 24 (SVR-24) and to evaluate statins as a possible modifying factor.
Method: Retrospective study of patients with HCV treated from January 2015 to December 2016, collecting different variables: age, sex, genotype, degree fibrosis, type of DAA, comorbidities, use of statins and analytical determinations: total cholesterol (TCh), triglycerides (TGL), HDL, LDL, insulin and HOMA at four different times: Basal (B), Final treatment (F), Week 12 after treatment (12) and Week 24 (24). To evaluate the influence of statins we use TCh.
Results: 332 patients treated (60.5% men), mean age 57 years. 26% had hypertension, 13% diabetes, 12.3% dyslipidemia and 27% liver cirrhosis. Only 5.45% of patients received treatment with statins prior to the start of treatment. The distribution of the genotypes was: 1a (27.5%), 1b (50%), 2 (2.5%), 3 (11%), 4 (9%). Mean viral load: 3,153,432 IU/ml. SVR-24 was reached in 98%. The baseline serum concentrations of TCh, TGL, HDL and LDL were 165.2, 135.7, 52.5 and 118.64 mg/dl respectively. In genotype 3, the mean baseline TCh concentrations were lower ($p < 0.005$) and the baseline HOMA was higher ($p = 0.029$). Overall, the mean serum concentration at the end of the TCh (F) treatment increased 18.65 mg/dl, 21.24 mg/dl at week 12 and 20.19 at week 24 compared to baseline values ($p < 0.0001$). The mean increase in LDL (F) was 26.03 and 22.81 mg/dl (12) ($p < 0.0001$). The atherogenic risk (TCh/HDL) increased from 3.46 (B) to 3.93 (F), 4.2 (12) and 3.8 (24) ($p < 0.005$) and coronary risk (HDL/LDL) increased 0.27 (24). In the non-statin group (mg/dl ± SD): TCh (B) 165.23 ± 35.15, TCh (F) 182.67 ± 40.5; TCh (12) 186.44 ± 36.21, TCh (24) 186.71 ± 36.65. In the statin group: TCh (B) 164.89 ± 35.15, TCh (F) 204.33 ± 40.5, TCh (12) 186.47 ± 36.21, TCh (24) 158.92 ± 36.65. The values of TCh (F) and TCh (24) were significant in the group of statins vs non-statins.
Conclusion: the low use of statins in patients with chronic hepatitis C suggests a metabolic blockade of HCV and variations in the lipid profile after antiviral treatment may reflect the physiological response to viral elimination. However, the increase in TCh, LDL and atherogenic risk may have a potential impact on atherosclerosis. Statins imply an additional block of lipid metabolism that is recovered with greater intensity in patients who suspend them. No effects of the type of DAA used on lipid changes were observed.

THU-402

Changes in serum neurotransmitters are associated with changes in patient reported outcomes and neurocognitive performance in patients with hepatitis C virus-genotype 1 who achieved sustained virologic response

L. Deavila[1], A.A. Weinstein[2], M. Curry[3], P. Golabi[1], J.M. Estep[1], C. Escheik[1], A. Birerdinc[1], M. Stepanova[4], L. Gerber[1,2,5], Z. Younossi[6].
[1]Inova Health System, Betty and Guy Beatty Center for Integrated Research, Falls Church, United States; [2]George Mason University, Center for the Study of Chronic Illness and Disability, College of Health and Human Services, Fairfax, United States; [3]Beth Israel Deaconess Medical Center, Boston, United States; [4]Center for Outcomes Research in Liver Disease, Washington DC, United States; [5]Inova Fairfax Hospital, Center for Liver Disease, Department of Medicine, Falls Church, United States; [6]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States
Email: zobair.younossi@inova.org

Background and Aims: Although neurotransmitters (NTs) in Hepatitis C Virus (HCV) infection have been shown to be associated with Patient Reported Outcomes (PROs) and neurocognitive performance (NP), changes in the relationships between NTs and PROs/NP in patients with Sustained Virologic Response (SVR) have not been assessed.
Method: HCV subjects without cirrhosis (N = 40, age: 45.3 ± 11.5, 48% male, 90% white) received 12 weeks of ledipasvir/sofosbuvir (LDV/SOF) or placebo followed by 12 weeks of LDV/SOF with 92% achieving SVR24. Baseline, and post-SVR PROs were assessed using Short-Form (SF-36), Chronic Liver Disease Questionnaire-HCV (CLDQ-HCV), Functional Assessment of Chronic Illness Therapy-Fatigue; and (2) NP: digit span/symbol span (working memory), Trail Making B/Color Word Interference (executive function), Hopkins Verbal Learning/Brief Visuospatial Memory tests (memory). Serum NTs (serotonin, BDNF, and GABA) were measured by ELISA at baseline and SVR24. Correlations among the NTs and PROs and NP were performed at baseline and at SVR24 using non-parametric Spearman correlations. Correlations of the amount of change from baseline (SVR24-baseline) was the correlation of interest.
Results: Relationships between NTs and PROs and NPs differed at baseline and SVR24. At baseline serum GABA and BDNF correlated with PROs of physical functioning ($r = 0.32$; $r = -0.40$, p's < 0.05). In contrast, Serotonin was related to perceptions of vitality, emotional well-being, fatigue, and activity/energy ($r = 0.32$ to 0.41; p's < 0.05). At SVR24, PROs improved and these relationships between NTs and PRO domains were no longer present. On the other hand, changes in magnitude and direction of the following remained significant: GABA was associated with the changes in measures of working memory, memory, executive function, fatigue and physical role ($r = 0.33$ to 0.47; $p = <0.05$). BDNF was associated with pain, physical composite score, physical well-being ($r = 0.4$ to 0.46; $p = <0.015$) and serotonin

correlated with general health and executive function (r = 0.34 to 0.40; p = <0.05).

Conclusion: After achieving SVR24, serum BDNF correlates with physical performance, while serum serotonin correlates with general health and executive function. During viremia, GABA levels associate with physical function. These data suggest that the relationships between NTs with PRO and NP seen during HCV viremia, change with SVR24 and the magnitude of these changes may have clinical relevance.

THU-403

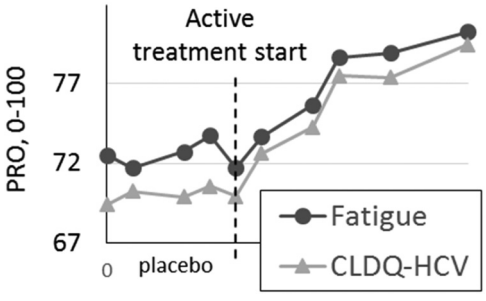
Patient-reported outcomes in chronic hepatitis C: The impact of placebo, active treatment, and sustained viral eradication

Z. Younossi[1], M. Stepanova[2], M.P. Manns[3], R. Reddy[4], S.C. Gordon[5], M. Bourliere[6]. [1]*Inova Fairfax Hospital, Department of Medicine, Falls Church, United States;* [2]*Center for Outcomes Research in Liver Disease;* [3]*Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany;* [4]*University of Pennsylvania;* [5]*Henry Ford Hospital;* [6]*Hopital Saint Joseph*
Email: zobair.younossi@inova.org

Background and Aims: Clearance of HCV infection is known to improve quality of life and other patient-reported outcomes (PROs). To longitudinally assess changes in PROs in patients with HCV infection who were initially randomized to placebo and then subsequently received SOF/VEL/VOX for 12 weeks in a "deferred treatment" study.

Method: HCV-infected patients who received 12 weeks of placebo in the POLARIS-1 study were subsequently treated with SOF/VEL/VOX (400 mg/100 mg/100 mg) daily for 12 weeks. During placebo treatment and active treatment periods, PROs were prospectively collected using SF-36v2, CLDQ-HCV, FACIT-F, and WPAI:SHP assessing 26 PRO domains.

Results: Of 147 HCV patients included, most were male (79%), white (82%), 33% had cirrhosis, and 99% had HCV genotype 1. The SVR-12 rate was 97%. During treatment with placebo, there were no significant changes in any PRO domains from patients' own baseline levels (all p > 0.05) except for the Worry domain of CLDQ-HCV. However, soon after the initiation of SOF/VEL/VOX, significant PRO improvements were noted in a number of PRO domains. By week 4 of active treatment, scores improved in 6/26 PRO domains (+2.4% to +8.1%, p < 0.05) and continued to improve until the end of treatment week 12 in 14/26 PRO domains (+2.0% to +8.3%, p < 0.05). Achieving SVR was associated with improvement in 24/26 PRO domain scores by post-treatment week 12 and in 23/26 domain scores by post-treatment week 24 (+3.2% to +14.9%). The greatest PRO improvements were observed in the domains of Vitality, Activity, and Presenteeism (>8% of a PRO range size). In multivariate analysis, being viremic was associated with significantly impaired PRO scores: β ranging from −2.4% to −8.5%, p < 0.05 for all but one PRO.



Conclusion: This study shows that PROs do not change during placebo treatment but significantly improve with active DAA treatment and with sustained viral eradication. These data provides strong evidence supporting the positive impact of HCV viral suppression on PROs.

THU-404

Universal access to DAA therapy paves the way for HCV control and elimination among people living with HIV in Australia

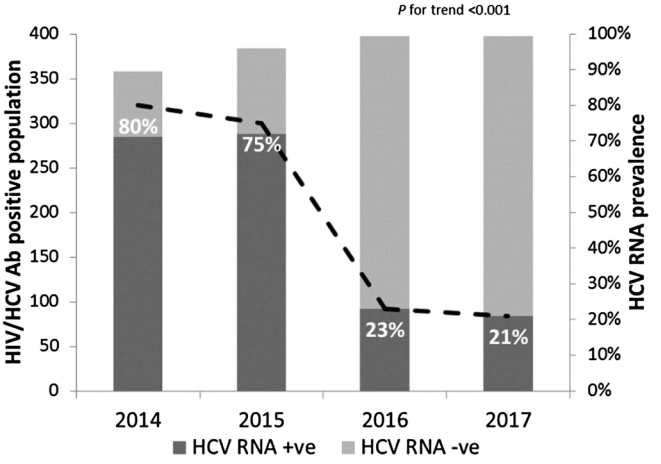
M. Martinello[1,2,3], S. Bartlett[1], G. Dore[1,2], R. Bopage[4,5], R. Finlayson[6], D. Baker[7], M. Bloch[8], J. Doyle[9,10,11], D. Shaw[12], K. Hajkowicz[13], P. Read[14], E. Filep[15], L. Lin[15], J. Yee[15], T. Applegate[15], M. Hellard[9,10], G. Matthews[15,16]. [1]*Kirby Institute, UNSW Sydney, Sydney, Australia;* [2]*St Vincent's Hospital, Darlinghurst, Australia;* [3]*Blacktown Mt Druitt Hospital, Blacktown, Australia;* [4]*The Albion Centre, Surry Hills, Australia;* [5]*UNSW Sydney, School of Public Health and Community Medicine, Sydney, Australia;* [6]*Taylor Square Private Clinic, Surry Hills, Australia;* [7]*East Sydney Doctors, Darlinghurst, Australia;* [8]*Holdsworth House, Sydney, Australia;* [9]*Burnet Institute, Melbourne, Australia;* [10]*Alfred Hospital, Melbourne, Australia;* [11]*Monash University, Department of Infectious Diseases, Clayton, Australia;* [12]*Royal Adelaide Hospital, Adelaide, Australia;* [13]*Brisbane Sexual Health Clinic, Brisbane, Australia;* [14]*Kirketon Road Clinic, Darlinghurst, Australia;* [15]*Kirby Institute, Sydney, Australia;* [16]*St Vincent's Hospital, Sydney, Australia*
Email: mmartinello@kirby.unsw.edu.au

Background and Aims: HCV elimination among people living with HIV may be possible in Australia, given population size (n = 2,500–3,000), high proportion diagnosed and linked to care (>80%), and unrestricted government-subsidised access to direct-acting antiviral (DAA) therapy (as of March 2016). The aim of this analysis was to assess HCV treatment uptake, outcomes, and HCV RNA prevalence among HIV/HCV co-infected adults enrolled in the Control and Elimination of HCV from HIV-infected individuals within Australia (CEASE-D) cohort study following the availability of DAA therapy.

Method: Cumulative HCV treatment uptake was defined as the proportion of individuals diagnosed with chronic HCV infection who ever initiated HCV treatment (censored 13 October 2017). Annual (2014–2016) HCV treatment uptake was defined as the proportion of individuals with chronic HCV who initiated treatment per year. Sustained virological response was assessed in those who had completed 12 weeks post treatment follow-up (SVR12). Factors associated with DAA uptake in 2016 and 2017 were evaluated by logistic regression analysis. HCV RNA prevalence was calculated per study year, accounting for new diagnoses, treatment outcome, reinfection post SVR and death.

Results: Of 402 HIV/HCV antibody-positive individuals enrolled (mean age 49, SD 10), 95% were male (80% gay and bisexual men [GBM]), 13% had cirrhosis, and 22% had ever received interferon-based therapy. Injecting drug use (IDU) ever and current was reported by 80% and 36%, respectively, predominantly (meth) amphetamine (ever 66%, current 30%). The principal modes of HCV transmission were IDU (54%) and sexual exposure in GBM (28%). Cumulative HCV treatment uptake among individuals ever diagnosed with chronic HCV infection was 85% (95%CI 81%, 88%); 67% had received interferon-free DAA regimens. Annual HCV treatment uptake increased from 7% (95%CI 5%, 11%) and 10% (95%CI 7%, 14%) in 2014 and 2015, respectively, to 78% (95%CI 73%, 83%) in 2016 (p < 0.001). Among those treated, SVR12 was 70%, 86% and 92% in 2014, 2015 and 2016, respectively. No clinical or demographic factors, including current IDU, were associated with DAA uptake. HCV RNA prevalence decreased significantly between 2014 and 2017, from 80% (95%CI 75%, 84%) to 21% (95%CI 17%, 25%) (p < 0.001) (Figure).

Conclusion: High uptake and efficacy of government-subsidised DAA therapy has permitted rapid treatment scale-up with a marked reduction in HCV RNA prevalence among people living with HIV, paving the way for HCV elimination in this population.



THU-405

The Rapid-EC study – A feasibility study of point-of-care testing in community clinics targeted to people who inject drugs in Melbourne, Australia

B. Williams[1], A. Pedrana[1,2], J. Howell[1,2,3,4], J. Doyle[1,5], A. Thompson[3,4], F. Bramwell[6], D. Membrey[6], M. Mcpherson[7], C. Layton[6], B. Draper[1], J. Roney[8], N. Latham[1,9], M. Hellard[1,2,10]. *[1]Burnet Institute, Disease Elimination Program, Melbourne, Australia; [2]Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia; [3]St Vincent's Hospital, Department of Gastroenterology, Melbourne, Australia; [4]University of Melbourne, Department of Medicine, Melbourne, Australia; [5]Alfred Health and Monash University, Infectious Diseases, Melbourne, Australia; [6]Cohealth, Melbourne, Australia; [7]North Richmond Community Health, Melbourne, Australia; [8]Alfred Hospital, Infectious Diseases, Melbourne, Australia; [9]Monash University, Department of Infectious Diseases, Melbourne, Australia; [10]The Alfred and Monash University, Department of Infectious Diseases, Melbourne, Australia*
Email: margaret.hellard@burnet.edu.au

Background and Aims: Increasing the number of people who inject drugs (PWID) accessing hepatitis C virus (HCV) diagnosis and treatment is essential to Australia's success in eliminating HCV. Point-of-care (POC) diagnostics may reduce barriers to HCV care by allowing same-day diagnosis and facilitating testing in locations already frequented by PWID, such as needle and syringe exchange programs (NSPs). The Rapid-EC study was conducted to assess the feasibility and acceptability of POC testing for HCV in three community clinics with NSPs.

Method: Clients of the NSP service, who were not engaged in HCV care, were invited to participate. Participants underwent OraQuick HCV antibody mouth swab test (20 minutes to result); those positive were offered venepuncture for the Xpert HCV viral load (105 minutes to result). Participants were offered same-day results delivered on site, via phone or text message, or on return to the service. Participants were invited for follow-up review and those diagnosed with chronic HCV were assessed for treatment by a nurse and linked to community or specialist prescribers. Analysis of treatment uptake is ongoing. Participants also completed demographic, behavioural and acceptability surveys.

Results: A total of 174 participants completed POC testing for HCV antibodies, of whom 150 (86%) had a reactive result. Of these, 140 (93%) underwent a POC HCV RNA test, of which 76 (54%) had detectable RNA. The median age of participants was 41 years, 118 (67%) were male, 154 (88%) had injected drugs within six months and 93 (53%) had shared injecting equipment within six months. Of the 67 participants for whom a four-week period had elapsed since HCV diagnosis, 40 (60%) had been reviewed and linked to care in that time. Only 7 (5%) participants waited on-site to receive their POC RNA result, while 85 (61%) opted to receive their result via phone call or text message. The majority (85%) of participants preferred POC compared to standard HCV testing.

Conclusion: Provision of POC testing at community clinics with NSPs was feasible and acceptable to clients at high risk of HCV infection. Point-of-care tests streamlined HCV testing and enhanced linkage to care opportunities, however the ability to provide same-day diagnosis with current tests is limited. The utility of HCV POC diagnostics may be improved by reducing time to result and number of tests to diagnosis.

THU-407

Evaluation of APRI index to identify cirrhosis prior to direct-acting antiviral HCV treatment

J. Doyle[1,2], B. Harney[1,2], D. Brainard[3], A. Osinusi[3], L. Stamm[3], M. Hellard[4], A. Thompson[5,6]. *[1]Monash University and The Alfred, Department of Infectious Diseases, Melbourne, Australia; [2]Burnet Institute, Australia; [3]Gilead Sciences, Foster City, United States; [4]Burnet Institute, Melbourne, Australia; [5]St Vincent's Hosptial Melbourne, Melbourne, Australia; [6]University of Melbourne, Melbourne, Australia*
Email: joseph.doyle@monash.edu

Background and Aims: Direct acting antivirals have been shown to be effective in treating hepatitis C (HCV) regardless of cirrhosis stage. However identifying cirrhosis prior to treatment is still important for clinical care and follow up. Liver biopsy (LB) and transient elastography (TE) are standard of care but access is limited by cost and training. Aspartate aminotransferase to platelet ratio index (APRI) is requires only routine blood tests and is simple to calculate. We aimed to identify an APRI value where LB or TE may not be required to identify cirrhosis.

Method: An analysis of data pooled from 10 sofosbuvir-based interferon free clinical trials that included participants with and without cirrhosis was conducted. Participants who underwent cirrhosis screening by LB or TE were included in this analysis. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated for a range of APRI values and stratified by age (<50 or >50 years). Poisson regression adjusted for sex, body mass index, HCV genotype and IL28B genotype was used to identify associations with cirrhosis.

Results: APRI data and LB or TE results were available for 3,835 participants among whom 23% (n = 898) were identified to have cirrhosis. The mean age of participants was 54 years (range 18–85), 64% were male and 82% were white. Approximately 34% underwent LB and there was no significant difference in cirrhosis identification between LB and TE (χ^2 0.138 p = 0.71). APRI value ≤0.5 had an NPV of 92% to exclude cirrhosis (95% CI: 90–94) among participants aged >50 and a NPV of 98% (95%CI 96–99) among those aged <50. Participants aged >50 with an APRI value ≤0.5 were 77% less likely to have cirrhosis (adjusted prevalence ratio [aPR] 0.23, 95%CI 0.18–0.30) compared to those with an APRI >0.5. Among those aged <50, an APRI ≤0.5 was associated with being 90% less likely to have cirrhosis (aPR 0.10, 95%CI 0.04–0.20).

	APRI 0.5	APRI 1.0	APRI 2.0
Participants under 50 years old	n = 380	n = 663	n = 850
Sensitivity, % (95% CI)	95 (89–98)	77 (69–84)	38 (29–47)
Specificity	46 (41–49)	78 (75–80)	94 (92–96)
PPV	22 (18–25)	35 (30–41)	51 (40–61)
NPV	98 (96–99)	96 (94–97)	91 (88–92)
Participants over 50 years old	n = 847	n = 1835	n = 2535
Sensitivity	92 (89–93)	68 (65–72)	33 (30–37)
Specificity	37 (35–39)	75 (73–77)	95 (94–96)
PPV	34 (32–37)	50 (47–53)	72 (67–77)
NPV	92 (90–94)	87 (85–88)	80 (78–81)

Conclusion: In settings with limited access to liver biopsy or transient elastography, APRI could be used to triage further fibrosis assessment. An APRI of <0.5 among people over 50, and APRI <1.0 among under 50 year olds may an appropriate cut-off to rule out cirrhosis and avoid additional fibrosis testing.

THU-408

Hepatitis C treatment success in primary and tertiary care among people with HCV/HIV coinfection

J. Doyle[1,2], D. Iser[1], J. Sasadeusz[3], J. Roney[1], J. Cutts[2], A. Bowring[2], R. Winter[2], M. O'reilly[4], C. Fairley[5], E. Gane[6], J. Hoy[1], G. Matthews[7], N. Medland[8], R. Moore[9], M. Prins[10], B. Tee[11], M. Stoove[2], M. Hellard[1,2].
[1]Monash University and The Alfred, Department of Infectious Diseases, Melbourne, Australia; [2]Burnet Institute, Melbourne, Australia; [3]Melbourne Health, Melbourne, Australia; [4]Prahran Market Clinic, Melbourne, Australia; [5]Alfred Health, Melbourne Sexual Health Centre, Melbourne, Australia; [6]Auckland Hospital, Auckland, New Zealand; [7]Kirby Institute, Sydney, Australia; [8]Alfred Health, Melbourne Sexual Health Centre, Carlton, Australia; [9]Northside Clinic, Melbourne, Australia; [10]GGD Amsterdam, Amsterdam, Netherlands; [11]Centre Clinic, Melbourne, Australia
Email: joseph.doyle@monash.edu

Background and Aims: In Australia, subsided access to hepatitis C (HCV) direct-acting antivirals (DAAs) without disease stage restriction provides an opportunity to dramatically increase HCV treatment uptake. The co-EC study aims to eliminate HCV through community treatment of HIV coinfected gay and bisexual men in Melbourne, Australia.
Method: The co-EC study is an ongoing (March 2016–) nurse-managed, clinician-directed, non-randomised trial of therapy among HCV/HIV coinfected people. Assessment and work-up are performed by nurses at tertiary (n = 2) and primary care (n = 4) sites to facilitate prescription of DAAs by specialists or general practitioners. Routine clinical data, including haematological, biochemical and fibrosis assessment, is collected at baseline and post-treatment visits (SVR12).
Results: Overall 190 HIV positive individuals with chronic HCV infection (98% male, median age 47 years) were enrolled; 67% in primary care. At baseline, 98% of participants were on ART and 91% had a suppressed HIV viral load. In the cohort, 67% of participants had HCV genotype 1 and 27% genotype 3. The most common modes of HCV infection were sexual contact with a person of same sex (38%) and injecting drug use (31%). Thirty participants (16%) had previously been treated for HCV. Of the 16 (8.5%) who were cirrhotic, 10 (63%) were cared for in tertiary settings.
One hundred and sixty nine participants commenced treatment, with the majority prescribed sofosbuvir with daclatasvir (47%) or ledipasvir (46%). At their SVR12+ visit, HCV RNA by PCR was undetectable in 131/136 participants (96%, 95% CI 91–98%), comprising 86/91 (95%) patients seen in primary care and 45/45 (100%) patients seen in tertiary care (p = 0.109). All cirrhotic participants (11/11) were undetectable at SVR12 + . Three participants discontinued treatment and did not achieve SVR12: one due to non-adherence; one self-discontinuation due to side-effects; and one clinician advised discontinuation due to adverse events.
Conclusions: HCV treatment was safe and highly effective in this real-world cohort. Despite HCV/HIV coinfection traditionally requiring specialist management, our findings suggest that most people can be managed in primary care settings without referral. Nurses undertook the vast majority of patient care – facilitating treatment commencement and undertaking patient monitoring. This network also provides an opportunity for regular testing to detect HCV reinfection in community settings.

THU-409

REtrieval And Cure of Hepatitis C patients in the Utrecht province in the Netherlands: REACH

P. Kracht[1], J.E. Arends[1], K.J. van Erpecum[2], S.F.T. Thijsen[3], B. Vlaminckx[4], A. Weersink[5], M. Deege[6], P.H.G.M. Stadhouders[7], P.W. Friederich[8], M.A.M.T. Verhagen[9], G. Boland[10], A.I.M. Hoepelman[1].
[1]University Medical Center Utrecht, Internal Medicine and Infectious Diseases, Utrecht, Netherlands; [2]University Medical Center Utrecht, Gastroenterology and Hepatology, Utrecht, Netherlands; [3]Diakonessenhuis Hospital, Medical Microbiology and Immunology, Utrecht, Netherlands; [4]St Antonius Hospital, Medical Microbiology and Immunology, Nieuwegein, Netherlands; [5]Meander Medical Center, Medical Microbiology and Immunology, Amersfoort, Netherlands; [6]Saltro, Medical Microbiology and Immunology, Utrecht, Netherlands; [7]St Antonius Hospital, Gastroenterology and Hepatology, Nieuwegein, Netherlands; [8]Meander Medical Center, Gastroenterology and Hepatology, Amersfoort, Netherlands; [9]Diakonessenhuis Hospital, Gastroenterology and Hepatology, Utrecht, Netherlands; [10]University Medical Center Utrecht, Medical Microbiology and Immunology, Utrecht, Netherlands
Email: p.a.m.kracht@umcutrecht.nl

Background and Aims: The Netherlands may be one of the first countries to achieve elimination of the hepatitis C virus (HCV). Case finding of formerly identified yet untreated HCV patients is essential in this Dutch HCV elimination process. The Retrieval and Cure of Hepatitis C (REACH)-project aims to retrieve and cure all previously diagnosed and lost to follow-up (LFU) HCV patients in the Utrecht province in the Netherlands.
Method: All positive HCV diagnostic tests (anti-HCV Ig or HCV-RNA) from all four hospitals and one diagnostic center in the Utrecht province between 2006–2015 were linked to clinical records. Untreated patients with available contact information were deemed eligible for retrieval. Patients were classified as having a chronic HCV (cHCV, i.e. 2x positive HCV-RNA ≥ 6 months) or possible chronic HCV (i.e. positive HCV immunoblot without HCV-RNA available). Thus, selected patients were invited for reevaluation with (virology) blood tests, fibroscan measurement, qualitative interview to assess LFU reasons and subsequent direct-acting antiviral (DAA) therapy.

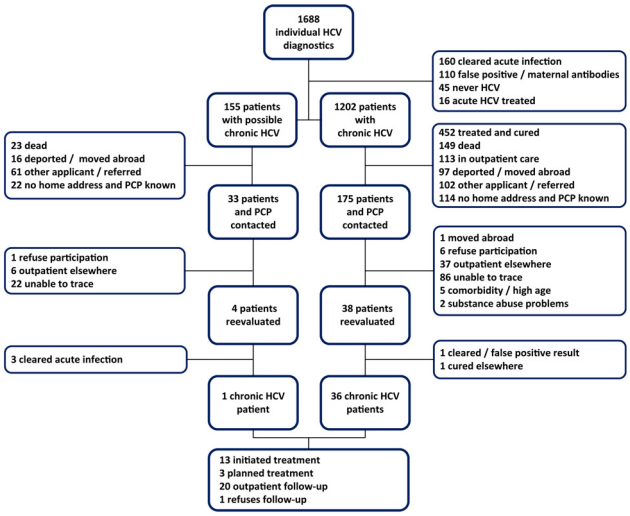


Figure 1: Flowchart: screening of HCV diagnostic tests. PCP, Primary care physician.

Results: Of the 1,688 patients with a positive HCV diagnostic test, 208 (12%) were eligible for retrieval and invited for screening (flowchart in Figure 1). The majority of patients (115/208, 55%) continued to live in the Utrecht province. Eventually, 42/208 (20%) visited the outpatient. After reevaluation, 37/42 patients (88%) had a persistent

cHCV infection characterized by a mean age 54 years (±9.4), 62% male gender, genotype 1a (48%), 1b (27%), 1c (3%), 2 (3%), 3 (8%) and 4 (11%) 14% cirrhosis, 84% treatment naïve, 78% history of intravenous drug use and 31% immigrants. Overall, 13 patients already initiated treatment, 3 are scheduled to start, 20 are in outpatient follow-up and 1 refused further appointments. The LFU from routine clinical practice of the 208 contacted HCV patients was not time dependent (median 13 patients per year, IQR 12–14). Main reasons for previous LFU by qualitative interviewing amongst the 37 traced HCV patients consisted of: deferral of treatment (43%) and substance abuse problems (19%).

Conclusion: In the REACH-project, 42 lost to follow-up chronic HCV patients, i.e. 20% of all individuals elligible for retrieval, were found through re-evaluation of positive HCV diagnostic tests. Therefore, re-evaluation of positive HCV diagnostics in combination with patient recall can be of value for the identification of previously diagnosed however yet untreated cHCV patients.

THU-410

Preliminary analysis of the Prime Study; A randomized controlled trial comparing the hepatitis C care cascade in primary care vs. tertiary care

A. Wade[1,2], J. Doyle[1,3], E. Gane[4], C. Stedman[5], B. Draper[1], D. Iser[3,6], S. Roberts[7,8], W. Kemp[2,3], D. Petrie[9], N. Scott[1], P. Higgs[1,2,10], P. Agius[1,2,11], J. Roney[3], L. Stothers[6], A. Thompson[6,12], M. Hellard[1,2,3].
[1]Burnet Institute, Disease Elimination Program, Melbourne, Australia; [2]Monash University, School of Public Health and Preventive Medicine, Melbourne, Australia; [3]The Alfred, Department of Infectious Diseases; [4]Auckland City Hospital, New Zealand Liver Transplant Unit; [5]Christchurch Hospital and University of Otago, Department of Gastroenterology; [6]St Vincent's Hospital Melbourne, Department of Gastroenterology, Melbourne, Australia; [7]The Alfred, Department of Gastroenterology, Melbourne, Australia; [8]Monash University, Department of Medicine, Melbourne, Australia; [9]Monash University, Centre for Health Economics; [10]Latrobe University, Department of Public Health; [11]Latrobe University, Judith Lumley Centre; [12]University of Melbourne, Department of Medicine
Email: amanda.wade@burnet.edu.au

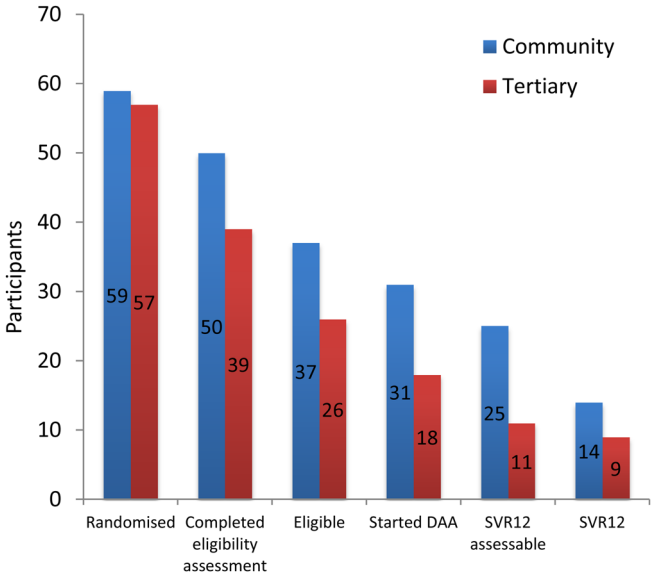
Background and Aims: In order to achieve the World Health Organisation hepatitis C virus (HCV) elimination targets, it is essential to increase access to treatment and retention in the HCV care cascade. The Prime Study is an Australasian study that aims to determine the effect of providing transient elastography (TE) and direct acting antiviral (DAA) treatment in the community on the proportion of people commencing treatment and achieving cure, especially amongst people who inject drugs (PWID).

Method: People with HCV infection were recruited at primary health care centres and randomized to receive eligibility assessment including TE (Australian sites only) and DAAs at their primary health centre (intervention arm), or the local tertiary hospital (standard of care (SOC) arm). Participants assessed as cirrhotic (liver stiffness ≥ 12.5 kPa) were ineligible and were referred to tertiary care. Study endpoints included key milestones in the care cascade; eligibility assessment, commencing DAA and achieving cure. Participants could exit the study at any milestone by failing to attend or declining to schedule further appointments.

Results: We report preliminary findings from the first 120 participants. 97% had ever injected drugs; 48% had injected in the last six months. 116 participants were randomized; 59 to the intervention arm and 57 to the SOC arm.

Of 59 participants in the intervention arm; 50 (85%) completed their eligibility assessment (37 were eligible, 13 were ineligible) and 9 exited the study. Of the 37 eligible participants, 31 commenced DAA and 6 exited the study. The overall treatment uptake rate, excluding ineligible participants, was 31/46 (67%). To date, 25 participants have reached their SVR12 time-point, of which 14 have completed an SVR12 test demonstrating cure and 11 are yet to have an SVR12 test.

Of 57 participants in the SOC arm; 39 (68%) completed their eligibility assessment (26 were eligible, 13 were ineligible) and 18 exited the study. Of the 26 eligible participants 18 commenced DAA and 8 exited the study. The overall treatment uptake rate, excluding ineligible participants, was 18/44 (41%). 11 participants have reached their SVR12 time-point, of which 9 completed an SVR12 test demonstrating cure and 2 are yet to have an SVR12 test.



Conclusion: Preliminary analysis suggests that providing liver assessment and DAA in the community may increase treatment uptake, including in PWID – a key to achieving the elimination targets.

THU-411

Strategic elimination: Efficacy of hepatitis C treatment in people who inject drugs in an urban, underserved clinic in the United States

C. Ramers[1,2], S. Rojas[2], M. Khasira[2], C. Cavanaugh[2], L. Asmus[3]. *[1]School of Medicine, Medicine/Infectious Diseases, La Jolla, United States; [2]Research, Special Populations, San Diego, United States; [3]Public Health, Public Health, San Diego, United States*
Email: christianr@fhcsd.org

Background and Aims: In 2014, only 16% of Americans living with Hepatitis C (HCV) had been treated and half of those cured. Statistical modeling suggests that in order to reach the World Health Organization's goal to treat 80% of those infected with HCV by 2030, scale up of treatment in people who inject drugs (PWID) is needed.

Method: Our urban, underserved clinic system of 23 sites and multiple mobile units started an HCV treatment clinic in 2013. Patients are screened in community drug rehab centers, methadone clinics, at mobile medical units, and needle syringe exchange programs using rapid point-of-care diagnostics followed by immediate phlebotomy for HCV RNA confirmation. Patient Navigators link HCV RNA positive individuals to care and guide them through complex barriers to care, i.e. transportation, health insurance authorization, linkage to drug/alcohol or mental health services. We collected disease and demographic information prospectively; and drug use information on a subset of patients. Non-invasive means were used to assess fibrosis staging, and patients were treated according to published guidelines.

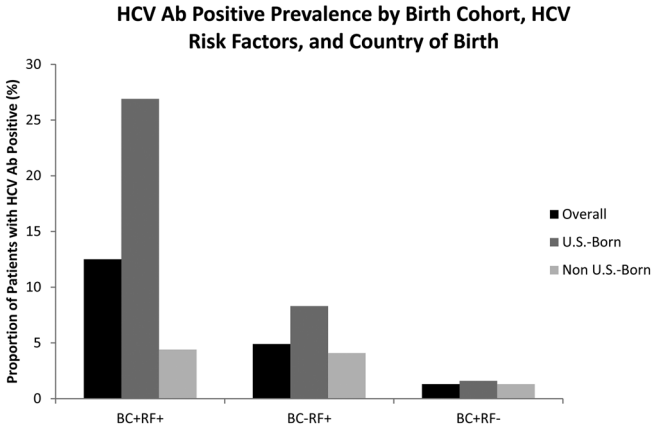
Results: Between 3/1/2013 and 9/30/2017, 413 patients with a detectable HCV RNA test provided information about their injection drug use habits. Most (92%) reported having ever injected drugs, and 50% reported injecting drugs within the previous12 months. Most of the sample was male (73%), Caucasian (39% non-Hispanic, 23% Hispanic) and the average age was 43 years. Of the 380 persons having ever injected drugs, 41% started HCV treatment, compared to 39% of those who had never injected drugs ($p = 0.856$). Of the 153 people injecting drugs in the prior 12 months, 24% started treatment compared to 50% in the group with no injection within 12 months ($p < 0.001$). There was no significant difference in virologic response between patients who had never injected drugs, had ever injected drugs and those who had injected within the past 12 months (99%, 100%, 90%, $p > 0.05$ for all comparisons). Overall, 99% had a sustained virologic response. Only 1 known re-infection has been diagnosed since the start of our program.
Conclusion: Injection drug use within 12 months is associated with decreased likelihood to initiate treatment, but not decreased cure rates. This supports the modeling theory of treatment as prevention. More research is needed to understand what modifiable factors or barriers might be addressed to increase treatment uptake in those who injected drugs in the past 12 months.

THU-412

Among 1945–1965 birth cohort patients with at least one additional hepatitis C virus risk factor, one in eight were positive for HCV antibody: an underserved safety-net population experience

G. Hirode[1], B. Liu[2], T. Bhuket[2], R. Wong[2]. *[1]Alameda Health System-Highland Hosp, Gastroenterology and Hepatology, Oakland, United States; [2]Alameda Health System – Highland Hospital, Gastroenterology and Hepatology, Oakland, United States*
Email: rowong@alamedahealthsystem.org

Background and Aims: Safety-net hospitals are enriched in high risk populations, providing an opportunity for high impact hepatitis C virus (HCV) screening. We aim to evaluate the impact of a pilot program integrating HCV screening into an outpatient endoscopy unit at an urban safety-net hospital.
Method: Consecutive adults undergoing outpatient endoscopy from July 2015-July 2017, who were not previously screened for HCV, were prospectively assessed for HCV screening eligibility using U.S. Preventative Services Task Force guidelines. HCV antibody positive (HCV Ab+) patients were categorized by birth cohort and presence of at least one HCV risk factor: 1945–1965 birth cohort with HCV risk factor (BC + RF+), non-1945–1965 birth cohort with HCV risk factor (BC – RF+) and 1945–1965 birth cohort without HCV risk factor (BC + RF–). Test completion and HCV Ab+ prevalence between groups were compared using chi-squared testing.
Results: Among 1,752 patients evaluated, 67.1% (n = 1,175) were eligible for HCV screening (mean age 57.9 ± 8.2 years, 48.1% male, 90.0% were 1945–1965 birth cohort, 25.7% with at least one HCV risk factor (2.6% HIV positive, 2.6% hepatitis B virus positive, 4.3% history of intravenous drug use, 14.0% previously incarcerated, 5.4% received a blood transfusion pre-1992)). Overall, 15.7% were BC + RF+, 10.0% were BC-RF+, and 78.8% were BC + RF–. Among patients offered testing, HCV Ab test acceptance was significantly higher in BC-RF+ patients compared to BC + RF– (93.9% vs. 82.5%, $p = 0.004$), whereas test completion was significantly higher in BC + RF– compared to BC+ RF+ patients (66.0% vs. 55.8%, $p = 0.03$). Among those who completed testing, overall HCV Ab+ prevalence was 3.4%. When stratified by birth cohort and HCV risk factors, HCV Ab+ prevalence was 12.5% in BC + RF +, 4.9% in BC-RF+, and 1.3% in BC + RF– ($p < 0.001$). When stratified by country of birth, HCV Ab+ prevalence was significantly higher in U.S.-born BC + RF+ vs. non-U.S.-born BC + RF+ patients (26.9% vs. 4.4%, $p = 0.005$), but no significant differences were observed in BC – RF+ patients (8.3% in U.S.-born vs. 4.1% in non-U.S. born, $p = 0.542$) or BC + RF– patients (1.6% in U.S.-born vs. 1.3% in non-U.S.-born, $p = 0.854$).



Conclusion: Among our pilot program integrating HCV screening into outpatient endoscopy, HCV Ab+ was 3.4% among those completing HCV testing. The highest HCV Ab+ prevalence was seen in patients who were born in 1945–1965 birth cohort and had additional HCV risk factors (BC + RF+:12.5%), particularly U.S.-born BR + RF+ patients (26.9%).

THU-413

Among patients being treated in addiction center, alcohol consumption increases the risk of hepatitis C seroconversion and the severity of hepatic fibrosis in those seropositive for hepatitis C virus

M. Doffoël[1,2], F. Habersetzer[2,3,4], T. Baumert[3,4], F.D. Nino[2], L. Jean-Philippe[2], E. Florence[2], H. Carmen[5], C. Frederic[2]. *[1]Pôle Hépato-digestif, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [2]SELHVA – Service Expert de Lutte contre les Hépatites Virales d'Alsace, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [3]Hôpitaux Universitaires de Strasbourg, Pôle Hépato-digestif, NHC, Strasbourg, France; [4]Inserm 1110, Strasbourg, France; [5]SOS Hépatites Alsace Lorraine, SOS Hépatites, Strasbourg, France*
Email: francois.habersetzer@chru-strasbourg.fr

Background and Aims: Drug abuse is a recognized risk factor for hepatitis C transmission among users of psychoactive substances, and excessive consumption of alcohol, which is frequently observed, may be associated with an increased risk of advanced hepatic fibrosis. This study in addiction treatment centers aimed to investigate the prevalence of hepatitis C virus infection and the severity of hepatic fibrosis and its correlation with alcohol consumption.
Method: Overall, 934 drug users from eight addiction centers were included between December 2012 and March 2016. They were divided into three groups based on their main addiction: (1) alcohol (n = 511); (2) drug abuse (n = 142); (3) alcohol and drug abuse (n = 281). Seropositivity rates for hepatitis C were compared between the three groups, as were significant ($F \geq 2$) and severe (F3–F4) fibrosis rates evaluated by FibroScan.
Results: The detection rate of hepatitis C was lower in Group 1 (62%) than in Groups 2 (85%) and 3 (81%) ($p < 0.001$). Hepatitis C seropositivity rates were, respectively, 4.4%, 30% and 42.3% in Groups 1, 2, and 3, and differed significantly between Group 1 and Groups 2 and 3 ($p < 0.001$) as well as between Groups 2 and 3 ($p = 0.02$). Significant fibrosis ($F \geq 2$) was observed in, respectively, 34%, 15% and 29% of users in Groups 1, 2 and 3, and differed significantly between Group 2 and Groups 1 and 3 ($p < 0.001$). The rate of severe fibrosis was lower in Group 2 (7%) than in Groups 1 (21%) and 3 (18%) ($p < 0.001$).
Conclusion: Between 7% and 21% of drug users consulting at addiction centers had severe hepatic fibrosis. The risk of severe fibrosis was 2.6 times greater among those addicted to alcohol. The seropositivity rate for hepatitis C increased with excessive alcohol consumption (+41%), suggesting a rise in risk behaviors.

THU-414

Prevalence and clinical characteristics of portal vein thrombosis in HCV related cirrhosis: a cohort of Egyptian patients

O. Alhadad[1], E.A. Sameea[1], M. Elsabaawy[1], O. Elshaarawy[1], M. Houseni[2]. [1]*National Liver Institute, Hepatology Department, Shebine Elkom, Egypt;* [2]*National Liver Institute, Radiology Department, Shebiene Elkom, Egypt*
Email: oelshaarawy@liver.menofia.edu.eg

Background and Aims: Portal vein thrombosis (PVT) is not an uncommon complication occurring during the course of liver cirrhosis, frequently in its advanced stages. We aim to estimate the prevalence of PVT and its clinical characteristics in a cohort of Egyptian HCV related cirrhotic patients.
Method: This prospective cohort study was conducted on 1,000 cirrhotic patients who were consecutively admitted at National Liver Institute (NLI) hospital, Menoufia University in the period from February 2017 to August 2017. All cases were investigated at least by abdominal ultrasound and Doppler study for presence as well as the extent of PVT and any focal lesion(s), and/ or any better modality like triphasic computed tomography (CT) scan or magnetic resonance imaging (MRI). Patients were divided into the PVT and non-PVT groups and accordingly, the clinical characteristics and complications associated with PVT in cirrhotic patients were analyzed.
Results: PVT was found in 216 (21.6%) out of the one thousand cirrhotic patients, consecutively admitted to our hospital and included in the study. Hepatocellular carcinoma associated PVT represented 72.7% (n = 157) of PVT group. Most of these patients (70.4%) and (85.2%) had complete PVT and were in the stage of hepatic decompensation respectively. In PVT group, 56% of patients had at least one episode of portal hypertensive bleeding, 33.8% had abdominal pain and 27.8% presented with jaundice. Portal bilopathy was diagnosed in two cases (%0.9). Extent of portal vein system occlusion to superior mesenteric vein was detected in 5.6% of patients with PVT (n = 12). There were significant differences between PVT and no PVT patients as regards platelet count, AST, ALT, total bilirubin, creatinine and alfa fetoprotein. In respect to complications; abdominal pain, portal hypertensive bleeding, jaundice and hepatic encephalopathy, no statistically significant differences were found between both groups. However, there was a significant association between ascites and PVT ($p < 0.001$). Male gender and presence of focal lesion were independent predictors of PVT development in HCV cirrhotic patients.

Table: Backward stepwise logistic regression analysis of factors associated with development of PVT in cirrhotic HCV patients.

	B 1	S.E.	Wald test	p-value	OR	95% C.I.	
						Lower	Upper
B 0	0.016						
Gender	−0.773	0.299	6.662	0.010	0.462	0.257	0.830
Presence of focal lesion	0.249	0.121	4.266	0.039	1.283	1.013	1.625
Portal Cavernoma	21.583	9323.808	0.000	0.998	2362861875.419	0.000	–

Conclusion: The PVT is as prevalent as 21.6% in a cohort of Egyptian patients with HCV-related cirrhosis and is significantly associated with ascites. The severity of liver disease, Presence of focal lesion and male gender are independent predictors of PVT.

THU-415

Outcomes of an opt-out strategy for Hepatitis C testing in the East Midlands prison estate

K. Jack[1], B. Thomson[2], W. Irving[2]. [1]*Queens Medical Centre, Hepatology, Nottingham, United Kingdom;* [2]*Queens Medical Centre, Microbiology, Nottingham*
Email: kathryn.jack@nottingham.ac.uk

Background and Aims: Prison populations in the UK have a high prevalence of hepatitis C (HCV) infection and are likely to support propagation of viral infection. In 2014, Public Health England (PHE) introduced a new and radical strategy of opt-out testing for blood borne virus infection, linked to the use of Dried Blood Spot (DBS) as the default sampling technique. The HCV elimination campaign is dependent upon a both a proactive testing and an accurate sampling process. We have evaluated the implementation and outcomes of this policy for HCV infection in the prison establishments in the East Midlands region of England.
Method: Seven prisons operationalized the policy of offering DBS testing for a 12 month period beginning in January 2016 and were included in the study. Details of the numbers of individuals entering each prison per three months were obtained via a Freedom of Information request to the UK Ministry of Justice and therefore provided an accurate denominator population. All DBS samples are sent to a single microbiology laboratory that routinely reported outcome data to the research team.
Results: 15,290 people entered the seven prisons during 2016, of whom 1,417 were tested using DBS (9.3%). Of those, 280 (19.8%) were noted to be small DBS samples but still tested, and 47 (3.3%) samples were rejected. Overall 108/1417 (7.6%) were found to be anti-HCV positive. The four prisons who predominantly received intake directly from the courts tested the lowest percentage of people: 2.4%, 2.6%; 5.3% and 10.9%, yet n = 93/523 (17.4%) tested anti-HCV positive. The three prisons who primarily received prisoners transferred from another establishment tested a higher proportion: 22%; 27% and 37.5% but only n = 15/879 (1.7%) tested anti-HCV positive.
Conclusion: Our study demonstrates that, despite the introduction of an opt-out testing strategy and the widespread uptake of DBS testing, rates of testing for HCV in East Midlands Prisons remains both low and variable. There was striking variability in both testing and positivity rates in prisons which received directly from the court system in comparison to those which received transfers solely from other prisons. The effect of the small DBS samples on the accuracy of the test results is not clear. Prison nurses require on-going training and support to undertake this sample collection technique effectively, and adequate resources to operationalize this policy.

THU-416

Evaluation of a hepatitis C virus core antigen assay in dried-blood spots: a cohort study

F. Lamoury[1], S. Bajis[1], D. Martinez[1], Y. Mowat[1], I. Jayasinghe[1], M. Martinez[1], P. Cunningham[2], B. Catlett[2], B. Jacka[1,3], P. Marks[1], J. Grebely[1], G. Cloherty[4], G. Dore[1], T. Applegate[1]. [1]*The Kirby Institute, UNSW Sydney, Viral Hepatitis and Clinical Research Program, Sydney, Australia;* [2]*St Vincent's Centre for Applied Medical Research, Sydney, Australia;* [3]*Centre de recherche du CHUM, Montreal, Canada;* [4]*Abbott Diagnostics, Chicago, United States*
Email: tapplegate@kirby.unsw.edu.au

Background and Aims: Simple and affordable tests that enable diagnosis of active hepatitis C virus (HCV) infection are required to scale up treatment. This study evaluated the performance of HCV core antigen (HCVcAg) detection in plasma samples and capillary-blood samples collected by dried blood spot (DBS).
Method: Plasma and DBS samples were collected from participants in an observational cohort enrolled at three sites in Australia (two drug treatment clinics and one homelessness service). This study evaluated the sensitivity and specificity of the ARCHITECT HCV Ag (Abbott Diagnostics) test for the detection of HCV core antigen (HCVcAg) in plasma and DBS compared with the Abbott RealTime HCV Viral Load assay on plasma. The sensitivity and specificity for the detection of HCVcAg (>3 fmol/l) for the detection of HCV RNA and diagnosis of HCV RNA >3,000 IU/ml were calculated for both plasma and DBS.
Results: Of 205 participants enrolled with sufficient sample available, 200 had paired HCVcAg results on plasma and capillary DBS samples, in addition to HCV RNA on plasma. Participants receiving HCV

therapy were excluded from analyses (n = 14). HCV RNA was detected in 29% of participants ([95% CI 22.6–36.1], 54 of 186). For detection of HCV RNA and diagnosis of HCV RNA (≥3,000 IU/ml) in plasma, the sensitivity of the ARCHITECT HCV Ag plasma assay was 98.1% (95% CI 90–100) and 100% (95% CI 93–100), respectively. For the detection of HCV RNA and diagnosis of HCV RNA (≥3,000 IU/ml) in plasma, the sensitivity of the ARCHITECT HCV Ag DBS assay was 90.7% (95% CI 80–97) and 92.5% (95% CI 82–98), respectively. The specificity for HCVcAg in plasma and DBS was 100% (95% CI 97–100), for both RNA thresholds. One participant had a viral load less than 3,000 IU/mL (424 IU/ml), and tested HCVcAg negative on plasma and DBS. Five HCV RNA positive samples were false negatives when assessed for HCVcAg in DBS (424, 3437, 28674, 85114, 26595 IU/ml).
Conclusion: These data indicate HCVcAg in plasma and DBS may be a suitable tool for HCV surveillance and diagnosis of chronic HCV infection, particularly in low- and middle-income countries. Further studies are required to evaluate the clinical performance of HCVcAg in individuals with low viral load, including those on HCV therapy.

THU-417
Antiviral treatment of hepatitis C improves glucose metabolism along the entire spectrum from normal glucose tolerance to diabetes

A. Gualerzi[1], M. Bellan[1], S. Bianco[1], M.T. Minh[1], C. Smirne[1], R. Bonometti[1], A. Re[1], S. Favretto[1], R. Minisini[1], G.P. Carnevale-Schianca[2], M. Pirisi[1]. [1]*Università del Piemonte orientale, Translational Medicine, Novara, Italy;* [2]*AOU Maggiore della Carità, SCDU Medicina Interna 1, Novara, Italy*
Email: rosalba.minisini@med.uniupo.it

Background and Aims: Insulin resistance (IR) complicates frequently chronic hepatitis C virus (HCV) infection, leading to an increased incidence of type 2 diabetes mellitus among infected patients. Indeed, it is well known that diabetes control of these patients benefits of successful treatment with either interferon-based regimens or direct antivirals (DAA). Whether the same applies to more subtle alterations of glucose metabolism is unknown. We aimed to fill this gap.
Method: The study population included 82 HCV RNA positive patients (48 males, median age 66 years, 73 with advanced fibrosis, 41 HCV-1b), attending the liver clinic of an academic hospital, not previously known to be diabetics. A standard oral glucose tolerance test (OGTT) was performed in all patients before starting DAA treatment and after its conclusion. OGTT results were interpreted according to the American Diabetes Association guidelines.
Results: Based on the results of the baseline OGTT, the majority of patients had evidence of abnormal glucose metabolism (N = 45, 54%; impaired fasting glucose (IFG) 10%, impaired glucose tolerance (IGT) 16%, IFG + IGT 12%, while 17% were diabetics). Conversely, only a minority of them (N = 37, 45%) were normally glucose tolerant. At the end of treatment, HCV RNA quantification was below the detection threshold (HCV RNA <12 UI/ml), for all the subjects enrolled. A significant decrease in glucose and insulin plasma concentrations was evident both at fasting and after 60 and 120 minutes, leading to a significant reduction in the Homeostasis model assessment (HOMA)-IR (from 3.42 [2.66–5.38] to 2.80 [1.78–3.95]); $p < 0.001$ and a corresponding increase in insulin sensitivity (ISI Belfiore from 0.49 [0.26–0.75] to 0.64 [0.42–0.91]; $p < 0.001$) despite a significant reduction in insulin secretion (EFP Stumvoll from 1363.0 [959.2–1730.0] to 1264.0 [975.8–1588.0]; p = 0,027). Moreover, a significant decrease in glycated hemoglobin was observed ($p = 0.008$), and two patients, formerly categorized as diabetics, did not satisfy criteria OGTT for diabetes anymore. The number of patients with normal glucose tolerance increased from 37 (45.1%) to 53 (64.6%); $p = 0.013$), which was paralleled by a reduced number of those satisfying criteria for prediabetic conditions (31 (37.9%) vs. 17 (20.8%); $p = 0.025$).
Conclusion: After treatment with DAA, glucose metabolism parameters of HCV infected patients improve early and affect the entire pathophysiologic spectrum of glucose metabolism.

THU-418
Lymphomas incidence in HIV/HCV coinfected versus HIV monoinfected patients over twenty-one years of follow up (1993–2014)

Á.M. de Cea, I. Rodríguez-Osorio, H. Meijide, J. Baliñas, J.D. Pedreira, M. de Los Ángeles Castro Iglesias. *Instituto de Investigación Biomédica de A Coruña (INIBIC)-Complexo Hospitalario Universitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), Grupo de Virología Clínica, Spain*
Email: alvaro.mena.de.cea@sergas.es

Background and Aims: Hepatitis C virus (HCV) in coinfected HIV patients could play a role in the development of lymphomas. The aim of this study was to evaluate the incidence of Hodgkin lymphoma (HL) and non Hodgkin lymphoma (NHL) in HIV-monoinfected and HCV coinfected (HIV/HCV) patients and to compare them with the general population and to analyze the time from HIV infection to lymphoma development.
Method: All lymphomas in HIV infected patients in follow up (FU) in a tertiary hospital were recorded. The period of time of the study was: 1993–2014. A data base was created where epidemiological, demographic, clinical and immunovirogical characteristics were recorded. Lymphomas incidence was evaluated and comparative analysis was done between HIV-monoinfected and HIV/HCV. The FU of the patients was done until last programmed visit, death or lost of FU. GLOBOCAN register was used to calculated the standard incidence rate (SIR) to compare with general population.
Results: A total of 2,318 patients where included (37% of them HIV/HCV), being a total of 27,086 patients-years. Lymphomas were identified in 63 cases: 59 NHL and 15 HL; of them, 37 were diagnosed in monoinfected patients and 27 in HIV/HCV, no differences between them were observed (OR:1.25, IC 95%:0.76–2.97). SIR in NHL in monoinfected was 15.6 (9.4–29.7) and in HIV/HCV 12.1 (6.8–23.4), while in HL for monoinfected patients was 17.2 (5.0–60.3) and 28.4 (8.3–98.8) in HIV/HCV. HIV monoinfected were diagnosed of lymphoma at the HIV diagnosis or first year after diagnostic in 64.9% of the cases, while in HIV/HCV this statement happened in 25.9%. Only 18.9% of monoinfected patients were on antiretroviral treatment at the diagnostic while 66.7% of the HIV/HCV ($p < 0.001$). The median of CD4 count at the lymphoma diagnostic was 36 cél/µl (10–212) in monoinfected vs 198 cél/µl (24–608) in HIV/HCV ($p < 0.001$). Over the FU 62.5% of the patients died (11 months [0–23] after lymphoma diagnostic). Of them, 52.5% mortality cause was lymphoma, with no significance differences observed between monoinfected and HIV/HCV. In HL, 13/15 of the cases achieved complete remission. Survival rate was better for HL than NHL (86.6% after 2 years of diagnosis vs 32.5%).
Conclusion: Lymphomas incidence (HL and NHL) observed in HIV-monoinfected and HIV/HCV is 15 times higher than in general population. Lymphomas in HIV/HCV developed latter and with a good immunovirological control. It is remarkable the high incidence of HL in HIV/HCV population. This data supports the presumption of a role of HCV chronic infection in the development of lymphomas in HIV-infected patients. It is necessary the HCV cure in this special and vulnerable population.

THU-419

Using hepatitis C viral load distribution data from a global database to derive the optimal limit of detection for a point-of-care diagnostic test

J Morgan Freiman[1], J. Wang[1], P. Easterbrook[2], G. Kamkamidze[3], M. Krajden[4], A. Loarec[5], F. Marinucci[6], N.V. Kinh[7], R. Njouom[8], S.S. Solomon[9], T. Tsertsvadze[10], L.F. White[11], C. Denkinger[6], B. Linas[12]. *[1]Boston University Medical Center, Infectious Diseases, Boston, United States; [2]World Health Organization; [3]Georgia Hepatitis C Elimination Program; [4]British Columbia Center for Disease Control; [5]MSF; [6]FIND; [7]TREAT Asia; [8]Center Pasteur of Cameroon; [9]Johns Hopkins University; [10]Infectious Diseases and Clinical Immunology Research Center; [11]Boston University School of Public Health; [12]Boston University Medical Center, Infectious Diseases, Boston,*
Email: j.morgan.freiman@bmc.org

Background and Aims: A low-cost point-of-care test (POCT) for hepatitis C virus (HCV) viraemia is a critical step toward HCV elimination. Our aim is to inform the limit of detection (LOD) for an affordable POCT.

Method: We established a cross-sectional dataset with HCV testing data from 8 countries. We included participants of all ages with HCV viraemia. We excluded individuals on HCV treatment. We analysed the distribution of HCV viral load for the first detectable HCV RNA available, and derived the LOD required to identify 97% of infections. We then performed multivariate logistic regression to identify characteristics associated with low-level viraemia in the bottom 3% of the distribution to investigate risk for false negative results with a less sensitive POCT.

Results: The dataset included 66,061 individuals with HCV viraemia from Canada (41.6%), Cameroon (4.8%), Georgia (44.8%), India (8.3%), Indonesia (0.2%), Malaysia (0.001%), Thailand (0.2%), and Vietnam (0.1%). The mean age was 48.3 years. The majority were male (75.8%), and genotype 1 infected (40%). There were 5.8% with HIV, and 10.8% with hepatitis B virus (HBV) co-infection. Fibrosis stage was known for 44.8%, among whom 11.5% were Metavir stage 4. HCV RNA showed a normal distribution with a 97% threshold value of 1130 IU/mL (95% CI 1125, 1140). The OR for low-level HCV viraemia among those with HIV was 1.05 (95% CI 1.01, 1.77). HBV co-infection was not significant. Multivariate analyses adjusting for age, country, genotype, sex, and fibrosis found an OR of 2.9 (95% CI 2.32, 3.63) among 18–30 year olds compared to those > 65, and an OR of 1.84 (95% CI 1.49, 2.26) for individuals in Cameroon compared to Canada. Females had an OR of 1.22 (95% CI 1.09, 1.36) compared to males. Lastly, the OR for fibrosis stage F4 was 2.59 (95%CI 2.06, 3.27) compared to stages F0-1. Despite higher ORs for low-level viraemia in these subpopulations, the threshold of 1,130 IU/ml held >95% sensitivity in all sub-groups.

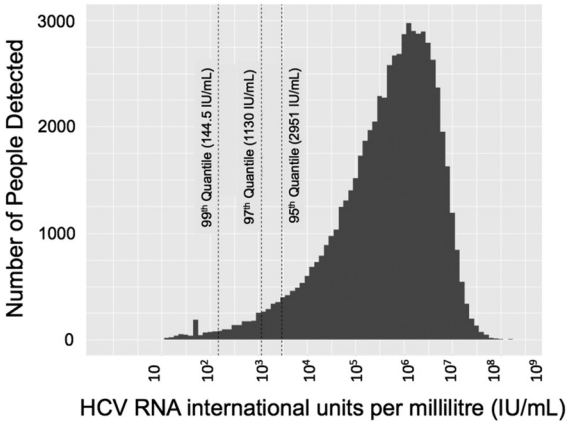


Figure: Frequency distribution of HCV RNA in international units per mililitre (IU/mL) among 66,061 patients with hepatitis C viraemia in a global database assembled from cohorts and laboratory data in the countries of Canada, Cameroon, Georgia, India, Indonesia, Malaysia, Thailand, and Vietnam.

Conclusion: In this global dataset, a POCT with a LOD of 1130 IU/mL would identify 97% of chronic HCV. Recently acquired infection with fluctuating viraemia likely contributed to the increased OR among 18–30 year olds. Additionally, as HCV predominantly replicates in hepatocytes low-level viraemia in advanced cirrhosis is expected. A criterion for an HCV POCT to have LOD = 1,130 IU/ml could facilitate affordable product development and expand the reach of HCV testing in resource-limited settings.

THU-420

Early HCV viral kinetics in the setting of transplantation of kidneys from HCV-infected deceased donors into HCV-negative recipients

D. Goldberg[1], R. Reddy[1], E. Blumberg[1], G. Cloherty[2], V. Holzmayer[2], M. Kuhns[2], R. Bloom[1], P. Abt[1], D. Sawinski[1], A. Sicili[1], M. Levine[1], A. Naji[1], P. Porrett[1], S. Nazarian[1], M. Kaminski[1], V.V. Deerlin[1], J. Smith[1], C. Gentile[1], P. Reese[1]. *[1]University of Pennsylvania, Philadelphia, United States; [2]Abbott Laboratories, East Windsor, United States*
Email: David.goldberg@uphs.upenn.edu

Background and Aims: Hundreds of organs from deceased donors with HCV are discarded each year, leading to proposals to transplant these organs into HCV-negative patients. Yet little is known about the transmissibility and kinetics of viral replication in this setting.

Method: THINKER (Transplanting Hepatitis C Kidneys into Negative Kidney Recipients; CT.gov # NCT02743897) is a single-center trial of transplanting kidneys from HCV-infected donors into HCV-negative recipients. Kidney transplant (KT) recipients were tested for HCV RNA on day 3 post- KT via the hospital assay (Roche Cobas Apliprep/ Taqman) and treated with Elbasvir/Grazoprevir when HCV was detected. Recipient blood was drawn with plasma extracted, frozen, and archived, and tested in batches using the Abbott RealTime HCV 0.5 ml Viral Load assay.

Results: Among 20 subjects, 12 (60%) had post-KT day 1 and/or 2 samples archived (8 did not have samples archived due to timing of KTs). Among 7 subjects with day 1 samples, HCV RNA was detectable in 5 cases on day 1 and was detectable in a sixth on day 3 [Table]. HCV RNA was detectable in all 5 subjects whose first HCV RNA was on post-KT day 2 [Table]. On day 3, 11 (91.7%) of subjects had a quantifiable HCV RNA; the twelfth had an undetectable HCV RNA on the Abbott platform, but a detectable but not quantifiable HCV RNA at the hospital lab and was started on treatment per protocol. Median time from initiation of Elbasvir/Grazoprevir to an undetectable viral load was 8 days (IQR: 6–12 days). KT recipients from donors with an HCV viral load ≥5 log all had detectable HCV within 48 hours.

Table: Table of viral loads (Abbott RealTime HCV assay)

Donor viral load, log IU/mL	Post-transplant							
	Day 1	Day 2	Day 3 (treatment start date)	Day 4	Day 5	Day 7 ± 1 day	Day 14 ± 3 days	Day 21 ± 3 days
5.1	1.7	1.84	2.95	2.74	1.54	–	0	0
5.1	1.41	2.35	3.02	2.97	2.29	–	0	0
3.8	0	0	1.36	–	1.81	–	–	0
N/A	1.0	1.85	2.58	–	–	1.59	0	0
N/A	1.56	3.01	3.29	–	–	1.46	–	0
5.5	–	1.83	2.58	–	1.0	0	0	0
5.5	–	1.76	2.73	1.84	–	1.0	0	0
7.3	3.31	3.71	3.86	–	2.56	1.94	0	0
5.4	–	1.1	1.29	1.81	1.08	0	0	0
5.4	–	1.76	2.24	1.32	1.42	1.0	0	0
6.0	–	1.0	1.28	1.1	–	0	0	0
3.1	0	0	0	0	0	0	0	0

Conclusion: During acute HCV infection via intentional transmission thru KT, HCV showed early viral positivity. Some donors had low viral loads, thus it is unclear if spontaneous HCV clearance might have occurred had we not started therapy after detection of HCV. Despite thymoglobulin induction, the time to HCV clearance on therapy was short, suggesting the potential for trials of shorter therapy duration in the future.

THU-421

Screening for neurocognitive dysfunction in non-cirrhotic chronic hepatitis C infection in an Irish academic unit

D. Ferguson[1,2], O. Strahan[3], P. O'gorman[4], M. Iqbal[5], J. Gormley[4], S. Mckiernan[6,7], R. Coen[8], C.P. Doherty[1,2], S. Norris[6,7]. [1]*University of Dublin, Trinity College Dublin, Academic Unit of Neurology, Dublin, Irland;* [2]*St. James's Hospital, Neurology, Dublin, Ireland;* [3]*University of Dublin, Trinity College Dublin, Psychology, Dublin, Ireland;* [4]*University of Dublin, Trinity College Dublin, Physiotherapy, Dublin, Ireland;* [5]*St. James's Hospital, Hepatology, Dublin, Ireland;* [6]*University of Dublin, Trinity College Dublin, Clinical Medicine, Dublin 8, Ireland;* [7]*St. James's Hospital, Hepatology, Dublin, Ireland;* [8]*St. James's Hospital, Mercer's Institute for Successful Ageing, Dublin, Ireland*
Email: dr.dwj.ferguson@gmail.com

Background and Aims: The reported prevalence of neurocognitive dysfunction in chronic hepatitis C (HCV) infection is 30%. In Ireland, between 30,000–50,000 people are believed to be infected with HCV, however, there is no Irish data on the prevalence of HCV-related neurocognitive dysfunction. The reversibility of neurocognitive dysfunction with viral eradication using newer HCV treatments is also unknown. We have designed the CANDI study (Hepatitis **C A**ssociated **N**eurocogntive **D**ysfunction in **I**reland) to address these questions. The first part of the study aims to determine the prevalence of neurocognitive dysfunction by screening all chronically infected, non-cirrhotic patients using the Brief NeuroCognitive Screen (BNCS).
Method: Since August 2016 we have been undertaking a prospective, cross-sectional, assessment of patients attending the hepatology service at St James's Hospital, (Dublin, Ireland). Screening involves an interview with the research team and administration of the BNCS and HADS (Hospital Anxiety and Depression Scale). Results are adjusted using age and education matched normative data. Inclusion criteria are as follows: age ≥ 18, hepatitis C virus RNA positive and capable of giving informed consent. Pertinent exclusion criteria include: co-infection with HIV and/or hepatitis B, visual/motor impairment and liver cirrhosis. Those who screen positive for impairment are then recruited to the CANDI study, a longitudinal study employing neuropsychological tests and neuroimaging techniques to investigate the impact of exercise and viral eradication with direct acting antivirals (DAA) on cognitive dysfunction.
Results: Between August 2016 and November 2017 580 subjects were screened and 431 were eligible for analyses. Of those, 48% screened positive for cognitive dysfunction. The majority were male (64.2%), the median age was 41 years and the median education attained was 11 years. Most subjects (65.8%) were born in Ireland. The most common method of HCV acquisition was from previous intravenous drug abuse (59.1%) and 34.2% are currently prescribed methadone. Factors associated with a positive screen for impairment included lower educational attainment, self-reported symptoms of cognitive dysfunction, screening positive for anxiety or depression using HADS and current prescription of methadone, anxiolytics or anti-depressants.
Conclusion: The interim results of this study highlight the importance of screening for cognitive dysfunction in non-cirrhotic HCV+ patients. Co-morbid conditions increase the burden of this problem. Future results from the CANDI study will address the potential reversibility of this neurocognitive dysfunction using an exercise intervention or viral eradication.

THU-422

Decrease in blood borne viral infections, liver fibrosis and drug use in a Danish prison population

J. Soeholm[1], D. Holm[2], B. Mössner[1], J. Hansen[1], P.B. Christensen[1]. [1]*Odense University Hospital, Department of Infectious Diseases, Odense, Denmark;* [2]*Odense University Hospital, Department of Clinical Immunology, Odense, Denmark*
Email: Jacob.Soeholm@rsyd.dk

Background and Aims: Our study aimed to describe the current prevalence of blood borne viral infections and liver fibrosis in Danish prison inmates and to characterize their drug use behaviors and opioid substitution therapy (OST) coverage.
Method: In seven Danish prisons, prisoners ≥18 years were offered participation in the study. Participation included a questionnaire, testing for blood borne viral infections by Dried Blood Spot sampling and Vibration-Controlled Transient Elastography as a marker for liver fibrosis.
Results: Among 1,098 prisoners, 801 (73%) participated. Of these 618 (77%) had snorted cocaine. Heroin use was reported in 146 (18%). Only 68 (8.5%) had ever injected drugs, 29 (3.5%) had injected while incarcerated and only one (0.1%) was currently injecting, compared to the 43%, 22% and 14% measured 20 years earlier in the same population. Median duration of injecting drug-use was 10 (IQR 4–18) years.
Of the people who inject drugs (PWID) 58 (85%) had received OST compared to 13% 20 years earlier.
The prevalence of chronic viral infections was: hepatitis C (HCVRNA) 3.2% (26/801), hepatitis B (HBsAg) 1.1% (9/801), and antiHIV 0.2% (2/801) compared to 29%, 4.3% and 0% 20 years ago. The prevalence of HCV among PWIDs was 28% compared to 56% 20 years ago.
Median age of the HCV infected prisoners was 44 (IQR 39–47) years, significantly older than non-infected prisoners (30 years, IQR 24–38) $p < 0.001$. Of the HCV infected prisoners 92% had previously been tested for HCV and 62% were aware of being infected.
Prisoners with viral hepatitis (n = 35) had significantly higher liver stiffness measurements with 68% < 7 kPa, 26% 7–10 kPa and 6% > 10 kPa compared to 95%<7 kPa, 2% 7–10 kPa and 3% > 10 kPa among non-infected prisoners (n = 763), p = 0.001.
Conclusion: We found a ninefold decline in the prevalence of HCV corresponding to a fourfold decline in PWIDs and a twofold decrease in prevalence of HCV among PWIDs in Danish prison inmates over the last two decades. There was a more than sixfold increase in OST coverage in the same period. The prevalence of fibrosis was low among the HCV infected prisoners probably reflecting a short duration of infection. Almost all prisoners with chronic hepatitis C had been tested previously but only two-thirds were aware of their infection.
The decreasing HCV prevalence in prisons suggests that the WHO target of 90% reduction in prevalence by 2030 may be within reach in Denmark.

THU-423

Strong correlation of hepatitis B virus prevalence among Mongolian adults 40 to 65 years old of age with HCC mortality rate: A result from the national general hepatitis screening program

U. Baatarsuren[1], M. Myanganbayar[1], S. Narankhuu[1,2], E. Enkhbayar[1], A. Imashkhan[1,3], O.-E. Battulga[1,4], B. Surenpurev[1], U. Dagva[1,2,3], O. Oidosambuu[3,4], A. Enkhbat[3,4], D. Boldbaatar[4], B. Dashtseren[4,5], M. Budeebazar[4,5], G. Jargalsaikhan[4,5], B. Rinchindorj[4,5], D. Zulkhuu[4,5], P. Bat-Ulzii[4,5], O. Lkhagva-Ochir[4,5], M. Enkhbat[4,5], Z. Davaadorj[4,5], B. Dendev[4,5,6], A. Dagvadorj[1,7], A. Murdorj[1,4,7], Z. Genden[1,4,8], D. Yagaanbuyant[1,4,6,8], A. Bungert[9], N. Dashdorj[1,4,8], N. Naranjargal[10]. [1]*Onom Foundation;* [2]*Medical Information Technology Association of Mongolia, Ulaanbaatar;* [3]*Mongolian Laboratory Network, Ulaanbaatar,* [4]*Liver Center, Ulaanbaatar, Mongolia;* [5]*Mongolian Society of Hepatology, Ulaanbaatar,* [6]*National Center for Communicable Diseases, Ulaanbaatar, Mongolia;* [7]*Mongolian Laboratory Network;* [8]*Mongolian Society of Hepatology;* [9]*Onom Foundation, ONOM FOUNDATION, Ulaanbaatar, Mongolia;* [10]*Onom Foundation, Head office, Ulaanbaatar, Mongolia*
Email: n.dashdorj@onomfoundation.org

Background and Aims: Mongolia has the highest mortality rate of hepatocellular carcinoma (HCC) in the world that is nearly twelve times higher than the global average. Our recent study revealed that approximately 400 thousand people are chronically infected with hepatitis B (HBV) or C virus (HCV) in Mongolia and they are at higher risk for developing liver cirrhosis and HCC. According to our recent

study, 60% of Mongolians with chronic HBV infection have hepatitis D virus. Within the Screening Campaign of the Hepatitis Prevention, Control, and Elimination (HPCE) Program, the Government of Mongolia, in cooperation with all relevant public and private stakeholders, is conducting a decentralized general population hepatitis B and C screening in Mongolia. Under the first-ever general population hepatitis screening program in the world, Mongolian citizens who are 40–65 years of age are being screened for hepatitis B and C in 2017. In the current study, we intended to determine the prevalence of hepatitis B (HBsAg), hepatitis C (anti-HCV) among people are 40 to 65 years and their correlation with HCC morbidity and mortality rate in Mongolia.

Method: Total of 286,898 and 287,249 people (~33.4% of Mongolian population in the 40–65 years of age cohort) were screened for anti-HCV and HBsAg, respectively, from June to October of 2017. HBsAg and anti-HCV in participants' venous bloods were detected using HBsAg and anti-HCV rapid diagnostic tests. All participants completed a structured demographic questionnaire. The Pearson's correlation test was used to determine a correlation between the prevalence of HBsAg, anti-HCV and mortality rates (2010 to 2016) in Mongolia.

Results: Overall, 26,193 (9.91%) and 49,389 (15.65%) people were positive for HBsAg and anti-HCV, respectively (Figure). The average HCC mortality rate between 2010 and 2016 was 77.73 ± 37.4 per 100,000 people. By correlating the prevalence with the HCC mortality rate, the Pearson's coefficients resulted at r = 0.64 and r = 0.20 for HBsAg and anti-HCV, respectively.

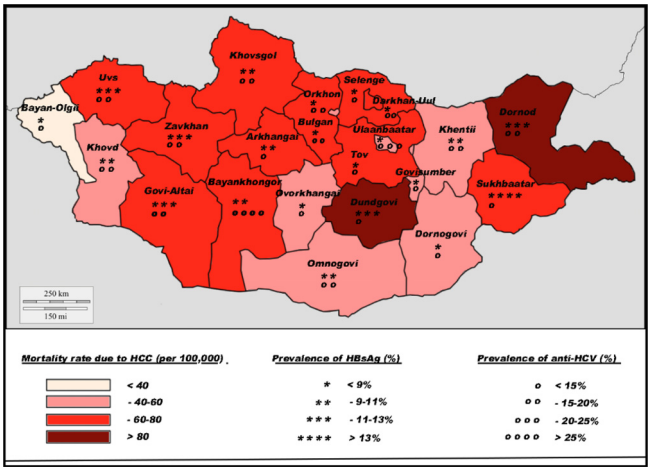


Figure: The mortality rates of HCC by provinces of Mongolia (per 100'000 people). Star and circular shapes denote the prevalence in percentage of HBsAg and anti-HCV positivity in each province. Color coding indicates HCC mortality rates in provinces.

Conclusion: HBV and HCV prevalences are at a similar level compared to recent nationwide prevalence study among Mongolian adults are 40–65 years old (9.91% vs 10.53% for HBV and 15.65% vs 16.17% for HCV). HBV prevalences in Mongolian provinces are strongly correlated with the HCC mortality rates. In contrast, high HCV prevalence showed more strong correlation with HCC mortality rate in Uvs Province in our previous study, indicating the difference between national and provincial differences. More studies need to be carried out and the results of this study need to be furthered refined.

THU-424

Identification of the fast progression and spontaneous regression liver fibrosis phenotypes by a serological collagen turnover profile

S.T. Hjuler[1], D.G.K. Rasmussen[2], M.J. Nielsen[1], D. Leeming[1], S. Gardner[3], Z. Goodman[4], K. Patel[5], D. Schuppan[6], M. Karsdal[7].
[1]Fibrosis Biology, Herlev, Denmark; [2]Fibrosis Biology; [3]Infectious Diseases Therapeutic Area Unit, United States; [4]Hepatic Pathology Consultation and Research, United States; [5]Centre for Liver Disease; [6]Institute of Translational Immunology, Research Center for Immune Therapy (FZI), University Medical Centre Mainz, Mainz, Germany; [7]Biomarkers & Research, Denmark
Email: stp@nordicbio.com

Background and Aims: Collagens are the main constituents of the extra cellular matrix (ECM) and the accumulating fibrotic tissue. There is a need for non-invasive biomarkers that can identify patients with progressive fibrosis and permit monitoring of the response to anti-fibrotic therapy. However, an equally important but often overlooked clinical need is the identification of patients with spontaneous fibrosis regression, as they should neither be included in clinical studies nor treated. Collagen biomarkers may provide a valuable tool for precision medicine.

Methods: Samples of patients with hepatitis C (baseline Ishak scores 2–4) receiving placebo treatment (n = 52) in a phase II trial of a PPAR agonist were included. We excluded the treatment arms of the study to avoid treatment bias. The patients followed with matched liver biopsies at baseline and 52 weeks follow-up, were analysed for serological biomarkers of collagen formation: Type 3 (PRO-C3), Type 4 (P4NP7S), Type 5 (PRO-C5), and markers of collagen degradation Type 3 (C3M), Type 4 (C4M), and Type 6 (C6M) and optimal cut offs were calculated for each biomarkers using the Youden-index. Progressors were defined as patients with an increase in Ishak score from baseline, regressors with a negative Ishak score from baseline.

Results: Logistic regression analysis including PRO-C3 and C6M could identify progressors with liver fibrosis (n = 11) with an AUROC of 0.91 ($p < 0.0001$) and positive and negative predictive values (PPV/NPV) of 54.5%/95.7%. The cut offs associated with progression for PRO-C3 was >22.4 ng/ml and for C6M it was >11.6 ng/ml. High levels of both PRO-C3 and C6M are associated with progression. Logistic regression analysis using PRO-C5, identified those individuals with regression of liver fibrosis (n = 5), with an AUROC of 0.78 $p = 0.0019$ with positive and negative predictive values (PPV/NPV) of 60.0%/95.74%. The cut off associated with regression for PRO-C5 was ≤239.9 ng/ml. Low levels of PRO-C5 are indicative of a regression phenotype.

Conclusions: High levels of markers reflecting Type 3 collagen formation and Type 6 collagen degradation at baseline predicted progressive fibrotic disease. Type 5 collagen formation at baseline could predict regression of disease. These data are the first to demonstrate that progressors and regressors can be identified by a biomarker panel of collagen remodelling. These models might prove efficient as tools to aid in patient identification and drug development.

THU-425

Field evaluation of Xpert (Cepheid) Hepatitis C Virus assay for RNA quantification in Genotype 6 predominant patient population in Cambodia

M. Iwamoto[1], A. Calzia[2], S. Yann[2], S. Pin[2], C. Lastrucci[3], S. Kimchamroeun[2], C. Dimanche[4], J.-P. Dousset[2], M.L. Paih[2], A. Dublineau[5], S. Balkan[6], T. Marquardt[7], J. Nouhin[8], F. Rouet[8], A. Loarec[1], D. Maman[5]. *[1]Médecins Sans Frontières, Epicentre, Phnom Penh, Cambodia; [2]Médecins Sans Frontières, Phnom Penh, Cambodia; [3]Médecins Sans Frontières, Paris, France; [4]Preah Kossamak Hospital, Hepato-Gasto Department, Phnom Penh, Cambodia; [5]Médecins Sans Frontières, Epicentre, Paris, France; [6]Médecins Sans Frontières, Medical,*

Paris, France; [7]Médecins Sans Frontières, Medical, Tokyo, Japan; [8]Pasteur Institute in Cambodia, HIV/Hepatitis Unit, Phnom Penh, Cambodia
Email: momoko.iwamoto@epicentre.msf.org

Background and Aims: GeneXpert® (Cepheid) is the only WHO prequalified platform for Hepatitis C Virus (HCV) Nucleic Acid Amplification Testing that is affordable for point-of-care (POC) use in resource-limited contexts. However, its field application in Southeast Asia is constrained by the lack of evidence on its performance among genotype (GT) 6 patients, which is one of the predominant GTs in the region. We therefore aimed to evaluate its field performance among GT6 predominant patient population.
Method: Two 4-module Xpert® machines were set up in an outpatient clinic setting on Jul 27, 2017. Between Aug 1, 2017 and Sep 6, 2017, 775 adult patients seeking HCV diagnosis at Médecins Sans Frontières' clinic inside the HepatoGastro Department of Preah Kossamak Hospital (Phnom Penh, Cambodia) were consecutively recruited. We tested fresh plasma samples for VL using GeneXpert® at POC, and venous samples were also sent to the reference laboratory (Pasteur Institute in Cambodia) for GT and VL testing using Cobas Ampliprep-Cobas TaqMan® HCV test v2.0 (Roche) as the gold standard test. We calculated the sensitivity, specificity, agreement of quantitative VL using the Bland-Altman method, error frequency, and turn-around-time (TAT).
Results: Among 769 consenting patients, 590 seropositive patients were enrolled into the study. The median age was 57; 60% were female; and the fibrosis stages by fibroscan® were 17% F0, 21% F1, 15% F2, 20% F3, and 25% F4. Of the seropositive patients, 77% (n = 454) had detectable VL above the limit of detection (LOD) using the Roche platform and 43% were GT6, 44% GT1, 8% GT2, and 5% indeterminate GT. Considering VL below the lower LOD as undetectable VL, the sensitivity of Xpert® compared to the Roche assay was 100% (95% CI 99.2, 100) and specificity was 98.5% (95% CI 98.4, 99.9). Mean difference between the two quantitative VL results was −0.01 (95%CI −0.05, 0.02) Log_{10} IU/ml for all 454 samples, and −0.07 (95%CI −0.12, 0.02) Log_{10} IU/ml for GT6 (n = 195). The limit of agreement (LOA) was −0.76 to 0.73 for all GTs, and −0.76 to 0.62 for GT6. Among the 454 detectable VL results, 29 (6.4%) Xpert VL results were outside the LOA, among which 7 (3.6%) were GT6. Frequency of error for all samples was 1.2% (7/590), and the median TAT for Xpert® was 0 days compared to 4 days using the gold standard test.
Conclusion: We demonstrated that Xpert® HCV assay has very good sensitivity, specificity, agreement of quantitative results, and TAT compared to the gold standard test in real-world, resource-limited clinical setting even among GT6 predominant HCV patient population.

THU-426

Screening for hepatitis C at the emergency department: Babyboomers should also be screened in Belgium

R. Bielen[1,2], C. Kremer[3], Ö. Koc[1,2,4], D. Hendrickx[3], P. Vanelderen[2,5], N. Hens[6,7], F. Nevens[8], G. Robaeys[1,2,8]. *[1]Ziekenhuis Oost-Limburg, Department of Gastroenterology and hepatology, Genk, Belgium; [2]Hasselt University, Faculty of Medicine and Life Sciences, Hasselt, Belgium; [3]Hasselt University, Faculty of Science, Center for Statistics, Diepenbeek, Belgium; [4]Maastricht University Medical Centre, Department of Medical Microbiology, School of Nutrition and Translational Research in Metabolism, Maastricht, Netherlands; [5]Ziekenhuis Oost-Limburg, Department of Anaesthesiology, Intensive Care, Emergency Medicine and Pain Therapy, Genk, Belgium; [6]Hasselt University, Interuniversity Institute for Biostatistics and statistical Bioinformatics, Diepenbeek, Belgium; [7]University of Antwerp, Centre for Health Economics Research and Modeling Infectious Diseases, Centre for the Evaluation of Vaccination, Vaccine & Infectious Disease Institute (WHO Collaborating Centre) and Unit of Epidemiology and Social Medicine, Antwerpen, Belgium; [8]University hospitals KULeuven, Department of Gastroenterology and Hepatology, Leuven, Belgium*
Email: rob.bielen@uhasselt.be

Background and Aims: The estimated prevalence of Hepatitis C viral infection (HCV) in Belgium is low (0.87%), and to date, there is no screening policy available. Several studies in Europe and in the United States have reported higher rates of HCV infection when screening is performed in emergency departments (ED) (2–3% and 10–18%,

Table 1: (abstract: THU-426): Age (by gender), drug use and high endemic birth country are significant risk factors in the final weighted model.

Parameter	Inclusion (HCVAb+)	Estimate	S.E.	*p*-value	Adjusted OR (95% C.I.)	
(Intercept)		-8.19	1.64	< .0001		
Female °1988-99 (18-29y)	182 (1)	0.26	1.92	0.892	1.29	(0.03;55.69)
Male °1978-87 (30-39y)	206 (2)	0.95	1.56	0.542	2.59	(0.12;54.88)
Female °1978-87 (30-39y)	195 (0)	-14.25	1.43	< .0001	6.51E-7	(3.97E-8;1.08E-5)
Male °1968-77 (40-49y)	224 (4)	2.33	1.57	0.138	10.37	(0.48;222.04)
Female °1968-77 (40-49y)	217 (1)	0.11	1.88	0.954	1.11	(0.03;45.08)
Male °1958-67 (50-59y)	322 (13)	3.36	1.50	0.025	**28.65**	(1.53;537.02)
Female °1958-67 (50-59y)	239 (4)	2.79	1.88	0.136	**16.22**	(0.42;631.76)
Male °1947-57 (60-70y)	325 (3)	3.46	1.73	0.040	**31.69**	(1.17;861.44)
Female °1947-57 (60-70y)	227 (2)	3.51	1.77	0.046	**33.45**	(1.07;1045.45)
Drug use (NIDU)	189 (6)	3.03	0.74	< .0001	**20.71**	(5.12 ; 83.94)
Drug use (IDU)	24 (15)	6.98	1.01	< .0001	**1069.77**	(152.29;7514.68)
Birth country (high endemic)	16 (3)	4.51	0.93	< .0001	**91.017**	(14.86 ; 557.32)
Birth country (low endemic)	519 (5)	-0.41	0.83	0.623	0.6630	(0.13;3.12)

respectively) and the Centre for Disease Control recommends screening for patients born in the baby boom period (1945–1965) in the United States. We aimed to study the prevalence of HCV in an ED population in Belgium (including the baby boom cohort) and to study the risk factors associated with HCV infection.

Method: We performed a monocentric, cross-sectional seroprevalence study between January and November 2017 in a large non-university hospital in Belgium (Ziekenhuis Oost-Limburg, Belgium). Patients between 18 and 70 years old who presented at the ED were eligible. After informed consent, patients completed a risk assessment questionnaire and were screened for HCV Ab (Abbott HCV 3.0 ELISA) with reflex HCV RNA testing (qRT-PCR). A multiple logistic regression model with post-stratification analysis for the age and gender distribution of the population of Middle-Limburg was used to study the risk factors for HCV infection. A post-hoc power analysis was performed in order to determine the probability of detecting an effect of a given size with a given level of confidence, given the observed sample sizes.

Results: Of 2,913 patients, 2,330 agreed to participate. Of the HCV Ab positive patients, 10 (32.3%) were previously cured, and 9 (29.0%) spontaneously cleared the virus. None of the 12 patients with chronic HCV infection were in follow-up at a hepatology department. We obtained enough power (≥0.8; 95% CI) for the analysis of the baby boom cohort, drug use, tattoos, and imprisonment. In the final weighted model, age (by gender), drug use, intravenous drug use and being born in a high endemic birth country were withheld as significant risk factors for HCV infection ($p < 0.05$, see table). In the final model, the specificity and sensitivity were 0.97 and 0.74, respectively, indicating good discriminative ability.

Conclusion: The prevalence of HCV Ab was higher than previously estimated for the general population in Belgium. However, HCV RNA prevalence was lower. None of the patients with chronic HCV infection were in follow-up at a hepatology department. Screening in drug users, immigrants from high-endemic countries and people born between 1948–1967 is recommended.

THU-427

Factors related to differential HCV therapy success or failure based on clinic location within a single health system: A possible role for increasing access to co-located support services?

J. Sherbuk[1], K. Mcmanus[2], E. Rogawski[3], T. Knick[4], Z. Henry[4], R. Dillingham[1]. *[1]University of Virginia, Division of Infectious Diseases and International Health, Charlottesville, United States; [2]University of Virginia, Charlottesville; [3]University of Virginia, Department of Public Health Sciences, Charlottesville, United States; [4]University of Virginia, Division of Gastroenterology and Hepatology, Charlottesville, United States*

Email: jes2nk@hscmail.mcc.virginia.edu

Background and Aims: The University of Virginia Health System (UVAHS) catchment area includes Appalachia, a region with the nation's largest increase in hepatitis C virus(HCV) infections, fueled by the opioid epidemic. At UVAHS, two specialty clinics provide treatment, gastroenterology/hepatology(GI) and infectious diseases (ID). Our aim was to determine the current state of care within the UVAHS and to identify demographic and behavioral factors that may influence achievement of sustained virologic response (SVR).

Method: A retrospective open cohort study was performed. The study population included individuals ≥18 years with a positive HCV test since 2010. Patient characteristics, including history of substance abuse based on ICD codes, were obtained from the UVA clinical data repository, an anonymized data warehouse.

Results: 5,186 individuals met inclusion criteria. Viral load (VL) was measured in 4,713(91%), and 3,991(85%) had a positive VL confirming chronic HCV. Among those with chronic HCV, 2,536(64%) were evaluated by a specialist, and 916(23%) achieved SVR. Of the 2,233 individuals evaluated by GI, 764(34%) achieved SVR. Of the 805 individuals evaluated by ID, 260(32%) achieved SVR. For the GI clinic, multivariate analysis revealed that outpatient diagnosis and proximity were associated with increased odds of SVR and substance abuse and indigent status with decreased odds (Table). For the ID clinic, male gender and outpatient diagnosis were associated with increased odds of SVR and age with decreased odds.

Table: Patient characteristics associated with SVR

Characteristic	GI		ID	
	OR(95% CI)	p	OR (95% CI)	p
Age ≥30 years	1.2 (0.8–1.8)	0.42	0.2 (0.2–0.8)	0.01
Male	0.9 (0.7–1.1)	0.28	1.5 (1.1–2.1)	0.02
History of substance abuse	0.4 (0.3–0.7)	<0.001	0.8 (0.5–1.5)	0.53
Outpatient diagnosis	1.5 (1.0–2.1)	0.03	1.9 (1.1–3.3)	0.03
Diagnosis in 2014–2017	1.1 (0.9–1.4)	0.23	1.3 (0.9–1.8)	0.19
Indigent	0.7 (0.6–0.9)	0.001	1.1 (0.8–1.6)	0.66
Proximity	1.7 (1.4–2.1)	<0.001	1.1 (0.8–1.6)	0.44

Conclusion: Patient characteristics associated with achieving SVR differed by clinic, though overall SVR rates were similar. Those with substance abuse and low income had lower odds of SVR in the GI clinic. The ID clinic is co-located with a Ryan White clinic, a federally-funded clinic that provides comprehensive care to people living with HIV. The ID clinicians can access established protocols and referral networks for social services, mental health treatment, and substance abuse counseling. The GI clinic does not have the same resources. Successful completion of HCV treatment for patients with social barriers including substance use and/or poverty may require additional support services not routinely available in GI practices. The Ryan White model of HIV care may be a useful template for building programs across health systems to address the HCV epidemic.

THU-428

Use of medications with clinically important drug-drug interactions with direct-acting antivirals for the treatment of chronic hepatitis C infection: Focus on ethinyl estradiol and HMG CoA reductase inhibitors

S. Corman[1], J. Liu[2], C. Nwankwo[2]. *[1]Pharmerit International; [2]Merck & Co., Inc*

Email: chizoba.nwankwo@merck.com

Background and Aims: The development of new direct-acting antivirals (DAAs) has expanded treatment options and improved outcomes in patients with chronic hepatitis C (CHC). However, clinically important drug-drug interactions (DDIs) with concomitant medications can limit therapeutic options for patients with comorbid conditions. Product labeling for some recently approved DAAs includes recommendations for avoidance and/or modified dosing of ethinyl estradiol-containing medications (including, but not limited to oral contraceptives) and HMG CoA reductase inhibitors ("statins"). The aim of this study was to estimate the proportion of CHC patients who would be impacted by these DDIs among Medicaid and commercially insured populations.

Methods: This is a retrospective cohort study using Truven MarketScan® Commercial Claims and Encounters and Medicaid claims data. The study included patients aged ≥18 years who were continuously enrolled in the respective health plan between January 1, 2015 and December 31, 2015. Patients with CHC were identified based on ICD-9 codes (70.44, 70.54). Study outcomes included the prevalence of ethinyl estradiol-containing medications among women (stratified by age 18–44 and ≥45), and the prevalence of statin use among both men and women, over 12 months.

Results: A total of 38,917 Medicaid and 26,035 commercially insured patients with CHC were included in the analysis. Of these, 48% of Medicaid patients and 39% of commercially insured patients were females. Among females of child-bearing age (18–44 years), 9.4% of Medicaid and 17.5% of commercially insured patients received ethinyl estradiol-containing medications during the study period (Table).

Table: (abstract: THU-428): Prevalence of use of ethinyl estradiol-containing medications and statins in patients with CHC

	Medicaid			Commercial		
	Males n = 20,166	Females 18–44 years n = 6038	Females ≥45 years n = 12,713	Males n = 15,888	Females 18–44 years n = 1586	Females ≥45 years n = 8561
Ethinyl estradiol-containing medication, n (%)	N/A	570 (9.4%)	10 (0.08%)	N/A	277 (17.5%)	55 (0.6%)
Statin, n (%)	3028 (15.0%)	221 (3.7%)	1946 (15.3%)	2286 (14.4%)	40 (2.5%)	932 (10.9%)
Ethinyl estradiol-containing medication or statin (%)	3028 (15.0%)	783 (13.0%)	1955 (15.4%)	2286 (14.4%)	313 (19.7%)	979 (11.4%)

The prevalence of statin use was approximately 15% in both males and females ≥45 years old who are insured by Medicaid, and was 14.4% and 10.9% in male and female commercially insured patients, respectively. Overall, 14.8% of Medicaid and 13.7% of commercially insured patients received at least one medication from either of the classes of interest.

Conclusions: Medications with clinically important DDIs assessed in this study are used in nearly 15% of patients with CHC. Clinicians caring for patients with CHC should consider these interactions when selecting DAA regimens.

THU-429

Strong increase of acute HCV infections in HIV-negative men having sex with men

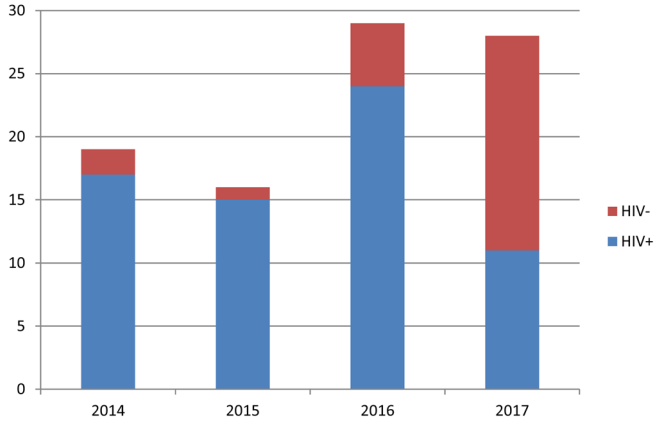
L. Cotte[1], M. Astrie[2], A.-C. Uhres[3], F. Bailly[4], S. Radenne[5], C. Ramière[6], C. Brochier[2], P. Miailhes[1], M.-A. Trabaud[6], J.-C. Tardy[6], M. Godinot[7], P. Chiarello[7], O. Guillaud[8], P. Pradat[2]. *[1]Hôpital de la Croix-Rousse – HCL, Infectious Diseases, Lyon, France; [2]Hôpital de la Croix-Rousse – HCL, Clinical Research Center, Lyon, France; [3]Hôpital de la Croix-Rousse – HCL, Pharmacy, Lyon, France; [4]Hôpital de la Croix-Rousse – HCL, Hepatology, Lyon, France; [5]Hospices Civils de Lyon, Hepatology Department, Lyon, France; [6]Hôpital de la Croix-Rousse – HCL, Virology Laboratory, Lyon, France; [7]Hôpital Édouard Herriot – HCL, Infectious Diseases, Lyon, France; [8]Hôpital Édouard Herriot – HCL, Gastroenterology, Lyon, France*
Email: laurent.cotte@chu-lyon.fr

Background and Aims: The epidemic of sexually transmitted HCV initially started in HIV-infected (HIV+) men having sex with men (MSM) reporting at-risk sexual practices such as Chemsex or other practices leading to mucosal trauma. Only anecdotal cases were reported to date in HIV-negative (HIV−) MSM.

Method: All acute HCV infections in MSM diagnosed in Lyon University Hospital from 2014 were identified from mandatory multidisciplinary discussions before DAA initiation and from database extraction for spontaneously cured infections. HIV status, at-risk practices for HCV (IV/ nasal drug use, participating in sex party, fisting), bacterial STI diagnosis within 3 months, HCV genotype and treatment status were retrieved from medical chart. Each patient gave written consent. The study was approved by the institution' Ethics Committee.

Results: From January 2014 to October 2017, 92 acute HCV infections (71 first infections, 21 reinfections) were observed in 86 MSM (63 HIV +, 23 HIV−). Median age (IQR) was 45 (36–52) years. Risk factors for HCV included IV drug, nasal drug, sex party, fisting and any drug or sexual risk in 34%, 31%, 66%, 22% and 83% respectively. All HIV+ MSM but one were receiving antiretroviral treatment. Median (IQR) CD4 cell count was 647 (510–758) cells/mm^3, and HIV viral load was <50 copies/ml in 95% of cases. Only 68% of HIV− patients were receiving PrEP at the time of diagnosis, while HCV was diagnosed at PrEP screening in 16% of cases. Genotype was 1a, 3a, 4d and unknown (spontaneous cure) in 53%, 5%, 33% and 9% of cases, respectively. The number of cases per year in HIV− MSM increased from 2 cases in 2014 to 17 cases in 2017 (figure). G4d decreased from 11 cases in 2014 to 5 cases in 2017, while G1a increased from 3 cases in 2014 to 19 cases in 2017. Spontaneous cure occurred in 11 cases (12%). Three patients were lost to follow up and 1 patient died from suicide. HCV treatment was initiated in 74 cases and is pending in 3 cases. SVR12 was observed in 43 cases, 2 patients were reinfected before SVR12, 1 patient relapsed and SVR results are pending in 28 cases.

Figure 1: acute HCV infections in MSM



Conclusion: The epidemic of sexually transmitted HCV infections in MSM in Lyon appears on the rise, both in HIV+ and in HIV− patients receiving or attending PrEP. Whether this increase is related to an increase in high-risk practices in PrEP users or to early identification of cases following systematic screening remains unclear. Screening of at-risk patients, harm reduction interventions and early treatment should be combined to contain this epidemic.

THU-430

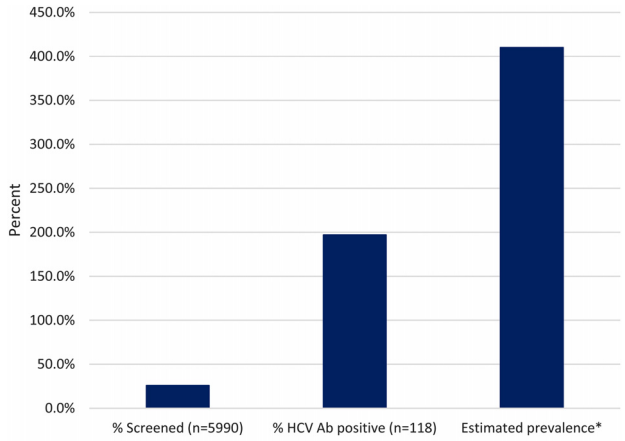
Implementation of a unique hepatitis C care continuum model in a resource limited setting

P. Mathur, E. Comstock, B. Emmanuel, D. Riedel, S. Kottilil. *Institute of Human Virology, University of Maryland School of Medicine*
Email: pmathur@ihv.umaryland.edu

Background and Aims: There has been a rapid evolution of chronic hepatitis C (HCV) treatment with the introduction of direct-acting antivirals. However, a lack of trained providers hinders the escalation of HCV treatment in resource-limited settings. Recently, we conducted the NIH ASCEND study, demonstrating that provider task-shifting is a safe and effective model to expand HCV treatment. We sought to translate the ASCEND model to Rwanda and evaluate the effectiveness of our training program internationally.

Method: An ASCEND-model didactic training program was established in Kigali, Rwanda for providers who had never treated HCV. Our training sessions focused on HCV diagnosis and management, as outlined by the AASLD and Rwanda National Guidelines. We evaluated the effectiveness of our training in three ways. First, each provider completed the same 10-question test (1 point each) before the didactic training and immediately after. Paired and independent *t*-test analyses were used to determine the difference in test score between pre- and post-training overall and by country in SAS 9.4. Second, we evaluated the number of patients screened for HCV after the training. Third, we identified the number of patients who were HCV antibody positive.

Results: We analyzed the pre- and post-test results for 11 new HCV providers in Rwanda and 18 in the U.S. (as part of the ASCEND study). The mean difference in score among Rwandan and U.S. providers was an increase of 17% (p = 0.03) and 21% (p = 0.005), respectively. In the paired analyses from pre-test to post-test, there was an overall increase of score by 20% (p < 0.0001), an increase of 17% (p = 0.008) among matched Rwandan providers, and an increase of 21%(p = 0.0014) among matched U.S. providers. During the follow-up phase of the study, 5,990 of 23,119 (26%) patients seen in Kigali were screened for HCV, and 118 (2%) had a positive antibody (Figure).



*Reference: Gupta et al. (2017). PLOS ONE 12(3): e0174148.

Figure: Number of patients screened for hepatitis C antibody and prevalence of HCV Ab in Rwanda, based on study findings. Our results estimate a lower prevalence than that which has been estimated in the literature.

Conclusion: The ASCEND model is highly effective in training new providers and can be applied to resource-limited settings, such as Rwanda. Our program provides insight into prevalence of HCV in an area where the epidemiology of HCV is relatively unknown. However, despite initiatives to increase HCV screening in Rwanda, our findings suggest there may be barriers to screening that have yet to be elucidated. Given Rwanda's significant accomplishments in the HIV era, the HCV care continuum can be successfully escalated using the ASCEND training model.

THU-431

The IL6-174 C/C genotype is associated with high quality of life scores in patients with chronic hepatitis C

D.A. Vieira[1], G.A. Rocha[2], L.R. Da Cunha[1], A.D. Gomes[2], R. Teixeira[1,3], D.M.M. Queiroz[2], L.D. Silva[1,3]. *[1]Viral Hepatitis Ambulatory, Instituto Alfa de Gastroenterologia, Hospital das Clínicas, Belo Horizonte, Brazil; [2]Laboratory of Research in Bacteriology, Faculdade de Medicina da Universidade Federal de Minas Gerais, Brazil; [3]Faculdade de Medicina da Universidade Federal de Minas Gerais (UFMG), Internal Medicine, Minas Gerais, Brazil*
Email: lucianadinizsilva@gmail.com

Background and Aims: Little is known about the association between cytokine genetic variations and health-related quality of life (HRQOL) in patients with chronic liver diseases. In chronic hepatitis C (CHC), single nucleotide polymorphisms (SNPs) in the promoter region of *IL10* has been associated with clearance of HCV and progression of hepatic disease. Furthermore, the presence of the *IL6*-174 G/G genotype (high-producing IL-6) was associated with a worse outcome of the chronic hepatopathy. Taking into account that the influence of these SNPs on the HRQOL of patients with CHC has not been studied, we investigated the frequency of *IL10*-1082G/A, -819C/T and -592C/A, and *IL6*-174G/C SNPs in CHC patients. We also evaluated their association with domains and summaries of HRQOL.

Method: One hundred and thirty-two consecutive patients (mean age 52.6 ± 11.4 years; 45.5% males; 81.8% non-cirrhotic patients and 18.2% with compensated cirrhosis) attending a referral centre for hepatitis and 98 age- and sex-matched healthy controls were evaluated using the Mini-International Neuropsychiatry Interview and the Medical Outcomes Study 36-Item Short-Form Health Survey. Cytokine genotyping was carried out by a pre-designed Taqman SNP genotyping assay. Multiple linear regression analyses were used to quantify independent associations between HRQOL summaries [physical component summary (PCS) and mental component summary (MCS)] and the variables of interest (clinical, psychiatric, sociodemographic, *IL6* and *IL10* SNPs). The study was approved by Ethics Committee of UFMG.
Results: The distribution of the genotypes followed the Hardy-Weinberg equilibrium. No single polymorphism was distributed differently between CHC patients and healthy individuals. In the multivariate analysis, educational level (>9 years of schooling) (β = 5.42; 95%CI = 1.97 to 8.86; p = 0.002) was positively associated with, but systemic arterial hypertension (HTN) (β = –4.50; 95%CI = –8.13 to –0.86; p = 0.02) was inversely associated with PCS scores. *IL6*-174 C/C (low-producing IL-6) genotype (β = 4.55; 95%CI = 0.45 to 8.65; p = 0.03) was positively associated with, but major depression disorder (β = –16.58; 95%CI = –21.29 to –11.86; p = <0.001) was inversely associated with MCS scores.
Conclusion: This is the first study to show that *IL6*-174C/C genotype (low-producing IL-6) is associated with high scores of MCS in patients with CHC.

THU-432

Has increased rollout of DAA therapy decreased the burden of late presentation and advanced liver disease in patients starting HCV therapy in Germany?

J. Rockstroh[1], C. Boesecke[1], P. Ingiliz[1], B. Florian[2], K.-G. Simon[3], L. Thomas[4], K. Schewe[5], J. Schulze, Z. Wiesch[6], D. Hüppe[7], S. Christensen[8], S. Mauss[2]. *[1]Bonn University Hospital, Department of Medicine I, Bonn, Germany; [2]Center for HIV and Gastroenterology, Düsseldorf, Germany; [3]Practice for Gastroenterology, Leverkusen, Germany; [4]Infektiologikum, Frankfurt, Germany; [5]Infektionsmedizinisches Zentrum Hamburg, Hamburg, Germany; [6]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [7]Practice for Gastroenterology, Herne, Germany; [8]CIM Infectious Diseases, Münster, Germany*
Email: christoph.boesecke@ukbonn.de

Background and Aims: Directly-acting agents (DAA) against HCV have impressively improved treatment outcome of HCV therapy including patients with cirrhosis. To date, it remains unclear if widespread DAA usage has already led to a reduction in HCV-positive patients presenting with advanced liver disease. More recently, a consensus definition of advanced liver disease has been developed which defines advanced liver disease due to chronic viral hepatitis as a patient with chronic hepatitis B, C or D who shows significant fibrosis (≥F3 assessed by APRI score >1.5, FIB-4 > 3.25, Fibrotest >0.59 or alternatively a transient elastography (FibroScan) >9.5 kPa) with no previous antiviral treatment. Therefore, we assessed the proportion of HCV-positive patients presenting with advanced liver disease at DAA treatment initiation over time in the German hepatitis C cohort (GECCO).
Method: The GECCO cohort is a multicenter cohort from 9 German sites. All treatment-naïve HCV mono- (n = 1.168) and coinfected (n = 282) patients (n = 1450) initiating DAA-based treatment since 2014 were analysed. Advanced liver disease was considered a liver stiffness ≥9.5 kPa in transient elastography (n = 1.036) or APRI score ≥1.5 (n = 414). Fisher's exact, chi-square and Mann-Whitney U test were used for statistical analysis.
Results: 938/1.450 (65%) patients were male, median age was 50 years (IQR:41–57). HCV genotype (GT) distribution was: GT1 60%, GT2 5%, GT3 29%, GT4 5%. 157/478 (33%) had IL28B C/C GT polymorphism.

Median baseline HCV RNA was 1.097.704 Mio IU/mL (989.320–1.243.600). Median baseline ALT was 69 U/l (66–73). Liver cirrhosis was present in 323/1.450 (22%). Median baseline CD4 was 596/ul (554–632). 353/1450 (24%) were on opiate substitution therapy (OST). Overall SVR rate was 95.8%.
In 2014 35% (94/272) of all patients presented with advanced liver disease. In the following years that proportion decreased to 24% (149/631) in 2015, to 26% (92/357) in 2016 and to 20% (37/357) in 2017 (p = 0.001).
Conclusion: In line with recommendations from clinical guidelines our real life data confirm that initially DAA therapy was prioritized to HCV patients with advanced liver disease. As a consequence the proportion of patients initiating DAA-based therapy with no or minimal HCV related liver disease has increased in recent years. The use of a consensus definition for advanced liver disease will contribute to both improving the epidemiological understanding of viral hepatitis and other liver diseases as well as testing policies and linkage to care.

Table: Distribution of DAA-treated HCV patients with/without advanced liver disease over time

year	% no/minimal fibrosis (n)	% advanced fibrosis (n)
2014 (n = 272)	65 (178)	35 (94)
2015 (n = 631)	76 (482)	24 (149)
2016 (n = 357)	74 (265)	26 (92)
2017 (n = 190)	80 (153)	20 (37)

THU-433
Cost-effectiveness of one-time screening for hepatitis C virus infection in Korean general population

K.-A. Kim[1], W. Chung[2], H.Y. Choi[3], E.S. Jang[4], M. Ki[3], S.-H. Jeong[4]. *[1]Inje University College of Medicine, Ilsan Paik Hospital, Internal Medicine, Goyang, Korea, Rep. of South; [2]Graduate School of Public Health, Seoul National University, Department of Public Health Science, Seoul, Korea, Rep. of South; [3]Graduate School of Cancer Science and Policy, National Cancer Center, Department of Cancer Control and Population Health, Goyang, Korea, Rep. of South; [4]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Department of Internal Medicine, Seongnam, Korea, Rep. of South*
Email: jsh@snubh.org

Background and Aims: In the new era of direct-acting antivirals (DAA) which are highly efficacious and widely applicable, screening and treating hidden hepatitis C virus (HCV) infection should be considered to control HCV infection. We aimed to evaluate the cost-effectiveness of HCV screening in the targeted Korean general population.
Method: We developed a Markov model simulating the natural history of chronic HCV infection using the data from published literatures, and other secondary sources. We analyzed the cost-utility of one-time screening and treatment with DAA in Korean general population aged 40–65 years from a payer's perspective and the impact of screening on HCV-related health events. Deterministic and probabilistic sensitivity analyses were performed to address the associated parameter uncertainty.
Results: Screening was associated with quality-adjusted life years (QALY) increase of 0.0015 and cost increase of $11.27 per a screened person, resulting in an incremental cost-effectiveness ratio (ICER) of $7,435 per QALY gained, compared with no screening. The introduction of screening was estimated to prevent 32 HCV-related deaths, 19 hepatocellular carcinoma and 15 decompensated cirrhosis per 100,000 screened persons. Sensitivity analyses revealed that ICERs ranged from $4,602 to $12,588 and were sensitive to screening costs, discount rates, and treatment acceptability. At a willing-to-pay of $27,205 per QALY, Korea GDP per capita in 2015, screening was optimal 98.8% of the time.
Conclusion: One-time HCV screening and treatment with DAA in Korean general population aged 40–65 years would be likely to be highly cost-effective, and significantly reduce HCV-related morbidity and mortality compared with no screening.

THU-434
Case finding can successfully re-engage persons lost to follow-up and increase treatment rates in hepatitis C virus services

Y. Gao-Du, S. Brocklesby, L. Corless. *Hull and East Yorkshire Hospitals NHS Trust, Gastroenterology, Herpetology and Endoscopy, Hull, United Kingdom*
Email: lynsey.corless@nhs.net

Background and Aims: The introduction of direct-acting anti-viral agents has transformed the therapeutic landscape of Hepatitis C virus (HCV) in the United Kingdom. Unfortunately however, the myriad challenges of historical treatments led to a sizeable proportion of patients being lost to follow up (LTFU) over the past decade, that are now at risk of progressive liver disease and onward transmission to others. As these patients are likely to derive benefit from currently available treatments we sought to actively re-engage them in care.
Method: Patients were identified through retrospective review of all positive HCV polymerase chain reaction (PCR) tests in our laboratory over 10 years. Letters were sent to primary care practitioners of those who had been LTFU for any reason advising re-referral and highlighting key benefits of new therapies. Available records of attenders and non-attenders were reviewed and analysed for demographic and clinical characteristics.
Results: Of 778 letters sent the majority (77.25%; n = 601) did not trigger a re-referral from primary care, 1 person declined referral and 1 had relocated. 177 (22.75%) were referred, but 104 of these (58.76%) subsequently did not attend. 34.46% (n = 61) of referrals have been seen, with a further 6.78% (n = 12) awaiting an appointment.
Attenders were predominantly male (77.04%; n = 47), with median age 44. Most were previously known to our service, but for 6.56% (n = 4), this was the first referral. The longest period since last contact was 7 years. 2 patients (3.28%) had cirrhosis requiring long-term follow-up. 27 (44.26%) had on-going mental health issues which may have previously precluded therapy. Attenders were significantly less likely to be active injecting drug users (IDU) than non-attenders (27.87% vs 50.96%; p = 0.00374).
37 of 61 attenders (60.66%) have started or are awaiting treatment. A further 15 (24.59%) are completing investigations prior to treatment decision. 4 (6.56%) had spontaneously cleared HCV and have been discharged, and 5 (8.20%) did not attend follow up.
Conclusion: A simple act of letter writing resulted in successful re-engagement of 7.8% of all LTFU to date. Over 85% of attenders have had, or are being worked up for curative therapy, and we also identified a small proportion with cirrhosis. The majority of referral requests resulted in no action from primary care, highlighting an opportunity to boost re-engagement by raising awareness of the individual and public health benefits of therapy. IDU remain hard to reach and are unlikely to re-engage in traditional settings in large numbers, therefore novel approaches should be considered.

THU-435
Direct acting anti-viral therapy rescues neutrophil dysfunction in hepatitis C infection by reduction of heamolysis

B. Leber[1,2], A. Horvath[3], B. Schmerboeck[1,2], A. Posch[4], A. Streit[4], W. Spindelböck[5], P. Stiegler[1], R.E. Stauber[6], V. Stadlbauer[5]. *[1]MEDICAL UNIVERSITY OF GRAZ, Surgery, Transplantation surgery; [2]Center of Biomarker Research in Medicine (CBmed); [3]Department of Gastroenterology and Hepatology, Medical University of Graz, Graz, Austria; [4]Medical University of Graz, Graz, Austria, Austria; [5]Medical University Graz, Internal Medicine; [6]Institute of Pathology, Graz, Austria*
Email: bettina.leber@medunigraz.at

Background and Aims: Hepatitis C (HCV) is a systemic disease that not only impacts on the liver but also shows extrahepatic manifestations from earlier stages of liver dysfunction. HCV induced immune

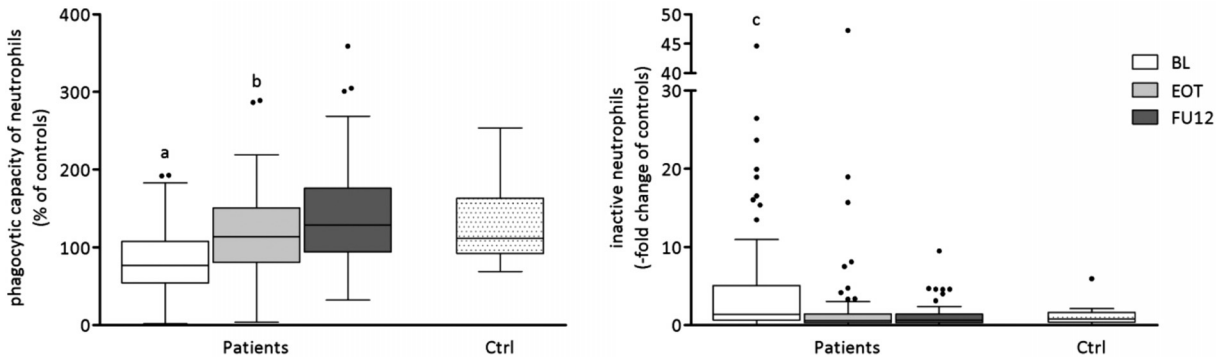


Figure: (abstract: THU-435): Influence of DAA therapy on neutrophil phagocytic capacity and inactive neutrophils of patients compared to control levels. a: $p < 0.001$ vs EOT, FU12 and Ctrl; b: $p = 0.001$ vs FU12; c: $p < 0.001$ vs EOT and FU12; $p = 0.004$ vs Ctrl; BL: baseline; EOT: end of anti-viral therapy; FU12: 12 weeks after EOT.

dysfunction that may lead to an increased risk of infection, is an underestimated extrahepatic manifestation.

Method: A real life cohort of 85 (mean age 57 ± 11 years; 34 female) patients undergoing DAA therapy (sofosbuvir combined with ribavirin or daclatasvir or simeprevir or ledipasvir or a combination of paritaprevir/ritonavir/ombitasvir and dasabuvir) between 4/2014 and 9/2015 was studied. Neutrophil phagocytosis was analysed at baseline, at end of therapy and after 12 weeks follow-up by flow cytometry (Phagotest). Data were compared to 21 healthy controls (mean age 58 ± 7, 12 female). For ex-vivo experiments isolated neutrophils of healthy volunteers and patients were used and incubated with serum of healthy controls and/or patients.

Results: Overall SVR rate was 86%, 66% had cirrhosis and 6 infections occurred during therapy. Baseline phagocytosis was significantly reduced and the number of inactive neutrophils was increased in HCV patients. Both recovered fully after DAA therapy (Fig.). Type of DAA regimen did not impact on neutrophil function. Ex-vivo experiments revealed serum components above 30 kDa to be responsible for neutrophil dysfunction in HCV patients and 3D gel electrophoresis pointed towards haemolysis as a potential mechanism for neutrophil dysfunction. Haptoglobin was investigated as marker of haemolysis during DAA therapy. Changes of haptoglobin levels during therapy mirrored the improvement of neutrophil function over time. Ribavirin delayed the improvement in haemolysis and neutrophil function.

Conclusion: DAAs are able to rescue HCV induced neutrophil dysfunction probably by reducing haemolysis and hence oxidative stress.

THU-436

Treatment of adolescents genotype 4 chronic HCV infected patients with Ledipasvir/Sofosbuvir combination: A real world experience

H.E. Khayat[1], I. Kamal[2], M.H. El-Sayed[3], H. Ayoub[3], M.E. Shabrawy[4], A. Rizk[4], R. Yehia[2], M. Maher[5], Y. Fouad[2], D. Attia[6]. *[1]Theodor Bilharz Research Institute, Hepatology, Gastroenterology and Endemic Medicine, Cairo, Egypt; [2]Faculty of Medicine, Menia University, Hepatology, Gastroenterology and Endemic Medicine, Menia, Egypt; [3]Faculty of Medicine, Ain Shams University, Pediatrics, Cairo, Egypt; [4]Faculty of Medicine, Cairo University, Pediatrics, Cairo, Egypt; [5]Egyptian Military Akademy, Hepatology, Gastroenterology and Endemic Medicine, Cairo, Egypt; [6]Faculty of Medicine, Beni-Suef University, Hepatology, Gastroenterology and Endemic Medicine, Benisuef, Egypt*
Email: dinaattia14@yahoo.com

Background and Aims: The efficacy and safety of Ledipasvir/Sofosbuvir in treatment-naïve adolescent (12–17 years) HCV genotype 1 patients was shown in few clinical trials. The aim of this study was to investigate the effectiveness and safety of Ledipasvir/Sofosbuvir in chronic HCV adolescent patients genotype 4 in the real-world.

Method: This prospective multicenter (6 centers) open label study included 144 adolescent chronic HCV patients with genotype 4 (mean age 14 ± 2, 69% males). All patients received a combination tablet containing 90 mg Ledipasvir and 400 mg Sofosbuvir once daily for 12 weeks. Laboratory and virological markers were evaluated at baseline, week4, week8 and week12 (EOT), and 12 weeks after end of treatment SVR12.

Results: SVR12 was observed in 142/144 patients (99%). The relapsers were previous naïve patients (n = 2/128, 2%) while the experienced patients showed 100% SVR12. ALT normalized at W4 with 88% decrease from baseline ($p < 0.001$), 89% decrease at W8 ($p < 0.001$) and 90% decrease at EOT ($p < 0.001$). AST also normalized at W4 with 86% decrease from baseline ($p < 0.001$), 86% decrease ($p < 0.001$) and 87% decrease ($p < 0.001$) at EOT. No serious side effects were associated. Headache was the most common side effect in all patients (20%). in the experienced patients, Pruritis (31%, $p = 0.007$), diarrhea (44%, $p < 0.001$) and skin rash (19%, $p = 0.002$) were higher than the naïve patients.

Conclusion: Ledipasvir/Sofosbuvir regimen is well tolerated and effective and can be used safely in treating adolescent patients with chronic hepatitis C genotype 4.

THU-437

Impact of a hepatitis C virus electronic medical record screening alert for baby boomers

R. Teply[1], S. Mukherjee[2], M. Goodman[2], T. Guck[2]. *[1]Creighton University; [2]Creighton University*
Email: robynteply@creighton.edu

Background and Aims: It is recommended all patients born between 1945 and 65 have a one-time screen for HCV, but adherence to this guideline is seriously deficient. To improve screening at a health system consisting of 35 primary care clinics, an electronic medical record (EMR) prompt was initiated to identify patients in need of screening. The purpose of this study was to evaluate the impact of the alert and compare the HCV antibody (Ab) positive patients identified prior to the alert to those after.

Method: Data was collected retrospectively for patients seen at a primary care clinic within a regional healthcare system in Midwest United States during June 1, 2016-November 30, 2016 ("Pre-Alert") and December 1, 2016-May 31, 2017 ("Post-Alert"). Data included number screened, demographics, laboratory measurements, referral for treatment and completion of appointment for treatment. Descriptive statistics were determined along with Chi-square and ANOVA tests to examine the differences between the groups.

Results: To date, data has been analyzed for 4 months before and after the alert with the full data set to be presented at the conference.

During the Pre-Alert time period, 29,703 patients were seen in primary care and 482 were screened for HCV (1.62%) with 20 patients found to be Ab positive (4.15%). During the Post-Alert period, 29,913 patients were seen and 5,685 were screened for HCV (19.00%) with 107 patients found to be Ab positive (1.88%). There were no statistical differences between the 2 groups in regards to race, gender, insurance provider, drug use or HCV viral load detection. The Pre-Alert group had 60% of patients with elevated liver tests whereas the Post-Alert group had 27% (p = 0.004). Mean AST to platelet ratio index (APRI) for the Pre-Alert group was 0.84 and Post-Alert was 0.45 (p < 0.001) and mean Fibrosis-4 (FIB-4) score for Pre-Alert group was 2.13 and Post-Alert was 1.55 (p = 0.076).

Conclusion: An alert within the EMR increased the rate of screening for HCV 10-fold for patients being seen in primary care. Five times the amount of HCV Ab positive patients were identified with the screening alert and most of which did not have elevated liver tests or a history of drug use. Such prompts should be implemented to improve screening and linkage to care rates for HCV.

NAFLD: Experimental and pathophysiology

THU-441

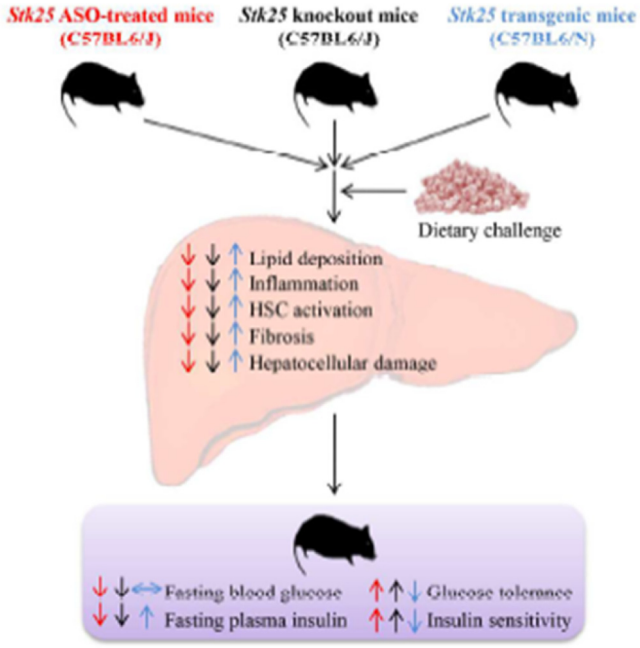
Stk25 antisense oligonucleotide treatment reverses glucose intolerance, insulin resistance, and NAFLD in mice

M. Mahlapuu[1], E.N. Duran[2], M. Aghajan[3], M. Amrutkar[4], S. Sütt[5], E. Cansby[5], S. Booten[3], A. Watt[6], M. Ståhlman[7], N. Stefan[8], H.-U. Haering[9], H. Staiger[10], J. Boren[11], H.-U. Marschall[12]. [1]*Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden;* [2]*Salhgrenska University Hospital, Lundberg Laboratory, Gothenburg, Sweden;* [3]*IONIS Pharmaceuticals, IONIS Pharmaceuticals;* [4]*Univ. of Oslo, Univ. of Oslo, Norway;* [5]*Inst. of Medicine, Univ. of Gothenburg, Sweden;* [6]*IONIS Pharmaceuticals, IONIS Pharmaceuticals, United States;* [7]*Department of Molecular and Clinical Medicine/Wallenberg Laboratory, University of Gothenburg, Sweden;* [8]*University of Tuebingen, Dept. of Internal Medicine, Tuebingen, Germany;* [9]*Med.Klinik u. Poliklinik der, Abt. Innere Medizin IV, Tuebingen, Germany;* [10]*University of Tuebingen, Medical Clinic, Internal Medicine IV, Tuebingen, Germany;* [11]*Dept of Molecular &, Wallenberg Laboratory, Goteborg, Sweden;* [12]*Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden*
Email: margit.mahlapuu@gu.se

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) contributes to the pathogenesis of type 2 diabetes and cardiovascular disease, and patients with nonalcoholic steatohepatitis (NASH) are also at risk of developing cirrhosis, liver failure, and hepatocellular carcinoma. To date, no specific therapy exists for NAFLD/NASH, which has been recognized as one of the major unmet medical needs of the 21st century. We recently identified serine/threonine protein kinase 25 (STK25) as a critical regulator of energy homeostasis and NAFLD progression. Here, we investigated the effect of antisense oligonucleotides (ASOs) targeting *Stk25* on the metabolic and molecular phenotype of mice after chronic exposure to dietary lipids.

Method: To evaluate the metabolic effect of *Stk25* ASOs *in vivo*, we treated mice on a high-fat diet (for 21 weeks) with *Stk25* ASO#1 or ASO#2 in PBS (50 mg/kg/week), or placebo (PBS), twice weekly for the last 6 weeks of the diet. The NAFLD progression in liver and whole-body glucose and insulin homeostasis were characterized. Furthermore, we genotyped 430 participants of the TÜF study for 11 common tagging SNPs covering major parts of the human *STK25* gene and assessed their associations with liver fat content measured by magnetic resonance spectroscopy.

Results: We found that *Stk25* ASOs efficiently reversed high-fat diet-induced systemic hyperglycemia and hyperinsulinemia, improved whole-body glucose tolerance and insulin sensitivity, and ameliorated liver steatosis, inflammatory infiltration, apoptosis, hepatic stellate cell activation, and nutritional fibrosis in obese mice. Moreover, *Stk25* ASOs suppressed the abundance of liver acetyl-CoA carboxylase (ACC) protein, a key regulator of both lipid oxidation and synthesis, revealing the likely mechanism underlying repression of hepatic fat accumulation by ASO treatment. We also found that STK25 protein levels correlate significantly and positively with NASH development in human liver biopsies, and several common non-linked SNPs in the human *STK25* gene are associated with altered liver fat, supporting a critical role of STK25 in the pathogenesis of NAFLD in humans.



Conclusion: This study provides preclinical validation for the metabolic benefit of pharmacologically inhibiting STK25 in the context of obesity and suggests that therapeutic intervention aimed at reducing STK25 function may provide a new strategy for the treatment of patients with NAFLD, type 2 diabetes, and related complex metabolic diseases.

THU-442

Decreased circulating peripheral blood mucosal associated invariant T cells is correlated with insulin resistance in patients with nonalcoholic fatty liver disease

J. Amer[1], D. Bakry[2], R.A. Sear[2], R. Safadi[3]. [1]*An Najah National University, Faculty of Medicine and Health Sciences, Nablus, Palestine;* [2]*Al-Quds University, Medical Laboratory Sciences, College of Health Professions, Jerusalem, Palestine;* [3]*Hadassah-Hebrew University, Faculty of Medicine, Jerusalem, Israel*
Email: j.amer@najah.edu

Background: Mucosal-associated invariant T (MAIT) cells comprise a subpopulation of T cells that can be activated by bacterial products and cytokines to produce IFN-γ. Little is known about the role of MAIT cells in fibrosis progressions in fatty liver disease.

Aim: To assess frequency and phenotype of MAIT cells with correlation of liver fibrosis severities in NAFLD patients.

Methods: Age, gender, BMI, serum vitamin-D levels, ALT, AST, serum-fasting-insulin levels, HbA1c, HOMA-IR score, TG, HDL, LDL and CRP were correlated with histological outcome (%steatosis, necro-inflammatory activity, fibrosis-scoring) in adult NAFLD cases lacking metabolic-syndrome or other liver etiologies (ANOVA). *In-vitro*, peripheral blood obtained from healthy donors (n = 17) and

NAFLD patients (n = 42, of them 20 with steatohepatitis). Using flow cytometry we identified MAIT cells by the expression of CD3, CD8, CD161 and TCR Vα7.2. For immune phenotyping we used markers like TNFα, CD69, CD38 and IL17.
Results: 42-cases fulfill inclusion/exclusion criteria, all are males, mean age at biopsy 39.4 ± 10.6y, BMI 29 ± 2.8. Ten had cirrhosis as scores were F4. Serum HOMA-IR found the most significant predictor for histological severity. Lower serum insulin levels significantly correlated with decreased hepatic-fat-content but increased liver-injury (CRP, fibrosis-scoring & necro-inflammatory-activity), IR (serum insulin levels, HbA1c & HOMA-IR score) and CRP. Healthy donors had 12.68% ± 1.11 MAIT cells and were significantly decreased in peripheral blood of patients with NAFLD to 10.62% ± 1.37, 3.9% ± 0.71, 1.66% ± 0.08 and 1.2% ± 0.21 with fibrosis grades of F1, F2, F3 and F4, respectively. Moreover, MAIT cells from patients showed higher expression of activation and exhaustion markers such as CD69 and CD38, respectively as compared to heathy donors. MAIT cells had also elevated IL-17 expression, a pro-fibrogenic cytokine as well as TNFα, a pro-inflammatory cytokine. These results were linearly correlated with fibrosis severities. The frequency of MAIT cells was negative correlation with HOMA-IR score ($r = -0.33$, $p = 0.02$).
Conclusion: Decreased expressions of peripheral blood MAIT cells in NAFLD patients were inversely correlated with the fibrosis stage. These results were associated with MAIT cells exhaustions and increased their TNFα and IL17 productions. Our data suggest MAIT cells might contribute to the development of fibrosis in NAFLD and represent a novel therapeutic target.

THU-443

Angiopoietin-2 as therapeutic target for pathological angiogenesis and inflammation in non-alcoholic steatohepatitis

S. Lefere[1], F. Van de Velde[2], S. Raevens[1], S. Van Campenhout[1], A. Vandierendonck[1], S. Neyt[3], C. Vanhove[4], A. Hoorens[5], C. Casteleyn[6], X. Verhelst[1], H. Van Vlierberghe[7], B. Lapauw[2], A. Geerts[7], L. Devisscher[7]. *[1]Ghent University, Gastroenterology and Hepatology, Ghent, Belgium; [2]Ghent University, Endocrinology, Ghent, Belgium; [3]Molecubes, Ghent, Belgium; [4]Ghent University, Institute Biomedical Technology, Medical Imaging and Signal Processing, Ghent, Belgium; [5]Ghent University, Pathology, Ghent, Belgium; [6]Ghent University, Morphology, Merelbeke, Belgium; [7]Ghent University, Gastroenterology and Hepatology, Ghent*
Email: sander.lefere@ugent.be

Background and Aims: Angiogenesis and inflammation are interconnected mechanisms that influence the progression of non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH). Previous studies have shown that angiopoietin-2 (Ang-2) mediates both these processes. Our aim was to investigate the role of Ang-2 and its potential as therapeutic target in NASH by using human samples, an *in vivo* mouse model and *in vitro* assays.
Method: Serum Ang-2 levels were determined in obese patients undergoing bariatric surgery (n = 105) with concomitant liver biopsy and in healthy controls (n = 30), and in mice fed the methionine choline deficient (MCD) diet. The Ang-2/Tie2 receptor inhibiting peptibody L1-10 (Amgen) was tested *in vivo* (4 mg/kg intraperitoneally three times weekly) in the MCD diet model in a preventive and therapeutic setting (starting at week 0 and after 2 weeks, respectively), and *in vitro* on endothelial MS1 cells. Liver histology and chemokine expression were assessed. The hepatic vascular bed was visualized using corrosion casts. FACS-isolated liver endothelial cells and monocytes were analysed by qRT-PCR.
Results: Serum Ang-2 levels were increased in patients with NASH compared to lean controls, obese patients without steatosis and patients with NAFL (all $p < 0.01$) and correlated with the severity of steatosis ($p < 0.05$), inflammation and ballooning (both $p < 0.001$), but not fibrosis. In line, serum, hepatic, and endothelial Ang-2 levels were increased in MCD diet fed mice ($p < 0.001$), correlating with markers of endothelial dysfunction and inflammation. Efficient *in vivo* dosing was confirmed by increased Ang-2 serum levels in L1-10 treated mice. MCD fed mice treated with L1-10 showed less inflammatory foci and ballooning hepatocytes compared to control treated mice ($p < 0.05$). Chemokine and endothelial dysfunction gene expression were similarly decreased following treatment. Fibrosis, assessed by sirius red area, was reduced. Liver endothelial cells and monocytes from L1-10-treated MCD fed mice expressed lower levels of dysfunction and inflammatory markers compared to cells from control treated mice. LPS-stimulated MS1 cells secreted pro-inflammatory cytokines and showed increased expression of endothelial dysfunction markers which was significantly less pronounced in cells treated with LPS + L1-10.
Conclusion: Angiopoietin-2 mediates the cross-talk between angiogenesis and inflammation in NASH, and is upregulated in humans and MCD fed mice. Our findings provide evidence for Ang-2 inhibition as a therapeutic strategy in NASH.

THU-444

Lipid-induced ASK1 activation in hepatocytes and Kupffer cells mediates the increased vulnerability of fatty liver to Ischemia/Reperfusion injury in mice

C. Imarisio[1], E. Alchera[1], C.B. Revanna[1], G. Valente[2], A. Follenzi[1], E. Trisolini[1], R. Boldorini[1], R. Carini[1]. *[1]University, Health Science, Novara, Italy; [2]University, Translational Medicine, Novara, Italy*
Email: chiara.imarisio@med.uniupo.it

Background and Aims: Steatosis enhances parenchymal injury and inflammation in liver exposed to ischemia/reperfusion (I/R). Several alterations, such as ER stress and increased ROS production are associated to such effects but a final and targetable pathogenic mechanism is still undetermined. This study investigates "in vitro" and "in vivo" a molecular mediator of the interplay among ER stress, ROS and cytotoxic/survival pathways and its role in the susceptibility of steatotic hepatocytes (HP) and Kupffer cells (KC) to hypoxia/reoxygenation (H/R) and of fatty liver to I/R injury and inflammation.
Method: Control or steatotic (treated with palmitic acid, PA) primary mouse HP and KC were exposed to H/R to "in vitro" simulate I/R exposure. C57BL/6 mice fed 9 weeks with control or High Fat diet underwent to a non-lethal partial hepatic I/R.
Results: In HP, PA increases H/R damage, induces ROS production and enhances the stimulation of the ASK1/JNK cytotoxic axis activated by the ER stress mediator TRAF2 during H/R. Prevention of ROS production nullifies the increased susceptibility of HP to H/R and the enhanced ASK1/JNK activation. ASK1 inhibition also completely protects JNK activation and HP damage. In KC, PA alone induces TRAF2 and a consequent ASK1 and p38 MAPK activation. PA also increases KC damage induced by H/R, but oppositely to HP, ASK1 inhibition enhances H/R damage by preventing the stimulation of the survival mediator p38 MAPK. In mice liver, steatosis induces the expression of activated ASK1 in KC, whereas upon I/R exposure, activated ASK1 expression is evident in both in KC and HP. "In vivo", ASK1 inhibition prevents ASK1, JNK and p38 MAPK activation and protects fatty mice liver from I/R-induced transaminases release and from the increase of TNF-alpha and iNOS.
Conclusion: Our results show that: (1) Lipids increase ASK1/JNK activation induced by ER in HP by rising cellular ROS; (2) Lipids activate ASK1/p38 MAPK in KC by promoting ER stress; (3) ASK1 is cytoxic for HP and protective for KC; (4) ASK1 inhibition protects I/R injury and inflammation of fatty liver. These observations indicate that steatosis, by stimulating ASK1, contextually promotes I/R induced liver injury and inflammation by increasing HP damage and protecting the resident hepatic macrophages (KC) and evidence the potentiality of ASK1 inhibitors as novel therapeutic agents to prevent hepatic damage and reduce inflammatory reactions consequent to fatty liver surgery.

THU-445

Role of rare pathogenic mutations in the development of hepatocellular carcinoma in patients with nonalcoholic fatty liver disease

S. Pelusi[1], A. Pietrelli[2,3], G.A. Baselli[1], P. Dongiovanni[2], M. Meroni[1], B. Donati[1], A.L. Fracanzani[1,2], R. Romagnoli[4], S. Petta[5], L. Miele[6], A. Grieco[6], E. Bugianesi[7], G. Soardo[8], R. De Francesco[3], S. Fargion[1,2], L. Valenti[1,9]. *[1]Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Università Degli Studi Di Milano, Milan, Italy; [2]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Internal Medicine and Metabolic Diseases, Milan, Italy; [3]Istituto Nazionale di Genetica Molecolare INGM, Romeo ed Enrica Invernizzi, Bioinformaticgroup, Milan, Italy; [4]Università di Torino, Liver transplant Center, general surgery 2U, AOU Città della salute e della scienza di Torino, Torino, Italy; [5]University of Palermo, Department of Gastroenterology and Hepatology Di.Bi.M.I, Palermo, Italy; [6]Università Cattolica del S. Cuore, Institute of Internal Medicine and Gastroenterology Area, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; [7]Università di Torino, Division of Gastroenterology, Department of MedicalSciences, A.O.U. Città della Salute e della Scienza, Torino, Italy; [8]University of Udine, Liver Unit, Internal Medicine, Department of Medical Area, Udine, Italy; [9]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Internal Medicine and Metabolic Diseases, Milan, Italy*
Email: serena.pelusi@unimi.it

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is increasingly being recognized as an underlying etiology of hepatocellular carcinoma (HCC), which however remains a relatively rare complication of the disease. Family history and genetic factors (such as the PNPLA3 I148M variant) play an important role in the pathogenesis of progressive NAFLD and HCC.
We examined by whole exome sequencing (WES) approach whether pathogenic and rare mutations predicted to alter protein sequence in candidate genes responsible for inherited liver disease or cancer syndromes are enriched in NAFLD-HCC.
Method: Clinical, biochemical data, personal and family history were collected in 72 HCC, 59 cirrhosis patients from different Italian tertiary centers and 50 local healthy controls without NAFLD. Pathogenic mutations were defined according to ClinVar database, developed to evaluate the genotype-phenotype relationships by integrating data from multiple sources, while enrichment in pathogenic variants was validated using public databases (1000 Genomes, n = 513).
Results: Already known rare pathogenic mutations in candidate genes were enriched in NAFLD-HCC: 40% of patients reported at least one mutation causing liver disease or cancer predisposition ($p < 0.05$ vs. healthy subjects, $p < 0.005$ vs. 1000G). Among the pathogenic mutations, the majority was located in genes involved in predisposition towards genetic liver disease (42%), cancer predisposition (33%) and lipid metabolism (10%).
Furthermore, in NAFLD-HCC patients we identified a significant enrichment of rare mutations (minor allele frequency < 0.001) determining an alteration in protein sequence predicted to alter its function, which resulted in a phenotype predisposing to liver disease (Table).
Supporting the pathogenicity of this second group of mutations, carriage of rare APOB mutations was associated with lower circulating triglycerides ($p = 0.001$) and higher HDL cholesterol ($p = 0.008$).
Conclusion: Rare pathogenic mutations in genes involved in liver disease and cancer predisposition are likely involved in determining predisposition to NAFLD-HCC development.

Gene	NAFLD-HCC (n = 72)	Controls^ (n = 563)	OR	95% C.I.	p value*
SQSTM1	3	1	24.0	2.5–234	0.0089
APOB	9	21	3.7	1.6–8.4	0.0104
EGF	2	0	39.9	1.9–840	0.0185
TERF2	3	2	12.2	2.0–74.3	0.0201
TSC2	4	5	6.5	1.7–25.0	0.0238
PNPLA3, 148MM	24	1°	24.5	3.2–188	0.002

*Evaluated by Burden test.
^Local controls and 1000G.
°Evaluated only in local controls, n = 50.

THU-446

Neurocognitive dysfunction in NAFLD occurs early and is associated with hyperammonemia, neurotransmitter defects, astroglial and microglial activation

N. Arias[1,2], F. De Chiara[1], E. Gómez-Lázaro[3], K.L. Thomsen[1,4], R. Jalan[1]. *[1]UCL Institute for Liver and Digestive Health, Royal Free Campus, London, United Kingdom; [2]Instituto de Neurociencias del Principado de Asturias, INEUROPA, Oviedo, Spain; [3]Basque Country University, Department of Basic Psychological Processes and their Development, San Sebastian, Spain; [4]Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus C, Denmark*
Email: karethom@rm.dk

Background and Aims: Memory, concentration and psychomotor dysfunction are frequently described in patients with non-alcoholic fatty liver disease (NAFLD) but the underlying mechanisms are poorly understood. The aim of this study was to characterize the neuropsychological disorders in a rodent model of NAFLD and relate this to the evolution of liver disease.
Method: 45 Sprague Dawley male rats were divided in three groups: chow (NC, n = 15), isocaloric diet (ICD, n = 15) and high-fat high-cholesterol diet (HFHC, n = 15) at different time points (4, 10 and 16 weeks). Severity of liver disease was assessed histologically. Ammonia levels, hepatic ornithine transcarbamylase (OTC) enzyme activity, neuropsychometric tests, brain neurotransmitters and brain astroglial and microglial activation were assessed.
Results: At 16 wks, the HFHC animals developed advanced fibrosis, which was not observed in NC or ICD animals. Progressive hyperammonemia was found from 10 wks in ICD (140 ± 7; $p < 0.01$) and HFHC (138 ± 8; $p < 0.01$), which was associated with progressive reduction in the activity of OTC (ICD: 0.32 ± 0.04, $p < 0.01$; HFHC: 0.25 ± 0.05, $p < 0.001$. Neuropsychometry: Progressive dysfunction was observed in the HFHC animals. Differences in depression and anxiety were found between ICD and HFHC groups at 16 wks compared to NC. Differences in social behavior were found in HFHC group at 4 and 16 wks, paired with differences in spatial working memory in HFHC group at 4 and 16 wks and ICD at 10 weeks, and a delay in the acquisition of spatial reference memory at 16 wks. Neurotransmitters: Dopamine and its metabolites were decreased in the prefrontal cortex in the HFHC group and, serotonin and noradrenaline and their metabolites increased in the hippocampus and striatum of ICD group, respectively. Immunohistochemistry: Microglial cells were activated and increased in the striatum, hippocampus and cerebellum from 10 wks onwards in ICD and HFHC groups. Astroglial changes were increased in the prefrontal cortex, striatum, cerebellum and CA1 subregion of the hippocampus in HFHC group at 10 and 16 wks.
Conclusion: The data show for the first time a temporal evolution of defects of the urea cycle and hyperammonemia that correlate with neurobehavioral disturbances and, microglial and astroglial activation in a clinically relevant rodent model of NAFLD even prior to cirrhosis stages. The data provide an explanation for the poor functioning of NAFLD patients and potential therapeutic targets.

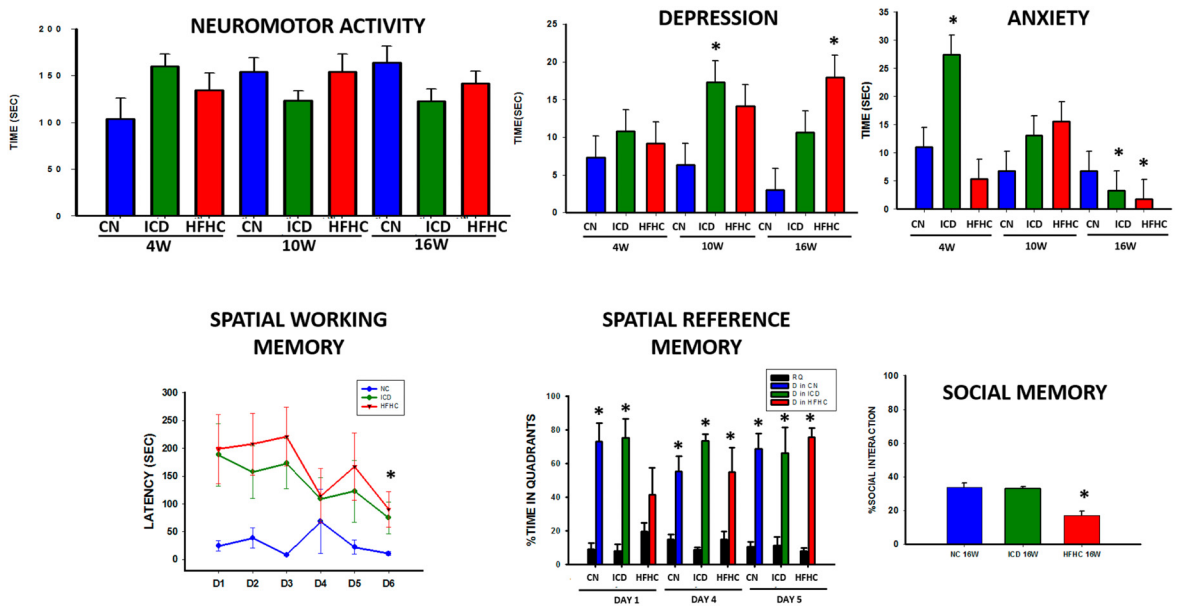


Figure: (abstract: THU-446)

THU-447

Metabolomic patterns associated with known genetic variants for hepatic steatosis and non-alcoholic steatohepatitisidentify biomarkers that may be of utility in predicting adverse liver outcomes

J. Mann[1,2], M. Allison[3], L. Wittemans[1], E.D.L. Rolfe[1], F. Imamura[1], N. Forouhi[1], L.A. Lotta[1], J.L. Griffin[4], A. Koulman[5], C. Langenberg[1], N.J. Wareham[1]. *[1]Institute of Metabolic Science, University of Cambridge, MRC Epidemiology Unit; [2]University of Cambridge, Department of Paediatrics; [3]Addenbrookes Hospital, Cambridge, Department of Hepatology; [4]University of Cambridge, Department of Biochemistry; [5]University of Cambridge, Department of Clinical Biochemistry*
Email: jakemann@doctors.org.uk

Background and Aims: Hepatic steatosis is a common, multifactorial condition strongly associated with obesity and insulin resistance. Not all individuals develop clinical liver disease and biopsy is used in risk stratification of patients with NAFLD. Non-invasive biomarkers for progression are needed. Several loci (rs738409 in PNPLA3, rs58542926 near TM6SF2, and rs641738 near MBOAT7) are associated with non-alcoholic steatohepatitis (NASH), fibrosis, and hepatocellular carcinoma independently of the metabolic syndrome. We aimed to use NASH-associated SNPs to identify biomarkers for NAFLD, in a cohort with detailed metabolic phenotyping.

Method: 9,135 participants from the Fenland Study were assessed for hepatic steatosis using ultrasound and had densely imputed genome-wide genotype data, including NASH-associated SNPs in PNPLA3, TM6SF2, and MBOAT7. All participants underwent DEXA scan for body composition analysis test. 504 metabolites were measured through a combination of targeted metabolomics (176 Biocrates panel, 37 fatty acids, 24 amino acids) and untargeted lipidomics (267

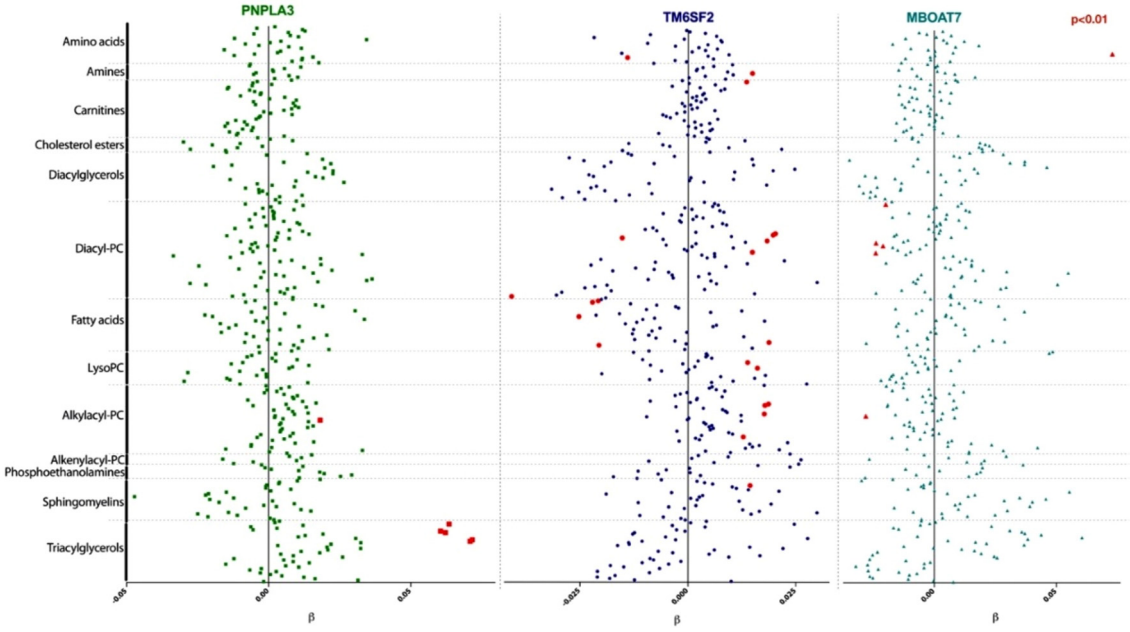


Figure: (abstract: THU-447)

species). Associations of metabolite levels with steatosis variants were assessed using linear regression adjusted for age, sex, ancestry, body fat percentage, hepatic steatosis, fasting glucose, blood lipids, and triglycerides, with $p < 0.01$ considered significant.
Results: Hepatic steatosis was present in 25.1% (2301/9135). Steatosis was independently associated with PNPLA3 (OR 1.4 (CI95% 1.2–1.5)), TM6SF2 (OR 1.3 (CI95% 1.1–1.5)), and MBOAT7 (OR 1.1 (CI95% 1.0–1.2)). Each SNP had a distinct metabolomic profile. The variant inPNPLA3 was associated with higher long-chain, polyunsaturated triacylglycerols, and TM6SF2 variant was associated with higher phosphatidylcholines (PC), whereas MBOAT7 was associated with lower PC, after correction for total lipids. Triacylglycerol C55:5 was the most significantly upregulated metabolite for PNPLA3 (β 0.07 ± 0.02, $p = 1.4 \times 10^{-3}$), whilst diacylphosphatidylcholine C36:2 was most significant for TM6SF2 (β 0.02 ± 0.01, $p = 5.2 \times 10^{-5}$).
Conclusion: Each NASH-associated SNP has a specific lipidomic profile independent of the metabolic markers of glycaemia, lipids and body adiposity is consistent with its reported mechanism of action. We have validated MBOAT7 as a risk factor for steatosis and characterised its metabolomic and lipidomic correlates. These require further assessment in biopsy-cohorts for use as disease-activity biomarkers.

THU-448
Gut barrier dysfunction contributes to the pathological progression of nonalcoholic fatty liver disease induced by high fat diet in mice

J. Peng, F. Huang, J. Leng, H. Tian, Y. Hu. *Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Institute of Liver Diseases, Shanghai, China*
Email: pengjinghua2004@163.com

Background and Aims: To discover the correlation between gut barrier function and the pathological progression of non-alcoholic fatty liver disease (NAFLD).
Methods: (1) Gut barrier dysfunction observation: fourty two C57BL/6J male mice, 12 weeks in age, were randomly divided into control (n

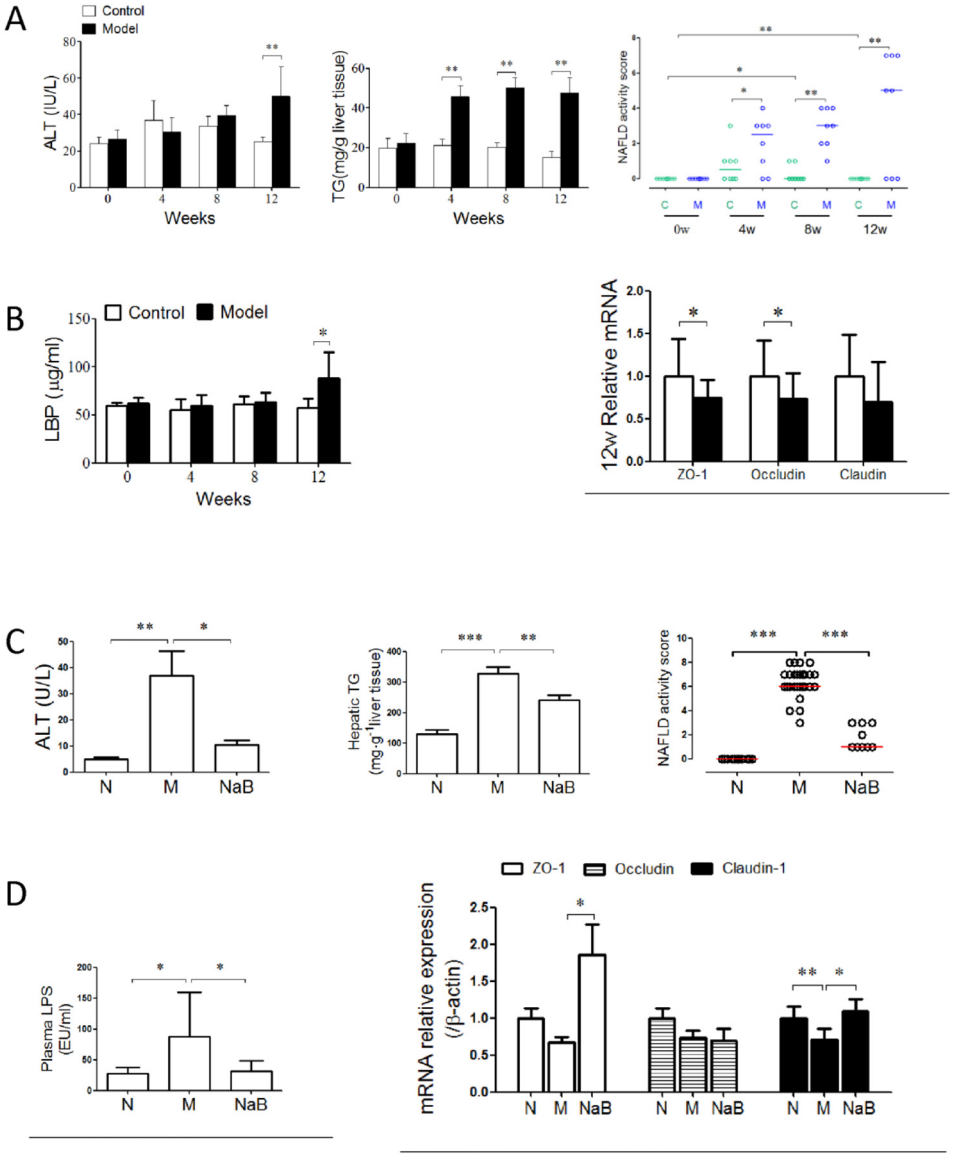


Figure: (abstract: THU-448): (A) Serum ALT, hepatic TG and NAS; (B) Serum LBP content, colonic tight junction mRNA expression; (C) Serum ALT, hepatic TG, NAS; (D) Plama LPS content, mRNA expression of colonic tight junction. ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

= 24, control diets, 10% energy originating in fat) and model group (n = 18, high-fat diets, 60% energy originating in fat). At the end of the 0, 4th, 8th and 12th week, mice were harvested. (2) Effects of gut barrier restoration by sodium butyrate (NaB) on NAFLD: thirty C57BL/6J male mice, 12 weeks in age, were randomly divided into control (n = 10, control diets), model group (n = 10, high-fat diets) and NaB group (n = 10, high-fat diets). After 12-week feeding, mice in NaB group were administrated with NaB (200 mg/kg body weight, daily) by gavage, the others with equal volume of sterile water. At the end of the16th week, mice were harvested.

Results: With 12-week high-fat diet feeding, non-alcoholic fatty liver (NAFL) progressed to non-alcoholic steatohepatitis (NASH), as well as increased hepatic triglycerides (TG) and serum alanine aminotransferase (ALT) (Fig. 1A). Simultaneously, sparse and shorten microvilli (data not shown) and decreased tight junction mRNA expression were observed in NASH mice (12-week high fat diet feeding), as well as increased serum LPS binding protein (LBP), the indirect marker of LPS gut-leakage (Fig. 1B). Supply with NaB, the energy source of the intestinal mucosal epithelial cells, the pathological progression in NAFLD was blocked (decreasing NAS, serum ALT and hepatic TG) (Fig. 1C), and LPS gut-leakage was also inhibited (Fig. 1D). Furthermore, NaB supplementation restored the tight junction mRNA expression in colon of the mice (Fig. 1D).

Conclusion: Gut barrier dysfunction contributes to the pathological progression of NAFLD.

THU-449

Inhibitionof IL-1 signaling in hepatocytes retains insulin sensitivity and protects fromhepatocellular injury in non-alcoholic fatty liver disease

N. Gehrke[1], B. Straub[2], N. Hoevelmeyer[3], A. Waisman[3], K.Y. Ook[4], D. Schuppan[5], W. Marcus[1], P.R. Galle[1], J. Schattenberg[1]. *[1]University Medical Center Mainz, Department of Medicine, Mainz, Germany; [2]University Medical Center Mainz, Department of Pathology, Mainz, Germany; [3]Institute for Molecular Medicine Mainz, Mainz, Germany; [4]Institute of Translational Immunology, Johannes Gutenberg-University Mainz, Mainz, Germany; [5]Institute of Translational Immunology, Research Center for Immune Therapy (FZI), University Medical Centre Mainz, Mainz, Germany*
Email: joern.schattenberg@unimedizin-mainz.de

Background and Aims: Despite recent evidence for a causative role of interleukin (IL)-1alpha and IL-1beta in the metabolic syndrome and related liver disease, the impact of IL-1 signaling in hepatocytes in the pathogenesis of non-alcoholic fatty liver disease (NAFLD) remains elusive. Our aim was to study the effect of IL-1 receptor type I (IL-1RI) deficiency in hepatocytes with regards to hepatic steatosis, inflammation and insulin resistance in mice with NAFLD.

Method: Using the Cre/loxP-system we generated transgenic mice lacking all signaling-capable IL-1R isoforms selectively in hepatocytes (Alb-Cre:IL-1RIHep−/−, IL-1RIHep−/−). Male IL-1RIHep−/− mice and wild type (wt) littermates aged 8–12 weeks were fed a high-fat, high-carbohydrate diet (HFD, 35.5% crude fat (58 kJ%)) and drinking water enriched with fructose (55% w/v) and glucose (45% w/v) for 12 weeks (n = 8 mice/group). Gender- and age-matched controls received a corresponding control diet (CD, 5.4% crude fat (13 kJ%)) and plain water (n = 4–7 mice/group).

Results: 12 weeks of HFD-feeding induced obesity and hepatomegaly in all mice, regardless of the genotype. Hepatic tissue analyses from mice fed with HFD revealed an increase in steatosis in comparison to CD-fed animals, but no difference was observed in steatosis induction and the hepatic expression of steatogenic factors including SREBP-1c, ACC, FAS and CPT1 between the genotypes. Despite comparable metabolic alterations on HFD including elevated serum triglycerides, total cholesterol, HDL, LDL and fasting glucose levels, D, insulin resistance was less pronounced in HFD-fed IL-1RIHep−/− mice as proven by intraperitoneal glucose tolerance test, lower insulin and HOMA-IR levels. The expression of the hepatic insulin receptor in IL-1RIHep−/− mice was augmented compared to the wt. In parallel, IL-1RIHep−/− mice were protected from hepatocyte injury as evident by lower ALT levels (20.0 vs. 40.9 U/l). Differences in liver injury were not attributable to the extent of hepatic necro-inflammation as hepatic mRNA levels of IL-1alpha, IL-1beta, IL-6 and CCL2 and macrophage infiltration detected by FACS were comparable between the genotypes.

Conclusion: In a high-fat, high-carbohydrate diet-fed mouse model the disruption of IL-1 signaling in IL-1RIHep−/− hepatocytes retains insulin sensitivity and dampens hepatocellular injury, suggesting that IL-1 suppression could be a promising strategy in the treatment of NAFLD.

THU-450

Mechanism for hypertriglyceridemia and effect of fibrate coadministration during acetyl-CoA carboxylase inhibitor treatment

L. Goedeke[1], J. Bates[2], D. Vatner[1], R. Perry[1], M.W. Ellis[3], T. Wang[2], M. Subramanian[2], R. Myers[2], A. Ray[2], G.I. Shulman[4]. *[1]Yale University School of Medicine, Internal Medicine, New Haven, CT, United States; [2]Gilead Sciences, Inc., Foster City, CA, United States; [3]Yale University School of Medicine, Cellular and Molecular Physiology, New Haven, CT, United States; [4]Yale University School of Medicine, Internal Medicine, Cellular & Molecular Physiology, HHMI, New Haven, CT, United States*
Email: gerald.shulman@yale.edu

Background and Aims: Inhibition of acetyl-CoA carboxylase (ACC) offers an attractive therapeutic strategy for NASH via simultaneous inhibition of fatty acid synthesis and stimulation of fatty acid oxidation. Clinical trials of liver directed ACC inhibitors (ACCi) have found beneficial effects on steatosis. However, elevated plasma triglycerides (TGs) have been observed in some patients. To understand the mechanism for these observations we evaluated the impact of an ACCi on lipid metabolism in diet-induced rodent models of NAFLD.

Methods: Male Sprague-Dawley rats were fed a high fat diet (60% Safflower oil) supplemented with 1% sucrose drinking water (HFSD) for 3 days and then treated with 10 mpk/day ACCi (GS-834356) or vehicle for 21 days. Hepatic TG production was assessed in overnight fasted rats injected with Poloxamer 407, while lipid clearance was measured in rats given an intravenous bolus of 20% Intralipid conjugated with ^{3}H-triolein. Male C57BL/6 mice were fed a fast food diet (FFD) for 5–8 months and then treated with ACCi ± a PPARα agonist, fenofibrate (0.1% in chow), or vehicle for 2–4 weeks.

Results: Oral administration of ACCi to HFSD-fed rats preferentially inhibited ACC enzymatic activity in the liver, reduced hepatic malonyl-CoA levels, and markedly reduced hepatic TG by ~75% ($p \leq 0.05$). Consistent with previous reports, liver-specific inhibition of ACC was associated with an increase in plasma TG levels (~30 to 130% depending on fasting length; $P \leq 0.05$). ACCi-mediated hypertriglyceridemia was attributed to a ~15% increase in hepatic VLDL release and ~20% reduction in lipoprotein lipase activity ($p \leq 0.05$). At the molecular level, these changes were associated with a significant increase in LXR/SREBP1 activation and decrease in PPARα activation. Similar observations, including a dose-dependent increase in plasma TGs, were made in FFD-fed mice. Importantly, combination treatment of FFD-fed mice with fenofibrate reversed alterations in LXR/SREBP1/PPARα, increased fatty acid oxidation and normalized plasma TG levels (all $p \leq 0.05$).

Conclusion: Liver-targeted ACC inhibition reduces hepatic steatosis but increases plasma TGs in rodent models of diet-induced obesity. The change in plasma TGs is mediated by disequilibrium in nuclear hormone receptor regulation that results in increased hepatic VLDL-secretion and reduced systemic TG clearance and was reversed with the PPARα agonist fenofibrate.

THU-451

Effect of exercise on gut microbiota and metabolic status modulation in an in vivo model of early obesity and NAFLD

S. Carbajo-Pescador[1], D. Porras[1], S. Martínez-Flórez[1], M.-V. García-Mediavilla[1], M.J. Cuevas[1], J.L. Mauriz[1,2], E. Nistal[1,3], J. González-Gállego[1,2], S. Sánchez-Campos[1,2]. [1]*Institute of Biomedicine (IBIOMED), University of León, León, Spain;* [2]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain;* [3]*Department of Gastroenterology. Complejo Asistencial Universitario de León, León, Spain*
Email: scarp@unileon.es

Background and Aims: Childhood obesity is one of the most serious public health concerns from this century, associated with metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) and gut microbiota alterations. Physical exercise improves obesity and NAFLD progression, modulating the gut microbial balance. We aim to investigate the effect of physical exercise on gut microbiota and the metabolic status of an *in vivo* model of early obesity, metabolic syndrome, and NAFLD.
Method: 21 days old male Wistar rats fed with control (C) or high fat diet (HFD) for 6 weeks followed a 5 weeks-interval aerobic training protocol. Body weight gain and metabolic markers were monitored. Lipid metabolism, pro-inflammatory and oxidative-related gene expression was assessed by RT-qPCR. The total bacteria concentration and the *Firmicutes*/*Bacteroidetes* ratio from faecal samples were assessed by qPCR.
Results: HFD increased body and adipose tissue weight gain (+14% and +44%, vs C, respectively), hepatic steatosis (NAFLD Index NAS:3.4), liver damage (AST:+12%; ALT:+45%, LDH:+36%, vs C), liver triglycerides (TG:+58%, vs C) and insulin resistance (HOMA-IR:+22%, vs C), impairing the gut-liver axis-related inflammation and leading to oxidative stress (TLR4:+286%; TNFα:+154%; NLRP3:+70%; CYP2E1: +380%, vs C). The increased intrahepatic lipid accumulation was associated with altered lipid metabolism-related gene expression (SREBP-1c:+94%; FAT/CD36:+95%; FAS:+57%, vs C). Exercise decreased body weight (−17%), insulin resistance (HOMA-IR:−37%), liver damage (ALT:−20%), NAS (−25%) and the intrahepatic lipid accumulation (−25%) as a result of its lipogenic metabolism modulatory capacity (SREBP-1c:−42%; FAT/CD36:−38%; FAS:−27%), reducing the subsequent lipotoxicity and the exercise ability to improve the inflammatory response induced by the gut-liver axis alteration (TLR4:−26%; TNFα: −5%; NLRP3:−3%; CYP2E1:−43%). HFD-fed rats showed lower intestinal bacteria concentration and higher *Firmicutes*/*Bacteroidetes* ratio, dysbiosis that was partially reverted by exercise.
Conclusion: We provide scientific evidences supporting the use of physical exercise protocols to modulate the intestinal microbiota in the management of childhood obesity and NAFLD development, via its anti-inflammatory, lipid metabolism modulatory and prebiotic capacities. Founded by LE063U16 (Junta de Castilla y León y Fondo Europeo de Desarrollo Regional (FEDER)) y GRS1428/A/16. CIBERehd is funded by Instituto de Salud Carlos III (Spain).

THU-452

The paracrine effect of visceraladipose tissue obtained at bariatric surgery on primary human hepatic stellatecells grown in human 3D healthy liver scaffolds

Z. Zhang[1], L. Meelberghs[2], L. Frenguelli[1], W. Al-Akkad[1], H. Korf[2], D. Cassiman[2,3], G. Mazza[1], M. Pinzani[1], K. Rombouts[1], S. Van Der Merwe[2,3]. [1]*University College London, Institute for Liver and Digestive Health, United Kingdom;* [2]*University of Leuven, Laboratory of Hepatology, Belgium;* [3]*University of Leuven, Gastroenterology and Hepatology, Belgium*
Email: k.rombouts@ucl.ac.uk

Background and Aims: Emerging data indicate that the progression from simple steatosis (NAFL) to non-alcoholic steatohepatitis (NASH) results from converging pathophysiological events originating in the liver, the adipose tissue, and the gastrointestinal tract. Adipose tissue is recognized as an endocrine organ that secretes adipokines controlling systemic metabolism and energy homeostasis. We previously showed that adipose tissue macrophages are activated in NASH and secrete pro-inflammatory cytokines which play a detrimental role during NAFL/NASH development. In this study the paracrine effect of human visceral adipose tissue (VAT) on primary human hepatic stellate cells (hHSC) cultured on 3D human liver scaffolds was explored.
Method: Freshly obtained VAT biopsies derived from obese patients and control patients undergoing bariatric surgery and cholecystectomy, respectively, were used for short-term culture (LEAN, NAFL and NASH patients). Similar-sized VAT explants were cultured in serum-free medium and conditioned medium was collected after 48 hrs. Human liver 3D scaffolds were obtained by the decellularization of healthy human liver unsuitable for transplantation. Primary hHSC were seeded for 7 days on 3D scaffolds and exposed to adipose tissue conditioned media (AT-CM) for 2 × 24 hrs. H&E staining was performed; RNA was extracted, followed by qPCR for pro-fibrogenic and pro-inflammatory genes.
Results: Primary hHSC homogeneously engrafted in the 3D scaffolds. No significant differences in the expression of pro-fibrogenic and pro-inflammatory genes was found in hHSC exposed to AT-CM derived from LEAN, NAFL and NASH patients and they were similarly upregulated when compared to non-treated cells. Importantly, within the group of samples from NASH patients, the upregulation of ACTA2 and COL1A1 was significantly more evident in samples with evident liver fibrosis. On the other hand, AT-CM derived from diabetic patients induced a significantly higher increase in pro-fibrogenic gene expression in hHSC 3D culture when compared with samples derived from non-diabetic patients, irrespective of the stage of liver fibrosis. HSC-related adipokines expression and characterization of the adipose tissue secretome is ongoing to further explore the mechanism of action on hHSC.
Conclusion: AT-CM-derived from NAFL and NASH patients, marked by different stages of hepatic steatosis, showed a paracrine effect on hHSC. This is the first study exploring the relationship between VAT and hHSCs on human liver 3D scaffold.

THU-453

Integrative analysis of NGS data highlight a genetic variant in ATG7 gene as a novel risk factor for nonalcoholic fatty liver disease progression

G.A. Baselli[1], A. Pietrelli[2], S. Pelusi[1], M. Meroni[1], A.L. Fracanzani[3], G. Soardo[4], E. Bugianesi[5], R. Romagnoli[6], S. Petta[7], L. Miele[8], S. Fargion[1,9], P. Dongiovanni[9], L. Valenti[1,9]. [1]*Università degli Studi di Milano, Department of Pathophysiology and Transplantation, Milan, Italy;* [2]*Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Internal Medicine and Metabolic Diseases, Milan, Italy;* [3]*Department of Pathophysiology and Transplantation, Ca'Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca'Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Italy;* [4]*University of Udine, Department of experimental and clinical Medical Sciences, Udine, Italy;* [5]*Università di Torino, Department of Medical Sciences, Torino, Italy;* [6]*AOU Città della Salute e della Scienza di Torino, Liver Transplant Center, General Surgery 2U, Turin, Italy;* [7]*University of Palermo, Department of Gastroenterology and Hepatology Di.Bi.M.I.S, Palermo, Italy;* [8]*Università Cattolica del S. Cuore, Institute of Internal Medicine and Gastroenterology Area, Rome, Italy;* [9]*Fondazione IRCCS Ca'Granda Ospedale Maggiore Policlinico, Internal Medicine and Metabolic Diseases, Milan, Italy*
Email: luca.valenti@unimi.it

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) represents an emerging cause of cirrhosis and hepatocellular carcinoma (HCC). NAFLD has a strong genetic component and the identification of causal variants underlying disease development and

progression could be important to improve early diagnosis and targeted therapies.
Next Generation Sequencing allows the analysis of entire exomes to underpin disease risk variants. However, an experiment highlights thousands of rare variants per sample leading to high rates of false positives. Variants prioritization methods are hence required.
In this study, we aimed to set up a pipeline to prioritize variants using in silico predictors from a whole-exome sequencing (WES) dataset to highlight novel risk factors for NAFLD progression.
Method:

(i) WES was conducted on a discovery cohort of 105 patients with advanced NAFLD (cirrhosis and/HCC), a preliminary validation cohort of 26 advanced NAFLD patients, and 50 healthy controls.
(ii) Variants were prioritized to select rare damaging variants in genes conserved in humans (Figure A).
(iii) Enrichment in the discovery cohort vs. general population (non-Finnish Europeans of ExAC and 1000G databases and our control group) was evaluated (Figure B).
(iv) Enrichment of variants highlighted in the discovery cohort was evaluated also in the validation cohort (Figure B).
(v) Statistical analysis was performed using R software.

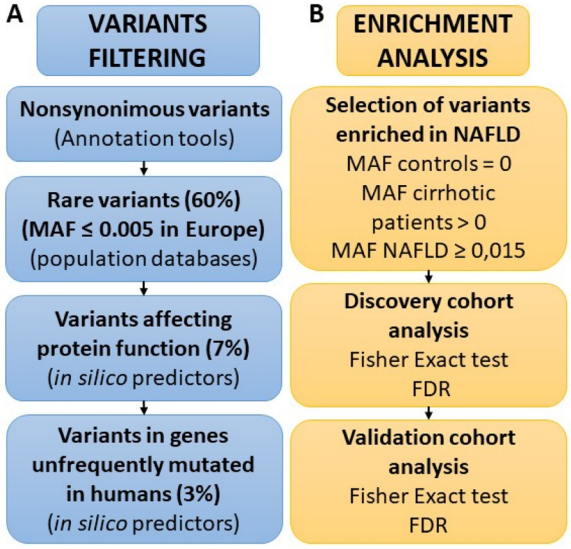


Figure: Filtering (A) and Analysis (B) pipelines.

Results: Enrichment analysis highlighted 8 variants as putative risk factors for liver disease progression. Among these, we found variants in genes of known interest for liver disease progression such as G6PD (FDR = 0.0004, OR = 25.1, CI: 7–69), NOTCH1 (FDR = 0.012, OR = 9.85, CI: 7–69) and ATG7 (FDR = 0.042, OR = 10.7, CI: 3–26).
The enrichment of the variant in ATG7 gene was conformed also in the validation cohort (FDR = 0.02, OR = 29.5, CI: 3–115). This variant resulted enriched in the two cohorts compared with the general population ($p = 4.6*10^{-5}$, OR = 13.8, CI: 4–34).
Conclusion: In conclusion, our analysis highlighted a loss-of-function variant in ATG7 gene and defective lipophagy as a new putative risk factor for progression of NAFLD to cirrhosis and HCC. ATG7 is involved in lipo-autophagy, a biological process of growing interest in the pathophysiology of NAFLD. Moreover, ATG7 deficient mice have been described to develop hepatomegaly and steatohepatitis, supporting an important role for ATG7 in progressive NAFLD.

THU-454
Effect of combined farnesoid X receptor agonist (INT747) and dipeptidyl peptidase-4 inhibitor (sitagliptin) on liver fibrosis
N. Shimozato[1], T. Namisaki[1], T. Akahane[1], K. Moriya[1], M. Kitade[1], H. Kawaratani[1], K. Kaji[1], Y. Okura[1], H. Takaya[1], Y. Sawada[1], N. Nishimura[1], S. Sato[1], S. Saikawa[1], K. Seki[1], M. Furukawa[1], T. Kubo[1], H. Yoshiji[2]. [1]*Japan;* [2]*Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan*
Email: shimozato@naramed-u.ac.jp

Background and Aims: The farnesoid X receptor (FXR) agonist, a bile acid-activated nuclear receptor, has been shown to improve the histologic features of non-alcoholic steatohepatitis (NASH); however, a satisfactory effect on liver fibrosis has not been achieved. We aimed to investigate the combined effect of FXR agonist (INT747) and dipeptidyl peptidase-4 inhibitor [DPP4-I (sitagliptin)] on liver fibrosis in a rat model of NASH.
Method: Fischer 344 rats were fed a choline-deficient L-amino-acid-defined (CDAA) diet for 8 weeks. The therapeutic effect of INT747 (30 mg/kg/day) and Sitagliptin (150 mg/kg/day) was evaluated along with liver fibrosis, lipopolysaccharide (LPS)-toll like receptor 4 (TLR4) regulatory cascade, and intestinal barrier function. The direct inhibitory effect of both INT747 and Sitagliptin on Ac-HSC was assessed in vitro.
Results: The F344 rats fed with CDAA diet developed marked liver fibrosis with deposition of collagen fibers. INT747 and Sitagliptin markedly suppressed CDAA diet induced liver fibrosis as compared with that in CDAA diet group (control group). The combination treatment of INT747 and Sitagliptin exerted a more potent inhibitory effect than either single agent. These inhibitory effects occurred almost concurrently with the suppression of immunohistochemical expression of α-SMA and mRNA expression of TGF-β1 and type-1 collagen-α1 in the liver. The suppressive effects of both agents on hepatic TLR4 mRNA expression were of a comparable magnitude to the observed effect on liver fibrosis, while no significant difference in intestinal TLR4 expression was observed. INT747 and combination treatment significantly attenuated CDAA induced increase in LPS-binding protein (LBP) mRNA expression and intestinal permeability. Semi-quantitative immunofluorescence microscopy revealed that INT747 and combination treatment improved CDAA-diet-induced delocalization and substantially decreased the expression of the tight-junction protein, intestinal zonula occluden-1 (ZO-1) in CDAA-diet-fed rats. In contrast, Sitagliptin had no significant effect on hepatic LPB expression, intestinal permeability or ZO-1 expression. The in *vitro* and in *vivo* inhibitory effects of INT747 and Sitagliptin on TGF-β1 and TLR4 mRNA expression in Ac-HSC were almost in parallel. Sitagliptin was found to directly suppress regulation of Ac-HSC.
Conclusion: INT747 and Sitagliptin have a synergistic repressive effect on liver fibrosis by reversing LPS-induced gut barrier dysfunction and suppressing HSC activation and proliferation, respectively. Combined treatment may represent a promising novel therapeutic approach for NASH.

THU-455
Efficacy of statins for the treatment of non-alcoholic steatohepatitis with mild portal hypertension
M. Bravo[1,2], I. Raurell[1,2], T. García-Lezana[2], M. Torres[2], S. Augustin[1,3], J. Genesca[1,3], M. Martell[1,2]. [1]*CIBERehd, Madrid, Spain;* [2]*VHIR – Vall d'Hebron Institut de Recerca, Liver Unit, Barcelona, Spain;* [3]*Hospital Universitari Vall d'Hebron, Barcelona, Spain*
Email: miren.bravo@gmail.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases in developed countries. Caused by liver fat deposition, it promotes inflammation and cell damage and may progress to cirrhosis. Statins are known for their lipid-lowering ability as well as for exerting pleiotropic effects that could prevent liver steatosis and non-alcoholic steatohepatitis (NASH). Our objective was to prove the efficacy of statins simvastatin

and atorvastatin in an experimental model of NAFLD with mild portal hypertension without fibrosis.
Method: Sprague-Dawley rats were fed with high fat diet combined with a glucose-fructose beverage (HFGFD), or control diet combined with water (CD). After 8 weeks, HFGFD animals were treated during 2 weeks with simvastatin (sim) (10 mg kg^{-1}·day^{-1}), atorvastatin (ato) (10 mg kg^{-1}·day^{-1}) or vehicle, maintaining the original diet. After treatments, hemodynamic parameters were registered and blood and tissue samples collected. Histological analysis of the liver samples and biochemical determinations in serum were performed.
Results: HFGFD animals developed obesity, showing a 20.27% of weight gain difference compared to CD rats. HFGFD also induced steatosis, ballooning and NASH (defined as NAFLD activity score ³3) in a higher proportion of individuals when compared to controls (13.3% NASH in CD *vs* 87.5% in HFGFD), but without fibrosis. Moreover, HFGFD animals showed a significant portal pressure increase compared with CD rats (10.47 ± 0.37 mmHg *vs* 8.30 ± 0.22 mmHg; $p < 0.001$) without changes in systemic hemodynamic. Biochemical analysis revealed a significant rise of alanine aminotransferase (ALT) ($p = 0.043$ *vs* CD) and triglycerides (TG; $p = 0.002$ *vs* CD) in HFGFD animals. Statin treatments had only mild side effects demonstrated by an increase in serum levels of creatine kinase (muscular toxicity) in some treated animals (7.7% of rats treated with sim and 12.5% of rats treated with ato), but absence of increases in serum levels of ALT in treated animals (hepatic toxicity). Moreover, atorvastatin treatment significantly reduced ALT levels ($p = 0.009$) compared to vehicle, despite maintaining the high fat diet, while TG levels were also significantly lower in both treated groups (sim, $p = 0.01$; ato $p = 0.024$). More importantly, HFGFD animals treated with both statins showed a significant portal pressure reduction (sim: 9.29 ± 0.25 mmHg, $p < 0.01$; ato: 8.85 ± 0.30, $p < 0.001$) compared with HFGFD treated with vehicle, as well as NASH reversion, revealed by a decrease of steatosis, ballooning and inflammation in the histological analysis (NAS score ³ 3 in 50% and 57% of treated individuals with sim and ato, respectively).
Conclusion: This study indicates that statins are effective drugs in reducing both portal hypertension and the histological alteration shown by a rat NASH model.
Project code: PI14/00331. ISCIII-FEDER CO-FUNDING.

THU-456
Whole exome sequencing identifies rare nonsense mutations enriched among patients with advanced fibrosis due to nonalcoholic steatohepatitis

P.R. Shea[1], A. Sanyal[2], S. Harrison[3], V. Ratziu[4], R. Loomba[5], S. Caldwell[6], S. Kleinstein[1,7], B. Mccolgan[8], M. Subramanian[8], J.G. Mchutchison[8], R. Myers[8], Z. Goodman[9], M. Abdelmalek[7], J. Bosch[10], N. Afdhal[11], D. Goldstein[1]. *[1]Institute for Genomic Medicine, Columbia University, New York, NY, USA; [2]Virginia Commonwealth University, Richmond, VA, USA; [3]Pinnacle Clinical Research, San Antonio, TX, USA; [4]Hôpital Universitaire Pitié-Salpêtrière, Paris, France; [5]University of California San Diego, La Jolla, CA, USA; [6]University of Virginia, Charlottesville, VA, USA; [7]Duke University School of Medicine, Durham, NC, USA; [8]Gilead Sciences, Inc., Foster City, CA, USA; [9]Inova Fairfax Hospital, Falls Church, VA, USA; [10]Inselspital, Bern University, Switzerland, and IDIBAPS, University of Barcelona, Spain; [11]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA*
Email: ps2878@cumc.columbia.edu

Background and Aims: Common genetic variation in the patatin like phospholipase domain containing 3 (PNPLA3) and transmembrane 6 superfamily member 2 (TM6SF2) genes have been associated with an increased risk of nonalcoholic fatty liver disease (NAFLD) and with the severity of nonalcoholic steatohepatitis (NASH) and fibrosis. However, common variation in these genes can only sufficiently explain a minor fraction of the estimated disease heritability. Thus, additional risk factors, such as rare genetic variants, may influence the risk of NAFLD and disease progression. To identify these rare genetic factors, we performed an exome-wide sequencing study of patients with advanced fibrosis due to NASH.
Method: Whole exome sequencing data was generated for 367 patients with NASH and bridging fibrosis (Ishak stage 3 or 4) or cirrhosis (stage 5 or 6) enrolled in two phase 2b trials of simtuzumab, a monoclonal antibody directed against lysyl oxidase-like-2 (LOXL2). Single variant and gene-based collapsing analyses were used to test for rare variants that were enriched or depleted in NASH cases relative to sequence data from 11,295 population controls. We also tested whether rare variants were associated with quantitative measures of fibrosis (e.g. Ishak fibrosis stage, hepatic collagen content by morphometry, and serum LOXL2 levels) and hepatic venous pressure gradient (HVPG) among cirrhotic subjects. All results were adjusted for multiple testing using a Bonferroni correction.
Results: Exome sequencing identified a total of 3,524,408 rare (<1% minor allele frequency) nonsynonymous variants, including 101,597 rare, loss-of-function mutations among cases and controls. Gene-based collapsing analyses identified a moderate study-wide significant enrichment of rare, loss-of-function mutations in the matrix extracellular phosphoglycoprotein (MEPE) gene among patients with advanced fibrosis due to NASH ($p = 8.19E{-}8$ by Fisher's exact test; Bonferroni threshold for significance after correcting for 18,652 genes, 2.68E–6). No significant associations were found between rare variation and any of the quantitative measures of fibrosis or HVPG in cirrhotic subjects.
Conclusion: We identified a novel, study-wide significant enrichment of loss-of-function mutations in the MEPE gene among patients with advanced fibrosis due to NASH. Replication and further functional study may provide insight into the role of MEPE nonsense mutations in predisposition to NAFLD and/or NASH.

THU-457
Nicotine enhances lipid accumulation and lipotoxicity in hepatocytes via suppression of autophagy

S. Yamashina, T. Aoyama, A. Uchiyama, K. Kon, K. Ikejima, S. Watanabe. *Juntendo University School of Medicine, Gastroenterology, Tokyo, Japan*
Email: syamashi@juntendo.ac.jp

Background and Aims: Previous clinical studies revealed that cigarette smoking enhances the progression of chronic liver diseases and carcinogenesis. It was reported that smokers were likely to have significantly more visceral fat accumulation than nonsmokers with similar body mass index, even though smokers were significantly less obese than nonsmokers. Treatment with nicotine activates mammalian target of rapamycin (mTOR) pathways which negatively regulates autophagy induction. Recently, it was shown that autophagy mediates lipid droplet degradation and lipolysis. The aim of this study was to identify the effect of nicotine on autophagic lipolysis in hepatocytes.
Method: Isolated hepatocytes from C57CL6J mice were cultured in media with 1 mM oleic acid for 6 hours. Subsequently, cells were washed by PBS three times and incubated in media with or without nicotine (10^{-5} M) for 12 hours. Some hepatocytes were incubated in media with both oleic acid and nicotine for 24 hours to evaluate cytotoxicity of nicotine. Cell viability was evaluated by WST-1 assay. Cells were formaldehyde-fixed and lipid accumulation was detected with LipidTOX™ lipid stain. Western blot analysis was performed to evaluate the expression of microtubule-associated protein1 light chain 3 (LC3), phospho-mTOR, perillipin in hepatocytes.
Results: Although accumulation of lipid droplets was observed in hepatocytes cultured in media with oleic acid for 6 hours, subsequent incubation in media without oleic acid for 12 hours decreased lipid accumulation in hepatocytes. On the other hand, addition of nicotine to media suppressed degradation of lipid droplet. Similarly, subsequent incubation in media without oleic acid and nicotine reduced perillipin expression increased by oleic acid; however nicotine treatment sustained an increase in perillipin expression due to oleic

acid. On the other hand, treatment with oleic acid for 6 hours enhanced the expression of phospho-mTOR and suppressed LC3-II expression in isolated hepatocytes. Subsequent incubation in media without oleic acid for 12 hours decreased the activation of mTOR; however, nicotine treatment maintained mTOR activation. Moreover, suppression of lipolysis due to nicotine was ameliorated by the co-incubation with mTOR inhibitor rapamycin. Treatment with only oleic acid did not affect cell viability; however, addition of nicotine to oleic acid decreased cell viability to 62.5 ± 2.42%. Interestingly, mTOR inhibitor rapamycin suppressed cell death by combination of nicotine and oleic acid to 73.8 ± 2.05%.
Conclusion: These results indicated that exposure to nicotine blunts lipolysis via suppression of autophagy. Moreover, it was suggested that suppression of autophagy by nicotine enhances cell death. In conclusion, suppression of autophagy due to nicotine may contribute the progression of liver diseases observed in smokers.

THU-458

Involvement of the CREB-E2F2-PPAR axis in non-alcoholic fatty liver disease development and progression to hepatocarcinoma

D.M. Congregado[1,2], I. Aurrekoetxea[1,2], B.G. Santos[2], D.S. de Urturi[2], M. Núñez[2], J.L.G. Rodríguez[2], F. Gonzalez-Romero[2], L.F. Ares[1,2], A. Iglesias[3], I. Bernales[4], P. Iruzubieta[5], V.G. de Juan[6], M. Varela-Rey[6], G.E. Olartekoetxea[1,7], L.M. González[7], S. Gaztambide[1,7], L.A.C. González[1,7], J. Crespo[5], M.L. Martínez-Chantar[6], X. Buque[1,2], A. Zubiaga[8], P. Aspichueta[1,2]. *[1]Biocruces Health Research Institute; [2]University of Basque Country UPV/EHU. Faculty of Medicine and Nursing, Physiology; [3]University of Basque Country UPV/EHU. Faculty of Science and Technology; [4]University of Basque Country UPV/EHU. SGIKER; [5]Marqués de Valdecilla University Hospital, Gastroenterology and Hepatology; [6]Center for Cooperative Research in Bioscience (CIC bioGUNE); [7]Cruces University Hospital; [8]University of Basque Country UPV/EHU. Faculty of Science and Technology, Genetics, Physical Anthropology and Animal Physiology*
Email: patrietal@hotmail.com

Background and Aims: Obese patients with non-alcoholic fatty liver disease (NAFLD) are at increased risk of developing hepatocellular carcinoma (HCC). However, the mechanisms that promote HCC development in NAFLD patients are not fully understood. Here we investigated the role of E2F2 transcription factor in NAFLD development and progression to HCC.
Method: E2F2$^{-/-}$ and control mice (WT) were used. Liver disease in mice was induced by administration of diethylnitrosamine (DEN) (25 mg/kg) at 14 days-old plus high-fat (HFD) or chow diet until sacrificed at 3 (3m) or 9 months-old (9m). A cohort of 67 obese patients, 15 of which exhibited normal liver (NL) and 52 NAFLD, and 18 samples from non-obese liver donors were used. Protein and lipid content, and metabolic fluxes were analyzed.
Results: In liver, according to oncomine database E2F2 expression is increased in tumoral vs non-tumoral human tissue. We observed that E2F2 expression is also higher in DEN-HFD induced HCC vs NL mice. The number and size of tumors and the content in neutral lipids were higher in 9m DEN-HFD WT mice than in the other WT groups. At 9m, E2F2$^{-/-}$ mice were resistant to HCC development and to lipid accumulation, which was linked to decreased lipogenesis and increased B-oxidation as the metabolic fluxes and the transcriptome showed. This metabolic profile was also evident when E2F2 was kd in HepG2 cells and in 3m mice, in which E2F2$^{-/-}$ mice were totally resistant to hepatoesteatosis. E2F2 protein levels were increased in obese NAFLD patients when compared to non-obese or obese NL subjects, in which E2F2 levels were already higher than in non-obese NL individuals. The anti-steatotic effect in E2F2$^{-/-}$ mice was linked to decreased PPARγ and increased PPGC1 levels, both controlled by CREB. CREB kd demonstrated its involvement in the regulation of lipogenesis and B-oxidation when E2F2 was also kd.
Conclusion: E2F2 is a master regulator of metabolism in obesity related liver disease progression. It regulates the CREB-PPAR axis, involved in the homeostasis of liver lipid metabolism. Deficiency of E2F2 avoids the lipid storage required for NAFLD development and progression to HCC, which points out the value of E2F2 as a therapeutic target.

THU-459

Akkermansia spp. mediates protection from obesity-associated NAFLD development in germ free mice following intestinal microbiota transplantation from high fat diet and quercetin treated donors

D. Porras[1], E. Nistal[1,2], S. Martínez-Flórez[1], J.L. Olcoz-Goñi[2,3], R. Jover[3,4,5], F. Jorquera[2,3], J. González-Gállego[1,3], M.-V. García-Mediavilla[1,3], S. Sánchez-Campos[1,3]. *[1]Institute of Biomedicine (IBIOMED), University of León, León, Spain; [2]Department of Gastroenterology. Complejo Asistencial Universitario de León, León, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain; [4]Experimental Hepatology Unit, IIS Hospital La Fe, Valencia, Spain; [5]Department of Biochemistry and Molecular Biology, University of Valencia, Valencia, Spain*
Email: dpors@unileon.es

Background and Aims: Dysbiosis and gut-liver axis alteration have been pointed as important contributors to obesity and non-alcoholic fatty liver disease (NAFLD) development. Modulation of intestinal microbiota (IM) emerge as a promising therapeutic strategy for obesity-associated NAFLD. This study aims to determine the effect of IM transplantation and quercetin supplementation in a high fat diet (HFD)-based NAFLD model in germ free mice (GFm).
Method: Donor mice were selected from conventional raised mice as follows: control (dC), control supplemented with quercetin (dCQ), responder and non-responder to the HFD (dHFD+ and dHFD−) and highest response to quercetin with HFD (dHFDQ). GFm were colonized with IM from donors and fed with HFD or control diet supplemented or not with quercetin for 16 weeks. Gut bacterial communities were identified by 16S-rRNA pyrosequencing.
Results: A remarkable higher detection of *Verrucomicrobia* phylum and *Akkermansia* genus was observed in HFD-fed dC, dCQ, dHFD− and dHFDQ-receiver groups, which were undetectable in dHFD+ recipients independently of the diet. Relative abundance of *Akkermansia* genus inversely correlated with body weight gain, NAFLD activity score and insulin resistance development (HOMA-IR). Evaluation of these parameters unveiled two protective metabolic phenotypes exhibited by dHFD− and dHFDQ-receiver groups and a predisposal to NAFLD development phenotype showed by dHFD+ transplanted mice. Gut-liver axis alteration was involved in predisposition to NAFLD as showed by enhanced expression of TLR4 and NLRP3 in dHFD+ recipients independently of the diet, associated to IM imbalance evidenced by reduced SCFAs (acetate, propionate and butyrate) production. dHFD−and dHFDQ microbiota transplantation reduced endotoxemia and ethanol production in HFD-fed mice attenuating gut liver axis activation and contributed to partially restore SCFAs profile. These alterations also correlated with *Akkermansia* abundance, positively for butyrate production and negatively for NLRP3 expression.
Conclusion: IM transplantation resulted in a definite microbiota composition establishment which determines susceptibility to NAFLD and metabolic syndrome development, highlighting the significant role of *Akkermansia* genus in the maintenance of a healthy metabolic profile, in a mechanism involving IM functionality and gut barrier integrity. Supported by BFU2013-48141-R, LE063U16 (JCyL and FEDER) and GRS 1428/A/16. CIBERehd is funded by ISCIII.

THU-460

Bile acid composition modulate insulin resistance in non-diabetic patients with NAFLD

C. Rosso[1], R. Younes[1], M. Eslam[2], F.W. Chen[2], M. Cucco[1], M. Gaggini[3], S. Coulter[2], F. Carli[3], C. Barbieri[3], V.D. Latta[3], M.L. Abate[1], G.M. Saracco[1], A. Gastaldelli[3], J. George[2], E. Bugianesi[1]. [1]*University of Turin, Department of Medical Sciences, Italy;* [2]*The Westmead Institute for Medical Research, University of Sydney, Storr Liver Centre, Australia;* [3]*Institute of Clinical Physiology, CNR, Cardiometabolic Risk Unit, Italy*
Email: ebugianesi@yahoo.it

Background and Aims: Bile acids (BAs) are signaling molecules involved in the pathogenesis of non-alcoholic fatty liver disease (NAFLD). BAs can modulate both glucose and lipid metabolism in insulin resistance (IR), a major pathogenic mechanism for the progression to non-alcoholic steatohepatitis (NASH). However, the association between BA composition and insulin sensitivity (IS)/IR has been not fully investigated yet. We aimed to assess the relationship between BA composition and sites and mechanisms of IR in non-diabetic NAFLD patients.
Method: 41 patients with biopsy-proven NAFLD were studied. Plasma BA composition was assessed by GC-MS. Adipose tissue IR (AT-IR), Hepatic IR (Hep-IR) and glucose clearance (GC) were derived from tracer studies. Visceral fat (VF) was assessed by NMR. Liver histology was scored according to Kleiner.
Results: Plasma levels of total primary BAs correlated with waist circumference (WC) ($r = 0.378$, $p = 0.014$), VF ($r = 0.406$, $p = 0.023$) and fasting C-peptide (C-pep) ($r = 0.301$, $p = 0.056$), while secondary BAs showed no correlation with anthropometric/metabolic parameters. Among primary BAs, GCA directly related to visceral adiposity and AT-IR while TCDCA was associated with visceral adiposity (WC and VF), insulin secretion (C-pep), IR in adipose tissue (AT-IR), liver (Hep-IR) as well as with hepatic steatosis and inversely related to muscle IS (GC) (Table 1). UDCA had no correlation with metabolic parameters while TUDCA (hydroxylated) was significantly correlated with visceral adiposity, IR at different sites and liver fat (Table 1).
Conclusion: In NAFLD patients, GCA, TCDCA and TUDCA are increased proportionally to IR at the main sites of insulin action (adipose tissue, liver and muscle) irrespective of diabetes. Since TCDCA is the most potent endogenous agonist of FXR, which upon activation improves insulin sensitivity, and TUDCA treatment in obese individuals has been found to improve insulin sensitivity, these increases may represent compensatory mechanisms to IR.
Funded by: Horizon2020 under grant agreement no.634413 for project EPoS.

THU-461

Pharmacological inhibition of the medium chain fatty acid receptor GPR84 reduces myeloid cell in filtration into injured liver and ameliorates steatohepatitis and fibrosis

T. Puengel[1], S. De Vos[2], O. Krenkel[1], P. Pujuguet[3], M. Auberval[3], F. Marsais[3], K.F. Shoji[3], L. Saniere[3], C. Trautwein[1], R. Brys[2], F. Tacke[1]. [1]*RWTH-University Hospital Aachen, Department of Medicine III, Aachen, Germany;* [2]*Galapagos NV, Mechelen, Belgium;* [3]*Galapagos SA, Romainville, France*
Email: tobias.puengel@rwth-aachen.de

Background and Aims: Expression of medium chain free fatty acid receptor GPR84 (G protein-coupled receptor 84) is induced in immune cells under inflammatory conditions. In view of the proposed roles for GPR84 in inflammation and leukocyte chemotaxis, we hypothesize that pharmacological blockade of GPR84 could represent a novel treatment option in NASH. We therefore evaluated the therapeutic inhibition of GPR84 by two novel, structurally distinct small molecule antagonists in mouse models of acute and chronic liver injury. Results were compared to Selonsertib, an apoptosis signal-regulating kinase 1 (ASK1) inhibitor currently evaluated in NASH patients.
Method: C57bl/6 wildtype mice were subjected to carbon tetrachloride (CCl4) injury, methionine-choline-deficient (MCD) diet for 8 weeks or choline-deficient & high-fat diet (CDAHFD) for 10 weeks. Mice were treated with two GPR84 antagonists (30 mg/kg QD PO) or Selonsertib (15 mg/kg BID PO) for the last 4 weeks of MCD or last 6 weeks of CDAHFD, respectively. Chemotaxis experiments were conducted with primary neutrophils and monocytes.
Results: *In vitro*, both GPR84 antagonists blocked neutrophil and macrophage chemotaxis induced by GPR84 activation. Upon acute liver injury (single CCl4 injection) in mice, treatment with both GPR84 antagonists resulted in a reduced necrotic liver area and significantly reduced hepatic recruitment of neutrophils, monocytes and monocyte-derived macrophages (MoMF), as evidenced by FACS analysis of intrahepatic leukocytes and F4/80 immunohistochemistry. Similarly, therapeutic application of the two GPR84 antagonists reduced blood monocytes as well as liver neutrophils and MoMF in the MCD model. Pharmacological GPR84 blockade ameliorated steatohepatitis and fibrosis, as assessed by histological NAFLD activity score and Sirius red staining, to a similar extent as Selonsertib. Similar anti-inflammatory and anti-fibrotic effects, including modulation of related gene expression pathways, were observed following GPR84 inhibition in the CDAHFD model.
Conclusion: Pharmacological blockade of GPR84 inhibits neutrophil and macrophage recruitment to the liver in models of acute and chronic liver injury. Therapeutic application in mouse liver fibrosis models ameliorated steatohepatitis and fibrosis, to a level comparable to the ASK1 inhibitor Selonsertib, corroborating the therapeutic potential of GPR84 antagonists in NASH.

Table 1 (abstract: THU-460)

Table 1.		Waist (cm)	VF (kg)	GC (ml/min kg)	C-pep (pmol/ml)	Insulin (mU/l)	HOMA	Hep-IR	AT-IR
Total primary BA	*r*	0.341	0.409	-0.158	0.360	0.275	0.244	0.261	0.261
	p	0.029	0.022	0.324	0.021	0.082	0.125	0.100	0.099
Glycocholic acid (GCA)	*r*	0.364	0.383	-0.237	0.442	0.341	0.328	0.296	0.367
	p	0.019	0.033	0.135	0.004	0.029	0.037	0.060	0.018
Taurochenodeoxycholic acid (TCDCA)	*r*	0.334	0.349	- 0.304	0.505	0.429	0.439	0.331	0.393
	p	0.033	0.050	0.050	0.001	0.007	0.006	0.042	0.014
Taurodeoxycholic acid (TUDCA)	*r*	0.339	0.209	-0.151	0.390	0.474	0.482	0.467	0.374
	p	0.030	0.258	0.347	0.012	0.002	0.001	0.002	0.016

THU-462

Non-alcoholic steatohepatitis impairs Kupffercell-mediated immune tolerance in the mouse liver

L.A. Orci[1], C. Toso[1], K. Mario[2], F. Slits[1], V. Delaune[1], G. Oldani[1], C. Gonelle-Gispert[1], L. Rubbia-Brandt[2], S. Lacotte[1]. [1]*Centre Médical Universitaire, Surgery, Geneva, Switzerland;* [2]*Centre Médical Universitaire, Pathology and Immunology, Geneva, Switzerland*
Email: stephanie.lacotte@unige.ch

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is increasingly recognized as a threat to human health. Although our understanding of NAFLD and non-alcoholic steatohepatitis (NASH) pathogenesis is improving, there is limited data on the function of resident Kupffer cells in this context, especially when considering their contribution to hepatic immune tolerogenicity.
Method: By using a unique isolation procedure, primary Kupffer cells, and not infiltrating liver monocytes, were studied in a mouse model of prolonged diet-induced liver steatohepatitis. We assessed Kupffer cell phenotype upon exposure to lipopolysaccharide or interleukin 4. We did phagocytosis and antigen presentation assays to investigate Kupffer cell function as scavenger cells and immune response initiators.
Results: Primary Kupffer cells circumscribe endotoxin-mediated inflammatory response by up-regulating anti-inflammatory genes such as arginase 1 and interleukin-10 (IL-10). In the chronically inflamed liver, Kupffer cells acquire immunomodulatory properties by reducing membranous expression of class II major histocompatibility complex (MHC, $p = 0.016$), and by enhancing co-inhibitory signalling (programmed-death ligand 1 [PD-L1], $p = 0.036$). While Kupffer cells isolated from mice with normal livers are capable of achieving endotoxin tolerance, our results indicate an impairment of this protective mechanism in the presence NASH-like parenchymal abnormalities.
Conclusion: Primary Kupffer cells are capable of achieving endotoxin tolerance, but in the chronically-inflamed fatty liver, although they acquire immunomodulatory phenotype, Kupffer cells are not sufficient to dampen immune-mediated damage. Therefore, loss of tolerance induced by ongoing liver insult may be a mechanism contributing to the worsening of NAFLD.

THU-463

BCAA and ER stress activate SREBP-1c cleavage and hepatic lipogenesis through mTOR

F. Phan, M. Flamment, M. Hu, I. Hainault, P. Ferré, F. Foufelle. *INSERM UMRS 1138, Centre de Recherche des Cordeliers, Paris, France*
Email: fabienne.foufelle@crc.jussieu.fr

Background and Aims: Liver plays a central role in energy homeostasis in response to variety of hormones and nutrients. In physiological conditions, upon food intake, insulin inhibits hepatic glucose production and induces *de novo* lipogenesis (DNL). In insulin resistant states, while the insulin action on the hepatic gluconeogenic pathway is impaired, its action on DNL remains intact or even exaggerated, a state referred to as selective insulin resistance. Several mechanisms have been proposed to explain the selective hepatic insulin resistance. We proposed that in obese rodents, the lipogenic transcription factor SREBP-1c is activated by ER stress thus inducing DNL in an insulin-independent way. Others proposed that bifurcation of insulin signaling after PKB, could explain selective insulin resistance with a branch increasing the activation of SREBP-1c by mammalian target of rapamycin complex 1 (mTORC1), and another branch decreasing gluconeogenesis via regulation of FoxO1. One of the nutritional factors that can activate mTORC1 signaling is the amino acids. Interestingly, it was shown that branched-chain amino acid (BCAA), shows strong correlation with insulin resistance (HOMA) in human study, and is especially increased in the plasma of obese individuals and ob/ob mice. In this study, we make the hypothesis that BCAA could stimulate mTOR signaling and the subsequent hepatic lipogenesis in primary hepatocytes.
Method: Primary rat hepatocytes were challenged with a mixture of BCAA or their metabolites BCKA or with ER stress inducers. Nuclear and microsomal extracts were performed to analyse SREBP-1c content. Western Blot were performed with total extracts to assess insulin signaling. RT-qPCR were performed to analyse the expression of gluconeogenic and lipogenic enzymes. Mice were orally forced fed with BCAA or vehicle and liver was collected to assess the same parameters.
Results: In this study, we showed that BCAA and their related metabolites BCKA could independently stimulate mTORC1 signaling, SREBP-1c proteolytic cleavage and the subsequent lipogenesis in primary hepatocytes while displayed no effects on gluconeogenesis. Further studies also demonstrated that BCAA may potentiate the insulin-induced or ER stress-induced SREBP-1c activation in an mTORC1-dependent way. Finally, we showed that force feeding of mice with BCAA leads to mTOR activation, SREBP-1c cleavage and transactivation of target genes.
Conclusion: Our results indicate that BCAA may play an important role in the mTORC1-centered lipogenesis and selective insulin resistance in liver.

THU-464

The vanin 1-cysteamine pathway regulates immune tolerance upon lipid-induced oxidative stress in non-alcoholic fatty liver disease

O. Govaere[1], J. Palmer[1], M. Zhuang[1], M.Y.W. Zaki[1], E. Scott[1], S. Cockell[2], A.K. Daly[1], Q. Anstee[1]. [1]*Newcastle University, Institute of Cellular Medicine, Newcastle upon Tyne;* [2]*Newcastle University, Bioinformatics Support Unit, Newcastle upon Tyne, United Kingdom*
Email: olivier.govaere@ncl.ac.uk

Background and Aims: Lipid-induced oxidative stress is considered a critical factor in the progression of non-alcoholic fatty liver disease (NAFLD). In response to lipid-loading hepatocytes release microparticles containing vanin-1, a pantetheinase that hydrolyses Vit B5 to cysteamine in the co-enzyme A pathway. Moreover, vanin-1 has been reported to modulate hepatic triglyceride levels and to be protective against acetaminophen-induced hepatoxicity. This study aims to investigate the role of the vanin-1/cysteamine pathway *in vitro* and *in vivo*, and to determine associations of *VNN1* genetic variations with the progression of NAFLD.
Method: *VNN1* rs4897612 genotype was assessed in a cohort of 465 patients with histologically characterised NAFLD. VNN1 expression was analysed using immunohistochemistry in fresh-frozen liver samples from patients with NAFLD and C57BL/6 mice fed a 20week high fat+/- sugar diet. To mimic hepatocyte-Kuppfer cell interaction, the hepatoma HepG2 and the myeloid Mono-Mac6 cell lines were challenged with oleic, linoleic, palmitic and stearic acid with or without cysteamine and LPS. Read-outs included Oil-Red-O staining, proliferation and ROS assays, ELISA and qPCR.
Results: The *VNN1* variant rs4897612 was associated with an increased risk of advanced hepatic fibrosis ($p = 4.9*10^{-3}$). In mouse vanin-1 showed a plasma membrane expression in hepatocytes which was increased upon high fat diet with or without sugar. Similar results were found in the human samples with strongest intensity in end-stage liver disease where immunopositivity in hepatic progenitor cells was seen. In HepG2 all fatty acids induced lipid accumulation but only linoleic acid significantly induced oxidative stress without inducing cell death. At a concentration of 1 mM linoleic acid a 5-fold increase in ROS levels ($p < 0.01$) was detected in the HepG2 together with an up-regulation in *VNN1*, *GPX1*, *KRT19* and *KRT23* expression ($p < 0.05$). Cysteamine significantly reduced oxidative stress and increased glutathione levels. *In vitro*, linoleic acid exposure primed the monocyte Mono-Mac6 cells for higher LPS-induced release of pro-inflammatory cytokines IL6 and IL8, an effect that was ameliorated by cysteamine treatment.
Conclusion: Our results suggest that under the influence of modifiers including Vanin-1, cysteamine levels can contribute to immune tolerance and thus reduce inflammatory potential in metabolic diseases like NAFLD.

THU-465

BAFF neutralization ameliorates the evolution of experimental NASH

S. Sutti[1], S. Bruzzì[1], G. Giudici[1], R.N. Naik[1], C. Bozzola[1], P. Schneider[2], E. Morello[3], M. Parola[3], E. Albano[1]. [1]*University of East Piedmont (UPO), Dept. of Health Sciences, Novara, Italy;* [2]*University of Lausanne, Dept. of Biochemistry, Epalinges, Switzerland;* [3]*University of Turin, Dept. of Clinical and Biological Sciences, Torino, Italy*
Email: salvatore.sutti@med.uniupo.it

Background and Aims: Recent studies have pointed out the importance of B-lymphocytes in supporting hepatic inflammation in nonalcoholic steatohepatitis (NASH). Moreover, the severity of human NASH correlates with the circulating levels of B-cell Activating Factor (BAFF; TNFSF13b), one of the cytokines that regulate B-cell survival and maturation. We thus investigated whether interfering with BAFF might modulate the evolution of experimental NASH.
Method: NASH was induced in C57BL/6 mice by feeding with a methionine-choline deficient (MCD) diet up to 4 weeks or with a choline deficient amino acid defined (CDAA) diet for 24 weeks. Mice received the BAFF neutralizing monoclonal antibody Sandy-2 (2 μg/g body weight) at the start and after two weeks of MCD diet.
Results: In preliminary tests, we observed that 1 week treatment Sandy-2 reduced by about 40% circulating and liver B-cells, specifically affecting the B2 subset, and prevented liver plasma cell maturation in mice fed with the MCD diet for 1 week. In the animals receiving the MCD diet for 4 weeks, BAFF neutralization ameliorated histological scores for steatosis and lobular inflammation as well as ALT release. Although Sandy-2 treatment did not appreciably affect the prevalence of liver infiltrating $CD4^+$ and $CD8^+$ T-cells, it significantly lowered Th-1 activation of liver $CD4^+$ T-lymphocytes, as evaluated by IFN-γ production. BAFF blockade also decreased the hepatic expression of pro-inflammatory mediators such as TNF, IL-12, CCL2 and CXCL10. Similarly, NASH severity was improved in mice overexpressing a soluble form of the BAFF/APRIL receptor Transmembrane Activator and Cyclophilin Ligand Interactor (TACI-Ig) receiving the CDAA diet. In these animals Sirius Red staining for collagen and the prevalence of α-smooth muscle actin (α-SMA)-positive activated hepatic stellate cells were also significantly reduced as compared to wild-type littermates and this paralleled with a lower hepatic expression of α1-procollagen, α-SMA and Transforming Growth Factor-β1 (TGF-β1).
Conclusion: Altogether, these data indicate that interference with cytokines controlling B-lymphocyte activation effectively prevents NASH progression, suggesting that BAFF inhibition with already available drugs could be a possible treatment for NASH.

THU-466

The multifactorial pathogenesis of nonalcoholic fatty liver disease: connecting inflammation and oxidation

F. Luciano-Mateo[1,2], N. Cabré[1,2], G. Baiges[1,2], A. Hernández-Aguilera[1,2], S. Fernández-Arroyo[1,2], J. Camps[1,2], J. Joven[1,2]. [1]*Unitat de Recerca Biomèdica, Hospital Universitari Sant Joan, Universitat Rovira i Virgili, Reus, Spain;* [2]*Instituto de Salud Carlos III (Grant PI15/00285 co-founded by the European Regional Development Fund (FEDER)), Madrid, Spain, Institut d'Investigació Sanitària Pere Virgili, Spain*
Email: fedranicaury.luciano@urv.cat

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is an immune-linked metabolic disease, which now represents the most frequent cause of chronic liver disease and probably the leading indication for liver transplantation in the years to come. However, the responsible mechanism unclear, we hypothesize that C-C motif chemokine ligand 2 deficiency (CCL2) enhance the metabolic alterations involved NAFLD. The lipid accumulation in the liver increases vulnerability to oxidative stress, lipid peroxidation, liver damage and inflammation. The study of the link between Chemokine (C-C motif) ligand 2 (CCL2), Paraoxonase-1 (PON1), and Low Density Lipoprotein receptor (LDLr) may help to better understand the role of these components in the NAFLD. The aim of this study was to evaluate the multifactorial pathogenesis of diet-induced fatty liver disease.
Method: Using triple deficient mice that combined the three cornerstones of the NAFLD: Inflammation, oxidation and hyperlipemia condition. These mice were deficient in CCL2, PON1 and LDLr (CPL KO) and double deficient mice PON1 and LDLr (PL KO). We used CCL2 KO, PON1 KO, LDLr KO and wild type (WT) as a control group. We performed an integrated analysis of the metabolic phenotypes occurring in two experimental diets treatments during 14 weeks. After this period, a histological and metabolomics analysis of their liver tissue by mass spectrometry (GC-EI- QTOF-MS) were performed.
Results: CPL KO mice were associated with significantly decreasing of steatosis, weight and adipose size and enhance metabolic alterations, mitochondrial dysfunction caused by the diet. All this combined with significative increases of F4/80 stained cell in the liver tissue. In contrast, PL KO mice were associated with opposite effect. It seems that this mechanism is involved in the manipulation of macrophages polarization, mitochondrial dysfunction, energy metabolism regulation and autophagy process. CCL2 deficient condition has a protective effect and preventing the development of these alterations.
Conclusion: We report that C-C motif chemokine ligand 2 (CCL2) is a potent targetable approach to limit NAFLD progression. Blocking CCL2 strongly protects from steatosis development, adipose tissue hyperplasia and manipulation of macrophage plasticity.

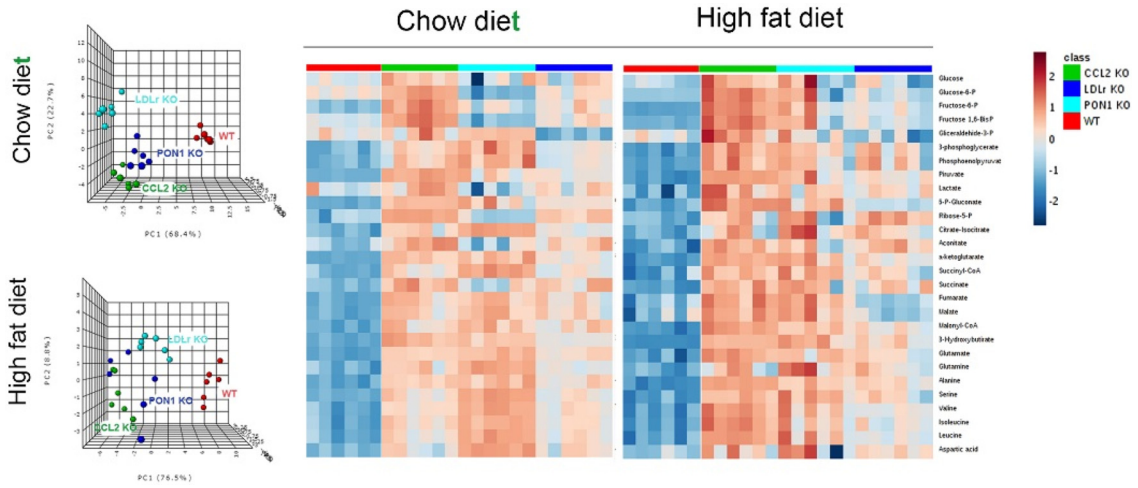


Figure: (abstract: THU-466)

THU-467

Expression of the chemokine CCL24 and its receptor in the sera and livers of patients with non-alcoholic fatty liver disease

Y. Maor[1], D. Haberman[2], M. Segal[3], A. Katav[3], S. Hashmueli[3], J. George[4], A. Mor[3]. [1]*Kaplan Medical Center, Institute of Gastroenterology and Hepatology, Rehovot, Israel;* [2]*Kaplan Medical Center, Heart Center, Rehovot, Israel;* [3]*Chemomab, LTD;* [4]*Kaplan Medical Center, Heart Center*
Email: halish@netvision.net.il

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease. Inflammation and fibrosis are the key pathological processes involved in the progression of NAFLD to non-alcoholic steatohepatitis (NASH). Chemokines play an important role in inducing inflammation and fibrosis and were found to be central in NASH progression. CCL24, a pro-inflammatory and pro-fibrotic chemokine, was recently found to be involved in the progression of inflammatory and fibrotic diseases and is tested for its involvement in NASH. Our aim was to study the levels of circulating CCL24 and its receptor-CCR3 in NAFLD patients' serum samples and liver biopsies and the association with its clinical features.
Method: Serum samples from NAFLD patients were analyzed for CCL24 levels using commercial ELISA kit (R&D systems). CCR3 levels in peripheral blood mononuclear cells were tested by flow cytometry. Immunohistochemistry staining was performed to evaluate CCL24 and CCR3 in liver biopsies.
Results: Our finding revealed significant elevation of CCL24 serum levels in NAFLD patients compared to healthy volunteers (718 ± 78 and 476 ± 36 pg/ml, respecitively, $p \leq 0.01$). Moreover, we used Fib4 score to divide the NAFLD population to subgroups according to disease progression. We found that CCL24 levels were increased by ~2 fold in high NAFLD Fib4 score patients (n = 23) compare to healthy volunteers (n = 20) ($p \leq 0.01$) and by 1.5 fold compare to low Fib4 score NAFLD patients (n = 28) ($p \leq 0.05$). CCL24 activity is mediated by its binding to its cognate receptor, CCR3. Thus, we assessed the levels of CCR3 expression in peripheral blood mononuclear cells isolated from NAFLD patients (n = 35) and healthy volunteers (n = 16). We found that CCR3 was significantly overexpressed in mononuclear cells isolated from NAFLD patients compared to healthy volunteers (3.81 ± 0.16% and 0.84 ± 0.1%, respectively, $p \leq 0.01$). Significantly higher hepatic expression of CCL24 and CCR3 using immunohistochemistry was revealed in NASH patients' liver biopsies with NAFLD Activity Score equal and higher than 5 compared with normal livers. Importantly ($p \leq 0.01$, $p \leq 0.05$, respectively).
Conclusion: This is the first evidence, that the chemokine CCL24 and its cognate receptor, CCR3, are significantly increased in NAFLD patients both in the circulation and in the liver. These results may indicate a potential involvement of CCL24-CCR3 axis in the pathogenesis of NASH, thus suggesting that CCL24 may serve as a potential prognostic tool and a therapeutic target for the treatment of patients with NASH.

THU-468

LJN452 (tropifexor) attenuates steatohepatitis, inflammation, and fibrosis in dietary mouse models of nonalcoholic steatohepatitis

B. Laffitte[1], E. Hernandez[1], Y. Kim[1], B. Liu[1], P. Rucker[1], D. Chianelli[1], D. Bao[2], J. Zoll[1], J. Xu[1], V. Molteni[1], P. Mcnamara[1], M. Badman[2]. [1]*Genomics Institute of the Novartis Research Foundation, La Jolla, United States;* [2]*Novartis Institutes for BioMedical Research, Cambridge, United States*
Email: blaffitte@gnf.org

Background and Aims: Farnesoid X receptor (FXR) agonists are investigational agents for the treatment of nonalcoholic steatohepatitis (NASH) and other chronic liver diseases. The bile acid-derived FXR agonist obeticholic acid (OCA) demonstrated efficacy in Phase II NASH trials, but also caused cholesterol elevation and pruritus. LJN452 is a highly potent non-bile acid agonist currently under Phase II development. Here, we compare the efficacy of LJN452 and OCA in two mouse models of NASH.
Method: STAM Model: Streptozotocin-injected 2-day old C57Bl/6J mice were placed on high-fat diet for weeks 4–12. From Week 9, mice received oral doses of LJN452 (0.03–0.3 mg/kg), OCA (25 mg/kg), or vehicle. Hematoxylin & eosin (H&E)-stained liver sections were assessed for nonalcoholic fatty liver disease activity score (NAS). Collagen deposition (fibrosis marker) was estimated by percent of Sirius-red positive area.
AMLN Model: C57Bl/6 mice were placed on high fat (40% kcal), fructose (22% by wt), and cholesterol (2% by wt) diet for 30 weeks. LJN452 (0.03–0.9 mg/kg), OCA (25 mg/kg), or vehicle was orally dosed for the last 4 weeks. Treatment effects were monitored by histopathology (H&E, Trichrome and IBA1 staining) and assessment of liver-damage markers (alanine/aspartate aminotransferases [ALT/AST]) levels and collagen type I, alpha1 (Col1a1) and tissue inhibitor of metalloproteinase 1 (TIMP1) mRNA levels.
Results: Compared with normal mice, STAM mice showed marked increases in NAS and fibrotic area. LJN452 treatment showed significant decrease in NAS at doses ≥0.1 mg/kg ($p < 0.0001$), whereas the effect of OCA tended was less marked. Significant dose-dependent reduction of Sirius Red-positive areas was observed with LJN452 ($p < 0.001$). In the AMLN model, LJN452, but not OCA, showed dose-dependent reduction in ALT/AST levels relative to controls. In addition, LJN452 reduced inflammation, steatosis, and fibrosis in AMLN mice. Steatosis and inflammation were completely resolved at LJN452 doses ≥0.3 mg/kg. LJN452 also dramatically reduced mRNA levels of fibrogenic markers Col1a1 and TIMP1. NASH mice exhibited hepatic inflammation as confirmed by IBA1+ staining of macrophages and Kupffer cells, which was dose-dependently reduced in LJN452-treated, but not OCA-treated, mouse livers.
Conclusion: Marked improvement in NASH endpoints with LJN452 in two distinct models suggests its potential as a treatment for NASH and warrants its further clinical investigation in NASH patients.

THU-469

EDP-305 modulates lipoprotein metabolism via distinct chromatin and microRNA regulatory mechanisms

M. Roqueta-Riverta[1], M. Chau[1], K. Garlick[1], Y. Li[2], Y.S. Or[3], L. Jiang[4]. [1]*Enanta Pharmaceuticals, Inc., Biology, Watertown, United States;* [2]*Enanta Pharmaceuticals, Inc., Pharmacology, Watertown, United States;* [3]*Enanta Pharmaceuticals, Watertown, United States;* [4]*Enanta Pharmaceuticals, Inc, Pharmacology, Watertown, United States*
Email: ljiang@enanta.com

Background and Aims: The Farnesoid X Receptor (FXR) has emerged as an attractive target for the treatment of NASH. EDP-305, a selective and potent small molecule FXR agonist, is currently being developed for the treatment of NASH. We previously demonstrated EDP-305 treatment results in different gene regulatory effects on lipoprotein metabolism *(LDLR, SRB1)* when compared to obeticholic acid (OCA). In this study, we sought to characterize transcriptional and post-transcriptional regulatory mechanisms by which EDP-305 regulates *LDLR* and *SRB1* expression.
Method: To examine the regulatory mechanisms of EDP-305 and OCA independent of drug potency, treatments were conducted near their respective EC_{50} concentrations (EDP-305: 50 nM; OCA: 500 nM) in human hepatocytes (hepatoma, HepaRG). *In vivo*, C57B6/J mice were treated daily by oral gavage for 5 days with EDP-305 (30 mg/kg) or OCA (100 mg/kg). Sonicated hepatocyte chromatin (~500 bp) was used for chromatin immunoprecipitation (ChIP-qPCR) assays to measure histone methylation and transcription factor enrichment at *LDLR* and *SRB1* promoters. miRNAs were isolated using the miRNAeasy kit (Qiagen).
Results: Under basal conditions, both *in vitro* and *in vivo*, EDP-305 exhibited higher *LDLR* and lower *SRB1* expression relative to OCA, despite equivalent expression of the FXR target, *SHP*. Thus, EDP-305 may have distinct transcriptional and post-transcriptional regulatory

mechanisms for *LDLR* and *SRB1* expression. At the transcriptional level, histone methylation and transcription factor binding were evaluated at the promoters of *LDLR* and *SRB1*. Post-transcriptionally, miRNAs targeting *LDLR* (mir-148a-3p) and *SRB1* (miR-96-5p) were measured.

At the LDLR promoter, EDP-305 treatment of hepatoma cells decreased the gene repressive mark of lysine-9 trimethylation at histone-3 (H3K9me3) by 40% ($p < 0.05$) while SREBP2 was enriched 2-fold ($p < 0.05$) relative to vehicle and OCA. In hepatoma cells under basal conditions, EDP-305 decreased mir-148a by 20% ($p < 0.05$) relative to vehicle, which coincided with increased levels of *LDLR* mRNA. In steatotic HepaRG cells, OCA decreased *LDLR* expression, whereas EDP-305 had no effect; this may be attributed to a 50% increase of mir-148a levels by OCA ($p < 0.05$ vs vehicle).

At the SRB1 promoter, OCA decreased H3K9me3 by 25% and mir-96 by 50% ($p < 0.05$ vs vehicle) allowing for increased *SRB1* transcription. In steatotic HepaRG cells, OCA similarly decreased mir-96 by 50% ($p < 0.05$ vs vehicle), while EDP-305 had no effect.

Conclusions: EDP-305 has distinct transcriptional and post-transcriptional regulatory mechanisms for *LDLR* and *SRB1* expression when compared to OCA. The EDP-305 mechanisms driving these lipoprotein-related gene regulatory differences may translate to a more positive lipoprotein profile in patients, making EDP-305 attractive for further investigation in NASH.

THU-470

CXCL16 promotes hepatocyte steatosis and fibrosis in nonalcoholic fatty liver disease via hepatocyte-stellate cell crosstalk

L. Jiang, J. Zhao. *302 Hospital, Department of Pathology*
Email: nnzadl@163.com

Background and Aims: Non-alcoholic liver disease (NAFLD), a common metabolic liver disease, attracts more and more attention in industrialized countries for its rapidly increasing prevalence. CXCL16, a chemokine with both secreting type and membrane type has been implicated in inflammatory and metabolic liver diseases. The effect of CXCL16 on mutual promotion between steatosis and fibrosis might push the progression of NAFLD in patients. In this study, we freshly investigated the contribution of CXCL16 to the steatosis and fibrosis during NAFLD progression.

Method: The study was comprised 104 NAFLD patients with different SAF scores. CXCL16 level in serum of patients was evaluated and its expression in liver biopsy was also detected. CXCL16 induced hepatocytes steatosis was stained by Oil Red O, meanwhile the TG and SOD level were calculated. Lipogenic genes and HSCs activation related factors were quantified by RT-PCR. Hedgehog signaling pathway was detected in CXCL16 influenced co-culture system. Activation of Hh signaling pathway was performed to investigate the function of Hh ligands in CXCL16 induced steatosis.

Results: CXCL16 is markedly increased in groups of steatosis and has siginificant difference among group S0-1, S2 and S3. We found that the difference is due to the data in patients with A or/and F score ≥ 2 in SAF score system. CXCL16 accumulates around hepatocytes with severe steatosis in patient liver biopsy specimens. CXCL16 induced severe steatosis in hepatocyte-stellate cell co-culture system. This induction suppressed respiration rate of hepatocytes and the steatosis related genes were also up regulated. TGF-β, COL1A1 and α-SMA were increased in activated HSCs and Hh ligands SMO, SHH, GLI1/2 and PTCH were down regulated in hepatocytes. Overexpression of SHH inhibited hepatocytes steatosis.

Conclusion: Collectively, our study demonstrates a freshly crosstalk between hepatocytes and HSCs regulated by CXCL16. These findings established CXCL16 as a part of the steatotic and fibrotic pathway in NAFLD progression. CXCL16 is a hopeful non-invasive detection index as well as a future potential therapeutic target to alleviate NAFLD.

THU-471

Inhibition of IL6 trans-signaling leads to NAFLD, mature-onset obesity and metabolic syndrome

T. Lanton[1], O. Levkovitch[1], S. Perles[2], J. Tam[3], S. Udi[3], J. Rachmilewitz[4], R. Abramovitch[1], S. Rose-John[5], E. Galun[1], J. Axelrod[1]. *[1]Hadassah Hebrew University Hospital, The Goldyne Savad Institute of Gene Therapy, Jerusalem, Israel; [2]Raziel Therapeutics, Raziel Therapeutics Ltd, Israel, Jerusalem, Israel; [3]The Institute for Drug Research, Faculty of Medicine, Obesity and Metabolism Laboratory, Jerusalem, Israel; [4]Hadassah Hebrew University Hospital, Hadassah Hebrew University Hospital, Jerusalem, Israel; [5]University of Kiel, Department of Biochemistry, Kiel, Germany*
Email: tali.lanton@mail.huji.ac.il

Background and Aims: Persistent IL6 production has been implicated in altered metabolic states such as exercise and HFD-induced obesity and fatty liver; however the causal role of IL6 and IL6 *trans*-signaling in particular in the spontaneous development of age-related obesity and fatty liver disease remains controversial. IL6 *trans*-signaling relies upon the release of the soluble IL6R (sIL6R), which binds IL6 to form an agonistic IL6/sIL6R complex. Here we have examined the hypothesis that IL6 *trans*-signaling plays a crucial role in the control of weight gain and glucose homeostasis in aging mice.

Method: Transgenic mice expressing high levels of the specific IL6/sIL6R antagonist, sgp130Fc, and wild type (WT) littermates were compared for weight gain, glucose homeostatis, and liver steatosis at 2, 6 and 14 months (mo) of age.

Results: Sgp130Fc mice, in comparison to WT littermate controls, displayed significant hyperphagia from an early age, followed by a dramatic rise in body weight and hyperglycemia by the age of 6 mo. Sgp130Fc mice displayed increased fat storage in the liver while reducing free fatty acid levels in the blood but not by altering hepatic triglyceride synthesis genes" expression. Interestingly, hepatosteatosis was not accompanied by increased inflammatory markers (e.g. TNF). Additionally, inhibition of IL6 *trans*-signaling lead to impaired glucose tolerance due to peripheral insulin resistance in aged mice without altering hepatic gluconeogenesis nor pancreatic secretion defects. Finally, antibiotics treatment rescued the animals from obesity and hyperglycemia indicating that the mechanism by which *trans*-signaling protects against mature onset-metabolic syndrome may involve the gut microbiota.

Conclusion: IL6/sIL6 protects mice against mature-onset obesity, hyperglycemia, and hepatosteatosis in a mechanism that may involve host immune response to the microbiota.

THU-472

Genetic and functional analysis of FGF21 in NAFLD/NASH

R. Gallego-Durán[1,2], F. Martin[3], J. Ampuero[4], J.A.D.C. Castillo[5], H. Pastor[1,2], M.J. Pareja[6], A. Gil-Gomez[1,2], A. Rojas[1], M. Carmen Rico[1,2], R. Millan[1,2], R. Montero-Vallejo[1,2], L. Alvarez-Amor[3], A. Rojas[3], M.T.A. Loste[7], J.A. Guerra[8], R.M. Hernandez[1,2], J.L.C. Panero[8], R.J. Andrade[9], J. Crespo[7], C. García-Monzón[10], M.R. Gomez[11]. *[1]Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, Sevilla, Sevilla, Spain; [2]Hospital Universitario Virgen del Rocío, Sevilla, UCM Digestive Diseases and CIBERehd; [3]Centro Andaluz de Biología Molecular y Medicina Regenerativa (CABIMER), Stem Cell Unit, Sevilla, Spain; [4]Institute of Biomedicie of Seville (IBIS), Sevilla, Spain; [5]Hospital Universitario Virgen de Valme, UCM Digestive Diseases, Sevilla, Spain; [6]Hospital Juan Ramón Jiménez, Huelva, Pathology Unit, Huelva, Spain; [7]IDIVAL, Hospital Universitario Marqués de Valdecilla, Santander, UCM Digestive Diseases; [8]Hospital Universitario Puerta de Hierro, Madrid, UCM Digestive Diseases, Madrid, Spain; [9]IBIMA, Hospital Universitario Virgen de la Victoria, Málaga, UCM Digestive Diseases and CIBERehd; [10]Hospital Universitario Santa Cristina, Madrid, UCM Digestive Diseases, Madrid, Spain; [11]Hospital Universitario Virgen del Rocio, Sevilla. Instituto de*

Biomedicina de Sevilla. CiberEHD., Hospital Universitario Virgen del Rocio, Sevilla, Spain
Email: mromerogomez@us.es

Background and Aims: Fibroblast Growth Factor 21 (FGF21) plays a central role in glucose and metabolic homeostasis. The main aim of this study was to evaluate the role of FGF21 in NAFLD/NASH.
Method: This study included: (i) FGF21 evaluation in liver tissue (n = 20, 10 simple steatosis (SS) and 10 NASH) and in peripheral mononuclear blood cells (PBMC) by qRT-PCR (iii) Circulating FGF21 levels assessment in 38 patients (19 NASH, 19 SS) by ELISA (iii) Evaluation of a single nucleotide polymorphism (SNP) located in FGF21 (rs838133) as well as the one discovered in PNPLA3 (rs838109). Kleiner, analysing liver fibrosis and NAS Score assessed liver damage. An additional semi-quantitative scale for significant fibrosis (F2-F4) was further employed (iv) Intrahepatic accumulation of fgf21 in C57BL/6J mice with high-fat diet and choline-methionine diet (HFD-MCD) by immunohistochemistry.
Results: (i) Hepatic FGF21 gene expression was found to be upregulated in NASH vs SS (3.45 + 4.0 vs 0.63 + 0.9). Further, it was found associated with BMI (r = 0.75; p = 0.004) and HOMA-IR values (r = 0.79; p = 0.001). No qRT-PCR products were detected in PBMC
(ii) NASH (2.17 + 0.77 vs 1.55 + 0.79) and ballooning patients (2.30 + 0.71 vs. 1.69 + 076; p = 0.045) showed increased FGF21 levels in serum, and were significantly correlated with NAS Score (r = 0.364, n = 38, p = 0.027). No patients showed FGF21 levels below quantification limit.
(iii) After multivariate analysis, variables independently associated with significant fibrosis were: A-allele of rs838133 [OR 3.91 (CI95% 1.09–14.06); p = 0.006]; age [OR 1.07 (CI95% 1.03–1.11); p = 0.001]; type 2 diabetes mellitus [OR 4.08 (CI95% 1.51–10.97)] and ALT [OR 1.03 (CI95% 1.01–1.04); p = 0.000]. AUROC obtained for significant fibrosis prediction was 0.89 [IC95% CI 0.85–0.95]
(iv) Hepatic fgf21 expression in HFD-MCD mice were found increased vs controls (p < 0.001), accordingly to the hepatic injury.
Conclusion: FGF21 expression, both hepatic and circulating, was found increased in NASH patients. Bearing AA genotype of FGF21 confers susceptibility to significant fibrosis development. In the HFD-MCD model, increased expression of fgf21 was found associated to liver injury. These results highlighted the role of FGF21 as a biomarker and a therapeutic target in NAFLD/NASH.
Acknowledgements: Consejería de Salud de la Junta de Andalucía (PC-0148-2016-0148).

THU-473

Divergent effects of RIP3 and MLKL inhibition on HF diet induced steatosis

W. Saeed[1], D.W. Jun[1], E. Kim[1], K.S. Jang[2], B.-K. Kang[3], E.C.J. Jang[4], S.B. Ahn[5], M.M. Kim[3], J.Y. Jeong[6], J.H. Sohn[6]. *[1]Hanyang University School of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [2]Hanyang University School of Medicine, Pathology; [3]Hanyang University School of Medicine, Radiology; [4]Soonchunhyang University College of Medicine; [5]Eulji University College of Medicine, Internal Medicine; [6]Hanyang University, College of Medicine, Guri Hospital, Internal Medicine*
Email: noshin@hanyang.ac.kr

Background and Aims: Although, effect of receptor-interacting serine-threonine kinase 3 (RIP3) inhibition has been evaluated in high fat (HF) and MCD diet induced steatosis models. However, whether mixed lineage kinase domain-like (MLKL), RIP3 downstream target, would also depict the similar results is currently unknown. We, therefore, compared the results of RIP3 and MLKL inhibition using HF diet induced steatosis model.
Method: HF diet was fed for 12 weeks to WT, RIP3$^{(-/-)}$KO and MLKL$^{(-/-)}$ KO mice. After 12-weeks, the animals were sacrificed. NAS score was assessed using mice liver tissue. Gluocse tolerance test, indirect caloric metric analysis and PET-Scan was performed in MLKL-HF mice. qRT-PCR analysis for de novo lipid synthesis markers (SREBP1c, FAS, SCD1), VLDL secretion markers (Xpb1, ApoB, MTTP, PDI) and inflammation markers (TNF-α, IL6), and fat browning markers (UCP1, Ppargc1a, Dio2) was performed using mice tissue. Oleic acid (OA) treated primary hepatocytes from WT, RIP3KO mice and HepG2 cells treated with RIP3 and MLKL inhibitors were stained using Nile Red staining. The liver tissue from human NAFLD patients was immunostained for MLKL expression and MLKL immunoreactivity (IR) score correlation with NAS score was assessed.
Results: HF diet fed RIP3$^{(-/-)}$ mice showed significant weight gain. RIP3$^{(-/-)}$ mice had increased serum ALT, liver weight and liver/body

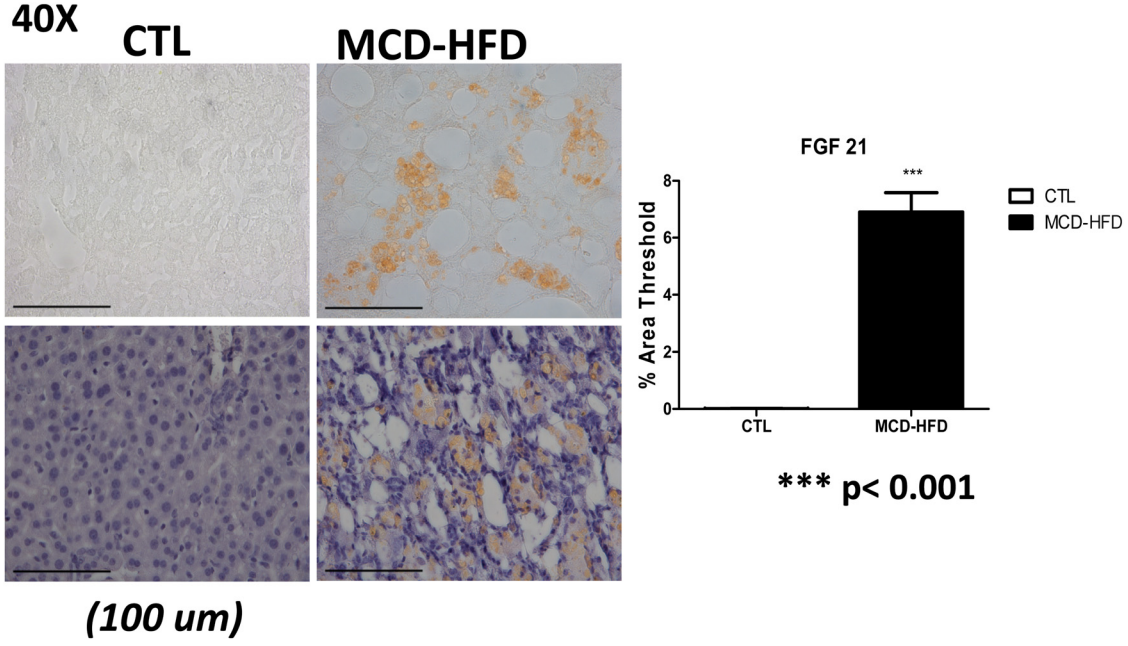


Figure: (abstract: THU-472): Fgf21 immunohistochemistry findings in HFD-MCD mice livers *vs* control group (p < 0.001).

weight ratio compared to wild type mice. RIP3$^{(-/-)}$ mice had decreased hepatic inflammation while increased fatty change, and liver tissue triglyceride; however, total NAS score was same between WT and RIP3$^{(-/-)}$ mice. RIP3$^{(-/-)}$ mice had significantly decreased VLDL secretion markers. MLKL IR score increased in human NAFLD patients and MLKL IR score was correlated with steatosis, lobular inflammation, ballooning degeneration, and NAS score. MLKL$^{(-/-)}$ and WT mice had overall the same body weights; however, interestingly, MLKL$^{(-/-)}$ mice had significantly decreased serum ALT, serum TG, liver weight, fatty change, lobular inflammation, ballooning degeneration and overall NAS score. In contrast to RIP3$^{(-/-)}$KO mice, MLKL$^{(-/-)}$ mice had significantly decreased lipid de novo synthesis markers (SREBP1c, FAS, SCD-1). Adipose tissue F4/80 staining showed decreased crown-like structures in MLKL$^{(-/-)}$ mice. Adipose tissue browning markers, PET-Scan, indirect caloric analysis, and GTT results were the same between WT and MLKL$^{(-/-)}$ mice. OA treated RIP3$^{(-/-)}$ primary hepatocytes had increased Nile Red staining compared to WT hepatocytes. RIP3 inhibitor (Gsk843) treated HepG2 cells showed increased while MLKL inhibitor (Necrosulfonamide) treated HepG2 cells showed decreased Nile red staining.

Conclusion: Both RIP3$^{(-/-)}$ and MLKL$^{(-/-)}$ mouse showed protective effect on hepatic inflammation, but RIP3 and MLKL inhibition depicts divergent effects on hepatic steatosis.

THU-474

Micro RNA 199a-3p attenuates hepatic lipogenesis through regulating specific protein 1

Y. Cheng. *Hospital for Infectious Diseases of Pudong New Area Shanghai China, Department of Liver Disease, Shanghai, China*
Email: drchengyang@126.com

Background and Aims: Emerging studies have demonstrated that microRNAs (miRs) are profoundly involved in non-alcoholic fatty liver disease (NAFLD) and related metabolic diseases. Previously, we revealed a repertoire of miRs dysregulated in NAFLD by high-throughput sequencing. Here, we showed that microRNA-199a-3p was down-regulated in the livers of C57BL/6J mice fed a high-fat-diet (HFD) and oleic acid/palmitic acid-induced Hepa1-6 cells.

Method: Male C57BL/6J mice were fed with HFD and divided into different groups randomly. A group of mice were injected intravenously through the tail vein with the adenovirus expressing a miR-199a-3p mimic or mouse Sp1 and negative control adenovirus vector. Hepa1-6 cell were cultured in routine DMEM supplemented with 10% fetal bovine serum. The NCTC1469 cells were cultured in low-glucose DMEM. Oleate (OA) and palmitate were used to induce the fat overloading cells. The Hepa1-6 cells at 80% confluency were exposed to a long train mixture of OA and PA (HFFA) at a final ratio of 2:1 and final concentration of 1 mM for 24 hr. The miR-199a-3p mimics and inhibitors as well as the negative control (NC) were used for transfection. Quantitative Real-time PCR and Western blot analysis were adopted. Tissues stained with Oil Red O were visualized under a microscope. Hepatic and cellular TG measurement were detected by kits. The luciferase activities were measured consecutively by using the Dual Luciferase Reporter Assay System.

Results: Gain-of-function and loss-of-function studies demonstrated that microRNA-199a-3p exhibited a suppressive role in hepatic lipogenesis. Adenoviral mediated microRNA-199a-3p expression in C57BL/6J mice largely attenuated triglyceride (TG) accumulation and expression of lipogenic genes. Furthermore, we identified Specificity Protein 1 (Sp1) as the functional target of miR-124. Restoration of Sp1 expression largely compromised the effect of microRNA-199a-3p on hepatic TG metabolism.

Conclusion: Taken together, our findings uncover a novel function of microRNA-199a-3p/Sp1 axis in NAFLD and provide a mechanism underlying perturbations of hepatic TG homeostasis.

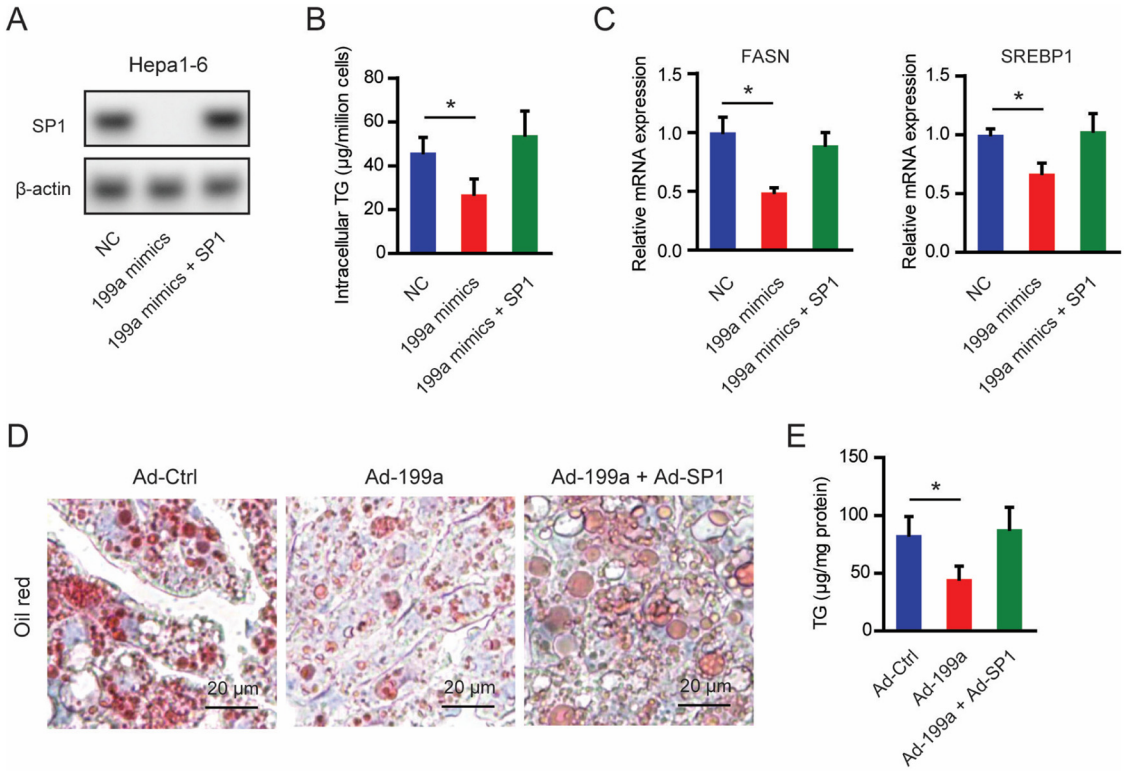


Figure: Restoration of Sp1 abolishes the effect of miR-199a-3p.

THU-475

RIPK1 depletion exacerbates progression of liver fibrosis in high fat diet induced non-alcoholic steatohepatitis (NASH) in mice

M. Farooq, C. Piquet-Pellorce, S. Dion, M.S. Eugenio, K. Santamaria, A. Filliol, M.-T. Dimanche-Boitrel, M. Samson, J. Le Seyec. *IRSET - U.1085 Inserm, Rennes, France*
Email: michel.samson@univ-rennes1.fr

Background and Aims: Non-alcoholic steatohepatitis (NASH) is an emergent chronic liver disease with a high prevalence in occidental countries. NASH can further progress into liver fibrosis, cirrhosis and hepatocellular carcinoma. Hepatocyte death carried through different death ligands plays key role in fibrotic progression. Previously, we showed that RIPK1, a protein kinase known to be involved in pathways related to both cell survival and death, exhibits a protective role in TNFα and FasL-induced hepatocyte death. Our new study aimed to investigate the role of RIPK1 in NASH.
Method: To decipher the role of RIPK1 in NASH, we took advantage of $RIPK1^{LPC-KO}$ mice which are deficient for RIPK1 only in liver parenchymal cells. NASH was induced by feeding both $RIPK1^{LPC-KO}$ animals and their WT ($RIPK1^{fl/fl}$) littermates with High Fat Diet (HFD). Mice were slaughtered at 3, 5 and 12 weeks of HFD feeding and were compared to mice fed with normal chow diet. Cytometry was performed to analyze the recruitment of inflammatory cells during the course of NASH. Plasma cytokine levels were measured by LEGENDplex™. Liver damage was assessed by histological staining and serum transaminase dosages. Liver fibrosis was quantified after Sirius red labelling.
Results: Irrespective of their genotype, mice fed with HFD, showed elevated levels of ALT and liver to body weight ratio during the development of NASH. Important liver infiltrations of immune cells, including NKT cells, were detected at week 3 of HFD. Then, after 5 and 12 weeks of treatment, the number of total immune cells decreased with a total loss of NKT cells. However, some cells such as macrophages and cytotoxic lymphocytes remained over-represented. This inflammation and immune cell infiltration were accompanied by higher plasma doses of cytokines such as TNFα and CCL2. IL-27 and IFNγ were specifically increased at week 3 of HFD. Despite similar inflammatory responses, more fibrosis was significantly evidenced at week 12 in $RIPK1^{LPC-KO}$ as compared to their WT littermates. These findings were further supported by more elevated mRNA expression of TGFBi and TIMP2 (genes indicative of fibrosis) in $RIPK1^{LPC-KO}$ compared to WT mice.
Conclusion: Our results show that RIPK1 in hepatocyte limits the progression of liver fibrosis during NASH.

THU-477

Clinical-grade human liver mesenchymal stem cells reduce NAS score and fibrosis progression in advanced stage NASH pre-clinical model through immunomodulation

M.M. Binda, E. Corritore, L. Menchi, T. Baran, Y. Greiling, S. Michel, J. Tchelingerian, G. Mazza, E. Sokal. *Promethera Biosciences, Mont-Saint Guibert, Belgium*
Email: mercedes.binda@promethera.com

Background and Aims: Nonalcoholic steatohepatitis (NASH), a severe form of nonalcoholic liver diseases (NAFLD), is one of the prominent liver diseases worldwide. There is currently no approved drug for its treatment and liver transplantation is the only therapeutic approach for advanced NASH. Mesenchymal stem cells (MSCs) are promising candidates to modulate the pro-inflammatory and pro-fibrogenic environment of chronic liver because of their immunomodulatory properties. HepaStem, adult human liver-derived MSCs isolated from organs unsuitable for transplantation can be GMP-manufactured, cryopreserved and reconstituted at the bedside as an off-the-shelf product. We previously showed that HepaStem can significantly reduce NAS score and collagen deposition in early stage NASH STAM™ model with necropsy at week 9 (Gellynck K *et al.* 2016). Safety and tolerability have been shown in a phase I/II clinical trial in patients with metabolic disorders. The aim of this study is to evaluate the efficacy of HepaStem in an advanced stage NASH pre-clinical model.
Method: The preclinical NASH mouse model was induced by 2 hits such as streptozotocin at 2 days of age and high-fat diet from 4 weeks of age (first cell infusion at week 10 and necropsy at week 13 STAM™ model). The potency of HepaStem was compared to a vehicle co-administered with immunosuppression (cyclosporine) in order to reduce the potential xenogenic response of the recipient to human cells. As outcome, a NAFLD activity score system, which contains the steatosis, inflammation and ballooning scores, was evaluated.
Results: In an advanced stage NASH model, cell-based treatment (1 and 3 IV injections 12.5×10^6 cells/kg) significantly and dose-dependently decreased NAFLD activity score (22.4% vs 32.6% reduction, $p < 0.05$ and $p < 0.001$, respectively), which was mainly attributed to a significant reduction in inflammation and thus supporting the proposed mechanism of action (Inflammation score: vehicle vs 3 doses of HepaStem: $p < 0.01$). In addition, HepaStem (1 and 3 IV injections 12.5×10^6 cells/kg) cell-based treatment tended to reduce the fibrotic area thus suggesting an inhibition of disease progression in a more advanced NASH model.
Conclusion: In line with our previous results (Gellynck *et al.* 2016), we confirm that clinical grade liver progenitor cells have anti-NASH and may have anti-fibrosis effects in an advanced pre-clinical NASH model. This observation provides significant evidences to open new phase I/II studies including also more severe NASH patients as well as to apply MSCs for the treatment of chronic liver disorders.

Reference

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THU-478

Ablation of Interleukin-4 Receptor alpha in macrophages ameliorated steatohepatitis and fibrosis in murine model of non alcoholic steatohepatitis (NASH)

M. Ashfaq-Khan[1], M. Aslam[2,3], M. Senkowski[2], M. Nick[1], S.Y. Weng[1], D. Schuppan[1,4]. *[1]Institute of Translational Immunology, University Medical Center, Mainz, Germany; [2]Institute of Translational Immunology, University Medical Center Mainz, Mainz, Germany; [3]Shaheed Benazir Bhutto Women University, Peshawar, Pakistan; [4]Division of Gastroenterology, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, United States*
Email: m.ashfaq_biotech@yahoo.com

Background and Aims: The role of immune cell populations in NASH-related inflammation and fibrosis remains controversial. However, targeting of specific receptors that switch immune cell phenotypes is attractive. We aimed to study the role IL-4 receptor alpha (IL-4Rα) which represents a central switch to generate Th2 T cells and M2 macrophages upon stimulation with interleukin (IL)-4 and IL-13 in a representative mouse model of NASH.
Method: 8-week-old male Balb/C wild type mice and Balb/C mice with general or macrophage specific deletion of IL-4Rα (Balb/C IL-$4R^{-}/^{-}$ and $LysM^{cre}$IL-$4R\alpha^{-}/^{lox}$) mice were fed a choline-deficient, L-amino acid-defined (CDAA) diet for an additional 12 weeks. Thereafter mice were sacrificed, and liver tissues sections were snap frozen and fixed in paraformaldehyde for further analysis.
Results: There was significant decrease in the liver weights of both the KO strains (Balb/C IL-$4R^{-}/^{-}$ and $LysM^{cre}$IL-$4R\alpha^{-}/^{lox}$) compare to the wild type mice. H&E and Sirius Red stained sections revealed a significant reduction of the NAS score (adapted for mice) from 7 to 5 and extent of fibrosis in Balb/C IL-$4R^{-}/^{-}$ B and Balb/C $LysM^{cre}$IL-$4R\alpha^{-}/^{lox}$ mice compared to the wild type controls. Hydroxyproline assay revealed significant reduction of fibrosis in CDAA fed IL-4R KO mice (both general and myeloid specific) compare to the CDAA fed

wild type control. In wild type mice, steatosis was >66% and macrovesicular, whereas steatosis in the IL-4Rα knockout mice was reduced and more concentrated in zone 3 with more microvesicular fat. Fibrosis score was 2.X in the wildtype vs <1 in both knockout strains. Specifically, CD68+ macrophages were significantly decreased in both L-4Rα compared to the wildtype mice ($p \leq 0.0096$), paralleled by significantly suppressed hepatic transcript levels for Col1a1, Tgfb and Tnfa.

Conclusion: We showed that 1. Ablation of the IL-4Rα alpha on macrophages as well as in general, comparably suppressed steatosis, inflammation and fibrosis in the CDAA model of NASH; 2. IL-4Rα targeted therapies, including inhibition of IL-4 and IL-13 is a potential therapy of fibrotic NASH.

THU-479

Combined administration of obeticholic acid (OCA) and GFT-505: additive histological improvements in mice with diet-induced and biopsy-confirmed non-alcoholic steatohepatitis (NASH)

J. Roth[1], S. Veidal[2], R. Papazyan[1], K. Rigbolt[2], M. Feigh[2], M. Young[1].
[1]*Intercept Pharmaceuticals, Inc., San Diego, United States;* [2]*Gubra, Horsholm, Denmark*
Email: jonathan.roth@interceptpharma.com

Background and Aims: OCA is a farnesoid X receptor (FXR) agonist and GFT-505 is a dual PPARα/δ agonist. Both have demonstrated efficacy in NASH and their endogenous targets are complementary. Using a prevention paradigm in a CDAA/high cholesterol model, a prior report noted benefits when both were co-administered (Ratziu et al. 2017; J of Hepat 66: S95–S332). The present study used (1) a therapeutic paradigm to examine individual and combined effects upon established diet-induced NASH, and (2) expression analyses to uncover pathways activated by combined FXR/PPAR administration.

Method: *Lep*$^{ob/ob}$ mice were fed the AMLN NASH diet or chow for 12W, biopsied and randomized (n = 12/group) to receive Vehicle (0.5% CMC, PO, QD), OCA (30 mpk), GFT-505 (3 or 10 mpk) or their combination for a further 8W while remaining on the NASH diet. Fractional area (%) calculations were performed for steatosis, galectin-3 (inflammation) and collagen 1a1 (fibrosis). Post-treatment, a portion of liver was collected for RNA Seq.

Results: Monotherapy with OCA or GFT-505 improved all histological parameters and both combinations exerted greater effects than either monotherapy ($p < 0.05$ vs. OCA and GFT-505; table). Monotherapy with FXR or PPARα/δ agonism elicited distinct expression profiles and the combination led to additive decreases in inflammatory and fibrotic genes and pathways.

	Steatosis (%)		Galectin-3 (%)		Collagen-1a1 (%)	
Treatment (mpk)	Baseline	Post-Rx	Baseline	Post-Rx	Baseline	Post-Rx
Vehicle	38.8 ± 2.5	31.8 ± 3.2	10.8 ± 1.0	10.2 ± 1.8	5.5 ± 1.7	13.8 ± 2.4
OCA (30)	38.8 ± 4.1	15.2 ± 3.2*	11.3 ± 1.9	6.8 ± 1.0*	6.0 ± 2.3	10.5 ± 1.5*
GFT-505 (3)	38.8 ± 2.8	22.8 ± 3.8*	10.9 ± 1.6	7.7 ± 2.5	5.7 ± 1.7	9.7 ± 2.7*
GFT-505 (10)	38.6 ± 4.4	19.3 ± 5.6*	11.5 ± 1.5	6.1 ± 1.8*	5.6 ± 2.3	8.9 ± 2.0*
OCA + GFT-505 (3)	36.3 ± 3.3	4.7 ± 3.1*,#	10.2 ± 1.7	3.6 ± 1.2*,#	5.4 ± 2.4	6.3 ± 1.5*,#
OCA + GFT-505 (10)	38.3 ± 1.1	2.4 ± 1.7*,#	10.3 ± 1.8	3.4 ± 0.6*,#	5.1 ± 2.0	6.0 ± 1.2*,#

*p < 0.05 vs. vehicle controls.
#p < 0.05 vs. both monotherapies.

Conclusion: OCA or GFT-505 monotherapy improved multiple histological parameters and combination therapy elicited clear additive (or greater) effects with normalization of steatosis and inflammation to levels below baseline and prevention of fibrosis progression. Histologic additivity was associated with additive improvements for individual genes and core NASH pathways. These preclinical findings provide additional proof-of-concept for combined FXR/PPAR-based therapies using a different NASH model and treatment regimen.

THU-480

Evaluation of the rodent Octodon degus as a pre-clinical model of liver fibrosis

S. Brockbank[1], P. Cogram[2], D. Leeming[3], S.T. Hjuler[3], S. Cruwys[4].
[1]*Grunenthal, Innovative Medicines Unit;* [2]*GeN, Chile;* [3]*Nordic Bioscience, Fibrosis Biology and Biomarkers, Copenhagen, Denmark;* [4]*Grunenthal, Innovative Medicines Unit, Aachen, Germany*
Email: sarah.brockbank@grunenthal.com

Background and Aims: Models of NASH, driven by mechanisms which reflect pathogenesis of human disease and which exhibit advanced steatohepatitis combined with insulin resistance are in short supply. Attempts to recapitulate human disease often involve the use of non-physiological drivers over a long duration. The *Octodon degus* is naturally insulin resistant caviomorph rodent which can readily develop diabetes mellitus on a diet of simple fruit sugars, and in a preliminary study administration of an atherogenic diet (AD) induced fatty liver disease. This study aims to characterise the rodent *O degus* as a natural preclinical model for the study of NASH.

Method: Adult O degus (aged 12m) were included in the study. One group (n = 10) was fed AD (0.25% Cholesterol/6% Palm Oil), titrated from 0.5% to complete AD over 6 weeks (weeks 1 & 2 @ 50%, week 3 & 4 @ 70% and week 5 & 6 @ 100% AD). The control group (n = 10) was fed with standard chow diet. Blood was obtained at basal, 2, 4 and 6 weeks for assessment of clinically relevant serum biomarkers (Pro-C3, C3M). At termination (6 weeks) blood profile of lipids, hepatic enzymes and histological analysis of the liver was undertaken using 3 stains: hematoxylin-eosin, Masson's trichrome and oil red.

Results: Animals retained weight over the duration of the study, while those on the high fat diet showed a 2 fold increase in liver-to-body weight ratio ($p < 0.0001$). The high fat diet induced a notable hepatic steatosis at 6 weeks and increased liver triglyceride concentration 2 fold ($p < 0.0002$), total cholesterol (150% increase, $p < 0.0001$) and LDL increased by 5 fold ($p < 0.0001$) whereas HDL was significantly decreased ($p < 0.0001$). The blood hepatic profile showed significant increases ($p < 0.0001$) in γ-glutamyltransferase, aspartate aminotransferase and alanine aminotransferase. Serum biomarkers (Pro-C3, C3M) were significantly increased on AD and fibrosis induced after 6 weeks, as assessed by histology.

Conclusion: Here we describe the O degus as a natural model of NASH which develops over a short duration and replicates features of the human disease. Features including insulin resistance, advanced steatohepatitis and fibrosis, along with elevation of clinically relevant biomarkers make this a potential preclinical model for drug discovery programs and translation to the clinic.

THU-481

Impact of proprotein convertase subtilisin/kexin type 7 genetic variation in patients with non-alcoholic fatty liver disease

P. Dongiovanni[1], M. Meroni[2,3], A. Cespiati[2,3], G.A. Baselli[4], R. Rametta[4], S. Pelusi[2,3], V. Borroni[2], A.L. Fracanzani[5], S. Badiali[6], J. Pihlajamaki[7], S. Romeo[8], S. Petta[9], A. Craxi[9], V. Nobili[10], S. Fargion[3,11], L. Valenti[3,11].
[1]*Fondazione IRCCS Cà Granda, Milano; University of Milan, Italy, Internal Medicine, Milano, Italy;* [2]*Fondazione IRCCS Cà Granda, Ospedale Policlinico, Milano, Department of Pathophysiology and Transplantation, University of Milan, Milano, Italy;* [3]*University of Milan, Milano, Italy;* [4]*Fondazione IRCCS Cà Granda, University of Milan, Italy, Internal Medicine, Italy;* [5]*Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Italy;* [6]*Fondazione IRCCS Cà Granda, Ospedale Policlinico, Milano, Surgery, Milano, Italy;* [7]*University of Eastern Finland, Kuopio, Finland, Department of Public Health and Clinical Nutrition, Finland;* [8]*University of Gothenburg, Molecular and Clinical Medicine, Sweden;* [9]*University of Palermo, Department of Gastroenterology, Italy;* [10]*Bambino Gesu Pediatric Hospital, Rome, Hepatometabolic Unit, Italy;*

[11]*Fondazione IRCCS Cà Granda, Ospedale Policlinico, Milano, Department of Pathophysiology and Transplantation, University of Milan, Italy*
Email: luca.valenti@unimi.it

Background and Aims: Inherited factors modify the risk of non-alcoholic fatty liver disease (NAFLD), steatohepatitis (NASH) and liver fibrosis by regulating hepatocellular lipid handling. Deregulation of iron and lipoprotein metabolism are typical features of NAFLD. The rs236918 G > C intron variant in the Proprotein Convertase Subtilisin/Kexin Type 7 (PCSK7) gene has been associated with liver fibrosis in hereditary hemochromatosis and its variation influences circulating lipid levels. Aim was to examine the impact of the rs236918 PCSK7 variant on iron metabolism, metabolic traits and liver disease in patients at risk of NASH.
Method: We genotyped rs236918 in 1801 European NAFLD patients from the Liver Biopsy Cross-Sectional Cohort (LBC). Liver damage was assessed according to NAS, PCSK7 hepatic expression by qRT-PCR, protein and circulating levels by Western blot and ELISA respectively, in a subset (n = 78).
Results: The C allele was associated with higher transferrin saturation (Estimate: +4.82; 0.34–9.29; p = 0.035) and circulating triglycerides (Estimate: +0.09; 0.007–0.17; p = 0.03). Concerning liver damage, while it had no effect on steatosis and ballooning, the C allele was independently associated with more severe lobular inflammation at multivariate analysis (Table 1). However, this did not translate in more severe fibrosis. PCSK7 was more expressed in hepatocytes than in hepatic stellate cells (p < 0.05) and gene expression correlated with *de novo lipogenesis* (p < 0.05). The rs236918 variant affected hepatic expression levels of PCSK7 alternative mRNA transcripts. Furthermore, carriers of C allele showed increased PCSK7 protein in the liver and in the circulation compared to non-carriers (p < 0.01, n = 72), and circulating PCSK7 was correlated with serum triglycerides.

Table 1: Impact of PCSK7 rs236918 variant on hepatic lobular inflammation in 1801 NAFLD patients from the LBC

	Estimate	95%CI	*p adjusted
Age, yrs	–0.0008	–0.007 to 0.005	0.80
Sex, M	+0.17	0.07–0.27	0.001
BMI, Kg/m^2	–0.02	–0.03 to –0.01	0.0002
T2DM, yes	+0.33	0.22–0.44	<0.0001
PNPLA3, I148M	+0.42	0.29–0.56	<0.0001
TM6SF2, E167K	+0.28	0.03–0.54	0.03
MBOAT7, T allele	+0.10	–0.02 to 0.23	0.11
PCSK7, C allele	+0.22	0.02–0.42	0.03

Conclusion: The PCSK7 rs236918 G > C variant may bridge hepatic inflammation with deregulation of iron metabolism and dyslipidemia in NAFLD patients. The mechanism may be related to increased PCSK7 protein levels, suggesting PCSK7 as a new therapeutic target for metabolic disorders.

THU-482

Expression profiling of 728 miRNAs in a NASH model identifies excellent correlations of hepatic and circulation miR-34a levels with histological lesions in rats and men

G. Cordonnier[1], F. Texier[1], N. Benoit[1], D. Nathalie[1], F.B. Sudrick[1], J. Brozek[1], R. Hanf[1], A. Sanyal[2]. [1]*GENFIT sa, Loos, France;* [2]*Virginia Commonwealth University, Richmond, United States*
Email: genevieve.cordonnier@genfit.com

Background: Changes in the hepatic expression of miRNAs might be instrumental in the development of non-alcoholic steatohepatitis (NASH) and fibrosis.
Aim: In order to identify miRNAs for non-invasive diagnosis of NASH, the aim of this animal study was to screen for miRNAs showing good correlations of both hepatic and circulating levels with histological lesions. Suitable miRNAs were tested for their clinical utility as new circulating biomarkers of NASH in a cohort of NAFLD patients.
Method: Wistar rats were fed a control diet (CSAA), or a choline deficient amino acid diet (CDAA) with or without 1% cholesterol for 11 weeks. Hepatic expression of 728 mature rno-miRNAs was analyzed using Affymetrix miRNA chip V4.0. The most differentially expressed miRNAs (CDAA + chol vs Control) were quantified by RT-qPCR in liver and plasma samples to assess correlations with NASH histological scores and fibrosis. Diagnostic performances of circulating levels of selected miRNAs were then compared in a cohort of NAFLD patients (GOLDEN study; n = 269).
Results: Expression array analysis of rat liver extracts revealed that 79 miRNAs were upregulated and 17 were downregulated in diseased livers (CDAA + chol vs control, FC ≥ 1.5, p ≤ 0.05). The two most upregulated miRNAs were miR-132-3p (51.7 fold, p < 0.0001), miR-34a-5p (26.2 fold, p < 0.001), while miR-122a-5p expression was not affected. RT-qPCR analyses showed that i) both hepatic and plasma levels of miR-34a strongly increased with NASH histological scores (NAS, steatosis, lobular inflammation, hepatocyte ballooning) and fibrosis stage, ii) for miR-122a, there was a weak negative correlation between hepatic levels and histological scores but, in contrast, there was a strong positive correlation when considering plasma levels. In NAFLD patients, serum level of miR-34a-5p increased with NAS and fibrosis stage whereas serum level of miR-122a-5p increased with NAS, but not with fibrosis stage. Finally, when measuring serum levels, miR-34a-5p was more potent than miR-122a-5p and miR132-3p in detection of patients with active disease and significant fibrosis (NAS ≥ 4 and F ≥ 2): AUROC = 0.74 vs 0.59 vs 0.58.
Conclusion: Hepatic miRNA expression is profoundly modified in NASH, supporting a major role in NASH and liver fibrosis. Compared to other miRNAs and notably miR-122a-5p, both hepatic and circulating levels of miR-34a are significantly correlated with the hepatic lesions, making serum miR-34a a potent biomarker with clinical utility for non-invasive diagnosis of NASH.

THU-483

Discovery of Inhibitors of NLRP3 inflammasome assembly for the treatment of NASH and liver fibrosis

J. Veal[1], C. Mcbride[1], M. Lazic[1], D. Povero[1], G. Ambrus[1], A. Santini[1], R. Stansfield[1], L. Trzoss[1], C.D. Johnson[2], J. Stafford[1], A. Feldstein[2]. [1]*Jecure Therapeutics Inc., San Diego, United States;* [2]*University of California at San Diego, Pediatrics, La Jolla, United States*
Email: jveal@jecuretx.com

Background and Aims: Persistent NLRP3 inflammasome activation has been shown to result in caspase-1 dependent hepatocyte pyroptosis and transdifferentiation/activation of hepatic stellate cells. Here we describe the discovery of novel small-molecule inhibitors of the NLRP3 inflammasome that have the potential to block the progression of NASH and liver fibrosis.
Method: Phenotypic screening was used to identify selective inhibitors of the NLRP3 inflammasome. Compounds were tested on human peripheral blood mononuclear cells (PBMCs), human Kupffer cells (KCs), and mouse bone marrow-derived macrophages (BMDMs). Secreted levels of IL-1β, IL-18 and TNFα were measured in response to distinct inflammasome activators. Effects on pyroptotic cell death and caspase activation were evaluated, and immunofluorescence imaging was used to characterize the mechanism of action of the inhibitor class. Pharmacokinetic profiles of selected compounds were determined in mice. In vivo efficacy studies were performed in *Nlrp3*$^{A350V/+}$*CreT* Muckle Wells Syndrome (MWS) and diet-induced NASH models.
Results: We identified novel molecules that dose dependently inhibited the cellular release of IL-1β and IL-18, following NLRP3 inflammasome stimulation. Lead molecules JT194 and JT349 demonstrated sub-100 nM cellular potency. Production of TNFα was not affected by the compounds. IL-1β secretion was blocked by the inhibitors when cells were stimulated by NLRP3 activators, nigericin or ATP, but not by NLRP1, AIM2 or NLRC4 specific stimuli. Inhibition of cellular caspase-1 activity, but not caspase enzymatic function, was

also observed. Analysis of cell viability in treated PBMCs and BMDMs showed a cytoprotective effect consistent with an anti-pyroptotic phenotype. Immunofluorescence for ASC in stimulated cells detected Nlrp3-ASC specks whose formation were abrogated by JT194 and JT349 treatment, revealing an activity of these compounds on the assembly of the NLPR3 inflammasome complex. Dosed orally in mice, JT194 and JT349 each provided excellent plasma exposure, and in vivo blockade of IL-1β production was demonstrated following a single dose below 5 mg/kg in a mouse acute LPS + ATP challenge model. In both *Nlrp3*$^{A350V/+}$*CreT* mouse and diet induced NASH models, daily oral administration of JT194 was well tolerated and significantly inhibited markers of inflammation and liver fibrosis.
Conclusion: Our studies identified novel compounds JT194 and JT349 that potently and selectively inhibited NLRP3 inflammasome activation in vitro and in vivo. These NLRP3 assembly inhibitors demonstrated favorable pharmacokinetics in mice suitable for oral administration, and efficacy was observed in advanced NASH and liver fibrosis studies. The results support advancement of NLRP3 inflammasome inhibitors into further safety studies and ultimately into clinical trials.

THU-484
Four-and-a-half LIM-domain protein affects diet induced (hepatic) steatosis and lipid droplet formation
J. Sommer, C. Hellerbrand. *Friedrich-Alexander University Erlangen-Nürnberg, Institute of Biochemistry, Erlangen, Germany*
Email: claus.hellerbrand@fau.de

Background: The four-and-a-half LIM-domain protein 2 (FHL2) is expressed in almost all tissues, including the liver, and exerts tissue- and cell context- specific functions. It acts as transcriptional cofactor and has already been shown to interact with >50 proteins, amongst them signaling cascade proteins as well as proteins involved in the regulation of proliferation and apoptosis. Some studies revealed a role of FHL2 in liver disease and hepatocellular carcinoma, but its impact on (hepatic) lipid metabolism or non-alcoholic fatty liver disease (NAFLD) has not yet been studied.
The aim of this study was to investigate the role of FHL2 in NAFLD.
Methods and Results: Starting 8 weeks after birth, male FHL2 wildtype (wt) and knockout (FHL2$^{-/-}$) mice (littermates) were fed with a Western-type diet (WTD) containing 38% fat, 30% sucrose and 0.2% cholesterol for 19 weeks. Controls were fed with standard chow. Basal body weight did not differ between genotypes. However, WTD-induced weight gain was decreased in FHL2$^{-/-}$ compared to wt mice, although food-consumption and fatty-acid (FA) concentration in faeces did not differ, indicative for similar FA-uptake. Glucose tolerance was not impaired in WTD-fed FHL2$^{-/-}$ mice in contrast to their wt counterparts, which exhibited starting insulin resistance. Adipose tissue mass was massively increased in WTD-fed FHL2$^{-/-}$ mice and revealed significantly increased expression of fat-specific protein 27 (FSP27), annexin A6 (Anxa6) and genes of the perilipin family, which are all modulating lipid droplet formation and maturation as well as their lipolysis. Also in the liver, triglycerides (TG) levels were significantly decreased in FHL2$^{-/-}$ mice compared to wt mice, while cholesterol and bile acids (BA) levels did not differ between genotypes. Despite reduced steatosis, WTD-induced pro-inflammatory gene expression was lower in FHL2$^{-/-}$ mice compared to wt mice. Also *in vitro*, primary hepatocytes (mpH) isolated from FHL2$^{-/-}$ mice had lower basal TG levels compared to wt mpH. Similarly, siRNA-mediated FHL2 suppression in the human hepatoma cell line HepG2 caused reduced cellular TG levels. Interestingly, *in vitro* as *in vivo* lipid droplets appeared significantly smaller in FHL2 depleted hepatocytes, and fitting to this, revealed decreased perilipin 2 (Plin2) expression.
Conclusion: FHL2 quantitatively and qualitatively affects (diet) induced (hepatic) steatosis. Analysis of the underlying mechanisms may lead to the identification of new prognostic markers or therapeutic targets for the development and progression of NAFLD.

THU-485
Hepatic effects of NS-0200 (Leucine-Metformin-Sildenafil) in an obese mouse model of diet-induced and biopsy-confirmed NASH
M. Zemel[1], O. Flores[1], K. Rigbolt[2], M. Illemann[2], P.S. Petersen[2], M. Feigh[2]. *[1]NuSIrt Biopharma, R&D, Knoxville, United States; [2]Gubra, Hersholm, Denmark*
Email: mzemel@nusirt.com

Background and Aims: NS-0200, a combination of leucine (Leu) with low-doses of metformin (Met) and sildenafil (Sil) that synergize to activate Sirt1-AMPK signaling, is currently in clinical investigation for the treatment of nonalcoholic steatohepatitis (NASH). The objective of the present study was to compare the histopathological effects of NS-0200 with two related leucine combinations (leucine-metformin and leucine-sildenafil) and to compare the effects of the combinations on relevant gene-regulatory pathways in an obese rodent model of diet-induced and biopsy-confirmed NASH (the Gubra DIO-NASH mouse).
Method: NASH was induced by feeding C57BL/6J mice a diet high in trans-fat, fructose and cholesterol (AMLN diet) for 35 weeks. This was followed by liver biopsy to confirm NASH and fibrosis ≥ stage 1. Col1a1 staining was used for stratification of mice into treatment groups for 12 weeks: vehicle; low-fat chow reversal; Leu (1.2 g/kg)+ Sil (1.25–5.0 g/kg); Leu + Met (50 mg/kg)+ Sil (1.25–5.0 mg/kg); or chow vehicle (no NASH induction). Following termination, liver steatosis, inflammation, ballooning and fibrosis stages were assessed, liver Col1a1 and Galectin-3 measured by immunohistochemistry and morphometry and a number of metabolic parameters were measured. The liver was analyzed using RNAseq.
Results: Leu + Met, Leu + Sil and Leu + Met + Sil significantly regressed steatosis, inflammation and ballooning at all doses, and approached the efficacy of the low-fat chow reversal diet. However, only Leu + Met + Sil effectively regressed fibrosis at the lowest Sil dose, with comparable effects only at the highest doses of Leu + Sil in the absence of Met; Leu + Met exerted no independent effect on fibrosis. Col1a1 staining was reduced by Leu + Met + Sil comparable to the effects of chow reversal, while Leu + Met and Leu + Sil exerted no significant effects. Intervention with the Leu + Met + Sil induced robust gene expression profile changes, with notable significant inhibition of stellate cell activation and monocyte recruitment pathways, while Leu + Met and Leu + Sil exerted only minor effects on a small number of genes.
Conclusion: These data indicate that Leu + Met, Leu + Sil and Leu + Met + Sil (NS-0200) all significantly regress steatosis, inflammation and ballooning in this DIO-NASH model, while only NS-0200 exhibited a robust reduction in Col1a1 protein and gene expression, as well as in stellate cell activation pathways, resulting in significant fibrosis regression.

THU-486
Comorbidity-specific augmented hepatic injury in a murine model of obesity-induced NAFLD and peritoneal sepsis
P. Horn[1,2], S. Vlaic[3], R. Steidl[4], M. Bläss[4,5], R.A. Claus[1,4]. *[1]Center for Sepsis Control and Care, Jena University Hospital; [2]Department of Internal Medicine IV, Jena University Hospital; [3]Research Group Systems Biology/Bioinformatics, Leibniz Institute for Natural Product Research and Infection Biology (Hans Knöll Institute), Jena; [4]Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena; [5]Institute of Precision Medicine, Medical and Life Sciences Faculty, Furtwangen University, Villingen-Schwenningen*
Email: paul.horn@med.uni-jena.de

Background and Aims: Obesity and non-alcoholic fatty liver disease (NAFLD) are increasingly prevalent in the general population and may have a major impact on development and resolution of sepsis-induced hepatic organ dysfunction. Though increased sepsis-induced mortality has been shown in animal models of obesity, underlying mechanisms and specific influence of NAFLD on liver dysfunction in sepsis have not been studied yet. We aimed to implement a murine

comorbidity model of obesity-induced NAFLD and polymicrobial sepsis to study comorbidity specific signaling pathways.
Method: Six weeks old male C57BL/6 mice were fed with control diet (CD) or high fat diet (HFD) for twelve weeks to induce a metabolic-syndrome (MeS)-like phenotype. Mice were repeatedly weighted and intraperitoneal glucose tolerance test was performed. Sepsis was induced by peritoneal contamination and infection (PCI). At baseline, six and 24 hours after sepsis induction, blood and liver samples were collected. We measured laboratory markers of organ function and metabolism, performed H&E liver histology and real-time quantitative PCR (RTqPCR). Using microarray transcriptome data, we performed gene enrichment analyses of differentially expressed genes.
Results: By HFD we induced a MeS-like phenotype, constituting increased body weight, impaired glucose tolerance and hypercholesterolemia. This was accompanied by severe liver steatosis without alterations in ALT or bilirubin levels at baseline. Peritoneal sepsis lead to a significantly increased 72 h mortality in the HFD group (93% vs 47%, $p = 0.022$). We observed increased levels of ALT and bilirubin 24 h after sepsis induction in HFD, indicating increased sepsis-induced hepatic injury. In contrast, renal function was not altered in HFD compared to CD mice 24 h after sepsis induction. Gene enrichment analysis of differentially expressed genes associated with HFD-specific impact on sepsis revealed comorbidity specific regulation predominantly in metabolic pathways besides regulation of inflammatory processes. Compared to CD, we observed a more sustained effect of HFD on sepsis-induced downregulation of hepatic Cyp1a1 and Mrp2 mRNA in confirmatory RTqPCR, pointing towards a more reduced drug metabolism capacity in NAFLD comorbidity.
Conclusion: We evaluated a comorbidity model of obesity-induced NAFLD and peritoneal sepsis reflecting higher mortality rate and increased severity of sepsis-induced hepatic injury. It may serve to discover comorbidity-specific signaling pathways and new therapeutic targets.

THU-487
The anti-inflammatory and anto-fibrogenic effects of namodenoson in NAFLD/NASH animal models

P. Fishman[1], A. Salhab[2], S. Cohen[1], J. Amer[2], I. Itzhak[1], F. Barer[1], R. Safadi[2]. *[1]CanFite Biopharma; [2]Hadassah University Hospital*
Email: pnina@canfite.co.il

Background and Aims: Namodenoson is a novel drug candidate, currently in Phase II clinical study for the treatment of NAFLD/NASH. The drug targets the Gi protein associated A3 adenosine receptor (A3AR), known to mediate differential effects on pathological and normal cells. Namodenoson is an A3AR small molecule agonist that acts as a robust anti-inflammatory agent in the Con. A induced liver inflammation model and at the same time possesses an hepato-protective effect in ischemia-reperfusion and partial hepatectomy models. Based on this dual effect, it has been assumed that namodenoson will positively act as an anti-NAFLD/NASH agent.
Method: NASH model was induced in C57BL/6 mice by injection of streptozotocin two days after birth followed by high fat diet feeding since age of 4 weeks. Namodenoson or vehicle administered orally along 6–9 weeks of age. Hepatic fibrosis model was induced in C57BL/6 mice by intraperitoneal Carbon Tetrachloride (CCl_4) injections, twice weekly, for 6 weeks. Namodenoson 100 μg/kg was injected intra peritoneally. 24 hours after each CCl_4 dosing.
Results: In the NASH model, the namodenoson treated group showed a significant decrease in steatosis, ballooning and lobular inflammation compared to the vehicle treated one. Furthermore, the drug reduced liver-to-body weight ratio ($p = 0.05$) and decreased ALT and Triglyceride levels. Moreover, a significant decrease in CK-18 and increase in adiponectin were also noted. In the CCl_4 model, normal macroscopic liver with no ascites was observed in the namodenoson treated group, and a decrease in ALT serum levels was found as well. Activated pro-fibrogenic NKT ($NK1.1^+$ $CD3^+$ $CD107a^+$) cell numbers were increased from 16.8 ± 3% (naïve) to 76 ± 1.2 ($p < 0.0001$) following CCl_4 induction and alleviated to 14.9 ± 11.4% ($p = 0.001$) after namodenoson therapy. Down-regulation of A3AR protein expression level was followed by a decrease in p-STAT-1, PI3K and αSMA in the liver extracts derived from the namodenoson treated animals.
Conclusion: The robust anti-NAFLD/NASH effect of namodenoson was mediated via a molecular mechanism leading to a decrease in αSMA and CK-18. These data together with the anti-steatotic effect, are positioning namodenoson as a potential drug candidate to combat this liver disease.

THU-488
Histopathologic assessment of fatty liver progression in a rodent model of chronic intake of high-fat diet, ethanol or both

A.R. Mendoza[1], A. Campos-Espinosa[1], M. Galicia-Moreno[2], B. León-Mancilla[2], T.A. Arévalo-Sánchez[1], K.Z.M. Ávila[3], I.I. Romero-Bello[1], R.O. Dorothy[2], A. Pérez-Torres[4], C. Guzman[1], G. Gutierrez-Reyes[2]. *[1]Hospital General de México, Unidad de Medicina Experimental, Laboratorio de Hígado, Páncreas y Motilidad, Mexico City, Mexico; [2]Universidad Nacional Autónoma de México, Facultad de Medicina, Laboratorio de Hígado, Páncreas y Motilidad, Mexico City, Mexico; [3]Universidad Nacional Autónoma de Méx, Laboratorio de Hígado, Páncreas y Mo, Mexico City, Mexico; [4]Universidad Nacional Autónoma de México, Facultad de Medicina, FSIPyM Depto. Biología Celular y Tisular, Mexico City, Mexico*
Email: carova@prodigy.net.mx

Background and Aims: Obesity is highly prevalent risk factor for non-alcoholic fatty liver disease (NAFLD) worldwide. In developing and developed countries, chronic alcohol intake, another cause of fatty liver and cirrhosis, is common among obese patients. Both etiologies have been independently studied for fatty liver disease and fibrosis development, and share physiopathologic mechanism during disease progression. We aimed to describe the histopathologic liver features of the coincidence of these insults in the mouse with chronic intake of a high-fat diet (HF), ethanol (OH) or both.
Method: C57BL/6 male mice aged 10 weeks and weighing 25 ± 2 g were randomly assigned to received either Chow (control diet, C) or HF (19% lard) and water or OH (20% v/v). Four groups were obtained and maintained for 4 or 6 months. Two additional groups were included with an initial insult (HFD or OH) during 4 months followed by a secondary insult (OH or HFD) during further 4 or 6 months. Both food and beverage were allowed *ad libitum*. Weight gain, food and beverage intake were recorded. Liver samples were collected in tissue-tek or neutral buffered formalin and embedded in paraffin. Paraffin sections were stained by hematoxyline-eosin, Masson's tricrhome and Wilder for reticular fibres. Frozen tissue-tek sections were stained by Oil Red O.
Results: Weight gain was higher in mice receiving HF, food intake was decreased in those drinking OH. Histological changes were observed according to the experimental group. No evident signs of steatosis were observed in COH group; however reticular fibres were present at the sinusoidal space. At 4 months, livers in the HF group showed microvesicular steatosis with 30.6 ± 5.6% of fat and by 6 months 39.5 ± 4.4% of fat accompanied by ballooning and inflammation were observed. Mice receiving both insults simultaneously showed increased macro and microvesicular steatosis in zones 1 and 3 of the acinus. Interestingly, mice receiving a primary insult of OH followed by an insult of HF (COH→HFW) exhibited the highest amount of liver fat compared to insults alone, exhibiting macrovesicular steatosis (4 months: 35.4 ± 2.6; 6 months: 54.7 ± 6.5%) and ballooning by 6 months. In contrast, the group with a primary insult of HF followed by OH (HFW→COH) showed low steatosis and reticular fibres.
Conclusion: Steatosis and other architectural changes in the liver depend on the interaction of the insults received. High fat diet is able to induce NASH after appropriate time. The order of the insults matters, in HFW→COH, reversion of steatosis induced by HF occurred

during OH exposition but not the opposite, in COH→HFW reticular fibre were still present after HF exposition. Our data suggest that, at least in mice, a chronic alcohol intake period followed by an obesogenic diet induces severer steatosis when compared to independent insults.

Acknowledgement: This work was partially funded by Conacyt (CB-221137) México.

THU-489

Nicotinamide, not N1 methylnicotinamide, ameliorates hepatic steatosis via NAD-depended sirtuin activation

S. Morizono[1], K. Ohe[2], S. Kiso[3], K. Tanabe[4], N. Ookubo[5], N. Togawa[6], M. Enjoji[2], M. Nakamuta[7]. *[1]Saiseikai Fukuoka General Hospital, Department of Gastroenterology, Japan; [2]Faculty of Pharmaceutical Sciences, Fukuoka University, Department of Clinical Pharmacology, Fukuoka, Japan; [3]Graduate School of Medicine, Osaka University, Department of Community Medicine, Suita, Japan; [4]LSI Medience Corporation, Medical Solution Promotion Department, Tokyo, Japan; [5]LSI Medience Corporation, Planning and Coordination Department, Tokyo, Japan; [6]Mitsubishi Chemical Corporation, Bio-Device Group,Tsurumi R&D Center, Tokyo, Japan; [7]National Hospital Organization Kyushu Medical Center, Department of Gastroenterology, Fukuoka, Japan*
Email: morizono@saiseikai-hp.chuo.fukuoka.jp

Background and Aims: Nicotinamide (NAM), a metabolite of NAD catalyzed by Sirts, is reutilized for NAD synthesis via nicotinamide mononucleotide (NMN) by nicotinamide phosphoribosyltransferase (Nampt) (Fig. 1). NAM is also converted to N^1 methylnicotinamide (MNAM) by nicotinamide N-methyltransferase (Nnmt) using S-adenosylmethionine (SAM). SAM is a major methyl group donor and is involved in the production of polyamine, phosphatidylcholine, and sarcosine (methylglycine) as well as MNAM. MNAM produced by Nnmt was reported to improve hepatic steatosis (Nat Med. 2015;21:887). On the other hand, the knockdown of Nnmt was reported to protect the liver from hepatic steatosis (Nature. 2014;508:258). We first investigated whether NAM has a protective effect on hepatic steatosis, and then whether NAM works through the NMN~NAD or MNAM pathway.

Method: C57BL/6J mice (n = 20) were divided into four groups and fed with: normal diet (ND); ND + NAM (NAM mixed with ND to 0.1% wt/wt); high fat diet (HFD); HFD + NAM for 8 weeks. The contents of NAM-related materials in the liver, NAM, NAN, NAD, MNAM, SAM, S-adenosylhomocysteine (SAH), spermidine, glycine, sarcosine were measured by LC/MS (Fig. 1). The expression of NAD metabolism-related genes was evaluated by real-time RT-PCR. Finally, microbiota analysis was performed using a deep sequencer.

Results: NAM histologically ameliorated hepatic steatosis as well as body weight gain caused by HFD. With regard to hepatic NAM-related contents, NAD was decreased in HFD + NAM compared to HFD, while MNAM, SAM, SAH, spermidine, glycine, and sarcosine were unchanged. The gene expression of Nnmt was unchanged but that of Nampt was increased in HFD + NAM compared to HFD. These results indicated that NAM converted into NMN rather than MNAM to supply NAD, leading to the activation of Sirts. In line with this, NAM enhanced the expression of Sirt 3, 4, and 5, known for their involvement in lipid metabolism (e.g. beta oxidation in the mitochondria) as well as Sirt 1. Furthermore, NAM enhanced the expression of beta oxidation- and ketone body formation-related genes; oppositely, it suppressed that of fatty acid synthesis-related genes. In microbiota analysis, adding NAM to HFD reduced Proteobacteria and Bacteroidetes, and increased Farmacutes and Actinobacteria at phylum level. Interestingly, Coriobacteria and Erysipelotrichi class was increased in Actionbacteria, and Farmacutes phylum, respectively.

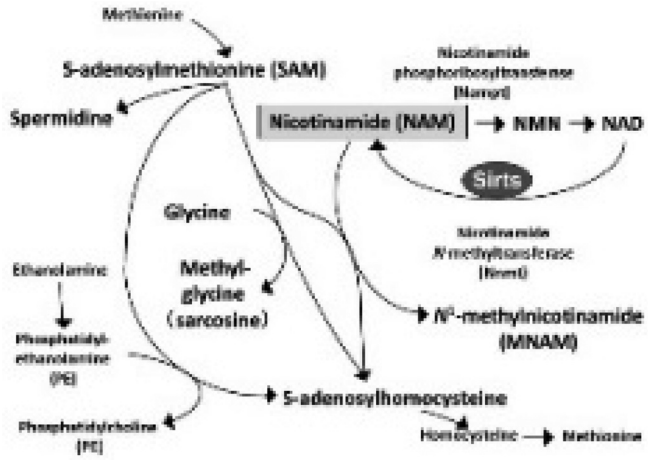


Figure 1:

Conclusion: NAM but not MNAM ameliorated hepatic steatosis through the activation of Sirts, leading to enhanced fatty acid oxidation and suppressed fatty acid oxidation, and also changed microbiota composition. Our results suggest that NAM might have a novel therapeutic application for NAFLD/NASH.

THU-490

Elafibranor and obeticholic acid differentially alter NASH and lipid metabolism in diet-induced NASH mouse and hamster models

F. Briand, E. Brousseau, N. Faresse, M. Pont, C. Costard, I. Urbain, M. Quinsat, T. Sulpice. *PHYSIOGENEX, France*
Email: f.briand@physiogenex.com

Background and Aims: Non-alcoholic steato-hepatitis (NASH) mouse models present limitations for evaluating drugs, due to a different lipid/bile acids metabolism as compared with human. To overcome this issue, we developed a Diet-induced NASH (DIN) hamster model with features of human-like lipid/bile acids metabolism. Here we evaluated the benchmarks elafibranor (GFT505) and obeticholic acid (OCA), in both DIN mouse and hamster models.

Method: Effects of GFT505 and OCA both at 15 mg/kg/day were evaluated in DIN C57BL6/J mice fed a high fat/cholesterol/fructose rich diet, or DIN hamsters fed a cafeteria diet. Fasting lipids assays, liver histology and NAS scoring were performed at the end of treatment.

Results: In the DIN mouse, OCA and GFT505 significantly reduced total NAS score (both $p < 0.001$ vs. vehicle), including reduced steatosis, hepatocyte ballooning, and fibrosis, while inflammation was only reduced by OCA. Plasma total cholesterol (TC) and LDL-C levels were reduced by 33% and 45% with OCA (both $p < 0.001$ vs. vehicle). GFT505 did not change plasma TC but reduced plasma triglycerides (−32%) and strongly increased plasma ketone bodies (+307%) levels (both $p < 0.001$ vs. vehicle), in line with an inhibition of diet-induced body weight gain.

In the DIN hamster, both OCA and GFT505 reduced total NAS score, including significant reduction in inflammation and trends towards lower ballooning scores, while no significant change was observed for liver steatosis and fibrosis. Hamsters treated with OCA showed significantly higher plasma cholesteryl ester transfer protein activity by 18%, higher LDL-C levels by 27%, and lower HDL-C levels by 20% vs. vehicle. Trends towards lower LDL-receptor and higher SR-BI hepatic protein levels were also observed. GFT505 reduced plasma TC, triglycerides and free fatty acids levels by 13, 10 and 16%, while plasma ketone bodies levels increased by 35% (all $p < 0.05$ vs. vehicle).

Conclusion: OCA and GFT505 differentially alter lipid metabolism and NASH depending on the DIN model. While both drugs markedly improved lipid profile and NASH in DIN mice, moderate improvements were also seen in DIN hamsters. Importantly, the DIN hamster

is the only model showing the same dyslipidemic effect observed in humans treated with OCA. For better translation to human, drug development should not be limited to mouse, but rather extended with models showing a lipid and NASH profile closer to human, such as the DIN hamster.

THU-491

Characterization of ASK1 signaling in human NASH liver and human hepatic stellate cells

G. Budas, F. Wu, S. Turner, A. Zagorska, L. Li, D. Breckenridge. *Gilead Sciences Inc, Foster City, United States*
Email: grant.budas@gilead.com

Background and Aims: Selonsertib is a first-in-class, small molecule inhibitor of ASK1 that is in clinical development for the treatment of NASH. ASK1 is a redox-sensitive kinase that is activated by diverse pathological stimuli including oxidative stress. Activation of ASK1 causes phosphorylation and activation of JNK and p38 MAP kinases, which are known to promote liver fibrosis by inducing hepatocyte apoptosis, hepatic inflammation and myofibroblast activation. In the current study, we evaluated ASK1 pathway activity and cell-specific localization in human NASH liver biopsies and characterized ASK1-dependent signaling and gene expression in human hepatic stellate cells (HSCs).
Method: Liver biopsies were obtained from patients enrolled in a Phase 2 trial evaluating the safety and efficacy of selonsertib in NASH (GS-US-384-1497). Multiplex immunofluorescence was used to evaluate hepatic p-p38 (a marker of ASK1 activation), and its co-localization with markers of activated myofibroblasts including alpha-smooth muscle actin (α-SMA) and fibroblast activated protein (FAP). To characterize ASK1-regulated genes in human HSCs, LX-2 cells were transfected for 24 hours with an adenoviral construct containing human ASK1 in the absence or presence of selonsertib (1μM), then subjected to RNA-seq to delineate differentially expressed genes (fold-change >2 compared to adenoviral vector control, $p < 0.05$). Pathway enrichment analysis was used to identify major gene signatures regulated by ASK1.
Results: p-p38 was localized to hepatocytes, immune cells and fibroblasts in human NASH liver biopsies. Multiplex immunofluorescence demonstrated that p-p38 was co-localized with cells positive for both FAP and α-SMA, indicative of ASK1 pathway activity in activated myofibroblasts. Adenoviral overexpression of ASK1 in human HSCs increased p38 and JNK phosphorylation and resulted in a significant upregulation of stress-response genes including those associated with cytokine-mediated pro-inflammatory signaling (IL-1β, IL-11, and IL-17F, all $p < 0.05$ vs. control). Selonsertib blocked ASK1-induced p38 and JNK phosphorylation and normalized ASK1-dependent gene expression.
Conclusion: ASK1 pathway activity is increased in human NASH and localizes to hepatocytes, immune cells and activated hepatic myofibroblasts. ASK1 overexpression in HSCs causes upregulation of genes associated with stress response and pro-inflammatory signaling. These data provide mechanistic insight into the pathological role of ASK1 in NASH and support the evaluation of selonsertib in patients with NASH and advanced fibrosis.

THU-492

CD4+ RORgt+ T cells, CD4+ T-bet+ T cells, CD4+ CD25+ Foxp3+ T cells and CD8+ T cells are differentially altered in liver and adipose tissue of mice fed a high-fat high-fructose diet in a time-dependent manner

M. Van Herck[1,2], L. Vonghia[1,2], P. Michielsen[1,2], C. Bridts[3], D. Ebo[3,4], J. De Man[1], B. De Winter[1], S. Francque[1,2]. *[1]University of Antwerp, Laboratory of Experimental Medicine and Pediatrics, Division of Gastroenterology and Hepatology, Antwerp, Belgium; [2]Antwerp University Hospital, Gastroenterology and Hepatology, Edegem, Belgium; [3]University of Antwerp, Translational Pathophysiological Research, Division of Immunology and Allergology, Antwerp, Belgium; [4]Antwerp University Hospital, Immunology and Allergology, Edegem, Belgium*
Email: mikhail.vanherck@uantwerpen.be

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a multisystem condition in which the liver, adipose tissue and the immune system are involved. T cells form a part of the adaptive immune system and can be subdivided in several subsets with differential functions. We investigated the involvement of $CD8^+$ cytotoxic T cells, T helper 1 cells (Th1, $CD4^+$ T–bet$^+$ RORγt$^-$), T helper 17 cells (Th17, $CD4^+$ T–bet$^-$ RORγt$^+$) and regulatory T cells (Treg, $CD4^+$ $CD25^+$ $Foxp3^+$) in the pathogenesis of NAFLD.
Method: Male 8-week old C57BL/6J mice were fed control diet (CD) or high-fat high-fructose diet (HFHFD) for 10, 15, 20 or 25 weeks (n = 6–8 per group). Liver tissue was assessed histologically and the NAFLD Activity Score (NAS) was calculated. T cell subsets were characterized in liver, abdominal and subcutaneous adipose tissue (AAT, SAT) via flow cytometry. $CD8^+$ and $CD4^+$ cells were expressed as percentage of $CD45^+$ $CD3^+$ cells. T–bet$^+$ RORγt$^-$, T–bet$^-$ RORγt$^+$ and $CD25^+$ $Foxp3^+$ cells were expressed as percentage of $CD3^+$ $CD4^+$ cells. For statistical analysis, mice were grouped into two time points (10–15 weeks and 20–25 weeks).
Results: Compared to CD mice, HFHFD mice became obese [Mdn body weight 44.2 g (IQR 9.3) vs. 32.2 g (IQR 4.1)] and developed NAFLD [Mdn NAS 4.0 (IQR 2.5) vs. 0.0 (IQR 1.0)]. Comparing HFHFD mice to CD mice, T-bet$^-$ RORγt$^+$ cells were present in larger numbers in liver tissue as of 10–15 weeks (Table 1). Conversely, T-bet$^+$ RORγt$^-$ cells were less numerous in liver tissue as of 10–15 weeks. This effect dissipated, however, as of 20–25 weeks. In AAT of HFHFD mice, $CD25^+$ $Foxp3^+$ cells were more numerous as of 10–15 weeks. In both AAT and SAT of HFHFD mice, $CD8^+$ cells were more abundant, but only as of 20–25 weeks. Interestingly, in AAT of HFHFD mice, a correlation existed between NAS and $CD8^+$ cells ($r = 0.575$, $p < 0.01$).

Table 1: Median percentages of tissue T cells

Median percentages of tissue T cells (IQR)	CD	HFHFD	p
Liver T-bet$^-$ RORγt$^+$ T cells			
10–15 weeks	0.6 (2.1)	3.0 (1.8)	<0.05
20–25 weeks	0.9 (1.4)	2.7 (4.5)	<0.01
Liver T-bet$^+$ RORγt$^-$ T cells			
10–15 weeks	3.2 (7.1)	0.7 (0.6)	<0.001
20–25 weeks	1.9 (1.2)	1.0 (3.2)	N.S.
AAT $CD25^+$ $Foxp3^+$ T cells			
10–15 weeks	2.0 (2.8)	17.2 (25.7)	<0.01
20–25 weeks	2.5 (3.9)	6.7 (5.7)	<0.01
AAT $CD8^+$ T cells			
10–15 weeks	17.2 (7.8)	19.1 (10.8)	N.S.
20–25 weeks	22.6 (10.7)	36.4 (7.1)	<0.001
SAT CD8+ T cells			
10–15 weeks	27.0 (12.5)	33.8 (5.6)	N.S.
20–25 weeks	29.0 (18.6)	38.0 (9.7)	<0.01

Conclusion: Differential T cell subsets seem to be implicated in various tissues involved in NAFLD in a time-dependent manner. In an early stage, $CD4^+$ T–bet$^-$ RORγt$^+$ Th17 cells were more abundant and $CD4^+$ T–bet$^+$ RORγt$^-$ Th1 cells less abundant in liver tissue of HFHFD mice, whereas $CD4^+$ $CD25^+$ $Foxp3^+$ Treg cells were more numerous in AAT of HFHFD mice. In a later stage, $CD8^+$ T cells became more abundant in both AAT and SAT of HFHFD mice. Additionally, $CD8^+$ T cells in AAT seemed to be associated with progression to a more severe disease state.

THU-493

Treatment with the Adra2a antagonist, Yohimbine, reduces fibrosis progression and liver inflammation in a NASH fibrosis rat

H. Jones[1], S.E. Andreasen[2], A. Habtesion[1], P.L. Eriksen[2], N. Davies[1], R. Jalan[1], K.L. Thomsen[2], R. Mookerjee[1]. [1]*UCL, Institute for Liver and Digestive Health, London, United Kingdom;* [2]*Aarhus University Hospital, Department of Hepatology and Gastroenterology, Denmark*
Email: helen.jones@ucl.ac.uk

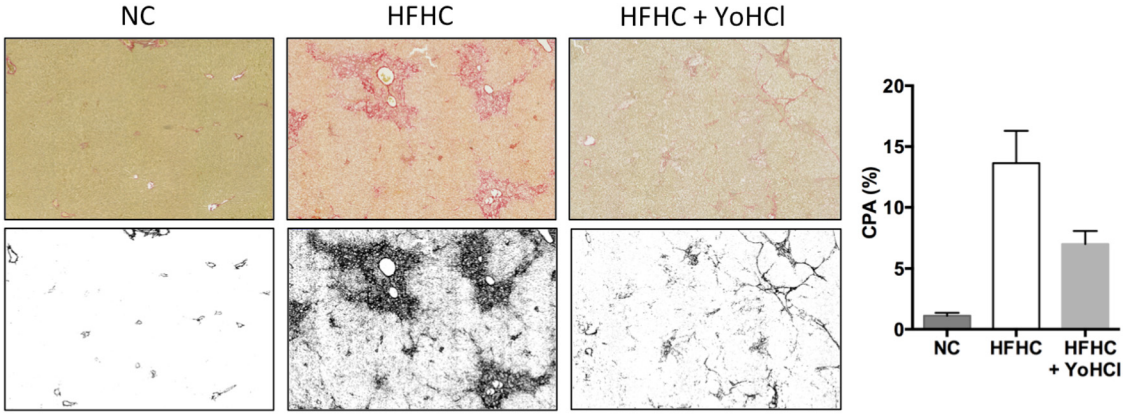
Background and Aims: Fatty liver disease (NAFLD) is increasing worldwide and is a disease spectrum from mild steatosis to non-alcoholic steatohepatitis (NASH) to cirrhosis. Fibrogenesis in NAFLD is key and correlates with long term morbidity and mortality. New treatments that slow fibrosis are needed. Noradrenaline, through alpha 2a subtype adrenergic receptors (Adra2a), may trigger development and progression of NAFLD. We previously showed blocking Adra2a signaling reduces hepatic stellate cell (HSC) activation and contractility in bile duct ligated rats. Here we studied whether blocking Adra2a, using the antagonist Yohimbine hydrochloride (YoHCl), can reduce fibrosis progression in a diet-induced NAFLD fibrosis rat model.
Method: Male Sprague Dawley rats were fed either high fat high cholesterol- inducing NASH- (HFHC; 65% kcal fat + 2% g cholesterol), or normal chow (NC; 7.5% kcal fat) diet ad libitum for 16 weeks. Rats in the HFHC group were randomized to receive YoHCl (titrated to 0.4 mg/kg daily) in drinking water for the final 8 weeks. Subsequently, formalin fixed liver sections were stained with picrosirius red. The fat proportion area (FPA) and collagen proportionate area (CPA) were measured on digitized sections using ImageJ.
Results: HFHC diet markedly increased Adra2a mRNA expression in liver tissue. HFHC diet also increased liver/body weight ratio (6.51 (0.89) vs. 2.76(0.25); $p < 0.0001$), and plasma AST (333(34.0) vs. 106 (24.5) U/L; $p < 0.0001$) compared to NC. Furthermore, the HFHC fed animals had higher FPA (23.7(3.37) vs. 1.89(1.28) %; $p < 0.0001$) and CPA (13.6(6.50) vs. 1.12(0.53) %; $p = 0.0005$) than controls. Hepatic proteome array analysis showed the HFHC group had higher levels of cytokines and chemokines involved in induction (IL1a, IL3, GM-CSF) and chemotaxis of immune cells (Ccl3, Cx3Cl1, CxCl1, CxCl5). Treatment with YoHCl in HFHC rats reduced liver/body weight ratio (5.73(0.44); $p = 0.034$), and AST levels (260.2(65.8) U/L; $p = 0.019$). Importantly, CPA (7.02(2.56) %; $p = 0.0397$) was reduced by YoHCl, and was associated with reduced cytokine and chemokine levels.
Conclusion: This study demonstrates that Adra2a antagonism reduces fibrosis progression in NAFLD, associated with reduced immune activation. This suggests Adra2a antagonism may slow progression of NAFLD with potential therapeutic translation in NAFLD and NASH patients that warrants further investigation.

THU-494

Elafibranor and nitazoxanide synergize to reduce fibrosis in a NASH model

R. Walczak[1], B. Carole[1], N. Benoit[1], E. Descamps[1], D. Nathalie[1], S. Megnien[1], D. Hum[1], B. Staels[2,3,4,5], S. Friedman[6], R. Loomba[7], S. Harrison[8]. [1]*GENFIT, Department of Research, Loos, France;* [2]*Univ. Lille - EGID;* [3]*Inserm U1011;* [4]*CHU Lille;* [5]*Institut Pasteur de Lille;* [6]*icahn School of Medicine at Mount Sinai, Division of Liver Diseases, New York, United States;* [7]*NAFLD Research Center, UCSD, Division of Gastroenterology, La Jolla, United States;* [8]*Pinnacle Clinical Research Center, San Antonio, United States*
Email: robert.walczak@genfit.com

Background and Aims: Drug combinations are increasingly required for the successful treatment of complex liver diseases. In NASH, drug combination has recently emerged as a new treatment paradigm to increase the proportion of patients that reach all treatment goals. Among these goals, NASH resolution and improvement of fibrosis are of tantamount importance. The ideal NASH medication will both reverse NASH histology and stop the progression of fibrosis in patients at high risk of cirrhosis and complications.
Elafibranor (ELA), a PPARα/δ agonist can reverse NASH histology and decrease fibrosis, especially in patients with advanced disease (GOLDEN-505 phase 2b trial), and is currently being evaluated in the RESOLVE-IT phase 3 trial. We have recently identified nitazoxanide (NTZ), a phase-2 ready drug candidate with a good safety profile in man as a potent anti-fibrotic agent, by using an unbiased phenotypic screening approach.
The aim of this proof of concept study is to assess ELA/NTZ combination in a disease model of NASH to establish its potential value for treating human disease.
Method: A NASH phenotype was induced in C57Bl/6J mice by feeding a cholesterol-supplemented CDAA diet (CDAA/c) for 12 weeks. Histological evaluation of NASH and fibrosis was performed in a blinded fashion. Additional biochemical and molecular analyses were also performed on relevant biomarkers. Animals received ELA alone (1 mg/kg/day), NTZ alone (100 mg/kg/day) or ELA/NTZ combination for the entire study period of 12 weeks.
Results: Histological examination revealed a severe NASH phenotype with maximal scores for steatosis and inflammation in mice fed the CDAA/c diet. Hepatocyte ballooning was also present. NASH histology was accompanied by perisinusoidal fibrosis (F2) and the picrosirius positive area occupied between 4% and 6% of the liver parenchyma. Liver fibrosis area was reduced by 41% and by 32% in mice treated with ELA and NTZ, respectively. Similarly, hepatic collagen content was reduced by 31% and 33% in mice administered with ELA and NTZ, respectively. As established by the EOHSA model, ELA/NTZ



Picro sirius red stained liver (top) and corresponding collagen area quantified (bottom)

Figure: (abstract: THU-493)

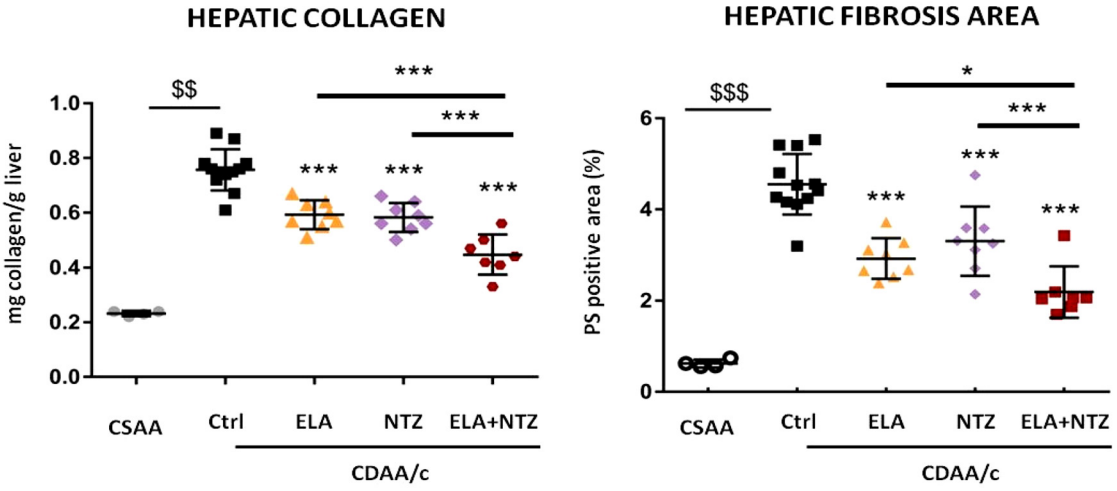


Figure: (abstract: THU-494)

combination showed a synergistic reduction of both fibrosis area (60%) and collagen content (59%), as compared to each single drug. Steatosis, inflammation and ballooning were partially improved by ELA but NTZ as a single drug had no effect on NASH histology. However, steatosis and ballooning were moderately improved in mice that received ELA/NTZ combination as compared to mice that only received ELA.
Conclusion: Elafibranor and nitazoxanide synergize *in vivo* to reduce liver fibrosis in a model of advanced NASH, opening interesting perspectives for further clinical development.

THU-495

LXR inverse agonists inhibit de novo lipogenesis and reduce intestinal lipid and cholesterol absorption in a NAFLD mouse model

C. Kremoser, U. Deuschle, C. Gege, O. Kinzel, H.D. Krol, M. Albers, M. Birkel, E. Hambruch. *Phenex Pharmaceuticals AG, Heidelberg, Germany*
Email: claus.kremoser@phenex-pharma.com

Background/Aims: Nuclear receptors LXR alpha and beta are both involved in the control of *de novo* lipogenesis and of lipid and fatty acid uptake in various tissues including small intestine and liver. We have developed potent synthetic LXR inverse agonists, PX25593 and PX25788, which block transcriptional activity of both LXRs. Both compounds display anti-steatotic effects in a mouse NAFLD model. Through stable and radioactive isotope labeling we could demonstrate that these effects are exerted through a combined inhibition of liver and intestinal *de novo* lipogenesis which also results in a reduced intestinal lipid and cholesterol uptake. This offers a new opportunity to address NAFLD clinically through LXR inverse agonists.
Method/Results: PX25593 and PX25788 were both characterized as potent synthetic LXR inverse agonists (LXRa/b EC50s: '593 = 2 nM/1.2 nM; '788 = 17 nM/19 nM). A key difference between these compounds is their distribution between liver and plasma ([liver]/[plasma] ratio at 4 h after oral administration: '593 = 3; '788 = 34). Hence, PX25788 can be regarded as a liver-selective LXR inverse agonist whereas PX25993 has a longer blood residence time. C57BL/6J mice which were prefed on a 60% kcal Survit-type high fat diet for 14 days and then dosed with PX25593 (3 and 10 mg/kg/d), PX25788 (10 and 30 mg/kg/d) and Tropifexor ((=LJN-452, a clinical stage potent FXR agonist) 3 mg/kg/d) for 28 days. Liver triglycerides were reduced by all compounds ('593 3 mg/kg: −33% ± 7; '593 10 mg/kg −41% ± 7; '788 10 mg/kg −31% ± 10; '788 30 mg/kg −30% ± 8; LJN-452 −73% ± 2). Plasma lipid and lipoprotein analysis yielded a differential reduction in HDLc by the treatments ('593 3 mg/kg: −13% ± 3; '593 10 mg/kg −35% ± 8; '788 10 mg/kg + 24% ± 4; '788 30 mg/kg + 14% ± 5; LJN-452 −52% ± 6). Plasma triglyceride reduction was observed to varying extents ('593 3 mg/kg: −19% ± 11; '593 10 mg/kg −21% ± 6; '788 10 mg/kg −3% ± 10; '788 30 mg/kg + 8% ± 10; LJN-452 −37% ± 7). A short term mechanistic study in C57 mice on HFD for four days demonstrated that LXR inverse agonists as well as Tropifexor reduced intestinal lipid and cholesterol uptake as well as inhibited liver-borne de novo lipogenesis (DNL).
Conclusion: LXR inverse agonists, similar to FXR agonists are capable of reducing liver fat in animal models. Like FXR agonists they reduced DNL in intestine and liver and markedly reduced intestinal lipid and cholesterol uptake. Thus, LXR inverse agonists might offer a new treatment option for NAFLD/NASH which potentially lacks the FXR-associated liabilities like HDLc lowering.

THU-496

Maternal obesity programs offspring's liver immune cells intra-uterine

J. Li[1,2], P. Cordero[3], A. Solanki[4], M. Vinciguerra[5], T. Crompton[4], J.A. Oben[1]. *[1]Institute for Liver and Digestive Health, London, United Kingdom; [2]Institute of Child Health, London, United Kingdom; [3]Institute for Liver and Digestive Health, United Kingdom; [4]Institute of Child Health, United Kingdom; [5]Center for Translational Medicine (CTM) International Clinical Research Center (FNUSA-ICRC) St. Anne's University Hospital, Brno, Czech Republic*
Email: jiawei.li.10@ucl.ac.uk

Background and Aims: Non-alcoholic Fatty Liver Disease (NAFLD) is now one of the leading causes for liver transplant. Based on developmental programming theory, insults and stimuli at critical periods have impact on the adult health status of offspring. Previously, our studies have shown that subjecting an offspring to maternal obesity peri-natally interacts with the post-natal diet, increasing the risk of developing NAFLD, with hepatic immune cells alteration suggested to play a role. The role however, of maternal obesity on pre-natal offspring livers is unclear.
Aims: To study the influence of maternal obesity on pre-natal offspring liver development, and the role of the immune system.
Method: Adult wild-type (WT) female mice were subjected to either control (Con) or high fat/high-sugar (Ob) diet for 8 weeks, and were then time-mated with a male stud. At Embryonic Day 14.5 (E14.5) and 17.5 (E17.5), all foetuses were harvested and the livers were analysed for their immune profile by flow cytometry, and transcriptomic changes by real-time polymerase chain reaction.
Results: At E17.5, the WT foetuses from the Ob mothers had, unexpectedly, a lower body mass compared to foetuses from the Con mothers. At E14.5, there is no weight difference between the foetuses from the two groups. However, the foetal livers subjected to maternal

obesity *in utero* have reduced cell numbers in both E14.5 and E17.5. Flow cytometric analysis showed an increased presence of granulocytes and natural killer (NK) cells foetal livers subjected to maternal obesity (Ob) compared to controls. This was accompanied by a relative increase in the markers of injury and inflammation: tumour necrosis factor-alpha and transforming growth factor beta-1.
Conclusion: Offspring are affected by maternal obesity pre-natally with an unexpected reduction of body mass at E17.5, and reduced liver cell number at both E14.5 and E17.5. Markers indicating liver were also elevated, along with changes of immune cells in the liver. This suggests maternal obesogenic status may predispose offspring for NAFLD by affecting the foetal immune development.

THU-497
Elafibranor restores lipogenic gene expression in a human skin stem cell-derived non-alcoholic fatty liver disease (NAFLD) model
J. Boeckmans[1], A. Natale[1], K. Buyl[1], J. De Kock[1], V. Rogiers[1], T. Vanhaecke[1], R.M. Rodrigues[2]. *[1]Vrije Universiteit Brussel (VUB), In Vitro Toxicology and Dermato-Cosmetology (IVTD), Brussels, Belgium; [2]Vrije Universiteit Brussel (VUB), In Vitro Toxicology and Dermato-Cosmetology (IVTD), Brussels*
Email: joost.boeckmans@vub.be

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a leading cause of chronic liver disease. It ranges from uncomplicated hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis and cancer. NASH is the first stage in the spectrum of NAFLD which is associated with increased health risk. No anti-NASH drug has been approved so far as discovery and development are largely hampered by the lack of adequate human-based *in vitro* systems that recapitulate the human pathophysiology.
Earlier, we showed that hepatic cells derived from human skin precursors (hSKP-HPC) represent a unique *in vitro* model for the investigation of drug-induced NAFLD. In this study we use hSKP-HPC to construct a human-relevant metabolically-induced NAFLD system that aims to mimic the progression of simple steatosis to NASH. As a proof-of-principle, the applicability of the hSKP-HPC-based disease model is evaluated in the context of anti-NAFLD drug discovery.
Method: In the current study, hSKP-HPC exposed to insulin (100 nM) and glucose (4500 mg/L) represent the *in vitro* steatosis model. NASH conditions were created by additional exposure to sodium oleate (65 µM) and palmitic acid (45 µM) in combination with a pro-inflammatory fibrotic cytokine cocktail (50 ng/mL TNF-alpha + 25 ng/mL IL-1beta + 8 ng/mL TGF-beta). Furthermore, the phase III anti-NASH drug elafibranor (Genfit) was tested in both *in vitro* systems.
Results: Gene expression analysis revealed a typical lipogenic gene expression profile concordant with human data: key lipogenic genes (*ACC*, *FAS* and *SREBP-1c*) were upregulated in the steatosis stage, but downregulated in the NASH model (24 h exposure; one-way ANOVA, $p < 0.05$). Gene expression changes were accompanied by an increased lipid load and caspase-3/7 activity in the NASH condition and a gradual increase in ATP production (72 h exposure).
In the steatotic setup, elafibranor (10 µM) restricted the increased expression of *SREBP-1c*, *ACC* and *FAS* (24 h treatment; student t-test, $p < 0.05$). Under NASH conditions, elafibranor induced the expression of *ACC* and *FAS* and tended to reverse NASH to a steatotic stage.
Conclusion: These first data provide the fundamental basis to further explore hSKP-HPC as a valuable *in vitro* model for anti-NAFLD drug discovery.

THU-498
The interplay between liver and muscle begins much earlier than cirrhosis. A diet-induced animal model
F.M. Trovato, P. Castrogiovanni, M.A. Szychlinska, F. Purrello, G. Musumeci. *University of Catania, Department of Clinical and Experimental Medicine, Internal Medicine Unit, Catania, Italy*
Email: trovatofrancesca@gmail.com

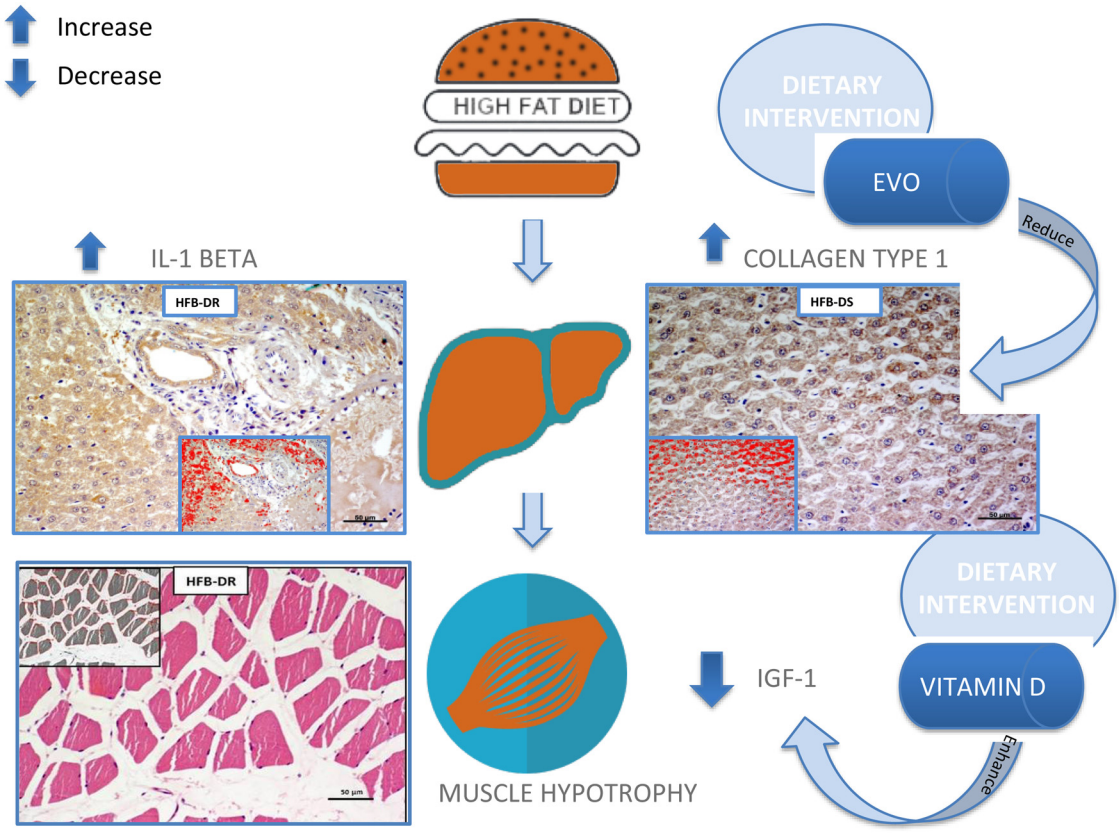


Figure: (Abstract: THU-4498)

Background and Aims: The growth hormone/insulin-like growth factor 1(IGF1) axis is involved in skeletal muscle metabolism. NAFLD and advanced fibrosis are associated with sarcopenia, and decreased levels of Vitamin D (VitD) and IGF1 and mutual relationship were reported. We aimed to evaluate whether different dietary profiles, containing or not VitD, may exert different effects on liver and muscle morphology, which may contribute to explain sarcopenia in NAFLD. In order to detect early defects induced by high fat diet, we decided to use a 10 weeks period of diet exposure.
Method: Twenty-eight male rats were fed by different dietary regimens for 10 weeks: **R**, regular diet; **R-DS** and **R-DR**, regular diet with respectively VitD supplementation (DS) and restriction (DR); **HFB-DS** and **HFB-DR** (41% energy from fat), high fat (butter) diet; **HFEVO-DS** and **HFEVO-DR** (41% energy from fat), high fat (Extra-virgin olive oil-EVO) diet. Collagen I in the liver and IL1 beta, VitD receptor (VDR), IGF1 in both liver and muscle were evaluated by immunohistochemistry. Perimeter of muscle fibers was measured by morphometric analysis; NAFLD severity was assessed by the NAFLD Activity Score (NAS).
Results: No difference was found in weight and NAS, that in all groups was between 0 and 2. Collagen I was more expressed in HFB-DS and HFB-DR, while in R and R-DS groups it was almost absent. HFEVO, DR or DS, seems to be protective against collagen I expression, in comparison with HFB. VitD did not show effect on collagen I. IL1 was higher in the liver and muscle of group HFD and HFEVO vs R, R-DS and R-DR ($p < 0,01$). Inside the R groups, the DR had a greater expression of IL1, so that VitD seems protective ($p < 0,01$). Muscle fibers perimeter analysis showed a highly significant hypertrophy in groups R-DS and HFEVO-DS ($p < 0,01$), and a statistically highly significant hypotrophy in group HFB-DR ($p < 0,01$): accordingly VitD supplementation showed trophic effect. However, VitD restriction did not show any detrimental effect vs. controls. HFEVO has no different effect on muscle trophism from the R diet. As expected, VDR was expressed more in groups DS in comparison with the respective DR. IGF1 was mostly expressed in R groups vs both HFB and HFEVO ($p < 0,01$). Liver and muscle IL1 were inversely, while VitD and IGF1 were directly related to muscle fibers perimeter. Liver collagen was directly related to dietary fat content, IL1 in muscle and liver, while IGF1 was inversely related to fat content and IL1 in muscle.
Conclusion: Even short-term high fat diets increase IL1 both in liver and muscle, thus reducing the expression of IGF1 in muscle. Moreover, EVO seems protective against collagen I expression in the liver. Vitamin D has a trophic effect on muscle fibers, probably through the interaction with IGF1. According to our results, liver and muscle damages begin early in rats fed with high fat diet and are modifiable by dietary intervention.

THU-499

Hyperreactivity to vasoconstrictors in a rat model of non-alcoholic fatty liver disease

D. van der Graaff[1,2], W. Kwanten[1,2,3], J. De Man[1], B. De Winter[1], P. Michielsen[1], S. Francque[1,2]. [1]*Laboratory of Experimental Medicine and Pediatrics (LEMP), Gastroenterology & Hepatology, Wilrijk (Antwerp), Belgium;* [2]*Antwerp University Hospital, Department of Gastroenterology and Hepatology, Edegem, Belgium;* [3]*Massachusetts General Hospital & Harvard Medical School, Department of Radiation Oncology, Boston, United States*
Email: denise.vandergraaff@uantwerpen.be

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has become the most prevalent chronic liver disease. Prior to development of inflammation or fibrosis, the intrahepatic vascular resistance (IHVR) is increased, impairing hepatic blood flow and potentially causing disease progression. Similar to the mechanisms in cirrhosis, hyperreactivity to vasoconstrictive agents is a potential mechanism. Therefore, our aim was to study the effects of alpha 1-adrenergic mediators and endothelin-1 (ET-1) on the IHVR in severe steatosis.
Method: The IHVR was studied by measuring the transhepatic pressure gradient (THPG) in an *in situ ex vivo* perfusion model. The THPG was studied in Wistar rats ($n \geq 6$/group) fed a methionine-choline-deficient diet, inducing severe steatosis after 4 weeks, and in rats fed a control diet. The effects of the alpha 1-adrenergic agonist methoxamine (Mx, 10^{-6}–3×10^{-4} M), the alpha 1-adrenergic antagonist prazosin (PRZ, 10^{-7}–10^{-4} M) and the vasoconstrictor ET-1 (10^{-12}–3×10^{-10} M) were studied in dose-response experiments. Subsequently, flow-pressure curves were constructed investigating the effects of 10^{-5} M Mx and 10^{-10} M ET-1 at different flows (10–50 ml/min).
Results: The basal THPG in steatotic livers was significantly increased compared to controls.

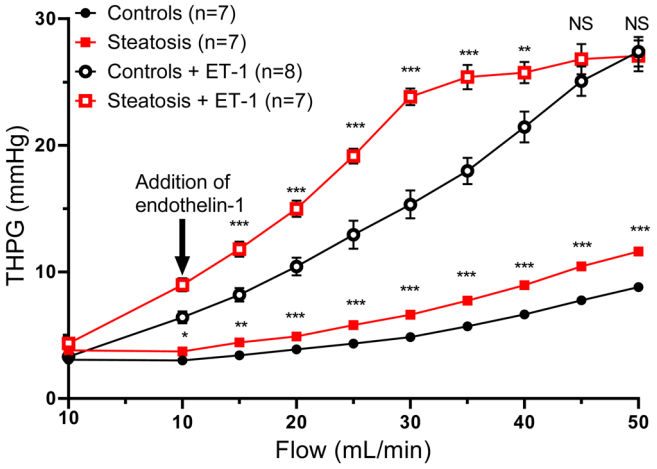


Figure 1: Flow-pressure curves presenting the THPG (mean ± SEM) in control and steatotic rats with and without the addition of ET-1.
The THPG was significantly higher in steatosis compared to controls at all flows (10–50 ml/min). Addition of ET-1 enhanced the THPG in controls and steatosis.
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$ significantly different from controls; NS: not significantly different from controls

Dose-response curves showed a significantly increased vascular sensitivity and responsiveness of steatotic livers to Mx (EC50 = $10^{-5.0}$ M, T_{max} = 9.8 mmHg) compared to controls (EC50 = $10^{-4.8}$ M, T_{max} = 8.2 mmHg [$p < 0.05$]). In flow-pressure experiments, the THPG of steatotic livers showed a significantly increased reactivity to Mx at all flows. PRZ did not alter THPG in both controls and steatosis.
ET-1 induced a dose-dependent increase of the THPG in both controls and steatosis, with significantly increased sensitivity and responsiveness to ET-1 in steatosis (20.3 ± 1.3 mmHg at 3×10^{-10} M) compared to controls (14.9 ± 1.4 mmHg at 3×10^{-10} M, $p < 0.001$). Flow-pressure experiments confirmed the hyperreactivity to ET-1 in steatotic livers with a more rapid and higher increase in THPG and the maximum THPG was reached at significantly lower flows compared to controls (controls 15.3 ± 1.1 mmHg, steatosis 23.8 ± 0.6 mmHg at 30 mL/min, $p < 0.001$, Figure 1).
Conclusion: The reactivity to both Mx and ET-1 is significantly increased in steatotic rat livers compared to controls, pointing towards an hyperreactivity to vasoconstrictors as a cause of the observed (and repeatedly confirmed) increased THPG associated with NAFLD.

THU-500

Role of mitofusin-2 in NAFLD and targeting by miRNAs

A. Simão[1], M.B. Afonso[1], P. Rodrigues[1], A.J. Amaral[2], M. Gama-Carvalho[2], A. Zorzano[3], C.M.P. Rodrigues[1], R. Castro[1].
[1]*Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal;* [2]*BioFIG - Center for Functional and Integrative Genomics, Faculty of Sciences, Universidade de Lisboa, Lisbon, Portugal;* [3]*Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain*
Email: adlsimao@ff.ul.pt

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) associates with intracellular lipid accumulation in the liver. Recent evidence supports a functional role for both miRNA and mitochondrial dysfunction in regulating NAFLD pathogenesis. In particular, deregulation of mitochondrial dynamics proteins, like mitofusin-2 (Mfn2), were recently described in obese and diabetic patients, while liver-specific Mfn2 silencing in mice promotes numerous metabolic abnormalities. Our aims were to profile global liver miRNA expression changes during NAFLD and correlate them with the development of mitochondrial dysfunction in experimental and human NAFLD.
Method: C57BL6/N mice were fed either a standard or a fast food (FF) diet for 25 weeks, or a methionine and choline-deficient (MCD) diet for 2 and 8 weeks. Liver RNA from 8 weeks MCD-fed mice was run in TaqMan miRNA arrays. Liver biopsies were obtained from NAFLD patients with steatosis or nonalcoholic steatohepatitis (NASH). mRNA and protein expression were analysed by qRT-PCR and immunoblotting, respectively. miRNA targeting was evaluated by dual-luciferase reporter assays in HepG2 cells.
Results: FF-fed mice developed steatosis, inflammation and insulin resistance. MCD-fed mice developed progressive steatohepatitis and fibrosis. Liver Mfn2 mRNA and protein levels were significantly decreased in both MCD- and FF-fed animals, comparing with control diet-fed mice. Inversely, expression of dynamin-related protein-1 (Drp1), a mitochondrial fission protein, was found increased. In humans, liver Mfn2 protein levels decreased from steatosis to NASH. Twenty-five miRNAs were found significantly increased in the liver of MCD-fed mice. Inversely, 27 miRNAs were decreased. Among the increased miRNAs, 4 have at least one targeting Mfn2 3'UTR binding site in Mfn2 mRNA (miR-134, miR-125a, miR-222 and miR-34a). Dual-luciferase reporter assays confirmed targeting of Mfn2 by miR-125a, miR-222 and miR-34a in liver cells. Further, overexpression of either of these miRNAs in HepG2 cells inhibited Mfn2 expression.
Conclusion: Altogether, inhibition of Mfn2 constitutes a key mitochondrial dysfunction event during NAFLD triggering and progression. A better understanding of miRNAs modulated during NAFLD that directly target Mfn2 might aid in the elucidation of novel molecular pathways for therapeutic intervention. (SFRH/BD/104160/2014, FCT, PT and Gilead Sciences International Research Scholars Program 2015).

THU-501

Diseased human 3D microtissues as building blocks for complex metabolic in-vitro systems

O. Frey, B. Yesildag, R. Kostadinova, S. Messner, P. Guye. *InSphero AG, Schlieren, Switzerland*
Email: patrick.guye@insphero.com

Background and Aims: NAFLD, obesity, insulin resistance, metabolic syndrome, and Type 2 Diabetes are closely connected clinical pathologies. Further, insults, as for example inflammatory stimuli, contribute to the progression of NAFLD to NASH, an increasing healthcare burden in developed countries and major indication for liver transplant. Studying the etiologies for this group of diseases, with the goal of developing novel therapeutic approaches, presents multiple challenges, such as having readily available organotypic, human tissues with inducible disease states, as well as simple and robust methods for studying organ-organ interactions.
Method: We developed a new generation of screening-compatible 3D microtissue models that emulate the healthy and various diseased states of human liver and pancreatic islets, adaptable to a unique standard multi-well microtissue plate format and novel microphysiological system (MPS) to accommodate interconnected culture and assay of such microtissues. The MPS design enables culturing of microtissues under physiological flow conditions, with the flexibility to interconnect and culture different types of microtissues for a variety of pre-clinical testing applications. The full polystyrene device is based on SBS-plate standards, includes 8 separate channels, each channel containing up to 10 microtissue compartments. Thus, up to 10 same or different microtissues can be interconnected and cultured in 8 identical or different conditions in parallel per plate. Such a setup enables microfluidic linking of, for example, liver and islet microtissues and investigation of organ-organ interactions.
Results: Organotypic liver and islet tissues are metabolically active, highly accessible to experimentation, and importantly, immune competent. Starting from their healthy state, we demonstrate induction of liver steatosis by exposure to high Glucose/Insulin media supplemented with dietary fatty acids (imaging/lipidomics). Treatment with inflammatory agents stimulate molecular events leading to NASH, as shown by induction of liver fibrosis markers (qRT-PCR, imaging, ELISA). Moreover, we demonstrate modulation of glucose-stimulated insulin secretion by Tolbutamide and Exendin-4 under physiological flow conditions, highlighting the unprecedented insights achievable with advanced physiologically relevant in-vitro systems.
Conclusion: We demonstrated that complex metabolically competent 3D microtissues are able to mimic human liver and islet disease states and are thus a physiological relevant in vitro drug discovery tool.

THU-502

A novel microtissue-based 3D human liver NASH model for drug discovery

J. Rupp, T. Strassfeld, S. Steiert, P. Guye, S. Messner, R. Kostadinova. *InSphero AG, Schlieren, Switzerland*
Email: radina.kostadinova@insphero.com

Background and Aims: Non-alcoholic steatohepatitis (NASH), an advanced form of non-alcoholic fatty liver disease (NAFLD), is defined as the presence of hepatic steatosis with inflammation and hepatocyte injury. NASH can eventually lead to advanced fibrosis, liver cirrhosis and liver failure. At present, there are no approved and safe therapies for NASH. The most frequently used in vitro model to study the effect of anti-NASH drugs are simple mono-layer cultures of hepatic stellate cells (HSCs) and hepatocytes, which are not relevant enough to account for the complex mechanism of the disease. We aimed to develop a physiological relevant 3D Human Liver NASH model, amenable for drug safety screening.
Method: 3D Human Liver Microtissues were engineered to incorporate all the relevant primary human liver cell types responsible for the development of the disease: hepatocytes, HSCs, Kupffer cells (KCs) and liver endothelial cells (LECs). The resulting 3D InSight™ Human Liver NASH model has been induced by treatment of the tissues with Free Fatty Acids (FFA) such as Oleic and Palmitic acids (1:1), LPS and TGF-β1 for 7 days. We characterized the tissues under basal and induced liver disease conditions on morphological and phenotypic levels by Nile-Red staining of incorporated lipids using confocal microscopy, immunostaining techniques, gene-expression analysis, and cytokine release.
Results: Using cell type specific markers and immunohistochemistry we demonstrated the presence of various cell types such as hepatocytes, HSC, KCs and LECs during the cultivation and treatment period. Treatment of the tissues with FFA, LPS and TGF-β1 for 7 days induced lipid accumulation in the hepatocytes as well as increased secretion of pro-inflammatory markers such as MCP-1, IL-6 and TNF-α. The treatment of the 3D microtissues with the described NASH inducers increased the mRNA and protein expression of the α-smooth

muscle actin (α-SMA), a marker of the activated HSCs and of the extracellular matrix proteins such as collagen type I.
Conclusion: We demonstrated that FFA, LPS and TGF-β1 treatment induced liver inflammation, steatosis and fibrosis in vitro, making this model an ideal tool for anti-NASH drug discovery.

THU-503
Modeling NAFLD using 3D bioprinted human liver tissue

D. Carter[1], S. Presnell[1], B. David[2], A. Chen[1]. [1]*Organovo, R&D, San Diego, United States;* [2]*University of California, Department of Medicine, San Diego, United States*
Email: achen@organovo.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a chronic condition that originates as lipid accumulation within hepatocytes (steatosis) and progresses into nonalcoholic steatohepatitis (NASH), characterized by lipid accumulation, inflammation, oxidative stress, and fibrosis. NAFLD is now recognized as the most common cause of chronic liver disease in the western world, with an estimated prevalence of 25% worldwide, and is projected to become the leading indication for liver transplant by 2025. Despite decades of research, the mechanisms of NAFLD progression, therapeutic approaches and non-invasive diagnostics are still resoundingly absent. The study of steatosis and NASH has traditionally utilized rodent models, which are time consuming to generate and do not fully recapitulate the complex phenotypes associated with the human disease. Furthermore, current 2D cell culture models lack relevant liver cell types, do not accurately display diseased phenotypes, and have limited utility due to rapid loss of cell viability and function. Thus, there is a significant need for a more predictive human multicellular 3D *in vitro* model to study the progression of steatosis into NASH.
Method: ExVive™ Human Liver Tissue, a human *in vitro* 3D bioprinted liver model comprising primary human hepatocytes, hepatic stellate cells, and endothelial cells exhibits a complex multicellular architecture similar to that of native liver and retains metabolic competence and liver-specific functions for at least 4 weeks in culture. To mimic the proposed pathogenesis of NASH via a "Two-Hit Hypothesis", immune competent tissues containing Kupffer cells were exposed to steatogenic cues via a nutrient overload approach of simple sugars and fatty acids, followed by inflammatory stimulation using prototypical inducers.
Results: Preliminary evidence suggests that steatosis can be induced via chronic exposure to lipids in the presence of high glucose. Treated tissues exhibit increased incidence of lipid vesicles positive for Oil Red O and the lipid droplet-associated protein, Perilipin 5, and increased triglyceride content. Incorporation of both hepatic stellate and Kupffer cells into the tissues, concomitant with activation via inflammatory inducers and nutrient overload, leads to activation of stellate cells, inflammatory cytokine release, and an increase in extracellular matrix deposition and fibrosis, characteristic of NASH.
Conclusion: Together, these features suggest that 3D liver tissues hold promise for the study of complex, chronic conditions such as NASH, enabling better understanding of disease processes, discovery of novel therapeutics, biomarkers, and the safety assessment of drugs in a disease-relevant background.

THU-504
The changing profile of extracellular vesicles in non-alcoholic fatty liver disease progression and their role in signalling to hepatocytes

L. Ban[1], S. Sutanto[1], A. Tao[1], S. Martinez-Huenchullan[1,2], B.R. Maharjan[1], N. Shackel[3], S. Mclennan[1,4]. [1]*University of Sydney, Greg Brown Diabetes and Endocrine Lab, Sydney Medical School, Sydney, Australia;* [2]*Universidad Austral de Chile, School of Physical Therapy, Faculty of Medicine, Valdivia, Chile;* [3]*University of New South Wales, Faculty of Medicine, Sydney, Australia;* [4]*NSW Health Pathology, Sydney, Australia*
Email: lban4851@uni.sydney.edu.au

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a prevalent comorbidity of obesity, however current diagnostic tools are often unreliable or impractical, and so tissue biopsy remains the gold standard. Extracellular vesicles (EVs) are submicron, membrane-bound structures that are released from activated or stressed cells, and have been shown to be involved in paracrine and endocrine signalling. This study aimed to investigate the potential of EVs as biomarkers in NAFLD, and their role in mediating the disease.
Method: Six-week old male C57Bl/6 mice were randomly assigned to receive high-fat diet (HFD; 45%kcal fat) or standard laboratory chow for 10, 20, 30 or 50 weeks. Physical profile, plasma biochemistry, and liver histology and phenotype were analysed at the conclusion of each time-point. Plasma EVs were isolated by ultracentrifugation and enumerated by nanoparticle tracking analysis. The uptake of EVs into a hepatocyte cell line (AML12) was assessed by flow cytometry, while changes in the gene expression of cells upon exposure to EVs (1000/ul) were assessed by real-time PCR.
Results: Within the HFD cohort, there was a progressive increase in liver weight and worsening histological severity of NAFLD across the time-points. This was reflected in the liver gene expression of inflammation and matrix remodeling markers by real-time PCR. Plasma insulin was consistently increased in HFD (all time-points: $p < 0.001$), while ALT was increased from 20 weeks onwards (20–50 weeks: $p < 0.0001$). Plasma EVs fluctuated across the duration of HFD, with a peak at 20 weeks ($p = 0.0001$ vs 10 weeks) followed by a gradual decline. Interestingly, AML12 hepatocytes were most responsive to EVs from 50 weeks HFD ($p = 0.009$ vs chow), which was associated with an increase in TNF mRNA ($p = 0.004$). In contrast, gene expression of molecules associated with matrix remodeling declined with exposure to HFD-derived EVs from 20 weeks diet onwards (collagen I: $p < 0.002$, TIMP1: $p < 0.001$ vs 10 week HFD). Similar trends were observed upon exposure to chow EVs, suggesting an age-dependent change in hepatocyte mediated tissue remodeling.
Conclusion: Intercellular communication by EVs may be an important event in NAFLD progression. While absolute number of plasma EVs fluctuate with diet duration, this doesn't necessarily reflect the level of responsiveness of cells. EVs mediate an inflammatory phenotype but suppress the tissue remodeling response in hepatocytes, suggesting a role in global feedback mechanisms to control organ-specific pathology.

THU-505
RIP3-dependent signalling contributes to non-alcoholic fatty liver disease-related hepatocarcinogenesis

M.B. Afonso, P.M. Rodrigues, A. Simão, M.M. Gaspar, R.E. Castro, C.M.P. Rodrigues. *Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal*
Email: mbafonso@ff.ulisboa.pt

Background and Aims: Hepatocellular death, inflammation and fibrosis are implicated in the pathogenesis of non-alcoholic steatohepatitis (NASH), including development and progression to hepatocellular carcinoma (HCC). Necroptosis is a highly immunogenic regulated cell death routine that depends on receptor-interacting protein 3 (RIP3) kinase activity. We aimed to evaluate the role of necroptosis in the pathogenesis of non-alcoholic fatty liver disease (NAFLD)-driven carcinogenesis.
Method: C57BL/6 wild-type (WT) or RIP3-deficient ($RIP3^{-/-}$) mice were fed a choline-deficient L-amino acid-defined diet (CDAA; n = 14) or a control choline-sufficient L-amino acid-defined (CSAA; n = 14) diet for 66 weeks, with subsequent histological and biochemical analysis of hepatic damage and carcinogenesis. Insulin resistance and oxidative stress were also investigated.
Results: CDAA-fed WT mice exhibited all the main histological features of liver injury associated with NASH, namely steatosis, hepatocellular ballooning, immune cell infiltration, and fibrosis. RIP3 deficiency ameliorated CDAA-induced inflammation and fibrosis, and decreased the NAFLD activity score. In agreement, hepatic gene

expression of pro-inflammatory mediators was also significantly decreased in CDAA-fed RIP3$^{-/-}$ mice, compared with WT. Intriguingly, RIP3$^{-/-}$ mice displayed increased body weight gain with time, as well as insulin resistance at 66 weeks as assessed by homeostasis model assessment-estimated insulin resistance and decreased insulin receptor substrate phosphorylation, compared with WT mice on CSAA or CDAA diet. RIP3$^{-/-}$ mice tended to show reduced incidence of macroscopic preneoplasic nodules, accompanied by significantly reduced Ki67 positive hepatocytes and increased proapoptotic Bax and cell cycle regulator cyclin-dependent kinase 2-associated protein 1 (CDK2AP1). Absence of RIP3 further hampered signaling pathways controlling tumor microenvironment and protected against oxidative stress and mitochondrial dynamic dysfunction.

Conclusion: Overall, RIP3 ablation halts long-term inflammation, fibrosis, hepatocyte proliferation, and genetic resistance of dysplastic hepatocytes to cell death, oxidative stress and tissue microenvironment changes associated with NASH-driven hepatocarcinogenesis. Targeting RIP3-dependent signalling might be a promising approach to arrest NAFLD progression to HCC, although complementary approaches may be required to control insulin resistance in obese patients. (Funding: PTDC/BIM-MEC/0895/2014; SAICTPAC/0019/2015).

THU-506

NAFLD in HIV mono-infection is a consequence of insulin resistance but not bacterial translocation

J. Maurice[1], P. Kelleher[2], M. Nelson[3], M. Thursz[1], M. Lemoine[1].
[1]*Imperial College London, Hepatology;* [2]*Imperial College London, Immunology;* [3]*Imperial College London, Infectious Disease*
Email: james.maurice@imperial.ac.uk

Background and Aims: Chronic non-communicable co-morbidities such as non-alcoholic fatty liver disease are an increasing concern in aging patients with HIV. Loss of gut-associated lymphoid tissue from HIV infection may contribute to bacterial translocation and the development of NAFLD. We aimed to investigate the role of bacterial translocation in the development of NAFLD, NASH and fibrosis in HIV mono-infected patients.

Method: Patients were prospectively recruited in a dedicated HIV liver clinic. Inclusion criteria were HIV mono-infection with biopsy-confirmed NAFLD, in the absence of alcohol excess, viral hepatitis or other causes of chronic liver disease. HIV infected patients with normal liver function and BMI <30 were used as controls. Fasted blood samples were collected. Bacterial DNA was extracted from whole blood and quantified using qPCR. Lipopolysaccharide (LPS) was measured using a cell reporter line expressing TLR-4 (HEK-Blue, Invitrogen). sCD14, sCD163, lipopolysaccharide binding protein (LBP) (RND Systems), leptin and adiponectin (Invivogen) were measured by ELISA. A subset of patients also conducted a PEG based gut permeability test. Liver histology was reported using the NASH CRN scoring system.

Results: Thirty cases (NASH n = 21, NAFL n = 9, age 47(38–55), male 97%, BMI 31(27–33)) and 30 controls (age 48(41–53), male 100%, BMI 25(23–28)) were included. NAFLD was not associated with bacterial DNA (3.72 vs 3.74 ng/ml, p = 0.772), LPS (0.024 vs 0.014 EU/ml, p = 0.176), sCD14 (6062 vs 5370 pg/ml, p = 0.074) or LBP (5.91 vs 5.85 ug/ml, p = 0.376), but was significantly associated with sCD163 (868 vs 738 ng/ml), leptin (13339 vs 4109, p < 0.001), reduced adiponectin (552 vs 1593 ng/ml p = 0.0091) and increased leptin:adiponectin ratio (13.9 vs 2.9 p < 0.001). There was no difference in patients with increased gut permeability measured by PEG between NAFLD and controls (18% vs 16%, p = 0.94). In a sub-analysis by disease severity in cases with NAFLD, no markers distinguished NASH from NAFL, but significant fibrosis (≥F2) was associated with sCD14 (6614 vs 5478 pg/ml p = 0.016), and leptin (16651 vs 6870 pg/ml p = 0.004).

Conclusion: NAFLD in HIV mono-infection is a consequence of insulin resistance and not bacterial translocation.

THU-507

Hepatic steatosis potentiates irinotecan-induced hepatocellular injury via dysregulation of irinotecan-metabolizing enzymes

A. Mahli[1], A. Koch[1], W. Thasler[2], C. Hellerbrand[1]. [1]*Friedrich-Alexander University Erlangen-Nürnberg, Institute of Biochemistry, Erlangen, Germany;* [2]*Ludwig-Maximilians-University Munich, Grosshadern Tissue Bank and Center for Liver Cell Research*
Email: claus.hellerbrand@fau.de

Background and Aims: Inclusion of irinotecan (IX) in preoperative chemotherapy regimens is associated with the risk to develop steatohepatitis known as chemotherapy-associated steatohepatitis (CASH) which increases the risk of perioperative morbidity and mortality. Observational clinical studies indicate that obese patients have a higher risk for developing CASH. However, the underlying mechanisms are elusive.

The aim of this study was to analyze the impact of hepatic steatosis on the hepatotoxicity of irinotecan.

Methods and Results: Lipid accumulation in primary human hepatocytes (PHH) was induced by incubation with the fatty acid oleate. Subsequently, steatotic and control hepatocytes were incubated with up to 50 µM irinotecan (IX). In this dose range, IX alone had only minimal hepatotoxic effects but lipid accumulation enhanced synergistically the hepatotoxic effects of IX. Moreover, the effects of IX on cellular triglyceride content, as well as lipid peroxidation, oxidative stress and ERK-mediated pro-inflammatory gene expression were significantly enhanced in fat-loaded hepatocytes compared to control cells. Furthermore, the expression of carboxylesterase 2 (CE2), which metabolizes IX to its active metabolite SN38, was significantly induced in fat-loaded hepatocytes while the expression of UDP-glucuronosyltransferase UGT1A1 (the main hepatic enzyme responsible for IX-inactivation) was significantly reduced in fat-loaded hepatocytes. Next, we applied IX to mice with hepatic steatosis (induced by feeding a high-fat diet for 4 weeks) and control mice. In mice with fatty livers, IX treatment further increased hepatocellular lipid accumulation and induced a significantly higher increase of serum transaminases and hepatic oxidative stress, ERK-activation and inflammation compared to control mice. Furthermore, hepatic expression of CE2 was induced and UGT1A1-expression was reduced in steatotic murine livers. This altered hepatic CE2 and UGT1A1 expression pattern was confirmed in patients with non-alcoholic fatty livers.

Conclusion: Our data indicate that irinotecan and steatosis synergistically induce pathological mechanisms in hepatocytes *via* dysregulation of IX-metabolizing enzymes which lead to higher hepatic levels of its toxic metabolite SN38. These findings may have important implications for prediction, prevention and treatment of irinotecan-induced CASH particularly in obese individuals.

THU-508

Glutaminase 1 targeting in non-alcoholic steatohepatitis

J. Simón[1], M. Núñez[2], P.F. Tussy[1], L. Barbier-Torres[1], D.F. Ramos[1], B.G. Santos[2], F.L. Otsoa[1], V.G. de Juan[1], C. Alonso[3], P. Iruzubieta[4,5], S.M.V. Liempd[5], A. Castro[3], M. Varela-Rey[1], J. Falcon-Perez[5], E. Villa[6], J. Crespo[4], S.C. Lu[7], J. Matos[1], P. Aspichueta[2], T.C. Delgado[1], M.L. Martínez-Chantar[5]. [1]*CIC bioGUNE, CIBERehd, Liver Disease Laboratory, Deroi, Spain;* [2]*University of Basque Country & Biocruces Health Research Institute, Physiology, Faculty of Medicine and Nursering, Leioa & Barakaldo, Spain;* [3]*Owl Metabolomics, Derio, Spain;* [4]*Marqués de Valdecilla Universitary Hospital, Digestive unit, Santander;* [5]*CIC bioGUNE, Metabolomics Platform, Derio, Spain;* [6]*University of Modena and Reggio Emilia, Gastro c/o AOU, Modena, Italy;* [7]*Cedars-Sinai Medical Center, Division of Gastroenterology, Los Angeles, United States*
Email: jsimon@cicbiogune.es

Background and Aims: Non-alcoholic fatty liver disease (NAFLD), comprehends a group of conditions and has an estimated worldwide prevalence of 25% of the adult population (Younossi et al., 2016). Its first stage, steatosis, is characterized by an accumulation of lipids in

the liver. If steatosis progresses into inflammation and fibrosis it turns into non-alcoholic steatohepatitis (NASH). Although first stages are rather benign conditions, NAFLD can turn into cirrhosis and hepatocellular carcinoma (HCC) (Ascha et al., 2010). Despite dietary and lifestyle interventions are enough to resolve the disease in the earliest stages, sometimes long-term compliance of the patients is so hard that pharmacological approaches are needed to target NAFLD. In fact, a huge economical effort of a billion US$ was estimated in 2015 with only novel experimental approaches and emerging therapies available.

Our group has focused on Glutaminase 1 (GLS1) whose main substrate, glutamine (Gln), has an altered metabolism in liver disease. GLS, located in the mitochondria, is the main regulator of Gln catabolism into glutamate (Glu) and ammonium. It has 2 isoforms: liver-type glutaminase (GLS2) and kidney-type glutaminase (GLS1). The higher affinity isoform, GLS1, has been shown to be regulated by cMyc and overexpressed in many cancer cell types (Yu et al., 2015). It also has been found to be overexpressed in earlier stages of HCC such as cirrhosis.

Method: GLS1 expression and activity was studied in NASH patients. Mice were fed a lipogenic diet (0.1% MCD diet) and targeted silencing of GLS1 was performed through tail vein injection of 4 nmol siCtrl/siGLS1 RNA using Lipofectamine 3.0®. Primary hepatocytes have been obtained through perfusion and targeted silencing was performed using 50 nM siCtrl/siGLS1 RNA and 0.4%v/v Darmaphect®.

Results: Gln/Glu ratio was decreased in serum from a cohort of 467 NASH patients, suggesting an increased Gln catabolism. Related to this, we have characterized GLS1 overexpression in NASH both in human patients and mice. We also have shown lower lipid accumulation when targeted silencing of GLS1, both in mice and primary hepatocytes. Reduced ROS levels have been found in cells and *in vivo* silencing of GLS1, showing to be a consequence of a decreased TCA cycle activity, a lower β-oxidation and a reduced ETC activity. The mechanism underlying these effect has been investigated.

Conclusion: Targeted silencing of GLS1 reduces ROS through a decrease in ECT and TCA activity and a lower β-oxidation. As a consequence, less glutathione is required and serine availability may be increased restoring phospholipid levels and finally restoring VLDL export implying a lower lipid accumulation in the liver.

THU-509

Epigenetic modification of urea cycle enzymes in NAFLD animal models and patients: Implications for novel therapeutic approaches

F. De Chiara[1], R. Jalan[1], G. Marrone[1], S. Heeboll[1], C. Montoliu[2], S. Hamilton-Dutoit[3], M. García-Torres[4], F. Andreola[5], K. Rombouts[5], H. Grønbæk[6], V. Felipo[7], R. Mookerjee[5], K. Louise Thomsen[5,6].

[1]University College of London UCL, ILDH, London, United Kingdom; [2]Fundación Investigación Hospital Clínico de Valencia, Instituto de Investigación Sanitaria-INCLIVA, Spain; [3]Aarhus University Hospital, Institute of Pathology, Denmark; [4]Unidad de Digestivo, Hospital Clínico de Valencia, Medicina, Universidad de Valencia, Spain; [5]University College of London UCL, ILDH, United Kingdom; [6]Aarhus University Hospital, Hepatology and Gastroenterology, Denmark; [7]Centro Investigación Príncipe Felipe de Valencia, Laboratory of Neurobiology, Spain

Email: francesco.chiara@ucl.ac.uk

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease ranging from steatosis, through non-alcoholic steatohepatitis (NASH) to cirrhosis. We have previously shown reduced function of urea cycle enzymes (UCE) in an experimental diet-induced NASH model. The resulting hyperammonemia contributes to hepatic stellate cell activation and risk of progression of fibrosis. We hypothesised that changes in function and expression of UCE are as a consequence of epigenetic modifications. The aims of this study were to investigate the potential mechanisms underlying these changes by assessing the methylation status of UCE promoter genes both in rats and humans.

Method: Rats were fed a high-fat, high-cholesterol diet (HFHC) for 10 months resulting in advanced experimental NASH and then changed to normal chow for 2 months to recover. In humans, we obtained liver biopsies from 20 patients with steatosis and 15 NASH patients. We measured the urea cycle enzymes' gene and protein expression, the OTC activity and ammonia concentrations. Also, we assessed the promoter methylation status of the UCE, ornithine transcarbamylase (OTC) in rats and OTC and carbamoyl phosphate synthetase (CPS1) in human.

Results: In NASH rats, gene ($p < 0.01$ vs. 10 and 12 m) and protein expressions of OTC and CPS1 as well as the enzyme activity of OTC were reduced ($p < 0.01$ both). Reversal of NASH by changing the diet to normal chow restored these changes ($p < 0.01$ vs. 12 m). Methylation of the OTC promoter gene ($p < 0.01$ both) was partially restored by reversal of the diet ($p = 0.02$ vs 12 m) and this was associated with reduced severity of NASH. In humans, NASH patients had significantly lower OTC enzyme activity and protein expression compared to controls ($p < 0.05$). This was associated with increased ammonia concentrations in both plasma and liver tissue ($p < 0.05$). Several sites upstream of the start codon in the OTC and CPS1 promotors were hypermethylated in NASH patients compared with controls.

Conclusion: Experimental and human NASH was associated with a reversible reduction in gene and protein expression and activity of UCE resulting in hyperammonemia. The promoter region of the genes for OTC, and in humans also CPS1, showed increased methylation indicating that hypermethylation of UCE may be the mechanism underlying the reduction in urea synthesis. Our investigations describe for the first time, a link between NASH, function of UCE and hyperammonemia that provides potential new targets for therapy.

THU-510

Ammonia: A novel target for the prevention of NAFLD progression in NASH

F. De Chiara[1], K.L. Thomsen[2,3], A. Habtesion[3], N. Davies[4], A. Hall[3,5], K. Rombouts[3], F. Andreola[3], H. Jones[3], R. Mookerjee[3], R. Jalan[3]. *[1]Royal free Hospital, ILDH, London, United Kingdom; [2]Aarhus University Hospital, Hepatology and Gastroenterology, Denmark; [3]University College of London UCL, ILDH, London, United Kingdom; [4]ILDH, UCL, United Kingdom; [5]Royal Free London NHS Foundation Trust, Sheila Sherlock Liver Centre, United Kingdom*

Email: francesco.chiara@ucl.ac.uk

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver diseases ranging from steatosis, through non-alcoholic steatohepatitis (NASH) to cirrhosis. Fibrosis is the most important factor contributing to NAFLD-associated morbidity and mortality and reduction in fibrosis is the main aim for treatment. Urea synthesis is down regulated in NASH resulting in hyperammonemia, which activates hepatic stellate cells (HSCs); the main cell type responsible for hepatic fibrosis. Therefore, we aimed to investigate whether lowering of ammonia prevents development of fibrosis in an animal model of NASH.

Method: Male Sprague Dawley rats ($n = 10$/group) were subdivided into 5 groups and fed, normal chow (NC), an isocaloric (IC) diet, a high fat, high cholesterol (HFHC) diet or the HFHC or IC diet plus the ammonia lowering drug ornithine-phenylacetate (OCR002) for up to 16 weeks. At the end of the study, biochemical parameters were measured, and histological staining was employed for detection of changes in hepatic architecture and collagen accumulation. Hepatic pro-fibrotic markers such as Col1A1, MyosinIIA, MyosinIIB and alpha-SMA were assessed. In liver tissue, activity of the urea cycle enzyme (UCE), ornithine transcarbamylase (OTC) was quantified. Plasma and liver markers of cell death was assessed with ELISA and TUNEL.

Results: In liver tissue, the HFHC diet induced massive and progressive downregulation of OTC activity compared with NC ($p < 0.05$), which was followed by progressive hyperammonemia. The

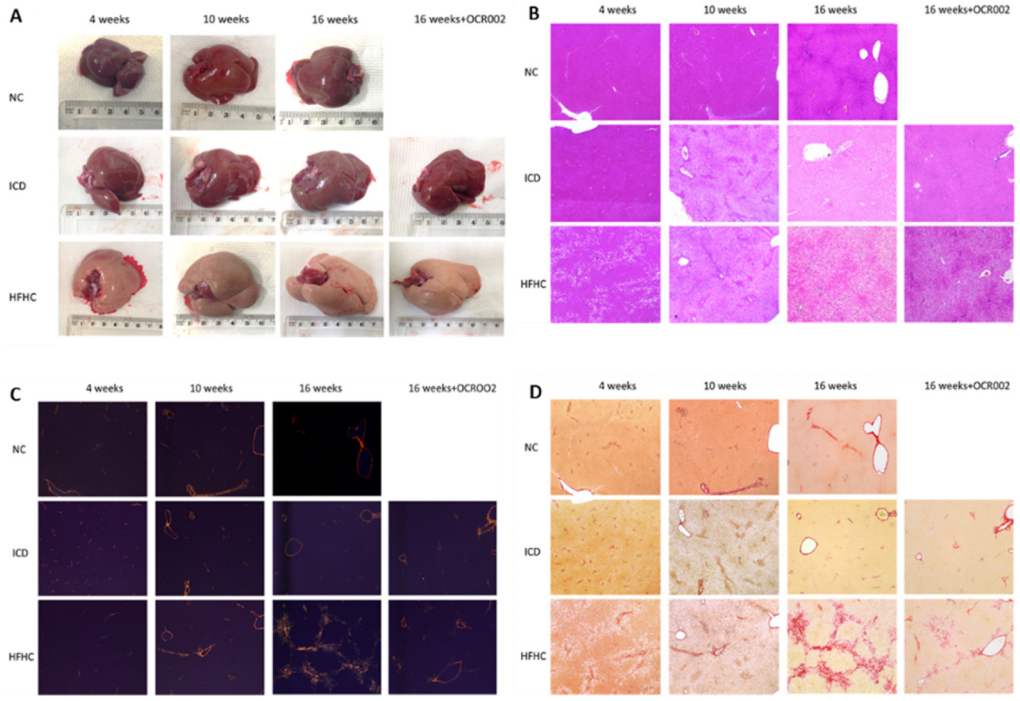


Figure: (abstract: THU-510): (A) Naked-eye assessment; (B) Hematoxylin and eosin; (C) Circularly polarized light; (D) Picro-siriusi red staining.

HFHC fed group showed cell death markers at 4, 10 and 16 weeks vs NC ($p < 0.05$). Hepatocyte lipid accumulation caused by HFHC diet led to dramatic increase of Col1A1, MyosinIIA, MyosinIIB and α-SMA protein expression in liver tissue compared with NC (2 or higher fold increase). High levels of ammonia and cell death markers in HFHC animals were confirmed in the plasma ($p < 0.05$). OCR-002 treated animals had significantly lower hepatic and serum ammonia, lower cell death markers in liver and plasma, and a reduced severity in fibrosis (HFHC vs HFHC + OCR-002, $p < 0.05$).

Conclusion: The above data show that experimental NASH is associated with early and progressive reduction in the activity of urea cycle enzyme OTC resulting in hyperammonemia, increased liver cell death markers, and hepatic stellate cell activation which exacerbates fibrosis. Reduction in ammonia concentrations with OCR-002 prevents hepatocyte cell death and progression of fibrosis supporting a rationale for targeting ammonia as a potential treatment for NASH.

THU-511

During aging osteopontin deficiency increases vulnerability to non-alcoholic fatty liver disease progression and the associated extrahepatic metabolic complications

B.G. Santos[1], F. Gonzalez-Romero[1], M. Nuñez-García[1], D.M. Congregado[1,2], D.S. de Urturi[1], V.G. de Juan[3], M.L. Martínez-Chantar[3], I. Aurrekoetxea[1,2], X. Buque[1,2], P. Aspichueta[1,2]. *[1]Faculty of Medicine and Nursing, Univesity of The Basque Country, Department of Physiology, Leioa, Spain; [2]BioCruces Health Research Institute, Barakaldo, Spain; [3]Center for Cooperative Research in Bioscience (CIC bioGUNE), CIBERehd, Derio, Spain*
Email: patrietal@hotmail.com

Background and Aims: Osteopontin (OPN), a cytokine part of the senescence associated secretory phenotype, overexpresses in liver fibrosis and hepatocellular carcinoma. Non-alcoholic fatty liver disease (NAFLD) is common in the elderly and carries more metabolic complications than in younger individuals. Here we investigated the involvement of OPN in the development and progression of aging related NAFLD and the extrahepatic metabolic complications.

Method: OPN deficient mice (OPN-KO) mice and their control littermates (WT) of 3, 10 and 20 month-old were used. A group of mice was fed a high-fat diet (HFD) for 16 weeks until sacrificed at 20 months-old. Immunohistochemistry analysis, lipid concentration, de novo lipogenesis and beta oxidation fluxes were analyzed.

Results: During aging circulating and liver OPN levels increased at 10 month-old and maintained high in 20 month-old WT mice, in which the increase in serum OPN was even higher when fed a HFD. The number of senescent hepatocytes, liver p21 and E2F1 protein levels, which controls de novo lipogenesis in liver, were higher in 10 month-old OPN-KO mice than in their control mice. p53 levels increased at 20 month-old just in OPN-KO. Liver triglycerides (TG), diglycerides and cholesteryl esters, de novo lipogenesis fluxes and fatty acid synthase levels together with serum TG levels were higher in 10 month-old OPN-KO mice than in WT mice. Liver lipid storage maintained stable in 20 months-old OPN-KO mice liver, in which fibrosis was increased as compared to their age-matched WT mice. Feeding a HFD to 16 month-old mice induced similar weight gain in both genotypes, but led to a higher metabolic dysregulation in OPN-KO mice; the HFD worsened insulin sensitivity, increased serum TG levels and adipose tissue lipolysis. Even though the HFD did not induce the liver lipid storage of the WT mice, Sirius red staining and F4/80 protein levels were higher.

Conclusion: OPN deficiency during aging induces a premature age related phenotype. It plays a protective role in the metabolic dysregulation of aging. E2F1 transcription factor could be involved in liver lipid storage and the associated extrahepatic metabolic complications in OPN-KO mice.

THU-512

Discovery and validation of new modulators of necroptosis using phenotypic high throughput screening of a large compound library

H.M. de Sousa Brito[1], V. Marques[1], M.B. Afonso[1], D. Brown[2], U. Börjesson[3], N. Selmi[3], M. Fitzek[4], C.M.P. Rodrigues[1]. [1]*Research Institute for Medicines, iMed.ULisboa, Faculty of Pharmacy, University of Lisbon, Cellular Function and Therapeutic Targeting, Lisboa, Portugal;* [2]*Astrazeneca, Hit identification, Waltham, United States;* [3]*Astrazeneca, Hit identification, Mölndal, Sweden;* [4]*Astrazeneca, Hit identification, Cambridge, United Kingdom*
Email: hugobrito1@gmail.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the Western world, representing an important public health concern. Disruption of the equilibrium between cell death and proliferation may be at the origin of NAFLD pathogenesis. We have previously shown that regulated necrosis or necroptosis plays a key role in non-alcoholic steatohepatitis (NASH). Here we aim to discovery novel, selective and potent inhibitors of necroptosis, which might evolve to potential therapeutic strategies. Benefiting from privileged research collaborations on target innovation between academia and pharma industry, we have gained access to a high-quality, large compound pharma collection of over 250,000 compounds.
Method: Compounds were screened at 30 μM for their ability to block TNF-α-induced necroptosis (30 μM; 8 h) in murine fibrosarcoma L929 cell line, using a bioluminescent cytolysis assay.
Results: From the full library screening, valid data was achieved for 251,879 compounds. For hit selection, exclusion criteria included qualitative and quantitative parameters, ZScore and percentage of cell death inhibition. A cut off threshold of >30% inhibition of cell death by tested compounds and a ZScore <−10, led to 3,353 active hits, corresponding to 1.3% hit rate for the full library. For positive hits, dose-response curves were built using a 10-point concentration range of 0.004–100 μM to quantitatively assess inhibitory potency of selected compounds in murine L929 and human Jurkat T FADD(−/−) cell lines. Further selection comprised exclusion criteria of pEC50 < 5 (EC50 < 10 μM) in both cell lines, leading to 1,000 actives at 29.8% hit rate. Next, using Jurkat E6.1 cells stimulated with cycloheximide (0.5 μg/ml; 8 h) for apoptosis induction, selected compounds were tested in caspase-3/-7 enzymatic activity assays using a 4-point concentration range of 0.03–30 μM, active hits protecting from apoptosis were excluded. Moreover, 33 and 21 compounds showed RIPK1 and RIPK3 inhibitory kinase activity, respectively, although the vast majority protected from necroptosis through yet undetermined mechanisms of action. 109 compounds were selected based on chemically clusters and EC potency.
Conclusion: Target identification and hit to lead medicinal chemistry is now expected to deliver optimized molecules that will then be evaluated in experimental murine models of NASH.
Funding: PTDC/BIM-MEC/0895/2014; SAICTPAC/0019/2015; SFRH/BD/110672/2015.

THU-513

Pharmacological inhibition of myeloperoxidase attenuates non-alcoholic steatohepatitis-induced liver fibrosis in mice

A. Koop[1], N. Thiele[1], D. Steins[1], T. Diedrich[1], E. Michaëlsson[2], J.S.Z. Wiesch[1], A.W. Lohse[1], J. Heeren[3], J. Kluwe[1]. [1]*University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany;* [2]*AstraZeneca R&D;* [3]*University Medical Center Hamburg-Eppendorf, Institute of Biochemistry and Molecular Cell Biology, Hamburg, Germany*
Email: a.koop@uke.de

Background and Aims: Myeloperoxidase (MPO) activity has been associated with obesity, arterial hypertension and cardiovascular disease all of which are outcome-relevant comorbidities of non-alcoholic steatohepatitis (NASH). Moreover, MPO-positive cells are present in the histology of NASH. Our aim was to explore the therapeutic potential of MPO inhibition in a mouse model of NASH.
Methods: MPO levels were assessed by ELISA in the sera of healthy controls and patients with non-alcoholic fatty liver disease (NAFLD). C57/Bl6J mice were fed a high-fat, high-carbohydrate (HFHC) diet to induce NASH. After several weeks, a subgroup of mice was sacrificed to characterize the baseline NASH phenotype. Another subgroup was switched to a HFHC diet containing the MPO inhibitor AZM198, provided by Astra Zeneca, while the control group was continued on HFHC diet without the inhibitor. The NASH phenotype was characterized by histology, qPCR and ALT levels. We performed 2 independent experiments with different timelines: For a short-term experiment mice received baseline HFHC feeding for 10 weeks, and 16 weeks baseline feeding for a long-term experiment, each followed by 8 weeks on HFHC diet with or without AZM198.
Results: MPO serum levels were elevated in patients with NAFLD compared to healthy controls. Also, mice fed a HFHC diet displayed significantly elevated MPO serum levels and increased numbers of MPO-positive cells on liver histology compared to mice on a chow diet. Reduced MPO-mediated liver damage was demonstrated by decreased 3-Chlorotyrosin-staining in AZM198-treated mice in both experiments. In the long-term experiment, alpha smooth muscle actin (aSMA) and sirius red staining demonstrated a significant decrease in liver fibrosis in AZM198-treated mice compared to control mice. This could be confirmed in the short-term experiment by aSMA staining, while collagen deposition was too mild at this time point for sirius red quantification. However, in AZM198-treated mice, qPCR revealed a decreased expression of fibrosis-related genes (Col1a1, TIMP1) and ALT levels were significantly lower compared to controls at the early time-point. Hepatic steatosis assessed by oil-red o staining was significantly decreased in AZM198-treated mice in both experiments. AZM198 had no effect on HFHC diet-induced weight gain or insulin resistance in either experiment.
Conclusion: Our data indicate that pharmacological MPO inhibition attenuates the progression of NASH including NASH-induced liver fibrosis in mice.

THU-514

Angiopoietin-like protein 8 is a novel vitamin D receptor-targeted lipogenic gene associated with non-alcoholic fatty liver

Á. Gónzalez-Rodriguez[1,2], P. Petrov[3,4], E.D. Pozo-Maroto[1,2], C. Guzmán[3], J.R. de Cía[1,2], J. Vargas-Castrillón[1,2], A. Saez[1,2], E. Rey[1,2], M.E. Miquilena-Colina[1], O.L. Iacono[5], J.V. Castell[3,4], R. Jover[3,4], C. García-Monzón[1]. [1]*Instituto de Investigación Sanitaria Princesa, Research Unit, University Hospital Santa Cristina, Madrid, Spain;* [2]*CIBERehd, Madrid, Spain;* [3]*Instituto de Investigación Sanitaria La Fe, Experimental Hepatology Unit, Valencia, Spain;* [4]*CIBERehd, Valencia, Spain;* [5]*Hospital del Tajo, Gastroenterology Unit, Aranjuez, Spain*
Email: garciamonzon@hotmail.com

Background and Aims: Circulating vitamin D (VD) deficiency (VDD) and increased hepatic VD receptor (VDR) expression have been reported in patients with non-alcoholic fatty liver disease (NAFLD) but whether a relationship between serum VD and its hepatic receptor exists as well as the significance of VD/VDR signalling in NAFLD setup remain to be elucidated.
Method: Serum VD and bile acid (BA) concentrations, and hepatic mRNA levels of VDR and VD/VDR-related genes were evaluated in patients with biopsy-proven non-alcoholic fatty liver (NAFL) and in subjects with histologically normal liver (NL). We also aimed to uncover novel VDR target genes and the potential mechanisms for VDR upregulation in human hepatocytes.
Results: Prevalence of VDD was similar in NAFL patients (60%) and subjects with NL (57.3%) whereas hepatic mRNA levels of VDR, cytochrome P450 (CYP) 2R1, CYP27A1, CYP3A4 and angiopoietin-like protein 8 (ANGPTL8) were significantly higher in NAFL patients than in NL subjects. Noteworthy, hepatic VDR mRNA levels correlated inversely with serum VD concentrations and positively with liver

ANGPTL8 mRNA as well as with both serum triglycerides and total cholesterol levels but only in NAFL patients. Moreover, a significant increase in serum conjugated BA, largely glycine-conjugated litho-cholic acid (LCA), was observed in NAFL patients. In addition, we demonstrated in cultured human hepatocytes that ANGPTL8 mRNA is induced upon VDR activation with VD and/or LCA, and that free fatty acids and insulin are able to upregulate both VDR and ANGPTL8 gene expression.
Conclusion: In a setting of low VD and high BA circulating levels, VDR signalling is increased in the liver of NAFL patients which could contribute to NAFL setup by upregulating lipogenic target genes, such as ANGPTL8, in human hepatocytes.

THU-515
The liver-specific deletion of the respiratory chain inhibitor MCJ attenuates NAFLD progression by enhancing hepatic beta-oxidation

L. Barbier-Torres[1], T.C. Delgado[1], P. Iruzubieta[1,2], D.F. Ramos[1], V.G. de Juan[1], M. Varela-Rey[1], P.F. Tussy[1], I. Zubiete-Franco[1], J. Simón[1], F.L. Otsoa[1], D.M. Congregado[3], B.G. Santos[3], X. Buqué[3], J. Crespo[2], S.C. Lu[4], J. Matos[5], P. Aspichueta[3], J. Anguita[6,7], M. Rincón[8], M.L. Martínez-Chantar[9]. *[1]CIC Biogune, Liver Disease Laboratory, Derio, Spain; [2]Marqués de Valdecilla University Hospital, Digestive Unit, Santander; [3]University of Basque Country & Biocruces Health Research Institute, Physiology, Faculty of Medicine and Nursering, Leioa & Barakaldo, Spain; [4]Cedars-Sinai Medical Center, Division of Gastroenterology, Los Angeles; [5]CIC bioGUNE, Director, Derio; [6]CIC bioGUNE, Macrophage and Tick Vaccine Lab, Derio, Spain; [7]Ikerbasque, Ikerbasque Foundation for Science, Bilbao, Spain; [8]University of Vermont, Robert Larner College of Medicine, Disivion of Immunobiology, Burlington, VT, United States; [9]CIC bioGUNE, Liver Disease Lab, Derio, Spain*
Email: dfernandez.ciberehd@cicbiogune.es

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide affecting over one-third of the population in the U.S. NAFLD comprises a broad range of clinical disorders from steatosis and non-alcoholic steatohepatitis (NASH) to cirrhosis and liver cancer. The molecular mechanisms underlying NAFLD progression are not completely understood and the tools for its early diagnosis are limited. Mitochondrial alterations have been described in a variety of chronic liver diseases including NAFLD. MCJ, also known as DNAJC15, is localized at the inner mitochondrial membrane where it binds and inhibits the electron transport chain complex I.
Method: MCJ expression and activity was studied in NAFLD patients. There were studied MCJ-KO mice and MCJ-wt mice after a targeted silencing of MCJ through tail vein injection of 4 nmol siCtrl/siMCJRNA using Lipofectamine 3.0®. Primary hepatocytes have been obtained through perfusion and targeted silencing was performed using 50 nM siCtrl/siMCJ RNA and 0.4%v/v Darmaphect®.
Results: In this work, we studied the role of MCJ in the pathogenesis of NAFLD and investigated the effect that the absence of MCJ exerts in the progression of the disease. MCJ expression is increased in human NAFLD. Moreover, MCJ silencing protected against hepatic lipid accumulation, liver injury and inflammation in the methionine-choline deficient diet mouse model of NASH. Loss of MCJ led to increased β-oxidation and enhanced mitochondrial respiration, TCA cycle function and glycolysis rate, which maintained mitochondrial function and ATP production. This metabolic adaptations were able to couteract the cytotoxic effects of fat accumulation on mitochondria and ultimately on hepatocytes.
Conclusion: Overall, MCJ emerges as a key regulator of NAFLD paving the way for new therapeuthical approaches.

THU-516
Targeting the NAFLD metabolome and the shaping of precision medicine for patients with NASH

M. Iruarrizaga-Lejarreta[1], I. Martínez-Arranz[1], M.C. Morrison[2], M. Varela-Rey[3], D.F. Ramos[3], L. Delacruz-Villar[3], M. Noureddin[4], M.L. Martínez-Chantar[3], R. Kleemann[2], C. Alonso[1], S.C. Lu[4], J.M. Mato[3]. *[1]OWL Metabolomics, Derio, Spain; [2]TNO, Metabolic Health Research, Leiden, Netherlands; [3]CIC bioGUNE, CIBERehd, Derio, Spain; [4]Cedars-Sinai Medical Center, Division of Digestive and Liver Diseases, United States*
Email: jmmato@cicbiogune.es

Background and Aims: NASH therapy is being developed under the "one drug treats all patients" paradigm. We show here, that a better characterization of the NAFLD metabolome reveals the existence of distinct NASH subtypes, providing the base for personalized treatment.
Method: We have compared the serum metabolome of three mouse models of NASH [Mat1a−/−, methionine and choline deficient diet (MCD), and high-fat fed Ldlr−/−.Leiden mice] with the metabolome of a cohort of 535 individuals with biopsy proven diagnosis of NAFLD.
Results: Analysis of the data indicates the existence of two major NAFLD phenotypes, each of them characterized by a specific metabolic alteration. One (named M-subtype), comprising 40% of the patients and showing a metabolic profile compatible with low hepatic SAMe, impaired VLDL secretion, increased fatty acid uptake and normal de novo lipogenesis (DNL); and a second phenotype (named L-subtype), including 32% of the patients, showing a metabolic profile compatible with normal SAMe and VLDL secretion, and increased DNL. Treatment with obeticholic acid improved NASH in the Leiden mouse model but had no effect in the MCD model, confirming the need of developing a personalized treatment in NASH.
Conclusion: These results indicate, that serum metabolomic profiling will give the opportunity to identify those patients that respond better to a specific treatment.

THU-517
The pathophysiological significance of nerve growth factor in non-alcoholic fatty liver disease via FXR upregulation

M.-S. Tsai[1], Y.-H. Kao[2], T.-C. Chiu[2], Y.-C. Lin[2], P.-H. Lee[2]. *[1]E-Da Hospital, Department of Surgery, Kaohsiung, Taiwan; [2]E-Da Hospital, Department of Medical Research, Kaohsiung, Taiwan*
Email: drmstsai@gmail.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has become the most common cause of liver disease not only in the western world, but also a major health concern in industrialized countries worldwide. Nerve growth factor (NGF) is a prototypic neurotrophin previously shown to exert hepatoprotective effect in cholestatic disease. Whether NGF is involved in liver metabolic disease remains obscure. This study investigated the regulatory role of NGF in farnesoid X receptor (FXR) expression during NAFLD development.
Method: The expression and histological expression patterns of NGF propeptide (proNGF) and FXR were studied in human liver tissues with NAFLD (n = 100). The mechanism underlying NGF-regulated FXR expression was studied in cultured primary and clone-9 hepatocytes.
Results: Downregulation of proNGF and FXR was simultaneously noted in human NAFLD livers. Immunohistochemistry indicated that NGF and FXR were mainly localized in parenchymal hepatocytes. Correlation analysis indicated strong and positive correlation between the hepatic NGF and FXR expression levels. In vitro mechanistic studies demonstrated that exogenous NGF treatment significantly increased FXR expression in primary hepatocytes. NGF receptor blocker pretreatment demonstrated that both NGF receptors, TrkA and p75 NTR, were involved in the NGF-induced FXR upregulation.

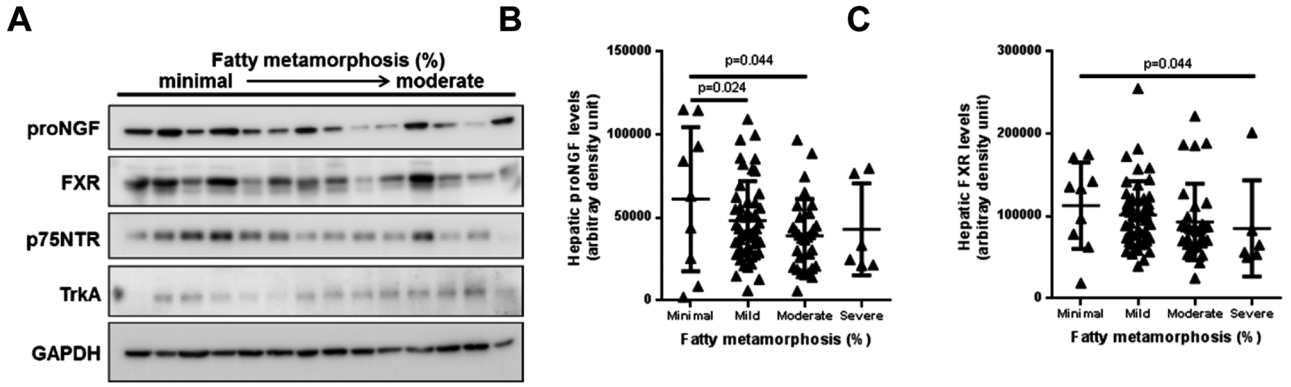


Figure: (abstract: THU-517): The pathophysiological role of NGF in the NAFLD development via FXR upregulation. (A) Expression of NGF precursor (proNGF), FXR, and NGF receptors in human NAFLD livers with minimal or moderate fatty metamorphosis. (Minimal:<5%; Mild: 5–33%; Moderate: 33–66%; Severe:>66% of fatty area) (B) Densitometry measurement of proNGF and FXR protein levels. (C) Pearson's correlation analysis between hepatic proNGF and FXR levels.

Conclusion: NGF and FXR downregulation was concomitantly evidenced in human NAFLD livers. NGF upregulates hepatic FXR expression through NGF-NGFR signaling axis.

THU-518

Modulation of the NLRP3 inflammasome pathway mediates the anti-inflammatory action of indoleamine dioxygenase in experimental NASH

B. Piombanti, E. Vivoli, F. Marra. *University of Florence*
Email: fabio.marra@unifi.it

Background and Aims: The inflammasome pathway is implicated in the pathogenesis of NAFLD, but its regulatory mechanisms are only partially understood. Indoleamine 2,3-dioxygenase (IDO-1), generates kynurenine degrading tryptophan, and is involved in immune regulation and tolerance. In this study, we analyzed the possible cross-talk between the IDO and inflammasome pathways in the setting of experimental NASH.
Method: In mice, steatohepatitis was induced by feeding for 4 weeks a diet deficient in methionine and choline (MCD), with or without administration of 1-methyl-D-triptophan (1MT, 5 mg/ml), an inhibitor of IDO. Cultured RAW264.7 murine macrophages were used for in vitro experiments.
Results: Inhibition of IDO with 1MT was associated with increased expression of proinflammatory genes, including CCL2, IL-1beta, and iNOS. In addition, 1MT treatment was associated with downregulation of components of the NLRP3 inflammasome, including NLRP3, ASC, and IL-1beta. RAW264.7 were treated with low-dose LPS together with 1MT to inhibit IDO. In these conditions, IDO inhibition was associated with up-regulated secretion of IL-1beta, and increased expression of NLRP3 inflammasome components.
Conclusion: We demonstrate the novel interaction between the IDO pathway and NLRP3 inflammasome in murine macrophages and in a mouse model of steatohepatitis. This cross-talk may contribute to explain the complex inflammatory picture observed in NASH.

THU-519

The role of dendritic cells in different stages of non-alcoholic fatty liver disease

O.L. Ramírez-Pérez[1], B. Barranco-Fragoso[2], R. Pichardo-Bahena[3], V.C. Cruz-Ramón[1], P. Chinchilla-López[1], S. Canizales-Quinteros[4], N. Méndez[1]. *[1]Medica Sur Clinic and Foundation, Liver Research Unit, Mexico City; [2]National Medical Center "20 de Noviembre" ISSSTE, Gastroenterology Department, Mexico City, Mexico; [3]National Institute of Rehabilitation, Department of Pathology, Mexico City, Mexico; [4]The National Institute of Genomic Medicine, Genomics Unit, Mexico City, Mexico*
Email: oscartuzos94@gmail.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause of chronic liver disease worldwide. The pathogenesis has not been completely elucidated but it has observed that multiple inflammatory and non-inflammatory factors are implicated. The oxidative stress induces hepatic cell injury, with subsequent inflammatory cell infiltration. Liver Dendritic Cells (DC) are a heterogeneous population of hepatic antigen-presenting cells; their main function is to induce T-cell mediated immunity by antigen processing and presentation to T cells. Nevertheless, the role of DC in NAFLD is incompletely defined. The aim of this study was to investigate the role of DC in fibrosis severity in NAFLD between patients with morbid obesity and obesity grade I.
Method: We enrolled 93 adult patients with NAFLD confirmed by biopsy. They were categorized into two groups; seventy-four morbid obesity patients and nineteen patients with obesity grade I. We collected clinical, biochemical and anthropometric variables. The degree of fibrosis was evaluated in all patients using the liver biopsy and the inflammatory activity was assessed according to the NAS Score System (NAS). In addition, the expression of DC were detected by immunohistochemistry using CD11c.
Results: We have summarized the main results in the Table 1 related to metabolic and anthropometric variables. We found that the expression of DC were similar in the morbid obesity group with and without fibrosis; however, in patients with grade I of obesity the DC expression was higher in group of fibrosis. On the other hand the mean of NAS score in all patients was 4. As we expected those patients with fibrosis and higher expression of DC were male and older.

Table 1: NAFLD patients according to the grade of obesity

	Patients with morbid obesity		Patients with obesity grade I	
	Non-fibrosis (n = 44)	Fibrosis (n = 30)	Non-Fibrosis (n = 9)	Fibrosis (n = 10)
Male, n (%)	13 (29.5)	10 (33)	3 (33)	5 (50)*, **
Age mean, SD	36.8 (9.5)	37.1 (9.9)	49.5 (12.8)	58.4 (4.2) **
Metabolic syndrome n (%)	29 (66)	16 (53)	4 (44)	4 (40) *
BMI (Kg/m^2) mean, SD	45.4 (6.9)	44.1 (6.0)	30 (1.4)	30.2 (2.77)
Glucose (mg/dL) mean, SD	100.7 (27.3)	99.3 (26.6)	103.7 (28.1)	113.4 (39.8) **
Triglycerides (mg/dL) mean, SD	174.5 (96)	136.3 (589	261 (209.6)	166.3 (88.5) **
ALT (U/L) mean, SD	42.5 (32)	38.9 (24)	35.5 (10.93)	57.9 (30.7) **
DC (CD11C) n(%)	29 (66)	20 (67)	8 (88)	10 (100)*

All presented as mean (SD) T Student test, *Proportions Chi-Square Test **p < 0.05.

Conclusion: We found that DC are expressed mostly in patients in the early stage of fibrosis and we believe that this kind of cells are important in the progression of the non-alcoholic steatohepatitis (NASH). We speculated that since the DC are involved in the immune response. Its role in the liver inflammation is important in the progression of NAFLD. However more studies are needed to define the molecular mechanism implicated in this process.

THU-520

Evolving alterations of hepatic macrophage population in the disease progression of non-alcoholic ateatohepatitis in a mouse model

X. Zhou, F. Yang, B. Ye, G. Ying, Y. Yang, H. Zhu, Z. Chen. *Zhejiang University, State Key Laboratory of Infectious Disease Diagnosis and Treatment, Institute of Infectious Diseases, First Affiliated Hospital, School of Medicine, Hangzhou, China*
Email: 11418232@zju.edu.cn

Background and Aims: NAFLD (non-alcoholic fatty liver disease) becomes one of the most common forms of chronic liver disease. The aim of the study was to investigate the role of liver macrophages in the development of liver inflammation and injury caused by non-alcoholic steatohepatitis (NASH).
Method: In the study, an experimental mouse model of NASH was established by MCD diet feeding. During the 4 weeks of MCD diet, content and subtypes of hepatic macrophages and serum cytokines were detected weekly.
Results: The percentage of F4/80+ macrophages in liver MNCs (mononuclear cells) increased on the 1st week and kept on a high level in the following weeks. And the increased macrophages were $CD11b^+$ $F4/80^+$, which were thought to be recruited from the peripheral blood. Further, we found that CD206+ $F4/80^+$ M2 macrophage increased and peaked on the 1st week, and gradually fell to a level lower than normal at the 4th week. In contrast, the level of iNOS, an M1 marker, began to increase on the 3rd week as the progression of NASH. And the level of serum pro-inflammatory cytokines such as TNF-α and IL-6, and anti-inflammatory cytokines such as IL-10, was altered in parallel with macrophage polarization.
Conclusion: These observations suggested that the macrophage recruitment and polarization were associated with NASH progression.

THU-521

Partial hepatectomy and hemodynamics: insights from numerical modeling on vascular response

C. Audebert[1], P. Bucur[2], M. Bekheit[3], N. Boissier[1], D. Drasdo[1], J.-F. Gerbeau[1], E. Vibert[3], I. Vignon-Clementel[1*]. *[1]Inria and Sorbonne Université UPMC, France; [2]CHRU Hop. de Tours, France; [3]Inserm and AP-HP Hop. Paul Brousse, France*
*Presenting and corresponding author

Background and Aims: Partial hepatectomy triggers hemodynamics changes, which causes and consequences are still matter of debate. The precise link between liver architecture, perfusion and function remains to be fully elucidated. The aim of this work is to qualitatively and quantitatively characterize the link between architecture and hemodynamics in the context of partial hepatectomy, based on mathematical models of systemic and hepatic hemodynamics.
Method: Partial hepatectomy was performed in a swine model, during which multimodality data were collected (CT imaging, continuous pressures and flow rates, histological material, …) (Bucur et al. 2017). First, hemodynamics after 75% partial ablation was simulated in a whole-body dynamic model (Audebert et al. JBM 2017). The model parameters were calibrated with pre-operative hemodynamics measurements. The impact of blood infusion or blood volume change on hemodynamics was analyzed. Changes in hepatic artery pressure and flow cardiac pulsatility were also studied with a whole-body hemodynamics model, where arteries from the heart to the liver were modeled with a spatially more precise mathematical model (1D Euler equations) (Audebert et al. CMAME 2017). Finally, the first post-operative day was studied with a multiscale model. The resistance of the model representing the micro-circulation of the liver was estimated from a more precise model of the micro-circulation based on histological analysis (Hoehme et al. PNAS 2010). In addition, different mechanisms impacting hemodynamics were studied (organ vascular dilation, liver micro-circulation changes …). All the simulations were compared to measurements made on the first post-operative day after 75% partial ablation on swine.
Results: The model quantitatively captures the typical increase of portal pressure, increase of liver portal to venous pressure 'gradient', slight decrease of portal flow and major decrease in arterial flow, for a 75% hepatectomy. The 75% decrease in hepatic arterial flow can be explained by the resistance increase induced by the surgery, without hepatic arterial buffer response (HABR) mechanism being needed to account for this change. The different post-operative states, observed in swine experiments, are reproduced with the proposed model. An architectural change of the liver vascular structures appears to be the cause of the hepatic artery hemodynamics pulsatility change, rather than just a mass reduction due to 75% hepatectomy. This hypothesis is compatible with a lesser change observed when going from 75% to 90% hepatectomy. Finally, the multiscale study makes apparent the need to take into account the microcirculation but also systemic vascular responses to understand the early days of liver regeneration.
Conclusion: An explanation for the major hemodynamics changes and inter-subjects post-operative hemodynamics variability is thus proposed for partial hepatectomy. The presented framework enables us to make hypothesis on the probable vascular mechanisms that can take place during the first days of regeneration. Moreover, it can be easily adapted to other species circulations and to different pathologies (e.g. cirrhosis – Audebert et al. IEEE Trans.Biom.Eng. 2018). Clinical translation is on-going.

EASL JOURNAL OF HEPATOLOGY

Posters Friday, 13 April 2018

Nurses' research in Hepatology

FRI-001

A six month follow-up study to determine the clinical utility and patient acceptability of fibroelastography in detection and treatment of alcohol-related liver disease

L. Owens[1,2], A. Thompson[2], C. Siju[1,3], P. Richardson[1]. [1]*Royal Liverpool University Hospital, Hepatology, Liverpool, United Kingdom;* [2]*University of Liverpool, Wolfson Centre for Personalised Medicine, Liverpool, United Kingdom;* [3]*University of Liverpool, Medical School, Liverpool, United Kingdom*
Email: lynno@liv.ac.uk

Background and Aims: It is axiomatic that all alcohol-related death is preventable. Furthermore, 1/3 of all deaths from liver disease are attributed to alcohol, and these deaths are increasing. One reason for this is that alcohol-related liver disease (ARLD) remains under-recognised and undertreated. We suggest that early detection by means of fibroelastography (FE) in alcohol treatment clinics (ATC) is an ideal opportunity for early detection of ARLD in a high risk population with no previous diagnosis.
Aim: To determine the clinical utility and patient acceptability of FE to identify the presence of liver fibrosis.
Method: An observational prospective clinical audit. The primary outcome was to detect the presence of fibrosis using FE, and a secondary outcome was to measure FE change over time related to alcohol consumption. Patients were also asked to complete a satisfaction survey including a question "Did knowing your fibroscan result encourage you to reduce or stop drinking". Participants**:** Acute hospital, ATC patients attending for treatment of an alcohol-use disorder with no previous history of ARLD.
Results: Of the 428 patients screened Dec 2015 – Sept 2017; 314 had no evidence for fibrosis with a Kpa score <8, 47 had a score ≥8 and <12, 19 had a score ≥12, <19.4 and 48 had a score ≥19.5. Sixty-three participants had FE at baseline and six month follow-up. At baseline, patients had an average daily consumption of 18.2 (SD = 10.5) UK units and a mean FE result of 11.9Kpa (SD = 11.9); F0-1 = 30, F1-2 = 15, F2-3 = 7, F3-4 = 11. At six months, there was a positive relationship between units consumed and FE result, such that a reduction in units was associated with a decrease FE score (B = 0.36, 95%CI = 0.16 to 0.57; p = 0.01). Of 120 patients surveyed 117 stated that knowing the FE score helped motivate them to reduce their drinking.
Conclusion: Nurse-led ATC setting is a valuable and effective setting for the early detection of ARLD utilising FE. Importantly, we identified 67 patients with an FE score consistent with cirrhosis and no previous history of ARLD. Furthermore, reductions in alcohol consumption were associated with reductions in fibrosis. The FE score is therefore potentially useful as an objective measure for comparisons over time, and perhaps more importantly is a useful clinical tool for patient feedback in motivation to reduce/stop drinking, and provides objective evidence for the positive effects of alcohol reduced drinking.

FRI-002

Pilot study: Evaluation of the role of the coordinating nurse in the management of patients with hepatocellular carcinoma and treated with chemoembolization

J. Devictor[1], W. Aurélie[2], Y. Mouelhi[3], B. Mohamed[4], F. Durand[1].
[1]*hôpital beaujon, hépatologie, Clichy, France;* [2]*Centre hospitalier de Lens, Lens, France;* [3]*Aix-Marseille Université, Faculté de Médecine La Timone, Marseille, France;* [4]*Hôpital Beaujon, Oncologie, Clichy, France*
Email: julie.devictor@aphp.fr

Background and Aims: Hepatocellular carcinoma is a significant public health problem with an annual incidence of 16.4/100,000 adults. In a context of constant healthcare adaptation, the management of these patients has been revamped. The notion of "care pathway" has been introduced and led to the creation of new positions such as complex care pathway coordinating nurses. We wanted to determine whether the presence of the coordinating nurse improves care efficiency for patients with hepatocellular carcinoma treated with chemoembolization.
Method: A comparative and retrospective cohort pilot study was carried out in two french university hospitals. The coordinating nurse position was effective in center A but not in center B. Clinical and coded medical data from 107 patients with hepatocellular carcinoma and treated for the first time with trans-arterial chemoembolization (TACE) between January 1rst, 2015 and January 31rst, 2015 were collected (center A: 62/center B: 45). Center A was using two different approaches for TACE (DC Beads and lipiodol), whilst center B only lipiodol TACE. There was no significant difference observed regarding tumor features: the average tumor size was 4.68 ± 3.08 cm in center A and 3.60 ± 3.56 cm in center B. The average number of nodules was 2.95 ± 2.01 in center A and 2.47 ± 1.46 in center B. All treated patients were Child A or B7. Higher proportion of Child B patients were observed in center B compared to center A (37.8% and 19.4% respectively).
Results: Univariate then multivariate analysis, adjusted for possible confounding factors such as disease stages, showed that the average length of stay in hospital of patients hospitalized for their treatment was significantly shorter in the center with coordinating nurses: 2.98 ± 1.91 days in center A vs. 4.67 ± 4.25 days in center B (p = 0.01). There was no significant difference for re-admissions and early emergencies. No differences were observed regarding tumor features, patients' characteristics or treatment approaches.
Conclusion: The anticipation and regulation missions of the coordinating nurse may contribute to improving care efficiency. However, a center effect cannot be excluded. These results will be confirmed by a planned prospective multicentric study. Interesting results from such studies can promote the nursing role in our health system while the position of advanced practice nurse soon to be implemented in France.

FRI-003

Patient education results in better sustained virological response to anti-viral therapy in a high number of patients with chronic hepatitis C than conventional care

François Habersetzer[1,2,3], M. Doffoël[1,3], C. Frederic[3], F.D. Nino[3], L. Jean-Philippe[3], E. Florence[3], H. Carmen[4], T. Baumert[1,2]. [1]*Pôle Hépato-digestif, Hôpitaux Universitaires de Strasbourg, Strasbourg, France;* [2]*Unité 1110, INSERM, Strasbourg, France;* [3]*SELHVA, Service Expert de Lutte contre les Hépatites Virales d'Alsace, Hôpitaux Universitaires de Strasbourg, Strasbourg, France;* [4]*SOS Hépatites Alsace Lorraine, SOS Hépatites, Strasbourg, France*
Email: francois.habersetzer@chru-strasbourg.fr

Background and Aims: Patient education may add benefit to chronic hepatitis C management and improve response to anti-viral therapy. This study aimed to evaluate the factors associated with participation in a patient education program for the treatment of chronic hepatitis C and the program's impact on treatment effectiveness.
Method: Overall, 453 consecutive patients were treated with direct-acting anti-viral therapy (DAA) between April 2014 and December 2016. Of these, 30 were treated with pegylated interferon, ribavirin, and sofosbuvir, and 423 with DAA alone, with or without ribavirin. All patients were proposed to take part in a patient education program.
Results: Altogether, 312 patients took part in the patient education program (69%). The number of nurse-led consultations varied between one and six per patient. On univariate analysis, the patients who participated in patient education were younger ($p < 0.001$) and more often in a precarious situation, migrants, or drug users ($p < 0.0001$). They also were receiving psychiatric or addiction treatment and lived near the hospital ($p < 0.0001$) more often. Treatment for the first time and treatments with pegylated interferon were also more common ($p < 0.01$). On multivariate analysis, four factors were associated with participation in a patient education: precarious situation (OR = 25.76), pegylated interferon therapies (OR = 5.93), place of residence (OR = 5.52), and first treatment (OR = 2.70).
All treatments taken together, sustained virological response for 12 weeks or more (SVR 12) was higher among patients who participated in patient education (94.2%) than those who did not (89.3%) ($p = 0.06$). This superiority was also observed in patients treated with DAA ± ribavirin (94.7% *vs.* 88.6%; $p = 0.009$). In patients who participated in patient education, SVR was independent of precarious situation, migrant status, and drug use, being around 95%.
Conclusion: Most patients treated for chronic hepatitis C agreed to patient education, thereby improving the rate of sustained virological response among patients treated with DAA.

FRI-004

Reliability and validity study of the Turkish version of the chronic liver disease questionnaire

F. Celik, H. Bektaş. *Akdeniz University, Antalya, Turkey*
Email: feryacelik@gmail.com

Background and Aims: The aim of this study was to adapt of the Chronic Liver Disease Questionnaire to Turkish and determine the validity and realibility of the scale.
Method: This methodological study was conducted between November 24, 2016 and April 5, 2017 at the Gastroenterology Clinic and Gastroenterology Policlinic of the Akdeniz University Hospital with 235 chronic liver patients. "Personal Information Form", "Child-Pugh Scoring System Form", "Chronic Liver Disease Questionnaire (CLDQ)" and "Chronic Liver Disease Quality of Life Scale 2.0" were used as data collection tools. This project received ethical approval from the ethics committee of Akdeniz University Clinical Research Ethics Committee and obtained permission from Center for Outcomes Research in Liver Diseases and individuals.
Results: Half of the participants are men, half of the patients diagnosed with cirrhosis. In evaluating the validity analysis; scope validity, validity according to a reference, structure validity methods were used. As a result of the validity analysis, it was determined that the scale consists of six sub-dimensions. There was no substance removed from the original scale. In evaluating the reliability analysis, internal consistency, invariance, assessment of substance analyzes was used. The overall Cronbach alpha coefficient of the scale was 0.95, and the Cronbach alpha values of the subscales ranged from 0.53 to 0.94. In the internal consistency evaluation, the correlation coefficient between the two applications ($r = 0.79$) was found to be high in the test re-test analysis results. When substance analyzes were examined, it was found that the mean of the substances were close to each other, when the average of the upper and lower groups were examined, the discriminatory properties of the substances were high and the behaviors to be measured in the symptoms of chronic liver diseases were found to be reliable.
Conclusion: The Chronic Liver Disease Scale was a valid and reliable tool to measure the quality of life of chronic liver disease patients by determining the frequency of symptoms in chronic liver diseases. It was suggested that the Turkish version of the Chronic Liver Disease Scale should be be used in symptomatic evaluation of chronic liver disease.

FRI-005

Using healthcare professionals' views to update and improve the Royal College of Nursing Caring for people with liver disease: A competence framework to deliver quality person centred care

L. Greenslade[1], M. Clayton[2]. [1]*Royal Free Hospital, Hepatology Department, London, United Kingdom;* [2]*University of Leeds, School of Healthcare, Leeds, United Kingdom*
Email: lynda.greenslade@nhs.net

Background and Aims: Liver disease is the third most common cause of premature mortality in the United Kingdom (UK). Two National Confidential Enquiry into Patient Outcome and Death (NCEPOD) reports on alcohol related liver disease and upper gastrointestinal bleeding raised concerns about suboptimal care of patients with complications of cirrhosis. Reflecting concerns that many healthcare professionals (HCPs) have poor understanding of how to identify and treat those with liver disease leading to poor quality care. Increased HCPs awareness of alcohol, viruses and obesity related liver disease can support the public health agenda in tackling rising rates of liver disease.
In 2013 the Royal College of Nursing (RCN) *Caring for people with liver disease: a competence framework for nursing* was published to help improve HCPs knowledge and skills identifying those at risk of developing liver disease; and care for those with existing liver disease. A recent review of the framework included how HCPs had used the framework and what other factors might improve future use by HCPs.
Method: A detailed survey sent to members of the RCN Gastrointestinal Nursing Forum to capture views of nurses throughout the UK who had experience of using the framework. This feedback was used to inform the revised edition.
Results: There was a range of responses from those surveyed ($n = 93$) with mostly positive feedback including narrative quotes. Identified barriers to implementation included perceived difficulty in fitting the right competence to the right patient; some nurses found the translation of theory into practice a challenge due to external issues such as time and level of seniority. Many wanted help with signposting and further examples of how to use the framework. An unexpected bonus was the use of the framework to develop and support new clinical roles and redefine original job descriptions to be more person centred. Many nurses said they could add existing liver nurse teaching packages into the implementation of the framework. The section on how to implement the framework in practice was strengthened by mirroring the nursing process of assessment, planning, implementing and evaluation to assist nurses to feel more confident in completing the competence framework.
Conclusion: The revised edition should further support all nurses who work with people with or at risk of liver disease to be able to identify and develop person centred liver care throughout the spectrum of care from early identification and prevention to end of

life care ensuring that quality care is embedded into practice for all liver patients.

FRI-006

Hepatitis C treatment in prisons through a nurse-led program with telemedicine

A. Olsson[1], K. Roos[1], S. Larsen[1], K. Lindahl[2], C. Gahrton[2], A. Oksanen[1], F. Öhrn[3], S. Aleman[2], K. Said[1]. *[1]Karolinska University Hospital, Dep. of upper GI diseases, Stockholm, Sweden; [2]Karolinska University Hospital, Dep. of Infectious Diseases, Stockholm, Sweden; [3]Karolinska University Hospital, Center for Innovation, Stockholm, Sweden*
Email: annika.el.olsson@sll.se

Background and Aims: Hepatitis C virus (HCV) infection is highly prevalent in prison population. Until now, several barriers to the HCV treatment for incarcerated as e.g. substantial side effects of previous interferon-based treatment, and the need of prisoner movement for assessing the care have led to treatment of only a small fraction of the incarcerated. With introduction of new direct acting antivirals (DAAs), there is an opportunity to treat HCV infected persons with mild side effects, high cure rate and short treatment time. The barrier with transport of prisoners needs though to be overcome with local delivery of HCV care to prisons.
The main objective of this project is to facilitate the assessment of liver fibrosis and treatment of HCV for prisoners through a nurse-led program.
Method: This is a nurse-led program with implementation of telemedicine in eight prisons of Stockholm County, Sweden. Planning, implementation and administration is handled by a project team consisting of two registered nurses and one part-time administrator, in collaboration with physicians, at Dep. of upper GI diseases/Dep. of Infectious Diseases at Karolinska University Hospital. The program includes: 1. The team has developed educational lectures for health care personal at prisons through video-link. 2. The initial consultation of the HCV infected patient, including liver elasticity measurement with portable FibroScan, is performed by a nurse at the local prison. 3. Consultation by physician via telemedicine. 4. Nurse-supervised HCV treatment for patients who meet the treatment criteria (at present at least F2 fibrosis).
Results: Through a collaboration between Karolinska University Hospital and The Swedish Prison and Probation Service, 42 incarcerated patients (74% men, 26% women) have been included so far in the program. Liver elasticity measurements have showed following distribution of fibrosis: 62% F0-F1, 26% F2, 7% F3 and 4% F4. Start of DAA treatment has been initiated in 13 persons. The final results of the project are planned to be analyzed at the end of 2018.
Conclusion: This is a project designed to enhance the care of HCV patients in prison settings, with new paths of delivering individualized care in a key population for targeting HCV epidemics. Program with delivery of HCV care to local prisons need to be part of HCV elimination plan.

FRI-007

Comparison of different models of nursing care delivery in the management of hepatitis C treatment among people who inject drugs

G. Rudel[1], V. Finessi[1], A. Nottaris[1], M. Borojevic[2], P. Messina[1], A. Moriggia[1,2]. *[1]Epatocentro Ticino, Lugano, Switzerland; [2]Ingrado Addiction Clinic, Viganello, Switzerland*
Email: giovanna.rudel@epatocentro.ch

Background and Aims: Hepatitis C Virus (HCV) treatment can be successfully administered in People Who Inject Drugs (PWID) if delivered in adequate settings with multidisciplinary models of care.
Method: We described the role of nurses in three different settings of HCV treatment for PWID in Southern Switzerland: (1) tertiary center for liver disease with specifically trained nurses; (2) integrated treatment "all under one roof" in addiction center; (3) directly observed therapy. We analyzed and compared HCV therapy results and characteristics of the patients in the three groups.
Results: Hundred and thirty-four PWID started HCV treatment and were included in the analysis. Among 66 treated patients with available results at the moment of the abstract submission, an interim analysis was completed: mean age was 48 years, 24% (16) were women and 27% (18) failed a previous HCV therapy. Most of the patients (41) were treated in a tertiary clinic for liver disease with the support of nurses with expertise in PWID management (Model 1). One patient was lost of follow up, 3 had a virological failure and 37 (93% of those who completed treatment) met a sustained virological response 12 weeks after end of treatment (SVR12). Twenty-one patients were treated in an addiction center through an integrated care model involving HCV specialist doctor, psychiatrist, nurses and psychosocial support "all under one roof" (Model 2). Of those, 2 died during treatment for reasons unrelated to HCV therapy, 1 stopped treatment for nonadherence, 1 had a virological failure and 17 (94% of those who completed treatment) met SVR12. Only 4 patients were treated as a directly observed therapy during their stay in a stationary rehabilitation center (Model 3). All of them completed the treatment successfully and reached the SVR12 (100%).
Conclusion: Our observation suggests a similar efficacy among the three models of treatment of HCV among PWID. It is important to offer different models of management of HCV, to be able to remove the barriers to access to care in this population.

FRI-008

Is the presence of fat and fibrosis a higher mortality risk factor versus cardiovascular disease?

A.M. Hefner, T. Hassanein. *Southern California Liver Centers, Coronado, United States*
Email: ahefner@livercenters.com

Background and Aims: The epidemic of fatty liver around the world is well recognized. The primary cause of death in this population is cardiovascular disease. Recent data clearly identifies advanced liver fibrosis as the main risk factor of death from NASH. These patients are primarily seen by the primary care physician. To help stratify patients with fatty liver who are at risk of dying from liver diseases we used Fibroscan® as a screening tool. We screened patients and classified them into 3 groups; Group 1 = high fat and liver fibrosis; Group 2 = high fat without liver fibrosis; and Group 3 = high fat and cardiovascular disease and no liver fibrosis.
Method: Between March 6, 2017 and May 29, 2017, 1,650 patients attending a primary care clinic, who have no known history of liver disease, were asked to participate in the screening program. 1,026 individuals agreed to be screened and their demographics, past medical history, and current medications were recorded, as well as their laboratory tests.
Results: 1,026 consecutive patients in a primary care office received a Fibroscan®. There were 376 (36.6%) males and 650 (63.4%) females. The mean age was 44.6 ± 16.8 years. The results are presented in Table 1. A breakdown by age of ≥50 showed that the presence of a risk factor for cardiovascular disease increases by 5 times and is a clinical significant, unlike the presence of significant fat and fibrosis.

Table 1

CAP	<250	≥250
n=	433	593
Fibrosis ≥ 7kPa	5%	10.6%
Presence of Diabetes	2.3%	3.7%
Cardiovascular Risk	12.2%	15.7%

Conclusion: The accumulation of fat alone is unlikely to be the sole stimulus to fibrosis and inflammation. We found co -morbidities of hypertension and hyperlipidemia indicating cardiovascular risk as the main risk factors for mortality and not the presence of significant fat and fibrosis.

FRI-009

Nurse-led clinic for liver cirrhotic patients: Effects on health-related quality of life

M. Hjorth[1], D. Sjöberg[2], E. Kaminsky[3,4], A. Svanberg[3,5], S. Langenskiöld[3], F. Rorsman[6]. *[1]Medical science, Department of medical science, Falun, Sweden; [2]Cerntre for Clinical Research, Dalarna, Falun, Sweden; [3]Uppsala universitet, Department of Public Health and Caring Sciences, Uppsala, Sweden; [4]Mälardalens högskola, School of Health, Care and Social Welfare, Västerås, Sweden; [5]Högskolan Dalarna, School of Health, Care and Social Welfare, Falun, Sweden; [6]Uppsala University, of Gastroenterology and hepatology, Uppsala, Sweden*
Email: maria.hjorth@ltdalarna.se

Background and Aims: Liver cirrhosis affects health-related quality of life (HRQoL) even in early stages. Morbidity is especially high when the disease decompensates, when self-care actions become essential. For the patient, nurse-led clinics in secondary prevention in other chronic diseases has contributed to:

(1) better symptom control
(2) decreased need of inpatient care
(3) improved HRQoL

Firm evidence supporting the role of nurse-led clinic in the management of patients with liver cirrhosis is lacking. In order to improve HRQoL in patients with liver cirrhosis, we decided to compare structured nurse-led clinics, founded in Orem self-deficit theory and motivational strategies, with a group of patients receiving standard care according to clinical routine.

Method: A pragmatic, multicentre randomized controlled study comparing two follow-up models:

Intervention group: Scheduled visits to a nurse-led clinic in addition to visits to physician at gastroenterology departments. Intervals of visits to the nurse-led clinic depends on disease severity (Table 1).

Control group: Standard care at gastroenterology departments.

The areas of the nursing intervention is:

I. Monitoring risk factors due to disease deterioration
II. Information and motivation to perform self-care and medical treatment
III. Nutrition assessment and support
IV. Motivation of life-style changes essential for preventing or delaying disease progress
V. Psychosocial care

Eligible patients are adults with diagnose of liver cirrhosis (n = 500) at six Swedish gastroenterology departments. Primary outcomes are the summary component of the physical and mental domain of HRQoL as measured by RAND-36 at enrolment, and after one and two years.

Results: Recruitment is ongoing and scheduled to continue until 2019.

Liver transplantation and hepatobiliary surgery: Clinical aspects

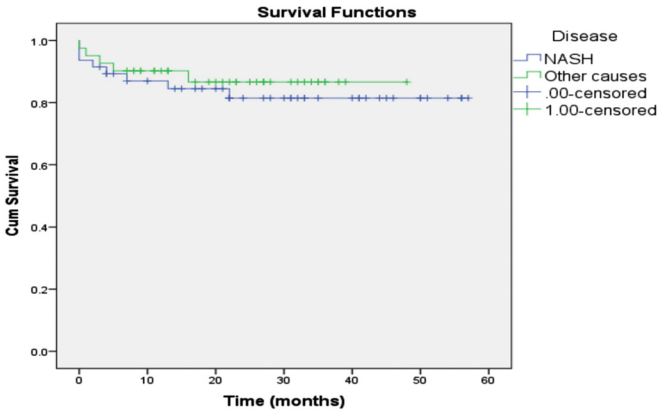
FRI-016

Outcomes of liver transplantation in patients with non-alcoholic steatohepatitis: High recurrence rate in ultrasound and transientelastography

A. Eshraghian[1], M.R. Fattahi[1], S. Nikeghbalian[2], S.A. Malek-Hosseini[2]. *[1]Shiraz University of Medical Science, Gastroenterology and hepatology; [2]Shiraz University of Medical Science, Transplant surgery*
Email: eshraghiana@yahoo.com

Background and Aims: Non-alcoholic steatohepatitis (NASH) is a rapidly increasing indication for liver transplantation surpassing other causes of liver cirrhosis. Recurrence of diseases like auto-immune hepatitis and primary sclerosing cholangitis have been reported after liver transplantation. This study aimed to investigate outcomes including recurrence of disease after liver transplantation in patients with NASH.

Method: In a cross-sectional study, adult (>18 years) patients with liver cirrhosis underwent liver transplantation at Shiraz Transplant Center, Shiraz, Iran between January 2011 and March the 2017 were included. Recurrence of steatosis in patients with NASH was evaluated by ultrasound and transient elastography (TE). Kaplan-Meier curve was used for analysis of post-transplant survival of patients.



Results: Totally 1950 patients were included. 71 patients with NASH underwent liver transplantation during the study period. 14 patients passed away during the study period. Mean post-transplant survival was 42.38 ± 2.35 months in NASH patients and 47.71 ± 2.98 in non-NASH patients (p = 0.558). From 57 patients underwent ultrasound evaluation in a mean follow-up of 15.5 ± 12.6 months after liver transplantation, 33 (57.8%) patients had recurrence of hepatic steatosis. 12 patients had grade II and III and 21 patients had grade I steatosis. In univariate analysis, lower high density lipoprotein (HDL), higher low density lipoprotein (LDL) and warm ischemic time

Table: (abstract: FRI-009)

Study group		Visit intervals: Intervention group		Visit intervals: Control group	
Disease severity		Nurse-led clinic	Physician	Nurse-led clinic	Physician
Compensated disease		1 visit/year	According to clinical routine, minimum 1 visit/year	No visits	According to clinical routine
DeCompensated disease	Within past 12 months	1–2 visit/month			
	Previous decompensation, without symptoms of decompensation	Every 3rd month			

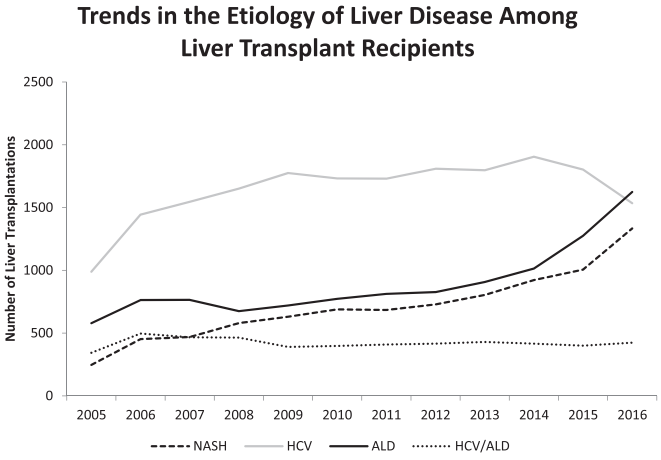
were associated with recurrence of hepatic steatosis ($p < 0.05$). In regression analysis, none of these factors were independent predictor of recurrence in our study population ($p > 0.05$). From 18 patients underwent TE, one patient had no steatosis (S0), 2 patients had S1 steatosis, 3 patients had S2 steatosis and 12 patients had S3 steatosis. 13 patients had different degrees of liver fibrosis. Post-transplant hypertension (OR: 5.3; $p = 0.016$), diabetes mellitus requiring insulin therapy (OR: 4; $p = 0.034$) and higher body mass index (BMI) ($p = 0.015$) were associated with significant fibrosis in TE.
Conclusion: Long-term survival of patients with NASH is comparable with other causes of liver cirrhosis. Recurrence of steatosis both in TE and ultrasound is prevalent and patients with hypertension, DM on insulin therapy and high BMI are susceptible to significant fibrosis.

FRI-017
Can liver transplantation or hepatic resection achieve cure for hepatocellular carcinoma?
A. Cucchetti[1], C. Sposito[2], T. Yang[3], V. Mazzaferro[2], L.D. Carlis[4], J. Zhou[5], S. Roayaie[6], S. Feng[3], M. Cescon[1], S.D. Sandro[4], H. Yifeng[5], P. Johnson[7], A. Pinna[1]. *[1]Alma Mater Studiorum – University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; [2]Fondazione IRCCS Istituto Nazionale Tumori di Milano, Gastrointestinal surgery and liver transplantation, Milan, Italy; [3]Second Military Medical University, Eastern Hepatobiliary Surgery Hospital, Shangai, China; [4]University of Milano-Bicocca and Niguarda-Cà Granda Hospital, General Surgery and Abdominal Transplantation Unit, Milan, Italy; [5]Zhongshan Hospital, Fudan University, Liver Surgery Department, Liver Cancer Institute, Shangai, China; [6]White Plains Hospital – Montefiore Health System, Liver cancer program, New York, United States; [7]University of Liverpool, Department of Molecular and Clinical Cancer Medicine, Liverpool, United Kingdom*
Email: aleqko@libero.it

Background and Aims: Hepatic resection (HR) and liver transplantation (LT) are considered potentially curative therapies for hepatocellular carcinoma (HCC). However, their impact on the life-term has never been investigated. *Statistical cure* occurs when the mortality of a specific population returns to values of that of the general population. The present study aims to provide such estimate after HR and LT for HCC in different clinical scenarios.
Method: Data from 3286 HCC patients treated with LT ($n = 1218$) or HR ($n = 2068$) in 7 tertiary referral hospitals were used to estimate statistical cure. Disease-free survival (DFS) was the primary survival measure, defining cure as the chance of being alive without tumor equivalent to that of the general population matched by age, sex, year and race. Overall survival (OS) was a secondary measure, defining the only chance of being alive, regardless of tumor recurrence, equivalent to that of the matched general population. Distinct multivariable non-mixture (DFS) and mixture (OS) cure models were built for LT and for HR and results within different morphologic criteria were compared. Variations of estimated cure fractions after LT were also adjusted for different drop-out risks in waiting-list to provide an intention-to-treat analysis. Differences between cure fractions were measured through effect size.
Results: Five and 10-year DFS rates were 73.3% and 66.0% after LT, and 33.6% and 19.2% after HR. On this ground, the whole cure fraction after LT was 74.1% and after HR was 24.1% (effect size >0.8). Considering DFS, LT outperformed HR in all transplant criteria considered (effect size >0.8), especially for multiple tumors (effect size > 0.9) and even in presence of a drop-out risk up to 20% (effect size >0.5). Considering OS, 5 and 10-year rates were 77.1% and 67.4% after LT, and 57.3% and 33.9% after HR. On this ground, the cure fraction after LT marginally increased to 75.8% and that after HR increased to 40.5%. Using OS, the effect size of LT over HR in terms of cure decreased (effect size ~0.5), became small (effect size <0.2) when the drop-out risk increased toward ~20%, and even negligible for single tumors <5cm.
Conclusion: As other malignancies, statistical cure can occur even for HCC, primarily with LT and secondarily with HR, depending on waiting-list capabilities and efficacy of treatments of tumor recurrence after HR. In presence of high drop-out risks, HR can be considered as the first treatment option for single tumors <5cm

FRI-018
Alcoholic liver disease surpasses hepatitis C virus in 2016 to become the leading indication for liver transplantation among adults without hepatocellular carcinoma in the United States
J. Wang[1], B. Liu[2], T. Bhuket[2], R. Wong[2]. *[1]California Pacific Medical Center, Medicine, United States; [2]Alameda Health System – Highland Hospital, United States*
Email: rowong@alamedahealthsystem.org

Background and Aims: The success of direct acting antivirals for hepatitis C virus (HCV) is expected to decrease the burden of HCV on adults awaiting liver transplantation (LT). To further investigate this, we aim to evaluate recent trends in etiology of liver disease among LT recipients in the U.S.
Method: Using data from the 2005–2016 United Network for Organ Sharing LT registry, overall trends in etiology of liver disease among adult LT recipients were evaluated, with specific focus on HCV, nonalcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), and combined HCV/ALD. Annual liver disease etiology-specific trends in LT recipients were stratified by sex, race/ethnicity, and presence of hepatocellular carcinoma (HCC), and differences in LT trends were evaluated using Student's t-test.
Results: Among 45,966 adult LT recipients (72.6% male, 74.4% non-Hispanic white, 8.6% African American, 14.8% Hispanic, mean age at LT 56.2 ± 7.9, 24.9% with HCC), 45.1% had HCV, 24.2% ALD, 19.0% NASH, and 11.7% HCV/ALD. The number of LT recipients with HCV peaked in 2014 (1905 patients) and has been declining since, and 2016 was the first year in which ALD surpassed HCV to become the leading indication for LT (2016: ALD, 1624; HCV, 1535; NASH, 1334; HCV/ALD, 424). The number of NASH patients receiving LT increased by 440% (from 247 in 2005 to 1334 in 2016). While ALD also became the leading indication for LT in 2016, among females, NASH surpassed HCV to become the leading indication for LT in 2016. ALD also surpassed HCV in 2016 as the leading indication for LT in non-Hispanic whites and Hispanics, whereas HCV remained the leading indication for LT among African Americans, accounting for 63.8% of LT. Among patients without HCC, similar trends were observed and HCV declined to the third leading indication for LT in 2016, accounting for 21.8% of LT, compared to 29.5% for NASH and 40.2% for ALD, $p < 0.01$. However, among patients with HCC, HCV remained the leading indication for LT in 2016, accounting for 58.6% of LT, compared to 20.1% for NASH and 12.2% for ALD, $p < 0.01$.



Conclusion: HCV as an indication for LT in the U.S. peaked in 2014 and has been declining. 2016 was the first year where ALD surpassed

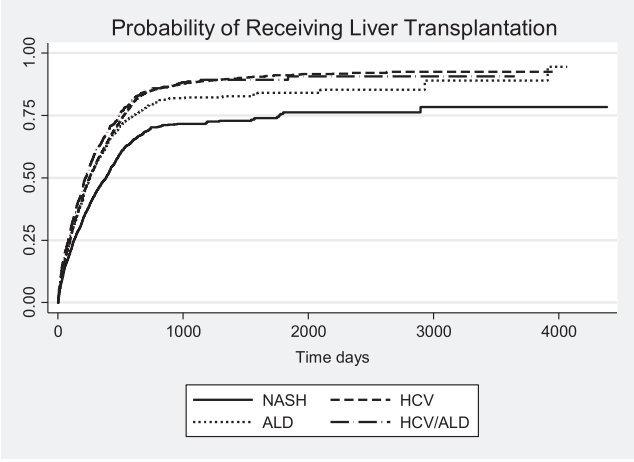
HCV as the leading indication for LT among patients without HCC, with the exception of African Americans where HCV remains the leading indication. NASH became the leading indication for LT among women. HCV remains the leading indication for LT among HCC patients.

FRI-019

Among adults with hepatocellular carcinoma awaiting liver transplantation, Asians, Hispanics, and patients with nonalcoholic steatohepatitis have disproportionately lower likelihood of receiving liver transplantation

J. Wang[1], B. Liu[2], T. Bhuket[2], R. Wong[2]. [1]*California Pacific Medical Center, Medicine, San Francisco, United States;* [2]*Alameda Health System - Highland Hospital, Gastroenterology and Hepatology, Oakland, United States*
Email: rowong@alamedahealthsystem.org

Background and Aims: Liver transplantation (LT) remains one of the primary curative options for patients with unresectable hepatocellular carcinoma (HCC). While HCC is a leading etiology for LT in the U.S., the demand for LT far outweighs the supply of donor organs in many regions, and disparities in receipt of LT persist. We aim to evaluate disparities in receipt of LT among U.S. adults with HCC with a focus on sex-specific, race/ethnicity-specific, and etiology-specific disparities.
Methods: Using data from the 2005–2016 United Network for Organ Sharing LT registry, probability of receiving LT among U.S. adults with HCC on the LT waitlist was stratified by race/ethnicity (non-Hispanic white, African American, Hispanic, Asian), sex, and liver disease etiology (nonalcoholic steatohepatitis (NASH), hepatitis C virus (HCV), alcoholic liver disease (ALD), or HCV/ALD). Comparison of LT rates between groups utilized Kaplan Meier methods and log-rank testing. Multivariate Cox proportional hazards models evaluated for independent predictors of receiving LT.



Results: Among 24,044 HCC patients listed for LT (77.3% male. 63.8% non-Hispanic white, 16.2% Hispanic, 10.3% African American, 9.7% Asian), 59.2% had HCV, 22.1% NASH, 10.4% ALD, and 8.4% HCV/ALD. Compared to females with HCC, males were significantly more likely to receive LT within 1 year (61.9% vs. 59.0%, $p = 0.01$). Compared to non-Hispanic whites (65.0%), significantly lower rates of receiving LT within 1 year were observed in African Americans (60.8%, $p < 0.001$), Hispanics (52.9%, $p < 0.001$) and Asians (51.1%, $p < 0.001$). When evaluating by liver disease etiology, HCC patients with HCV/ALD were most likely to receive LT within 1 year (65.6%) and NASH patients were least likely (48.6%). On multivariate regression, males were significantly more likely to receive LT than females (HR 1.09, 95% CI 1.04–1.14, $p = 0.001$). Compared to non-Hispanic whites, Asians (HR 0.86, 95% CI 0.77–0.95, $p = 0.003$) and Hispanics (HR 0.77, 95% CI 0.73–0.81, $p < 0.001$) were significantly less likely to receive LT. Compared to HCC patients with HCV, NASH-HCC patients (HR 0.65, 95% CI 0.61–0.68, $p < 0.001$) and ALD-HCC patients (HR 0.80, 95% CI 0.75–0.85, $p < 0.001$) were significantly less likely to receive LT.
Conclusion: Among U.S. adults with HCC awaiting LT, significant disparities in receipt of LT were observed, with the lowest rates of receiving LT seen among females, among Asians and Hispanics, and among HCC patients with NASH and ALD.

FRI-020

Risk factors for dropout from the liver transplant waiting list under locoregional treatment

H.A. Lee[1], Y.S. Seo[1], T.H. Kim[1], Y.-S. Lee[1], S.J. Suh[2], Y.K. Jung[1], J.H. Kim[1], H.J. Yim[1], J.E. Yeon[1], K.S. Byun[1], S.H. Um[1]. [1]*Korea University, College of Medicine, Department of Internal Medicine, Korea, Rep. of South;* [2]*Korea University Ansan Hospital, Department of Internal Medicine, Ansan-si, Gyeonggi-do, Korea, Rep. of South*
Email: gandorie@gmail.com

Background and Aims: Liver transplantation (LT) has been recognized as the most effective treatment for hepatocellular carcinoma (HCC) in carefully selected patients. In new liver allocation policy, patients with HCC have 6-month delay in granting Model for End-Stage Liver Disease (MELD) exception points. However, it may not be fair, because of the risk of dropout by progression of HCC within 6 months in some patients.
Method: All patients who were diagnosed as United Network for Organ Sharing (UNOS) stage 1 or 2 of HCC between January 2004 and December 2012 were included. Patients who received surgical resection or LT as a primary treatment and who did not receive any treatment for HCC were excluded. Patients with baseline MELD score ≥22 were also excluded because they have a higher chance of receiving LT with their own MELD score. Patients who developed extrahepatic progression within 1 years were considered as high risk group of early recurrence after LT.
Results: A total of 586 patients with UNOS stage 1 or 2 of HCC were included. Age was 59.9 ± 10.3 years and 409 patients (69.8%) were men. Chronic hepatitis B virus infection was the most common underlying liver disease (380 patients, 64.8%), followed by chronic hepatitis C virus infection (104 patients, 17.7%) and alcoholic liver disease (66 patients, 11.3%). MELD score was 9.9 ± 3.0. Number of tumors was 1.3 ± 0.6 and size of the maximum nodule was 2.0 ± 0.9 cm. Serum alpha-fetoprotein (AFP) level was 1.3 ± 0.8 $\log_{10}$ ng/ml. Cumulative incidence of eDO by downstaging approach was 0.7%, 4.1%, 7.2%, and 12.0% at 3, 6, 9, and 12 months, respectively. Within 6 months, 24 patients reached eDO by downstaging approach. On multivariate logistic regression analysis, size of the maximum nodule (≥4 cm) was the only independent factor for eDO within 6 months. Extrahepatic progression was developed in 16 (2.7%), 45 (7.7%), and 73 (12.5%) patients at 11.3% at 1, 2, and 3 years, respectively. On multivariate analysis, size of the maximum nodule (≥4 cm) and serum AFP level (>100 ng/ml) were independent predictors for extrahpeatic progression within 1 year.
Conclusion: HCC progressed to above the Milan criteria during 6 months in 4.1% of patients with UNOS stage 1 or 2. Granting MELD exception points at the time of enrollment would be needed for patients with high risk of eDO (maximum size ≥4 cm). Nontheless, in patients with maximum size ≥4 cm and high serum AFP level (>100 ng/ml), high caution is needed, because of the risk of early progression after transplantation. Considerations about risk factors of dropout and posttransplant prognosis would reduce disparity between HCC patients and non-HCC patients in LT allocation system.

FRI-021

Outcome of liver grafts procured from hepatitis C-positive donors in the era of direct-acting antiviral drugs: a preliminary single centre experience

S. Martini[1], F. Calvo[1], C. Chialà[1], F. Tandoi[2], S. Mirabella[2], A. Ottobrelli[1], A. Amoroso[3], M. Salizzoni[2], G.M. Saracco[1], R. Romagnoli[2].
[1]Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, Turin, Italy; [2]Liver Transplant Center and General Surgery 2U, AOU Città della Salute e della Scienza di Torino, Turin, Italy; [3]Regional Transplant Center, Piedmont, AOU Città della Salute e della Scienza di Torino, Turin, Italy
Email: sivima21@hotmail.com

Background and Aims: Organ shortage continues to push the transplant community to expand the donor pool and HCV-positive donors represent a precious resource. We aimed to evaluate clinical and virological outcomes of HCV antibody (Ab)-positive donors compared with negative ones, in the era of direct-acting antivirals (DAA).

Method: Between August 2014 and August 2016, 213 adult cirrhotic patients underwent a first liver transplant (LT) in our Centre, with grafts from brain-dead donors; 83 recipients (39%) were HCV Ab-positive and 11 (13%) received a HCV Ab-positive graft.

At retrieval of HCV Ab-positive donors: 4 tested HCV RNA negative and were allocated to 4 HCV Ab-positive HCV RNA-negative recipients (on DAA until LT); 3 grafts did not show fibrosis; 7 were fibrosis stage 1/6 or 2/6 and 1 was 3/6, according to Ishak score.

Immunosuppression regimen was based on tacrolimus, mycophenolate mofetil and steroids (tapered to suspension in 6 months).

Virological and clinical outcomes were recorded until October 31, 2017.

Results: *Eleven HCV Ab-positive donors vs 72 HCV Ab-negative donors*: median age 52 *vs* 63 years (p = 0.04); BMI 24 *vs* 26 Kg/m^2; HBcAb positive 27% *vs* 13%; moderate macrosteatosis 0% *vs* 10%, donor risk index 1.73 *vs* 1.87, cold ischemia time 432 *vs* 405 minutes (all p: ns).

Eleven HCV Ab-positive recipients of HCV Ab-positive donors (group A) vs 72 HCV Ab-positive recipients of HCV Ab-negative donors (group B): median age 57 *vs* 57 years; median BMI 26 *vs* 26 Kg/m^2; MELD at LT 9 *vs* 12; hepatocellular carcinoma (HCC) rate 91% *vs* 71%; HCV RNA negative 36% *vs* 65% (all p: ns).

All 7 HCV viremic recipients of HCV viremic donors achieved sustained virological response (SVR) at 48 weeks after the end of therapy (6 out of 7 patients underwent preemptive DAA therapy).

One of the 4 HCV non-viremic donor/recipient pairs relapsed the recipient genotype (4d) and achieved SVR48 after re-treatment.

All 66 surviving recipients in group B achieved SVR48 with pre- (79%) or post-LT (21%) DAAs.

Group A vs B post-LT outcome: 1-year and 2-year graft and patient survival: 100% *vs* 92% and 100% *vs* 89%, respectively; median hospitalization time 11 *vs* 13 days; early allograft dysfunction according to Olthoff 9% *vs* 35%; 1-year treated acute rejection: 9% *vs* 4.5%, 1-year biliary complications: 36% *vs* 27%; HCC recurrence 0 *vs* 3% (all p: ns); 1-year and 2-year liver stiffness 7.8 *vs* 6.3 kilopascal (kPa) (p = 0.09); 6.1 *vs* 6.2 kPa, (p = 0.49), respectively.

Conclusions: Preliminary data in our HCV-positive recipients, suggest comparable clinical, virological and 2-year liver stiffness between liver grafts from HCV Ab-positive and Ab-negative donors, even with HCV-viremic bridging fibrosis graft, provided that DAA therapy is started as soon as possible after LT.

FRI-022

Preemptive direct-acting antiviral therapy in naive or NS5A-relapser liver transplant recipients: a single centre experience

S. Martini[1], C. Chialà[1], F. Calvo[1], F. Tandoi[2], D. Patrono[2], D. Cocchis[2], A. Ottobrelli[1], M. Salizzoni[2], G. Maria Saracco[1], R. Romagnoli[2].
[1]Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, Turin, Italy; [2]Liver Transplant Center and General Surgery 2U, AOU Città della Salute e della Scienza di Torino, Turin, Italy
Email: sivima21@hotmail.com

Background and Aims: In HCV-positive patients with active replication at liver transplant (LT), the best timing for direct-acting antiviral (DAA) treatment is still matter of debate. Immediately post-LT, HCV RNA levels fall sharply and this period could represent a unique opportunity to cure HCV infection, before rebound of viremia. We aimed to evaluate efficacy and safety of preemptive DAA therapy in LT recipients (DAA-naïve or relapsers to prior NS5A inhibitor treatment).

Method: Between January 2016 and May 2017, 63 adult HCV-positive cirrhotic patients underwent a first LT in our Centre, with a graft from brain-dead HCV-negative donor.

Immunosuppression regimen was based on tacrolimus, mycophenolate mofetil and steroids (tapered to suspension in 6 months).

Twenty recipients (20/63, 32%) underwent preemptive DAA therapy (15 DAA-naïve patients received sofosbuvir plus ledipasvir or daclatasvir ± ribavirin for 12 weeks; 5 NS5A-inhibitor relapsers received sofosbuvir plus velpatasvir plus ribavirin for 24 weeks), starting from the day of LT, and represent our study population.

Clinical and virological outcomes were recorded until October 31, 2017.

Results: Recipients: median age 56 years, BMI 26 kg/m^2; MELD at LT 12 (interquartile range 9–17), hepatocellular carcinoma (HCC) rate 60%, HCV RNA at LT 5.6 Log IU/ml; HCV genotype (GT) 1a: 5 patients; GT1b: 9 patients (1 NS5A-relapser), GT3: 3 patients (1 NS5A-relapser) and GT4 3 patients (all NS5A-relapsers); *IL28B* C/C: 25%. Median LT waiting-list time: 10 days.

Donors: median age 63 years, BMI 26 Kg/m^2, none with macrovesicular steatosis ≥30%, 15% HBcAb positive, donor risk index 1.48, cold ischemia time 415 minutes.

Post-LT follow-up: median hospitalization time: 13 days, early allograft dysfunction according to Olthoff: 25%, 30-day treated acute cellular rejection: 10%.

All grafts and patients are alive after a median follow-up of 335 days (range 155–643 days), 1 patient with HCC recurrence at 10 months after-LT (exceeding Milan criteria on explant pathology).

Within week 4 post-LT all patients were HCV RNA <15 IU/ml; all 15 DAA-naïve patients achieved a sustained virological response (SVR) at 12 weeks after the end of therapy; the 5 NS5A relapsers are all negative at the end of therapy, with 1 patient reaching SVR4 and 1 SVR12.

No patient had to discontinue DAA therapy post-LT.

Conclusions: In our 20 HCV-positive patients (15 naïve and 5 NS5A inhibitor relapsers) with a median LT waiting time of 10 days, preemptive DAA therapy (since the day of LT) was safe and well tolerated and HCV RNA <15 IU/ml was achieved within week 4 after LT in all of them. All the 16 patients who reached 12 weeks of follow-up after the end of therapy, are SVR12.

FRI-023

Donor-specific anti-HLA antibodies are not associated with non-anastomotic biliary strictures, but both are independent risk factors for graft loss after liver transplantation

A.C. den Dulk[1], X. Shi[2], C. Verhoeven[3], J. Dubbeld[4], F.H.J. Claas[5], R. Wolterbeek[6], S. Brand-Schaaf[5], H.W. Verspaget[1], A.F. Sarasqueta[7], L. van der Laan[3], H. Metselaar[2], B. van Hoek[1], J. Kwekkeboom[2], D. Roelen[5]. [1]*Leiden University Medical Center, Gastroenterology and Hepatology, Leiden, Netherlands;* [2]*Erasmus Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands;* [3]*Erasmus Medical Center, Surgery, Rotterdam, Netherlands;* [4]*Leiden University Medical Center, Surgery, Leiden, Netherlands;* [5]*Leiden University Medical Center, Immunohematology and Blood Transfusion, Leiden, Netherlands;* [6]*Leiden University Medical Center, Medical Statistics and Bioinformatics, Leiden, Netherlands;* [7]*Leiden University Medical Center, Pathology, Leiden, Netherlands*
Email: bvhoek@lumc.nl

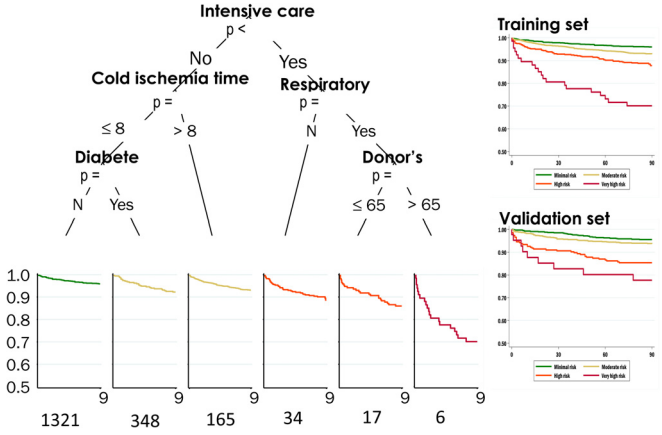
Background and Aims: Donor-specific alloantibodies (DSA) have been associated with rejection and shorter graft survival after orthotopic liver transplantation (OLT). We examined the role of DSA in non-anastomotic biliary strictures (NAS) after OLT.
Method: Patients receiving first OLT who developed NAS ($n = 68$) and a control group without NAS ($n = 83$), with pre-OLT and 12 months post-OLT serum samples were included. DSA were specified using the Luminex single antigen test. Risk factors for NAS and graft survival were analysed.
Results: The presence of preformed DSA was not significantly different between patients with NAS and controls ($p = 0.89$). After 12 months, 26.5% of NAS patients and 16.9% of controls had generated de novo DSA ($p = 0.15$). Neither de novo class I DSA nor de novo class II DSA were associated with NAS. De novo DSA generally developed after the diagnosis of NAS. Time-dependent regression analysis identified both NAS (aHR 8.05, CI 3.28–19.77, $p < 0.01$) and de novo class II DSA (aHR 2.84, CI 1.38–5.82, $p < 0.01$) as independent risk factors for graft loss.
Conclusion: Preformed or de novo DSA were not associated with the development of NAS. However, NAS as well as de novo class II DSA were independent risk factors for graft loss after OLT.

FRI-024

Short-term suvival after liver transplantation depends on the matching of graft and recipient caracteristics

E. Levesque[1], E. Audureau[2], A. Winter[3], C. Antoine[4], J.P. Daures[5], P. Landais[3], D. Azoulay[6], C. Duvoux[7], C. Feray[7], O. Group[8]. [1]*Henri Mondor Hospital, Anesthesia, Creteil, France;* [2]*Henri Mondor Hospital, Santé Publique, Creteil, France;* [3]*CHU Montpellier, Santé Publique, Montpellier, France;* [4]*Agence De Bioemedecine, Saint Denis La Plaine, France;* [5]*Institut Mutualiste, Clinical Research, Montpellier, France;* [6]*Henri Mondor Hospital, Liver Surgery, Creteil, France;* [7]*Henri Mondor Hospital, Hepatology, Creteil, France;* [8]*Henri Mondor Hospital, Santé Publique*
Email: eric.levesque@aphp.fr

Background and Aims: Liver transplantation offers an immediate benefit for decompensated cirrhosis while it offers a differed advantage for hepatocellular carcinoma. No matching rules other than blood group exists in most allocation systems.
Method: 5509 consecutive cirrhotic adult patients receiving a first liver graft between 2009 and 2015 were analysed through cox model and through unsupervised decision tree analysis. The training and the validation sets comprised 3905 and 2004 patients. Criteria was 90-days mortality post transplant.
Results: Cox analysis showed that presence in ICU, artificial ventilation, kidney failure, cold ischemic time were independent risk factors for short-term mortality. Decision tree analysis confirmed ICU as the main predictor. In patients in ICU, those who were ventilated had 30% of mortality if the donor was older than 65y and of 15% if not. In those not in ICU, the cold ischemic time less that 8 hours gave excellent results. These findings were reproduced in the validation set.



Conclusion: Cox analysis evidenced variables with an average effect in the whole population and point to the importance of organ failures at the time of LT. Decision tree analysis indicated matching between graft and candidate characteristics which may reduce the short-term mortality. Cold ischemic times remains the best predictor for excellent short-term results.

FRI-025

Rescue allocation in the french nationwide liver graft cohort

C. Feray[1,2], A. Winter[3], M. Disabato[4], P. Compagnon[4], C. Jacquelinet[5], J. Pierre Daures[6], D. Azoulay[4], P. Landais[7], O. Group[8]. [1]*Henri Mondor, Hepatology, Creteil, France;* [2]*INSERM, U955 Team 18, Creteil, France;* [3]*Montpellier University, Montpellier, France, Department Of Biostatistics, UPRES EA2415, Clinical Research University Institute, Montpellier, France;* [4]*Henri Mondor, Liver Surgery and Transplantation, Creteil, France;* [5]*Stratégie, Agence de Biomedecine, Saint Denis, France;* [6]*Institut Mutualiste, Clinical Research, Montpellier, France;* [7]*Montpellier University, Montpellier, France, Department Of Biostatistics, UPRES EA2415, Clinical Research University Institute, Montpellier, France;* [8]*APHP, DRC, Paris, France*
Emil: cyrille.feray@gmail.com

Background and Aims: Liver transplantation is hampered by the shortage of donor leading to the use of graft from donors with extended criteria (ECD) such as age or ischemia times, defining the donor risk index (DRI). In France, each graft is patient-Oriented (PO) according to a national score. In some occasions, a graft may be refused by all transplant teams to which it is offered and then attributed to a transplant team or Center-Oriented (CO), which in turn chooses the most appropriate candidate for this rescue allocation (RA).
Method: Patients receiving PO or CO liver graft were compared for recipient and donor covariates. A propensity score (PS) including covariates explaining the allocation type in order to make comparable groups was determined using logistic regression. Retained recipient's covariates were: age, sex, MELD at transplant and hepatocellular carcinoma (HCC). The PS was validated considering its ability to provide balanced groups. Cases were weighted using the PS, considering the Inverse Probability of Treatment Weighting (IPTW) method in a Cox model and using several covariates for adjustment. Analyses were performed using R statistical software version 3.3.0.
Results: 5516 adults received a liver graft from 2009 to 2014 in France; 5218 recipients were selected and 336 (6.4%) received a graft through a CO offer (G1). These patients received a graft from older donors ($p < 0.01$), had lower MELD ($p < 0.01$), and more frequently with an HCC ($p < 0.01$). The survival were similar between CO and PO patients. Using PS, we showed that the risk of mortality was increased

in CO patients compared to PO patients (HR 1.18 [95% CI: 1.09–1.28]). However, in 25% of centers, for which transplanted patients had a CO offer, in more than 6.5% of cases, this increased risk did not appear (HR: 0.95 [95% CI : 0.84–1.07]). Better result was observed between these centres than in the others (HR: 1.37 [95% CI: 1.21–1.54]) in which DRI of CO donor graft were lower.

Conclusion: Although PO graft came from ECD, survival of PO and CO liver grafts were similar suggesting that centres chose appropriate candidates for PO liver grafts. This confirmed small series published on this issue. However, PS cox model demonstrated that CO graft induces an intrinsic risk of mortality and this was only observed for centres with low usage of such grafts.

FRI-026

Role of interventional radiology in the scenario of liver transplantation

M.B. Pitton[1], T. Zimmermann[2], J. Mittler[3], S. Schotten[1], R. Klöckner[1], P. Galle[2], G. Otto[3], H. Lang[3], C. Düber[1]. [1]*University Medical Centre of Mainz, Diagnostic and Interventional Radiology, Mainz;* [2]*University Medical Centre of Mainz, Internal Medicine, Mainz, Germany;* [3]*University Medical Centre of Mainz, Visceral Surgery, Mainz, Germany*
Email: michael.pitton@unimedizin-mainz.de

Background and Aims: To analyze the role of Interventional Radiology (IR) in the complex scenario of liver transplantation (LTx).

Method: Patients with history of liver transplantation (LTx) were included in our analysis. Patients were analyzed for number and type of interventional procedures in the scope of liver transplantation. The institutional data bases were searched for all interventional procedures during the time on the waiting list, in the immediate perioperative phase as well as during follow-up after LTx. The interventional procedures were categorized in image-guided punctures (e.g. biopsies, drainages), local tumor treatment (eg. tumor ablations, TACE, SIRT), biliary interventions (e.g. percutaneous biliary drainages in ischemic or ischemic-type biliary lesions [IBL / ITBL]), vascular interventions (portal, venous, arterial recanalization or embolization), TIPS, and others. The numbers end time points of interventional procedures during the patient's course were analyzed.

Results: Between 1996 and 2016 a total of 815 patients received liver transplantation in our centre. 24.4% of patients had no interventions at all. 44.7% of patients received interventions during time on the waiting-list (in 20.4% ≤3 procedures per patient, in 24.3% >3 procedures per patient, e.g. TACE etc.). 23 patients (2.8%) received procedures within the immediate perioperative phase (≤3 days after LTx). During 30d-follow-up, a total of 60% of patients received some IR-procedures: in 28.7% only one per patient, however, 3.6% of patients received >3 procedures per patient (range 4–8).

Conclusion: Interventional procedures are an integral part in the scenario of liver transplantation and cover the whole scope of IR, particularly TIPS and local tumor treatment before LTx, peri-/postoperative vascular issues, as well as biliary interventions in IBL/ITBL during follow-up.

FRI-027

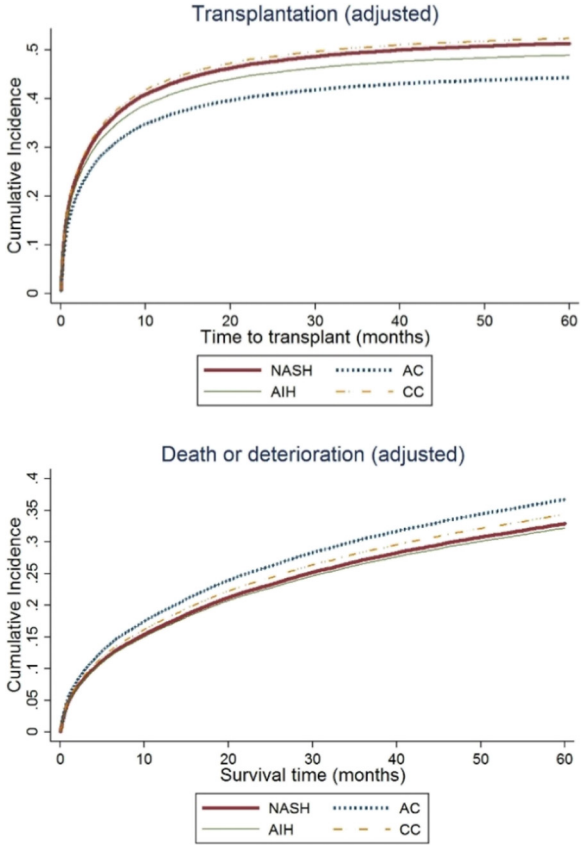
Incidence of waitlist removal and transplantation rates are similar in NASH, cryptogenic and autoimmune hepatitis cirrhosis

P.J. Thuluvath[1], Y. Savva[2]. [1]*Mercy Medical Center & University of Maryland School of Medicine, Medicine, Baltimore, United States;* [2]*Mercy Medical Center, Medicine, Baltimore, United States*
Email: thuluvath@gmail.com

Background and Aims: Cirrhosis secondary to nonalcoholic steatohepatitis (NASH) has become the 3rd most indication for liver transplantation (LT) in the USA. Patients with NASH cirrhosis are relatively older and have multiple comorbidities. Although post-LT survival of patients with NASH is acceptable, we hypothesized that they are more likely to be removed from the waitlist because of clinical deterioration or death, and therefore less likely to be transplanted when compared to those with cryptogenic (CC), alcoholic (AC) or autoimmune hepatitis (AIH) cirrhosis.

Method: To test the above hypothesis, we analysed the United Network for Organ Sharing (UNOS) data from 2002 to 2016. After excluding those with liver cancer (HCC) and multiple-organ transplants, the study included 8,656 NASH, 6,550 CC, 17,857 AC and 2,839 AIH. The absolute risk (unadjusted cumulative incidence) for removal from list due to death/deterioration or transplantation was analysed using a cumulative incidence competing risk method.

Results: In the first three years on the waiting list, the risk for death/deterioration was 32% (CI 31–33) for NASH, 30% (CI 29–31) for AC or CC, and 25% (CI 23–26) for AIH. The factors increasing the risk of waiting list death/deterioration were poor performance status (HR = 1.73), encephalopathy (HR = 1.20), diabetes (HR = 1.12), dialysis (HR = 1.11), high MELD score (HR = 1.11), being Hispanic (HR = 1.10), older age (HR = 1.03) and a low serum albumin (HR = 0.98). After controlling for known demographic and disease confounders, the relative risk of death/deterioration was 13% higher for AC (SHR = 1.13) when compared to NASH, but the other two groups had the same risk as NASH. During the first three years on the waiting list, the incidence of receiving a transplant was 49% (CI 48–50) for NASH, 48% (CI 47–49) for CC, 45% (CI 44–45) for AC, and 47% (45–49) for AIH. The factors associated with a lower incidence of LT were dialysis (HR = 0.48), being a female (HR = 0.82), not White (HR = 0.92 for Blacks, HR = 0.73 for Hispanics, and HR = 0.77 for Asians), having a higher albumin (HR = 0.98) and higher serum creatinine (HR = 0.98). The factors that increased the incidence of LT were a poor performance status (HR = 1.32), encephalopathy (HR = 1.18) and a high MELD score (HR = 1.14). The adjusted cumulative incidence of transplantation was 19% lower for AC (sub-distribution HR [SHR] = 0.81) and similar for CC and AIH when compared to NASH.



Conclusion: In this study, we found that NASH, CC and AIH had similar risk of removal from waitlist and similar incidence of transplantation and but those with AC had a higher risk of wait list death/removal and lower incidence of transplantation.

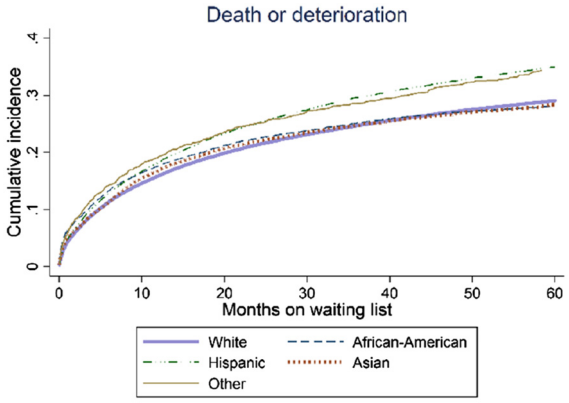
FRI-028

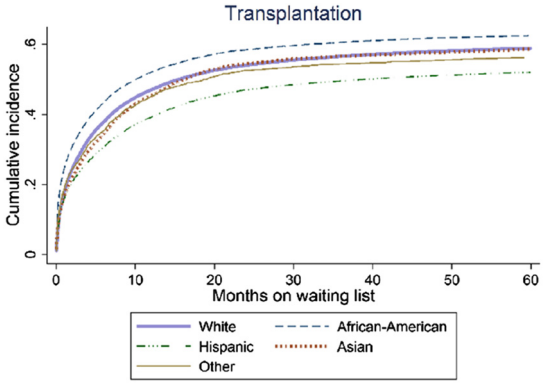
Liver transplant waitlist mortality, transplantation rates and post-liver transplant outcomes in Hispanics

P.J. Thuluvath[1], Y. Savva[2]. [1]*Mercy Medical Center & University of Maryland School of Medicine, Medicine, Baltimore, United States;* [2]*Mercy Medical Center, Medicine, Baltimore, United States*
Email: thuluvath@gmail.com

Background and Aims: It has been previously reported that African American (AA) have a lower post-liver transplant (LT) survival compared to Whites (Lancet 2002; 359; 287–93). In the USA, Hispanics are the fasting growing population, and yet there is a paucity of data on waitlist mortality, transplantation rates and post-LT outcomes of this population.

Method: In this study, we examined UNOS data between 2002 and 2016 to determine the relative outcomes of Hispanics compared to Whites. Kaplan-Meier estimator was used to construct removal due to death/deterioration, transplantation and post-transplant survival curves. Multivariate Cox proportional hazard regressions were used to study the association between the risk factors.





Results: During this period, 19,217 Hispanics, 92,892 Whites, 11,534 AA, 5,914 Asians and 1,638 "Others" were listed for LT. Cumulative incidence of removal from the waitlist either due to death or deterioration was highest for Hispanics, and similar for Whites, AA and Asians (Figure 1). Transplantation rates were lowest for Hispanics, and highest for AA followed by Whites and Asians (Figure 2). After adjusting for clinical characteristics and other confounders, adjusted waitlist removal was 26% higher for Hispanics, and transplantation rates were 22% lower for Hispanics compared to Whites. Donor quality based on Donor Risk Index (DRI) was similar for all groups. 1-year and 5-year post-LT graft and patient survival was similar for Hispanics (90% and 75% respectively) and Whites (89% and 75% respectively). As in previous reports, survival was lowest for African Americans.

	Patient survival (%)					Graft survival (%)				
	White	AA	Hispanic	Asian	Other	White	AA	Hispanic	Asian	Other
30 days	0.97	0.96	0.97	0.97	0.97	0.96	0.94	0.95	0.95	0.96
1 year	0.89	0.87	0.90	0.92	0.90	0.87	0.84	0.88	0.89	0.89
2 years	0.85	0.79	0.85	0.88	0.86	0.82	0.76	0.83	0.85	0.85
3 years	0.81	0.75	0.82	0.84	0.83	0.79	0.72	0.79	0.82	0.81
5 years	0.75	0.67	0.75	0.80	0.77	0.72	0.64	0.73	0.77	0.75
10 years	0.58	0.52	0.62	0.69	0.59	0.56	0.49	0.59	0.67	0.59

Conclusion: This study based on a large dataset shows that Hispanics are more likely to be removed from the waitlist, less likely to be transplanted, and yet have similar post-LT outcomes when compared to Whites.

FRI-029

Pretransplant Karnofsky Performance Status is an independent predictor of post-liver transplant survival

P.J. Thuluvath[1], A. Cherry[2], A. Thuluvath[3], Y. Savva[2]. [1]*Mercy Medical Center & University of Maryland School of Medicine, Medicine & Surgery, Baltimore, United States;* [2]*Mercy Medical Center, Medicine, Baltimore, United States;* [3]*Johns Hopkins University, Medicine, Baltimore, United States*
Email: thuluvath@gmail.com

Background and Aims: Karnofsky Performance Status (KPS) has been used for almost 70 years in clinical practice as a subjective "eyeball" assessment of overall performance status of patients. KPS score, administered by the provider, assign scores to patients on a scale of 0–100%, in increments of 10, where 100% is normal activity and 0% is dead. In this study, our objective was to determine whether KPS score is an independent predictor of post-LT survival after adjusting for other known confounders.

Method: We included all adult patients listed with UNOS from 2006 to 2016 (UNOS started collecting KPS scores in a consistent manner since 2006). We grouped patients into 3 groups based on KPS score: 10–40% severe disability, 50–70% mild to moderate disability and 80–100% minimal or no disability. Kaplan-Meier survival analysis was done to examine graft and patient survival. Multivariate Cox regression was used to analyze the independent effect of KPS on survival after adjusting for other variables including age, sex, race, disease etiology, BMI, organ failures, stage 3–4 hepatic encephalopathy, MELD scores and donor risk index (DRI). We adjusted for stage 3–4 hepatic encephalopathy (HE) as it may influence assessment of KPS.

Results: During the study period, 18,673 patients with severe disability, 22,293 with moderate disability and 13,159 with minimal or no disability were transplanted. The graft and patient survival of these patients are shown in the figures 1 & 2. The graft and patient survival differences were significantly lower (log-rank $p < 0.0001$) in in those with poor KPS scores. This patient survival was lowest for those with KPS score <40 and highest for those with scores 80–100% [1-yr (86, 91, 93%), 2-yr (81, 86, 89%) for the 3 groups]. Cox regression analysis showed that KPS is an independent predictor of graft and patient (see table) survival. Other independent predictors of graft and patient survival were age, race, presence of stage 3 or 4 HE, disease etiology and DRI,

	Level	HR (unadjusted)	p-value	HR (adjusted)	p-value
Age		1.02 (1.017–1.021)	<0.01	1.02 (1.016–1.021)	<0.01
MELD score		1.01 (1.004–1.007)	<0.01	1.01 (1.005–1.009)	<0.01
Encephalopathy (3–4)		1.10 (1.063–1.144)	<0.01	1.05 (1.002–1.091)	0.04
KPS score	80–100	1.00		1.00	
	50–70	1.18 (1.130–1.238)	<0.01	1.17 (1.116–1.232)	<0.01
	≤40	1.44 (1.371–1.505)	<0.01	1.48 (1.395–1.566)	<0.01
Donor Risk Index		1.29 (1.242–1.338)	<0.01	1.34 (1.286–1.389)	<0.01

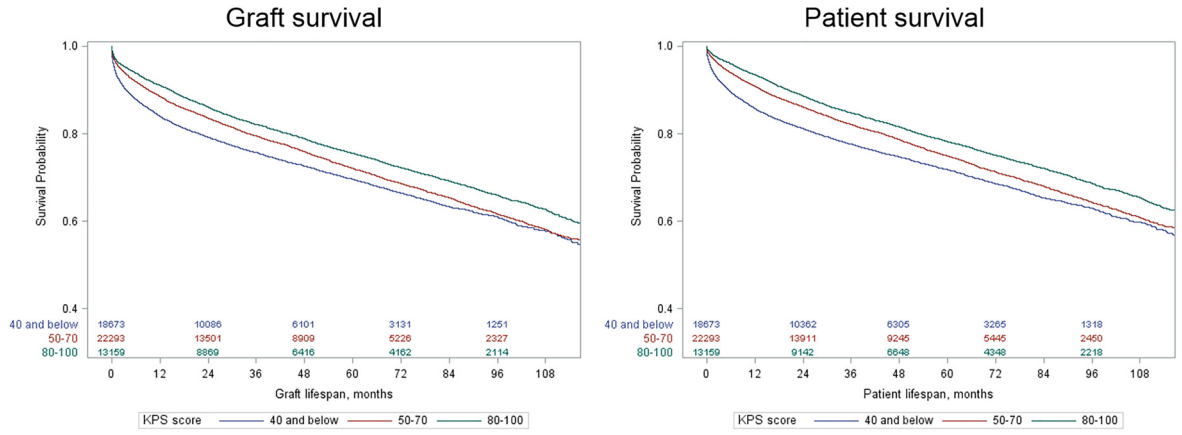


Figure 1 & 2: (abstract: FRI-029)

Race and aetiology of liver disease were also independent predictors of survival (not shown).

Conclusion: Karnofsky Performance Status (KPS) is an independent predictor of graft and patient survival after adjusting for other important predictors of survival including age, race, HE, disease etiology and DRI.

FRI-030

Survival benefit of liver transplantation in Catalonia: A 2007–13 analysis

J. Colmenero[1], J. Lombardo[1], N. Trota[2], G. Crespo[1], I. Bilbao[3], A. Rafecas[4], X. Xiol[5], L. Castells[6], C. Baliellas[5], P. Ruiz[1], S. Biggins[7], C. Fondevila[8], J. Tort[2], M. Navasa[1]. *[1]Hospital Clínic, Barcelona, Liver Transplant Unit, Barcelona, Spain; [2]OCATT, Generalitat de Catalunya; [3]Hospital Vall d'Hebron, Barcelona, Transplant Surgery; [4]Hospital de Bellvitge, Barcelona, Transplant Surgery; [5]Hospital de Bellvitge, Barcelona, Hepatology, Barcelona; [6]Hospital Vall d'Hebron, Barcelona, Hepatology; [7]University of Washington Medical Center, Seattle; [8]Hospital Clínic, Barcelona, Liver Transplant Surgery, Spain*
Email: jcolme@clinic.ub.es

Background and Aims: The survival benefit (SB) of liver transplantation (LT) is the comparative risk of death after LT compared to remaining on the waiting list (WL). Observational studies suggest that the mortality risk after LT is greater for LT candidates with MELD < 14 and lower for those with MELD > 17. We aimed to investigate the SB of LT in Catalonia (7.5M people).

Method: Data was extracted from the Catalan Organization of Transplantation. WL and post-LT mortality at 1-year was studied among 990 adult patients with ESLD listed for LT (07/2007–12/2013). Liver allocation was based on the last MELD score and 3996 MELD score updates were analyzed. Candidates with hepatocellular carcinoma (single ≥ 3cm, 2–3 nodules or treatment failure) received 19 MELD points (+1point/3m). Refractory ascites and hepatic encephalopathy were *not* granted with exception points. Candidates with acute liver failure or MELD exceptions at listing were excluded while those with exception points after listing, or removed from the WL due to improvement or living donor LT were censored. Time-dependent Cox regression models were fitted to compare mortality for LT candidates and recipients at equal duration since listing adjusted for age, sex, race, diagnosis, and MELD.

Results: Overall, covariate-adjusted mortality risk of LT recipients was 79% lower than candidates (HR = 0.25; 95%CI= 0.18–0.34; p < 0.001), supporting a significant SB of LT. Forty percent of candidates had hepatitis C virus infection. The WL drop-out rate (death/*too-sick*) was 8.9% and the probability of survival at 1-year after LT was 90.2%. The SB after LT varied across the range of MELD score: post-LT mortality risk was markedly higher than WL mortality for MELD 6–11 (HR = 6.72; 95%CI= 1.29–35.0; p = 0.024). Conversely, a significant SB of LT was observed at a MELD ≥ 19 (Figure) and the magnitude of SB increased markedly at a MELD ≥ 23 [MELD 19–23: HR = 0.426, p = 0.0076; MELD 24–26: HR = 0.047, p < 0.001; MELD 27–29: HR = 0.074, p < 0.001; MELD ≥ 30: HR = 0.078, p < 0.001]. LT candidates with MELD 12–14 and MELD 15–18 showed a reduction on the mortality risk after LT, but it was not statistically significant (HR = 0.792 (0.15–3.31) and HR = 0.556 (0.23–1.32), p = 0.662 and p = 0.179 respectively). Only 5% of LT candidates with MELD scores <12 at listing progressed to a MELD ≥ 19.

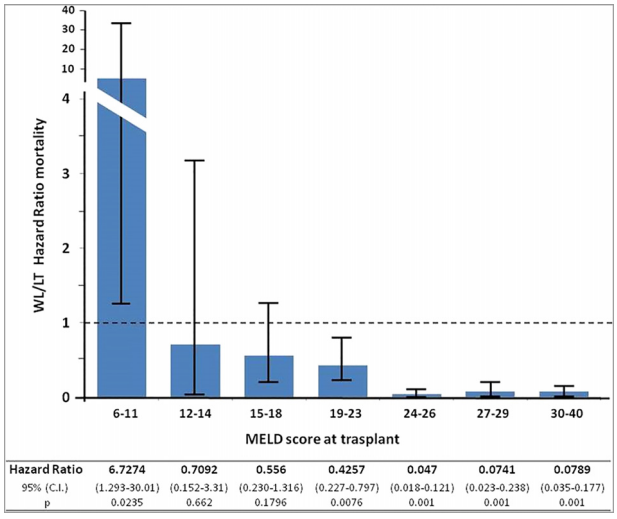


Figure 1: Comparison of mortality risk expressed as hazard ratio by MELD for recipients of liver transplantation (LT) compared to candidates on the waiting list (WL). A hazard ratio of less than 1 favors LT.

Conclusion: LT carried a significant SB for ESLD recipients. Candidates with low MELD scores (<12) did not have SB after LT while those at a MELD score ≥19 had significant SB after LT. In our cohort, the SB of LT for candidates with MELD 12–18 did not reach statistical significance. These results support our MELD-based current criteria for listing (MELD ≥ 12) and our current organ allocation policy.

FRI-031

The survival benefit of hepatic resection in advanced cases for intrahepatic cholangiocarcinoma: a surveillance, epidemiology and end results (SEER) analysis

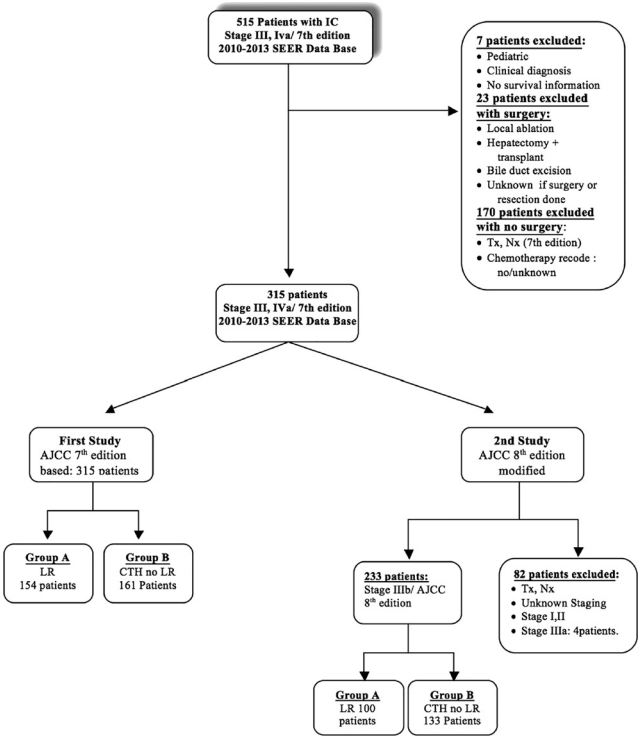
M. Moustafa, U. Cillo, E. Fasolo. *Padua University Hospital, Liver Transplant and HBP Surgery Unit, Padua, Italy*
Email: dr_ezzo81@hotmail.com

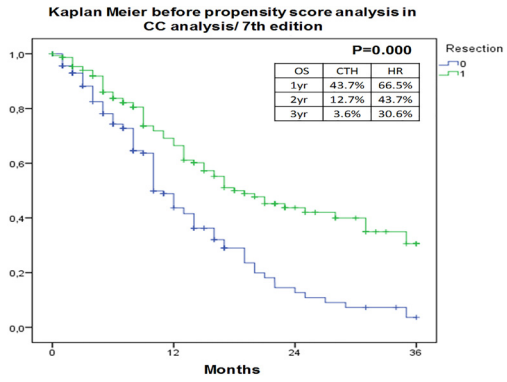
Background and Aims: Liver resection (LR) is the cornerstone in the treatment of Intrahepatic Cholangiocarcinoma (IC). However, it is a

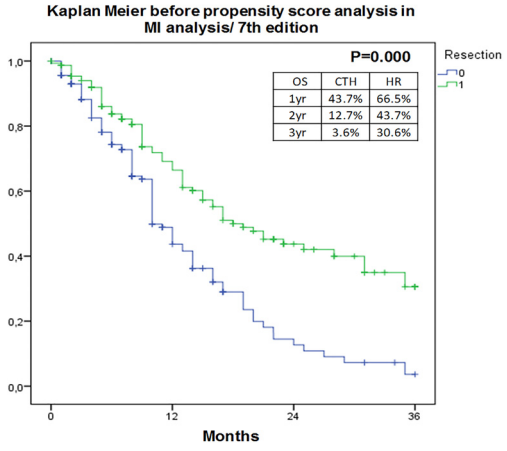
controversial solution for advanced lesions not only due to surgical technical aspects but also its survival benefit remains questionable. The aim of this study is to verify the survival benefits of LR in advanced stages of IC based on the 7th and 8th editions of American Joint Committee on Cancer (AJCC) Staging System, and to identify prognostic factors that directly influence patients' survival after LR.

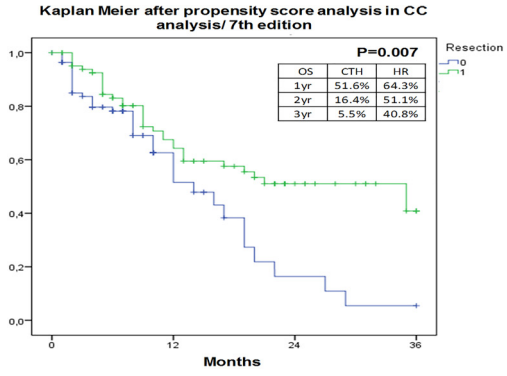
Method: A retrospective cohort study was performed using the Surveillance, Epidemiology, and End Results (SEER) database to identify stage III and IVa of IC patients based on the 7th edition of AJCC staging system. 315 patients were enrolled in this study, during the period 2010–2013 and classified into 2 groups; group A includes 154 patients who underwent LR and group B includes 161 patients who received only chemotherapy. The selected population has been classified according to the AJCC 8th edition. 233 patients out of 315 were enrolled and classified into group A with LR and Group B with CTH. To account for missing data, two sets of analyses were performed; complete cases (CC) data set and multiple imputation (MI). The survival was estimated and compared in the two groups using the Kaplan-Meier method with log-rank test. The patients in group A and B were matched and propensity score (PS) analysis performed for both 7th and 8th edition modules in both CC and MI data set. A Cox proportional hazards model were developed using relevant clinic-pathologic variables to determine the prognostic factors.

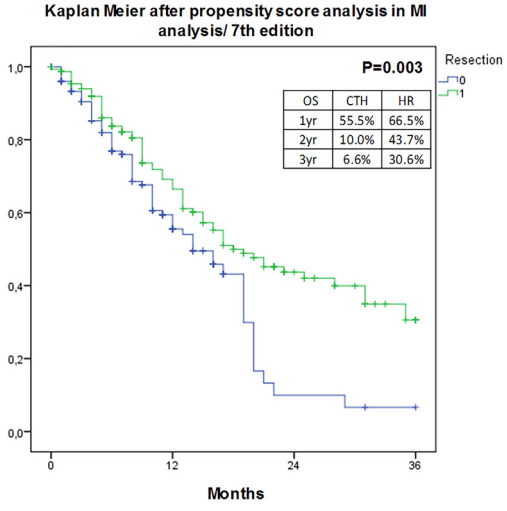
Results: In CC/ AJCC 7th edition data set with PS analysis the median survival was 35 months (12.5–57.4) 95% CI, and 1, 2, and 3years survival rates were 64.3%, 51.1%, and 40.8%. In matched group B, the median survival was 14 months, (9.1–18.8) 95% CI and the 1, 2, and 3years survival rates were 51.6%, 16.4%, and 5.5% for matched group B patients (p = 0.007). In CC/AJCC 8th edition with PS analysis the median survival for group A was 17 months (8.1–25.8) 95% CI and 1, 2, and 3years survival rates were 57.8%, 43.4% and 32.6%. In group B, the median survival was 12 months (8.7–15.2) 95% CI and the 1, 2, and 3years survival rates were 46.6%, 7.4%, and 3.7% for matched group B patients (p = 0.013). In CC/AJCC 7th edition data set; poor prognosis has been shown in patients above 65 years old (HR 1.804, 95% CI 1.139–2.858, P.012), Multi focal lesion (HR 1.588, 95% CI 0.950–2.654, P 0.077) and positive lymph node (HR 1.885, 95% CI 1.012–3.513, P 0.046).

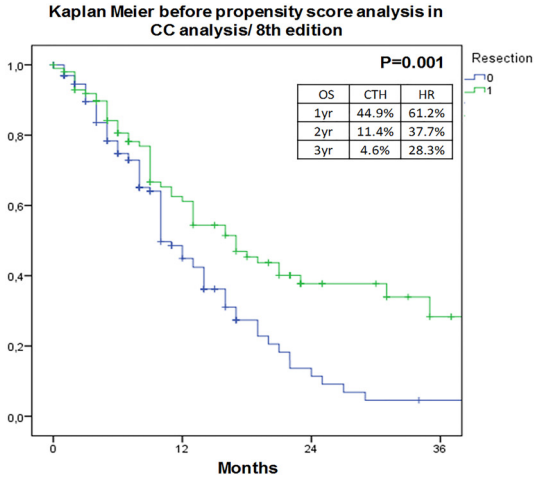


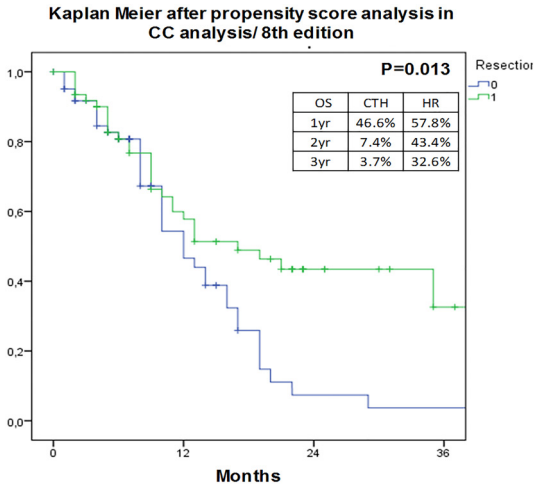












Conclusion: LR has showed a significant survival benefit over chemotherapy for IC stage III and IVa of the 7th edition and some survival benefit in stage IIIb of 8th edition of AJCC staging system. Poor outcome has been observed in patients >65 years and with multifocal lesions and lymph node metastasis.

FRI-032

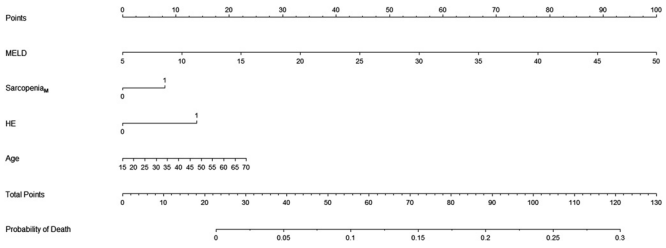
A nomogram with sarcopenia surpasses the MELD score in predicting waiting list mortality in cirrhotic liver transplant patients: a competing risk analysis in a national cohort

J. van Vugt[1], L. Alferink[2], S. Buettner[1], M. Gaspersz[1], D. Bot[3], S.D. Murad[4], S. Feshtali[5], P. van Ooijen[6], W. Polak[7], R. Porte[8], B.V. Hoek[9], A. van den Berg[10], H. Metselaar[11], J. Ijzermans[12]. *[1]Erasmus MC, Surgery, Rotterdam, Netherlands; [2]Erasmus Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; [3]LUMC, Dietics, Netherlands; [4]Erasmus MC, Hepatology, Rotterdam, Netherlands; [5]LUMC, Radiology, Netherlands; [6]UMCG, Radiology, Netherlands; [7]Erasmus MC, University Medical Center Rotterdam, Department of Surgery, Division of HPB and Transplant Surgery, Rotterdam, Netherlands; [8]UMCG, Surgery, Netherlands; [9]LUMC, Hepatology, Leiden, Netherlands; [10]UMCG, Hepatology, Groningen, Netherlands; [11]Erasmus Medical Center, Gastroenterology and Hepatology, Rotterdam, Netherlands; [12]Erasmus MC, Department of Surgery, Rotterdam, Netherlands*
Email: j.l.a.vanvugt@erasmusmc.nl

Background and Aims: Frail patients with low MELD scores may be underprioritised. Low skeletal muscle mass (i.e. sarcopenia) has been identified as risk factor for waiting list mortality and a recent study proposed to incorporate sarcopenia in the MELD score (i.e. MELD-Sarcopenia score). We aimed to investigate the association between sarcopenia and waiting list mortality, and to validate the MELD-Sarcopenia score (i.e. MELD + 10.35*Sarcopenia).

Method: We identified consecutive patients with cirrhosis listed for liver transplantation in the Eurotransplant registry between 2007–2014 and measured skeletal muscle mass on computed tomography (CT). A competing risk analysis was used to compare survival of patients with and without sarcopenia, and concordance (c) indices were calculated to assess performance of the MELD and MELD-Sarcopenia score. We created a nomogram of the best predictive model.

Results: We included 585 patients with a median MELD score of 14 (IQR 9–19), of which 254 (43.4%) were identified as having sarcopenia. Median waiting list survival was shorter in patients with sarcopenia than those without ($p < 0.001$). This effect was even more pronounced in patients with MELD ≤15. The discriminative performance of the MELD-Sarcopenia score (c-index 0.820) for 3-month mortality was lower than MELD score alone (c-index 0.839). Apart from sarcopenia and MELD score, other predictive variables were occurrence of hepatic encephalopathy before listing and recipient age. A model including all these variables yielded a c-index of 0.851 (figure).



Conclusion: Sarcopenia was associated with waiting list mortality in liver transplant candidates with cirrhosis, particularly in patients with lower MELD scores. The MELD-Sarcopenia score was successfully validated in this cohort. However, incorporating sarcopenia in the MELD score had limited added value in predicting waiting list mortality.

FRI-033

Tacrolimus cumulative exposure after liver transplantation is associated with a progressive derangement of renal function despite routine dose adjustments

M. Rodríguez-Perálvarez[1], M. Guerrero[1], L.D. Luca[2], B. Gros[1], D. Thorburn[2], D. Patch[2], R. Westbrook[3], R. Fernández[1], P. Aguilar[1], J.L. Montero[1], J. O'beirne[4], J. Briceño[1], M.D.L.M. Garcia[1], E. Tsochatzis[4]. *[1]Reina Sofía University Hospital, IMIBIC, CIBERehd, Hepatology and Liver Transplantation, Spain; [2]Royal Free Hospital and UCL, UCL institute for liver and digestive health and Sheila Sherlock liver unit, London, United Kingdom; [3]Royal Free Hospital, London, United Kingdom; [4]Royal Free Hospital and UCL, UCL institute for liver and digestive health and Sheila Sherlock liver unit, United Kingdom*
Email: ropeml@hotmail.com

Background and Aims: Liver transplant (LT) patients who develop renal impairment receive tacrolimus minimization. We aimed to evaluate cumulative tacrolimus exposure as a determinant of progressive derangement in kidney function.

Method: A consecutive cohort of patients who underwent LT in two European institutions (2008–2013) and received tacrolimus-based immunosuppression were included. Death within the first 90 days post-LT was the main exclusion criterion. All measurements of tacrolimus trough concentrations within the first 6 months after LT were recorded in each patient. Cumulative tacrolimus exposure was expressed as the area under curve of trough concentrations (AUCtc), which was calculated by the Wagner-Nelson equation. Patients were stratified in low AUCtc (<25 percentile), intermediate AUCtc (25–75 percentile) and high AUCtc (>75 percentile). The AUCtc at 3 and 6

months after LT was correlated with the delta creatinine (Cr) within the same intervals.
Results: 456 patients were included (mean age 52.1 ± 10, 28.3% women). Major etiologies of liver disease were hepatitis C (n = 164; 36%) and alcoholic cirrhosis (n = 151; 31.1%). Pre-LT MELD was 17.9 ± 7.2. Prevalence of renal impairment (Cr > 1.5 mg/dl at least twice with at least one month interval) was 24.8% at 3 months and 27.6% at 6 months after LT. Artificial renal support was required in 8.8% of patients. As part of routine dose adjustments, patients with renal impairment received low AUCtc more frequently, both at 3 months (46.9% vs 22.1%; p < 0.001) and at 6 months (41.3% vs 20.2%; p < 0.001). However, the AUCtc was associated with a progressive increase of serum Cr. At 3 months, delta Cr was 0.25 mg/dl in patients with high AUCtc, 0.17 mg/dl in patients with intermediate AUCtc and 0.10 mg/dL in patients with low AUCtc (p < 0.001). At 6 months, delta Cr was 0.29mg/dl in patients with high AUCtc, 0.18 mg/dl in patients with intermediate AUCtc and 0.17 mg/dL in patients with low AUCtc (p = 0.002). A high AUCtc predicted a progressive increase of serum Cr even in the subgroup of patients without renal impairment: Delta Cr 0.21 mg/dl vs 0.15mg/dl at 3 months, and Delta Cr 0.24 mg/dl vs 0.14 mg/dl at 6 months (p = 0.002 and p = 0.006 respectively).
Conclusion: AUCtc estimates cumulative exposure to tacrolimus and is associated with a progressive increase of serum Cr in spite of routine dose adjustments. Tacrolimus minimization should be universally applied, even for patients with an initially preserved renal function.

FRI-034
Evolution and impact of obesity in patients on the liver transplant waiting list
G. Lassailly[1], M. Favre[2], F. Artru[2], O. Goria[3], E. Nguyen-Khac[4], A. Louvet[2], Stéphanie Truant[2], E. Boleslawski[2], G. Lebuffe[2], F.-R. Pruvot[2], P. Mathurin[2], S. Dharancy[1]. *[1]Liver unit, CHRU Lille, Lille, France; [2]CHRU Lille, 59000, Lille; [3]CHU Rouen, 76000, Rouen, France; [4]CHU Amiens, 80000, Amiens, France*
Email: mathilde.favre@chru-lille.fr

Background and Aims: Obesity increases worldwide and impacts global morbi-mortality. As an example, NASH is now the second cause of liver transplantation (LT) in the US and the third cause of HCC. We aimed at deciphering the evolution and the impact of obesity in patients on the waiting list for LT.
Method: Data between 1990 and 2017 were extracted from the prospective CRISTAL database of the Agence de biomedicine (French Transplant Agency). All patients were registered and followed in our transplant center. Three periods of time were analyzed: 90–97; 97–2007 and 2007–2017. To study the impact of obesity on the access to LT, only the MELD era was studied to avoid allocation bias.
Results: 1393 registrations occurred between 97–17. Characteristics of patients were: age 54 [45–61], BMI 25.3 kg/m² ± 4.8, gender (F:33%), MELD 15.7[9.6–24.7], CPT score 9[7–11]. BMI and the prevalence of obesity significantly increased during the 3 period of time: 22 ± 4.3 vs 24.3 ± 3.9 vs 26.5 ± 4.9 kg/m² and 3.7% vs 7% vs 22.9% (p < 0.0001) respectively. Access to transplant was lower for obese patients 72.9% vs 81% (p < 0.03) than lean patients (BMI < 30 kg/m²). Death and drop out from the waiting list increased with obesity grade (G1 = 23.8%; G2 = 37.1%; G3 = 40%, p = 0.04). Obese patients were older (57 vs.53y) more diabetic (38 vs 26%) and frequently registered for HCC (51.5 vs 39%) [p < 0.01 for all]. MELD (20 vs 20) and CPT (9 vs 9.3) did not differ between the 2 groups. Using univariate analysis, age, gender, BMI, bilirubin, CTP score, alcoholic cirrhosis and hepatic encephalopathy were associated with increased death and drop out. Using multivariate analysis, BMI (CR −0.059 ± 0.02, p = 0.007), HCC (−0.74 ± 0.26 p = 0.005) and CPT score (−0.13 ± 0.06; p = 0.047) and trend for age (CR −0.02 ± 0.01; p = 0.05) were associated with increased death and drop out from the list. Surprisingly, in sensitivity analysis, obese patients registered for HCC had same access to transplant than non-obese (72 vs 77%, p = 0.4). Conversely, obese patients without HCC dropped out more frequently than non-obese (26.5% vs 17.1%, p = 0.04) and trended to disclose more severe liver disease MELD (median 24 vs 20.8, p = 0.08).
Conclusion: The worldwide increase of obesity during the past 3 decades has impacted our waiting list. Obesity was associated with a lower access to liver transplantation.

FRI-035
A beneficial weekend effect? Weekend liver transplantation isassociated with reduced graft and transplant failure
N. Halliday[1,2], K. Martin[3], D. Collett[3], E. Allen[3], D. Thorburn[4]. *[1]University College London, Institute of Immunity and Transplantation, London; [2]Royal Free Hospital, Sheila Sherlock Liver Centre, London, United Arab Emirates; [3]NHS Blood and Transplant, Statistics and Clinical Studies, Bristol, United Kingdom; [4]Royal Free Hospital, Sheila Sherlock Liver Centre, London, United Kingdom*
Email: neilhalliday@doctors.org.uk

Background and Aims: Liver transplantation (LT) is a time critical procedure, as graft cold ischaemic time needs to be minimised and the timing of organ retrieval often cannot be scheduled, hence many procedures occur "out-of-hours'. There is concern that adverse clinical outcomes are associated with weekend and night-time clinical activity. We sought to determine whether weekend or night-time LT was associated with poorer outcomes in the UK.
Method: Rates of graft failure and transplant failure (the occurrence of graft failure and/or death) at 30 days, 1 and 3 years following LT were determined for adult, liver only recipients from all seven UK transplant centres between 2000–2014. A risk adjusted Cox regression model was constructed and outcomes correlated with weekend (5pm Friday to 9am Monday) or night-time (7pm to 7am) LT.
Results: 8816 transplants were included and baseline characteristics between weekend and weekday groups were similar.
In the unadjusted analyses the hazard ratio (HR) for graft failure was the same for weekend transplantation at all time points (HR at 30 days 0.85, p = 0.08; 1 year 0.91, p = 0.16; 3 years 0.92, p = 0.16) but lower for transplant failure at 30 days (0.82, p = 0.01; 0.91, p = 0.09; 0.93, p = 0.12) compared to weekdays. In the risk-adjusted model the hazard of graft failure was lower at early time points (HR 0.81, p = 0.02; 0.87, p = 0.06; 0.892, p = 0.06) and for transplant failure at all time points (0.77, p = 0.001; 0.86, p = 0.01; 0.89, p = 0.02) with weekend LT. For patients without transplant failure at 30 days, there was no weekend effect on LT outcomes.
Night-time transplantation was associated with a higher hazard of graft or transplant failures at all time points in the unadjusted analyses. However, in the unadjusted analyses no differences were observed for outcomes with night-time transplantation or graft retrieval.
Conclusion: Weekend and night-time LT are non-inferior to weekday transplantation and there are potentially benefits with weekend LT in the UK, which are dependent upon peri-transplant factors. These data suggest that the current UK model of liver transplant services avoids adverse outcomes at perceived periods of risk.

FRI-036
Long-term post-transplant liver biopsies of children: central perivenulitis is associated with circulating donor-specific antibodies and tissue C4D deposition
L.N. Souza[1], A. Sanchez-Fueyo[2], A. Dhawan[3], A. Quaglia[4]. *[1]Institute of Liver Studies, Department of Transplantation Immunology and Mucosal Biology (DTIBM), London, United Kingdom; [2]Institute of Liver Studies, MRC Transplant Centre, King's College London University, London; [3]Paediatric Liver, GI and Nutrition Centre, London, United Kingdom; [4]Institute of Liver Studies, Pathology, London, United Kingdom*
Email: k1344108@kcl.ac.uk

Background and Aims: Abnormalities in long-term post-transplant liver biopsies are common. The role of donor-specific alloantibodies

(DSA) in chronic allograft pathology is not completely understood. Our aim was to study the association between post-transplant DSA, C4d immunohistochemistry and chronic allograft histological injury in paediatric liver transplant recipients undergoing a protocol liver biopsy at least 8 years after transplantation, clinically stable and with normal liver function tests.

Method: Post-transplant allograft core needle biopsies were assessed by two histopathologists using semi-quantitative score for inflammation and fibrosis. Immunohistochemistry for C4d was performed with Cell Marque mono-polyclonal antibody and the stain assessed through a semi-quantitative score. Patients" serum was retrieved from our biobank and tested for the presence of circulating DSA.

Results: Fifty-nine patients underwent protocol biopsy between 8.7 and 15.4 (average 12.0) years post-transplant. Recipients age at biopsy ranged from 9.6 to 17.1 (average 15.0) years. Thirty-one children were male. Forty patients (67.8%) had histological abnormalities: twenty-four (42.1%) unexplained chronic hepatitis, 24 (42.1)% significant portal fibrosis (defined as at least bridging), 2 (3.4%) established rejection and 1 patient had chronic cholangiopathy. Thirty-six children had serum and donor's HLA data available for DSA testing. Twenty-five (of 36, 69.4%) had circulating DSA: 19 directed at class II HLA antigens, 3 at class I, and 4 at both classes. The presence of class II DSA with mean fluorescent intensity >10,000 was associated with significant portal fibrosis, present in 90% of patients with these antibodies ($p = 0.002$). There was a link between C4d in portal vein branches and DSA ($p = 0.009$), and all 6 patients who showed moderate or strong C4d deposition in portal veins had circulating DSA. C4d was not sensitive, thought, as 76% of DSA+ recipients had negative or weak C4d positivity in portal vein branches. Furthermore, all patients with DSA and concomitant C4d deposition (focal or diffuse) in portal vein had central perivenulitis (CP) on biopsy ($p = 0.018$). However, 25% of patients without DSA and C4d also had central perivenulitis.

Conclusion: 67.8% of children who underwent liver transplantation developed significant histological injury by the time of biopsy, despite being clinically stable with normal liver function tests. DSA were present in 69.4% of patients, in most cases directed at class II HLA antigens. Circulating class II DSA in high titres were associated with fibrosis. Moderate/strong C4d deposition in portal vein branches was a specific but not sensitive indication of circulating DSA. Central perivenulitis may represent a sensitive although not specific histological indication of chronic antibody-mediated allograft damage in stable transplanted children.

FRI-037

DAA therapy improves early post-liver transplant survival and induces significant changes in wait-list composition

G. Crespo[1], N. Trota[2], M.-C. Londoño[1], E. Mauro[1], C. Baliellas[3], L. Castells[4], José Castellote[3], J. Tort[2], X. Forns[1], M. Navasa[1]. *[1]Hospital Clínic, Liver Unit, CIBERehd, IDIBAPS, Barcelona, Spain; [2]Organització Catalana de Transplantaments, Barcelona, Spain; [3]Hospital Bellvitge, Liver Unit, L'Hospitalet de Llobregat, Barcelona, Spain; [4]Hospital Vall d'Hebron, Liver Unit, CIBERehd, Barcelona, Spain*
Email: gcrespo@clinic.ub.es

Background and Aims: The availability of direct-acting antivirals (DAA) has dramatically changed the treatment and prognosis of patients with chronic hepatitis C. We aimed to evaluate the impact of DAA on the liver transplant (LT) waiting list and the early post-transplant survival.

Method: We included all patients admitted in the waiting list for a primary LT between 1/1/2008 and 31/12/2016 in Catalonia, Spain, using data from the Registry of the Organització Catalana de Trasplantaments (OCATT). Time span was divided into two periods according to the availability of different antiviral therapies: 2008–2013 (IFN-based therapies) and 2014–2016 (DAA). Changes in the indications of LT and aetiology of baseline liver disease, as well as post-LT patient survival, were evaluated according to the year of inclusion and transplantation, respectively.

Results: We included 1483 patients admitted in the waiting list during the study period. Inclusions in the waiting list due to HCV-related liver disease significantly decreased: from 52% in 2008–2013 to 40% in the second period (28% in 2016), particularly those indications related to decompensated cirrhosis ($p < 0.0001$). In contrast, NASH-related inclusions increased significantly, from 4% to 8% ($p = 0.002$) (12% in 2016). Three year post-LT patient survival improved significantly in the second period in the whole cohort (82% vs 91%, $p = 0.002$). The latter was explained by a significant survival increase in anti-HCV positive patients (76% vs 91%, $p = 0.001$), but not in HCV-negative patients (88% vs 91%, $p = 0.359$). Using Cox regression multivariate analysis, HCV serology, time period and donor age were independent predictors of patient survival in the whole cohort; while time period and donor age were independently associated with survival in HCV-positive recipients.

Conclusion: DAA therapy is associated with significant changes in the composition of the LT waiting list and more importantly, results in improved early post-transplant survival.

FRI-038

Long-term subclinical inflammatory lessions in liver transplant recipients

M.-C. Londoño[1], L. Neves Souza[2], R. Miquel[2], A. Quaglia[2], L.P. Llovet[3], M. Navasa[3], A. Rimola[1], A. Sanchez-Fueyo[4]. *[1]Hospital Clínic Barcelona, Liver Unit, Spain; [2]Institute of Liver Studies at King's College Hospital, MRC Transplant Centre, King's College London University, United Kingdom; [3]Liver Unit, Hospital Clínic, Spain; [4]Institute of Liver Studies, King's College London, MRC Transplant Centre, King's College London University, London, United Kingdom*
Email: mlondono@clinic.ub.es

Background and Aims: Sub-clinical inflammatory changes are commonly described in long-term transplant recipients undergoing protocol liver biopsies. The pathogenesis of these lesions and their contribution to progressive allograft fibrosis remain unclear. Therefore, the aim of the study was to determine the prevalence of histological abnormalities in long-term surviving liver recipients and to investigate the molecular profiles of sub-clinical inflammatory changes.

Method: Between 1989 and 1999, 654 liver transplantations (LT) were performed on 589 recipients at Hospital Clínic Barcelona. Patients with recurrence of underlying liver disease, severe biliary or vascular complications, chronic rejection, or ALT >2-fold ULN were excluded. 312 patients were dead and 121 were lost to follow-up. 67 patients underwent extensive laboratory testing and a liver biopsy. Transcriptome profiling was performed on RNA extracted from FFPE liver biopsies employing the next generation sequencing Ion AmpliSeq platform.

Results: Median time since LT to liver biopsy was 155 months (118–268). Most of the patients were on monotherapy with cyclosporine, tacrolimus or mycophenolate at low through levels (mean CyA 38 ng/ml [0–143], FK 1.7 ng/ml [0–4.2]). Six patients (9%) had cirrhosis, 5 (8%) had chronic rejection and 8 (12%) patients had moderate/severe hepatic steatosis. Among the remaining patients the most frequently observed histological abnormality was portal inflammation, present in 45 biopsies (67%). Employing *Weighted Gene Correlation Network Analysis*, we identified 2 modules of genes (Cyan and Pink modules) that significantly correlated with portal inflammation, interface hepatitis and portal fibrosis observed in liver biopsy. Biopsies were assigned into 2 groups according to the level of expression of these modules (High and Low). High group was enriched in canonical pathways associated with allograft rejection and immunopathology (similar to patients with T cell mediated rejection, TCMR). Contrary to what was observed in the low group, after a median follow-up period of 6.8 years, patients in the high group have significantly lower platelet counts and high fibrosis score (FIB-4).

Conclusion: The prevalence of significant histological abnormalities in highly selected long-term surviving liver transplant recipients is high. Samples with portal inflammatory infiltrates exhibit transcriptional changes that greatly overlap with those of TCMR.

FRI-039

Utility of FDG-PET/CT in pre-transplantation workup of the potential liver recipient with hepatocellular carcinoma

S.Y. Yi[1], J.H. Shim[1], G.W. Song[2], G.H. Choi[1], K.M. Kim[1], Y.-S. Lim[1], H.C. Lee[1], Y.-H. Chung[1], Y.S. Lee[1], S.-G. Lee[1]. [1]*Asan medical center, Division of Gastroenterology, Department of Internal Medicine, Seoul, Korea, Rep. of South;* [2]*Asan medical center, Division of Hepatobiliary Surgery and Liver Transplantation, Department of Surgery, Seoul, Korea, Rep. of South*
Email: s5854@amc.seoul.kr

Background and Aims: There is no consensus approach to the decision-making regarding suitability for liver transplantation (LT) in patients with hepatocellular carcinoma (HCC). Positron emission tomography-computed tomography using ^{18}F-fluorodeoxyglucose (FDG PET/CT) has been found to provide helpful information for determining post-LT prognosis in HCC patients. We aimed to assess the performance of FDG-PET/CT for detection of metastatic disease or other malignancy in potential liver recipients with HCC.
Methods: This retrospective study included 423 adult liver transplant candidates with HCC who underwent both FDG-PET/CT and conventional imaging studies such as chest-abdomen-pelvis CT examinations and bone scintigraphy, together with upper and lower gastrointestinal endoscopy, as pre-transplant workup. All patients had no history of cancer other than HCC. The diagnostic performance of FDG-PET/CT was quantitatively evaluated by the calculation of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).
Results: Out of the 423 patients, 338 (79.9%) were male with a median age of 55 years (54.03–55.43). In terms of extrahepatic evaluation, FDG-PET/CT detected a total of 163 lesions in 142 patents, which consisted of 132 benign and 31 malignant-looking lesions. The number of lesions suspicious for metastatic HCC was initially 24. Further diagnostic procedures confirmed 3 pulmonary, 7 skeletal, and 7 lymphatic metastases in 3, 7, and 7 patients, respectively; and 1 gastrointestinal stromal tumor (GIST) and 1 lung cancer in 1 and 1 patient, respectively. Among the 17 metastases, 4 were suspected to be a metastatic focus only by FDG-PET/CT, not by conventional scanning. All 2 cases of colorectal cancers diagnosed by sigmoidoscopic screening were detected on neither FDG-PET/CT nor abdomen/pelvis CT images. False positive FDG-PET/CT results were identified in 12 patients with benign lesions: 1 Warthin's tumor of the parotid gland, 3 inflammatory nodules of the lung, 2 degenerative bone lesions, 4 reactive lymphadenopathies, 1 focal bladder wall thickening, and 1 prostatic hyperplasia. No false negative errors occurred in FDG-PET/CT, while 1.2% in conventional studies (1 GIST and 4 bone metastases). Taken together, the performance of FDG-PET/CT in detecting metastatic or primary cancer in our series was measured with sensitivity of 90.48%/89.47%, specificity of 97.04%/97.04%, PPV of 61.29%/62.96%, and NPV of 99.49%/99.49% on per-lesion/per-patient basis.
Conclusion: Our results indicate that whole-body FDG-PET/CT, when coupled with colonic examination, is effective for identification of extrahepatic disorders before LT in patients with HCC, and may fully replace multiple organ-specific imaging tests. The future cost-effectiveness study is warranted for the rational use of FDG-PET/CT in potential LT candidates with HCC.

FRI-040

Long-term outcome of donor biliary complications following living donor liver transplantation

H.Y. Woo[1], I.S. Lee[2], J.H. Chang[2], S.H. Bae[2], J.Y. Choi[2], S.K. Yoon[2]. [1]*Pusan National University Hospital, Departments of Internal Medicine, BUSAN, Korea, Rep. of South;* [2]*The Catholic University of Korea, Department of Internal Medicine, College of Medicine*
Email: who54@hanmail.net

Background and Aims: Biliary complications are the most common donor complication following living donor liver transplantation (LDLT). The aim of this study is to investigate the long-term outcomes of biliary complications in right lobe adult-to-adult living donor liver transplantation donors, and to evaluate the efficacy of endoscopic treatment of these donors.
Method: The medical charts of right lobe donors who developed biliary complications between June 2000 and January 2008 were retrospectively reviewed.
Results: Of 337 right lobe donors, 49 developed biliary complications, including 36 diagnosed with biliary leakage and 13 with biliary stricture. Multivariate analysis showed that biliary leakage was associated with the number of right lobe bile duct orifices. Sixteen donors, five with leakage and 11 with strictures, underwent endoscopic retrograde cholangiography (ERC). ERC was clinically successful in treating eight of the 11 strictures, one by balloon dilatation and seven by endobiliary stenting. Of the remained three, two were treated by rescue percutaneous biliary drainage and one by conservative care. Of the five patients with leakage, four were successfully treated using endobiliary stents and one with conservative care. In overall, total 35 improved with conservative treatment. All inserted stents were successfully retrieved after a median 264 days (range 142–502 days) and there were no recurrences of stricture or leakages during a median follow-up of 10.6 years (range 8–15.2 years).
Conclusion: All donors with biliary complications were successfully treated non-surgically, with most improving after endoscopic placement of endobiliary stents and none showing recurrence on long term follow-up.

FRI-041

Impact of surgical margin according to AFP ratebefore hepatectomy for hepatocellular carcinoma

Frédéric Marques[1], E. Boleslawski[2], O. Ciacio[1], D. Cherqui[1], M.-A. Allard[1], N. Golse[1], D. Castaing[1], René Adam[1], J.-M. Regimbeau[3], J.-Y. Mabrut[4], F.-R. Pruvot[2], D. Samuel[1], E. Vibert[1]. [1]*AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire;* [2]*Service de Chirurgie et Transplantation hépatique - Hôpital CLAUDE HURIEZ - CHU Lille;* [3]*Service de Chirurgie Digestive - Hopital Amiens Sud - CHU Amiens;* [4]*Lyon Croix Rousse*
Email: eric.vibert.pbr@gmail.com

Background and Aims: When surgical resection is decided for the treatment of hepatocellular carcinoma (HCC), surgical margins are essential to remove potential satellite nodules associated to microvascular invasions. It remains unclear if resection with narrow margins (<1cm) could be sufficient for some patients and which tumors need to be resected with wide margins (≥1cm) to prevent recurrence. The aim of this study was to determine if the width of resection margin necessary to prevent recurrence could be determined by preoperative alpha-fetoprotein (AFP) rate.
Method: From April 2012 to January 2016, all patients who underwent a first hepatectomy for HCC were included in a multicentric prospective database and analyzed retrospectively. Patients with no extrahepatic disease were included. Patients with remnant tumor after resection (R2) were excluded. We first studied if preoperative AFP rate was correlated to recurrence and pejorative pathological features. Univariate and multivariate analysis of prognostic factors for time to recurrence (TTR) were conducted and we studied the impact of the width of resection margins (<1cm or ≥1cm) in low and high AFP rate patients (≤100 or >100ng/ml).

Results: 397 patients from 5 centers met the selection criterias. 98 patients (25%) had a high AFP rate. Patients with AFP > 100 had significantly larger tumors (p < 0.001), more frequently microvascular invasions (p = 0.01), satellite nodules (p = 0.013) and poorly differentiated tumors (p = 0.014). In multivariate analysis, the only independent preoperative predictive factor for TTR was AFP > 100 (p < 0.001). In High AFP group, TTR was impacted by surgical margins (p = 0.040). Median TTR for patients with narrow margins was 8 months. TTR for patients with wide margins did not reach the median. In Low AFP group, TTR was not impacted by surgical margins (p = 0.625). Patients with narrow and wide resection margins had a median TTR of 38 and 32 months respectively.

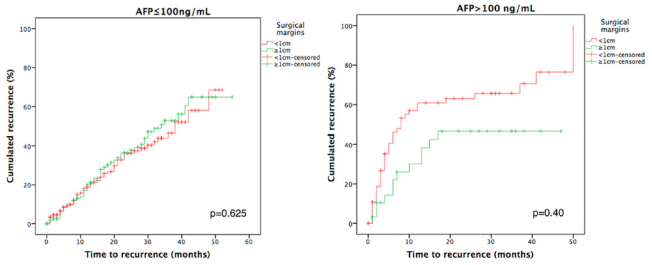


Figure 1: Impact of surgical margins on time to recurrence according to AFP rate

Conclusion: Our study confirmed that AFP > 100 ng/ml is an independent predictive factor of HCC recurrence, associated to invasive pathological features such as microvascular invasion, satellite nodules and poorer tumor differentiation. This study showed that tumors associated with a preoperative AFP > 100 ng/ml should be resected with a wide margin to prevent recurrence. At the opposite, the width of resection margin did not impact survival or recurrence in patients with a preoperative AFP ≤ 100.

FRI-042
Upper limb lean mass by Dual Energy Xray Absorptiometry is associated with increased mortality in men with advanced cirrhosis

M. Sinclair[1,2], R. Hoermann[2], A. Peterson[1], A. Testro[1], P. Angus[1,2], P. Hey[1], B. Chapman[1], P. Gow[1,2]. *[1]Austin health, Liver Transplant Unit, Australia; [2]The University of Melbourne, Medicine, Melbourne, Australia*
Email: mariejsinclair@gmail.com

Background and Aims: Sarcopenia is common in cirrhosis, and accelerates as MELD score rises. Low muscle area at the L3 level on CT scan is an independent predictor of mortality in cirrhosis; this association is strongest in men. Dual Energy X-ray Absorptiometry (DEXA) body composition is not well studied in cirrhosis, but has the advantages of low cost, low radiation dose, and analysis of all body compartments. This study examines the relationship between DEXA lean mass measures including appendicular (APLM = lean mass of arms + legs) and total lean mass (TLM) on clinical outcomes in cirrhotic men awaiting liver transplantation.
Method: We retrospectively reviewed DEXA scans performed during liver transplant assessment of men between September 2001 and November 2016. Baseline clinical data including presence of ascites and MELD score were recorded. DEXA lean mass measures were adjusted for height as previously described. We retrieved clinical outcomes including mortality, sepsis and time-to-outcome. Cox regression was used to identify predictors of outcome.
Results: 421 men with median age 53.4 years [95% CI 49.1; 59.3] and median MELD 16 [12; 20] were studied. Median follow-up was 2533 days [1157; 3823]. 27.6% of patients died, 24.2% suffered major sepsis and 74.3% were transplanted. APLM was inversely associated with overall mortality (HR 0.78 [0.62; 0.98], p = 0.034). Lean mass of arms (HR 0.37 [0.16; 0.83], p = 0.015) rather than legs (HR 0.77 [0.58; 1.03], p = 0.079) was responsible for this association. TLM was not associated with mortality, but increased with MELD score (r=+0.22, p < 0.001) in conjunction with increasing prevalence of ascites (OR for ascites 1.20 [1.15; 1.25], p < 0.001 for each unit increase in MELD). APLM displayed no relationship with MELD score (r = 0.0, p = 0.96) but arms lean mass fell with rising MELD score (r = –0.28, p < 0.001). Neither APLM, leg lean mass nor TLM were associated with sepsis, however a trend was noted for arms lean mass (HR 0.55 [0.30; 1.02], p = 0.056).
Conclusion: Upper limb lean mass by DEXA scan is strongly associated with mortality in men awaiting liver transplant and is inversely associated with liver disease severity. DEXA scans cannot differentiate water (either ascites or peripheral oedema) from muscle, which likely explains the counterintuitive positive association between TLM and MELD score, and the lack of association between either TLM or leg lean mass and outcome. These data suggest that upper limb lean mass is the best DEXA measure of muscle mass in cirrhotic men, and represents a novel, reliable, low cost estimate of sarcopenia in this cohort.

FRI-043
MELD dynamics predicts waitlist outcomes in patients awaiting liver transplantation

B.H. Kim, A. Mannalithara, A. Kwong, W.R. Kim. *Stanford University, Division of Gastroenterology and Hepatology, Stanford, United States*
Email: wrkim@stanford.edu

Background and Aims: Recent advances in the treatment have enabled to alter prognosis of patients with liver disease. Dynamic changes in Model for End-Stage Liver Disease (MELD) among waitlist candidates may provide insight into liver disease trajectories. The aim of this study was to determine whether a change in MELD score over 12 weeks is predictive of transplant-free survival among adult liver transplantation (LT) candidate with end-stage liver disease.
Method: From the United Network for Organ Sharing dataset, adult liver transplant candidates listed from 1/JAN/2010 to 5/DEC/2014, aged 18 years or more, had never undergone LT and not listed for multiorgan transplantation were identified. Patients with hepatitis C-related cirrhosis, non-alcoholic steatohepatitis (NASH), or alcoholic cirrhosis were considered eligible; however, those who listed as status 1A or receiving an exception score were excluded. The change in MELD score over 12 weeks on subsequent transplant-free survival was assessed by the multivariable proportional hazards regression analysis.

Table 1: Incidence rates of death or liver transplantation per 100 people per year (95% CI) in patients who experienced change in MELD score over 12 weeks.

	Initial MELD		
Change in MELD score	10–14	15–20	21–25
Decrease by ≥ 2	15 (13–18)	33 (30–36)	83 (77–90)
No change (± 1)	24 (22–26)	53 (50–57)	102 (95–110)
Increase by 2–5	42 (38–46)	118 (111–126)	251 (228–276)
Increase by 6–10	95 (81–111)	269 (240–302)	704 (605–820)
Increase by 11+	268 (210–341)	718 (608–848)	1730 (1422–2105)

Results: Among 23,075 eligible candidates consisting of 15,591 men and 7,484 women, 11,804 (51.2%) had hepatitis C, 4,258 (18.5%) NASH and 7,013 (30.4%) alcoholic cirrhosis. Of these patients, 6,491 (28.1%) had MELD 10–14, 6,973 (30.2%) had MELD 15–20 and 2,954 (12.8%) had MELD 21–25. The incidence of LT or mortality increased as the initial MELD score increased as shown in Table 1. For each initial MELD strata, those who experienced a decrease by 2 or more points over 12 weeks had lower incidence compared with those who had no change, while those with a rising MELD score showed progressively higher incidence according to the degree of increase. Patients who had initial MELD of 10–14 and experienced a decrease by 2 or more

points had a significantly lower risk of LT or mortality with incidence rate ratio of 0.62 (95% confidence interval [CI] 0.52–0.76). This was consistent for other initial MELD strata; 0.61 (95% CI 0.55–0.68) for MELD 15–20 and 0.82 for MELD 21–25 (95% CI 0.73–0.91).
Conclusion: Reduction of MELD score by 2 or more points over 12 weeks decreases the risk of LT or death – by approximately 40% compared to those whose MELD remained stable. As effective therapeutic agents become increasingly available for patients with viral and non-viral liver disease, the longitudinal trajectory of MELD scores may inform management decisions in patients with hepatic decompensation.

FRI-044
Effects of liver transplantation (LTx) on health-related quality of life (HRQoL) in patients with PBC
M. Krawczyk[1,2,3], Małgorzata Koźma[4], A. Szymańska[5], K. Leszko[4], M. Przedniczek[4], K. Mucha[5,6], B. Foroncewicz[5], L. Paczek[5,6], B. Moszczuk[6], P. Milkiewicz[4,7], R.-W. Joanna[4]. *[1]Department of Medicine II, Saarland University Medical Center, Homburg, Germany; [2]Laboratory of Metabolic Liver Diseases, Center for Preclinical Research, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland; [3]Department of Medicine II, Saarland University Medical Center; Homburg, Germany; [4]Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery, Medical University of Warsaw, Warsaw, Poland; [5]Department of Immunology, Transplantology and Internal Medicine, Transplantation Institute, Medical University of Warsaw, Warsaw, Poland; [6]Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Warsaw, Poland; [7]Translational Medicine Group, Pomeranian Medical University, Szczecin, Poland*
Email: marcin.krawczyk@uks.eu

Background and Aims: Patients with primary biliary cholangitis (PBC) are known to have a significantly decreased health related quality of life (HRQoL). They suffer from not only pruritus and fatigue, but several other aspects of their well-being are also affected. As clearly shown, treatment with UDCA does not improve HRQoL (Mells et al Hepatology 2013;58:273–83) and in these who develop advanced liver cirrhosis, liver transplantation (LTx) remains the only curative option. Here we investigated HRQoL in two cohorts of patients with PBC who underwent LTx and compare their results to healthy subjects.
Method: Generic SF-36 and disease-specific PBC-40 questionnaires were used in 107 PBC patients (F/M = 99/8, mean age 63 ± 7 years) with mean 91 months after LTx (group 1). They were also implemented in 26 patients (F/M = 23/3, mean age 59 ± 6 years) in whom they were taken before and within a shorter period (mean 12 months) after LTx (group 2). Control group comprised 60 matched healthy controls.
Results: When compared to controls, patients with prolonged period after LTx (group 1) showed a significant impairment of their HRQoL measured with SF-36. It included physical functioning, physical role, emotional role and physical component score domains. In group 2, where HRQoL questionnaires were available before and after LTx, a significant improvement in virtually all domains of SF-36 was seen. Also a significant amelioration of symptoms assessed with PBC-40 was seen in this group including both pruritus (7.8 ± 5.5 vs. 3.7 ± 4.3; p = 0.009) and fatigue (32.7 ± 11.9 vs. 24.2 ± 10.7; p = 0.002). There was no difference in HRQoL between patients in group 1 and 2.
Conclusion: Patient with PBC and prolonged period of time after LTx have worse HRQoL than their matched controls. On the other hand, LTx leads to significant improvement of HRQoL in PBC which is notable within a short period after LTx and does not improve any further later on.

FRI-045
Filamin a expression predicts early recurrence of hepatocellular carcinoma
M. Donadon[1], L.D. Tommaso[2], C. Soldani[1], B. Franceschini[1], L. Vigano[1], M. Cimino[1], M. Roncalli[2], A. Lleo[3], G. Torzilli[1]. *[1]Humanitas University, Department of Hepatobiliary and General Surgery, Rozzano (MI), Italy; [2]Humanitas University, Department of Pathology, Rozzano (MI), Italy; [3]Humanitas University, Department of Internal Medicine and Hepatology, Rozzano (MI)*
Email: ana.lleo@humanitas.it

Background and Aims: The risk of recurrence of hepatocellular carcinoma (HCC) after hepatectomy is very high and predictive markers of early recurrence (ER) are not available. The overexpression of Filamin A (FLNA), a cytoskeleton protein with scaffolding properties, has recently been associated with progression in different tumors. The aim of this study was to test the expression of FLNA in a cohort of patients operated for HCC.
Method: A retrospective cohort of patients who underwent curative hepatic resection at Humanitas Clinical and Research Center between January 2004 and December 2014 was analyzed. FLNA was tested using a tissue-microarray in the extra-tumoral, peri-tumoral, and intra-tumoral tissue compartments. The endpoint was the role of FLNA expression in predicting ER of HCC after hepatectomy. Analyses were performed according to the REMARK guidelines.
Results: A total of 113 patients were included in the study. FLNA was expressed only in the peri-tumoral and intra-tumoral tissue but not in the extra-tumoral normal tissue. Several variables, including T-stage, tumor number, tumor size, type of viral hepatitis, type of hepatectomy, and intra- and peri-tumoral immune-reactivity to FLNA were significantly associated with ER by univariate analysis. With multivariate analysis, only T-stage (HR = 2.108; p = 0.002), tumor number (HR = 1.586; p = 0.023), intra-tumoral (HR = 2.672; p < 0.000) and peri-tumoral immune-reactivity to FLNA (HR = 2.569; p < 0.000), significantly correlated with ER. The logistic regression analysis revealed that advanced T-stage (OR = 2.985; p = 0.001), HCV-infection (OR = 1.219; p = 0.008), and advanced tumor grading (OR = 2.781; p = 0.002) were associated with intra-tumoral FLNA immune-reactivity.
Conclusion: FLNA expression predicts recurrence of HCC after hepatectomy. This finding provides important insights that would help physicians to personalize follow-up strategies and develop a new therapeutic target.

FRI-046
Patients with 18F-FDG PET-positive hepatocellular carcinoma and elevated values of alpha-fetoprotein and C-reactive protein have an extraordinary high risk of tumor recurrence following liver transplantation
A. Kornberg[1], U. Witt[1], J. Kornberg[2], K. Müller[3], H. Friess[1], K. Thrum[4]. *[1]Technical University Munich, Klinikum rechts der Isar, Department of Surgery;, [2]Ludwig-Maximilians-University, Department of Anesthesiology; [3]Friedrich-Schiller-University Jena; [4]Helios Klinikum Berlin, Institute of Pathology*
Email: arnokornberg@aol.com

Background and Aims: Biological tumor aggressiveness rather than macromorphology of hepatocellular carcinoma (HCC) determines outcome following liver transplantations (LT). Recently, standard procedures such as ^{18}F-FDG positron emission tomography (PET), alpha-fetoprotein (AFP) and C-reactive protein (CRP) were suggested to describe tumor biology of HCC. The aim of this study was to assess the prognostic significance of combining ^{18}F-FDG PET data with serum values of AFP and CRP for selecting appropriate liver transplant patients.
Method: We performed a retrospective observational trial including 123 patients that were identified from a prospectively maintained LT database. All of them underwent pre-LT ^{18}F-FDG PET to distinguish between PET-negative and PET-positive tumors. The most optimal cut-off values of AFP (100 ng/ml; Area under the curve [AUC] = 0.826;

r = 0.042; 95%Confidence Interval [CI] 0.743–0.909) and CRP (0.8 mg/dl; AUC = 0.824; r = 0.039; 95%CI 0.747–0.901) for predicting HCC recurrence were determined by receiver operating characteristic analysis. Recurrence-free survival (RFS) rates were determined using the Kaplan-Meier method. Uni- and multivariate analyses using Cox's proportional hazards model were performed to identify pre-LT available clinical predictors of RFS.

Results: Median post-LT follow-up was 73 months (range: 5–184). Tumor recurrence rate was 23.6%. In multivariate analysis, only CRP < 0.8 mg/dl (Hazard ratio [HR] = 9.3; 95%CI 2.199–41.035; p = 0.003), AFP < 100 ng/ml (HR = 4.3; 95%CI 1.754–10.563; p = 0.001) and PET-negativity (HR = 4.2; 95%CI 1.491–11.867; p = 0.007) were identified as independent predictors of RFS, whereas macromorphologic tumor features were not independently significant. Five year RFS rates were 93.5% in ^{18}F-FDG-non-avid patients (n = 77) and 100% in PET-positive patients with low AFP/CRP levels (n = 8), defining a low biological risk group (n = 85). In contrast, it was only 32.7% in PET-positive patients with high CRP and/or AFP levels (log ran < 0.001; n = 38; high risk group), respectively. The special subset of patients with a triplet of unfavorable biological features (PET-positive + AFP > 100 ng/dl + CRP > 0.8 mg/dl; n = 16) demonstrated a 5 year RFS rate of 0%. Hazard ratios for predicting RFS were 16.9 for patients with low biological risk (95%CI 6.384–44.521), and 3.2 for meeting MC tumors (95%CI 1.471–7.109). Application of tumor biological variables instead of macromorphology increased transplant eligibity by 23.2%.

Conclusion: Combining ^{18}F-FDG PET with serological parameters of tumor viability, such as AFP and CRP improves prognostic accuracy and increases the number of eligible liver transplant patients. Thus, strict macromorphologic tumor burden limits may be crossed.

FRI-047

Multi-frequency bioelectrical impedance output correlates to liver disease severity, nutritional status and functional capacity

R. Sinha[1], J. Foo[2], P. Hayes[1]. [1]*Royal Infirmary and The University of Edinburgh, Scottish Liver Transplant Unit, Edinburgh, United Kingdom;* [2]*College of Medicine & Veterinary Medicine, The University of Edinburgh, Medical School, The Chancellor's Building, 2nd Floor, Edinburgh, United Kingdom*
Email: rohit.sinha@nhs.net

Background and Aims: Malnutrition and poor physical endurance is highly prevalent in patients with advanced liver disease requiring liver transplant and bear significant impact on morbidity and mortality. Traditional assessment of nutritional status is subjective and has limitations. Additionally, measurement of physical fitness with cardiopulmonary exercise (CPEX) cannot be extended globally to all patients. Bioelectrical impedance analysis (BIA) is increasingly used to measure body composition, malnutrition and clinical progression of various diseases. The aim this study is to assess the clinical usefulness of BIA as a bedside tool for assessing nutritional status, functional exercise capacity and relationship to severity of liver disease.

Method: This is a retrospective, observational cross-sectional study of 68 consecutive patients who underwent liver transplant assessment at our centre between the period of January 2017 and July 2017. Acute liver failure cases were excluded. Various clinical, biochemical, nutritional assessment [Dry BMI, albumin and mean arm muscle circumference (MAMC)] and functional assessment [Hand-grip strength (HGS) and CPEX data – maximal oxygen consumption (VO2 max) and anaerobic threshold (AT)] data were collected. All patients underwent body composition assessment on a multi-frequency BIA – Seca analyser 515 device, and outputs [Total Body Water, Extracellular Water, Fat Mass Index, Fat-free Mass Index, Skeletal Muscle Mass and Phase Angle] were considered. Correlation analysis was carried out using Spearman's rho correlation. Multivariate stepwise linear regression analyses were used to determine the independent predictors of the severity of liver disease (MELD) and functional exercise capacity (AT) respectively.

Results: 63.2% were males and median age was 59.5 (IQR 11.5) years. The results showed strong correlations between BIA parameters, in particular PA and CPEX data. PA correlated positively with VO2 max (r = 0.521, p < 0.01) and AT (r = 0.440, p < 0.01). PA was positively correlated with HGS (r = 0.548, p < 0.01). PA strongly correlates to serum albumin (r = 0.503, p < 0.01), dry BMI (r = 0.296, p < 0.05) and MAMC (r = 0.380, p < 0.01). PA showed a negative correlation with UKELD (r =-0.408, p < 0.01) and MELD (r=-0.431, p < 0.01). In the linear regression model, AT was primarily predicted by PA (beta = 0.281, p < 0.001) and MELD was by PA (beta=-0.420, p < .001)

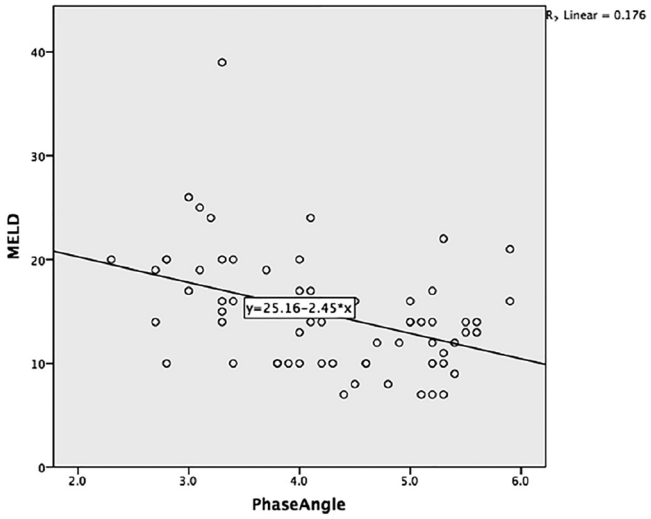


Figure 1: A positive correlation between Phase angle (PA)

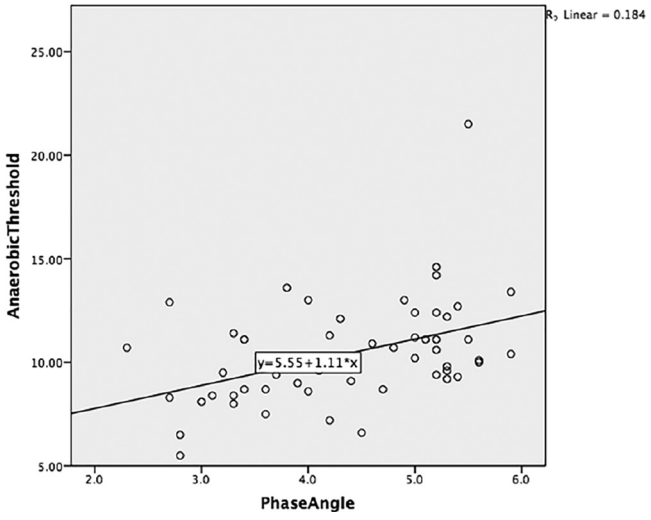


Figure 2: A negative correlation between Phase angle (PA) and severity of Functional capacity liver disease

Conclusion: BIA offers non-invasive, relatively inexpensive, portable bed-side assessment. PA correlates strongly to nutritional status, functional capacity and severity of liver disease. Further prospective studies are required to validate our finding.

FRI-048

Pregnancy outcomes and reproductive health after liver transplantation

C. Lindenmeyer[1], G. Flocco[1], L. Bell[2], R. Baird[2], V. Sanghi[3], R. Lopez[4], A. Mccullough[1]. [1]*Cleveland Clinic, Gastroenterology and Hepatology, Digestive Disease and Surgery Institute, Cleveland, United States;* [2]*Cleveland Clinic, Lerner College of Medicine, Cleveland, United States;* [3]*Cleveland Clinic, Internal Medicine, Cleveland, United States;* [4]*Cleveland Clinic, Quantitative Health Sciences, Digestive Disease and Surgery Institute, Cleveland, United States*
Email: christina.lindenmeyer@gmail.com

Background and Aims: Contemporary advances in liver transplantation (LT) have steadily increased post-LT survival. As patients are now expecting to live longer, fertility has become a major component of the patient's quality of life. However, our current understanding of the implications of LT and immunosuppressant medications on mother, fetus, and graft remains limited. In addition, previous data suggest that pre-LT, post-LT and prenatal counseling regimens are non-standardized and poorly implemented. This study attempts to expand our understanding of reproductive health in female LT recipients.
Method: This is a single center retrospective cohort study of female LT recipients who were less than the age of 50 at the time of LT. An online survey was utilized to collect self-reported immunosuppressive therapy, fertility counseling, and fertility and pregnancy outcomes. Women with hysterectomy, oopherectomy, tubal ligation and primary amenorrhea were excluded. Demographic and medical data were collected from the electronic medical record. Generalized linear mixed models were used to compare pre- and post- LT pregnancy characteristics. Binary variables were modeled using a logit link and ordinal variables were modeled using a cumulative logit link; a random effect was included in the models to account for multiple pregnancies in the same subject.
Results: 175 living women under the age of 50 were identified for enrollment. To date, 62 women have completed the survey. The average age at time of LT was 34 ± 12 years and 8 subjects underwent LT under the age of 18. Twenty-five women reported between 1–10 pre-LT pregnancies and 10 women reported between 1–6 post-LT pregnancies. Only 2 women reported pregnancies both before and after LT. Thirteen percent (n = 6 of 48 respondents) of women reported active attempts at pregnancy post-LT and only 4% (n = 2) of these women were successful (3 and 6 pregnancies each). Of the 42 women who were not actively attempting to achieve pregnancy post-LT, 8 (19%) did. There was no significant difference between rates of pre- or post-LT gestational diabetes, pre-eclampsia, eclampsia, spontaneous abortion, graft rejection or graft failure. Pre-term birth was significantly more common in pregnancies post-LT than pre-LT (75% vs. 41%; p = 0.007). Twenty-three percent of women (n = 12 of 53 respondents) reported receiving pre-LT fertility and pregnancy counseling, and 21% of women (n = 11) received any counseling after LT. Forty percent of women (n = 21) used any form of contraception after LT, and of the patients who received counseling, only 15% of women (n = 8) were counseled on contraceptive methods post-LT.
Conclusion: Ongoing study is needed to further characterize changes in fertility post-LT, to identify risk factors associated with post-LT fertility and pregnancy complications, and to standardize fertility counseling strategies for women undergoing LT.

FRI-049

Is a telehealth-to-home group lifestyle intervention a feasible and safe option for specialist liver clinics?

I. Hickman[1,2], S. Keating[3], A. Hannigan[2], L. Elvin-Walsh[2], A. Barnett[2], C. Salisbury[3], M. Jarrett[4], J. Fawcett[4], I. Croci[3], K. Campbell[2,5], J. Coombes[3], G. Macdonald[6]. [1]*Mater Research Institute – University of Queensland, Brisbane, Australia;* [2]*Princess Alexandra Hospital, Nutrition and Dietetics, Brisbane, Australia;* [3]*University of Queensland, School of Human Movement and Nutrition Science, Brisbane, Australia;* [4]*Princess Alexandra Hospital, Queensland Liver Transplant Service, Brisbane, Australia;* [5]*Bond University, Faculty of Health Sciences and Medicine, Gold Coast, Australia;* [6]*Princess Alexandra Hospital, Gastroenterology and Hepatology, Brisbane, Australia*
Email: i.hickman@uq.edu.au

Background and Aims: Addressing obesity and cardio-metabolic complications presents a challenge for clinical care in liver disease. We piloted the feasibility of a 12-week group-based telehealth-to-home cardioprotective lifestyle (Mediterranean diet and individualised aerobic and resistance exercise) intervention for liver transplant recipients. The study aimed to identify the feasibility of delivering the telehealth lifestyle intervention and accuracy of home-based clinical outcome measures.
Method: Feasibility was assessed by recruitment rate, sessions completed, adequacy of technology, attrition and adverse events/safety. Accuracy of home-based assessment including waist circumference, repeated chair stand, 6 minute walk test (6MWT) was assessed by comparing clinician (face-to-face) and repeated by the participant unsupervised at home (within approximately 1 week of clinician assessment) using Bland-Altman analysis. All patients were >6 months post transplant.
Results: Recruitment rate was 24% (n = 28 of 119 eligible), age 21–68 years and 64% males. Reasons for not participating included being too busy or unwell or already eating/exercising well. Attrition was 11% (3/28). Of the 87 sessions completed to date, 91% of patients rated confidence with home technology ≥8/10. Staff reported technology was adequate for delivering the intervention >90% of the time. Completion of scheduled sessions was 91% for nutrition and 56% for exercise. Only 46% (13/28) participants agreed to repeat clinical measures at home. Of these, the mean difference and limits of agreement between researcher and participants were: Waist, 1.0 ± 2.6cm (−4.0 to 6.0cm); Chair Stand, 0.4 ± 1.7s (−3.1 to 3.8s); 6MWT, 64 ± 7.2m (−134 to 147m). There were no study-related adverse events.
Conclusion: Group telehealth-to-home is a feasible option to provide lifestyle intervention from a specialised liver clinic and patients can accurately self-assess outcomes at home. Considerations when establishing a telehealth service for lifestyle include the need for technical support related to patient orientation to internet connection, clinical support for risk assessment of complex patients and exploring enablers to support more patients to perform functional outcome measures at home.

FRI-050

Pre-liver transplant visceral adipose tissue predicts the early development of metabolic syndrome post-transplant

A. Woodward[1], M. Wallen[2], J. Ryan[1], L. Ward[2], J. Coombes[2], G. Macdonald[1]. [1]*Princess Alexandra Hospital, Woolloongabba, Australia;* [2]*The University of Queensland, Saint Lucia, Australia*
Email: aidanjwoodward@gmail.com

Background and Aims: Post liver transplantation metabolic syndrome (PTMS) is a significant independent risk factor for cardiovascular disease. Risk factors for developing PTMS include pre-transplant diabetes, obesity and increasing age. Low muscle mass, excess adipose tissue, and poor cardiorespiratory fitness are risk factors for metabolic syndrome in the general population which have had limited evaluation post liver transplantation. Our aim was to assess the role of these variables in predicting the early development of PTMS.
Method: A retrospective cohort study was performed by assessing consecutive adult patients for inclusion who received a liver transplant by the Queensland Liver Transplant Service between August 2012 and June 2016. We included seventy-seven patients for analysis. Demographic, anthropometric and metabolic data were collected pre-transplant and at 3 months post-transplant. Metabolic Syndrome was defined in accordance with international guidelines. Pre-transplant Computed Tomography (CT) skeletal muscle (SMA), visceral adipose (VAT) and subcutaneous adipose (SAT) areas were

measured at the level of the 3rd Lumbar vertebrae using ImageJ software (NIH, Bethesda, MD, USA). Skeletal Muscle Index (SMI) was calculated by correcting the SMA for height, squared. Cardiorespiratory fitness [using the ventilatory threshold (VT)] was determined from a cardiopulmonary exercise test.
Results: The median age was 56.0 years [interquartile range 51.0–59.0] with 58 (77%) males. Primary liver disease aetiology was hepatitis C (57%) followed by primary sclerosing cholangitis (13%) and alcohol (12%). Thirty patients (40%) had a diagnosis of hepatocellular carcinoma. Ten patients (13%) developed early onset PTMS by 3 months post-transplant. Patients who developed PTMS had higher pre-transplant body mass index (BMI) ($p = 0.012$), VAT ($p = 0.001$) and SAT ($p = 0.008$). There was no difference in VT ($p = 0.772$) or SMI ($p = 0.313$) between those who did or didn't develop PTMS. Univariate logistic regression found that BMI ($p = 0.019$), VAT ($p = 0.004$) and SAT ($p = 0.01$) were significant predictors for the development of PTMS. After multivariate analysis, only VAT remained a significant predictor (Odds ratio 1.02, 95%CI 1.00–1.04; $p = 0.042$). A sensitivity and specificity analysis determined that the optimal cut-off value for VAT predicting PTMS was >153.4cm^2 (Sensitivity 80%; Specificity 80%).
Conclusion: Pre-transplant VAT is independently associated with the early development of PTMS. Body composition analysis using cross-sectional imaging prior to liver transplant can assist with risk stratification for PTMS. These patients could be targeted for interventions to prevent this, either pre- or early post-liver transplantation.

FRI-051

Follow-up of non-HLA and anti-HLA antibodies: Importance in graft failure after liver transplantation

S. Iacob[1], V. Cicinnati[2], M. Maschmeier[2], H. Schmidt[2], S. Beckebaum[2]. *[1]Fundeni Clinical Institute, Bucharest, Romania; [2]University Hospital Munster, Munster, Germany*
Email: msiacob@gmail.com

Background and Aims: Patient and graft survival after liver transplantation (LT) has strongly improved in the last decades. However, new data are emerging regarding causes of graft failure. Studies indicate that humoral response to both HLA and non-HLA antigens have a detrimental effect on allograft survival. The aim of our study was to investigate clinical and immunological risk factors for graft failure at 5 years following LT.
Method: A total of 174 LT recipients were enrolled in the study. Patients underwent biopsy for histologic and C4d examinations. Assessment of sMICA, sMICB and sULBP2 was realized by enzyme linked immunosorbent assay. Screening for anti-HLA class I, class II or MICA antibodies was performed using Luminex technology. Graft failure was defined as histologically proven liver cirrhosis or allograft dysfunction requiring relisting for LT or leading to death. Cox proportional hazards regression model was used to identify predictors of graft failure after LT.
Results: In the univariate analysis, the following factors were identified as risk factors for graft failure at 5 years: increasing donor age ($p = 0.0002$), as well as the increasing recipient age ($p = 0.04$), presence of disease recurrence after LT ($p = 0.03$), presence of donor specific anti-HLA II antibodies >5000MFI ($p = 0.001$), high serum levels of sMICA ($p = 0.01$) and ULPB2 ($p < 0.0001$), positive complement-dependent cytotoxic crossmatches at LT ($p = 0.0003$), presence of positive C4d staining liver biopsies ($p < 0.0001$). In multivariate analysis, C4d deposition ($p < 0.0001$) and increased donor age ($p = 0.001$) were independent predictors for graft failure at 5 years after LT.
Conclusion: C4d deposition and advanced age of the donor (>66 years) correlated with allograft injury among LT patients.

FRI-052

CXCL9 and CXCL10 gene polymorphisms are associated with earlier onset of acute cellular rejection after liver transplantation

A. Ostojic[1], A. Markotic[2,3], T. Kelava[3,4], A. Mrzljak[1,4]. *[1]University Hospital Merkur, Liver Transplant Centre, Zagreb, Croatia; [2]University Clinical Hospital Mostar, Mostar; [3]Croatian Institute for Brain Research, Laboratory for Molecular Immunology, Zagreb, Bosnia and Herzegovina; [4]School of Medicine, University of Zagreb, Zagreb, Croatia*
Email: anna.mrzljak@gmail.com

Background and Aims: Despite the improvement and optimization of immunosuppressive protocols, acute cellular rejection (ACR) is still a frequent complication after liver transplantation. Recent studies showed that increased concentrations of chemokines CXCL9 and CXCL10 are associated with the ACR occurrence. The aim of this study was to examine the association of CXCL9 and CXCL10 single nucleotide polymorphisms with ACR after liver transplantation.
Method: DNA was isolated from the whole blood of 215 patients transplanted due to alcoholic liver disease from 1/2009 to 3/2017 in University Hospital "Merkur", Zagreb, Croatia. Polymorphisms of CXCL9 (rs10336) and CXCL10 (rs3921) were determined by polymerase chain reaction using commercially available TaqMan SNP assays. ACR was defined as biopsy proven (Banff score ≥3) within 6 months after liver transplantation. All patients received the same immunosuppressive protocol comprising of calcineurin inhibitors, steroids (discontinued after 3 months) and mycophenolate mofetil.
Results: 59 patients with ACR and 156 patients without ACR were included into the study. There were no statistically significant differences in age, sex or MELD score at the time of transplant between rejection and non-rejection groups. Genotypes were in Hardy-Weinberg equilibrium ($p > 0.05$), with strong linkage disequilibrium ($D' = 0.99$, $r = 0986$) between CXCL9 and CXCL10. In the rejection group 22 (37.3%) patients had GG, 25 (42.4%) had AG and 12 (20.3%) had AA genotype of the CXCL9 polymorphism, with similar genotype distribution observed in the non-rejection group, in which 54 (34.6%) patients had GG, 75 (48.1%) had AG and 27 (17.3%) had AA genotype. Lack of association between CXCL9 genotypes and incidence of ACR was found in codominant, dominant, recessive, overdominant or log-additive model ($p > 0.05$). Similar results were obtained for CXCL10 genotypes. On the other hand, we observed significant association between both CXCL9 and CXCL10 genotypes and the time of ACR occurrence. Patients with CXCL9 genotype AA developed ACR earlier (median 5 days (IQR 4.0–7.5)) than patients with the GG genotype (median 8 days (IQR 6.0–18.3)) ($p = 0.003$), with similar results for CXCL10 gene (CC vs GG; $p = 0.005$).
Conclusion: Single nucleotide polymorphisms of CXCL9 (rs10336) and CXCL10 (rs3921) are not associated with the incidence of acute cellular rejection after liver transplantation, but are associated with the time of ACR onset.

FRI-053

Post-transplantation outcomes in cirrhosis secondary to granulomatous liver diseases

A. Thuluvath[1], Y. Savva[2], P.-H. Chen[1]. *[1]The Johns Hopkins School of Medicine, Medicine, Baltimore, United States; [2]The Mercy Medical Center, Medicine, Baltimore, United States*
Email: athuluv1@jhmi.edu

Background and Aims: Cirrhosis is a rare complication of sarcoidosis, and cirrhosis from other granulomatous diseases is even rarer. The published center specific data available are limited to case series. Therefore, we examined the UNOS data from 2002–2016 to determine post liver transplant outcomes of those who were transplanted for sarcoidosis and other granulomatous diseases.
Method: The patients with sarcoidosis were defined as individuals with a primary diagnosis code of 4210 (cirrhosis: other specify, e.g., histiocytosis, sarcoidosis, "granulomatous"), which were further specified as sarcoidosis at the time of listing. We compared this

group with a mixed group that may include many with sarcoidosis too; this is a group with a diagnosis code of 4210 but without explicitly stating sarcoidosis as the primary diagnosis. We excluded 100 (10%) individuals with HCC, 91 (9.1%) with Hepatitis C or B and 88 (8.8%) listed for multi-organ transplants. Only the data for the first transplant were used. The final sample size included 117 recipients with a firm diagnosis of sarcoidosis and 255 individuals with "granulomatous liver diseases" (not specified as sarcoidosis). Kaplan-Meier survival estimates were done for graft and patient survival and log rank test was used to estimate the differences.

Results: The sarcoidosis group had more black patients, as well as more patients with diabetes. Otherwise there were no noteworthy differences between the two groups. The graft and patient survival rates at 1, 3, 5 and 10 years were similar between the two groups, with more than 69% of patients surviving at 5 years and 58% surviving at 10 years.

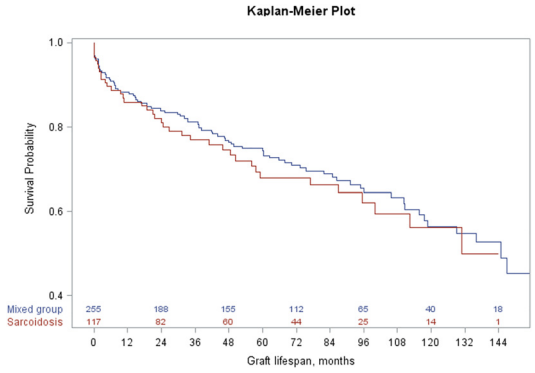


Figure 1: Graft survival in sarcoidosis and mixed group

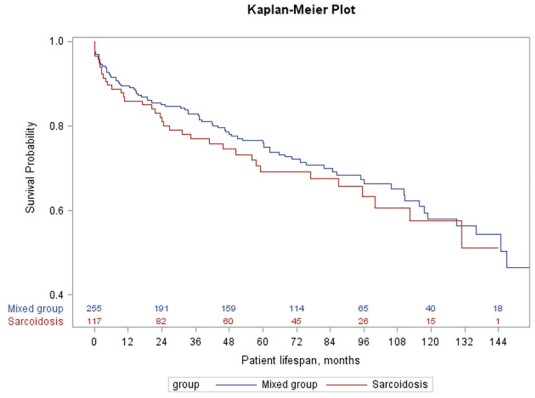


Figure 2: Patient survival in sarcoidosis and mixed group

Conclusion: The above data show that patients who are transplanted for sarcoidosis or other granulomatous liver diseases (most of whom may have sarcoidosis) have similar survival outcomes. Moreover, survival outcomes of both groups are similar to the published outcomes for those who are transplanted for other indications.

FRI-054
The effect of immunosuppression on coagulation in patients after liver transplantation

S. Bedreli[1], K. Piras-Straub[1], A. Achterfeld[1], A. Katsounas[1], F. Saner[2], G. Gerken[1], K. Herzer[1]. *[1]University Hospital Essen, Department of Gastroenterology and Hepatology, Essen, Germany; [2]University Hospital Essen, Department of General, Visceral and Transplantation Surgery, Essen, Germany*
Email: kerstin.herzer@uk-essen.de

Background and Aims: Everolimus (EVR) is an immunosuppressive (IS) agent commonly used in patients after liver transplantation (LT). However, there are concerns whether mTor inhibitors may impair coagulation and cause thromboembolic events after solid organ transplant. The present investigation aimed to identify coagulation disorders after use of EVR.

Method: We evaluated 51 patients who underwent a conversion of their IS regimen after LT either to EVR in combination with low dose tacrolimus (TAC; n = 26) or to extended-release TAC (n = 25). Common coagulation parameters, rotational thromboelastometry (ROTEM), as well as anti-coagulation and fibrinolysis factors were measured at baseline, 1 and 6 months after conversion. Statistical analysis was performed with paired t-test, one-way ANOVA and Tukey's multiple comparison test. Statistical significance was assumed for $p < 0.05$.

Results: Compared to baseline, there was a significant increase of von Willebrand factor (vWF), fibrinogen and factor VIII ($p < 0.0001$ respectively) 1 month after conversion to EVR. Furthermore, there was an increase in ROTEM-parameters, such as maximal clot firmness (MCF, $p = 0.0001$ for EXTEM, $p = 0.0006$ for INTEM, $p < .0001$ for FIBTEM). Maximum lysis (ML) was lower one month after conversion to EVR ($p < 0.0001$ for EXTEM, $p = 0.0004$ for INTEM and $p = 0.0002$ for APTEM). In those patients who were converted to extended-release TAC we could not observe any changes in coagulation parameters. Evaluation of so far 17 patients with EVR and 10 with TAC after 6 months shows a persistently significant increase of vWF ($p = 0.0005$), fibrinogen ($p < 0.0001$) and factor VIII ($p = 0.0017$) after conversion to EVR. ROTEM-parameters, such as MCF, also increased ($p < 0.0001$ for EXTEM, $p = 0.0003$ for INTEM, $p = 0.0003$ for FIBTEM). ML was lower after conversion to EVR ($p = 0.0001$ for EXTEM, $p = 0.0008$ for INTEM and $p = 0.002$ for APTEM). In general, coagulation parameters did not change between 1 and 6 months after start of EVR. In patients who were converted to extended-release TAC, there were no significant changes on coagulation parameters at all.

Conclusion: Application of EVR seems to activate coagulation to a procoagulant state in patients after LT. However, it remains uncertain whether these changes are transient or may persist and could in deed result in thromboembolic events. Ongoing clinical observation will clarify whether these changes of coagulation have a clinical impact in patients after LT.

FRI-055
99mTechnetium-MebrofeninHepatobiliary Scintigraphy predicts portal hypertension in Child-Pugh Acirrhosis

T. Chapelle[1], G. Roeyen[1], V. Hartman[1], B. Bracke[1], H. Ivan[2], T. Vanwolleghem[3], D. Ysebaert[1], S. Francque[3]. *[1]UZA, Dept. of Hepatobiliary, Transplantation and Endocrine surgery, Edegem, Belgium; [2]UZA, Nuclear Medicine, Edegem, Belgium; [3]UZA, Gastroenterology and Hepatology, Edegem, Belgium*
Email: thiery.chapelle@uza.be

Background and Aims: The Child-Pugh (CP) score and the Model for End Stage Liver Disease (MELD) are commonly used to estimate the risk of liver resection in cirrhosis. Liver resection is usually considered safe in CP grade A, whereas MELD scores ≥ 9, 10 or 11 predict post-hepatectomy liver failure (PHLF). Portal hypertension, measured by Hepatic Venous Pressure Gradient (HVPG) ≥ 10 mmHg, predicts a higher risk for PHLF. Differentiation between 5 and 6 CP points (Grade A) does not distinguish between low and high risk patients within this group. ^{99m}Technetium-Mebrofenin Hepatobiliary Scintigraphy (HBS) corrected for body surface area (HBS^{BSA}) assesses the functional reserve of the liver and may be of added value in differentiating the additional surgical risk of portal hypertension (PHT) in cirrhosis CP grade A.

Method: 99 patients with cirrhosis were divided into 3 groups according to the CP classification, grade A, B or C. The predictive value of MELD, HBS and HBS^{BSA} for CP grade and HVPG <10mmHg was evaluated.

Results: MELD, HBS and HBS^{BSA} predicted the different CP-grades. In CP grade A, only HBS and HBS^{BSA} were predictive of HVPG. Our research further revealed a cut-off value for HBS^{BSA} >3.6%/min/m² to be predictive of HVPG <10mmHg.

Table 1: Median HBS, HBS^{BSA} and MELD score for HVPG < 10mmHg and ≥ 10mmHg in Child-Pugh A *and* in Child-Pugh B/C

		HVPG < 10mmHg	≥ 10mmHg	p
Child-Pugh A	(n)	31	17	
HBS	%/min	9.18 (4.61–13.88)	7.19 (2.43–10.30)	0.001
HBS^{BSA}	%/min/m²	5.23 (2.56–7.95)	3.28 (1.13–5.20)	<0.001
MELD		8 (3–14)	8 (6–14)	0.974
Child-Pugh B or C	(n)	14	37	
HBS	%/min	3.84 (1.81–10.60)	2.48 (0.41–10.00)	0.005
HBS^{BSA}	%/min/m²	2.12 (0.97–6.76)	1.23 (0.17–5.34)	0.003
MELD		11.50 (6–18)	16 (2–28)	0.005

Abbreviations: HBS: Hepatobiliary Scintigraphy; HBS^{BSA}: HBS corrected by body surface area; MELD: Model for End Stage Liver Disease; HVPG: hepatic venous pressure gradient

Conclusion: HBS^{BSA} may identify patients with a HVPG <10mmHg in Child A cirrhosis. As HBS^{BSA} is predictive for PHT, it helps to determine if liver resection can be performed with low risk for PHLF. Hence, it might help to avoid invasive HVPG measurement prior to liver resection in Child A.

FRI-056

Chronic rejection in children: Risk factors, diagnosis and outcome

A. Cheng[1], K. Mysore[1,2], K. Hosek[2], R. Himes[1,2], D. Schady[3], J. Goss[1,2], T. Miloh[1,2]. *[1]Baylor College of Medicine, [2]Texas Children's Hospital, Transplant; [3]Texas Children's Hospital, Pathology*
Email: tamir.miloh@bcm.edu

Background and Aims: Chronic rejection (CR) is the leading indication for long term graft loss. We discuss our centre's experience with diagnosis and management of CR.
Method: Electronic medical records were searched for histologically confirmed CR (ductopenia, aberrant cytokeratin-7 of periportal hepatocytes with absent ductular proliferation and minimal portal inflammation) between years 2000–2016. Clinical data was extracted and compared to patients without CR. Standard immunosuppression induction included tacrolimus and steroids.
Results: Of 435 patients, 17 (3.9%) had CR over an average follow up of 7.4y: 5 had biliary atresia, 2 each: Alagille, other cholestasis, autoimmune hepatitis, indeterminate acute liver failure and 1 each: OTC deficiency, CF, A1AT deficiency, and hepatoblastoma. Median age at LT was 1.8y (4m–17y), similar to control. Median age of CR was 5y (2–21 y) with range of 3m–14y post LT. Demographics in CR vs control included male (59% vs 51% NS), Hispanic (41% vs 46%), African Americans (35% vs 12%), Caucasians (12% vs 36%) $p < 0.0001$ and public insurance (71% vs 64% NS). Whole graft (76% vs 85%) and ABO incompatible (6% vs 5%) (NS). On average, patients had 2.8 episodes of acute cellular rejection (ACR) prior to CR and 13 had acute on chronic rejection. In 5 cases tacrolimus (TAC) was reduced; 4 PTLD and 1 PRESS. Presenting symptoms were: 41% asymptomatic; 42% icterus, 42% splenomegaly, 24% ascites and 12% had pruritus. At CR average ALT 242 IU/l, AST 190 IU/l, GGT 603 IU/l, total bilirubin 4.6 mg/dl, conjugated bilirubin 3.7 mg/dl, albumin 3.4, platelet count 192K, INR 1.3 and 9 (53%) had positive ANA. Prior to CR the TAC medication level variability index (MLVI) was 4.2. Therapy included monotherapy; Rapamune (Rapa) 3, combination Rapa + Mycophenolate (MMF) 4 or prednisone 2, TAC + MMF 1 or Pred 1 and 6 on triple therapy. Rapa trough averaged 4.9. Outcomes included mortality in 4 patients (3 multi-organ failure 1 unknown) at average 9.3y, 1 re-transplanted after 1.5y, 2 sustained normalization of liver enzymes and the remainder 10 had fluctuating lab values.
Conclusion: CR was infrequent in our population. Risk factors included non adherence (high MLVI), ACR, ANA, ethnicity and intentional TAC dose reduction. Most patients were treated with additional immunosuppressants and only minority normalized graft function. Further research is required to identify risk factors, effective therapy and prevention of chronic rejection.

FRI-057

Hyperglycemia-triggered S1P-S1PR3 signaling worsens liver ischemia/reperfusion injury by regulating M1/M2 polarization

J. Rao[1], C. Yang[2], F. Cheng[3], S. Yang[4], L. Lu[5], X. Wang[3]. *[1]the First Affiliated Hospital of Nanjing Medical University, Liver Surgery/Liver Transplantation Center, Nanjing, China; [2]the First Affiliated Hospital of Nanjing Medical University the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [3]the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [4]the First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [5]the First Affiliated Hospital of Nanjing Medical University, nanjing*
Email: raojh@njmu.edu.cn

Background and Aims: Hyperglycemia/Diabetes is an adverse risk factor for hepatic ischemia/reperfusion injury (IRI) during liver transplantation or hepatectomy; however, the underlying mechanism remains unclear. Sphingosine 1-phosphate (S1P)/S1P receptor (S1PR1–3) system has been implicated in the pathological of variety organs damage. The aim of this study was to clarify whether and how (S1P)/S1P receptor (S1PR1–3) system is involved in hyperglycemia-exacerbated liver IRI.
Method: Diabetic patients and streptozotocin (STZ)-induced diabetic mice were involved in vivo. Bone marrow-derived macrophages (BMDMs) were used in vitro.
Results: S1P-S1PR3, not S1P-S1PR1 and S1P-S1PR2 signaling pathway, was specifically activated in liver tissues and Kuppfer cells (KCs) from diabetic patients and STZ-induced diabetic mice. CAY-10444, as an antagonist of S1PR3, effectively attenuated hyperglycemia-exacerbated liver IRI based on hepatic biochemistry, histological liver damage, and inflammatory responses. Interestingly, diabetic mice administrated with CAY-10444 expressed higher levels of M2 markers and lower levels of M1 markers compared with untreated diabetic mice. What's more, diabetic mice administrated with CAY-10444 also enhanced Stat3- and Stat6-signaling pathway activation. In vitro, hyperglycemia triggered S1P-S1PR3 signaling, promoted TLRs activation, and enhanced synthesis and release of pro-inflammatory cytokines in BMDMs. S1PR3 knockdown (KD) expressed lower levels of M1 markers and produced lower TNF-a, IL-6 but higher IL-10 in response to TLR ligands compared with the controls. In addition, S1PR3 KD had also enhanced Stat3- and Stat6-signaling pathway activation, but diminished Stat1-signaling pathway activation, in response to TLR4 stimulation.
Conclusion: This study demonstrates hyperglycemia specifically triggers S1P-S1PR3 signaling, promotes inflammatory responses, and exacerbates liver IRI by facilitating M1 polarization and inhibiting M2 polarization.

FRI-058

Stabilization of acute-on-chronic liver failure patients before liver transplantation predicts post-transplant survival

P. Huebener[1], M. Sterneck[1], K. Bangert[2], A. Drolz[2], A.W. Lohse[1], S. Kluge[2], L. Fischer[3], V. Fuhrmann[2]. *[1]University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Department of Intensive Care, Hamburg; [3]University Medical Center Hamburg-Eppendorf, Department of Hepatobiliary Surgery and Transplantation, Hamburg*
Email: p.huebener@uke.de

Background and Aims: Acute-on-chronic liver failure (ACLF) is a severe complication of liver cirrhosis and associated with excess

short-term mortality rates. Orthotopic liver transplantation (OLT) is a potentially life-saving therapeutic modality for ACLF patients, but selection of transplant candidates with acceptable post-OLT outcomes is challenging. The aim of this study was to assess the risk of OLT in patients with ACLF, and to determine parameters that predict post-OLT survival in this patient cohort.
Method: We retrospectively analyzed all 250 patients with liver cirrhosis who underwent their first OLT between 2009 and 2014 at our institution, and assessed post-transplant outcomes.
Results: Of 250 cirrhotic liver transplant recipients, 98 patients fulfilled the diagnostic ACLF-criteria in the 3-month pre-transplant period. Compared to non-ACLF patients, ACLF was associated with significantly higher short-term morbidity and mortality after OLT (90-day patient survival 96.1% non-ACLF versus 72.4% ACLF patients, $p < 0.0001$). Clinical improvement in the pre-transplant period, as defined by recovery of at least one previously failed organ system, was observed in 37 of 98 ACLF patients, mostly within several days after diagnosis. Most notably, clinical improvement prior to OLT was associated with excellent post-transplant survival rates that approximated non-ACLF OLT recipients. Following the 90-day post-transplant period, patient survival and long-term graft functions were comparable between ACLF and non-ACLF OLT recipients for up to five years.
Conclusion: Given the dismal prognosis of ACLF, our results indicate that ACLF patients can be transplanted with comparably good outcomes, in particular patients who improve under conservative therapeutic measures.

FRI-059
High mortality after liver transplantation for cirrhotic patients with previous spontaneous peritonitis occurring within one year prior to transplantation
M. Elnegouly[1], E. Matevossian[2], K. Lange[2], S. Thorban[2], M. Abdelhafez[1], R.M. Schmid[1], M. Guba[3], A. Umgelter[1]. *[1]Klinikum rechts der Isar der Technischen Universität München, 2nd Medical Department, Munich, Germany; [2]Klinikum rechts der Isar der Technischen Universität München, Department of Surgery, Munich, Germany; [3]Großhadern Clinic, University of Munich, Department of General, Visceral and Transplant Surgery, Munich, Germany*
Email: mayada.elnegouly@tum.de

Background and Aims: Infection is a leading cause of acute-on-chronic liver failure (AoCLF) and death in patients with end-stage liver disease. Spontaneous Bacterial Peritonitis (SBP) is the commonest infection in those group of patients. In urgency based liver allocation systems high MELD scores resulting from AoCLF may prioritize patients after infection for transplantation (OLT). Post-OLT mortality of these sicker patients may be higher. The aim of the study is to evaluate the impact of SBP occurring within one year before transplantation on mortality within one year after transplantation.
Method: A retrospective analysis of all liver transplants for cirrhotic patients at a German University Center since introduction of MELD-based allocation was performed. The association between SBP during one year before transplantation and mortality within one year after transplantation was analyzed.
Results: A total of 147 patients (107 (72.8%) male, mean age 57 ± 9 years) were included. Child-Pugh-class was A in 15 (17.0%), B in 57 (38.8%) and C in 65 (44.2%). Laboratory MELD at allocation was 18 (13–24). Ten patients had laboratory MELD scores >35, 49 (33.3%) patients had exceptional MELD scores, mostly (n = 40 (27.3%)) for HCC within Milan criteria. 26 patients had at least one episode of SBP one year prior to transplantation. The most recent episode of SBP was culture-positive in 10 (38.5%) patients yielding gram-positive cocci in 5 and gram-negative rods in another 5.
Mortality during one year after transplantation was 25.2%. Mortality of patients with (n = 26) or without (n = 121) SBP during one year before transplantation was 61.5% and 17.4%, respectively ($p < 0.001$). In univariable analysis, mortality after OLT was associated with Age (OR 1.067; 95% confidence interval (CI) 1.014–1.122; p = 0.012), MELD (OR 1.046; 95% CI 1.009–1.084; p = 0.014) and SBP (OR 7.619; 95% CI 3.038–19.110; $p < 0.001$).
In multivariable analysis including MELD, SBP and age, only age (OR 1.104; 95% CI 1.040–1.172; p = 0.001) and SBP (OR 9.354; 95% CI 3.049–28.718; $p < 0.001$) were independently associated with mortality
Conclusion: SBP defines a subset of patients with a higher mortality after OLT.

FRI-060
Sofosbuvir-based antiviral therapy in patients with HCV recurrent infection after liver transplant had a high rate of SVR but can be a trigger to a graft rejection
A. Araujo, M.T. Michalczuk, A.B. Lopes, M.R. Álvares-Da-Silva. *Hospital de Clinicas de Porto Alegre, Department of Gastroenterology, Brazil*
Email: alexandredearaujo12@gmail.com

Background and Aims: Recurrent HCV infection after liver transplant (LT) has a negative impact on graft and patient survival. The aim of this study is to describe the efficacy and safety of Sofosbuvir (SOF-based) regimens in the treatment of recurrent HCV after LT. liver transplant.
Method: This study included 68 adults with recurrent HCV after LT, treated with different SOF-based regimens between March 2015 and December 2016. The choice of regimens, their duration and use of ribavirin (RBV) was performed by their treating physician. The efficacy of antiviral treatment was assessed by sustained viral response 12 weeks after the end of treatment (SVR12), according to intention-to-treat analysis.

Table 1: Baseline characteristics of the study population

Patients characteristics	n = 68
Genotype	
1	36 (52.9%)
1a	16
1b	15
2	
3	2 (3%)
	30 (44.1%)
Male	48 (70.6%)
PEG experienced	46 (67.6%)
Cirrhosis	7 (10.2%)
Decompensated cirrhosis	2 (3%)
F3	4 (5.8%)
SOF + DCV	63 (92.6%)
SOF + SMV	3 (4.4%)
SOF + RBV	2 (3%)
RBV use	56 (82.3%)
12 weeks treatment	66 (97%)

SOF: sofosbuvir; DCV: daclatasvir; SMV: simeprevir; RBV: ribavirin

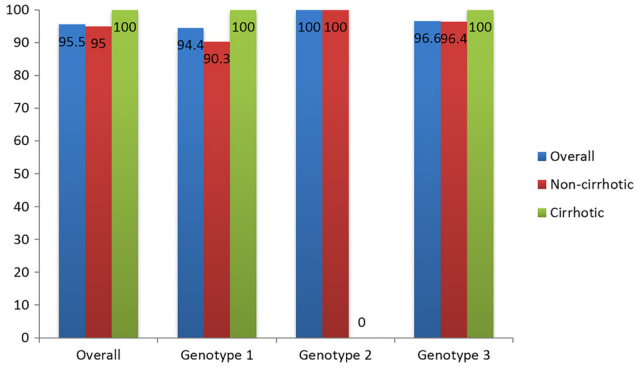


Figure 1: SVR12 according HCV genotype and cirrhosis status

Results: The most frequent HCV genotypes were 1 and 3 (n = 35, 51.4% and n = 31, 45.6%, respectively). 22 patients were treatment naïve

Table 2: (abstract: FRI-060): Characteristics of four patients with severe graft rejection after HCV clearance

Patient	Age (years)	Gender	Time to DAA therapy after LT (months)	Immunos supressive regimen	Antiviral therapy	Liver biopsy	Treatment	Outcome
1	68	F	10	Tac + MMF+ Ev	SOF + DCV+ RBV	PCR	IS4	Remission
2	59	M	52	Tac	SOF + DCV+ RBV	TCR (RAI 6)	IS4	CR
3	47	M	42	Tac	SOF + DCV+ RBV	TCR (RAI 5)	MPT + IS4	Remission
4	57	M	15	Tac + MMF	SOF + DCV+ RBV	TCR (RAI 7)	MPT + IS3	Remission

DAA: Direct-activing Antiviral Therapy; Tac: Tacrolimus; MMF: Mycophenolate Mofetil; Ev: Everolimus; IS4:Tac + MMF+ Ev + Prednisone; PCR: Plasma-Cell Rejection; TCR: T-Cell Mediated Rejection; RAI: Rejection Activity Index; CR: Chronic Rejection; MPT: Methylprednisolone Pulse Therapy; IS3:Tac + MMF + Prednisone

(32.3%) and 7 had cirrhosis (10.2%). SOF + daclatasvir (DCV) was the most commonly used regimen (n = 63, 92.6%). Most patients used RBV (n = 56, 82.3%) and were treated for 12 weeks (n = 66, 97%). Overall SVR12 was 95.5% (65/68 patients). Three patients had virological failure. Three patients had serious adverse events, however, no one discontinued treatment prematurely. Anemia was the most frequent adverse event (n = 34, 50%). Four patients had severe graft cellular rejection after HCV elimination, while maintaining stable immunosuppression.

Conclusion: SOF-based therapy is highly effective and safe to treat HCV recurrence after LT. The lymphocytic exhaustion induced by the persistent HCV antigenic exposure could be restored after HCV clearance with DAA. This form of immune reconstitution could be the trigger to T-Cell mediated graft rejection and needs further studies.

FRI-061

Donor liver small droplet macrovesicular steatosis is associated with reduced graft survival after liver transplantation

F. Ferri[1], A. Molinaro[2], E. Poli[1], L. Parlati[3], B. Lattanzi[1], G. Mennini[1], F. Melandro[1], F. Nudo[1], F. Pugliese[1], F. Maldarelli[1], A. Corsi[1], M. Riminucci[1], M. Merli[1], M. Rossi[1], S.G. Corradini[1]. [1]*Sapienza Università di Roma, Roma, Italy;* [2]*Università di Göteborg, Sweden;* [3]*Hospital Cochin, Paris, France*
Email: flaminia.ferri@gmail.com

Background and Aims: Modern hepatic steatosis classification includes large droplet macrovesicular (L-MaS), small droplet macrovesicular (S-MaS) and true microvesicular (MiS). Based on previous classification simply describing macrovesicular and microvesicular steatosis, donor livers with ≤30% of hepatocytes with macrosteatosis, which should represent L-MaS, are considered safe to be transplanted, while microsteatosis is usually not considered a risk factor for graft loss. Microsteatosis is differently associated with the type and severity of hepatocellular damage, according to the presence or absence of hepatitis c virus (HCV) infection. Thus, we analyzed the impact of steatosis on post-transplant liver graft survival, separately in HCV-RNA negative (HCV-) and positive (HCV+) recipients.

Method: We retrospectively analyzed 206 routinely performed pre-ischemia graft biopsies in consecutive adult patients submitted to deceased-donor liver transplantation in our Center between 2001 and 2011. Steatosis was defined as follows: L-MaS as one or few large vacuoles in the cytoplasm with nuclear displacement; S-MaS as few or discrete vacuoles in the cytoplasm without nuclear displacement; MiS as intracytoplasmic accumulation of numerous, tiny and undiscernable vesicles with a foamy appearance. Graft ATP content was measured by bioluminescence assay.

Results: Only 2 grafts had MiS and were excluded from the statistical analysis. The maximum L-MaS was 40% (6 grafts). A S-MaS ≥40% was present in 9 grafts. The median follow-up was 2432 and 2264 days respectively for the HCV – (n = 122) and HCV+ (n = 82) patients. At Cox regression analysis, in the HCV – group S-Mas >15% was independently associated with overall graft loss (HR 2.386, 95% CI 1.176–4.841, p = 0.005), after normalization for several recipient, donor and intraoperative variables. No association of graft survival was found with L-MaS in the HCV – group and with both S-MaS and L-MaS in the HCV+ group. In HCV – but not in HCV+ recipients, the first three post-operative days serum AST peak positively correlated with S-MaS. Graft S-MaS >15% was associated with reduced graft ATP content.

Conclusion: A donor liver graft S-MaS >15% is associated with low graft ATP content. S-MaS is associated with clinical signs of severe ischemia reperfusion damage and with reduced graft survival only in HCV – recipients. These data are relevant for organ allocation and because the percentage of HCV – recipients is rapidly increasing.

FRI-062

Liver transplantation in HIV patients: a descriptive cohort study

S.C. Branco[1], J. Martins[2], J. Gandara[3], V. Lopes[3], J. Daniel[3], H.P. Miranda[3], S. Ferreira[3]. [1]*Medicina Interna;* [2]*Medicina Interna, Portugal;* [3]*Unidade de transplantação hepática e pancreática*
Email: sara.castellobranco@gmail.com

Background and Aims: With the widespread use of highly antiretroviral therapy, survival of the HIV-infected patients has improved over the last years. Conversely, end stage liver disease has become an important cause of death among these patients and liver transplantation (LT) is becoming the best treatment option for selected cases. The aim of this study was to describe the clinical characteristics of the HIV-infected patients at time of evaluation for LT and the outcomes of LT.

Methods: All HIV patients referred for their first LT evaluation at Centro Hospitalar do Porto between 2009 and 2017 were included in this retrospective, descriptive cohort study.

Results: Forty-four HIV patients were evaluated for LT, with 11 (25%) listed for LT and 33 (75%) not listed. Two patients (4,5%) died during the evaluation process and 13 (29,5%) were too early for listing. The median age was 46 (±7) years. The major HIV risk factor was the use of intravenous drugs (84%). The underlying cause of liver disease was hepatitis C (89%) and the majority of patients had detectable HCV RNA (74%). Eighteen patients (41%) were declined for listing and the major reasons were psychosocial (44%) and HIV related (38%). The median MELD score at first evaluation and at LT were 10 (±5) and 15,3 (±7), respectively. All patients listed were transplanted (except for one who is still waiting) and the average time between the first evaluation and LT was 16,5 months. Within the transplanted patients, 50% died and the median MELD score at first evaluation and at LT in this subgroup was 11,6 (±5) and 17,8 (±8), respectively.

Conclusion: After the first major decompensation of their liver disease, HIV-infected patients have a rapid progression to death. Thus, it is extremely important to recognize the clinical characteristics of these population and the ideal referring time for LT. As previously reported, attention should be paid to the MELD score as it is a predictor for death and a crucial tool to indicate LT.

Fibrosis

FRI-063

Functional relevance and pro-fibrogenic properties of mucosal-associated invariant T cells (MAIT) during chronic liver diseases

P. Hegde[1,2], E. Weiss[1], Valérie Paradis[1,2,3], J. Wan[1,2], M. Mabire[1,2], S. Sukriti[4], P.-E. Rautou[5], M. Albuquerque[1,2,3], O. Picq[1,2], A. Gupta[1,2], G. Ferrere[1,2], Hélène Gilgenkrantz[1,2], B. Kiaf[6], A. Toubal[6], L. Beaudoin[6], P. Letteron[1,2], R. Moreau[1,2,5], A. Lehuen[6], S. Lotersztajn[1,2,5]. *[1]Inserm UMR-1149, Centre de Recherche sur l'Inflammation, 75018 Paris, France; [2]Sorbonne Paris Cité, Laboratoire d'Excellence Inflamex, Faculté de Médecine, Site Xavier Bichat, Université Paris Diderot, Paris, France; [3]Département de Pathologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; [4]Institue of Liver and biliary Sciences, Molecular and cellular medicine, India; [5]Département Hospitalo-Universitaire (DHU) UNITY, Service d'Hépatologie, Hôpital Beaujon, Assistance Publique-Hôpitaux de Paris, Clichy, France; [6]Inserm U-1016, CNRS UMR 8104, Institut Cochin, université Paris-Descartes, Paris, France*
Email: sophie.lotersztajn@inserm.fr

Background and Aims: Persistent chronic inflammation along with immune dysfunction is a major driving force of chronic liver disease progression to fibrosis. Mucosal-Associated Invariant T (MAIT) cells are unconventional T cells characterized by the invariant TCR-chain, Vα7.2 in humans (Va19 in mice) and restricted by the non-classical MHC-1b molecule, MR1. Owing to their involvement in the pathogenesis of various infectious, autoimmune and chronic inflammatory diseases, we hypothesize that MAIT cells may be involved in immune-dysfunction associated with liver fibrosis.
Method: MAIT ($CD161^{hi}$ $Va7.2^{+}$) cells were analyzed in the PBMC of cirrhotic patients (decompensated (n = 59), compensated (n = 15)) of alcoholic and non-alcoholic origin, in comparison with healthy donors (n = 47) by FACS. Liver MAIT cells were analyzed by FACS and immunofluorescence labeling. Functional relevance of MAIT cells was studied in mice deficient ($MR1^{-/-}$) or enriched (Vα19TCRTg) in MAIT cells, following chronic challenge with CCl_4 or bile duct ligation. Interactions between human MAIT cells and human hepatic myofibroblasts (HMF) were studied in *in-vitro* co-culture experiments.
Results: MAIT cell frequency was reduced in PBMC from cirrhotic patients and was independent of cirrhosis etiology and severity. Peripheral MAIT cells from cirrhotic patients displayed an activated phenotype with increased CD25 and CD69, and produced increased levels of intracellular IL-17 and granzyme B. Despite their reduced frequency, MAIT cells in cirrhotic livers preferentially accumulated along the fibrotic septa. However cirrhotic liver MAIT cells showed an activated phenotype as evidenced by increased intracellular IL-17 production. Moreover, cirrhotic MAIT cells displayed exhaustion features, as revealed by increased expression of TIM-3 and PD-1 compared to MAIT cells from control livers. *In vivo*, following chronic administration of CCl_4 or bile duct ligation, Vα19TCRTg mice showed exacerbated fibrosis and accumulation of fibrogenic cells, while $MR1^{-/-}$ mice were resistant. Profibrogenic properties of MAIT cells were related to mitogenic effects on HMF, as demonstrated in co-culture experiments. HMF expressed MR1, and MAIT cell-induced proliferation of HMF was reduced by an anti MR1 antibody.
Conclusion: Our results reveal a novel pro-fibrogenic role for MAIT cells in liver injury and identify MAIT cells as a novel target for anti-fibrogenic therapy.

FRI-064

Effects of a PEGylated fibroblast growth factor 21 variant on steatosis, inflammation, and fibrosis in a mouse model of non-alcoholic steatohepatitis

B. Zinker[1], S. Boehm[1], S. Gao[1], A. He[1], B. Strassle[2], P. Morin[3], R. Christian[3], J. Krupinski[3]. *[1]Bristol-Myers Squibb, Pennington, United States; [2]Bristol-Myers Squibb, Lawrenceville, United States; [3]Bristol-Myers Squibb, Lawrenceville*
Email: bradley.zinker@bms.com

Background and Aims: Analogues of fibroblast growth factor 21 (FGF21), a key regulator of lipid and glucose metabolism, improve insulin sensitivity, lipid profiles, steatosis, and fibrosis in preclinical and clinical studies of non-alcoholic steatohepatitis (NASH). Here, the effects of a PEGylated-FGF21 variant (PEG-FGF21v) were examined in the choline-deficient amino acid-defined, high-fat diet (CDAHFD) mouse model of NASH and liver fibrosis.
Method: C57BL/6J mice were fed either normal chow or a CDAHFD (60% kcal from fat, 0.1% methionine), which induces NASH. Mice (10/group) received twice weekly (BIW) subcutaneous (SC) injections of 0.6 mg/kg PEG-FGF21v for either 4 or 8 wks after 4 wks on CDAHFD, or for 4 wks after 8 wks on CDAHFD. Control mice were fed normal chow or CDAHFD, and were given vehicle BIW SC corresponding to the diet and treatment (tx) durations above. Mice were maintained on their respective diets until sacrificed; their plasma and livers were harvested for biochemical, histological, and gene expression analyses.
Results: Mice fed a CDAHFD (4 wks) compared with normal chow showed increased hepatic triglycerides (TG) and reduced adiponectin levels (−30% to −40%). In CDAHFD-fed mice (4 wks), PEG-FGF21v tx for 4 or 8 wks reduced TG similar to mice on normal chow, reduced body weight (12%–22% vs vehicle tx), and improved adiponectin levels compared with vehicle tx (48%–139%; $p < .05$). PEG-FGF21v tx vs vehicle tx significantly reduced hepatic steatosis (−60% to −80% change by morphometry [CBM] on H&E-stained liver sections [SLS]), microgranulomatous inflammation (−40% CBM on MAC-2 IHC-SLS), and fibrosis (−15% to −50% CBM of trichrome-SLS; and −62% to −75% change in hydroxyproline content) in CDAHFD-fed mice (all $p < .05$). Additionally, gene expression markers of fibrosis (eg, *Col1a1*, *Col1a2*, *Col3a1*, *Itga2*, *Lox*) and inflammation (eg, *Spp1*, *Tnf*, *Ccl2*, *Ccl3*) were reduced with PEG-FGF21v tx vs vehicle tx ($p < .05$). After 8 wks of a CDAHFD, 4 wks of PEG-FGF21v tx compared with vehicle tx reduced hepatic steatosis, fibrotic and inflammatory gene markers (all $p < .05$), but had no effect on liver fibrosis.
Conclusion: In a CDAHFD mouse model of NASH, tx with PEG-FGF21v increased plasma adiponectin, and reduced body weight, hepatic steatosis, inflammation, and fibrosis (by histology and hydroxyproline content) and gene expression of markers of fibrosis and inflammation. These data further support the benefits of PEG-FGF21v analogues for the tx of NASH.

FRI-065

Cholesterol-mediated expression of ganglioside GD3 acetylation contributes to liver fibrogenesis

C. Vallejo[1,2], V. Ribas[1,2,3], D. Robles[1,2], S. Torres[1,2], J. Ramos[1], J. Caballeria[2,3,4], M. Elena[2,4], José Fernandez-Checa[4], M.C. Garcia-Ruiz[4]. *[1]Instituto de Investigaciones Biomédicas de Barcelona-CSIC; [2]IDIBAPS; [3]Centro de Investigación Biomédica en Red (CIBERehd); [4]Liver Unit-Hospital Clinic i Provincial de Barcelona-UB*
Email: carmen.garcia@iibb.csic.es

Background and Aims: Liver fibrosis is an indication of advanced chronic liver disease caused by different etiologies, including NASH that can lead to progressive liver dysfunction and failure. Cholesterol (chol), and particularly mitochondrial-chol accumulation, has emerged as a key factor in NASH. Moreover, cholesterol has been shown to promote liver fibrogenesis through activation of hepatic stellate cells (HSC). Ganglioside GD3 is a glycosphingolipid that induces apoptosis by a dual mechanism involving MMPT and inactivation of NF-κB-dependent survival program. Recent findings

have shown that GD3 acetylation by O-acetyl disialoganglioside synthase (OAcGD3S) antagonizes the proapoptotic actions of ganglioside GD3. As the relationship between cholesterol and the status of ganglioside GD3 in liver fibrosis has not been explored, our aim was to investigate the effects of nutritional cholesterol feeding in GD3 synthesis and acetylation and in HSC and impact in liver fibrogenesis.

Method: Free cholesterol levels in HSC were induced by incubation of HSC with cholesterol and an inhibitor of ACAT. Eight weeks old male C57BL/6J mice were fed a 60% high fat diet enriched in 0.5% with cholesterol (HFHC) for up to six months. Expression of a-SMA, Col1A1, TGFb, PDGF, GD3 levels and OAcGD3S were analyzed by WB and IHC. The impact of OAcGD3S silencing was examined in the activation of HSC in vivo and in mice fed HFHC. Moreover, OAcGD3S expression was monitored in human biopsies from subjects with chronic liver disease.

Results: Cultured HSC challenged with cholesterol increased HSC activation and stimulated the levels of ganglioside GD3 and its acetylated form. Mice fed a HFHC diet showed increased liver damage, hepatomegaly, and inflammation. HFHC feeding increased StARD1 expression and cholesterol levels in HSC and translated in enhanced levels of a-SMA, Col1A1, TGFb, and PDGFRb (protein and mRNA). Liver tissue hydroxyproline levels, carbonylated proteins, Sirius red and DHE staining revealed increased levels in samples from HFHC-fed mice. The gene expression and IHC time-course of aSMA, PCNA, GD3 and 9-O-acetyl GD3, showed a progressive and extensive expression from 1 to 6 months. In vivo OAcGD3S silencing through intravenous adenovirus administration prevented HSC activation and GD3 acetylation, resulting in reduced liver fibrogenesis markers. In vitro studies indicated that TUDCA ameliorated cholesterol-mediated HSC activation, pointing to cholesterol-induced ER stress as a key mechanism linking cholesterol to GD3 acetylation in HSC biology and liver fibrosis. Importantly, samples from patients with chronic liver disease exhibit increased GD3 and GD3 acetylated expression.

Conclusion: Dietary cholesterol induced liver damage and fibrogenesis is mediated, in part, through GD3 acetylation, suggesting that OAcGD3S emerges as a potential target to regulate liver fibrosis.

FRI-066

Inducible ablation of TGFß receptor type 2 limited to hepatic stellate cells potently inhibits liver fibrosis and attenuates inflamation

O. Molokanova[1], K. Schönig[2], S.-Y. Weng[1], X. Wang[1], S. Ohngemach[3], A. Nikolaev[4], D. Strand[5], L. Eshkind[3], D. Schuppan[6], S. Lorenz[5].
[1]University Medical Center, Johannes Gutenberg University, Mainz, Germany, Institute of Translational Immunology, Mainz, Germany; [2]Central Institute of Mental Health, Medical Faculty Mannheim / Heidelberg University, Mannheim, Germany, Department of Molecular Biology, 68159 Mannheim, Germany; [3]University Medical Center, Johannes Gutenberg University, Mainz, Germany, Translational Animal Research Center (TARC), Mainz, Germany; [4]University Medical Center, Johannes Gutenberg University, Mainz, Germany, Institute of Molecular Medicine, Mainz, Germany; [5]University Medical Center, Johannes Gutenberg University, Mainz, Germany, Dept. of Medicine I, Mainz; [6]Institute of Translational Immunology, Research Center for Immune Therapy (FZI), University Medical Centre Mainz, Mainz, Germany
Email: lemol1970@gmx.de

Background and Aims: Transforming growth factor β (TGFβ) is a central fibrogenic activator of hepatic stellate cells and myofibroblasts (HSC). However, TGFβ also profoundly modulates almost all other cell types, including immune cells, and its general genetic ablation causes early lethality in mice due to severe intestinal inflammation. We therefore generated and tested a conditional knock-out mouse of TGFßRII in activated HSC, to assess the effect on liver fibrosis and inflammation.

Method: An activated myofibroblast/fibroblast (HSC) specific promoter driven Col3a1-CreERT2 mouse was generated by microinjection of a purified, linearized Col3a1-CreERT2 BAC DNA fragment into the pronucleus of C57BL/6N oozytes. The Col3a1-CreERT2 mice were bred with TGFbR2 flox/flox mice to generate Col3a1CreERTΔTGFbR2fl/fl mice. The bi-transgenic mice were treated with escalating doses of oral CCl4 for three weeks to induce advanced parenchymal liver fibrosis. A group of Col3a1CreERTΔTGFbR2fl/fl mice was treated with tamoxifen, to activate Cre recombinase and induce TGFßRII gene excision (5 injections during the three week fibrosis induction). Matched wildtype mice treated with tamoxifen served as additional controls. Livers were analyzed using histology, immunohistochemistry, biochemical and morphometrical determination of collagen, and qPCR.

Results: In the induced Col3a1-CreERTΔTGFbR2fl/fl mice Sirius red stained collagen area was reduced by 47% (both $p < 0.001$), total liver collagen (hydroxyproline content) by 40% ($p < 0.01$), and α-SMA positive HSC were suppressed by 57% ($p < 0.001$). This was accompanied by a significant dowregulation of key fibrogenic transcripts. Notably, histological inflammatory infiltrates, necro-apoptotic hepatocytes and serum ALT and AST significantly reduced in the conditional HSC-TGFßRII ablated vs the control mice.

Conclusion: 1. We generated the first (activated) HSC-specific inducible knockout mice. 2. HSC-specific disruption of TGFß signaling using Col3a1CreERTΔTGbR2fl/fl mice potently inhibits fibrosis progression. 3. Notably, the HSC-specific TGFbR2 ablation also attenuated hepatic inflammation, a detrimental side-effect of general TGFß blockade, possibly via beneficially affecting the structure and function of the extracellular matrix as coactivator of inflammation. 4. Inhibition of TGFßRII, when targeted to HSC, is a highly promising antifibrotic therapy.

FRI-067

Caspase-8 is a gender-specific modulator of chronic cholestatic liver disease in female Mdr2 knockout mice.

J. Jung, D. Lambertz, U. Haas, R. Sonntag, C. Trautwein, C. Liedtke.
University Hospital RWTH Aachen, Department of medicine III, Aachen, Germany
Email: julia.hennings@rwth-aachen.de

Background and Aims: Females are more susceptible to hepatic cholestasis, but the underlying mechanisms are incompletely understood. Mdr2 knockout ($Mdr2^{-/-}$) mice are a well-established animal model of human primary sclerosing cholangitis (PSC) also comprising enhanced fibrosis susceptibility in female mice. We aimed to investigate the impact of extrinsic apoptosis in PSC by deleting Caspase-8 in hepatocytes of $Mdr2^{-/-}$ mice.

Method: $Mdr2^{-/-}Casp8^{\Delta hepa}$ double knockout mice were generated in a C57Bl/6 background by crossing $Mdr2^{-/-}$ mice with animals lacking Caspase-8 in hepatocytes ($Casp8^{\Delta hepa}$). Cre-negative littermates ($Mdr2^{-/-}Casp8^{f/f}$) and C57Bl/6 WT mice were used as reference. Male and female animals were analyzed for liver fibrosis by quantification of hepatic collagen deposition at the age of 12, 26 and 52 weeks. Expression of genes related to inflammation, cell death, proliferation and cancer was determined by qPCR.

Results: In good agreement with earlier studies we detected increased liver fibrosis in female compared to male $Mdr2^{-/-}$ mice at the age of 26–52 weeks. Unexpectedly, deletion of Caspase-8 in male $Mdr2^{-/-}$ mice did not affect the degree of liver fibrosis at any age investigated. However, in female $Mdr2^{-/-}$ at the age of 26 weeks, concomitant inactivation of Caspase-8 triggered approximately 2fold increased gene expression of Tumor Necrosis Factor alpha (TNF) and Receptor-interacting serine/threonine-protein kinase 3 (RIPK3). Of note, both genes are involved in regulating inflammation and programmed cell death including apoptosis and necroptosis. In contrast, basal TNF and RIPK3 gene expression was not different between male and female WT or $Mdr2^{-/-}$ mice suggesting that the observed gender disparity observed in $Mdr2^{-/-}Casp8^{\Delta hepa}$ mice was

provoked specifically by Caspase-8 deletion. In addition, we found a significant correlation between the fibrosis level in 26 week old Mdr2$^{-/-}$Casp8$^{\Delta hepa}$ mice and gene expression levels of RIPK3, Cyclin E2 (involved in cell cycle regulation) and c-myc (related to fibrosis and cancer). In agreement with these findings, loss of Caspase-8 significantly enhanced liver fibrosis exclusively in female Mdr2$^{-/-}$ mice at the age of 52 weeks reflecting a stage of advanced disease progression.
Conclusion: Caspase-8 is dispensable for initiation and progression of liver injury in male Mdr2$^{-/-}$ mice. However, ablation of Caspase-8 triggers significantly elevated liver fibrosis in female Mdr2$^{-/-}$ mice which precedes enhanced gene expression of TNF and RIPK3. Thus Caspase-8 can be considered as a gender-specific modulator of death pathways in the cholestatic liver.

FRI-068
Novel pro-fibrotic properties of macrophage migration inhibitory factor in non-alcoholic steatohepatitis is associated with a shift in natural killer T cell populations
D. Heinrichs[1], E.F. Brandt[1], P. Fischer[1], J. Koehncke[1], T. Wirtz[1], S. Djudjaj[2], P. Boor[2], R. Bucala[3], D. Kroy[1], F. Schumacher[1], H. Wasmuth[1], C. Trautwein[1], Jürgen Bernhagen[4], M.-L. Berres[1].
[1]University Clinic RWTH Aachen, Medical Department III, Aachen, Germany; [2]University Clinic RWTH Aachen, Department of Pathology; [3]Yale University School of Medicine, Rheumatology Section of the Department of Internal Medicine; [4]Klinikum der Universität München, Department of Vascular Biology
Email: dheinrichs@ukaachen.de

Background and Aims: The cytokine macrophage migration inhibitory factor (MIF) shows inflammatory properties and has chemokine-like functions. In previous models of chronic liver injury, MIF shows anti-fibrotic and anti-steatotic properties via the receptor CD74 and the stress kinase AMPK. Because the pathophysiology of chronic non-alcoholic steatohepatitis is associated with liver fibrosis, we here investigated the role of MIF on liver fibrosis in the methionine-choline deficient (MCD)-diet-model. This model combined fibrosis formation and steatohepatitis within the liver of the mice.
Method: *Mif* gene-deficient (*Mif*$^{-/-}$), hepatocyte-specific *Mif* gene-deficient (*Mif*$^{\Delta hep}$) and wild-type mice were fed an MCD diet. Fibrosis was analyzed histologically by Sirius Red stainings, by hydroxyproline content and intrahepatic mRNA expression of fibrosis-related genes. Immune cell infiltration was determined by flow cytometry analysis. *In vitro* stimulation experiments with recombinant MIF were performed in isolated murine NKT cells. Furthermore, mRNA expression patterns of fibrosis marker and NKT marker from NASH patients were correlated.
Results: In contrast to prior findings in hepatotoxic fibrosis models, *Mif*$^{-/-}$ and *Mif*$^{\Delta hep}$ mice showed decreased fibrosis after MCD diet as assessed by histology and hepatic collagen levels. Reduced liver fibrosis was associated with a strong down-regulation of fibrosis-relevant genes in *Mif*$^{-/-}$ and *Mif*$^{\Delta hep}$ mice and a substantial reduction of stellate cell activation. FACS analysis revealed no difference in monocyte or lymphocyte infiltration between *Mif*$^{-/-}$ and wild-type mice; however, the NKT cells were skewed to type II subpopulation in *Mif*$^{\Delta hep}$ mice. *In vitro* studies show a direct effect of recombinant MIF on NKT cell polarization. MIF favored the pro-fibrotic type I NKT subtype. Gene expression analysis between fibrosis marker and NKT subtype marker show strong correlations in human NASH patients.
Conclusion: In the metabolism-driven MCD liver fibrosis model, MIF exacerbates liver fibrosis. Our new results show a yet undiscovered relation of MIF and NKT cell subsets within the liver. NKT cell subsets are skewed towards the pro-fibrotic type I NKT subtype by MIF. These findings offer a novel mechanism through which MIF affects liver disease dependent on the pathogenic context.

FRI-069
High density lipoproteins production induced by selective intestinal LXR activation protects against the progression of liver injury by shifting M1 to M2 Kupffer cell phenotype
I. Pierantonelli[1], C. Pinto[1], C. Rychlicki[1], D.M. Giordano[1], L. Trozzi[1], M. Marzioni[1], A. Benedetti[1], G. Svegliati-Baroni[1,2]. *[1]Università Politecnica delle Marche, Department of Gastroenterology and Hepatology, Ancona, Italy; [2]Università Politecnica delle Marche, Obesity Center, Ancona, Italy*
Email: pierantonelli_irene@libero.it

Background and Aims: Liver fibrosis is the result of wound healing response during chronic liver injury. Liver X receptor (LXR) exerts anti-inflammatory and anti-oxidant effects, but its activation is associated with hypertriglyceridemia and liver steatosis, due to hepatic fatty acid synthesis. However, its selective induction in the gut might regulate hepatic inflammation and fibrogenesis via specific gut-liver signaling.
Method: Mice with an intestinal constitutive LXRα activation (iVP16LXRα) and their controls (iVP16) were exposed to i.p. injection of carbon tetrachloride twice a week for 8 weeks.
Results: iVP16LXRα mice showed a lower expression of the hepatic pro-inflammatory genes NF-kB, TNF-α, IL-6 and MCP-1 ($p < 0.005$; $p < 0.05$; $p < 0.05$ and $p < 0.005$ respectively vs iVP16) that was associated with reduced macrophage infiltration by immunohistochemistry for the macrophage marker F4–80 ($p < 0.05$). The suppression of liver inflammation was coupled with decreased fibrogenesis, measured by immunohistochemistry for α-SMA and by TGF-β expression (both $p < 0.005$ vs iVP16). Reduced hepatic stellate cells activation in iVP16LXRα decreased collagen deposition, quantified by morphometry for Sirius Red staining ($p < 0.0005$) and hydroxyproline content ($p < 0.05$). Gut selective activation of LXRα induced the synthesis of high density lipoproteins (HDL), as shown by increased gene expression of intestinal ABCA1 and by the quantification of plasmatic lipoproteins (both $p < 0.005$), without affecting mucosal inflammation (evaluated by H&E and immunohistochemistry for CD3). These beneficial effects did not induce metabolic side effects, as shown by hepatic expression of SREBP1c and its downstream target FAS and by the quantification of hepatic triglyceride content. The anti-inflammatory effect of HDL was demonstrated by the shift from pro-inflammatory (M1) to anti-inflammatory (M2) hepatic macrophage phenotype, as shown by STAT6-dependent increase of Arginase-1 (both $p < 0.0005$ vs iVP16). The anti-inflammatory properties of HDL were confirmed *in vitro* when Kupffer cells activation, measured by gene expression of TNF-α, IL-6, IL1β and MCP-1 ($p < 0.05$) was restored by HDL pre-incubation.
Conclusion: Specific intestinal LXRα activation might represent a new target for the treatment of liver fibrosis by modulating macrophage response to injury, thus reducing hepatic inflammation without the occurrence of the side effects related to hepatic LXR induction.

FRI-070
Increased expression of pregnancy-associated plasma protein-A in activated hepatic stellate cells is a potential therapeutic target and serum marker of hepatic fibrosis
F. Kim, C. Hellerbrand. *Friedrich-Alexander University Erlangen-Nürnberg, Institute of Biochemistry, Erlangen, Germany*
Email: claus.hellerbrand@fau.de

Background: Pregnancy-associated plasma protein-A (PAPP-A) was firstly discovered as a placental protein present in the circulation of pregnant women. Recently, we have discovered PAPP-A as a tumor promotor in hepatocellular carcinoma applying causal modeling (PLoS Comput Biol. 2015;11(5):e1004293). PAPP-A is a metalloproteinase that specifically cleaves insulin-like growth factor (IGF) binding proteins (IGFBPs). The IGF-system is known to play a role in hepatic fibrosis, however, the expression and function of PAPP-A in chronic liver disease is unknown.

The aim of this study was to analyze the expression and function of PAPPA in liver fibrosis.
Methods and Results: Quantitative RT-PCR analysis revealed significantly increased PAPP-A expression in different murine models of hepatic fibrosis (TAA-induced liver injury A, bile duct ligation, dietary NASH-models). Furthermore, PAPPA expression revealed a significant correlation with collagen I and alpha-smooth-muscle expression in human hepatic tissue specimens from patients with chronic liver disease, and PAPPA serum levels were significantly increased in patients with cirrhosis as compared to individuals without liver disease. Fitting to this, PAPPA expression significantly increased in hepatic stellate cells (HSC) during *in vitro* activation, and siRNA-mediated PAPPA suppression in activated HSC resulted in reduced PAPPA secretion into the supernatant. Furthermore, PAPPA suppressed HSC showed significantly reduced proliferation. Next, we isolated primary HSC from PAPPA-deficient (PAPPA-/-) and wildtype (wt) control mice. Histomorphological analysis and monitoring of markers of HSC activation revealed a significantly retarded *in vitro* activation process in PAPPA-/- HSC. Furthermore, fully activated PAPPA-/- HSC revealed significantly reduced proliferation. In addition to PAPP-A, we newly discovered strong expression of IGFBP-4 in activated HSC, and analysis of human activated HSC isolated from 14 different donors revealed a significant correlation between PAPP-A and IGFBP-4 expression. In the model of bile duct ligation, PAPPA-/- revealed significantly reduced HSC activation and fibrosis.
Summary and Conclusions: PAPP-A expression and secretion increase during HSC activation, and our data suggest that this leads to an autocrine induction of HSC proliferation, potentially via cleavage of IGFBP-4 and consecutive release of (bioactive) IGF. Future studies need to examine the potential of PAPP-A as a therapeutic target, and the impact of inter-individual differences in PAPP-A/ IGFBP-4 for the development and progression of hepatic fibrosis. Furthermore, circulating PAPP-A levels could have potential as potential novel biomarker for hepatic fibrosis.

FRI-071

Oncostatin M regulates the role of macrophage during progression and resolution of hepatic fibrosis

M. Matsuda, M. Tanaka. *National Center for Global Health and Medicine, Regenerative Medicine, Tokyo,*
Email: michimtd@gmail.com

Background and Aims: Hepatic macrophages (HM) contribute both fibrosis progression and resolution. However, underlying mechanism regulating these opposing roles of HM is to be elucidated. We have recently reported Oncostatin M, a member of IL-6 family cytokines, causes fibrosis progression by regulating cooperation between hepatic stellate cell (HSC) and macrophages during chronic liver injury (CLI) (Hepatology 2017). Base on these findings, this study aims to elucidate the role of OSM in fibrosis resolution by focusing on origin and phenotype of HM.
Method: Hepatic fibrosis was developed by the administration of 0.03% thioacetamide in drinking water for 12 weeks. After cessation of TAA, spontaneous resolution of fibrosis was evaluated. Continuous expression of OSM in the normal liver was enabled by hydrodynamic tail vein injection (HTVi). HSC and HM was isolated and cultured to examine the effect of OSM. HM was further divided into F4/80^{hi} CD11b^{lo} resident macrophage (KC) and F4/80^{lo} CD11b^{hi} infiltrating macrophage (infM) based on FACS and IHC analyses. In adoptive transfer experiments, bone-marrow-monocytes/macrophages (BM) were isolated by using anti-Ly6C, Ly6G and CD115 antibodies.
Results: During TAA-induced fibrosis progression, OSM was continuously produced by immune cells in the chronically injured liver. Compared to wild type mouse (WT), OSM deficient mouse showed less severe fibrosis. Conversely, continuous expression of OSM in normal liver by HTVi (OSM-HTVi) induced fibrosis with HSC activation. *In vitro* analyses showed OSM up-regulates fibrogenic genes including TGF-beta1 in HM, leading collagen production from HSC. FACS and IHC analyses on subpopulation of HM suggested that infM is more responsible than KC for OSM-induced fibrosis. Consistently, blocking infiltration of macrophage by CCR2 inhibitor administration prevented fibrosis progression and HSC activation in OSM-HTVi. These findings suggested BM earned fibrogenic phenotype by OSM stimulation in the liver. Then we examined the role of OSM in fibrosis resolution phase. WT mouse developed severe fibrosis with 12 weeks administration of TAA and even after cessation of TAA, residual fibrosis and prolonged OSM expression was observed for at least one week. During this phase, adoptive transfer of WT BM had no effect or even exacerbated the fibrosis compared to spontaneous resolution. In contrast, adoptive transfer of OSM receptor knockout BM promoted resolution of fibrosis, suggesting BM can exert fibrolytic potential if there were no OSM signal.
Conclusion: Continuous expression of OSM is a risk factor for fibrosis during CLI and even after cessation of causative agents of CLI. OSM not only induces fibrogenic potential but also suppresses fibrolytic potential of monocyte/macrophage. OSM could be a therapeutic target for CLI patients with prolonged fibrosis even after elimination of causative agents.

FRI-072

Selective NDRP1 E3 ubiquitin ligase overexpression in inflammatory macrophages using functionalized carbon nanoparticles promotes fibrosis regression in cirrhotic mice

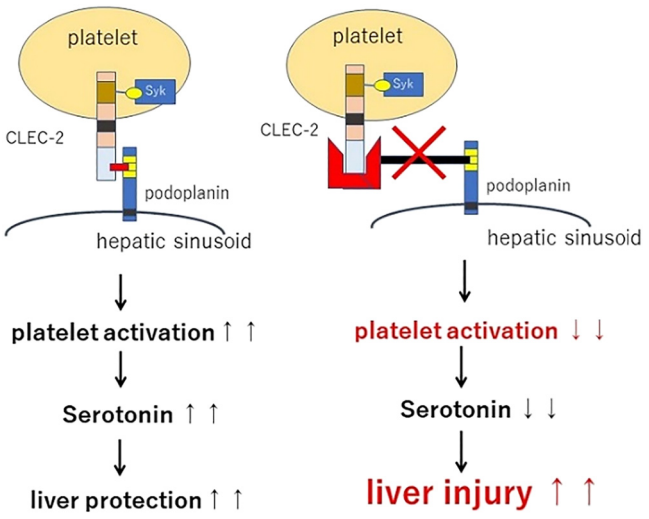
P. Melgar-Lesmes[1,2,3], A. Luquero[1], E. Edelman[2], W. Jiménez[1,4].
[1]*University of Barcelona, Barcelona, Spain, Department of Biomedicine, Spain;* [2]*Massachusetts Institute of Technology, Cambridge, MA, Edelman lab, Spain;* [3]*Hospital Clinic de Barcelona, Fundació Clínic per a la Recerca Biomèdica, Spain;* [4]*Hospital Clínic Universitari, IDIBAPS, CIBERehd, Barcelona, Spain, Biochemistry and Molecular Genetics Service, Spain*
Email: pmelgar@clinic.cat

Background and Aims: Hepatic macrophages are important in all stages of chronic liver disease; their activation is prognostic for survival in patients with cirrhosis. Macrophages also mediate wound repair and fibrosis by regulating extracellular matrix turnover. We investigated whether NRDP1 E3 Ubiquitin ligase might switch inflammatory M1 into pro-regenerative M2 macrophages to promote fibrosis regression in cirrhotic mice.
Method: Carbon nanoparticles, typically used to selectively stain macrophages, were covalently attached to PAMAM G5-dendrimer, and characterized by dynamic light scattering and electron microscopy. Carbon-dendrimer nanoparticles transported plasmid DNA (pDNA) expressing NRDP1 under CD11b promoter, and high constitutive levels of the fluorescent reporter GFP. Murine macrophages RAW 264.7 were used to test the uptake, functionality and activity of carbon-dendrimer-pDNA nanoparticles (CDDN) at transforming M1 to M2 macrophages. Cirrhosis was induced in ten Balb/c mice by i.p. injection of CCl_4 for 9 weeks twice a week. Cirrhotic mice received an i.v. injection of NRDP1 or scrambled-control CDDN (50 µg/Kg) every 3 days for 9 days. Tissue samples were analyzed for fibrosis by Sirius Red staining, M1 gene expression profiles and metalloproteinases by Real-Time PCR.
Results: *In vitro*: Stimulation of RAW 264.7 macrophages with TNF-α increased carbon nanoparticle uptake 7-fold (92.3 ± 1.1 vs. 13.6 ± 2.1%, $p < 0.01$). CDDN efficiently and selectively delivered NRDP1 plasmid into inflamed macrophages promoting switch to M2 subset, highlighted by the high presence of mannose receptor and increased gelatinase activity. *In vivo*: Cirrhotic mice treated with NRDP1 CDDN drastically reduced liver fibrosis (1.5 ± 0.3 vs. 11.1 ± 1.0 fibrosis area%, $p < 0.001$) and hepatic expression of markers of M1 macrophage phenotype (IL1-β: 0.5 ± 0.1 vs. 1.0 ± 0.1, $p < 0.01$; NOS2: 0.2 ± 0.0 vs. 1.1 ± 0.1, $p < 0.01$; COX-2: 0.4 ± 0.1 vs. 1.1 ± 0.1 fold change, $p < 0.05$), while increasing collagenase MMP-9 expression (2.6 ± 0.5 vs. 1.1 ± 0.1 fold change, $p < 0.05$) and recovery of parenchymal structure.

Conclusion: These outcomes show new mechanistic insights into NRDP1 regulating the behavior of macrophages in fibrosis regression, and offer an innovative strategy to combat cirrhosis.
Work funded by the Ministry of Economy, Industry and Competitiveness (MINECO), Spain. Reference: SAF15-64126-R.

FRI-073
Platelet c-type lectin-like receptor reduces cholestatic liver injury in mice
S. Maruyama[1], H. Kono[1], S. Furuya[2], D. Ichikawa[1]. [1]*universitiy of yamanashi hospital, first department of surgery, chuo-yamanashi;* [2]*University of Yamanashi, First Department of Surgery, Chuo, Japan*
Email: hkouno@yamanashi.ac.jp

Background and Aims: Bile duct obstruction is caused by various factors, and lead to liver dysfunction and death due to serious complications. It was recently reported that platelets reduced cholestatic liver damage, but its mechanism has not been unclear. In addition, it was recently found that c-type lectin-like receptor (CLEC-2), new platelet receptor different from known receptors, activated platelets by binding with ligand podoplanin. CLEC-2-podoplanin interactions induced powerful platelet activation through the tyrosine kinase-dependent pathway, and facilitated tissue regeneration. Therefore, the aim of this study was to evaluate the role of CLEC-2 on cholestatic liver injury in mice.
Method: Mice (C57BL/6J, male, 9 weeks age) were intraperitoneally administered anti-CLEC-2 antibody (2A2B10) every week for deleting CLEC-2 on platelets. Then, mice were subjected to left and middle bile duct ligation(LMBDL) procedure. Mice were sacrificed 1 week later (2A2 B10-BDL group). In addition, control antibody + laparotomy alone (sham group), anti-CLEC-2 antibody + laparotomy only (2A2B10-sham group), and control-antibody + LMBDL (BDL group) were also prepared. we compared to these groups.
Results: Serum T-Bil and transaminase significantly increased in 2A2B10-BDL group, and hepatocellular necrosis also increased histologically compared to BDL group. The mRNA expression of inflammatory markers (TNF-alpha, IL-6) and fibrosis markers (Timp1, Epcam1, TGF-beta, and Col1a1) significantly increased in 2A2B10-BDL group compared to BDL group. In addition, histologically expression of MPO, Sirius red, and alpha-SMA increased in 2A2B10-BDL group. In BDL group, podoplanin was strongly expressed in hepatic sinusoid compared to sham group. Serum serotonin level, protecting from cholestatic liver injury, significantly increased in BDL group compared to sham group. In contrast, serum serotonin level did not increase in 2A2B10-group. These results suggested that anti-CLEC-2 antibody suppressed the platelet activity and the release of serotonin, as a result, the bile acid regulation failed and then caused hepatic injury.



Conclusion: Platelet activation via new platelet receptor CLEC-2 reduced cholestatic liver injury. Podoplanin expressed in hepatic sinusoid and serotonin released from platelets play an important role for reducing cholestatic liver injury in mice.

FRI-074
AXL increase in NASH patients and anti-fibrotic efficacy of AXL inhibition in experimental NASH
A. Tutusaus[1], E.D. Gregorio[1], B. Cucarull[1], H. Cristobal[1], I. Graupera[2], G. Gausdal[3], A. Holmes[3], J. Lores[4], P.G. de Frutos[1], M. Mari[1], A. Morales[1,5]. [1]*IIBB-CSIC/IDIBAPS, Barcelona, Spain;* [2]*Unidad de Hepatología, Hospital Clinic, IDIBAPS, CIBEREHD, Barcelona, Spain;* [3]*Bergenbio AS, Norway;* [4]*Department of Biomedicine, Centre for Cancer Biomarkers, University of Bergen, Bergen, Norway;* [5]*barcelona Clínic Liver Cancer, Barcelona, Spain*
Email: amorales@clinic.ub.es

Background and Aims: GAS6 and the TAM receptor tyrosine kinases AXL and MERTK regulate the activation of hepatic stellate cells (HSC) during hepatic fibrogenesis as observed in animal studies and in vitro. Serum levels of GAS6 and AXL are elevated in a number of hepatic etiologies, however GAS6/AXL/MERTK levels in nonalcoholic steatohepatitis (NASH) are unclear. The distinctive subcellular signaling of the GAS6/TAM receptors during NASH development and the efficacy of AXL intervention to prevent diet-induced liver fibrosis remains to be explained. Several inhibitors against TAM receptors are in clinical development. The selective small molecule AXL kinase inhibitor BGB324 is currently being evaluated in Phase 2 clinical trials.
Method: Human activated HSC cells (LX2) and RAW264.7 cells were exposed to LPS, TGF-beta, AXL activation, and selective AXL kinase inhibitor (BGB324, BerGenBio AS). Mice were fed a high-fat diet choline-deficient with methionine restriction (HFCD) or methionine-choline-deficient diet (MCD) for 8 weeks. Serum levels of Gas6, AXL and MERTK were measured by ELISA. The collagen content was measured by Sirius Red staining and image-analysis software. HSC activation, liver inflammation and cytokine/chemokine production were measured by qPCR, mRNA array analysis, Western Blot and ELISA.
Results: Among individuals with different degrees of nonalcoholic liver disease (steatosis / fibrosis / cirrhosis), only cirrhotic patients displayed increased Gas6 and MERTK serum levels. However, AXL values were significantly elevated in all NASH groups in parallel to disease progression. Consistent with AXL influence in HSC transdifferentiation, human LX2 cells expression of profibrogenic genes after AXL activation was blocked by BGB324 treatment. AXL and MERTK control of inflammatory response was analyzed in activated human THP-1 macrophages. While Gas6 reduced LPS-induced gene expression, AXL inhibition did not affect it. Finally, HFCD-fed mice developed significant hepatic steatosis and fibrosis, and exhibited increased AXL serum levels, recapitulating human NASH observations. Besides inhibiting AXL, BGB324 administration increased circulating GAS6, favoring GAS6 liver protection via MERTK signaling. Oral administration of BGB324 to HFCD-fed mice reduced liver fibrosis and hepatic inflammation. Analogous protection was provided by BGB324 in animals receiving MCD diet.
Conclusion: AXL serum levels are an early marker of NASH that correlates with disease development. Stimulation of AXL signaling in HSCs is sufficient to induce HSC activation and expression of profibrotic genes in vitro. In experimental NASH models, therapeutic administration of the AXL inhibitor BGB324 diminishes liver fibrosis by blocking HSC activation and reduces hepatic inflammation possibly due to GAS6 hepatoprotective action.

FRI-075

Platelet-derived growth factor receptor alpha deprived hepatocytes attenuate thioacetamide induced liver fibrosis in mice

J.II. Lee[1], K.S. Lee[1], H.W. Lee[1], W.-K. Lee[2], H.Y. Chang[3]. [1]*Yonsei University College of Medicine, Internal Medicine, Seoul, Korea, Rep. of South;* [2]*Inha Univeristy College of Medicine, Biomedical Sciences, Incheon, Korea, Rep. of South;* [3]*Gangnam Severance Hospital, Medical Research Center, Seoul, Korea, Rep. of South*
Email: mdflorence@yuhs.ac

Background and Aims: Platelet-derived growth factor receptor (PDGFR)-alpha expression is very low in normal liver. It dramatically increases in cirrhotic liver where activated hepatic stellate cells (HSCs) are suggested to be responsible for this increment. Although normal hepatocytes scarcely express PDGFR-alpha, cancerous hepatocytes may have up-regulated PDGFR-alpha expression. Since hepatocellular carcinoma is very often preceded by liver fibrosis, we hypothesized that upon repetitive liver insult, PDGFR-alpha on abnormal hepatocytes might play an important role in liver fibrosis by means of cell-to-cell crosstalk between hepatocytes and HSCs.
Method: Hepatocytes were isolated from normal and thioacetamide (TAA) induced cirrhotic liver respectively for assessment of PDGFR-alpha expression on hepatocytes. Then, we generated conditional knock-out mice from C57BL/6 mice where PDGFR-alpha was deleted on hepatocytes. Liver fibrosis was induced by injecting TAA for 8 weeks. Hep3B cells were transfected with siRNA (PDGFR-alpha or control) and co-cultured with LX2 cells.
Results: PDGFR-alpha expression was increased on hepatocytes from cirrhotic liver compared with that from normal liver. After PDGFR-alpha on hepatocytes was deleted, TAA induced liver fibrosis was significantly attenuated in mice. Although expressions of *transforming growth factor beta* and *Smad2/3* were enhanced after deletion of hepatocyte PDGFR-alpha, this was compensated by increased inhibitory *Smad7* expression, resulting in decreased liver fibrosis. From the co-culture system, LX2 cells, cultured with PDGFR-alpha siRNA infected Hep3B cells, showed decreased *PDGFR-alpha* expression as well as attenuated *alpha-smooth muscle actin (SMA)* and *collagen 1 (Col1) alpha* expression.
Conclusion: Deleting PDGFR-alpha on hepatocytes resulted in attenuated TAA induced liver fibrosis. This suggests that although PDGFR-alpha is scarcely expressed on normal hepatocytes, in the event of chronic liver injury, PDGFR-alpha on hepatocytes plays an important role, facilitating liver fibrosis.

FRI-076

Platelet deactivation attenuates CCL4 induced liver fibrosis progression in mice

A. Bhat[1], S. Mg[1], A. Parasar[1], A. Rastogi[2], S.K. Sarin[1,3]. [1]*ILBS, Molecular and cellular medicine, New Delhi, India;* [2]*ILBS, Department of Histopathology, New Delhi, India;* [3]*ILBS, Department of Hepatology, New Delhi, India*
Email: shivsarin@gmail.com

Background and Aims: Platelet activation induces liver fibrosis by PDGF-B dependent fibrogenic activation of hepatic stellate cells, and use of aspirin significantly attenuates the liver fibrosis progression by deactivating platelets in the animal model. The aim of this study is to further investigate the molecular mechanism of platelet deactivation by aspirin in liver fibrogenesis.
Method: Forty-two male C57/B6 mice were randomly divided into the control group (n = 7), ASA group (n = 7), CCL4 group (n = 14), and CCL4 + ASA group (n = 14). CCL4-induced fibrotic mice received 0.5μl/g bw of 50% carbon tetrachloride (CCL4) by intraperitoneal injection i.p. twice a week for 10 weeks while two different doses of Aspirin were given in drinking water. We compared the liver injury in both low (5mg/kg) and the moderate dose (50mg/kg) post euthanization after 10 weeks. Both hematoxylin-eosin and Masson's trichrome staining were performed to observe pathological changes in liver tissue. Liver fibrosis was evaluated by histology, biochemical determination of liver enzymes, collagen content and QRT-PCR.
Results: The aspirin-treated group displayed a decrease in platelet counts as compared to the control groups. Further, Alanine aminotransferase, aspartate aminotransferase, and total bilirubin were found to be higher in CCL4 group as compared to the aspirin-treated group. Assessment of Hepatic fibrosis by METAVIR score showed a significant decline in fibrotic areas and hydroxyproline contents in the aspirin-treated group as compared to CCL4 group ($p < 0.01$). Moreover, usage of aspirin at moderate-doses significantly improved the long-term fibrosis outcomes in the CCL4 model of liver fibrosis. Platelet deactivation by aspirin revealed a significant correlation with the expression levels of collagen type I as well as alpha-smooth muscle actin, a marker of HSC activation. Quantitative RT-PCR results revealed a downregulation of PDGFR expressions in the aspirin-treated group as compared to the CCL4 model group.

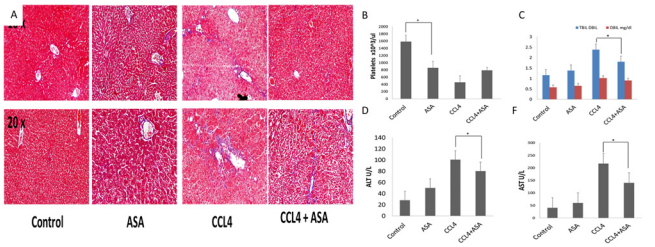


Figure 1 **Hepatoprotective effect of platelet inhibition in CCl4 induced hepatic injury. (A)** Representative photomicrographs of liver histology from normal healthy mice, ASA alone, CCl4 + vehicle alone and CCl4 + ASA. Mice were given repeated injections of CCl4 for 10 weeks in CCL4 model group. (**B-E**)Platelet number, Serum aminotransferases, direct and total bilirubin levels are plotted. Grading of hepatic fibrosis was evaluated on a scale of 1–4 as follows: 1, scattered; 2, mild; 3, moderate and 4, marked. The histological changes were assessed in 200× magnification fields of slides stained with H&E and Masson's trichrome.

Conclusion: Platelets may promote fibrosis during liver injury and pharmacological targeting of platelet activation could be beneficial and strongly attenuate fibrosis progression.

FRI-077

Combination of an FXR agonist and an ACC inhibitor increases anti-fibrotic efficacy in rodent models of NASH

J. Bates, D. Hollenback, A. Zagorska, G. Budas, J. Liles, H. Liu, K. Liu, S. Kusam, R. Brockett, D. Newstrom, I. Mikaelian, T. Wang, A. Ray, D. Breckenridge. *Gilead Sciences, Inc., Research, Foster City, United States*
Email: jamie.bates@gilead.com

Background and Aims: GS-9674 a selective, non-steroidal Farnesoid X Receptor (FXR) agonist (FXRag), and GS-0976, a liver-directed Acetyl-CoA Carboxylase (ACC) inhibitor (ACCi), are currently being investigated in clinical trials for NASH. FXR activation inhibits bile acid synthesis, and increases bile salt export. ACC 1 and 2 catalyze the rate limiting step of *de novo* lipogenesis (DNL) and inhibit mitochondrial fatty acid oxidation (FAO), respectively, which is hypothesized to promote lipotoxicity in NASH. We evaluated the potential efficacy of combination therapy agonizing FXR and inhibiting ACC in rodent models of NASH.
Method: Male C57BL/6 mice were administered a fast food diet (FFD) enriched in fat, cholesterol, and sugar for 6 months and treated with vehicle, FXRag, ACCi, or FXRag + ACCi from months 5 to 6 (n = 14–16/group). Endpoints included quantification of hepatic triglycerides (TG), plasma ALT, and hepatic gene expression by NanoString (*Col1a1* and *Timp1*). Male Wistar Han rats were fed a choline deficient high fat diet (CDHFD) for 12 weeks and administered vehicle, FXRag, ACCi, or FXRag + ACCi from week 6 to 12 (n = 15–16/group). Fibrosis and fibroplasia were assessed by picrosirius red (PSR) staining and α-SMA

IHC, respectively, with quantitative image analysis. Plasma TIMP-1, HA and PIIINP were quantified by ELISA.
Results: Hepatic triglycerides, serum ALT, and expression of fibrosis related genes *Col1a1* and *Timp1* were increased in vehicle treated FFD mice compared to mice on standard diet. FXRag + ACCi caused significant reductions in hepatic triglycerides and ALT (47% and 74%, respectively; $p < 0.001$), and liver gene expression of *Col1a1* and *Timp1* (80% and 74% reduction, respectively; $p < 0.0001$). *Col1a1* and *Timp1* expression were significantly reduced relative to either monotherapy ($p < 0.05$). Compared to normal diet, CDHFD significantly increased hepatic fibrosis at 6weeks (3% PSR area) and at 12 weeks (8% PSR area). FXRag + ACCi inhibited progression of fibrosis by 73% ($p < 0.001$) and α-SMA area by 85% ($p < 0.01$). Plasma levels of TIMP1, PIIINP, and HA were increased by CDHFD and were reduced by >98% by FXRag + ACCi ($p < 0.05$). The combination significantly inhibited α-SMA area and plasma PIIINP more than either monotherapy ($p < 0.05$).
Conclusion: Combining therapies targeting complementary mechanisms resulted in increased anti-fibrotic efficacy in rodent models of NASH. These data support investigation of a combination of GS-9674 and GS-0976 in patients with NASH.

FRI-078

Non-invasive phenotyping of hepatic fibrosis using unsupervised machine learning

J. Brag[1], Y. Nakano[1], R. Cabrera-Lozoya[1], E. Oubel[1], M. Wagner[2], O. Lucidarme[2]. [1]*Median Technologies, R&D, France;* [2]*Pitié Salpêtrière Hospital, Radiology, Paris, France*
Email: johan.brag@mediantechnologies.com

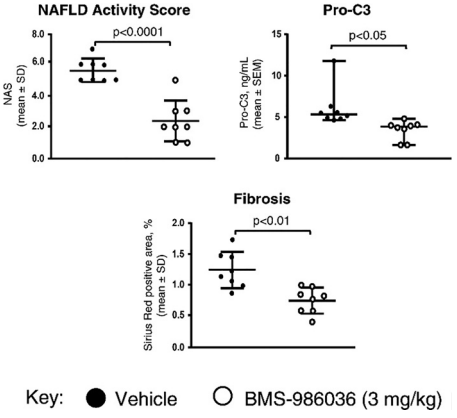
Background and Aims: Diagnosis and severity assessment of chronic liver diseases typically relies on histopathological analysis from biopsy samples. With novel anti-viral and NASH therapies there is a need for reliable non-invasive assessment of hepatic fibrosis. Earlier studies have shown that radiological signatures reflect biological phenotypes from tomographic images such as computed tomography. The aim of this study is to demonstrate the feasibility of applying routine CT imaging protocols, combined with unsupervised machine learning, to the non-invasive phenotyping of hepatic fibrosis.
Method: Two hundred patients with focal liver lesions referred for ex-vivo liver resection or transplantation at the academic hospital Pitié-Salpêtrière in Paris underwent a non-contrast CT exam as well as a standard triphasic contrast CT scan. The patients also had tissue samples surgically excised and graded for fibrosis by histopathology per the METAVIR score (F0-F4).
The liver was automatically segmented from the CT scans. Radiological signatures were automatically extracted from more than 10,000 individual 1 cm^2 size patches using a moving window scanning the entire liver. A similarity metric, (EMD) was used to compute the distance between radiological signatures. An unsupervised machine learning algorithm was used to group the patch signatures into clusters based on similarity with reference signatures corresponding to various tissue types and fibrosis score.
Robustness of the radiological signatures was tested against variations in reconstruction algorithms, equipment models and slice thickness as well as variations in intensity and contrast injection. Temporal stability was also assessed using test-retest procedures at different time points. The ability of the radiological signatures to discriminate between malignant and non-malignant tissue types and fibrosis classes was also evaluated.
Results: The signatures were generally insensitive to variations in equipment configuration, reconstruction or slice thickness as well as to variations in intensity or contrast with a distance variability of less than 5%. Local or temporal distance variations from matched tissue samples were also small compared to variations across tissue types. Tissue classification tests using unsupervised clustering showed classification ranging from 50 to 90% of patches correctly classified based on pathology data. Substantial heterogeneity of fibrosis distribution throughout the liver was also apparent.
Conclusion: Unsupervised machine learning can be applied to the non-invasive phenotyping of hepatic fibrosis and hepatocellular carcinoma. Radiological signatures extracted from contrast CT images reflect underlying tissue cellular biology. Unsupervised machine learning can be used for the classification and staging of hepatic fibrosis and hepatocellular carcinoma.

FRI-079

BMS-986036, a PEGylated fibroblast growth factor 21 analogue, reduces fibrosis and Pro-C3 in a mouse model of non-alcoholic steatohepatitis

Y. Luo[1], J. Krupinski[2], S. Gao[2], E. Charles[3], R. Christian[3]. [1]*Bristol-Myers Squibb, Pennington;* [2]*Bristol-Myers Squibb, Pennington, United States;* [3]*Bristol-Myers Squibb, Lawrenceville, United States*
Email: yi.luo@bms.com

Background and Aims: Non-alcoholic steatohepatitis (NASH) is characterised by steatosis, inflammation, and liver cell injury with or without fibrosis. BMS-986036 is a PEGylated recombinant analogue of human fibroblast growth factor 21 (FGF21) with a prolonged half-life and has been shown to improve insulin sensitivity, lipid profiles, steatosis, and biomarkers of liver injury and fibrosis in clinical studies. This study examines the effect of BMS-986036 treatment (tx) in a mouse model of NASH.
Method: In the STAM (Stelic) mouse model, male C57BL/6 mice were injected with streptozotocin 2 days after birth and placed on high-fat diet (57% kcal fat) at 4 wks of age. STAM mice develop evident steatohepatitis at 7 wks of age that later progresses to fibrosis and hepatocellular carcinoma, a disease profile that resembles NASH in humans. Mice were dosed at 7 wks of age with vehicle or 3 mg/kg BMS-986036 ($n = 8$/arm) for 2 wks by twice-weekly subcutaneous injection. Plasma and livers were collected for biochemical and histological analysis at the end of tx. Liver fibrosis was measured by Sirius Red staining and the non-alcoholic fatty liver disease activity score (NAS) was evaluated according to NASH Clinical Research Network histological criteria. Statistical analyses were performed using Student's t-test.
Results: Compared with vehicle, BMS-986036 tx significantly improved whole blood glucose (–30%; $p < .001$), body weight (–7.9%; $p < .05$), and liver/body weight ratio (–20%; $p < .01$), as well as liver and plasma triglycerides (–68% and –58%, respectively; both $p < .001$). BMS-986036 tx also decreased mean grades for steatosis, lobular inflammation, and hepatocellular ballooning (all $p < .005$ vs vehicle), resulting in a lower mean NAS (5.63 for vehicle vs 2.38 for BMS-986036; $p < .0001$; figure). BMS-986036 tx significantly decreased the mean serum fibrosis biomarker Pro-C3 by 44% (3.4 vs 6.1 ng/mL for vehicle; $p < .05$). Finally, BMS-986036 tx significantly decreased mean liver fibrosis, determined by Sirius Red-positive area, by 40% (0.75% vs 1.25% for vehicle; $p < .01$).



Conclusion: BMS-986036 tx for 2 wks in the STAM mouse model of NASH resulted in significant improvements in lipid and metabolic profiles, histological indicators of NASH, fibrosis-associated biomarkers, and liver fibrosis. These results suggest that BMS-986036 impacts several key drivers of NASH pathogenesis and fibrosis and support further clinical studies of BMS-986036 in patients with NASH and advanced fibrosis.

FRI-080

Human amnion epithelial cells reduce liver fibrosis via effects on macrophages phenotype and liver progenitor cells in murine liver injury

M. Alhomrani[1,2,3], J. Correia[1,4], N. Kuk[1,4], R. Lim[2,5], W. Sievert[1,4].
[1]*Centre for Inflammatory Disease Monash University, Melbourne, VIC, Australia;* [2]*Hudson Institute of Medical Research, Melbourne, VIC, Australia;* [3]*Medical College, Taif University, Taif, Saudi Arabia;* [4]*Gastroenterology and Hepatology Unit, Monash Medical Centre, Monash University, Melbourne, VIC, Australia;* [5]*Department of Obstetrics and Gynecology, Monash University, Melbourne, VIC, Australia*
Email: majid.g.alhomrani@monash.edu

Background and aim: Chronic liver disease is characterised by progressive hepatocyte injury, inflammation and accumulation of extracellular matrix. Treatment for end stage liver disease is limited to liver transplantation. Liver progenitor cells (LPC) are bipotent cells induced during liver injury that can regenerate both hepatocytes and cholangiocytes. In addition, macrophages play a pivotal role in fibrogenesis and fibrosis resolution. Classically, macrophages are classified into M1 (pro-inflammatory macrophages) and M2 (pro-resolution macrophages). Recently, Ly6C expression has been used to identify distinct macrophage populations; Ly6C^{hi} (inflammatory) and Ly6C^{low} (resolution). We are developing a therapy for chronic liver fibrosis using human amnion epithelial cells (hAECs). The choline-deficient ethionine- supplemented (CDE) diet is a non-invasive and quick method to induce liver injury and LPC proliferation. Here, we aimed to investigate the effect of hAECs on macrophages and LPC during liver injury induced by CDE diet.
Methods: Male C57Bl/6J mice (6–8-weeks) were fed a CDE diet for up to 42 days; 2 or 4 million hAECs were infused intra-peritoneally 24h following initiation of the CDE diet. Outcomes were assessed at days 1, 3, 5, 14, 21 and 42 of the CDE diet following hAEC administration. The extent of liver fibrosis was determined by Sirius red staining and computer assisted morphometry was used to quantify the percentage of positively stained liver (expressed as % fibrosis area). LPC activation was determined by staining with wide spectrum screening cytokeratin (Pan-CK). Macrophages were further identified and characterised using flow cytometery sorting and PCR. Monocyte-derived macrophages (MDM) were distinguished from resident hepatic macrophages (Kupffer cells) based on expression CD45^{+} CD11b^{Hi} F4\80^{intermediate} Ly6G^{-} CD3^{-} B220^{-} NK1.1^{-}. Further, MDM were divided into two subpopulations based on high and low Ly6C expression.
Results: In CDE treated mice, hAEC significantly reduced liver fibrosis compared to untreated mice. hAEC decreased the number of proinflammatory (Ly6C^{hi}) MDM cells and increased the number of anti-inflammatory and tissue remodelling (Ly6C^{low}) MDM cells at days 1 and 42. hAEC also enhanced the expression of MMP12 and MMP13 in Ly6C^{Low} sorted cells. LPC numbers were reduced significantly in hAEC treated mice.
Conclusion: This is the first study to assess the efficacy of cell-based therapy on LPC and macrophage LyC6 phenotype. hAEC therapy significantly reduced liver fibrosis, induced a resolution Ly6C^{Low} macrophage phenotype and significantly decreased the number of LPC. Our data confirm the potential efficacy of hAECs as an effective therapy in liver fibrosis.

FRI-081

Stimulation of soluble guanylate cyclase inhibited fibrosis and inflammation in human liver microtissues and in an animal model of liver disease

K. Hall[1], S. Bernier[1], S. Jacobson[1], G. Liu[1], R. Sarno[2], V. Catanzano[2], J. Sheppeck[3], J. Hadcock[4], M. Currie[5], J. Masferrer[5]. [1]*Ironwood Pharmaceuticals, Pharmacology, Cambridge, United States;* [2]*Ironwood Pharmaceuticals, DMPK, Cambridge, United States;* [3]*Ironwood Pharmaceuticals, Medicinal Chemistry, Cambridge, United States;* [4]*Ironwood Pharmaceuticals, Cambridge;* [5]*Ironwood Pharmaceuticals, Pharmacology, Cambridge*
Email: khall@Ironwoodpharma.com

Background and Aims: Liver fibrosis in nonalcoholic steatohepatitis (NASH) is a risk factor for liver failure. Liver disease is associated with endothelial dysfunction and reduced nitric oxide (NO), the endogenous ligand of soluble guanylate cyclase (sGC). Drugs known as sGC stimulators activate the NO-sGC-cGMP signaling pathway, which modulates vascular function, metabolism, inflammation and fibrosis. Human liver microtissues (HLMs) and the carbon tetrachloride (CCl_4) liver fibrosis model were used to assess the antifibrotic/anti-inflammatory activity of sGC stimulators and explore their mechanism of action
Method: The sGC stimulators IWP-597 and IW-1973 were used in 2 studies: (1) HLMs (InSphero) composed of human hepatocytes, Kupffer and stellate cells, were treated with TGF-beta and IWP-597 for 48 h. (2) CCl_4 was administered to rats by PO dosing for 2 wk, then CCl_4+IW-1973 for 6 wk. mRNA levels were determined by bDNA, PCNA protein levels by Western blot, Ki67 by immunohistochemistry (IHC), and MCP-1 levels by ELISA.
Results: TGF-beta-treatment of HLMs increased expression of alpha-SMA mRNA, a key fibrosis marker, by 1.6x after 48 hours. IWP-597 treatment inhibited this increase in a dose-dependent fashion. All doses significantly inhibited TGF-beta-induced MCP-1 secretion relative to control. The antifibrotic and anti-inflammatory responses to IWP-597 observed in the HLMs were consistent with the effects of IW-1973 in the CCl_4 rats, suggesting similar responses to sGC stimulation between these two models. sGC expression was restricted to stellate-derived myofibroblasts in fibrotic livers from the CCl_4-model; we hypothesized that myofibroblast proliferation explained sGC's increase in fibrotic livers which was decreased in IW-1973 treated animals. PCNA, a proliferation marker, was 6.4x higher in fibrotic livers than in normal livers; IW-1973 treatment yielded lower PCNA expression, similar to levels in normal livers. Ki67 IHC revealed that proliferation of hepatocytes and myofibroblasts was increased in fibrotic livers. Proliferation was significantly reduced in the IW-1973 group.
Conclusion: In human liver microtissues, sGC stimulation reduced markers of fibrosis and inflammation compared to control. In the rat CCl_4 fibrosis model, in addition to decreasing fibrosis and inflammation, IW-1973 treatment reduced sGC expression and proliferation of hepatic cells. Several sGC-regulated proliferation factors are being explored as mechanistic candidates

FRI-082

Zoledronic Acid suppresses tumour associated macrophages andmyeloid derived suppressor cells in murine HCC

M. Aslam[1,2,3], M. Ashfaq-Khan[1], A. Qureshi[4], M. Nick[1], M. Senkowski[1], S.Y. Weng[1], K.Y. Ook[1], D. Schuppan[1]. [1]*Institute of Translational Immunology, University Medical Centre, Mainz, Germany;* [2]*;* [3]*Shaheed Benazir Bhutto Women University;* [4]*Dow university of medical sciences*
Email: m.ashfaq_biotech@yahoo.com

Background and Aims: HCC is associated with chronic inflammation leading to recruitment of bone marrow derived cells, mainly tumour associated macrophages (TAM, M2) and myeloid-cell derived suppressor cells (MDSC). Both cell types markedly suppress anti-HCC immune responses and are present in all stages of HCC. Zoledronic acid (ZA) is used in patients with osteoporosis to inhibit osteoclasts,

i.e., bone macrophages with TAM-like properties. We hypothesized that ZA can polarize tumour promoting TAM and MDSC towards M1 macrophages with anti-tumour activity.
Method: Mouse bone marrow derived in vitro M1 or M2 polarized macrophages () were exposed to increasing concentrations of ZA. Transcript levels of M1 markers (TNFα, IL-1β, iNOS, TIMP1) and M2 markers (Fizz1, ARG1, VEGF, YM1, MRC1, MMP-9) were determined by qPCR. IL-12 and SOCS3 (M1), IL-10 and VEGF (M2) secretion were measured by ELISA. Mice bearing a syngenic HCC (DEN/Mdr2KO model) received 3 doses of 100µg ZA/kg BW or vehicle control intraperitoneally weekly for a period of one month from age month 5–6. After four weeks of treatment mice were sacrificed to measure hepatic tumor number and volume and livers were assessed by H&E histology, IHC and qPCR.
Results: ZA dose-dependently decreased M2 (Fizz1, ARG1, STAT6, YM1, MRC1, MMP-9) and increased M1 macrophage (iNOS, TNF-alpha, IL-1beta, SOCS3) specific transcript levels without affecting cell viability in vitro. This was paralleled by a significant upregulation of IL-12 and dowregulation of IL-10 protein secretion into the cell supernatant. Compared to vehicle controls, treatment of DEN/Mdr2KO mice with ZA reduced tumour number and volume by 33.3% and 68%, respectively ($p < 0.004$). Tumour cell proliferation as evaluated via Ki-67-positive cells was significantly blunted by ZA. Staining of YM-1 and glypican positive M2 and CD68 positive total macrophages of ZA treated HCC liver sections showed a significant upregulation of M1 > M2 macrophages and reduced numbers of TAM. ZA significantly downregulated hepatic transcript levels the TAM/MDSC markers CSF-1, VEGF, TGFβ1, Cox2, Hif1α, CCL2, CCL3, CCL5 and CCL17.
Conclusion: 1. ZA exhibits potent macrophage (and MDSC) repolarizing activity (M2 towards M1) in- vitro and in-vivo, thereby increasing anti-HCC immune responses and limiting angiogenesis. 2. Since ZA has a well-known clinical safety profile, it should be assessed alone or in combination with other anti-cancer agents in patients with HCC.

FRI-083
Rapamycin and Zoledronic acid exert a potent antifibrotic effect in murine biliary fibrosis
M. Aslam[1,2], M. Ashfaq-Khan[1], A. Qureshi[3], M. Senkowski[1], M. Nick[1], S.Y. Weng[1], K.Y. Ook[1], D. Schuppan[1]. *[1]Institute of Translational Immunology, University Medical Centre, Mainz, Germany; [2]Shaheed Benazir Bhutto Women University, Pakistan; [3]Dow university of medical sciences, Pakistan*
Email: m.ashfaq_biotech@yahoo.com

Background and aims: There is an urgent need for effective antifibrotic therapies for biliary fibrosis. The *in vivo* microenvironment, especially macrophages, can modulate hepatic stellate cell (HSC) activation. We therefore assessed the antifibrotic efficacy of a combination of two clinically used drugs, Zoledronic acid (ZA) and Rapamycin (RA), that affect macrophage polarization and putative fibrogenic activation.
Methods: Mdr2-knockout (Mdr2KO) mice that had received one dose of diethylnitrosamine (DEN) at day 5 after birth were treated from month 5–6 (stage of advanced fibrosis with emerging HCC) with 1) ZA alone (100µg/kg body weight i.p., thrice weekly), 2) RA alone (5mg/kg body weight in the chow), 3) the combination of both drugs. A fourth group of Mdr2KO mice (without DEN and no signs of HCC) was treated with the combination. The degree of fibrosis and extent of inflammation was quantified histologically using staining with H&E, Sirius Red, for αSMA and CD68. Collagen deposition was confirmed by hydroxyproline determination. Real time PCR was performed to analyze the hepatic expression of fibrosis-related and macrophage-specific target genes produced by KCs (TNF-α, CCL2, TGFβ1, HIF1α and several MMPs), liver SECs(VEGF) involved in the activation of HSCs thereby progression of liver fibrosis.
Results: Compared to the untreated controls and to animals treated with the single drugs alone, Mdr2KO KO mice that received the ZA/RA combination for only one month demonstrated a twofold reduced collagen deposition, with elimination of bridging fibrosis ($p < 0.0001$). This was accompnied by a similar reduction of αSMA expression and a significant suppression of profibrogenic transcripts like Col1a1, Col3a1, Asma, Tnfa, and of markers of M2 macrophage polarization, including Hif1a and Mmp9. Moreover, the number of YM-1 relative to CD68 positive macrophages was significanatly
Conclusion: The combination of RA and ZA, two agents with macrophage modulating activity, induces a remarkable regression of even advanced biliary fibrosis. This antifibrotic effect goes along with a marked antitumorous activity. Since both drugs are used in the clinic for other indications, with a reasonable safety profile, their clinical testing should be considered in patients with fibrotic and (pre) cancerous PSC and other unaddressed indications.

FRI-084
EDP-305, a highly selective and potent farnesoid X receptor agonist, favorably regulates the expression of key fibrogenic genes in vitro and in vivo
Y. Li[1], J. Shang[2], M. Chau[2], M. Roqueta-Riverta[2], K. Garlick[2], P. An[3], K. Vaid[3], Y. Popov[3], Y.S. Or[4], L. Jiang[5]. *[1]Enanta Pharmaceuticals, Inc., Pharmacology, Watertown, United States; [2]Enanta Pharmaceuticals, Inc., Biology, Watertown, United States; [3]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, United States; [4]Enanta Pharmaceuticals, Watertown, United States; [5]Enanta Pharmaceuticals, Inc, Pharmacology, Watertown, United States*
Email: ljiang@enanta.com

Background and Aims: Fibrosis drives disease progression in people with advanced nonalcoholic steatohepatitis (NASH). EDP-305, a potent Farnesoid X Receptor (FXR) agonist, is currently being developed for the treatment of NASH. Herein, we report the anti-fibrotic activity of EDP-305 *in vitro* and *in vivo*. The effect of EDP-305 on post-transcriptional regulatory mechanism via microRNA29a (miR29a) was also characterized.
Method: To investigate the effects of EDP-305 on liver fibrosis *in vitro*, primary human hepatic stellate cells (HSC) were induced with 5 ng/ml of transforming growth factor beta (TGFβ) and co-treated with DMSO or EDP-305 for 18 hours. The *in vivo* anti-fibrotic effect of EDP-305 was investigated using mice with methionine/choline-deficient diet (MCD)-induced steatohepatitis and peri-sinusoidal fibrosis. EDP305 (10 mg/kg) was orally administered to mice 4 weeks after MCD-induced early fibrosis was established and treatment duration was 4 weeks. The expression of essential genes involved in modulating the pathogenic fibrogenic response associated with NASH was analyzed by RT-PCR.
Results: EDP-305 significantly ($p < 0.05$) decreased expression of α-smooth muscle actin (α-SMA), collagen type 1 α2 (COL1A2), collagen type 3 α1 (COL3A1), metallopeptidase inhibitor 1 (TIMP1) and metallopeptidase inhibitor 2 (TIMP2) by 68%, 42%, 57%, 80%, and 65%, respectively, *in vitro* in HSC cell cultures. Consistent with *in vitro* observations, these key fibrogenic genes were also significantly down-regulated by EDP-305 in mice. Moreover, EDP-305 favorably upregulated miR29a, a crucial player in fibrosis. EDP-305 increased miR29a expression by 89% when compared to the vehicle control, which led to 70% reduction of hepatic collagen content, in mice with MCD-induced fibrosis.
Conclusions: EDP-305 exhibits potent anti-fibrotic activity *in vitro* and *in vivo*. Moreover, EDP-305 can favorably upregulate miR29a, a key post-transcriptional regulator of profibrotic genes. These results warrant further clinical study of EDP-305 for the treatment of NASH.

FRI-085

Fibrosis involves increased fibroblast and hepatocyte collagen species, reflecting the interstitial and basement membrane matrix: Restoration of the local tissue milieu with FXR agonism

J. Roth[1], S. Veidal[2], R. Papazyan[1], K. Rigbolt[2], M. Feigh[2], M. Karsdal[3], D. Leeming[3], M. Young[1]. *[1]Intercept Pharmaceuticals, Inc.; [2]Gubra, Horsholm, Denmark; [3]Nordic Bioscience, Herlev, Denmark*
Email: jonathan.roth@interceptpharma.com

Background and Aims: Fibrosis involves an induction of both basement membrane (BM) and interstitial matrix components. Most NASH pharmacology studies focus exclusively on the myofibroblast-derived fibrillar collagens, type I collagen (Col1) and type III collagen (Col3). By contrast, the role of hepatocyte and endothelial-derived BM proteins like the network forming type IV collagen (Col4) in disease progression/regression are not well understood. Previously, INT-767 reduced Sirius Red staining (Col1 and Col3) and Col1 immunoreactivity. We assessed INT-767's impact on major components of the BM and its remodeling and regeneration, including Col4 and laminin (LAM), using histological, molecular and biomarker assessments.
Method: *Lep$^{ob/ob}$* mice were fed the AMLN NASH diet for 12W, biopsied and randomized to receive vehicle or INT-767 10 mg/kg for 8W. Hepatic collagen and BM-related gene expression were measured by RNA-Seq. Fractional area (FA%) calculations were performed for Col1a1, LAM and Col4 (BM). Serum P4NP7S (a marker of Col4 formation) was sampled during diet induction, at baseline prior to treatment, and after 4W and 8W of INT-767.
Results: INT-767 reduced mRNA levels of BM proteins including Col4, BM-40, nidogens, laminins, and fibrillins vs vehicle controls. Consistent with transcriptional changes, INT-767 reduced FA% hepatic Col1a1 (-38%), LAM (-39%) and Col4 (-19%) vs. controls (all $p < 0.05$). P4NP7S (ng/ml) increased during diet-induction (from 86 to 104 at baseline) and continued to rise in vehicle-treated mice (to 141 and 152, at 4W and 8W; all $p < 0.05$). INT-767 reduced levels of P4NP7S at 4W (115) and 8W (113; both $p < 0.05$). Circulating P4NP7S correlated with endpoint hepatic levels of Col1a1 ($p = 0.015$, R^2=0.2125).
Conclusion: We demonstrated that fibrosis is not only associated with increased Col1 and Col3 of the fibroblasts, but also a significant thickening of the BM involving a completely different functional type of collagen, Col4. INT-767 treatment reduced Col4 and LAM, the major components of the BM which are likely contributors to improvements in endpoint fibrosis. For Col4, these changes were evident at the mRNA level and linked to circulating P4NP7S. Notably, P4NP7S was also associated with improved fibrosis as assessed by Col1a1. These preclinical findings raise the possibility that FXR agonism restores both fibroblast and hepatocyte/epithelial cell phenotypes to ultimately improve liver function.

FRI-086

Possible liver regeneration and anti-fibrogenic effect of NOTCH1 selective inhibitor in the diseased liver model

M. Kitade, K. Kaji, H. Yoshiji. *Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan*
Email: kitademitsu@yahoo.co.jp

Background and Aims: Recently several arguments have arisen in the true potential of hepatic progenitor cells (HPC) on regeneration of diseased liver. We hypothesized that HPC shifts their differentiation fate towards "too biliary" direction by NOTCH signal, and this may prevent HPC to provide new hepatocytes (HC) in the diseased liver. We speculated that NOTCH1 selective inhibition may contribute efficient HPC-derived hepatocyte repopulation which results in a more efficient liver regeneration in the diseased liver.
Method: We employed a small molecule NOTCH1 inhibitor (N1inh) developed by Interprotein Inc. We treated both 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC)- and carbon tetrachloride (CCL4)-induced mice liver injury model with N1inh and observed several serological and histological parameters related with liver regeneration.
Results: N1inh successfully gained both body and liver weight with recovery of liver function in both DDC and CCL4 models. Treatment with N1inh increased the number of A6-positive CK19-negative newly differentiated HC from HPC. Also, Ki-67 positive hepatocytes in the liver were significantly increased in N1inh-treated group which may reflect the increase of newly differentiated HC from HPC. We also found that N1inh-treated diseased livers exerted significantly less liver fibrosis development than compared with the livers without N1inh in both models. Our in vitro experiments revealed that N1inh did not affect proliferation of activated HSC-LX2, however, N1inh altered tubular formation of human umbilical vascular endothelial cells, suggesting that anti-angiogenic effect of N1inh may ameliorated liver fibrosis development.
Conclusion: Our experiments suggested that NOTCH1 selective inhibition in the liver could successfully augment not only differentiation of HPC towards HC but also amelioration of liver fibrosis development. Since both compensation of the loss of HC and hepatic fibrolysis are prerequisite for the effective liver regeneration, these dual functions of NOTCH1 inhibition could be a new possible therapeutic option for liver regeneration.

FRI-087

ACC inhibitor demonstrates potent anti-fibrotic activity in vitro and in vivo

J. Bates[1], S. Ghoshal[2], L. Wei[2], D. Hollenback[1], K. Liu[1], S. Kusam[1], M. Sulfab[1], H. Liu[1], R. Brockett[1], D. Newstrom[1], I. Mikaelian[1], T. Wang[1], G. Harriman[3], W.F. Westlin[3], J. Rocnik[3], H.J. Harwood[3], R. Kapeller[3], A. Ray[4], D. Breckenridge[4], B.C. Fuchs[2]. *[1]Gilead Sciences, Inc., Research, Foster City, CA, United States; [2]Massachusetts General Hospital, Division of Surgical Oncology, Boston, MA, United States; [3]Nimbus Therapeutics, Cambridge, MA, United States; [4]Gilead Sciences, Inc., Foster City, CA, United States*
Email: jamie.bates@gilead.com

Background and Aims: GS-0976, a liver-directed acetyl-CoA carboxylase (ACC) inhibitor is currently being investigated in clinical trials for NASH. ACC1 and 2 catalyze the rate-limiting step of *de novo* lipogenesis (DNL) and inhibit mitochondrial fatty acid oxidation (FAO), respectively, promoting lipotoxicity in NASH. We evaluated the direct antifibrotic efficacy of ACC inhibition in rat models of liver fibrosis and in isolated hepatic stellate cells (HSCs).
Method: Rats were fed a choline deficient high fat diet (CDHFD) for 12 weeks and administered vehicle, or 10 mg/kg ACCi (GS-834356, an analog of GS-0976) from weeks 6–12. Rats were injected weekly with DEN 50 mg/kg IP for 18 weeks and from weeks 13–18 were administered vehicle or 10 mg/kg ACCi, or in a separate study vehicle or 30 mg/kg ACCi. Hepatic fibrosis was assessed by quantitative morphometry of liver sections stained with picrosirius red (PSR) or α-SMA immunohistochemistry or by determination of hepatic hydroxyproline content. Primary human HSCs were treated for 48 hours with TGFβ (2ngmL) +/– GS-0976, after which HSC activation was assessed by collagen and α-SMA expression. DNL in HSCs was quantified by measuring the incorporation of ^{14}C-acetate into fatty acids.
Results: CDHFD significantly increased hepatic PSR and α-SMA at 6 weeks (3% and 1% area, respectively) and at 12 weeks (8% and 6% area, respectively) compared to normal diet ($p < 0.05$). ACCi treatment inhibited fibrosis progression as measured by PSR and α-SMA area by 62% and 44%, respectively ($p < 0.01$). DEN significantly increased hepatic PSR from 13 weeks (4% area) to 18 weeks (7% - 11%). 10 mg/kg and 30 mg/kg ACCi reduced the progression of fibrosis as assessed by PSR area (61% and 86% inhibition, respectively, $p < 0.05$) and liver hydroxyproline content (70% and 100% reduction, respectively, $p < 0.05$). In isolated stellate cells, TGFβ stimulated DNL and HSC activation. GS-0976 dose-dependently inhibited DNL, induction of HSC activation markers, and increased PPARγ expression.

Conclusion: ACC inhibition suppressed the activation of HSCs in vitro and reduced liver fibrosis in two rodent models, one of which was driven by a non-metabolic insult. These data demonstrate that, in addition to decreasing lipotoxicity in hepatocytes, ACC inhibition directly inhibits fibrogenesis in HSCs. The data support clinical evaluation of GS-0976 in patients with NASH and advanced fibrosis.

FRI-088

During the progression of liver fibrosis, myofibroblasts develop endoplasmic reticulum stress that both decreases their proliferation and increases their pro-angiogenic activity

E. Loeuillard[1], H.E. Mourabit[1], L. Lei[1], S. Lemoinne[1,2], C. Housset[1,2], A. Cadoret[1]. *[1]Inserm UMR_S 938, Centre de Recherche Saint-Antoine, UPMC Univ Paris 06, Paris, France; [2]Assistance Publique-Hopitaux de Paris, Hopital Saint-Antoine, Centre de Référence Maladies Rares des Maladies Inflammatoires des Voies Biliaires, Service d'Hépatologie, Paris, France*
Email: axelle.cadoret@inserm.fr

Background and Aims: Portal myofibroblasts (PMFs) are a sub-population of liver myofibroblasts. Compared with hepatic stellate cell-derived myofibroblasts, they derive from a smaller cell niche and proliferate much more. PMFs sub-population is predominant at early stages of biliary-type liver fibrosis and trigger angiogenesis during the progression of all types of fibrosis. Mechanisms regulating PMFs expansion and functions are poorly known. Endoplasmic reticulum (ER) stress was previously shown to regulate liver fibrosis. The aims of this study were to determine if ER stress occurs in PMFs and affects their functions.
Method: PMF were expanded in culture after isolation from control or 14-day bile duct-ligated (BDL) rats. PMFs from BDL rats were used as a model of *in vivo*-activated PMFs. *In vitro*, ER stress was induced or inhibited using tunicamycin and the PERK inhibitor GSK2656157, respectively. The degree of ER stress was determined using the markers CHOP, TRB3, GADD34.
Results: *In vivo*-activated PMFs obtained from BDL rats, displayed reduced proliferative and migratory capacities, together with increased pro-angiogenic properties, compared to control PMFs obtained from sham-operated rats. In BDL rats, CHOP expression was detected in peri-portal fibrotic areas of the liver. *In vivo*-activated PMFs showed ER dilatation and increased expression of ER stress markers of the PERK pathway. *In vitro*, tunicamycin-induced ER stress had no effect on the expression of myofibroblastic markers (alpha-SMA and collagen-1) in PMFs, but caused a significant reduction of proliferation and migration in these cells, as well as an increase in VEGF production by these cells and in their angiogenic properties, as assessed in matrigel plugs *in vivo*. GSK2656157 treatment of *in vivo*-activated PMFs reduced ER stress, which caused a decrease in VEGF expression and in their angiogenic properties. GSK2656157 treatment also partially restored the proliferative and migratory capacities of these cells.
Conclusion: ER stress occurs in PMFs during the progression of liver fibrosis and may contribute to this progression by stimulating their proangiogenic properties. However, ER stress also inhibits proliferation and migration of PMFs, and thereby may provide an incoherent feedback loop that restricts their expansion.

FRI-089

The antiretroviral rilpivirine induces hepatic regeneration in liver fibrosis and cirrhosis by modulating the STAT3/STAT1 balance

A. Martí-Rodrigo[1], Ángela B. Moragrega[1], P. Martí-Rodrigo[1], D. Castelli[1], N. Apostolova[1,2], Juan V. Esplugues[1,2,3], A. Blas-García[1,2]. *[1]Universitat de València, Pharmacology Department, Valencia, Spain; [2]CIBERehd, Valencia, Spain; [3]FISABIO-Hospital Universitario Dr. Peset, Valencia*
Email: alberto.marti-rodrigo@uv.es

Background and Aims: Liver fibrosis constitutes a serious health problem with no current cure and whose prevalence is rising worldwide. We have previously reported that chronic treatment with the antiretroviral rilpivirine (RPV), widely used in anti-HIV therapy, induces anti-steatotic, anti-inflammatory and anti-fibrotic effects in a nutritional mouse model of non-alcoholic fatty liver disease, though the underlying mechanisms are unknown.
Activation of STAT3 and STAT1 transcription factors in the liver induces different cellular responses depending on the cell population affected. Generally, parenchymal activation of STAT3 induces anti-fibrotic, anti-inflammatory and regenerative pathways, while its activation in hepatic stellate cells (HSCs) induces inflammation and fibrogenesis. Conversely, STAT1 in HSCs induces their inactivation and is pro-fibrogenic in hepatocytes.
We aimed to characterize the effect of RPV on the progression/regression of liver fibrosis, focusing on the regulation of STAT3- and STAT1-mediated signalling pathways
Method: Two different models of CCl_4-induced liver fibrosis were established in C57BL/6-WT mice to determine the effects of chronic RPV administration on the progression (4 weeks of CCl_4 and RPV) and regression (6 weeks of CCl_4 and the last two weeks of RPV) of liver fibrosis. Serum and enzyme activity determinations, histological studies and molecular biology techniques were carried out to assess liver inflammation, fibrosis and alterations of the STAT3/STAT1 ratio
Results: Liver fibrosis was clearly induced in both models. All the parameters of liver injury (AST, ALT and bilirubin), inflammation (macrophage infiltration, NFkB activation and MPO activity) and fibrosis progression (collagen deposition and vimentin expression) we evaluated were attenuated in RPV-treated mice with respect to controls. In addition, RPV modulated the STAT3/STAT1 balance in the liver and induced a clear inactivation of HSCs.
Conclusion: Beyond its well-known antiviral effect, RPV exerts a strong protective role in all our chronic liver injury models (NAFLD, fibrosis and cirrhosis). Although further studies are needed to clarify the mechanism involved in this off-target effect of RPV, our results are clinically relevant in that they highlight the therapeutic potential of RPV in the management of chronic liver diseases, particularly since this drug is known not to have a toxic profile.

FRI-090

Performance of quantitative collagen parameters for assessing longitudinal non-advanced liver fibrosis

Y. Wang[1], X. Liang[1], J. Sun[1], J. Yang[2], Y. Zheng[1], Y. Chen[1], J. Hou[1]. *[1]Southern Medical University Nanfang Hospital, Department of Infectious Diseases and Hepatology Unit, GZ, China; [2]Southern Medical University, School of Pharmaceutical Science, GZ, China*
Email: yanwang@i.smu.edu.cn

Background and Aims: Non-advanced fibrosis is a common scenario in therapeutic trials of chronic liver disease. However, current tools generally lack sufficient performance in detecting the longitudinal change. We aimed to evaluate whether using quantitative fibrous collagen parameters (q-FP) can be as accurate as but more sensitive than the standard histology for addressing this issue.
Method: A well-established CHB cohort (NCT00962533) with mostly the non-advanced fibrosis were used for this study. 301 subjects with paired liver biopsies were consecutively included. Of them, 139 subjects were used to establish the test and the rests for internal validation. Fibrosis change between baseline and 104 weeks of treatment was blindly assessed with Ishak fibrosis staging and q-FP.
Results: 70% subjects were Ishak F0-2 at baseline. Imaging data were collected yielding a dataset of 69 q-FPs per biopsy specimen, which then composed a single score, q-FS representing the overall fibrosis status. Using q-FP profile, variations of fibrosis response in different clinical settings could be extensively visualized (Figure). For diagnosing overall fibrosis endpoint, 67% (93/139) patients got decrease in their Ishak stages ($p < 0.0001$), and the decrease extent showed a significant association with baseline Ishak stage (OR 6.7, 95%CI 4.4–10.5, $p < 0.0001$); on q-FP analysis, 68% (94/139) patients achieved decrease in their q-FS ($p < 0.0001$), of which the extent also

demonstrated a significant association with baseline q-FS (Spearman ρ -0.7, 95%CI -0.7–-0.6, p < 0.0001). However, while q-FP identified the independent association between fibrosis regression and anti-viral efficacy (OR 3.0, 95%CI 1.4–6.5, p = 0.005), Ishak failed the detection (OR 0.6, 95%CI 0.3–1.3, p = 0.24). Moreover, on analysis of statistical consistency, there showed no difference between their diagnoses of fibrosis endpoint (difference 0.7%, 95%CI -9.2–10.6, p = 1.00). The indices of positive (p_{pos}) and negative (p_{neg}) agreement were 0.8 (95%CI 0.7–0.8) and 0.5 (95%CI 0.4–0.7), respectively, for which, the disagreement was identified more likely occurring to the baseline Ishak staging (p = 0.003), mainly involving some pairs with baseline moderate fibrosis, but had not relation to Ishak staging at week 104 (p = 0.55). In contrast, the disagreement had no significant relation to q-FP assessment, either at baseline (p = 0.18) or at week 104 (p = 0.78). Moreover, neither did the disagreement correlate to the biopsy size at baseline (p = 0.22) or at week 104 (p = 0.37). Eventually, these findings were verified by reviewing through the paired Ishak staging and q-FP score for every subject. The above results were confirmed in the validation subjects.

Conclusion: Compared with standard histology, q-FP could have an equivalent accuracy as well as a higher sensitivity in monitoring the longitudinal non-advanced fibrosis.

FRI-091

RNA-sequencing analysis of biopsies from chronic liver disease patients identifies gene signatures associated with progressive liver disease

D. Ramnath[1,2], K. Irvine[3,4], S. Lukowski[1,2], L. Horsfall[3,5], K. Loh[1,2], A. Clouston[3], P. Patel[3,5], A. Iyer[1,2], G. Lampe[6], J. Stow[1,2], K. Schroder[1,2], D. Fairlie[1,2], J. Powell[1,2], E. Powell[3,5], M. Sweet[1,2]. *[1]Institute for Molecular Bioscience, The University of Queensland, Brisbane; [2]IMB Centre for Inflammation and Disease Research, The University of Queensland, Brisbane, Australia; [3]Centre for Liver Disease Research, The University of Queensland, Brisbane, Australia; [4]Mater Research UQ, Translational Research Institute, Brisbane, Australia; [5]Department of Gastroenterology and Hepatology, Princess Alexandra Hospital, Brisbane, Australia; [6]Pathology Queensland, Princess Alexandra Hospital, Brisbane, Australia*
Email: d.ramnath@imb.uq.edu.au

Background and Aims: Liver fibrosis, resulting from injury- and inflammation-driven production and accumulation of extracellular matrix proteins, is characteristic of most type of chronic liver diseases (CLD). Although our understanding of the cellular and molecular mechanisms of liver fibrosis has greatly advanced, current methods

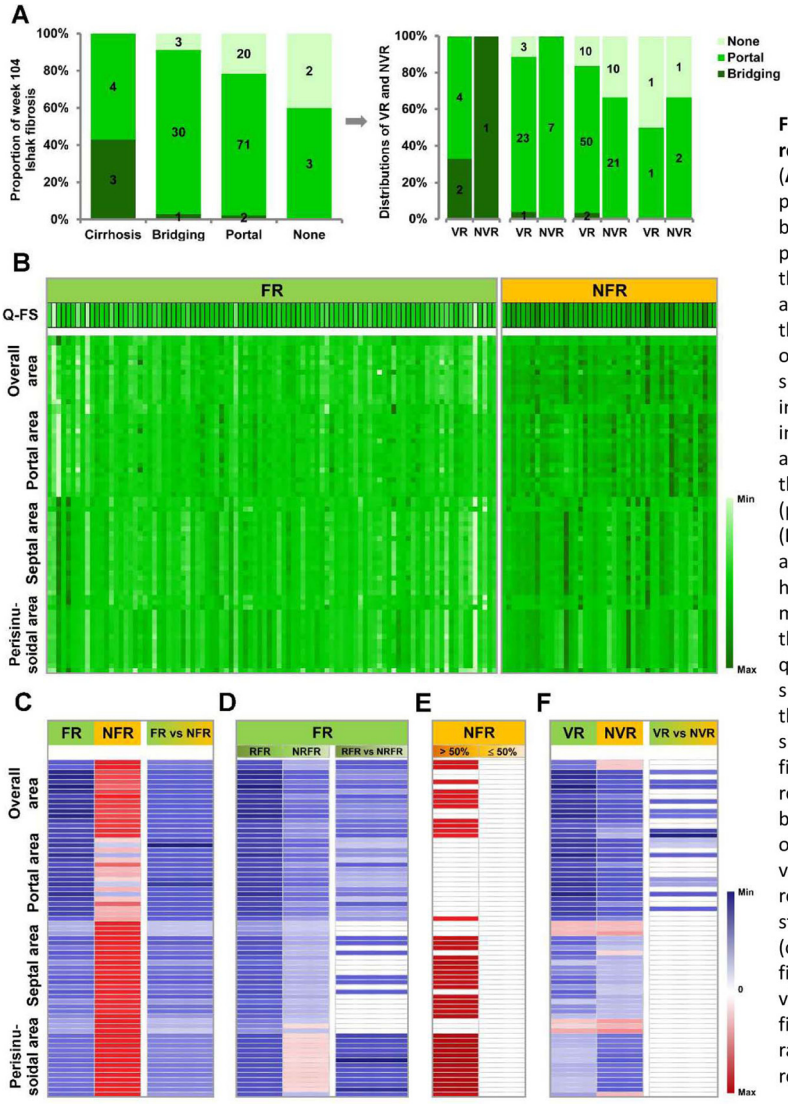


Figure. Ishak staging versus q-FP profiling of the fibrosis response in test subjects.
(**A**) Ishak staging data show the proportions of different patterns in the week 104 liver biopsies grouped by their baseline patterns. Numerals on each bar represent patients' number. Q-FP heat-map shows the data: (**B**) For the 139 individuals, the exact extent of fibrosis change across sublobule regions can be visualized precisely; of these, the FR subjects appeared more reduction in overall fibrosis than NFR subjects. (**C**) For the FR vs NFR subjects, all q-FPs of FR subjects had significant decrease in their values (p<0.05), and the most decrease localized in the portal area. (**D**) For the RFR vs NRFR subsets among FR subjects, the subset of RFR had their q-FPs in the portal and sinusoidal regions decreased more (p<0.05), and sinusoidal region had the most decrease. (**E**) For the subsets of >50% vs ≤50% increase in q-FS among the NFR subjects, 57% q-FPs of the '>50%' subset had a significant 3.1 ± 0.5-fold increase (p<0.05), which mostly localized in the septal and sinusoidal regions. For the '≤50%' subset, no region had significantly increased q-FPs. And (**F**) for the subjects achieving VR or NVR, VR subjects showed more reduction in overall fibrosis, and the significance was in the portal region (p<0.05); NVR subjects appeared more reduction in the sinusoidal fibrosis, but it was not significant. In the matrix, each cell represents the level of a Δq-FS or Δq-FP in an individual biopsy (panel B), or represents the mean level of a Δq-FP of the subgroups (panels C-F). Dark vs light green, or red vs blue in cells reflects high to low expression levels, respectively. Blank cell in panels C-F represents no statistical significance. Δq-FP (or Δ q-FS) = week 104 q-FP (or q-FS) – baseline q-FP (or q-FS). Q-FP, quantitative fibrosis parameter; Q-FS, quantitative fibrosis score; VR, virological remission; NVR, non-virological remission; FR, fibrosis regression; NFR, non-fibrosis regression; RFR, rapid fibrosis regression; NRFR, non-rapid fibrosis regression.

Figure 1: (abstract: FRI-090)

for diagnosing and treating liver fibrosis are limited. Existing non-invasive methods of liver fibrosis diagnosis involve transient elastography and certain serologic tests such as the enhanced liver fibrosis (ELF) score; however, these methods are not able to reliably detect fibrosis stage. Liver biopsy still remains the only effective way to accurately determine the stage of fibrosis, but it is an invasive procedure, which can be accompanied by complications such as internal bleeding. In this study, we aimed to identify the core gene signature associated with liver fibrosis to identify novel biomarkers and/or therapeutic targets for liver disease.

Method: In this study, we performed RNA-sequencing using liver tissue RNA from 69 chronic liver disease patients at different stages of fibrosis and with different aetiologies to identify gene signatures associated with advanced liver disease.

Results: RNA-sequencing analysis identified 171 genes that were differentially expressed between early versus advanced stages of fibrosis, 60 of which encoded extracellular proteins. By gene correlation analysis with matched patient ELF score data, we identified 52 genes that strongly correlate with advanced fibrosis. One such gene represents a candidate master transcriptional regulator of the pro-fibrogenic gene signature associated with liver fibrosis. By comparing gene profiles of HCV or HCV with steatohepatitis patient biopsies, we also identified a steatohepatitis-enriched set of genes associated with progressive fibrosis.

Conclusion: In summary, our approach of using samples from patients with different CLD aetiologies has enabled us to deconvolute the inherit heterogeneity that exists within clinical samples, and has led to the identification of a core set of liver fibrosis-associated genes. Several of these encode immune-related proteins that may represent tractable targets and/or biomarkers for chronic liver disease.

FRI-092

Interference of PTTG1 mRNA dramatically reduces portal hypertension and liver fibrosis in fibrotic rats

S.C. Restoy[1], V. Reichenbach[1], D. Oró[1], S. Marfa[1], G. Fernández Varo[1,2], S. Lamas[3], W. Jiménez[1,2]. *[1]Biochemistry and Molecular Genetic Service, Hospital Clínic de Barcelona, Institut d'Investigacions Biomèdiques August Pí i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Spain; [2]Department of Biomedicine, University of Barcelona, Barcelona, Spain; [3]Laboratorio Mixto Consejo Superior de Investigaciones Científicas (CSIC)-Fundación Renal Iñigo Álvarez de Toledo, Centro de Biología Molecular Severo Ochoa, Madrid, Spain.*
Email: scarvajal@clinic.ub.es

Background and Aims: Pituitary tumor transforming gene (PTTG1) encodes a protein with roles in gene regulation and migration. It is highly expressed in hepatocellular carcinoma promoting tumor progression and metastasis, however little is known about its role in pre-neoplastic stages. Recent studies suggest that PTTG1 could be implicated in liver fibrosis development. The aim of this study was to assess whether PTTG1 inhibition reduces the fibroproliferative process and ameliorates hemodynamics in a rat model of liver fibrosis by CCl_4 inhalation.

Method: 12 Wistar rats were induced to liver fibrosis by CCl_4 inhalation for 14 weeks and randomly treated with siRNA against PTTG1 or scramble siRNA (0.25 mg/kg) intravenously from the 9th to the 13th week. 6 healthy rats were used as control. Mean arterial pressure (MAP) and portal pressure (PP) were measured at the end of the study and serum and liver samples were collected. Liver fibrosis content was quantified by Sirius Red and biochemical parameters of liver damage were assessed in serum. Hepatic expression of PTTG1 and other fibrosis-related genes were analyzed by Real Time PCR.

Results: PTTG1 expression was markedly increased in the liver of fibrotic rats treated with scramble siRNA, while its expression in rats treated with siRNA against PTTG1 was similar to that observed in healthy rats, demonstrating the effectiveness of the treatment. PTTG1 inhibition dramatically reduced the liver fibrosis formation compared to fibrotic rats treated with siRNA (4.3 vs 10.0%). This was associated with a significant improvement in the hemodynamic function, reflected by a marked reduction in the PP in the rats subjected to PTTG1 inhibition (7.3 vs 10.4 mmHg). PTTG1 inhibition also reduced the hepatic expression of key genes related to liver fibrosis, such as MMP2 and PDGFRβ1. Interestingly, a close relationship was found between the hepatic expression of PTTG1 and DLK1 (r = 0.96), a key protein in the fibrogenic process through promoting HSC activation,

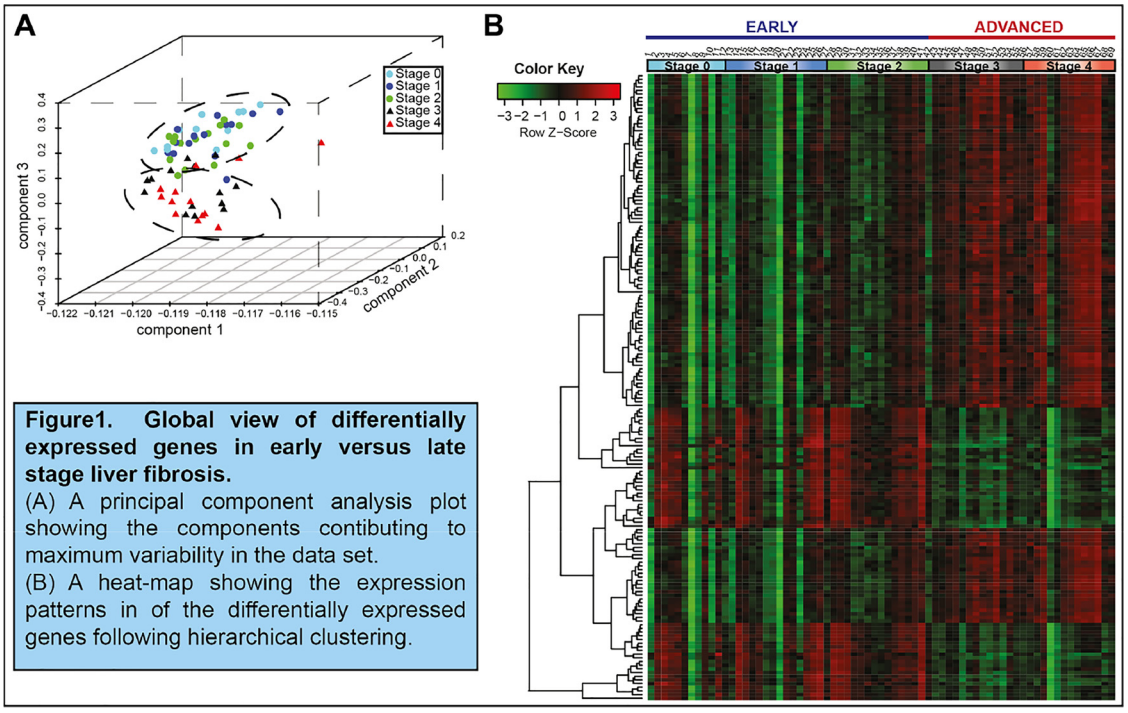


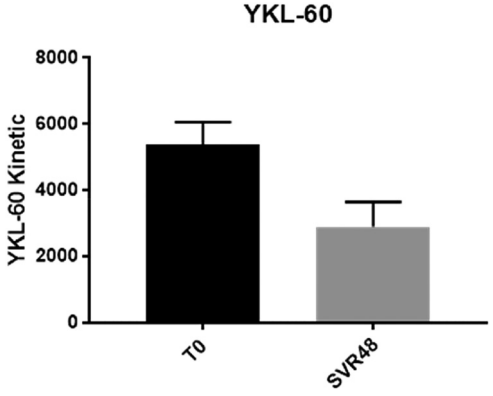
Figure1. Global view of differentially expressed genes in early versus late stage liver fibrosis.
(A) A principal component analysis plot showing the components contibuting to maximum variability in the data set.
(B) A heat-map showing the expression patterns in of the differentially expressed genes following hierarchical clustering.

Figure 1: (abstract: FRI-091)

and whose expression is tightly related to PTTG1. Hepatic expression of PTTG1 was also related with αSMA, Col1α2, Col3α1, TIMP1, TIMP2, and with GGT, AST and T-Bil serum levels.
Conclusion: These results demonstrate that PTTG1 play a critical role in the hepatic fibroproliferative process in an animal model of chronic liver injury, revealing this protein as a new target for the prevention and treatment of liver fibrosis.
Acknowledgements: Supported by grants from MINECO (SAF15-64126-R) and (BES2013-063685).

FRI-093
Direct fibrosis markers kinetic in patients undergoing antiviral treatment with DAA for chronic hepatitis C
C. Mazzarelli[1,2], M. Bruce[1], S. Imbert[1], M.D. Cannon[1], G. Dusheiko[1], K. Agarwal[1], I. Carey[1]. *[1]King's college Hospital, Institute of liver studies, London, United Kingdom; [2]ASST Ospedale Niguarda, Hepatology and Gastroenterology, Milan, Italy*
Email: chiaramazzarelli@hotmail.com

Background and Aims: Registration trials and real-life cohorts have demonstrated that a significant percentage of patients with decompensated liver disease may potentially experience clinical improvements following HCV eradication. Liver fibrosis is characterized by excess collagen deposition, decreased extracellular matrix degradation and activation of hepatic stellate cells. Different markers seem to be involved in liver fibrosis. Transforming growth factor beta (TGF-β), Hyaluronic acid (HA) and Osteopontin (OPN) are well-recognized as promoter of hepatic fibrogenesis. IL-6 is an inducer of the acute phase response as well it has been demonstrated to be involved in liver regeneration. YKL-40 is involved in matrix remodeling. We aimed to evaluate the kinetics of direct fibrosis biomarkers in HCV patients in relation to DAA antiviral treatment.
Method: 75 cirrhotic patients, treated with SOF + NS5A inhibitors (daclatasvir or ledipasvir) at King's College Hospital from 2015–17, were identified and divided into 3 different cohorts: 40 patients with a Child A cirrhosis, 18 patients with Child A cirrhosis but with a previous decompensating event and 17 patients with decompensated liver disease. Plasma levels of TGF-β, IL-6, HA and OPN were measured by ELISA at three different time-points: treatment baseline (T0), End of treatment (EOT) and 48 weeks after the EOT (SVR48). YKL-60 was evaluated at T0 and SVR48.



Results: Patients demographics and clinical characteristics of our cohorts were illustrated in table 1. Decompensated patients were younger (p = 0.01), had lower pre-treatment HCV-RNA (p = 0.08), more adverse events post-therapy (p < 0.01), higher incidence of HCC during or after treatment (p = 0.03), and a lower PLTs count (p < 0.01 compared to other groups). IL6, YKL-60 and TGF beta levels were similar between 3 groups at all time-points. Levels of HA differ between 3 groups and all time-point (p = 0.01, p=<0.01, p = 0.01), while OPN levels were similar at T0 and SVR48, but varied among 3 groups at SVR48. When compared for all patients between time-points IL-6 levels were similar at all time-points, for TGF-β and OPN levels were comparable between TO and EOT, however we observed a significant increase in TGF-β (p < 0.01) and OPN between T0 and SVR48 (p < 0.01) as well as EOT and SVR48 (p < 0.01 & p < 0.01). HA levels declined significantly between T0, EOT and SVR48 (p = 0.02, p = 0.09, p = 0.05), in contrast to a significant increase in YKL-60 levels between T0 and SVR 48 (p < 0.01).
Conclusion: HA is confirmed in our cohort as a strong marker of liver fibrosis stages. DAA treatment impacts fibrosis markers kinetics. Significant changes in HA can be observed quickly after the start of DAA treatment, while modification in TGF-β and OPN are slower and can be observed later after ending of treatment. Finally, YKL-60 decreased significantly along our cohort as expression of matrix remodeling.

FRI-094
SWAVE: Steady State Shear Wave Elastography for Fibrosis Evaluation in Liver Disease
C. Schneider[1], J. Lobo[1], M. Honarvar[1], E. Tam[2], R. Rohling[1], T. Salcudean[1]. *[1]University of British Columbia, Electrical and Computer Engineering, Vancouver, Canada; [2]LAIR Centre, Vancouver, Canada*
Email: caitlin.m.schneider@gmail.com

Background and Aims: Non-invasive liver elasticity measurements have previously been shown to be correlated with histologic liver fibrosis stage on biopsy. Measurement of the propagation speed of shear waves within the liver is directly related to the accumulation of fibrosis within the liver. Herein we present initial results of a new technology developed to non-invasively measure deep volumetric liver elasticity using steady state shear waves, known as shear wave absolute viboelastography, or SWAVE. This technology enables measurements of liver elasticity to a depth equal to the B-mode image, or in excess of 15 cm.
Method: The system consists of an ultrasound machine, a vibration device to excite shear waves in the patient and a 3D ultrasound transducer (m4DC7-3). The vibration device induces shear waves in the liver at four different frequencies between 40Hz and 70Hz simultaneously. The ultrasound volume is acquired through the ribs at the same location as a typical transient elastography (TE) measurement. Volumes are collected in a fan of approximately 15 degrees and taken at a depth of 15cm.
SWAVE (Sonic Incytes), TE (FibroScan®), and magnetic resonance elastography (MRE) were performed on a cohort of healthy volunteers. A second cohort of patients with chronic liver disease (Hepatitis C (HCV), Hepatitis B (HBV), or Non-alcoholic steatohepatitis (NASH)) were evaluated with SWAVE and TE.
Results: 12 healthy volunteers (mean age 37 years [range 25 to 49], 25% female) and 8 patients (mean age 56 years [range 34 to 65], 37% female, diagnosis of HCV (n = 3), HBV (n = 2) and NASH (n = 3)) were included in the study. Of the volunteers the mean elasticity and standard deviation measured with SWAVE was 3.9 ± 0.4 kPa, with TE was 4.5 ± 0.7 kPa and with MRE was 4.9 ± 0.3 kPa. Figure 1a compares the SWAVE, TE and MRE results. For the cohort of patients, the mean elasticity was 5.4 ± 0.7 kPa with SWAVE and 8.4 ± 1.5 kPa with TE, with staging ranging from F0-F3. Since each elastography measurement algorithm is unique, the correlation between the SWAVE and TE for all subjects is shown in Figure 1b. This correlation yields an R^2 value of 0.64.
Conclusion: These initial results demonstrate promise for SWAVE as a new technique for non-invasive fibrosis assessment in chronic liver disease. SWAVE is volumetric, works at depth, uses the same principle as MRE, and is suitable for point-of-care diagnosis and regular patient monitoring during and after treatment.

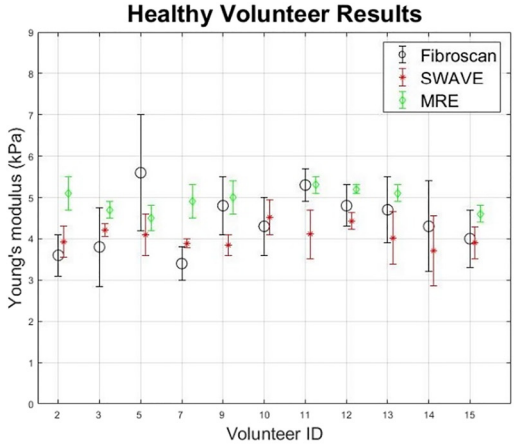


Figure 1a

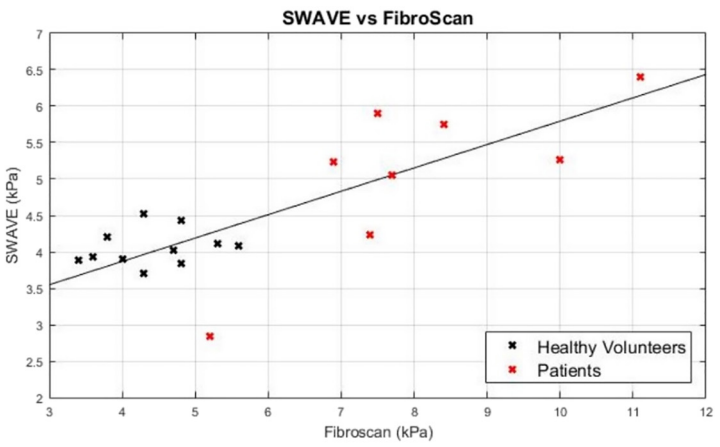


Figure 1b

Figure 1: (abstract: FRI-094)

FRI-095

A PEGylated fibroblast growth factor 21 variant improves hepatic steatosis in a mouse model of non-alcoholic steatohepatitis, as determined by magnetic resonance imaging-derived hepatic fat-fraction

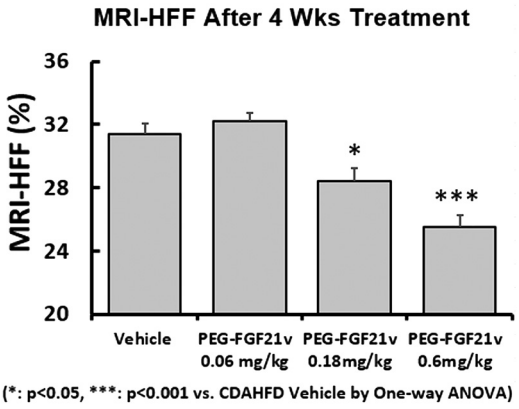
H. Tang, M. Fronheiser, S. Boehm, A. Pena, A. Shorts, B. Zinker, J. Krupinski, H. Malone, P. Chow, E. Charles, S. Du, W. Hayes. *Bristol-Myers Squibb, Lawrenceville, United States*
Email: haiying.tang@bms.com

Background and Aims: Non-alcoholic steatohepatitis (NASH), characterised by steatosis with inflammation and liver cell injury, can progress to fibrosis. Fibroblast growth factor 21 (FGF21) regulates energy and lipid metabolism; analogues have been shown to improve steatosis, biomarkers of liver injury and fibrosis, lipid profiles, and insulin sensitivity in clinical studies. This study evaluated the effects of a PEGylated-FGF21 variant (PEG-FGF21v) in a mouse model of NASH using magnetic resonance imaging-derived hepatic fat-fraction (MRI-HFF), a non-invasive imaging technique to assess hepatic steatosis.

Method: C57BL/6J mice were fed a control (10% kcal fat; n = 12) or a choline-deficient amino acid-defined, high-fat diet (CDAHFD; 60% kcal fat, 0.1% methionine; n = 48) for up to 8 wks, with baseline (BL) MRI performed at 4 wks on diet. Mice (12/arm) received twice-weekly subcutaneous PEG-FGF21v (0.06, 0.18, or 0.6 mg/kg) or vehicle after BL MRI, and were imaged again after 4 wks on treatment (tx), followed by sacrifice and liver collection for biochemical assessment of triglycerides (TG) and histological assessment of steatosis. MRI was performed on a Bruker Biospec 7T 20 cm system with an 86 mm volume coil and a phase array receive coil. MRI-HFF derived from the DIXON water-fat MRI technique was used to quantitate steatosis. Repeated measures ANOVA was used to test tx effects.

Results: Mice on CDAHFD developed liver steatosis with a mean MRI-HFF of 35.7%, 36.8%, 35.0%, and 36.4% in vehicle and PEG-FGF21v 0.06, 0.18, or 0.6 mg/kg tx groups, respectively, vs 10% ($p < .001$) in control mice at BL. Tx of CDAHFD mice with vehicle or PEG-FGF21v 0.06, 0.18, or 0.6 mg/kg for 4 wks resulted in absolute MRI-HFF reductions of 4.4%, 4.5%, 6.6% and 10.8% from BL, respectively, with significant improvements in hepatic steatosis with PEG-FGF21v 0.18 and 0.6 mg/kg vs vehicle tx (figure). MRI-HFF correlated with histology-determined steatosis (r = 0.93) and biochemical TG content (r = 0.93).

Conclusion: MRI-HFF accurately quantified hepatic steatosis in a mouse model of NASH, with strong correlation with histological and biochemical assessments of steatosis and hepatic TG, respectively. PEG-FGF21v significantly reduced MRI-HFF–assessed hepatic steatosis in a dose-dependent manner. These results support the use of MRI-HFF as an endpoint to evaluate efficacy in preclinical and clinical NASH studies, as well as further preclinical and clinical studies of FGF21 analogues for NASH.



FRI-096

AGAP2, a new player in TGF-beta signalling

A. Navarro-Corcuera[1,2], E. Ansorena[2], M.I. Elizalde[2], C. Montiel-Duarte[3]. [1]*Nottingham Trent University, School of Science and Technology, Nottingham, United Kingdom;* [2]*Universidad de Navarra, Biochemistry and Genetics, Pamplona, Spain;* [3]*Nottingham Trent University, School of Science and Technology, Nottingham, United Kingdom*
Email: amaia.navarrocorcuera2015@my.ntu.ac.uk

Background and Aims: Transforming growth factor β (TGFβ) is the main pro-fibrogenic cytokine involved in hepatic stellate cells (HSC) regulation, promoting its proliferation and migration, and increasing the production of extracellular matrix proteins. TGFβ-receptor (TGFβR) I and II can be internalised into the cells via clathrin-coated vesicles triggering Smad activation. AGAP2 (ArfGAP with GTPase domain, ankyrin repeat and PH domain 2) is a new proto-oncogene involved in tumorigenesis, promoting cellular proliferation and invasion through Akt activation. AGAP2 seems to be part of the actin remodelling system, and promotes the endosomal recycling of β_2-adrenergic receptors. Our aim was to investigate the role of AGAP2 in hepatic fibrosis in response to TGFβ. We analysed the gene expression profile of TGFβ-mediated fibrotic genes in the presence/absence of AGAP2. We also studied the implication of AGAP2 in HSC viability, proliferation, migration and TGFβR trafficking in response to TGFβ.

Method: LX-2 cells were transfected with scramble siRNA or with AGAP2 siRNA and stimulated with TGFβ to determine the genes induced by TGFβ through AGAP2: a RT^2 Profiler PCR Array of human fibrosis was performed. The role of AGAP2 in HSC viability was evaluated by RTCA iCELLigence™ instrument. The effects of AGAP2 in LX-2 proliferation and migration were analysed using IncuCyte® S3 Live-Cell Analysis System. Protein expression of AGAP2, Collagen-I, and phosphorylated Focal adhesion kinase (p-FAK) was analysed by Western-Blot. U-2 OS cell line was employed to perform live tracking of TGFβR trafficking with CLIP- and SNAP-tag technology.
Results: Within the array, 45% of genes showed ≥2-fold differential expression in scrambled LX-2 treated with TGFβ *versus* LX-2 without TGFβ. AGAP2 silencing prevented some gene expression changes induced by TGFβ. The genes MMP1, MMP9, IL1A, ILB and SERPINA1 were up-regulated in AGAP2 knocked-down cells treated with TGFβ, whereas ACTA2, COL1A2, COL3A1, EDN1 and LOX were down-regulated (Fig.1). The viability and proliferation were lower in AGAP2 knocked-down LX-2 treated with TGFβ. The wound-healing assay showed a significant difference in the reduction in wound size in scrambled cells treated with TGFβ. TGFβ treatment increased AGAP2, p-FAK and collagen-I protein levels in a time-dependent manner. TGFβ-mediated increase in p-FAK protein levels required the presence of AGAP2. p-FAK protein was also required to increase collagen-I protein expression and the absence of AGAP2 interfered with this process.

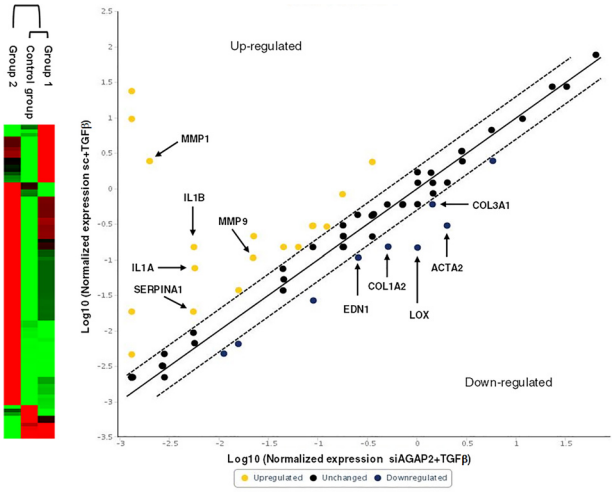


Figure 1 Potential targets of AGAP2 in response to TGFβ.

Conclusion: We show here for the first time that AGAP2 is a pro-fibrogenic gene involved in TGFβ-signalling. TGFβ increases collagen-I protein expression through p-FAK in an AGAP2-dependent manner. After TGFβ treatment, AGAP2 increases HSC viability, and promotes their proliferation and migration.

FRI-097

Role of the interleukin 15/macrophage axis in the immune response of liver fibrosis

M. Myllys[1], U. Albrecht[2], S. Dooley[3], S. Hammad[3], T. Weiß[4], H. Jan G.[1], P. Godoy[1]. *[1]IfADo - Leibniz Research Centre for Working Environment and Human Factors at the Technical University Dortmund, Systems toxicology, Dormund, Germany; [2]Universitätsklinikum Düsseldorf, Klinik für Gastroenterologie, Hepatologie und Infektiologie, Düsseldorf, Germany; [3]Medical Faculty Mannheim, Heidelberg University, Molecular Alcohol Research in Gastroenterology, Mannheim, Germany; [4]University Hospital Regensburg, Department of Pediatrics and Juvenile Medicine, Regensburg, Germany*
Email: myllys@ifado.de

Background and Aims: Interleukin-15 (IL-15) plays important roles in both innate and acquired immune responses by promoting the development and function of leukocytes. IL-15 and its cognate receptor IL-15Ralpha are expressed in multiple cell types including leukocytes, fibroblasts and epithelial cells. Previous studies using IL-15Ralpha-KO mice reported hepatoprotective effects of IL-15 in liver fibrosis and hepatitis. However, since this constitutive KO mouse line suffers from basal alterations in leukocyte physiology, more precise studies are required to understand the role of IL-15 in immune modulation on acute and chronic liver pathology.
Method:
Results: We observed increased IL-15 mRNA expression in diseased human liver tissue, and its expression levels correlated positively with disease severity. Also, serum levels of IL-15 were increased in patients with liver cirrhosis compared to healthy controls (p = 0.011). In line with this, we observed upregulation of IL-15 mRNA in mouse liver tissue after both acute and chronic liver damage by intraperitoneal CCl_4 administration. Furthermore, IL-15 induction was detected in hepatocytes but not in non-parenchymal liver cells after acute injury by CCl_4. A screening with multiple cytokines in vitro showed that TGF-beta can strongly induce IL-15 mRNA in primary mouse hepatocytes. The strong upregulation induced by this pro-fibrogenic cytokine suggested a potential pro-fibrotic role of IL-15. This hypothesis was supported by two experimental approaches. Firstly, stimulation of bone marrow-derived macrophages with IL-15 caused a strong induction of multiple pro-inflammatory cytokines including IL-28b, IL-13 and Gdf2. Secondly, liver fibrosis markers (sirius red and alpha-SMA expression) were reduced in IL-15 knockout in mice in comparison to wild type mice after chronic CCl_4 administration.
Conclusion: These results suggest that IL-15 may promote liver fibrosis by inducing pro-fibrotic cytokines in macrophages.

FRI-098

Establishment of an ex vivo model of human fibrotic liver slices culture: characterization of intrahepatic immune cells and TH17 cytokines

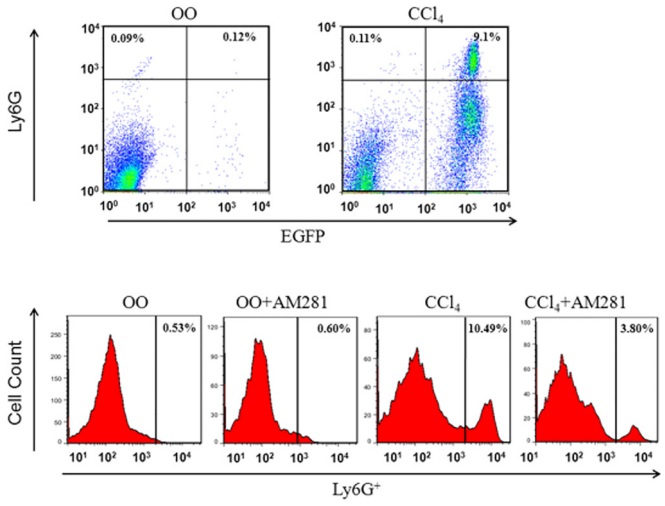
D. Kartasheva[1], J. Gaston[1,2], O. Scatton[3], J.-C. Vaillant[3], V.A. Morozov[4], P. Stanislas[1,2,5,6], S. Lagaye[1]. *[1]Institut Pasteur INSERM U1223, paris; [2]Université Paris-Descartes, Paris, France; [3]Hôpital Pitie-Salpétrière, Chirurgie Digestive, Hépatico Pancréatique et Transplantation Hépatique, Paris; [4]Robert Koch Institute, Berlin, Germany; [5]Hopital Cochin, service d'Hépatologie, Paris, France; [6]Institut Pasteur, Centre de Recherche Translationelle, Paris, France*
Email: sylvie.lagaye@inserm.fr

Background and Aims: To establish an ex vivo model of human fibrotic liver
Methods: Human fibrotic liver samples were collected after partial hepatectomy. Samples had from F2 to F4 fibrosis stage according to the METAVIR score. Liver slices (LS) obtained from human liver resection and cut in 350 µm-thick slices (2.7×10^6cells per slice), were cultivated for up to 21 days. Fibrotic liver slices (FLS) were infected or not with HCVcc supernatant infection [Con1/C3 (genotype1b)] (MOI = 0.1) (INF FLS). Human healthy liver slices (HLS) were used as controls. Ursodeoxycholic acid (UA) treatment (SOC) was tested on HLS and FLS cultures. The intrahepatic immune cells were extracted at day 0, 1. We evaluated the following fibrosis markers in HLS, in FLS and in INF FLS: expression of tumor growth factor β (TGFβ), Heat shock protein 47 (*Hsp47*), Alpha smooth muscle actin *(αSma), Procollagen1 A1 (Procl1A1), Matrix metalloproteinases 2, 9 (MMP-2, 9), Vascular Endothelial Growth Factor (VEGF),* which were checked by RT-qPCR and triglyceride production by ELISA assays. The immune cells were characterized by flow cytometry. IL-17A expression was determined by westernblot or ELISA assays.
Results: We succeeded to establish fibrotic livers slices culture up to day 21 with a viability rate of 55%. The TGFβ, Hsp47, αSma, Procl1A1, MMP-2, MMP-9, VEGF expression and a triglyceride production in HLS and FLS increased both but to a higher extent in FLS as compared

to HLS: a significant 6, 8, 5, 4, 5.2, 5, 5.2 fold increase, respectively as compared to controls with a triglyceride production higher in FLS [~ x 3.2]. HCV infection increased significantly, TGFβ, Hsp47, αSma, Procl1A1, MMP-2, MMP-9, VEGF expression and triglyceride production in NIFL and INF FLS to a higher extent in INF FLS as compared to controls. [at day 21, in INF FLS a significant 3, 3, 4, 2, 3, 2, 4, 2 fold increase as compared to NI FLS, respectively]. At day 0, 1, we could highlight the liver infiltration by the immune populations (LT CD4 +, CD8 +, NKT, MDSC). A higher IL-17A expression [~x4] was found in FLS compared to controls. FLS UA treatment gave a significant 2.5 fold decrease of TGF β expression.
Conclusion: The ex vivo model of human fibrotic liver slices culture supporting hepatocyte-specific gene expression for 21 days should be an easy tool for studying human liver fibrosis and evaluating the potency of new antifibrotic therapies, as immunotherapy, alone or in combination in the human liver tissue.

FRI-099
Endocannabinoid system contributes to activation of neutrophils in mouse chronic liver injury
X. Fan[1], L. Tian[1], X. Zhou[1], L. Yang[2], L. Yang[2], L. Li[2]. [1]*Capital Medical University, Department of Cell Biology, b, China;* [2]*Capital Medical University, Department of Cell Biology, Beijing, China*
Email: liliying@ccmu.edu.cn

Background and Aims: Neutrophil might be an initial factor that it triggers the inflammatory cascade. In recent research, more attention was focused on the role of neutrophil in sterile inflammatory disease process. Neutrophils are recruited to the site of liver injury shortly, thus mediating the early responses to tissue injury. The infiltration and accumulation of neutrophil in injured liver further contribute to the inflammation-associated damage by releasing reactive oxygen species (ROS), myeloperoxidase (MPO) and forming neutrophil extracellular traps (NETs). Our previous results showed that endocannabinoid system participated in liver injury. However, the concrete mechanism of endocannabinoids changing and function of neutrophil-expressed cannabinoid receptors (CBs) are unclear.
Method: Carbon tetrachloride (CCl_4) injection was used to induce chronic liver injury. The amount and activation of neutrophil in injured liver was measured by Fluorescence-activated cell sorting and RT-qPCR. *In vitro*, we isolated neutrophil from bone marrow. The expression of CB1 and CB2 were measured by gel electrophoresis and Western blot. Migration assays were performed by transwell chambers. The ROS, MPO release and NETs formation were detected by immunofluorescence and high content analysis.



Results: Here, we found Ly6G (neutrophil marker) and MPO expression and the amount of neutrophil were significantly elevated in CCl_4-induced mouse injured livers. Moreover their expression showed positive correlation with fibrosis parameter (procollagen α1(III)) and CB1/2 expression. *In vitro*, we found that both CB1 and CB2 were expressed in neutrophils at mRNA and protein levels. CB1 activation promoted the migration of neutrophils, but CB2 activation had no such effect. Pharmacological ablation of CB1 reduced ACEA-induced migration, whereas CB2 did not. Meanwhile, CB1-mediated migration was associated with cytoskeletal remodeling. Furthermore, activation of CB1 enhanced the releasing of ROS and MPO. Formation of NETs has been recently found in response to various stimuli. We noted CB1 activation contributed to NETs formation. *In vivo*, administration of CB1 antagonist AM281 markedly inhibited the recruitment and activation of Neutrophil to the injured liver and significantly attenuated liver injury.
Conclusion: Blockage of CB1 limited neutrophil infiltrations and over-activation, which might attenuates the inflammation enlargement and reduce fibrosis of injured liver.

FRI-100
Exosomes secreted by the hepatocytes can inhibit and reverse hepatic stellate cells stimulation
M. Safran[1], R. Masod[1], I. Tachlytski[1], M. Sultan[1], Z.B. Ari[2]. [1]*Chaim Sheba Medical Center, Liver Disease Center, Tel Hashomer, Israel;* [2]*Sheba Medical Center at Tel Hashomer, Center of Liver Diseases, Tel Aviv, Israel*
Email: michal.safran@sheba.health.gov.il

Background and Aims: In the normal liver, hepatic stellate cells (HSCs) constitute quiescent, vitamin A–storing cell. Upon activation by a specific stimuli released by an injured liver, HSCs undergo activation and differentiation into a myofibroblast-like cell, thereby inducing hepatic fibrosis. Recent findings demonstrated that activated HSCs have the ability to revert into their quiescent state. Our aims were to investigate the mechanisms adopted by the normal liver that maintained the HSCs in quiescent state and to try to elucidate the role of the hepatocytes in the process.
Method: Primary HSCs were purified from normal mice liver using enzymatic digestion. Mediums were collected from primary hepatocytes, primary kidney cells, hepatocytes cell-line or kidney cell-line. The purified HSCs were cultured with the different cells media for 24h or 96 hours. HSCs activation level was analyzed by the expression of αSMA and Col1a (qRT-PCR and Western blot analysis). HSCs were stained with Oil-Red-O as a marker of lipid accumulation and activation. Exosomes were purified from the hepatocytes using ultracentrifuge. The level of CD63, a marker of exosomes, was measured using western blot analysis. Exosomes size was measured either by Nanostream analysis or TEM. Exosomes secretion inhibitor GW4869 (20μM) was also used to inhibit exosomes production and to prevent the hepatocytes activity.
Results: We have shown that medium collected from normal hepatocytes have the ability to inhibit and even reverse the HSCs stimulation and prevent their differentiation toward myofibroblast like cells. Furthermore, using a cellulose membrane with a cutoff of 100kDa, we have demonstrated that the size of the particles responsible for the HSCs inhibition is larger than 100kDa. Using ultra-centrifuge we have purified the particles from the medium and by western blot, nanostrean and TEM analysis we have proven that the fraction contains exosomes. Using exosomes secretion inhibitor we have demonstrated that the exosomes are the active component in the medium and we have shown that purified hepatocytes secreted exosomes can inhibit the stimulation of primary HSCs.
Conclusion: We have demonstrated for the first time that in the normal liver hepatocytes can regulate HSCs stimulation and inhibit their differentiation toward fibroblast like cells. This inhibition is mediated by the exosomes, extracellular nanovesicles vesicles that

play a role in intercellular communication. Further exploration of our proposed mechanism for the exact role and reliability of exosomes as screening, diagnostic and treatment targets will facilitate the development of new therapeutic options that can be used to inhibit the development and progression of hepatic fibrosis

FRI-101

The anti-fibrotic effect of Aramchol on rat liver fibrosis induced by TAA and in vitro on primary hepatic stellate cells

R. Golan-Gerstl[1,2], M. Valitsky[1], R. Oren[1], E. Brazowski[3], L. Hayardeni[1], S. Reif[1,4]. *[1]Hadassah Medical Center, The Liver Unit, Jerusalem Israel; [2]Hadassah Medical Center, Pediatrics, Jerusalem, Israel; [3]Tel Aviv Medical Center, The Pathology Department, Tel Aviv, Israel; [4]Hadassah Medical Center, Pediatrics, Jerusalem, Israel*
Email: reginag@hadassah.org.il

Background and Aims: Cirrhosis is the end result consequence of wide variety chronic liver diseases; including nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH). Liver fibrosis results from an accumulation of extracellular matrix (ECM) following the activation and proliferation of hepatic stellate cells (HSCs). HSCs secrete pro-collagen, and also tissue inhibitor metalloproteinase (TIMP). Aramchol (arachidyl amido cholanoic acid) is a fatty acid-bile acid conjugate which has been shown to reduce liver fat content in nonalcoholic fatty liver disease (NAFLD) and is presently in a Phase 2b study for nonalcoholic steatohepatitis (NASH). In MCD diet model, Aramchol down regulated steatosis, inflammation and fibrosis. The total amount of collagen accumulated in the Aramchol treated mice was significantly lower than in the shame treated mice. The aim of this study was to investigate the direct anti fibrotic effect of Aramchol using Thioacetamide (TAA) rat model of fibrosis and in vitro model of activated primary HSCs.
Method: *In vitro:* HSCs were isoalted from rats by sequential digestion of the liver with Pronase and collagenase, followed by arabinogalactan gradient centrifugation. Proliferation, TGF-**β,** TIMP-1, collagen and αSMA levels were analysed in activated HSC. *In vivo:* Liver fibrosis was induced by intraperitoneal injections of TAA at a dose of 20mg/100g body weight twice-weekly intra peritoneal for up to 10 weeks. Rats were treated orally by gavage with Aramchol (1 mg/kg/day) or vehicle. Control TAA induced fibrosis rats were treated with vehicle for the same duration. At the end of the experiment, liver samples were obtained. A histological assessment of the livers was performed after staining with hematoxylin-eosin (H&E) and Mason trichrome staining. Evaluation of fibrosis was based on the Ludwig and Batts staining system
Results: TAA-treated animals developed cirrhosis. However, rats that received TAA and Aramchol 1mg/Kg showed marked macroscopic morphologic improvement. Microscopically, the TAA treatment group displayed a periportal fibrosis characterized by portal-portal septa surrounding the hepatic lobules and received a fibrotic score of 3.25 ± 0.21, whereas rats treated with the TAA and Aramchol demonstrated significantly lower fibrosis and scored 1.6 ± 0.2. No fibrosis was observed in the control rats or the group that received Aramchol alone. Consistently, Aramchol treatment improved liver histology as determined by a reduction of 40.2% in fibrosis score. PDGF treatment up regulated the HSCs number; this elevation was reduced following incubation with Aramchol (10 μM) compared to untreated cells. Moreover, following TGF-β stimulation, the expression of TIMP-1 collagen and αSMA were down regulated by Aramchol treatment.
Conclusion: The *in vivo* and *in vitro* results support the ameliorative effect of Aramchol on liver fibrosis.

FRI-102

25(OH) D3 alleviate liver NK cytotoxicity in early but not in late fibrosis model of Balb/c mice due to modulations in vitamin D receptor

J. Amer, A. Salhab, R. Safadi. *Hadassah Hebrew University Hospital, Jerusalem, Israel*
Email: johnnyamer@hotmail.com

Background & Aims: Low 25-Hydroxy-vitamin-D; "25(OH) D3" serum and vitamin D receptor (VDR) levels were recently correlated to advanced fibrosis in Chronic Hepatitis C (CHC). However, vitamin D receptor mechanism in liver fibrosis modulations is not well understood. We aimed to evaluate associations of VDR with NK cell modulations during fibrogenesis.
Methods: Carbon-tetrachloride (CCl_4) hepatic-fibrosis was induced in Balb/c mice for 4 weeks. Along 1th to 4th weeks; 25 (OH) D3 were i. p injected/2x week. Liver NK cells were isolated and were identified as resident ($CD49a^+/CD49b^-$) NK1.1. NK cells were further stained for CD107a (LAMP-1; Lysosomal-associated membrane protein 1) as activation marker. Liver proteins were quantified for VDR and αSMA expressions by western blot and RT PCR, respectively. Livers were also assessed histologically and serum ALT levels were estimated. *In vitro*, 25 (OH) D3 was incubated with pHSCs obtained from Balb/c WT-mice and assessed for αSMA intensities.
Results: Hepatic fibrosis increased along 4 weeks injections of CCl_4 as indicated by serum ALT levels and αSMA expressions ($P < 0.02$) as well as H&E staining of liver necro-inflammatory lesions. These results were associated with increased activations of NK1.1 CD107a. While 25 (OH) D3 administrations did not modulate fibrosis of early stages (weeks 2 & 3); 25(OH) D3 significantly worsen hepatic-fibrosis of late stage (week 4) as hepatic αSMA expressions and serum ALT levels increased. In week 4, no further activations of NK cells were seen following 25(OH)D3 injections and were associated with down-expressions of VDR (1.7 Fold, $P < 0.01$) indicating the inability of 25 (OH)D3 to ameliorate hepatic fibrosis were lost due to modulations in VDR. These results were correlated with changes in serum calcium levels; in early fibrosis model calcium levels were unchanged and while hypercalcemia were noticed in serum of the animals with advanced fibrosis. *In vitro*, pHSCs showed to have 3 sub-populations that differ in the size and granularity. Two of these populations were excluded as they do not express VDR and a low amount of αSMA. pHSCs subpopulation with high VDR (50% ± 12%) were further elevated with increased concentrations of 25 (OH) D3 ($p < 0.02$).
Conclusions: 25(OH) D3 alleviate liver NK cytotoxicity in early but not in late fibrosis model of Balb/c mice due to modulations in vitamin D receptor and calcium. Hypercalcemia associated with late fibrosis may inhibited levels of VDR, however, may not explain the profibrogenic effects of 25(OH) D3. While in the vitro data showed anti-fibrotic effects, more studies are needed to clarify the role of VDR in attenuation of liver fibrosis.

FRI-103

Role of the protein tyrosine kinase Mer (MerTK) in the cross-talk between macrophages and hepatic stellate cells

M. Pastore[1], G.D. Maira[1], A. Caligiuri[1], S. Petta[2], F. Marra[1]. *[1]DMSC, University of Florence; [2]University of Palermo, Department of Gastroenterology and Hepatology Di.Bi.M.I.S*
Email: fabio.marra@unifi.it

Background and Aims: One of the first events that defines the liver fibrogenic process is the activation of resident macrophages and the recruitment of further inflammatory cells such as monocytes/macrophages, resulting in the activation of quiescent hepatic stellate cells (HSCs) via paracrine pathways. MerTK, a receptor tyrosine kinase mainly expressed in macrophages, plays a key role in the initiation of efferocytosis, a process by which dying cells are removed by phagocytes. MerTK is overexpressed in murine models of

fibrogenesis and by human HSCs, where mediates profibrogenic actions. In addition, MerTK mutants are associated with higher protein expression are present with higher frequency in patients with NAFLD and significant fibrosis, and macrophages contribute to its expression. This study was undertaken to evaluate the potential effects of MerTK activation in macrophages on HSC phenotype modulation

Method: Primary human HSCs, isolated from human liver tissue and activated on plastic, and the immortalized monocytic line THP1 were employed. THP1 monocytes were differentiated into THP1 macrophages after treatment with phorbol 12-myristate 13-acetate (PMA). Inhibition of MerTK expression or activity was performed by knockdown with siRNA or with the specific inhibitor UNC569. Migration of HSCs was assessed by modified Boyden chamber. HSC viability was measured by MTT assay and gene expression were evaluated by

Results: Exposure of THP1 cells to PMA resulted in a dramatic upregulation of MerTK expression, at the gene and protein levels. Incubation with Gas-6, a MerTK ligand, caused time-dependent phosphorylation of MerTK on tyrosine residues. Exposure of HSCs to conditioned medium (CM) of differentiated, PMA-treated THP1 cells exposed to Gas-6 induced a significant increase in cell migration and in cell viability compared to control CM. Furthermore, the CM from Gas-6-stimulated THP1cells induced in HSCs an increase in the gene expression of profibrogenic factors compared to control CM. These effects were specifically related to MerTK activity/expression, as indicated by knockdown experiments and by pharmacologic inhibition

Conclusion: These data highlight a novel important role of MerTK in the fibrogenic responses, through a cross-talk between HSCs and inflammatory cells.

FRI-104

PBI-4547 decreases hepatic stellate cell activation via AMPK signaling pathway, and reduces fibrosis in carbon tetrachloride (CCL4)-induced hepatic fibrosis model

François Sarra-Bournet, B. Grouix, K. Hince, A. Felton, Mikaël Tremblay, S. Abbott, J.-S. Duceppe, B. Zacharie, P. Laurin, L. Gagnon. *Prometic Biosciences Inc., Laval, Canada*
Email: f.sarra-bournet@prometic.com

Background and Aims: Hepatic stellate cells (HSC) are considered a key player in the fibrogenic process of the liver. In response to liver injury, HSC become activated and transdifferentiate into myofibroblast-like cells, which display increased proliferation and collagen synthesis. Recent studies have shown that AMPK modulates HSC activation and inhibits transforming growth factor (TGF)-β1-induced fibrosis. In the present study, we investigated whether treatment with PBI-4547, a novel first-in-class orally active compound, could decrease *in vitro* HSC activation via AMPK, and ameliorate CCL4-induced fibrosis in mice.

Method: *In vitro*, primary human HSC were stimulated with TGF-β1 (10 ng/ml) in the presence or absence of PBI-4547 (20 and 10 μM) for 24 hours. AMPKα and α-SMA proteins were detected by Western blot. Expression of fibrotic and activation markers in stellate cell was investigated by qPCR. Liver fibrosis was induced in C57BL/6 mice by administration of 10% CCL4 in olive oil at 2 ml/kg, twice a week for eight weeks, and mice were treated with PBI-4547 (10 and 50 mg/kg) or vehicle. The degree of fibrosis in the liver was evaluated by histopathology and gene expression analysis.

Results: *In vitro*, TGF-β1-induced activation of HSC was decreased by PBI-4547, as shown by the significant inhibition of stellate cell activation marker α-SMA mRNA and protein expression. Profibrotic factor CTGF mRNA expression was also downregulated by PBI-4547. As evidenced by protein analysis, PBI-4547 significantly activated AMPK signalling in TGF-β1 activated HSC. After induction of hepatic fibrosis with CCL4, mice treated with PBI-4547 showed reduced liver fibrosis compared to CCL4 controls, as evaluated by histological analysis. The hepatocyte growth factor (HGF) tissue regeneration factor, upregulated in CCL4-treated mice, was also reduced by treatment with 50 mg/kg of PBI-4547. Moreover, PBI-4547 restored expression of peroxisome proliferator-activated receptor-γ (PPARγ), which was reduced in the liver of CCL4-animals and in TGF-β1-activated HSC.

Conclusion: This study demonstrated that PBI-4547 significantly reduced HSC activation through AMPK signalling pathway. PBI-4547 reduced collagen deposition in CCL4-induced liver. Ours results suggest that PBI-4547 may be developed as a novel therapeutic agent to treat hepatic fibrosis.

FRI-105

The wrong or "right" effects of HCV on cardiac function in patients with low-mild liver fibrosis: A case-control study

A. Dalbeni[1], S. Romano[1], E. Imbalzano[2], A. Tagetti[1], G. Torin[1], A. Mantovani[1], G. Cavallon[3], V. Paon[1], C. Fava[1], L.I. Prat[1,4], F. Capra[5]. *[1]Division of General Medicine and Hypertension, Medicine, Verona; [2]Division of Internal Medicine, Clinical and Experimental Medicine, Messina, Italy; [3]Azienda Ospedaliera Universitaria Integrata, Division of Liver Unit, Verona, Italy; [4]UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, United Kingdom; [5]University and Azienda Ospedaliera Universitaria Integrata of Verona, University of Verona, Italy*
Email: andrea.dalbeni@aovr.veneto.it

Background and Aims: Hepatitis secondary to hepatitis C virus (HCV) infection is one of the most common causes of viral hepatitis. Association between HCV infection and increased incidence of cardiovascular disease has already been described in literature: vascular and cardiac alterations related to HCV seem to be Cardiovascular disease incidence and HCV infection is described and a possible mechanism due to this vascular and cardiac alterations seems to be explained by HCV proinflammatory effects on endothelium and myocardium. Few studies describe echocardiographic modifications in subjects with HCV vs a control population. In particular, a modified systolic and diastolic left function seems to be present in HCV subjects. Only one study reported a right ventricular systolic dysfunction and pulmonary hypertension in HCV patients. In this study we examined right and left ventricular systolic function in patients affected by HCV infection in low-mild liver fibrosis stage.

Method: In this study we included 65 consecutive naïve HCV patients with low-mild liver fibrosis stage at Fibroscan referring to our clinic (Liver Unit) because of eligibility for HCV eradication with DAA (Directly Acting Antivirals) (mean age 58.0 ± 12.8; M 46%). We also included 60 age-sex-BMI and cardiovascular risk factors matched controls Transthoracic echocardiography was performed in all participants. Therefore, we aimed to analyse left and right ventricular systolic functions in HCV patients and in the control group and parameters were compared between these 2 groups.

Results: In the two groups the left ventricular function was similar. Left ventricular mass (LVM), dystolic function E/A, mitral annular plane excursion (MAPSE) and ejection fraction (EF%) showed no difference between the two groups. Also left atrial measures showed no difference in the two groups. Conversely, when we analysed the right sections, tricuspid annular plane excursion (TAPSE) and right atrium volume (RA), we found significant differences: TAPSE HCV (mean ± SD) was 14.8 ± 6.1 mm vs TAPSE controls 18.9 ± 1.9 mm ($p < 0.001$); RA HCV 36.9 ± 20.4 mm3 vs RA controls 25.2 ± 2.9 mm3 ($p < 0.001$). PAPs showed no differences. When we subdivided the HCV patients according to fibrosis stage (1, 2 or 3) or viral load (>800.000 copies) no differences were detectable in echocardiographic measures.

Conclusion: our study is the first case-control study that shows right-sided heart alterations due to the presence of HCV which do not seem to be linked to the severity of liver fibrosis and to viral load. Other studies are necessary to understand the right cameras modifications due to HCV infection.

FRI-106

BMS-986036, a PEGylated fibroblast growth factor 21 analogue for the treatment of non-alcoholic steatohepatitis: A population pharmacokinetics and exposure-response analysis

G. Tirucherai[1], M. Magnusson[2], C. Acharya[2], E. Charles[1], D. Shevell[1], R. Christian[1], Y. Luo[1]. [1]*Bristol-Myers Squibb, Lawrenceville;* [2]*Pharmetheus, Sweden*
Email: giridhar.tirucherai@bms.com

Background and Aims: Fibroblast growth factor 21 (FGF21) is a key regulator of energy and lipid metabolism. BMS-986036, a PEGylated analogue of human FGF21, decreased steatosis (hepatic fat fraction [HFF]) and improved biomarker (BM) responses of fibrosis (Pro-C3), adiponectin, and injury (ALT) in a phase 2 study of patients (pts) with non-alcoholic steatohepatitis (NASH); a population pharmacokinetic (PopPK) model was developed to assess the exposure response of BMS-986036 on key BMs.
Method: The PopPK model was developed from randomized, placebo (PBO)-controlled trials: MB130-001 (phase 1; single [0.3–60 mg] and multiple ascending doses [0.3–30 mg/d or 21 mg/wk] of BMS-986036 in healthy obese adults), MB130-002 (NCT02097277; phase 2; 1, 5, or 20 mg once-daily [QD], 20 mg once-weekly [QW] BMS-986036, or PBO QD in obese pts with type 2 diabetes), and MB130-045 (NCT02413372; phase 2; 10 mg QD or 20 mg QW BMS-986036, or PBO QD, in pts with NASH [stage 1-3 fibrosis]). Non-linear mixed effects modelling was performed (NONMEM VII). The PopPK model was used to describe the PK-pharmacodynamic (PD) relationship between BMS-986036 and HFF, ALT, Pro-C3, adiponectin, triglycerides, LDL, and HDL. PK-PD relationships were used to simulate BM response at various QD and QW dosing for 16 wks.
Results: The PK of SC BMS-986036 was adequately described by a two-compartment model with sequential zero- and first-order absorption, and first-order elimination from the central compartment. Duration of zero-order absorption, bioavailability, and central- and peripheral-volume of distribution supported interindividual variability terms. Direct- or indirect-response PK-PD models described the time course of BM responses. Simulations showed that BM responses were similar for QD and QW dosing at a similar total dose/wk (table).

Model-predicted % change in response at trough concentrations (baseline to wk 16), for QD and QW dosing of BMS-986036

BM	~10 mg/wk		~20 mg/wk		~40 mg/wk	
	1.5 mg QD	10 mg QW	3 mg QD	20 mg QW	6 mg QD	40 mg QW
	%					
HFF	−33.7	−24.8	−34.1	−29.7	−34.3	−31.9
ALT	−22.5	−16.7	−27.9	−22.6	−31.6	−26.7
ProC3	−8.3	−7.0	−13.7	−12.4	−20.3	−17.4
Adiponectin	14.1	11.4	21.3	18.3	28.9	24.0

Conclusion: PopPK-PD models described the PK and PD responses following QD and QW dosing of BMS-986036 in 3 trials. Simulations identified QW doses of BMS-986036 projected to have significant PD responses comparable with QD dosing (at a similar total dose/wk), supporting the use of a less frequent dosing regimen for future trials.

FRI-107

Primary human HSC cell phenotype is differently regulated by pro-fibrogenic and pro-inflammatory stimuli in cirrhotic and healthy human liver 3D ECM scaffolds

E. Caon[1], Z. Zhang[2], L. Frenguelli[1], W. Al-Akkad[1], G. Mazza[3], M. Pinzani[1], K. Rombouts[1]. [1]*University College London, Institute for Liver and Digestive Health, London, United Kingdom;* [2]*University College London, Institute for Liver and Digestive Health, London, United Kingdom;* [3]*Institute for Liver and digestive he, London, United Kingdom*
Email: k.rombouts@ucl.ac.uk

Background and Aims: Hepatic stellate cells (HSCs) are key mediators in liver fibrosis. A common platform to investigate HSCs activation is the usage of classical 2D cultures. However, the ECM microenvironment plays a crucial role in reason of the liver-specific 3D microarchitecture, which favours essential cell-ECM interactions. The aim of this study is to evaluate a novel in vitro 3D model based on human liver scaffolds in order to combine the advantage of the liver's specific 3D architecture as well as the preserved bioactive cues to achieve a more accurate in vitro phenotype of primary human HSCs.
Method: Human liver 3D scaffolds were obtained by the decellularization of healthy and cirrhotic livers. Scaffolds were repopulated with the hHSC cell line LX2 or with primary hHSCs ($0.25*10^6$) in serum-rich medium for 10 days. Cells were exposed to profibrogenic agents: PDGF-BB (1–10ng/mL), TGFbeta1 (2–5ng/mL) for 24hrs or LPS (1ng/mL) for 1–3hrs. In parallel, LX2 cells or primary hHSCs were grown in 2D cultures and treated as above. Histology was performed to compare hHSCs cell phenotype/engraftment in the 3D scaffolds. QRT-PCR was performed.
Results: Significant differences were observed in gene expression of hHSCs cultured on 2D vs 3D healthy scaffolds, especially when exposed to LPS, PDGF-BB and TGFbeta1. Human HSCs in 3D cultures treated with LPS showed a strong increase in Acta2, CYGB, COL1A1, IL-6 whereas LOX gene expression remained unchanged. TGFbeta1 induced a significant increase in Acta2, Col1A1 and LOX gene expression, but not CYGB and IL-6. In contrast, PDGF-BB significantly decreased Acta2 in comparison to non-treated hHSCs in 3D cultures. Furthermore, the HSC activation markers Acta2 and COL1A1 were significant upregulated in cirrhotic scaffolds compared to healthy scaffolds, whereas CYGB, LOX and IL-6 were not affected. In contrast, LX2 cells on cirrhotic scaffolds showed a downregulation of Acta2, Col1A1, and Col3A1 gene expression compared to LX2 cells on healthy scaffolds, indicating that, when cultured in a natural 3D ECM microenvironment, LX2 cells do not show the same gene expression pattern of primary hHSCs.
Conclusion: This study shows that primary hHSCs have different gene expression patterns when cultured in 3D scaffolds derived from healthy and cirrhotic human livers and in comparison to 2D cell culture. By using human tissue-specific 3D scaffolds, as models of human physiology and pathophysiology, specific and novel drug targets and biomarkers will be identified.

FRI-108

Integrin αvβ6-targeted near-infrared/positron emission tomography contrast agent for liver fibrosis imaging

Y.O. Kim[1], K.-S. Park[1], N. Engelbogen[2], M. Diken[3], Y. Popov[4], T. Ross[5], D. Schuppan[1,4]. [1]*University Medical Center of the Johannes Gutenberg University Mainz, Institute of Translational Immunology, Research Center for Immune Therapy (FZI), Mainz, Germany;* [2]*Johannes Gutenberg University Mainz, Germany, Institute of Nuclear Chemistry, Mainz, Germany;* [3]*University Medical Center of the Johannes Gutenberg University Mainz, Institute for Translational Oncology (TrOn), Mainz, Germany;* [4]*Beth Israel Deaconess Medical Center, Harvard Medical School, Division of Gastroenterology, Boston, United States;* [5]*Hannover Medical School, Department of Nuclear Medicine, Radiopharmaceutical Chemistry, Hannover, Germany*
Email: kimy@uni-mainz.de

Background and Aims: There is an urgent need for quantitative imaging of liver fibrosis. The integrin αvβ6 is highly upregulated on cholangiocytes that drive liver fibrogenesis. We therefore developed and validated a bimodal αvβ6-targeted contrast agent to quantitatively image liver fibrogenesis.
Method: We designed a dual-labeled cyclic peptide recognizing integrin αvβ6 based on a 9-mer cyclic RGD peptide, attaching a

functional group with sulfo-Cy5.5 and a Ga-68-chelator for near infrared (NIR) and PET imaging, resp. Binding specificity was tested in vitro on αvβ6-positive and -negative cell lines. In vivo uptake, biodistribution and clearance were studied in mouse models of biliary (Mdr2 KO) and parenchymal (CCl_4-induced) fibrosis compared to nonfibrotic controls. For NIR imaging, 20 µg (5.84 nM/mouse) of contrast agent were injected intravenously and whole body and organ imaging were performed at 20 min, and 2, 4, 6 and 12 h post injection. For micro-PET imaging the Ga-68-labeled construct (5 MBq/mouse) was injected and followed by micro-PET. Organ specific signals were also quantified using a gamma-counter. Fibrosis and target expression were assessed by determination of collagen content and αvβ6 protein expression by qRT-PCR.

Results: The dual-labeled cyclic peptide dose-dependently bound to αvβ6 expressing, but not to αvβ6 deficient cells (highest at 1 µM in 5.2-fold vs control; $p < 0.01$). The activity was blocked with excess unlabeled peptide. Mdr2 KO fibrotic mice displayed a 3-fold elevated hepatic collagen content ($p < 0.0001$) and a 43-fold increased αvβ6 mRNA expression compared to wildtype mice ($p < 0.05$). CCl_4-treatment induced a 3-fold elevated hepatic collagen content ($p < 0.0001$), and a 4.6-fold αvβ6 expression ($p < 0.05$). NIR imaging with the bimodal cyclic peptide revealed a liver-specific 3.4-fold ($p > 0.001$) and a 3.2-fold ($p > 0.01$) enhanced uptake in the fibrotic livers, respectively, 6 h post injection, compared to the non-fibrotic controls. Comparable results were obtained with micro-PET imaging using the Ga-68-radiolabeled bimodal cyclopeptide.

Conclusion: We designed a bimodal integrin αvβ6-specific fibrogenesis imaging agent based on a cyclic RGD peptide that can be used for NIR and PET-imaging in mice and for PET-imaging in patients. This opens the possibility of molecular imaging to quantify liver fibrogenesis in vivo and therefore to assess early treatment responses in patients treated with potential antifibrotic agents.

Liver development, physiology and regeneration

FRI-111

Glycosyltransferase GLT25D2 acts as a negative regulator of autophagy to promote acetaminophen-induced hepatotoxicity

J. Zhang[1], X. Zhang[1], H. Shi[1], Z. Duan[1], H. Wei[2], F. Ren[1]. [1]*Capital Medical University, Beijing Youan Hospital, Beijing, China;* [2]*Capital Medical University, Beijing Ditan Hospital, Beijing, China*
Email: renfeng7512@hotmail.com

Background and Aims: The glycosylation of proteins in acetaminophen-induced hepatotoxicity remains enigmatic. The aims of this study is to explore the role of the collagen galactosyltransferase GLT25D2 in pathogenesis of acetaminophen-induced hepatotoxicity.

Method: The mice were given a single intraperitoneal (i.p.) injection of acetaminophen. Livers tissues analyzed by histology, reverse-transcription polymerase chain reaction, western bolting, immunohistochemistry, and electron microscopy, respectively. Primary hepatocytes were isolated and analyzed. Liver biopsy samples from patients with acetaminophen overdose were analyzed by immunofluorescence staining.

Results: GLT25D2 expression was significantly elevated in the livers of mice exposed to acetaminophen. Knockout of GLT25D2 ameliorated the hepatocellular damage, evidenced by reduced serum alanine aminotransferase levels and well-preserved liver architecture compared with controls. Mechanistic investigations elucidate that GLT25D2 acts as a negative regulator of autophagy, whereby enhancing the susceptibility of hepatocytes to acetaminophen-induced cytotoxicity. Indeed, (1) knockout of GLT25D2 promoted autophagy and enhances autophagy flux in vitro and in vivo; (2) inhibition of autophagy reversed liver protection and hepatocyte protection of GLT25D2 knockout; (3) autophagy induced by GLT25D2

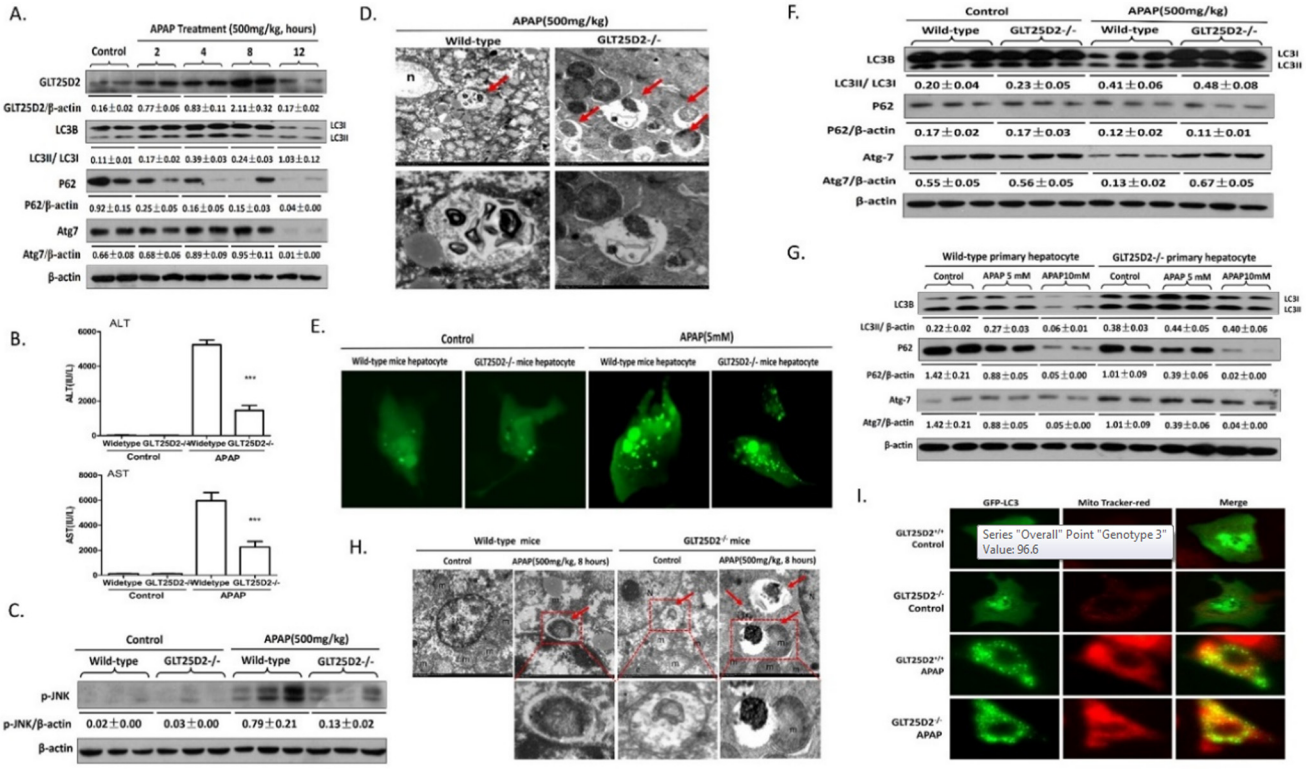
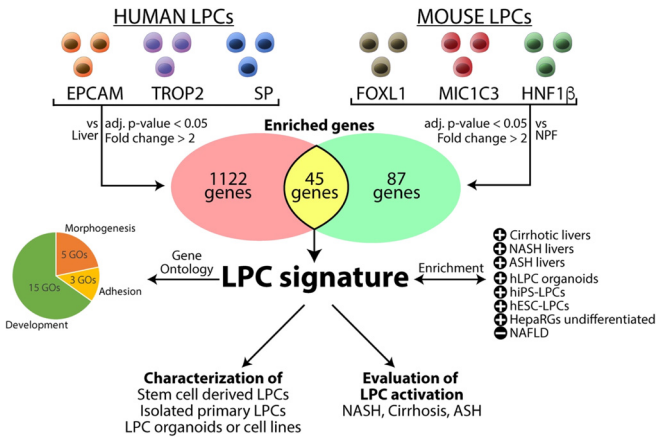


Figure 1: (abstract: FRI-111)

knockout seemed to be selective for damaged mitochondria. More importantly, the expression of GLT25D2 is significantly down-regulated in drug-induced liver injury patients.
Conclusion: The increased GLT25D2 suppresses autophagy to promote the occurrence and development of acute liver injury and suggest that GLT25D2 can be a potential therapeutic choice for acetaminophen-induced hepatotoxicity.

FRI-112
Generation of a unique liver progenitor cell gene signature to identify LPCs and LPC activation in chronic liver diseases
S. Verhulst[1], A. Ceulemans[2], P. Sancho-Bru[3], T. Roskams[2], L. van Grunsven[1]. [1]*Vrije Universiteit Brussel, Biomedical Sciences, Brussels, Belgium;* [2]*KU Leuven, Imaging and Pathology, Leuven, Belgium;* [3]*Institut d'Investigacions Biomèdiques August Pi i Sunyer, Barcelona, Spain*
Email: stefaan.verhulst@vub.be

Background and Aims: Chronic liver diseases are frequently associated with a ductular reaction. This includes the activation of liver progenitor cells (LPCs), especially in conditions in which hepatocytes are senescent. The extent to which LPCs contribute to liver regeneration is still a subject of debate. The different isolation methods and the use of diverse LPC markers to isolate, characterize and lineage-trace LPCs in healthy, damaged and regenerating livers is certainly one of the culprits. In this study we compared the gene expression profiles of different LPC populations, i.e different species and isolation methods as well as LPC cell lines, and established a gene signature that identifies LPCs and their activation.
Method: In this study, we analyzed online available gene expression profiles of human (enriched in EPCAM, TROP2 or side population) and mouse (enriched in HNF1b, FOXL1 or MIC1C3) LPCs. We compared their transcriptomes and analysed co-expressed genes by using supraHex and AmiGO. A unique LPC signature was created by pooling enriched genes from each LPC population using venn diagrams. Gene set enrichment analysis using this LPC signature was performed on different iPS- and ESC-derived LPCs, differentiated HepaRGs and on data sets from livers of patients with cirrhosis, ASH, NAFLD or NASH.
Results: Comparison between human and mouse LPC populations showed high similarities in genes involved in proliferation and development. Overlap of genes enriched in all LPC population resulted in 45 genes and contains well-known LPC markers but also genes never described in LPCs. LPCs derived from human iPS- or ESC-derived LPCs and undifferentiated HepaRGs showed a higher enrichment of our signature compared to previously established LPC signatures. Gene set enrichment analysis with the LPC signature of liver expression profiles of ASH, NASH and cirrhosis suggests that only these diseases are accompanied by a strong LPC activation.



Conclusion: We compared and characterized for the first time human and mouse LPC gene profiles and created a unique LPC signature through an unbiased approach. This signature can be used to identify primary LPCs, LPC cell lines or LPCs derived from iPS or hESCs and as a tool to evaluate LPC expansion in liver diseases. In the future, we would like to correlate the LPC signature with the outcome of the liver disease.

FRI-113
Osteopontin might be a central regulator of inflammation during postoperative liver regeneration in humans
D. Pereyra[1], S. Holzer[1], M. Herac[2], J. Stift[2], M. Finsterbusch[3], C. Brostjan[1], T. Grünberger[4], P. Starlinger[1]. [1]*Medical University and General Hospital of Vienna, Department of Surgery, Vienna, Austria;* [2]*Medical University of Vienna, Clinical Institute of Pathology, Vienna, Austria;* [3]*Medical University of Vienna, Institute of Pharmacology and Pathology, Vienna, Austria;* [4]*Rudolfstiftung Hospital, Department of Surgery, Vienna, Austria*
Email: N1342352@students.meduniwien.ac.at

Background and Aims: Osteopontin (OPN) was described as an important factor for liver regeneration (LR) in mice. However, a rat model investigating postresectional LR, showed development of necrosis and inflammation in OPN overexpressing livers. Of note, there is no human data on OPN after liver resection available. The present study was conducted to elucidate the role of OPN in patients undergoing liver resection. As YAP1 dependent sonic hedgehog (SHH) signaling was described as a possible determinant of OPN expression in fatty liver disease, we also aimed to assess whether this pathophysiologic model might be applicable to the setting of human postoperative LR.
Method: 48 patients were included in this investigation. Plasma OPN levels were investigated preoperatively and on the first (POD1) and fifth day after surgery (POD5). Further, 2 hours after induction of LR blood was collected from the liver vein and concentration of OPN was assessed. Additionally, liver biopsies were gathered at baseline and at 2 hours of LR. Gene expression was assessed using RT-PCR. Patients were followed up for morbidity and liver dysfunction (LD) after hepatic resection.
Results: Circulating levels of OPN significantly increased within 2 hours of LR in the liver vein ($p = 0.017$). Interestingly, there was a significant correlation of both SHH and YAP1 with OPN expression during regeneration ($r = 0.628$, $p = 0.005$; $r = 0.558$, $p = 0.016$; respectively). Further, patients with high induction of SHH showed significantly higher fold changes in mRNA of both YAP1 ($p = 0.035$) and OPN ($p = 0.044$). Postoperatively, OPN showed an increase on POD1 ($p = 0.001$), with a subsequent decrease up to POD5 ($p = 0.050$). Patients that developed LD showed significantly higher levels of OPN on POD1 ($p = 0.039$, AUC = 0.704). Ultimately, a cut-off at 250 ng/µl postoperative OPN was identified and patients above this cut-off were found to have a significantly higher incidence of postoperative LD (10.5% in OPN $\leq$ 250 ng/µl vs 52.4% in OPN > 250 ng/µl, $p = 0.005$).
Conclusion: Within this study, we were able to elucidate a central role of OPN, possibly expressed in a YAP1 and SHH dependent manor, during postoperative LR. While circulating OPN shows an initial increase already 2 hours after induction of LR in all patients, an excessive increase of OPN might lead to adverse effects in patients after liver resection. This made it possible to identify patients at risk for postoperative LD via OPN already on POD1.

FRI-114
Obeticholic acid improves fetal hypercholanaemia during cholestatic gestation
V. Pataia[1], G. Papacleovoulou[1], E. Jansen[2], L. Adorini[3], H.-U. Marschall[4], C. Williamson[1]. [1]*King's College London, Women and Children's Health, London, United Kingdom;* [2]*National Institute for Public Health and the Environment, Centre for Health Protection, Bilthoven, Netherlands;* [3]*Intercept Pharmaceuticals, San Diego, United States;* [4]*University of*

Gothenburg, Department of Molecular and Clinical Medicine, Gothenburg, Sweden
Email: vanessa.formigo_pataia@kcl.ac.uk

Background and Aims: Intrahepatic cholestasis of pregnancy is characterized by a supraphysiological elevation of maternal circulating bile acid levels, concomitant with a deranged lipid profile. Intrahepatic cholestasis of pregnancy leads to accumulation of bile acids in the fetal compartment and increasing bile acid levels are associated with increased risk of adverse fetal outcomes, including preterm birth, perinatal death and stillbirth. The most common treatment is ursodeoxycholic acid administration but not all patients respond. The semi-synthetic farnesoid x receptor agonist obeticholic acid (OCA) has shown efficacy in the treatment of cholestatic conditions such as primary biliary cholangitis, and is approved for this indication. In this study, we hypothesized that OCA administration during cholestatic pregnancy results in improved maternal and fetal bile acid and lipid profiles.
Method: Female C57BL/6 mice were fed either: a normal chow diet, a 0.5% cholic acid (CA)-supplemented diet (equivalent to 700 mg/kg/day), a 0.03% OCA-supplemented diet (Intercept Pharmaceuticals) (equivalent to 42 mg/kg/day), or a 0.5% CA + 0.03% OCA-supplemented diet for 1 week prior to mating and throughout pregnancy. Pregnant females were euthanized on day 18 of pregnancy and maternal and fetal body and organ morphometry were studied. The effects of CA and OCA feeding during pregnancy on maternal and fetal serum bile acid levels were investigated. Maternal and fetal serum and hepatic lipid levels were also assessed.
Results: OCA administration during gestation did not alter the maternal or fetal body weight or organ morphometry (n = 6–8). OCA administration during cholestatic pregnancy resulted in decreased bile acid levels in the fetal compartment (172.4 ± 15.5 μmol/l vs 246.1 ± 31.5 μmol/l, n = 4–6, $p < 0.05$). However, fetal BA levels remained higher in this group than in controls (6.8 ± 0.3 μmol/l, n = 4–6) and fetal dyslipidemia was not reversed (n = 4–6). OCA administration during cholestatic pregnancy did not reduce maternal bile acid levels or improve dyslipidemia (n = 4–6).
Conclusion: OCA administration during gestation did not have negative effects on maternal or fetal morphometry and improved fetal hypercholanemia during cholestatic gestation. As raising bile avid levels in intrahepatic cholestasis of pregnancy are correlated with increased rates of adverse fetal outcomes, further investigations into the potential use of OCA during cholestatic gestation are warranted.

FRI-115

In vivo functional genetics for liver regeneration and disease

V. Iakovleva[1], T. Wuestefeld[1,2], A. Potapova[1], S.H.J. Dass[1]. *[1]Genome Institute of Singapore, Stem Cell & Regenerative biology, Singapore, Singapore; [2]National Cancer Centre Singapore, SingHealth, Singapore, Singapore*
Email: Iakovlevav@gis.a-star.edu.sg

Background and Aims: We conducted functional genetic *in vivo* shRNA screens for modulators of liver regeneration taking advantage of the Fumarylacetoacetate hydrolase (FAH) knockout mouse model before. We further developed our approach conducting these functional genetic screens in wild-type (wt) mice opening functional *in vivo* genetic shRNA screens to any genetic background and genetically modified mice. We have already identified potential new therapeutic targets.
Method: We used hydrodynamic tail vine injection to deliver transposon-based constructs for the expression of GFP and shRNA together with a sleeping beauty transposase (SB13) expressing plasmid to C57Bl6 mice. We reached stable integration of our construct into the genome of around 10% of hepatocytes. As a proof of principle, we first tested this system using a library we researched before in FAH knockout mice. We applied chronic thioacetamide (TAA) treatment to induce chronic liver damage. After this time we harvested the liver, isolated genomic DNA, amplified the expression cassette and did Illumina based deep sequencing. We determined the relative abundance of each shRNA. Then, we calculated the fold change in abundance after chronic liver damage *in vivo* to the starting pool for each shRNA. We determined the limitations of the system regarding the potential pool size for screening purposes and conducted a novel screen using a shRNA library consisting of 2300 shRNAs targeting 1000 cDNAs.
Results: Using the previously published ROMA-HCCdel shRNA library in our wt mouse set-up recapitulates the results obtained in the FAH knockout mouse model. The top-enriched shRNAs perfectly overlap, indicating the feasibility of functional genetic screens for modulators of liver regeneration and disease in our novel set-up. Conducting the first *in vivo* functional shRNA screen in wild-type mice using a library of 2300 shRNAs, we identified new potential regulators of liver regeneration. Confidence in the screening results is reflected by enrichment of shRNAs for targets known to enhance regeneration as well as depletion of shRNAs for targets essential for regeneration. We also examined the maximal pool size for in vivo screening in this system. We could reliably retrieve more than 5000 shRNAs. This shows the potential for genome-wide screens using our system.
Conclusion: We established a novel and highly versatile *in vivo* functional screening set-up for identification of modulators of liver regeneration and disease. This system is scalable for genome-wide screens and therefore will allow identifying new therapeutic targets for liver disease.

FRI-116

Differentiation of human pluripotent stem cells into hepatocytes is more efficient in spheroids than in 2D culture

M. Antonietta[1,2], U. Pereira[2,3], Cécile Legallais[2,3], A. Dubart-Kupperschmitt[1,2]. *[1]UMR_S1193 INSERM/Université Paris-Sud, Villejuif, France; [2]Département Hospitalo-Universitaire Hépatinov, Villejuif; [3]Laboratoire de Biomécanique et Bioingénierie (BMBI), UMR CNRS 7338/ Université de Technologie de Compiègne, Compiègne, France*
Email: anne.dubart@inserm.fr

Background and Aims: The self-renewing abilities and differentiation potential of the human induced pluripotent stem cells (hiPSCs) appoint them as one of the most promising reliable source of hepatocytes for cell therapy, regenerative medicine and bio-engineering. Beside safety issues, the challenges regarding these applications are the number and the functionality of hepatocyte-like cells (HLCs). Moreover, 2D cultures appear restricted while 3D cultures offer easier upscaling and expected improved differentiation into HLCs, due to better cellular interactions. Here, we used hepatoblasts differentiated from hiPSCs to generate spheroids investigating cell survival, hepatocytic differentiation and functionality in 2D versus 3D cultures.
Method: hiPSCs were differentiated towards hepatocytic lineage and seeded at different stages of differentiation and different cell densities into inert micro-wells to induce their self-assembly. 2D cultures were performed as control. We studied cell aggregation rates comparing cell viability and expression of hepatic specific markers and functions along time.
Results: Hepatoblast stage (day 10) appeared to be the more suitable for the spheroid generation. Cells re-arranged themselves into aggregates of 100–120 μm in diameter 24h after seeding. Secretion of AFP and expression of ALB mRNA after 1 and 3 days of aggregation, respectively, attested the hepatic differentiation in 3D condition. In contrast ALB mRNAs was detectable only after 20 days of culture in the 2D controls where AFP expression and secretion persist along time. Immunostaining and ELISA confirmed the precocious expression of ALB and the rapid loss of AFP expression into the 3D systems in comparison with the 2D controls. Albumin secretion from spheroids regularly increased then reached a plateau after 7 days of culture with values threefold higher and statistically significant versus the 2D controls. Moreover, metabolic activity (Cytochrome

P450 and the phase II enzyme expression) and functionality (Periodic acid–Schiff and Oil Red O staining) of the spheroids were successfully assessed.
Conclusion: The 3D approach results in a quicker and more complete maturation of HLCs with respect to classical 2D cultures. Therefore, these spheroids can be used across multiple clinical and research applications especially as the cellular component for the development of bioartificial liver devices where they can replace single cells.

FRI-117

Hepatic autophagy potentiates ureagenesis and its enhancement protects against acute and chronic hyperammonemia

L. Soria[1], G. Allegri[2], D. Melck[3], N. Pastore[4,5], P. Annunziata[1], D. Paris[3], E. Polishchuk[1], E. Nusco[1], B. Thöny[6], A. Motta[3], J. Häberle[6], A. Ballabio[1,4,5,7], N. Brunetti-Pierri[1,7]. [1]*Telethon Institute of Genetics and Medicine, Pozzuoli, Italy;* [2]*Division of Metabolism, Universty Children's Hospital Zurich and Children's Research Center, Zurich, Switzerland;* [3]*Institute of Biomolecular Chemistry, National Research Council, Pozzuoli, Italy;* [4]*Department of Molecular and Human Genetics; Baylor College of Medicine; Houston, TX, USA;* [5]*Jan and Dan Duncan Neurological Research Institute, Texas Children's Hospital, Houston, TX, USA;* [6]*Division of Metabolism, University Children's Hospital Zurich and Children's Research Center, Zurich, Switzerland;* [7]*Department of Translational Medicine, Federico II University, Naples, Italy*
Email: brunetti@tigem.it

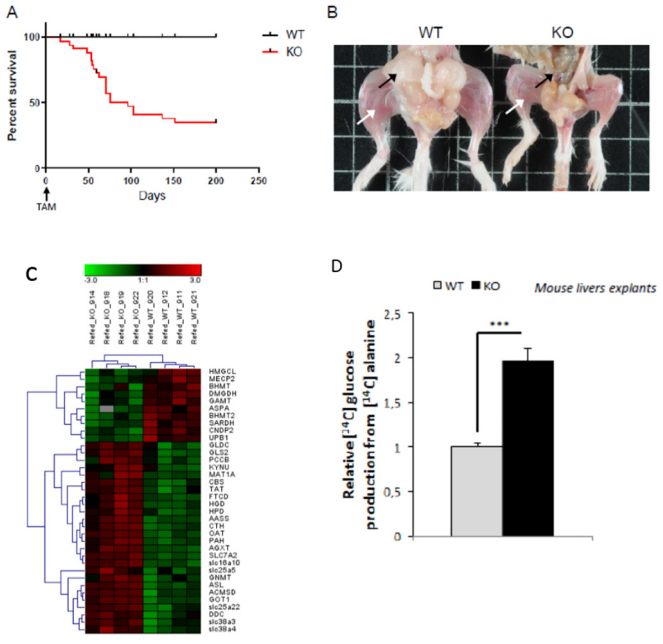
Background and Aims: Ammonia is a potent neurotoxin that is converted into urea by the healthy liver. Hyperammonemia is a common complication of a wide variety of both inherited and acquired liver diseases, such as urea cycle disorders, organic acidemias, or acute and chronic liver diseases. If not treated early and thoroughly, it results in encephalopathy and death. Available therapeutic options to treat hyperammonemia are often unsatisfactory. Autophagy is a lysosomal recycling pathway that plays a major role in metabolism. In this study, we investigated the role of hepatic autophagy in ammonia detoxification.
Method: Liver autophagy was investigated in well established mouse models of acute and chronic hyperammonemia in which C57BL/6 wild-type mice received intraperitoneal injections of ammonium chloride or were fed ad libitum with a diet supplemented with ammonium acetate (20% w/w), respectively. Ammonia detoxification was evaluated in mice with either induced or deficient autophagy. Pharmacological enhancement of autophagy was investigated in models of acute and chronic hyperammonemia, including thioacetamide-induced acute liver failure and ornithine transcarbamylase deficiency, the most frequent urea cycle disorder.
Results: Hepatic autophagy is triggered *in vivo* by hyperammonemia through an α-ketoglutarate-dependent inhibition of the mammalian target of rapamycin complex 1 (mTORC1). Ammonia detoxification capacity was impaired in mice with hepatic-specific suppression of autophagy. In contrast, autophagy enhancement by means of hepatic gene transfer of the master regulator of autophagy transcription factor EB (TFEB) or treatments with the autophagy activators rapamycin and Tat-Beclin-1 increased ureagenesis and protected against acute and chronic hyperammonemia. Moreover, stable isotope studies and liver metabolomic analyses suggested that during hyperammonemia autophagy potentiates ureagenesis by furnishing the urea cycle with key intermediates metabolites and preventing ammonia-induced depletion of ATP.
Conclusion: Our study suggests the novel concept that hepatic autophagy potentiates ureagenesis under both acute and chronic hyperammonemia. The enhancement of autophagy has potential for therapy of both primary and secondary causes of hyperammonemia. These findings may lead to development of new drugs promoting ammonia clearance in patients with hyperammonemia.

FRI-118

lkb1 inhibits the hepatic gluconeogenis by impeding the availability of amino acids

C. Perret[1], S. Charawi[2], J. Pierre-Alexandre[2], Raphaël Denis[3], T. Massire[4], B. Sultan[4], S. Nadia[4], S. Pierre[4], S. Mathilde[4], W. Maud[4], L. Marjorie[4], G. François[4], S. Luquet[3], P. Bossard[4]. [1]*Institut Cochin, Development Reproduction Cancer, Paris, France;* [2]*institut Cochin, Paris;* [3]*bfa University Paris 7;,* [4]*institut Cochin*
Email: Christine.Perret@Inserm.Fr

Background and Aims: Liver kinase B1 (LKB1) is a known inhibitor of hepatic gluconeogenesis. AMPK was proposed to be the kinase involved in this control, but recent reports demonstrated that the salt-inducible kinases (Sik) were the true gatekeeper effectors of *Lkb1*. However the mechanisms by which *Lkb1* controlled hepatic gluconeogenesis are still undefined.
Method: We developed a mouse model with a tamoxifen inducible hepatocyte-specific deletion of *Lkb1*. Mutant and control mice were analyzed by metabolic and proteomic approaches as well as IRM and indirect calorimetry.
Results: We confirmed that mice injected with tamoxifen to induce a hepatocyte-specific deletion of *Lkb1* revealed a fasted hyperglycemia two weeks after tamoxifen injection. In addition, we observed a striking phenotype at longer term. More than 60% of the mutant mice died in a cachexic context with a dramatic sarcopenia (Figure A-B). Analysis by IRM of the whole body composition in short-term mice (15 days after tamoxifen injection) showed a significant modification of the body composition of the mutant mice with a decrease of lean mass and an increase in fat mass although the body weight was unchanged. Proteomic analysis of liver of mutant and control mice identified the gluconeogenesis and amino acid metabolism as the TOP canonical pathways enriched in the liver of the *Lkb1* mutant mice. More specifically, there was a strong up-regulation of enzymes of the amino-acid catabolism and urea cycle in the liver of mutant mice, indicating that *Lkb1* played a critical role on the hepatic breakdown of the amino-acids (Figure C). The loss of lean mass that culminated in sarcopenia, combined with the hepatic breakdown of amino-acids observed in the *Lkb1* mutant mice suggested that *Lkb1* may control the availability of the amino-acids as gluconeogenic substrates. Using hepatocyte primary culture and liver explants, we showed that *Lkb1*-deficient hepatocytes have an increased capacity to synthetize glucose from the amino-acid, glutamine and alanine compared to controls (Figure D).



Conclusion: Altogether, our results showed that *Lkb1* inhibits gluconeogenesis by decreasing the availability of the amino acids as gluconeogenic precursors.

FRI-119

Liver biopsy derived induced pluripotent stem cells provide unlimited supply for the generation of hepatocyte-like cells.

D. Calabrese[1], G. Roma[2], S. Bergling[2], W. Carbone[2], V. Mele[1], S. Nuciforo[1], I. Fofana[1], B. Campana[1,3], D. Szkolnicka[4], D. Hay[4], J. Tchorz[5], T. Bouwmeester[5], S. Wieland[1], M. Heim[1,3]. [1]*University Hospital of Basel, Department of Biomedicine, Basel, Switzerland;* [2]*Novartis Institutes for BioMedical Research, Forum 1, Basel, Switzerland;* [3]*University Hospital of Basel, Division of Gastroenterology and Hepatology, Basel, Switzerland;* [4]*MRC Centre for Regenerative Medicine, Edinburgh, United Kingdom;* [5]*Novartis Institutes for BioMedical Research, Basel, Switzerland*
Email: diego.calabrese@unibas.ch

Background and Aims: Hepatocyte-like cells (HLCs) differentiated from induced pluripotent stem cells (iPSCs) have emerged as a promising cell culture model to study metabolism, biotransformation, viral infections and inherited liver diseases. However the derivation of iPSCs is restricted by ethical and procedural constraints. Furthermore, incomplete HLC differentiation remains a major challenge. iPSC may carry-on a tissue of origin dependent expression memory influencing iPSC differentiation into different cell types. Whether liver derived iPSCs (Li-iPSCs) maintain a liver specific gene expression profile is not known. It is also not known whether Li-iPSCs would allow the generation of more fully differentiated HLCs.
Method: Primary liver cells (PLCs) were expanded from liver needle biopsies and reprogrammed into Li-iPSCs using a non-integrative Sendai virus-based system. Li-iPSCs were differentiated into HLCs using established differentiation protocols. The HLC phenotype was characterized at the protein, functional and transcriptional level. RNA sequencing data were generated from the originating liver biopsies, the Li-iPSCs, fibroblast derived iPSCs, and differentiated HLCs, and used to characterize and compare their transcriptome profiles.
Results: PLCs were obtained from small pieces of liver biopsies and could be reprogrammed into Li-iPSCs. Li-iPSCs indeed retain a liver specific transcriptional footprint. Li-iPSCs can be propagated to provide an unlimited supply of cells for differentiation into Li-HLCs. Similar to HLCs derived from fibroblasts, Li-HLCs could not be fully differentiated into hepatocytes. Relative to the originating liver, Li-HLCs showed lower expression of liver specific transcription factors and increased expression of genes involved in the differentiation of other tissues.
Conclusion: PLCs and Li-iPSCs obtained from small pieces of human needle liver biopsies constitute a novel unlimited source for the production of HLCs. Despite the preservation of a liver specific gene expression footprint in Li-iPSCs, the generation of fully differentiated hepatocytes cannot be achieved with the current differentiation protocols.

FRI-120

Mechanisms of action of cortisol in steatotic and non-steatotic livers subjected to partial hepatectomy with vascular occlusion

E. Bujaldon[1], María E. Cornide-Petronio[1], E. Negrete-Sánchez[1], C.G. Ávalos De León[1], A.I. Álvarez-Mercado[1], J. Gulfo[2], Mónica Jiménez-Castro[3], F. Rotondo[1], J. Gracia-Sancho[4], C. Peralta[1,2]. [1]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Experimental Liver Surgery and Liver Transplantation, Barcelona, Spain;* [2]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain;* [3]*Transplant Biomedicals S.L., Barcelona, Spain;* [4]*Barcelona Hepatic Hemodynamic Laboratory, IDIBAPS, CIBEREHD, Barcelona, Spain*
Email: ebujaldonormaechea@gmail.com

Background and Aims: In clinical practice, partial hepatectomy (PH) under vascular occlusion, is a common technique used in hepatic surgery to avoid bleeding. Hepatic steatosis is a major risk factor in hepatic surgery, associated with high rates of complications and postoperative mortality. Cortisol is the main active hormone of the HPA axis, released as a response to stress, and it stimulates hepatocellular proliferation in PH without vascular occlusion. It is suggested that these effects rely upon the acetylcholine (ACh) signalling pathway. The aim of this study was to examine if the beneficial effects of cortisol, previously reported in PH, are applicable when vascular occlusion is necessary.
Method: Male Zucker rats, lean and obese, were used in the well-known model of 70% PH with vascular occlusion. We modulated the ACTH-cortisol pathway pharmacologically and studied levels of hepatic cortisol and enzymes involved in its metabolism, its relevance in hepatic injury and regeneration, as well as the underlying cortisol-ACh mechanisms in these animals.
Results: In this context, lean animals undergoing liver resection displayed no changes in cortisol, whereas cortisol levels in plasma and liver were elevated in obese animals due to an overexpression of cortisol-producing enzymes (11b-HSD1) and downregulation of cortisol clearing enzymes (5bR). Lean animals given exogenous cortisol showed high circulating cortisol but maintain low hepatic cortisol levels because of an upregulation of cortisol clearing enzymes (5aR1 and 5bR), thus avoiding its harmful effects on liver injury and regeneration. In obese animals, high plasmatic cortisol triggers a negative feedback loop through the HPA axis that maintains low circulating ACTH. However, it is not enough to counteract the rise in hepatic cortisol and consequently exacerbates tissue damage and regeneration failure. We also found that cortisol administration caused hepatic ACh accumulation in steatotic livers. ACh administration caused an increase in transaminases and lowered hepatic levels of PI3k/Akt and regenerative markers, exerting harmful consequences on hepatic injury and regeneration. These deleterious effects could be reverted with the administration of M3 muscarinic acetylcholine receptor antagonist, but not a7 nicotinic acetylcholine receptor antagonist.
Conclusion: In instances of PH under vascular occlusion, HPA fundamentals, hepatic cortisol levels and enzymatic shifts are all dependent on baseline liver status. Cortisol administration has virtually no impact on non-steatotic livers, whereas steatotic livers are actually harmed by exogenous cortisol. Strategies aimed to block cortisol activity in order to block ACh accumulation and/or blockade of M3 mAChR are probably worthwhile to protect steatotic livers and reduce the incidence of postoperative complications following PH under vascular occlusion.

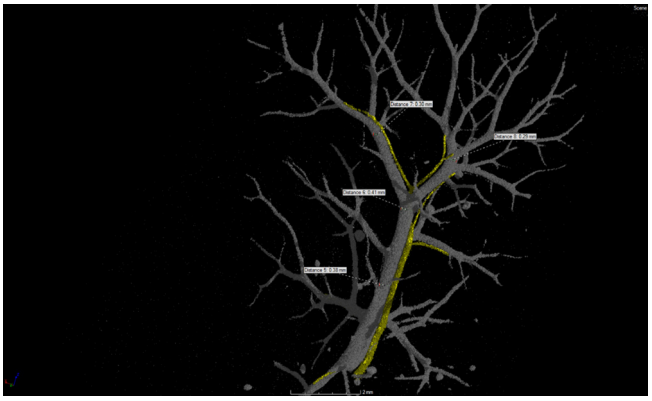
FRI-121

Double resin casting micro computed tomography (DUCT) of biliary and vascular system

S. Hankeova[1,2], T. Zikmund[3], M. Kavkova[3], A. Brinek[3], U. Lendahl[1], J. Kaiser[3], V. Bryja[2], E. Andersson[1]. [1]*Karolinska Institutet;* [2]*Masaryk University;* [3]*CEITEC - Central European Institute of Technology*
Email: simona.hankeova@ki.se

Background and Aims: DoUble resin Casting micro computed Tomography (DUCT) is a novel technique that aims to visualize two tubular lumenized structures at the same time. We applied DUCT to investigate the morphology of blood vessels and intra hepatic bile ducts (IHBDs) in a mouse model for Alagille syndrome (ALGS). ALGS is a multisystem pediatric disorder caused by a mutation in *JAGGED 1 (JAG1)* that is characterized by liver cholestasis due to a lack of IHBDs. Jag1 is a ligand in the Notch signaling pathway and is necessary for proper development of both blood vessels and IHBDs. To study ALGS liver disease we have developed a mouse model carrying a point mutation in *Jag1*, nicknamed Nodder (Jag1 H268Q, Ndr). Nodder mice are jaundiced at early postnatal stages and histological evaluation of liver shows IHBD abnormalities and missing hepatic arteries (Andersson *et al*, in press). Since blood vessels and IHBDs are 3D structures, histological sections do not provide sufficient information

to understand perfusion of whole liver by these structures, or their 3D interaction.
Method: DUCT employs injection of synthetic resin followed by micro computed tomography (μCT) to simultaneously assess multiple three dimensional (3D) networks. Hus it allows measurement and quantification of the architecture and perfusion of different systems and reveals the relationship between the two systems *in vivo*.
Results: The injection of two synthetic resins (MICROFIL®) with different radiopacities enabled us to reconstruct portal vein vascular branching in parallel with the IHBD network. DUCT revealed that homozygous Nodder portal vein branching is reduced with sprouting abnormalities, while bile ducts are tortuous and misplaced.



Conclusion: DUCT represents a unique tool to visualize the tubular systems and dissect out the relationships between any two lumenized structures in 3D.

FRI-122

Human skin-derived precusor cells: A potential source for cellular therapy of the liver

J.D. Kock[1], R.M Rodrigues[1], M. Najar[2], L. Verhoye[3], O. Govaere[4], L. Lootens[5], P.V. Eenoo[5], N. Sanders[6], L. Lagneaux[2], G. Leroux-Roels[3], T. Roskams[7], P. Meuleman[3], T. Vanhaecke[8], V. Rogiers[8]. *[1]Vrije Universiteit Brussel, In Vitro Toxicology and Dermato-Cosmetology, Brussels, Belgium; [2]Université Libre de Bruxelles, Laboratory of Clinical Cell Therapy, Belgium; [3]Universiteit Gent, Department of Clinical Chemistry, Microbiology and Immunology, Belgium; [4]Newcastle University, Institute of Cellular Medicine, United Kingdom; [5]Universiteit Gent, Doping Control Laboratory, Belgium; [6]Universiteit Gent, Laboratory of Gene Therapy, Belgium; [7]Katholieke Universiteit Leuven, Department of Imaging and Pathology, Belgium; [8]Vrije Universiteit Brussel, In Vitro Toxicology and Dermato-Cosmetology, Belgium*
Email: jdekock@vub.ac.be

Background and Aims: Often the only effective treatment for patients suffering from severe liver failure is orthotopic liver transplantation (OLT). Yet, the scarcity of donor organs and the complexity of the intervention significantly limits its general application. Therefore, new treatment options need to be urgently developed. Primary hepatocyte transplantations offer an alternative, but their limited availability, inability to significantly expand *ex vivo*, short life span and difficulties with cryopreservation necessitate the search for other sources of hepatic cells. A plausible solution could be offered by stem cell technology as these cells exhibit the ability of self-renewal and multi-lineage differentiation. Stem cell transplantation could be particularly interesting for patients suffering from severe liver dysfunction with no immediate chance of OLT. In this study, we investigated the potential of a multipotent human stem cell population, so-called human skin-derived precursor cells (SKPs), for the treatment of severe parenchymal liver damage.
Method: 0.5 million luciferase-positive SKPs were injected into the spleen of a transgenic murine model of liver deficiency (uPA$^{+/+}$/SCID). Ten weeks post transplantation, the SKP-derived hepatic grafts were characterized by dianabol metabolisation studies, bioluminescence imaging and immunohistochemistry. In many degenerative diseases, a pronounced inflammatory micro-environment is present that might increase the immunogenicity of SKP, facilitate their rejection and thus hamper their future therapeutic application. Therefore, *in vitro* and *in vivo* studies were performed to evaluate the immunogenicity of SKPs in the presence and absence of a pro-inflammatory environment.
Results: We found that SKPs successfully engraft, survive and repopulate the hepatic tissue in the uPA$^{+/+}$/SCID mouse model. Immunohistochemistry shows that SKPs acquire hepatic morphology, express hepatic markers and store glycogen. Most importantly, after oral administration of dianabol, *in vivo* generated SKP-derived hepatic grafts produce human-specific metabolites that can be detected in the urine of the chimeric mice demonstrating their *in vivo* human biotransformation capacity. In addition, we found that pro-inflammatory stimulation of SKPs does not increase their immunogenicity *in vitro* nor *in vivo*, but it evokes significant changes in their cytokine and growth factor secretion. In this context, we found that SKPs drastically increase their secretion of hepatocyte growth factor (HGF), a hepatotrophic factor, in the presence of inflammation. In-depth pathway analyses show that this increase in HGF is linked to the combined activation of CCL2, CSF2, IL6 and LIF.
Conclusion: Our data shows for the first time that SKPs can represent a potential source for cellular therapy of the liver.

FRI-123

PRMT5 deficiency results in liver abnormalities and impairs liver regenerationfollowing partial hepatectomy

Y.X. Tan[1], M. Caldez[1], N.K.M.V. Hul[1], C.L. Lee[1], P. Kaldis[1], E. Guccione[1,2]. *[1]Institute of Molecular and Cell Biology, Singapore; [2]Icahn School of Medicine at Mount Sinai*
Email: yxtan@imcb.a-star.edu.sg

Background and Aims: Arginine methylation is a major post-translational modification that regulates a myriad of biological processes including transcription, pre-mRNA splicing, mRNA translation and cell signalling. PRMT5 is the major mammalian type II arginine methyltransferase and plays an essential role in regulating gene expression and pre-mRNA splicing. Constitutive genetic ablation of PRMT5 caused early embryonic lethality (E3.5) and maintenance of its activity in proliferating cells is required for growth and survival. Therefore, it remains unclear if and how PRMT5 plays a role during hepatogenesis and in the adult liver during liver regeneration.
Method: PRMT5 was deleted specifically in the liver in PRMT5flox/flox ALB-Cre (PRMT5 LKO) mice or in hepatocytes only by injecting AAV8-TBG-Cre into adult PRMT5flox/flox mice (PRMT5 HKO). 70% partial hepatectomy was performed on these mice.
Results: PRMT5 LKO mice are born at Mendelian ratio and are viable and fertile through adulthood. However, they have slightly reduced body weight compared to control mice. Macroscopically, the livers of PRMT5flox/flox ALB-Cre mice have uneven surfaces, although liver-to-body weight ratio did not differ from control mice. Histological examination revealed marked multifocal hepatocellular (periportal, coalescing and random) hypertrophy accompanied by anisokaryosis, karyomegaly, binucleation and increased hepatocellular mitoses. Oval cell proliferation and bile duct hyperplasia were also observed. We detected small but significant increases in the ALT and ALP levels in PRMT5 LKO mice, suggesting mild liver dysfunction. On the other hand, deleting PRMT5 in adult hepatocytes in PRMT5 HKO mice did not result in liver abnormalities or dysfunction one month post deletion. During liver regeneration in wildtype mice, PRMT5 protein is upregulated, suggesting it may play a role in the regenerative process. Accordingly, following 70% partial hepatectomy, PRMT5 HKO mice have reduced liver to body weight ratio compared to control

mice one week post surgery. This correlated with reduced hepatocyte mitoses and increased steatosis at 36h and strong oval cell activation at 96h post liver resection.
Conclusion: Our data suggests that in the absence of PRMT5, hepatocytes are unable to proliferate and compensatory mechanisms such as cellular hypertrophy and oval cell activation are triggered. We are currently investigating the molecular mechanism(s) by which PRMT5 regulates hepatocyte proliferation.

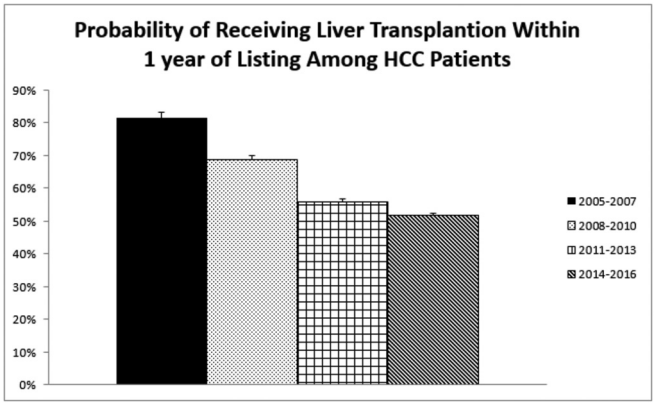
FRI-124
Bile duct organogenesis using ECM micropatterning
B. Latifa[1], M.-A. Elsa[2], F. Alexandra[2], F. Dominique[3], J.-C. Duclos-Vallée[4], P. Dupuis-Williams[1,5]. *[1]INSERM U1174, Université Paris Sud, ORSAY, France; [2]CEA/DRF/PCV/BIG, INSERM U1160, Paris, France; [3]Institut Pasteur, Paris, France; [4]Hôpital universitaire Paul Brousse, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France; [5]ESPCI, Paris, France*
Email: pascale.dupuis-williams@u-psud.fr

Background and Aims: Bile duct disease accounts for a significant part of liver transplants. Most biomimetic liver projects though, have precluded the construction of a functional bile duct system, mostly because of the difficulty of procuring cholangiocytes, the biliary epithelial cells. As a result, experimental models and mechanisms of tubulogenesis, which have been recently developed for kidney tubules and vascular networks are still lacking for bile ducts.
Tubulogenesis is a complex process that requires the orchestration of multiple molecular pathways including cell surface receptors, cell matrix, adhesion molecules, the cytoskeleton and vesicular transport. Interestingly, the recent input of bio-engineered microfabrication techniques like protein and cell micropatterning, stereolithography or microfluidics brought opportunities to rationalize bioengineered tissue construction.
The aim of our work is to identify in vitro conditions (extracellular matrices: ECM, topological constraints and needs for co-culture with ectopic cell types) that will allow the construction of functional single or interconnected biliary ducts from self-organization of cholangiocytes or liver precursor cells.
Methods and Results: Based on our previous work showing that biliary cells can self-organize into luminal structures when grown in appropriate 3D ECM, we further aimed to construct biliary structures of given topologies. This work explores how biliary cells may develop simple or complex 3D luminal structures whose topologies are defined in 2D by micropatterning or in 3D by stereolithography.
In a first step, biliary cells were grown in 2,5D on ECM surfaces of simple defined geometries obtained by micropatterning. This step allowed us to probe the ECM and topological conditions that favor the 3D self-organization of biliary cells into luminal organoids.
ECM conditions and critical dimensions inducing efficient self-organization of differentiated biliary cells into luminal spheres or single tubes have been identified. Further work aims in inducing organogenesis from hepatic progenitors and in co-culture conditions with hepatic or endothelial cells.
In a second step, biliary cells were grown in complex 3D hydrogel architectures built by stereolithography to induce the development of interconnected functional tubes, where cell proliferation, migration and coalescence conditions can be recorded. This work in progress contributes to the identification of topological cues for self-organogenesis of bile ducts cells from differentiated hepatic cells.
Conclusion: This work explores 3D self-organogenesis of biliary cells cultured in simple or complex micropatterned 2D or 3D topologies. We have already shown that biliary cells self-organize into luminal structures whose geometry can be controlled by restricting cell adhesion.

Liver tumours: Clinical aspects except therapy

FRI-127
While hepatocellular carcinoma (HCC) has become the leading indication for liver transplantation in the United States, the probability of receiving liver transplantation among adults with HCC has rapidly declined
J. Wang[1], R.G. Gish[2], B. Liu[3], T. Bhuket[3], R. Wong[3]. *[1]California Pacific Medical Center, Medicine, San Francisco, United States; [2]Stanford Health Care, Gastroenterology and Hepatology, Palo Alto, United States; [3]Alameda Health System - Highland Hospital, Gastroenterology and Hepatology, Oakland, United States*
Email: rowong@alamedahealthsystem.org

Background and Aims: The number of patients with hepatocellular carcinoma (HCC) listed for liver transplantation (LT) has been steadily increasing. However, demand for LT far outweighs the supply of donor organs, and results in disparities in receipt of LT that persist and may be increasing. We aim to evaluate overall trends in probability of receiving LT among U.S. adults with HCC with a focus on age-specific and insurance-specific disparities.
Method: Using data from the 2005–2016 United Network for Organ Sharing LT registry, probability of receiving LT among U.S. adults with HCC was stratified by age (age < 50, 50–59, 60–69, ≥70), year of listing (2005–2007, 2008–2010, 2011–2013, 2014–2016) and insurance type (private/commercial [PC], Medicare [MC], Medicaid [MA] and Veterans Affairs [VA]). Comparison of LT rates between groups utilized Kaplan Meier methods and log-rank testing. Multivariate Cox proportional hazards models evaluated for independent predictors of receiving LT.
Results: Among 24,044 HCC patients listed for LT (8.5% age <50 years, 43.0% 50–59 years, 43.6% 60–69 years, and 4.8% ≥70 years), the majority had PC insurance (56.2%), followed by MC (26.6%), MA (14.5%), and VA (2.7%). When stratified by age, probability of receiving LT within 1 year of listing was highest among HCC patients age 50–59 years (64.6%) and lowest among those age 60–69 years (58.1%), p < 0.01. When stratified by insurance, 1-year probability of receiving LT was highest among HCC patients with PC (63.6%) and lowest among those with MC (52.8%), p < 0.001. With later time periods, the probability of receiving LT for HCC patients declined dramatically (1-year probability, 81.5% in 2005–2007 vs. 51.7% in 2014–2016, p < 0.001). On multivariate regression, increasing age was not associated with likelihood of receiving LT. HCC patients in the most recent era (2014–2016) had significantly lower likelihood of receiving LT compared to 2005–2007 (HR 0.43, 95% CI 0.40–0.46, p < 0.001). Compared to HCC patients with PC, those with MA were significantly less likely to receive LT (HR 0.79, CI 0.75–0.84, p < 0.001).



Conclusion: Despite the increasing number of adults with HCC awaiting LT in the U.S., the probability of receiving LT has declined significantly, and HCC patients in 2014–2016 were 57% less likely to receive LT compared to 2005–2007. Furthermore, HCC patients with Medicaid insurance were significantly less likely to receive LT compared to patents with private/commercial insurance.

FRI-128

Two new blood tests for identifying patients with chronic liver diseases, at high risk of primary liver cancer

T. Poynard[1,2], V. Peta[3], M. Munteanu[3], J. Moussalli[1], M. Rudler[1], P. Lebray[1], J. Massard[1], R. Pais[1], L. Bonyhay[1], F. Charlotte[1], V. Thibault[1], O. Lucidarme[1], D. Eyraud[1], E. Savier[4], O. Scatton[1], M.A. Valantin[1], Y. Ngo[5], A. Ngo[5], F. Drane[5], F. Bismut[4], L. Fartoux[4], O. Deckmyn[5], P. Cacoub[4], O. Rosmorduc[4], C. Housset[6], D. Thabut[4], V. Ratziu[4]. *[1]APHP, Hepatology, Paris, France; [2]UPMC, UMR938; [3]BioPredictive, Research, Paris, France; [4]APHP; [5]BioPredictive; [6]UPMC*
Email: tpoynard@teaser.fr

Background and Aims: The identification of patients (pts) with chronic liver disease and a high-risk profile of primary liver cancer (PLC) is needed. We hypothesized that certain FibroTest (FT) components mediating hepatoprotection could be predictive of the development of PLC. The main aim was to assess the predictive value of two new blood tests in pts with chronic liver disease who underwent FT in the prospective FibroFrance cohort NCT01927133 since 1997.
Method: 2 panels of components were constructed (Patents pending) in a baseline population (P0) using AUROCs and logistic regression, one (HR-Test) to identify pts with a high-risk profile and one combining HR and alpha-fetoprotein (HR-AFP). Their prognostic values were longitudinally assessed using KaplanMeier, Cox model and AUROCs in pts who did not develop PLC at least 1 year (yr) after baseline (P1), and in a subpopulation who received at least 2 tests to assess intra-patient variability (P2).

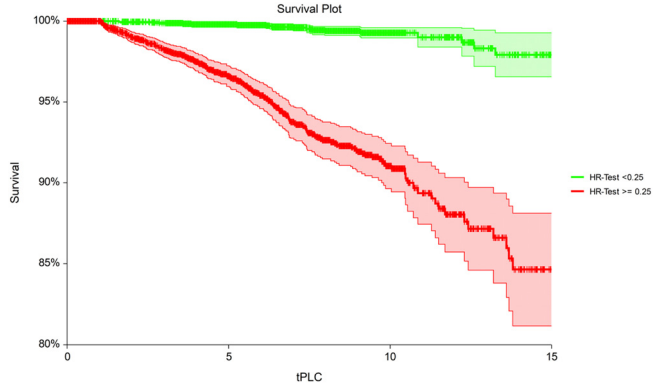


Figure 1: 15-year survival without occurrence of primary liver cancer (95% CI) in patients with HR-Test <0.25 versus those > = 0.25

Results: 9,925 pts were included in P0, 34%, 20%, 12%, 5% and 29% with CHC, CHB, NAFLD, ALD and other or mixed causes, respectively. The HR-Test for the diagnosis of 134 contemporaneous PLC had an AUROC (95%CI) = 0.903 (0.874–0.926) that was higher than FT .877 (0.845–0.903 p = 0.01) and AFP 0.810(0.725–0.862 p = 0.03). In P1, 226 incident PLC (98% HCC) occurred/9791 pts, with a 15-yr-survival without PLC (SwC)) 95%CI = 90% (88–92). Pts with an HR-Test <0.25 (HR- n = 6020) had SwC = 99.3% (99.0–99.6) at 10yr and 97.7% (96.2–99.1) at 15yr (28 PLC), compared to pts >=0.25 (HR+ n = 3771) 91.1% (89.6–92.5) at 10yr and 84.5% (80.9–88.1) at 15yr (198 PLC). The risk (hazard-ratio) of PLC was 12.7(9.6–16.6 p < 0.0001) times greater in the HR+ than HR- pts (Figure). PLC occurred less often in HR- than in HR+ pts, whatever the cause of liver disease: 14/1727 vs 114/1637, 6/1532 vs 27/475, 4/682 vs 20/416, and 2/159 vs 27/317, in CHC, CHB, NAFLD, and ALD respectively (all p < 0.001). HR-AFP had an AUROC = 0.860 (0.833–0.883) which was higher than that of single tests: AFP (0.740; 0.698–0.778; p = 0.01), HR1 (0.802; 0.772–0.828 p = 0.0001) and FT (0.813; 0.784–0.838 p = 0.0001). In P2, among 1818 pts with at least 2 repeated HR-tests, 16 incident PLC occurred at 10yr, (SwC = 70%; 49–91). When repeated 5.2yr (5.0–5.4) later, the HR-Test had a higher AUROC than the first test 0.851 (0.796–0.892) vs 0.772 (0.699–0.829) at baseline (p = 0.001). The results of Cox sensitivity analyses, which take into account the repeated tests, the impact of antiviral treatment, and HIV infection were similar. These results were confirmed by internal validation but external validation must be performed.
Conclusion: The HR-Test identified a group of pts at high risk of PLC among those with CHC, CHB, NAFLD and ALD. Combining the HR-Test and a specific cancer marker such as AFP significantly increased the value of a single test.

FRI-129

Contrast-enhanced ultrasound for non-invasive diagnosis of hepatocellular carcinoma: A comparison between CEUS LI-RADS and ESCULAP criteria in a large high-risk cohort of patients

A. Saviano[1], L. Riccardi[2], M.A. Zocco[2], T. Baumert[1,3], G.L. Rapaccini[2], M. Pompili[2], A. Gasbarrini[2]. *[1]Inserm Unit 1110; Institut de Recherche Sur Les Maladies Virales et Hépatiques, Strasbourg, France; Université de Strasbourg, Strasbourg, France; [2]Internal Medicine, Gastroenterology and Liver Disease Unit, Policlinico "A. Gemelli", Catholic University, Rome, Italy; [3]Institut Hospitalo-Universitaire, Pôle Hépato-Digestif, Nouvel Hôpital Civil, Strasbourg, France*
Email: saviano.ant@gmail.com

Background and Aims: Contrast-enhanced ultrasound (CEUS) for the non-invasive diagnosis of hepatocellular carcinoma (HCC) in patients with liver cirrhosis raised concerns for the risk of misdiagnosis with intrahepatic cholangiocarcinoma (ICC) and was removed as diagnostic technique from international guidelines. To address this issue, the American College of Radiology recently released the CEUS LI-RADS criteria for HCC diagnosis in liver cirrhosis. Other criteria, named ESCULAP (Erlanger Synopsis of Contrast-enhanced Ultrasound for Liver lesion Assessment in Patients at Risk) were also recently published and reported to have a better accuracy compared to CEUS LI-RADS. Aim of this study was to assess and compare, for the first time, the diagnostic accuracy of these criteria in a large independent cohort.
Method: Between 2005 and 2015, 181 nodules in 156 patients with chronic liver disease at high HCC risk were retrospectively collected in the Center of Liver Diseases at the Catholic University of Rome and were enrolled in this study. The diagnostic accuracy of the CEUS LI-RADS LR-5 and ESCULAP-4 categories for the diagnosis of HCC was assessed and compared. The 2005 AASLD criteria applied to HCC > 1cm were also evaluated. A comparison of the diagnostic performance of the categories CEUS LI-RADS LR-M (non-HCC malignancies) and ESCULAP-C (ICC diagnosis) was made. The diagnostic reference was histology or CT/MRI.
Results: The 58.6% of patients had HCV cirrhosis and the median nodule size was 1.8 cm (range 0.7–9.0 cm). HCC represented the 78.5% of diagnosis while ICC the 2.2%. LR-5 category (52% of nodules) had a positive predictive value (PPV) for HCC of 100% and a sensitivity of 58% with no risk of misdiagnosis with ICC. ESCULAP-4 (76% of nodules) had a PPV of 92% and a sensitivity of 77% for HCC. In this cohort, the 2005 AASLD criteria showed a PPV and a sensitivity for HCC diagnosis of 93% and 64%, respectively. No nodules could be classified as ICC using the ESCULAP-C category whereas all the non-HCC malignancies (included all the ICCs) were classified as LR-M according to CEUS LI-RADS.
Conclusion: CEUS LI-RADS LR-5 category has a high specificity and PPV for HCC diagnosis eliminating the risk of failure to diagnose ICC. ESCULAP criteria have higher sensitivity but lower specificity for HCC

diagnosis and do not avoid the risk of ICC misdiagnosis. A marked and/or early wash-out in CEUS (LR-M feature) is the most important feature for CEUS diagnosis of ICC arising in liver cirrhosis.

FRI-130

Tumour progression and recurrence after direct acting antiviral therapy for hepatitis C in patients with previously treated or active hepatocellular carcinoma

M. Wong, G. Mccaughan, S. Mason, B. Moore, D. Bowen, D. Koorey, S. Strasser. *Royal Prince Alfred Hospital, AW Morrow Gastroenterology and Liver Centre, Camperdown*
Email: may.wong1@health.nsw.gov.au

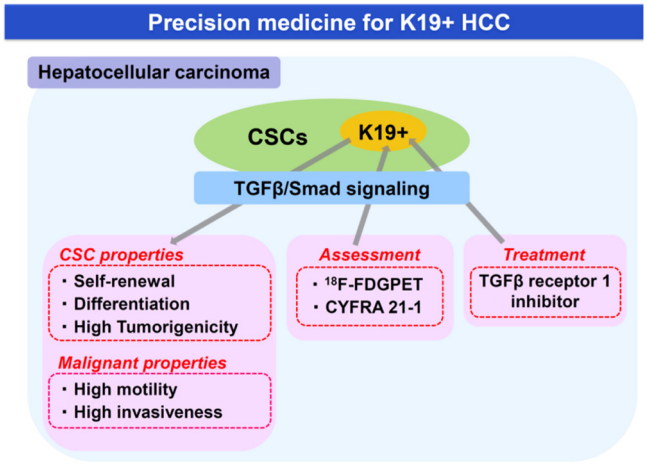
Background and Aims: Data on tumour recurrence rate in patients with previously successfully treated hepatocellular carcinoma (HCC) after direct acting antiviral (DAA) therapies are conflicting. Data on tumour progression in patients with active HCC at the time of DAA therapy are sparse. Furthermore, the significance of indeterminate nodules and its role in HCC development is unclear. We explore the incidence and pattern of HCC events, sustained virological response (SVR) rates and patient outcomes of individuals with a history of HCC who have had DAAs.
Method: All HCV patients with a prior history of HCC who started DAAs in a transplant-referral center were included. Clinical, laboratory and radiologic characteristics at DAA baseline and during followup (FU) were registered. Patients were grouped by HCC status at time of DAA therapy; complete response (CR), ongoing active disease (AD) and indeterminate nodules (IN). DAAs were administered for 12 or 24 weeks according to label.
Results: 80 patients with a prior history of HCC received DAAs between March 2014–2017. 40 had no evidence of active HCC (CR) before starting DAA. 30 had active HCC at time of DAA therapy (AD), and of those, 13 had residual disease from previously treated HCC. 9 had indeterminate nodules (IN). For those with CR, baseline BCLC stage at HCC treatment was BCLC-0/A in 94% and 32/40 received locoregional therapy (chemoembolization/ablation). Median time to DAA initiation post CR was 9.3 months. HCC recurrence was 22/40 (55%) at median 7.4 months (14/22 (64%) within 6 months after start of DAAs). In those with AD at time of DAAs, progression occurred in 25/30 (83.3%) at a median 7.6 months from start of DAAs. At the time of progression for patients with AD their tumor biology seemed to be more aggressive with instances of rapid progression to BCLC and D. 9 patients had IN at the time of DAA initiation; 4 developed HCC beyond six months from start of DAAs. With regard to rates of SVR, 97.4% of patients with CR achieved SVR, in comparison to 55.6% in those who still had active HCC, where a high relapse rate was observed. Overall, tumour-related mortality was seen in 4 patients; where 3 had recurrent HCC within 6 months of DAA initiation.
Conclusion: As previously reported, DAA treatment may be associated with high rates of rapid tumour recurrence in patients with prior HCC CR. Furthermore, patients with active HCC at the time of DAA therapy are at risk of rapid progression. Deferral of antiviral treatment in patients with HCC should be considered.

FRI-131

Identification of keratin 19-positive cancer stem cells associating human hepatocellular carcinoma using 18F-FDGPET and CYFRA 21-1

T. Kawai, T. Ishii, K. Yasuchika, S. Seo, S. Ogiso, Y. Miyauchi, R. Yamaoka, H. Kojima, T. Minami, K. Fukumitsu, S. Uemoto. *Graduate School of Medicine, Kyoto University, Department of Surgery, Kyoto city, Japan*
Email: u12323@kuhp.kyoto-u.ac.jp

Background and Aims: The current lack of tools for easy assessment of cancer stem cells (CSC) prevents the development of therapeutic strategies for hepatocellular carcinoma (HCC). We previously reported that keratin 19 (K19) is a novel HCC-CSC marker associated with transforming growth factor beta (TGFb)/Smad signaling, and that K19+ HCC-CSC could be a new therapeutic target of TGFb receptor 1 inhibitor. To develop precision medicine for K19+ HCC, we examined whether K19+ HCC-CSC can be tracked using PET with 18F-fluorodeoxyglucose (18F-FDGPET) and cytokeratin 19 fragment (CYFRA 21-1).
Method: K19 and glucose transporter-1 (GLUT1) expression were evaluated by immunohistochemistry in consecutive 255 HCC patients who underwent liver resection or liver transplantation. Preoperative SUV, tumor-nontumor SUV ratio (TNR), and preoperative serum CYFRA 21-1 level were compared in K19+/K19- patients. Using HCC cell lines encoding with a K19 promoter-driven enhanced GFP, 18F-FDG uptake, GLUT1 expression, and supernatant CYFRA 21-1 level were examined in FACS-isolated K19+/K19- cells.
Results: In HCC patients, K19 expression was significantly correlated with GLUT1 expression, FDG accumulation, and serum CYFRA 21-1 levels. ROC analyses revealed that among preoperative clinical factors, TNR (AUC = 0.87, $p < 0.001$) and serum CYFRA 21-1 (AUC = 0.81, $p < 0.001$) were most and second-most sensitive indicator of K19 expression in HCC tumors. In HCC cells, FACS-isolated K19+ cells displayed significantly higher FDG uptake and supernatant CYFRA 21-1. Moreover, gain/loss of function experiments confirmed that K19 regulates FDG uptake and CYFRA 21-1 level through TGFb/Smad signaling including Sp1 and its downstream target GLUT1.



Conclusion: 18F-FDGPET and CYFRA 21-1 can be used to predict K19 expression in HCC, and should thereby aid in the development of individual therapeutic strategies targeting K19+ HCC-CSC.

FRI-132

Hepatocellular carcinoma (HCC) after direct-acting antivirals (DAA) does not show differences at diagnosis compared with HCC after IFN-based treatments. Results of a national HCC Registry in Spain

C. Rodríguez de Lope[1], M.T. Ferrer[2], M. Sala[3], S. Pascual[4], A.M Matilla[5], I. Ortiz[6], P. Rendon[7], B. Figueruela[8], J. Fuentes[9], D.E.M. Arraez[10], A.G. Moya[11], A. Lué[12], B. Minguez[13], M.R. Alemany[14], F.M. Blazquez[15], C.Gónzalez Muñoz[16], F.P. Renedo[17], A. Raga[18], C. Fernández Marcos[19], J.M.R. Zabal[20], J.L. Lledó[21], C. Muñoz Codoceo[22], S. Montoliu[23], G. Pacheco del Rio[24], J.M.C. Suaña[25], G.J.S. Rodriguez[26], T.H. Alsina[27], I.E. Apestegui[28], M.J.D. Medina[29], A Ortega-Alonso[30], G.d.l.R. Bellvis[31], A.G. Ramirez[32], I. Castello[33], L.C. Garcia[34], M. Varela[35]. *[1]Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain; [2]Hospital Universitario Virgen del Rocio, Sevilla, Spain; [3]Hospital Universitario Germans Trias i Pujol, Badalona, Spain; [4]Hospital General Universitario de Alicante. CIBERehd, Alicante, Spain; [5]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [6]Hospital Dr. Peset, Valencia, Spain; [7]Hospital Universitario Puerta del Mar, Cádiz, Spain; [8]Hospital de Valme, Sevilla, Spain; [9]Hospital Universitario Miguel Servet, Zaragoza, Spain; [10]Hospital Universitario de Canarias, Santa Cruz de Tenerife, Spain; [11]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [12]Hospital*

Clínico Universitario Lozano Blesa, Zaragoza, Spain; [13]Hospital Universitari Vall d'Hebrón, Barcelona, Spain; [14]Consorci Sanitari de Terrassa, Terrassa, Spain; [15]Hospital Universitario de Basurto, Bilbao, Spain; [16]Hospital General Universitario de Valencia, Valencia, Spain; [17]Hospital Universitario Puerta de Hierro, Madrid, Spain; [18]Hospital Universitari Mutua de Terrassa, Terrassa, Spain; [19]Hospital Universitario de Burgos, Burgos, Spain; [20]Hospital Costa del Sol, Marbella, Spain; [21]Hospital Universitario Ramón y Cajal, Madrid, Spain; [22]Hospital 12 de Octubre, Madrid, Spain; [23]Hospital Universitario Joan XXIII, Tarragona, Spain; [24]Hospital Universitario La Ribera, Valencia, Spain; [25]Hospital de Mataró, Mataró, Spain; [26]Hospital Universitario Puerto Real, Cádiz, Spain; [27]Hospital San Pedro, Logroño, Spain; [28]Complejo Hospitalario de Navarra, Pamplona, Spain; [29]Hospital Clínico San Carlos, Madrid, Spain; [30]Hospital Clínico Universitario Virgen de la Victoria, Málaga, Spain; [31]Hospital Esperit Sant, Barcelona, Spain; [32]Hospital Universitario Lucus Augusti, Lugo, Spain; [33]Hospital Francesc de Borja, Valencia, Spain; [34]Hospital San Jorge, Huesca, Spain; [35]Hospital Universitario Central de Asturias, Oviedo, Spain
Email: carlorodriguez@humv.es

Background and Aims: Direct-acting antivirals (DAA) represent a revolution for the treatment of hepatitis C virus (HCV), with rates of sustained virological response (SVR) > 90%. Recent publications suggest that incidence of HCC after DAA could be increased and more aggressive due to an imbalance of the immune surveillance. Aim: analyze if HCV patients diagnosed with HCC have differences in tumor stage depending on the antiviral treatment received.
Method: We used data from the Spanish HCC-Registry supported by the AEEH and CIBERehd (prospective database of patients with primary liver tumors in Spain).
Results: Between March 1, 2016 and October 31, 2017, 35 centers registered 843 primary liver tumors: 809 (96%) HCC, HCV + 377; available information of previous antiviral treatment in 263: 125 had never received antiviral treatment and 138 had received at least one (27 IFN-based; 111 DAA). Last antiviral treatment started at a median of 338 days (range 12–3640) before HCC diagnosis. Patients that had received antiviral treatment had 1) higher SVR rate (80.4% vs 3.2%, $p < 0.001$); 2) earlier stages (BCLC 0-A 68.6% vs 48.8%; $p < 0.001$); 3) more radical treatments [resection, ablation, transplant] (61.4% vs 32.2%; $p < 0.001$); 4) higher albumin (4 vs 3.6 g/dl; $p < 0.001$); 5) lower INR (1.11 vs 1.18; $p = 0.028$); and 6) more frequently diagnosed under surveillance programs (80% vs 37.2%; $p < 0.001$). Considering only patients under surveillance, those with previous antiviral treatment were younger (60.1 vs 74.7 years, $p = 0.003$); earlier stages (BCLC 0-A 79.2% vs 52.4%, $p < 0.001$); more radical treatments (71.6% vs 33.3%, $p < 0.001$). Comparing patients according to the last antiviral treatment (IFN vs DAA), patients treated with IFN had larger main nodule (34 mm vs 25 mm, $p = 0.04$); more extrahepatic dissemination (23.1% vs 8.1%, $p = 0.028$); and higher AFP (16.4 vs 7.6 ng/ml, $p = 0.022$). These differences disappeared when considering patients under surveillance only.
Conclusion: Patients that have received antiviral treatment were diagnosed in earlier stages, partially because of better adherence to surveillance programs. Patients whose last treatment was DAA were diagnosed with smaller tumors, less extrahepatic spread and lower AFP compared to patients that had received IFN-based treatment. However considering only patients under surveillance, these differences disappeared. Surveillance is key for HCC detection in patients with cirrhosis even after successful antiviral treatment.

FRI-133

Regression of fibrosis stage after treatment in patients with HFE haemochromatosis and severe fibrosis at diagnosis: relevance to hepatocellular carcinoma

E. Bardou-Jacquet[1,2,3], M. Emilie[1], A. Gregory[3], G. Ramm[4], L. Ramm[4], M. Jeff[5], D. Jeannette[3], C. Andrew[6,7], L. Fabrice[1,8], T. Bruno[9], L. Powell[3], Y. Deugnier[1]. *[1]CHU Rennes, Liver disease department, Rennes, France; [2]CHU Rennes, National Reference Centre for Haemochromatosis and Iron Metabolism disorder, Rennes, France; [3]QIMR Berghofer Medical Research Institute, Iron Metabolism Laboratory, Brisbane, Australia; [4]QIMR Berghofer Medical Research Institute, Hepatic Fibrosis Group, Brisbane, Australia; [5]CHU Rennes, INSERM CIC1414, Rennes, France; [6]Faculty of Health Sciences, University of Queensland, Brisbane, Australia; [7]Envoi Specialist Pathologists, Brisbane, Australia; [8]CHU Rennes, INSERM CIC1414, France; [9]CHU Rennes, Pathology Department, France*
Email: edouard.bardou-jacquet@chu-rennes.fr

Background and Aims: HFE hemochromatosis treatment by removing iron through bloodletting is effective and is standard therapy. Regression of fibrosis stage following treatment has been reported, although reversal of cirrhosis itself remains controversial. Our aim was to assess fibrosis stage regression and the ensuing risk of hepatocellular carcinoma (HCC) in patients with HFE haemochromatosis after treatment.
Method: The Rennes and Brisbane databases of HFE C282Y homozygous patients were searched for patients with F3 or F4 fibrosis stage at diagnosis and at least one second liver biopsy (LB) during follow-up. Initial clinical and biological data were recorded. Follow-up information collected included HCC occurrence and fibrosis stage.
Results: Overall, 112 patients (89% males) were included (71 with F4; 41 with F3 fibrosis). At diagnosis, the median age was 46[40–53] years, serum ferritin was 2940[2000–4060] μg/l and transferrin saturation was 87[80–95] %. The median time between first and last LB was 9.25[3.5–15.3] years. Median follow-up time was 16.9[9.5–23.75] years. HCC developed in 35 patients during the study period (3 had F2, 1 had F3 and 30 had F4 fibrosis at last LB).
Of the F3/F4 patients at diagnosis, 44 (39%) had fibrosis ≤ F2 at last LB. HCC occurred in 31(45.5%) patients with F3/F4 fibrosis at last LB, versus 4(9%) patients with fibrosis ≤ F2 at last LB ($p < 0.001$). The incidences were, respectively, 29.4 and 4.6 per 1000 person-years.
Of the F4 patients at diagnosis, 14 (19.7%) had fibrosis ≤ F2 at last LB. HCC occurred in 31 (54.4%) patients with F3/F4 fibrosis at last LB, versus 3 (21.4%) patients with fibrosis ≤ F2 at last LB ($p = 0.03$). The incidences were, respectively, 35.3 and 12.0 per 1000 person-years.
In F3/F4 patients, multivariate analysis showed that younger age at diagnosis, and lower GGT were significantly associated with fibrosis regression to ≤ F2 at last LB. In F4 patients, multivariate analysis showed that fibrosis stage regression was associated with a reduced, HCC risk.
Conclusion: Our results show that in HFE hemochromatosis, fibrosis stage improves after treatment even in patients with severe fibrosis (F3 and F4). Further, while our study does not allow us to assess the question of cirrhosis reversibility, the reduction in fibrosis stage is associated with a significant reduction of HCC risk. Respective roles of duration of iron overload and fibrosis regression requires further investigation. Our findings are clearly relevant to surveillance for HCC and show the importance of aggressive therapy in such patients to reduce their iron burden.

FRI-134

Nonalcoholic fatty liver disease is the most common cause of hepatocellular carcinoma (HCC) in individuals without cirrhosis: A United States multicenter study

A. Delemos[1], L. Dakhoul[2], P. Roche[1], E. Miller[3], H.A. Sbeih[3], E. Mao[3], A. Scanga[4], E.V. Gomez[2], S. Gawrieh[2], N. Chalasani[2], J. Wattacheril[5]. *[1]Carolinas Healthcare System; [2]Indiana University School of Medicine; [3]MD Anderson Cancer Center; [4]Vanderbilt University Medical Center; [5]Columbia University College of Physicians and Surgeons*
Email: andrew.delemos@carolinas.org

Background and Aims: The etiologies and characteristics of HCC arising in patients with chronic liver disease but without cirrhosis are not well understood. The aims of this study were to (i) determine the frequency of non-cirrhotic HCC relative to cirrhotic HCC seen at 5 U.S. academic liver centers over time, and (ii) to compare patient and tumor characteristics among the two groups.

Method: Patients diagnosed with HCC between January 2000 through June 2014 were identified using center specific cancer registries. After confirming the diagnosis of HCC in the medical record, clinical information, tumor characteristics, and survival data were extracted. Patients were categorized as non-cirrhotic (when ascertained with either very high or high probability) or as confirmed cirrhosis as per Mittal S, et al. criteria (CGH 2016; 14: 124–131). The number of non-cirrhotic and cirrhotic HCC cases was compared over 5-year intervals (2000–2004, 2005–2009, and 2010–2014).
Results: A total of 2,454 patients with HCC were available for analysis. 2,095 HCC cases (85%) occurred in patients with cirrhosis, whereas 359 patients (15%) had HCC without underlying cirrhosis. The frequency of non-cirrhotic HCC decreased over time (2000–04, 23%; 2005–09, 18%; 2010–2014, 11%), while there was an increase in cirrhotic HCC (81.5%, 82.2%, and 89% for respective periods, $p < 0.001$). Non-alcoholic fatty liver disease (NAFLD) was the most common liver disease etiology (45%) in non-cirrhotic HCCs compared to viral hepatitis and alcohol (79%) in cirrhotic HCCs ($p < 0.001$). Patients with cirrhosis had higher mortality rate with a HR of 1.28 (1.12–1.47; $p < 0.01$). Selected characteristics of the two groups are shown below.

Table 1: Characteristics of HCC Patients with and without Cirrhosis

Variable	HCC with cirrhosis (n = 2095)	HCC without cirrhosis (n = 359)	P-value
Age, mean (SD)	62 (10)	64 (14)	<0.001
BMI, mean (SD)	28.6 (6.0)	27.3 (5.8)	<0.001
Female (%)	22	39	<0.001
Largest Tumor size (cm), mean (SD)	4.9 (3.7)	8.9 (4.9)	<0.001
Within Milan Criteria (%)	42	15	<0.001
Resection (%)	8.5	53	<0.001
Liver Transplantation (%)	21	3	<0.001
1-year survival rate (%)	56	66	0.001
5-year survival rate (%)	14.4	18.6	0.04

Conclusion: NAFLD accounts for nearly half of all non-cirrhotic HCCs in the US. A majority of non-cirrhotic HCCs fall outside the Milan criteria and seldom receive liver transplantation.

FRI-135

Clinical effectiveness of enhanced surveillance in "super-high risk" cirrhotics as evaluated in the ITA.LI.CA. Study Group

F. Pelizzaro[1], M. D'elia[2], G. Peserico[1], A. Meneghetti[2], A. Imondi[2], E.G. Giannini[3], F. Trevisani[4], F. Farinati[1]. *[1]Università Degli Studi di Padova, dip. Scienze Chirurgiche, Oncologiche e Gastroenterologiche, Università di Padova; [2]Università Degli Studi di Padova; [3]Università Degli Studi di Genova; [4]Università Degli Studi Di Bologna*
Email: giulia88.fish@gmail.com

Background and Aims: Surveillance of cirrhotics in the secondary prevention of HCC is mandatory but the ideal surveillance interval is still under discussion. The Japanese guidelines consider HCV/HBV-related cirrhotics as "super-high risk" patients, with shorter doubling time, and indicate an enhanced surveillance (3–4 months). Aim of the study were to evaluate the impact of a three-month enhanced surveillance (3MS) in patients with viral cirrhosis in terms of tumour stage, survival and direct costs.
Method: The multicenter ITA.LI.CA database (5849 HCC patients) was used. Inclusion criteria were: cirrhosis, viral etiology and diagnosis under surveillance (3MS versus 6MS). Overall 1576 cirrhotics met the definition of "super-high risk": 194 underwent 3MS, 1382 6MS. The survival analysis took into account the lead time bias (LTB) (by Schwartz's algorithm, Cancer 1961).
Results: The 3MS did not increase the proportion of lesions diagnosed as "very early" ($p = 0.622$) or within Milan Criteria ($p = 0.067$). In the 3MS patients a greater portion of HCC were multifocal ($p = 0.025$), probably due to an increased likelihood of the 3MS to diagnose more aggressive tumors. The survival of the 3MS patients was not significantly different, also when corrected for LTB ($p = 0.987$), with actually a shorter survival in the 3MS group (35 months, 95% CI 32–38, vs 42 months, 95% CI 37–43). These results were confirmed in the multivariate analysis. Micro-economic analysis estimated an increase of 1447 euros in the costs for each HCC while the cost for year of life saved was not computable.
Conclusion: In patients at "super-high risk" an enhanced 3MS does not improve tumor stage, feasibility of curative treatments and patients' survival, with an increase in direct costs. It can be concluded that "super-high risk" patients should be managed as all the population at risk at 6MS, as indicated by the European guidelines.

FRI-136

Patterns of glutamine synthetase expression as marker of beta catenin activation in hepatocellular adenomas

C. Balabaud[1], C. Sempoux[2,3], A.S. Gouw[4,5,6,7], D. Cappellen[8], B. Bisig[3], B.L. Bail[9], P. Bioulac-Sage[8]. *[1]Inserm U1053, Bordeaux; [2]CHUV, Institut Universitaire de pathologie, Lausanne, Switzerland; [3]CHUV, Pathology, Lausanne, Switzerland; [4]Groningen, Netherlands; [5]Pathology; [6]UMCG, Pathology, Groningen, Netherlands; [7]University Medical Center Groningen, Pathology, Groningen, Netherlands; [8]Inserm U1053, Bordeaux, France; [9]CHU Bordeaux, Pathology, Bordeaux, France*
Email: charles.balabaud@u-bordeaux.fr

Background and Aims: In hepatocellular adenomas (HCA) different types of b-catenin (b-cat) mutations have been identified by molecular analysis, occurring in exons 3 or 7/8 with different levels of b-cat pathway activation and risk of malignant transformation. The aim of the study was to describe the immunohistological patterns of Glutamine Synthetase (GS) as a surrogate marker of the different levels of b-catenin activation and to establish a genotype-phenotype correlation.
Method: HCA cases already classified by molecular analysis were collected from 3 centers. GS and CD34 were analysed in 19 b-cat activated HCA (b-HCA) and 23 b-cat activated inflammatory HCA (b-IHCA) identified by CRP expression. Cases had been previously classified according to their specific genotype (ex3 non S45; ex3 S45; ex7/8). GS staining was divided in 4 groups based on the immunohistological patterns: diffuse, "starry sky", "empty sky" but with GS patches around hepatic veins or elsewhere, and none of the above. Additional features were also taken into account: presence of a GS border, CD34 staining diffuse or not. The control group consists of IHCA and HNF1a inactivated HCA (H-HCA) without any b-cat mutation. The study was performed on sections from resection specimens containing tumoral and non-tumoral tissue in areas devoid of necrosis/hemorrhage.
Results: Cases with ex3 (non S45) mutations were characterized by diffuse GS (3b-HCA, 11 b-IHCA) and non-diffuse CD34 expression. Ex3 S45 b-HCA (9) showed a diffuse "starry sky" pattern with an obvious border and diffuse CD34 expression except in the border. The GS expression of b-IHCA ex3 S45 mutations (3) often shows GS patches combined with a "starry sky" pattern; CD34 was rarely diffuse. The GS pattern in ex7/8 b-HCA (7) is characterized by an obvious border but none or only a few solitary positive cells in the lesion. Ex7/8 b-IHCA (10) showed often a quite similar pattern with the b-IHCA S45 although with less "starry sky" component. In IHCA cases without any b-cat mutations, GS was frequently expressed around veins restricted to a few rows of hepatocytes, rarely wider which may resemble b-IHCA ex7/8 (5/46). Focal GS staining, usually faint, can sometimes be seen in atypical H-HCA (no steatosis), that is rare in all H-HCA (5/59).
Conclusion: GS staining is a good surrogate marker to identify all HCA with ex3 non S45 and typical "starry sky" S45 mutated HCA, both harboring higher risk of malignant transformation. In b-HCA/b-IHCA, the differentiation between ex3 S45 and ex 7/8 pattern depends on the extent of the "starry sky" component, more difficult in b-IHCA than in b-HCA. CD34 helps in interpreting GS patterns to suspect

possible b-cat mutation. In aberrant and inconclusive patterns, molecular analysis should be performed, particularly to differentiate S45 and 7/8, which is important for the patient management.

FRI-137

Usefulness of newly proposed albumin-bilirubin grade and its modification -Japan nationwide survey

A. Hiraoka[1], K. Michitaka[2], T. Kumada[3], N. Izumi[4], M. Kadoya[5], N. Kokudo[6], S. Kubo[7], Y. Matsuyama[8], O. Nakashima[9], M. Sakamoto[10], T. Takayama[11], T. Kokudo[12], K. Kashiwabara[13], M. Kudo[14]. *[1]Ehime Prefectural Central Hospital, Gastroenterology Center, Matsuyama, Japan; [2]Ehime Prefectural Central Hospital, Gastroenterology enter, Japan; [3]Ogaki Municipal Hospital, Department of Gastroenterology, Japan; [4]Musashino Red Cross Hospital, Department of Gastroenterology, Japan; [5]Shinshu University School of Medicine, Department of Radiology, Japan; [6]National Center for Global Health and Medicine, Department of Surgery, Japan; [7]Osaka City University Graduate School of Medicine, Department of Hepato-Biliary-Pancreatic Surgery, Japan; [8]School of Public Health, University of Tokyo, Tokyo, Japan, Department of Biostatistics, Japan; [9]Kurume University Hospital, Department of Clinical Laboratory Medicine, Japan; [10]Keio University School of Medicine, Department of Pathology, Japan; [11]Nihon University School of Medicine, Department of Digestive Surgery, Japan; [12]Graduate School of Medicine, University of Tokyo, Graduate School of Medicine, University of Tokyo, Japan; [13]School of Public Health, Graduate School of Medicine, The University of Tokyo, Department of Biostatistics, Japan; [14]Kindai University Faculty of Medicine, OSAKA, Japan*
Email: hirage@gmail.com

Background/Aim: For evaluation of hepatic function, Child-Pugh classification (CP) is used worldwide, while indocyanine green test (ICG-R15) is also examined in Japan. We examine the usefulness of albumin-bilirubin (ALBI) grade, a newly proposed method for assessment of hepatic function and graded by ALBI score calculated only with albumin and total-bilirubin, in hepatocellular carcinoma (HCC) patients.

Method: Of 64,928 naïve HCC patients included in a Japan nationwide survey (2001–2007), the records of 31,011 were subjected to analysis after exclusion for lack of data (CP-A/B/C = 24,599/5883/529) [tumor node metastasis stage (TNM) 1/2/3/4 = 4566/14,982/8793/2670] [resection/ablation/transcatheter arterial chemoembolization (TACE)/others = 13487/7669/7761/2094]. Their median age was 68 years old (IQR: 61–73 years) and 22,639 (73.0%) were male. Patients with hepatitis C virus were 19,873 (64.1%) and those without viral hepatitis were 8389 (27.1%). To compare ALBI, LD, and CP, values for predicting prognosis based on Japan Integrated Staging (JIS) score using CP/TNM, modified JIS (mJIS) with LD/TNM, and ALBI-TNM (ALBI-T) with ALBI-grade/TNM were evaluated. As a sub-analysis, we modified the 3 ALBI grades to 4 grades (mALBI) using ICG-R15 (30%) for more detailed evaluation of hepatic function and also evaluated the predictive value of mALBI/mALBI-T for prognosis.

Results: ALBI-score had a good correlation with ICG-R15 (r = 0.563, 95%CI: 0.550–0.570, p < 0.0001). The cut-off value for ICG-R15 (<30%) was an ALBI score of -2.270 (AUC: 0.828, 95% CI 0.823–0.833) and ALBI grade 2 could be divided into sub-grades (2a, 2b). For each grade of mALBI, prognosis was clearly stratified by TNM (p < 0.01). Akaike's information criterion (AIC) values for ALBI-T, mALBI-T, mJIS, and JIS were 157,696.4, 157,668.7, 157,630.9, and 157,591.4, respectively, for all patients. On the other hand, those were 41,054.6, 40,887.7, 41,094.1, and 41,107.9, respectively, for patients within the Milan criteria and treated curatively (resection or ablation) (n = 13,404). Kaplan-Meyer curves for patients with low ALBI-T and mALBI-T scores were always superior to those with the same mJIS and JIS scores.

Conclusions: Although ALBI and mALBI are calculated only with albumin and total-bilirubin, they showed a good ability to highlight patients with better hepatic function as compared to LD and CP. In addition, ALBI-T/mALBI-T had better predictive value regarding prognosis, especially for patients with early HCC who were treated in a curative manner.

FRI-138

Serological diagnosis of early HCC in NASH: A German multicenter study

J. Best[1], L. Bechmann[2], A. Dechêne[1], K. Pflanz[1], S. Bedreli[1], C. Schotten[1], T. Berg[3], J. Fischer[3], A. Vogel[4], H. Bantel[4], A. Weinmann[5], J. Schattenberg[5], Y. Huber[5], H. Wege[6], K. Schulze[6], J. von Felden[6], B. Dominik[7,8], R. Thimme[7], F. Sinner[2], K. Schuette[2], K.H. Weiss[9], S. Berhane[10], P. Johnson[10], G. Gerken[1], A. Canbay[2]. *[1]University Hospital Essen, Department of Gastroenterology and Hepatology; [2]Otto-von-Guericke University Magdeburg, Department of Gastroenterology,*

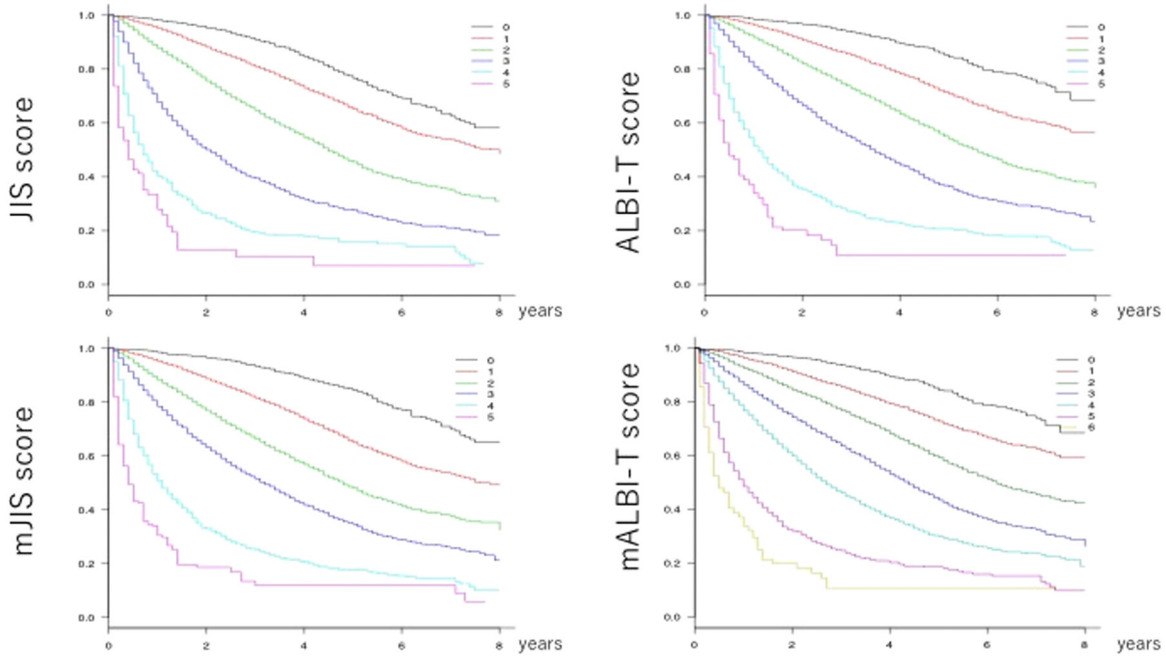
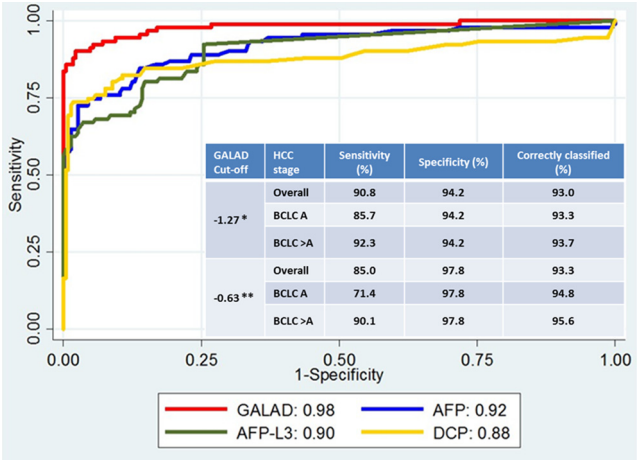


Figure 1: (abstract: FRI-137)

Hepatology and Infectious Diseases; [3]University Leipzig, Section of Hepatology; [4]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology; [5]University Medical Center Mainz, Department of Internal Medicine I; [6]University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine; [7]Medical Center University of Freiburg, Department of Medicine II; [8]Faculty of Medicine, University of Freiburg, Berta-Ottenstein-Programme; [9]University Hospital Heidelberg, Department of Internal Medicine IV; [10]University of Liverpool, Department of Molecular and Cancer Medicine
Email: ali.canbay@med.ovgu.de

Background and Aims: Hepatocellular carcinoma (HCC) is one of the leading causes of death in cirrhotic patients worldwide. There is increasing incidence of HCC in non-alcoholic steatohepatitis (NASH), even in the absence of cirrhosis. NASH is frequently associated with obesity resulting in poor performance of ultrasound surveillance in these patients. This creates an urgent need for serological approaches to ameliorate the current situation with HCC detection predominantly at advanced stages. Therefore, this study aims to explore whether the biomarkers AFP, AFP-L3 and DCP have the potential to be used in the screening setting in NASH patients in a German multicenter cohort.
Method: From 8 German centers, 121 NASH patients with newly diagnosed HCC and 224 NASH control patients were enrolled. AFP, AFP-L3 and DCP were measured using the µTASWako i30® automated immunoanalyzer. The diagnostic performance of biomarkers was measured as single parameters, in a logistic regression model and by ROC analysis. A diagnostic algorithm (GALAD) that combined gender, age and the three biomarkers mentioned above was tested in this NASH cohort.
Results: AFP, AFP-L3 and DCP showed comparable sensitivities and specificities for HCC detection. The GALAD score achieved an AUROC of 0.98 compared to individual application of AFP (0.88), AFP-L3 (0.92) and DCP (0.88) ($p < 0.0005$) (Figure 1). In early stage HCC (BCLC A) the GALAD algorithm again provided the highest overall AUROC (0.93) which was significantly superior to any of the individual markers.



GALAD Cut-off	HCC stage	Sensitivity (%)	Specificity (%)	Correctly classified (%)
-1.27*	Overall	90.8	94.2	93.0
	BCLC A	85.7	94.2	93.3
	BCLC >A	92.3	94.2	93.7
-0.63**	Overall	85.0	97.8	93.3
	BCLC A	71.4	97.8	94.8
	BCLC >A	90.1	97.8	95.6

Figure 1: This figure exhibits the ROC curves, sensitivities and specificities of the individual biomarkers and their combined utilization in the GALAD Score for HCC detection.
*This is the optimal GALAD cut-off for specificity and sensitivity for this dataset.
**This is the published optimal GALAD cut-off for specificity and sensitivity according to the original GALAD publication (Johnson PJ et al.; Cancer Epidemiol Biomarkers Prev; 2014; 23; 144–53).

Conclusion: This German multicenter NASH-HCC cohort demonstrates a high sensitivity and specificity of the GALAD score for HCC early cases and warrants future prospective study in the surveillance setting.

FRI-139

Deviations of the immune cell lanscape between healthy liver and hepatocellular carcinoma

N. Rohr-Udilova[1], K. Tsuchiya[2], M. Herac[3], J. Stift[3], M. Salzmann[4], E. Jensen-Jarolim[4,5], R. Schulte-Hermann[6], T. Reiberger[1], G. Oberhuber[3], G. Timelthaler[6], R. Eferl[6], M. Pinter[1], M. Peck-Radosavljevic[7], M. Trauner[1]. *[1]Medical University of Vienna, Internal Medicine III, Vienna; [2]Musashino Red Cross Hospital, Gastroenterology and Hepatology, Tokyo, Japan; [3]Medical University of Vienna, Clinical Institute of Pathology, Vienna, Austria; [4]Institute of Pathophysiology and Allergy Research, Medical University of Vienna, Center of Pathophysiology, Infectiology and Immunology, Vienna, Austria; [5]The Interuniversity Messerli Research Institute of the University of Veterinary Medicine of Vienna, Medical University of Vienna and University of Vienna, Comparative Medicine, Vienna, Austria; [6]Medical University of Vienna, Internal Medicine I, Institute for Cancer Research, Vienna, Austria; [7]Clinikum Klagenfurth, Division of Gastroenterology and Hepatology, Klagenfurth am Wörthersee, Austria*
Email: nataliya.rohr-udilova@meduniwien.ac.at

Background and Aims: Tumor-infiltrating immune cells are highly relevant for prognosis and identification of immunotherapy targets in hepatocellular carcinoma (HCC). The recently developed CIBERSORT method allows immune cell profiling by deconvolution of gene expression microarray data.
Method: We assessed the abundance of immune cells in 42 healthy human livers, 305 HCC samples and 82 HCC adjacent tissues by CIBERSORT analysis (Newman et al. 2015 Nat Meth 12: 453–457). The obtained immune cell profiles were calculated for each human patient and provided enumeration and activation status of 22 immune cell subtypes. Key CIBERSORT findings were validated by immunohistochemistry combined with tissue morphometric analysis in a tissue array constructed from a patient subgroup of an Austrian HCC cohort (tumor tissues and corresponding surrounding tissues, n = 53) and from healthy livers (n = 24).
Results: Activated mast cells, monocytes and plasma cells were decreased in HCC, while resting mast cells, total and naïve B cells, CD4 + memory resting and CD8+ T cells were increased when compared to healthy livers (Figure 1). Strong total immune cell infiltration into tumor tissue - but not into tumor-adjacent tissue - correlated with improved patient survival ($p = 0.04$). In particular, high intratumoral numbers of T cells and monocytes correlated with improved survival (HR = 2.71, 95%CI 1.23–5.99 and HR = 2.26, 95% CI 1.06–4.80 respectively, both $p < 0.05$). In contrast, intratumoral resting and total mast cells correlated with poor survival. Immunohistochemical staining of mast cell tryptase in the validation cohort confirmed the results from CIBERSORT: density of activated mast cells was in average 7.67 times (95% CI 3.15–12.2) lower in tumors as compared to corresponding adjacent tissues (n = 52, $p < 0.0001$). Healthy liver tissues showed the highest density of activated mast cells.

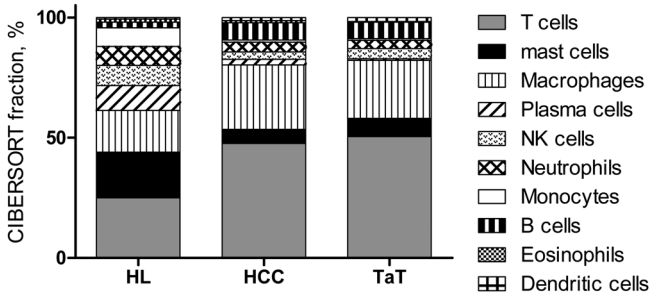


Figure 1: Immune cell composition of human healthy livers (HL), hepatocarcinoma tumor tissue (HCC) and tumor adjacent tissue (TaT) as determined by CIBERSORT methodology.

Conclusion: Deconvolution of gene expression data by CIBERSORT provides valuable information about immune cell composition and

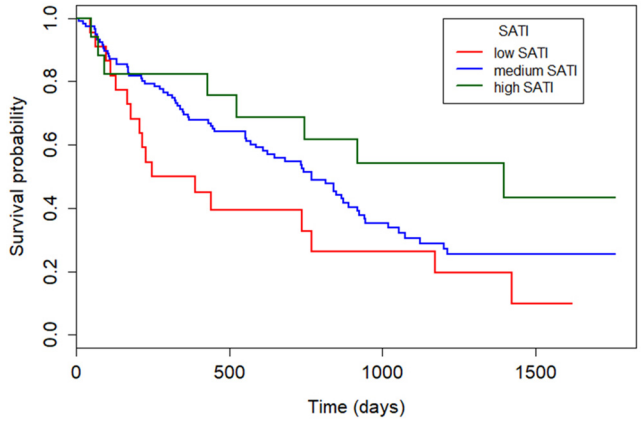
immune cell-based prognosis of HCC patients. The abundance of activated mast cells is diminished in HCC as compared to corresponding surrounding tissue or healthy liver tissue. The potential benefit of mast cell reactivation for HCC therapy should be further evaluated.

FRI-140

Subcutaneous adipose tissue is a predictor of survival in patients with hepatocellular carcinoma

L. von Koeckritz[1], P. Kolly[1], M. Maurer[2], S.-E. Birgit[1], A. Berzigotti[1], A.D. Gottardi[1], N. Semmo[1], S. Casu[1], S. Guido[1], V. Banz[1], J. Bosch[1], J.-François Dufour[1]. [1]*University Clinic for Visceral Surgery and Medicine, Inselspital, University of Bern, Switzerland, Bern, Switzerland;* [2]*Radiology, Inselspital, University of Bern, Switzerland, Bern, Switzerland*
Email: leona.vk@gmx.de

Background and Aims: Prognostic stratification in patients with hepatocellular carcinoma (HCC) is based on clinical parameters as tumor burden, liver function and performance status. Imaging features of body composition have been suggested to refine prognosis stratification in patients with cancers including HCC. However, data in European patients with HCC are scarce. This study aimed at evaluating whether skeletal muscle mass and regional fat distribution on computed tomography (CT) adds to the standard prognostic indicators, predicting overall survival (OS) of patients with HCC.
Method: This is a retrospective analysis of patients with HCC consecutively included in a prospective cohort at a tertiary European university hospital between 08/2010–10/2016. Patients with CT scan available at time of diagnosis were selected. Cross-sectional areas of skeletal muscle mass (SM), intramuscular adipose tissue (IMAT), subcutaneous (SAT) and visceral adipose tissue (VAT) were measured by CT (SliceOmatic software) at the level of the third lumbar vertebra and normalized to height (cm^2/m^2), to obtain indexes (I). Univariate and multivariate Cox regression analysis was used to assess the prognostic significance of standard predictors and imaging features for OS. Maximally selected rank statistics were used to define cut-off values to split the population into different groups according to their OS.
Results: 157 patients fulfilled inclusion criteria (male 81%, cirrhotic 80%, hepatitis C infected 30%, BCLC 0 + A/B/C/D 34/34/21/11%) and showed OS of 68% and 33% at 1 and 3 years, respectively. In the univariate analysis, VATI and SATI were associated with survival (HR 0.995, p = 0.044 and HR 0.992, p = 0.020, respectively), while SMI and IMATI were not. In the multivariate analysis only SATI remained significant when adding the BCLC stage (p = 0.046). Cut-off values for SATI of < 28, 28–110 and > 110 allowed splitting the population into 3 groups with mean OS of 596 days (95% CI 356–837), 1067 (853–1282) and 1290 (855–1724), respectively (p = 0.042) (Figure).



Conclusion: In this European HCC population low SATI, but not low SMI, is associated with poor survival. These results suggest that in the body composition subcutaneous fat is a better predictor of survival than muscle mass.

FRI-141

Macrotrabecular-massive hepatocellular carcinoma: a distinctive histological subtype with clinical relevance

M. Ziol[1,2], N. Poté[3,4], G. Amaddeo[5,6], A. Laurent[6,7], J.C. Nault[2,8], F. Oberti[9], C. Costentin[10], S. Michalak[11], B. Mohamed[12], C. Francoz[13], G.-P. Pageaux[14], J. Ramos[15], D. Thomas[16], A. Luciani[17], B. Guiu[18], V. Vilgrain[19], C. Aubé[20], J. Derman[21], C. Charpy[21], J. Zucman-Rossi[22], N. Barget[23], O. Seror[2,24], N. Ganne-Carrié[2,25], V. Paradis[4,12], J. Calderaro[6,21]. [1]*Hôpital Jean Verdier, Pathology, Bondy, France;* [2]*Inserm U1162, Functionnal Genomics of Solid Tumors;* [3]*Hôpital Beaujon, Pathology, Clichy, France;* [4]*INSERM, Université Paris Diderot, Centre de Recherche sur l'Inflammation;* [5]*Hôpital Henri Mondor, Hepatology, Créteil, France;* [6]*Insert U955, Team 18, Institut Mondor de Recherche Biomédicale;* [7]*Hôpital Henri Mondor, Surgery, Créteil, France;* [8]*Hôpital Jean Verdier, Hepatology, Clichy, France;* [9]*CHU Angers, Hepatology;* [10]*Hôpital Henri Mondor, Hepatology;* [11]*CHU Angers, Pathology;* [12]*Hôpital Beaujon, Pathology;* [13]*Hopital Beaujon, Hépatologie, AP-HP, France;* [14]*CHU Montpellier, FRANCE, Montpellier, France;* [15]*CHU Montpellier, Pathology;* [16]*CHU Grenoble, Hepatology;* [17]*Hôpital Henri Mondor, Medical Imaging;* [18]*CHU Montpellier, Medical Imaging;* [19]*Hôpital Beaujon, Medical Imaging;* [20]*CHU Angers, Medical Imaging;* [21]*Hôpital Henri Mondor, Pathology;* [22]*Inserm U1162, Functional Genomics of Solid Tumors;* [23]*Hôpital Jean Verdier;* [24]*Hôpital Jean Verdier, Medical Imaging;* [25]*Hôpital Jean Verdier, Hepatology*
Email: julien.calderaro@aphp.fr

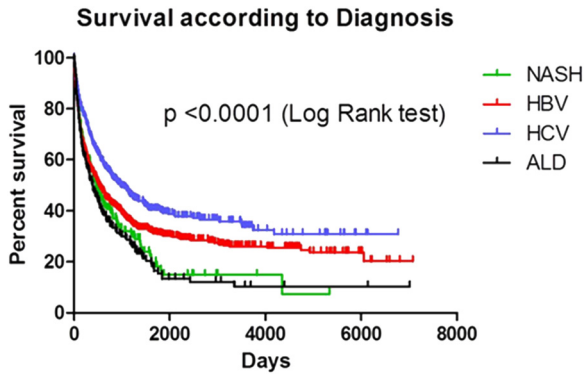
Background and Aims: We recently identified a novel histological subtype of hepatocellular carcinoma, designated as "macrotrabecular-massive" (MTM-HCC) and associated with specific molecular features. In order to assess the clinical relevance of this novel variant, we aimed to investigate its prognostic value in two large series of patients treated either by surgical resection or radiofrequency ablation (RFA).
Method: We retrospectively included 389 HCC surgical samples and 284 HCC liver biopsies from patients treated by surgical resection and RFA, respectively. Histological slides were reviewed by pathologists specialized in liver disease, and the MTM-HCC subtype was defined by the presence of a predominant (>50%) macrotrabecular architecture (more than 6 cells thick). The main clinical and biological features were recorded at baseline. Clinical endpoints were early and overall recurrence.
Results: The MTM-HCC subtype was identified in 14% of the whole cohort (19% of surgically resected samples, 8.5% of liver biopsy samples). Interobserver agreement for the diagnosis of MTM-HCC was good (k = 0.72) and excellent (k = 0.82) in the surgical and RFA series, respectively. This subtype was associated at baseline with known poor prognostic factors (tumor size, AFP level, satellite nodules and vascular invasion). Multivariate analysis showed that MTM-HCC subtype was an independent predictor of early and overall recurrence (surgical series: OR 2.90 (1.29–6.53), p = 0.01 and 2.83 (1.66–4.82), p < 0.001); RFA series: 2.37 (1.36–4.13), p = 0.002 and 2.19 (1.35–3.54), p = 0.001, respectively). Its prognostic value was retained even after patients' stratification according to common clinical, biological and pathological features of aggressiveness. The relative risk of relapse associated with MTM-HCC was also higher than those associated with classical HCC outcome predictors, such as AFP serum levels, vascular invasion or satellite nodules. No other baseline parameter was independently associated to recurrence in the RFA series.
Conclusion: The MTM-HCC histological subtype, reliably observed in 14% of patients eligible for a curative treatment, represents an aggressive form of HCC that may require more specific therapeutic strategies.

FRI-142

Improving survival in patients with hepatocellular carcinoma related to chronic hepatitis C and B but not in those related to non-alcoholic steatohepatitis or alcoholic liver disease: A 20 year experience from a national programme

I. Hassan, E. Gane, D. Prasad, A. Bartlett, O. Lithgow. *Auckland city hospital, New Zealand liver transplant unit, Auckland, New Zealand*
Email: ibrahim20.hassan20@gmail.com

Background and Aims: Hepatocellular carcinoma (HCC) is the most rapidly increasing cause of cancer mortality in New Zealand due to endemic hepatitis B (HBV) infection and recent hepatitis C (HCV) and obesity epidemics. The objectives of this audit are to describe the changing landscape of HCC referred to a national HCC service since1998, in particular changes in the underlying liver disease, rate of screening uptake and curative treatments and survival.
Method: All newly diagnosed cases of HCC referred to New Zealand liver transplant unit between 1998 and 2016 were included, with follow-up available until June 2017. Data on patient demographics, liver disease aetiology, screening status and HCC stage at diagnosis were collected from chart review. Data were also collected on transplantation, resection and ablation. Kaplan Meier survival estimates were derived from the national mortality database. Recruitment in and adherence with HCC surveillance were recorded.
Results: HCC diagnosis rates have increased from 25 cases in 1998 to 260 in 2016, an increase of 20% per annum. The total of 1683 HCC cases were divided into 3 cohorts (Era 1: Jan 1998 to Dec 2008; Era 2: Jan 2009 to July 2013; Era 3: August 2013 to June 2016), each comprising 561 patients.
During the study period, overall survival improved ($p = 0.005$). The proportion with screen-detected HCC was similar across the 3 cohorts (43% in Era 1, 42% in Era 2 and 47% in Era 3) as was the proportion who received curative therapy (35% in Era 1, 37% in Era 2 and 41% in Era 3). 5 and 10-year survival were higher in screen-detected cases (49% and 43%) than in non-screen detected cases (14% and 10%), $p < 0.0001$. Over the 3 eras, survival improved in the nonscreen-detected cases ($p = 0.002$) but not in the screen-detected cases ($p = 0.23$).
The most common underlying liver diseases were HBV (43%), HCV (26%), alcoholic live disease (ALD)(11%), and non-alcoholic steatohepatitis (NASH) (9%).Over the study period, the proportion with HBV has decreased from 56% to 32%, whilst the proportion with HCV has increased from 17% to 32% and NASH from 4% to 15%. Survival was higher in patients with HCV and HBV than is those with NASH or ALD – 5 and 10-year survival was 40% and 34% in HCV-HCC, 30% and 26% in HBV-HCC, 15% and 14% in NASH-HCC, 13% and 10% in ALD-HCC, $p < 0.0001$.



Conclusion: The improvement in survival in patients with HCC over the past 20 years likely reflects improved screening uptake and better management of the nonscreen-detected cases. Lower survival in NASH and ALD patients may reflect poor screening uptake and lack of awareness of risk factors in these patients.

FRI-143

Prospective evaluation of gadoxetic-acid MR for the non-invasive diagnosis of hepatocellular carcinoma in newly detected nodules <=2 cm in cirrhotic patients

A. Forner[1], A. Darnell[1], C. Ayuso[2], J. Rimola[1], M.Á. García-Criado[1], R. Vilana[1], L. Bianchi[1], María Reig[1], J. Bruix[2]. *[1]Hospital Clínic Barcelona. IDIBAPS. University of Barcelona. Spain, Barcelona Clínic Liver Cancer group (BCLC). Liver Unit; [2]Hospital Clínic Barcelona. IDIBAPS. CIBERehd University of Barcelona. Spain, Barcelona Clínic Liver Cancer group (BCLC). Radiology Department*
Email: aforner@clinic.ub.es

Background and Aims: To prospectively evaluate the diagnostic accuracy of gadoxetic-acid enhanced MR (Gd-EOB-DTP MR) for the non-invasive diagnosis of hepatocellular carcinoma (HCC) in nodules <2 cm detected by screening ultrasound (US).
Method: Between July 2012 and October 2015, we prospectively included asymptomatic Child-Pugh A-B cirrhotic patients with newly US-detected solitary nodule between 1–2 cm. Hepatic extracellular-contrast-enhanced MR (ECCE-MR) followed by Gd-EOB-DTP MR were obtained in less than 1-month interval. Two independent radiologists blindly reviewed the Gd-EOB-DTP MR studies and the diagnosis of HCC was assigned when the lesion showed arterial enhancement followed by portal venous phase wash-out and/or hypointensity on the hepatobiliary phase (HBP). The final HCC diagnosis was made by ECCE-MR according the accepted non-invasive criteria, or by biopsy in lesions with atypical vascular profile. We calculated the sensitivity, specificity and positive and negative predictive value (PPV, NPV) and their 95% confident interval. The protocol was approved by the Ethics Committee for Clinical Research.
Results: A total of 62 patients were included in the study. Final diagnoses were: HCC (n = 41), intrahepatic cholangiocarcinoma (ICC) (n = 2), colorectal metastases (n = 1) and benign conditions (n = 18). The sensitivity, specificity, PPV and NPV of Gd-EOB-DTP MR for HCC diagnosis were 56.1% [95%CI: 39.7–71.5], 90.5% [95%CI: 69.6–98.8], 92.0 [95%CI: 74.0–99.0], and 51.4 [95%CI: 34.4–68.1] respectively, while sensitivity of ECCE-MR was 63.4% [CI95%: 46.9–77.9]. The most specific contrast pattern for HCC diagnosis was homogeneous contrast uptake in arterial phase followed by washout in portal phase (95.2% [CI95%: 77.3–99.1], but it was penalized by a low sensitivity (41,5% [CI95%: 27.8–56.6]). Low rate of hypointense HCCs in the HBP (26 out of 41 HCC, 63.4%), suboptimal image acquisition in a relevant proportion of patients (37%) because of motion artifacts or incorrect arterial timing, and suboptimal liver uptake of contrast agent could justify the low sensitivity of Gd-EOB-DTP MR for HCC diagnosis.
Conclusion: Gd-EOB-DTP MR is not superior than ECCE-MR for non-invasive diagnosis of HCC in nodules <2 cm in cirrhotic patients.

FRI-144

Risk of early de-novo hepatocellular carcinoma (HCC) in patients with genotype-1b HCV compensated cirrhosis treated with 3 direct-acting antivirals (DAAs) - a real life, multicenter study

C.-M. Muzica[1,2], C. Stanciu[1], O. Stoica[3], I. Girleanu[1,3], L. Huiban[1,3], C. Alexandru[1,3], T. Cucureanu[1,3], A.-M. Singeap[1,3], S. Chiriac[3], A. Trifan[1,3]. *[1]Institute of Gastroenterology and Hepatology, Iasi, Romania, Gastroenterology, Iasi, Romania; [2]"Grigore T Popa ' University of Medicine and Pharmacy, Iasi, Romania, Gastroenterology, IASI, Romania; [3]"Grigore T Popa ' University of Medicine and Pharmacy, Iasi, Romania, Gastroenterology, Iasi, Romania*
Email: lungu.christina@yahoo.com

Background and Aims: Recent studies have reported an increased risk of HCC after treatment with 3-DAAs. The aim of our study was to evaluate the incidence and factors associated with *de- novo* HCC in patients with genotype-1b HCV compensated cirrhosis treated with 3-DAAs: real-life study.
Method: We prospectively analysed a cohort of patients with HCV-related liver cirrhosis treated with paritaprevir/ritonavir, ombitasvir

and dasabuvir (PrOD) ± ribavirin for 12 weeks between 01 December 2015 and 31 March 2017, in two tertiary referral centers from North-Eastern Romania. All patients with genotype-1b HCV-infected, treatment-experienced or naive patients with Child-Pugh class A cirrhosis assessed by Fibromax (cut off 0.71 for F4) or liver biopsy (F4 METAVIR) were evaluated pretreatment according to our National Protocol. Demographics, imaging, laboratory tests, end of treatment (EOT), and 12 weeks after therapy (sustained virological response - SVR) were assessed. All underwent surveillence by US, ALT, AST, alpha-fetoprotein (AFP) within six months after EOT.

Results: The study included 480 consecutive HCV-infected cirrhotic patients, predominantly female (54.8%), mean age 59.1 ± 8.3 years, with no prior history of hepatocellular carcinoma, who completed 12 weeks of treatment with PrOD and were followed by a median of 8 months after EOT. EOT virological response was 100% and SVR rate was 99.2%. Of these, 12 patients (2.5%) developed early *de-novo* HCC, predominantly males (61.5%) mean age 59.6 ± 7.8 years. The mean period between EOT and HCC diagnosis was 26.7 ± 4 weeks. The imaging findings revealed the predominance of unicentric lesions in 8 (61.5%) patients and the predominant localization of the lesions was in the VII liver segment (23%). At multivariate analysis, the only independent predictor of HCC was AFP ≥ 10 ng/ml at EOT.

Conclusion: The risk of *de-novo* HCC in patients with genotype-1b HCV compensated cirrhosis treated with PrOD ± ribavirin for 12 weeks, remains in range of the expected rate risk of that reported in untreated HCV patients with cirrhosis. An elevated AFP level at EOT (≥10 ng/ml) is the only significant predictor of HCC development.

FRI-145

Incidence of HCC in TIPS bearing cirrhotic patients

J.M. Garcia-Ortiz[1], A. Giraldez-Gallego[1], V. Nacarino-Mejías[2], J.M. Sousa-Martin[1], M. Teresa Ferrer[1], J. Ampuero[1], J.M. Pascasio[1].
[1]*Virgen del Rocio University Hospital, Digestive Diseases, Sevilla, Spain;* [2]*Virgen del Rocio University Hospital, Interventional Radiology, Sevilla, Spain*
Email: jm.garortiz@gmail.com

Background and Aims: For varied reasons, tranjugular intrahepatic portosystemic shunt (TIPS) has been proposed to have a possible role on the onset of hepatocellular carcinoma (HCC), although this statement has never been proved. Our aim was to know the cumulative incidence of HCC during long-term follow up of cirrhotic patients on whom TIPS has been placed.

Method: Retrospective observational study of a cohort of 88 TIPS bearing cirrhotic patients without previous HCC or liver transplant (LT), during a 7 years period. Follow-up consisted of conventional screening by Doppler-ultrasound with a periodicity of at least 6 months until death, LT, HCC diagnosis or loss to follow-up happened.

Results: Our sample was formed by 88 patients (71.6% male) with a mean age of 55.0 ± 10.7 years. Cirrhosis ethiology was alcohol (37.5%), HCV (37.5%), NASH (8%), HBV (5.7%) or others (11.3%). Median MELD was 12 (RIC 10–16.8). Indications for placing TIPS had been: acute variceal bleeding (33%), secondary profilaxis of variceal bleeding (36.4%), refractory ascites (13.6%) recurrent hydrotorax (6.8%). 34 patients (38.6%) had portal thrombosis –present or recanalized- and 4.5% (4/88) were HIV-infected.

After a medium follow-up of 24.1 ± 20.1 months, 23 patients had died (26.1%) and 16 had been transplanted (18.2%). 44/48 patients (47.7%) remained alive and without HCC, and only two patients (2.3%) were lost on follow-up. In 9/88 patients (10.2%) there was a *de novo* diagnosis of HCC.

None of the studied variables showed a statistically significant association with the onset of HCC, on univariant analysis. Nevertheless, patients who developed HCC were older (59.6 ± 8.0 vs 54.5 ± 10.9 years; p = 0,084) and had a longer follow-up (33.3 ± 21.6 vs.23.1 ± 19.8 months; p = 0.148) compared to those who did not.

The possibility of remaining HCC-free after TIPS (Kaplan-Meier) in months 6 and 12 was 98.7% and 97.1% respectively. After 2, 3 and 4 years of follow-up, the proportion of HCC-free patients consecutively reduced to 95.2%, 92.6% and 88.6%.

Conclusion: After rigorous screening of HCC in our sample of cirrhotic patients bearing TIPS because of previous severe portal hypertension complications, we established a cumulative incidence rate of 2.9% on year-1, 4.8% on year-2, 7.4% on year-3 and 11.4% on year-4. *De novo* HCC becomes a more relevant problem as liver transplant-free survival improves in our patients bearing TIPS.

FRI-146

Lymphoid infiltrate predicts prognosis of mass-forming intrahepatic cholangiocarcinoma undergoing complete liver resection

L. Vigano'[1], C. Soldani[1], A. Lleo[2], L. Di Tommaso[3], B. Franceschini[1], M. Cimino[1], M. Donadon[1], G. Torzilli[1]. [1]*Humanitas University, Department of Surgery - Division of Hepatobiliary & General Surgery;* [2]*Humanitas University, Department of Internal Medicine and Hepatology;* [3]*Humanitas University, Pathology*
Email: ana.lleo@humanitas.it

Background and aims: In colorectal cancer, the lymphoid infiltrate has shown a prognostic impact. Similar data have been reported for hepatocellular carcinoma. No study focused on intrahepatic mass-forming cholangiocarcinoma (MFCCC). To assess the presence of lymphoid infiltrate and its prognostic impact in patients undergoing liver resection for MFCCC.

Methods: All consecutive patients undergoing surgery for MFCCC between 2005 and 2015 were considered. The inclusion criteria were complete resection (R0/R1) and follow-up ≥12 months. Patients with operative mortality were excluded. Formalin-fixed, paraffin-embedded tissue sections from MFCCC were immunostained for CD3+, CD4+, CD8+, Foxp3+ and CD68+. The number of positive cells was quantified using a computer-aided image analysis system. The percentage of positive cells in the analyzed area was computed. Different cut-off values were tested as predictors of overall and recurrence-free survival (OS and RFS). For each marker, the value with the most significant p-value was included in the multivariable analysis of OS and RFS.

Results: Overall, 53 patients were analyzed. MFCCC were multiple in 10 (19%) patients, >50 mm in 26 (49%), and N+ in 12 (23%). 28 patients (53%) had T1 tumor.

After a median follow-up of 41 months, 5-year OS was 56.1% and 3-year RFS was 40.1%. At univariate analysis, the following lymphoid infiltrate values had a prognostic impact: CD3+ >0.10% (OS p < 0.001, RFS p < 0.001); CD8+ >0.10% (OS p = 0.044, RFS p = 0.001), CD4+ >0.30% (OS = 0.094, RFS p = 0.009), and Foxp3+ present (OS p = 0.097). CD68+ cells were not associated with prognosis. At the multivariable analysis, CD3+ value was a prognostic factor of both OS and RFS [> 0.10%, 5-year OS 66.9% vs. 18.2% if ≤0.10%, HR = 0.287, p = 0.049; 3-year RFS 48.1% vs. 9.1%, HR = 0.232, p = 0.001] and Foxp3+ was a negative prognostic factor of OS [present, 5-year OS 21.4% vs. 61.9% if absent, HR = 2.924, p = 0.044] (Figure).

CD3+ values stratified prognosis in T1 patients (5-year OS 73.9%/14.3%, p < 0.001; 3-year RFS 60.8%/14.3%, p < 0.001), in N+ patients (OS 71.4%/0%, p = 0.028; RFS 42.9%/0%, p = 0.011) and in patients without lymph node metastases (RFS 49.7%/20.0%, p = 0.062).

Conclusions: The lymphoid infiltrate impacts prognosis of MFCCC after complete surgery. CD3+ infiltrate is associated with higher survival and lower recurrence risk, while Foxp3+ is associated with worse prognosis. CD3+ infiltrate allows to refine prognosis in early tumors and across different N stages.

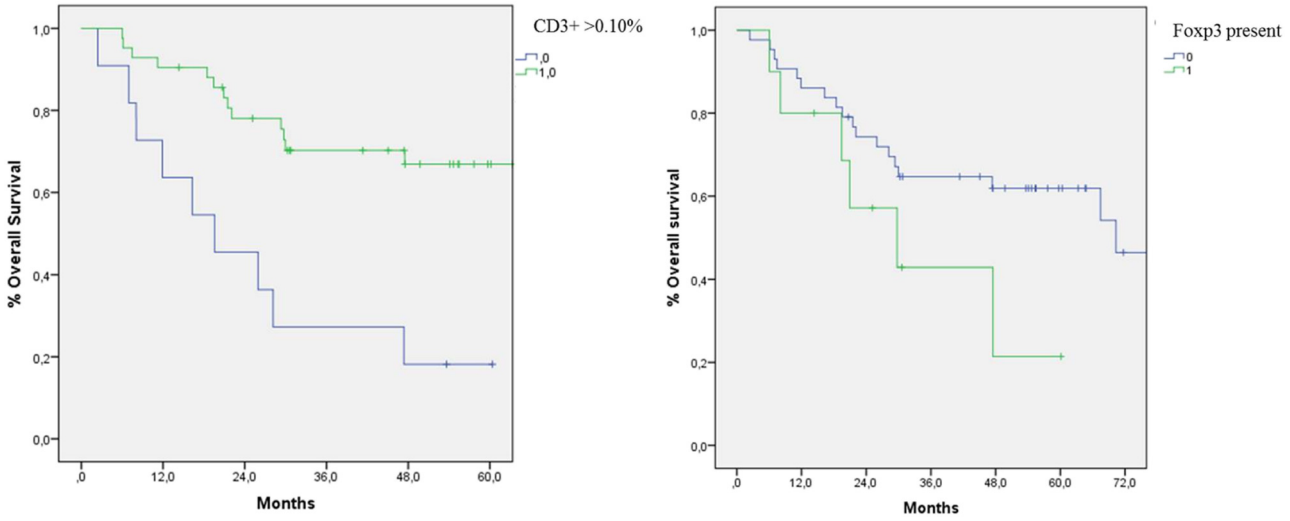


Figure 1: (abstract: FRI-146): Overall survival curves of MFCCC patients according to $CD3^+$ and to $Foxp3^+$ infiltrate.

FRI-147

Clinical correlates of the genetic variability of the CD274 gene (Programmed Cell Death-Ligand 1) among patients with hepatocellular carcinoma

F. Daffara, L. Salmi, M.N. Barbaglia, V. Mulas, D. Camatta, M.T. Minh, M.E. Burlone, R. Minisini, M. Pirisi. *Università del Piemonte orientale, Translational Medicine, NOVARA, Italy*
Email: rosalba.minisini@med.uniupo.it

Background and Aims: A deranged Programmed Death-Ligand 1 (PD-L1, a protein encoded by the *CD274* gene) pathway is an important mechanism of immunological escape exploited by different cancers. Specifically, PD-L1 germline mutations modulate outcome and response to therapy in non-small cell lung cancer. Our aim was to verify the clinical correlates of three single nucleotide polymorphisms (SNPs) on the CD274 gene among patients with hepatocellular carcinoma (HCC).
Method: The study population included n = 387 patients: n = 214 with HCC (Group A: 162 males, median age 71 years, cirrhosis in 97% and hepatitis C in 56%) and n = 164 with cirrhosis, similar for age and sex distribution (Group B: 118 males, median age 72 years, and hepatitis C in 63%) to Group A. All were genotyped for the following SNPs: rs2279136, rs4143815 and 8923A/C. The status of all these patients was known and documented up to (and including) the censor date of 31 Jul 2017.
Results: The study population did not depart from what expected based on the Hardy-Weinberg equilibrium for any of the three SNPs. For rs2279136, the allelic frequencies in Group A vs. Group B were 0.39 and 0.61 vs. 0.41 and 0.59, respectively for the ancestral and variant gene (p = 0.941); for rs41438156, they were 0.70 and 0.30 vs. 0.71 and 0.29 (p = 0.935); for 8923A/C, they were 0.57 and 0.73 vs. 0.52 and 0.48 (p = 0.137). Patients in group A did not show differences based on the rs2279136 and 8923A/C genotypes with regard to age at diagnosis, gender distribution, hepatitis C etiology, major tumor node size, number of tumor nodes, Milan-in criteria, serum alpha-fetoprotein concentration and neutrophil-to-lymphocyte ratio. However, carriage of the variant gene for the rs4143815 was associated with younger age at diagnosis, obtained at a median of 73 years (interquartile range, 65–79) for G/G homozygotes, 70 years (62–76) for G/C heterozygotes, and 68 years (59–73) for C/C homozygotes (p = 0.032). Moreover, there was a trend for higher number of nodules at diagnosis in the same direction (p = 0.070). Finally, median survival in Group A was 24 months; at logrank test, survival probabilities in Group A were not statistically different based on carriage of any of the germline mutations, either analyzed genotypically or using a dominant or a recessive model.
Conclusion: Carriage of the rs4143815 germline mutation may affect the natural history of HCC superimposed on cirrhosis by predisposing to its earlier and multinodular occurrence.

FRI-148

Gp38+ hepatic progenitor cell-derived large extracellular vesicles in biliary cancers - a novel liquid biopsy marker?

S. Urban[1], M. Krawczyk[1], A. Willms[2], J. Ligocka[3], H. Sänger[1], K. Jankowski[4], M. Krawczyk[3], K. Zieniewicz[3], W. Patkowski[4], R. Schwab[2], A. Wöhler[2], S. Gehlert[5], J.M. Banales[6], P. Milkiewicz[7], F. Lammert[1], V. Lukacs-Kornek[1], M. Kornek[1]. *[1]Saarland University Medical Center, Saarland University, Department of Medicine II, Homburg, Germany; [2]German Armed Forces Central Hospital, Department of General, Visceral and Thoracic Surgery, Koblenz, Germany; [3]Medical University of Warsaw, Department of General, Transplant and Liver Surgery, Warsaw, Poland; [4]Medical University of Warsaw, Department Internal Medicine and Cardiology, Warsaw, Poland; [5]Institute of Cardiovascular Research and Sport Medicine, German Sport University Cologne, Department of Molecular and Cellular Sport Medicine, Cologne, Germany; [6]Biodonostia Health Research Institute – Donostia University Hospital, University of the Basque Country (UPV/EHU), CIBERehd, Ikerbasque, Department of Liver and Gastrointestinal Diseases, San Sebastian, Spain; [7]Medical University of Warsaw, Liver and Internal Medicine Unit, Department of General, Transplant and Liver Surgery, Warsaw, Poland*
Email: miroslaw.kornek@uks.eu

Background and Aims: Large extracellular vesicles (EVs), so-called microparticles (MPs), are cell-derived membrane vesicles that harbor the same surface antigens as their parental cells. Recently, we showed that tumor-associated MPs (taMPs) could be used to discriminate hepatic cancers from cirrhosis. To further distinguish biliary cancer (CCA and GbC) from HCC and other cancer entities, we utilized this minimal-invasive MP approach with surface marker compositions based on gp38/podoplanin, a recently described novel marker for liver progenitor cell subpopulations (Eckert. C. et al. 2016, Lukacs-Kornek et al. 2017 JHEP).
Method: The presence of $gp38^+$ progenitor cells was confirmed in various organs in wild type C57Bl/6J mice by FACS. TaMPs from patients' sera were isolated by sequential ultracentrifugation at 2,000

and 20,000xg. To identify taMP populations FACS was applied. In total, 43 HCC, 26 NSCLC and 91 biliary cancer patients were enrolled in the study. 47 cirrhosis patients and 46 healthy individuals served as controls.
Results: i) Recently described liver progenitor marker gp38 was evaluated in additional organs in order to assess their potential as biomarkers for biliary cancer. Indeed, $gp38^+EpCAM^+$ and $gp38^+EpCAM^+CD133^+$ cells were found in murine liver, lung and gallbladder. ii) $AnnexinV^+EpCAM^+ASGPR1^+$ taMPs pinpointed liver cancers (HCC and CCA) and distinguished these from NSCLC and cirrhosis. Of note, gp38 in the combinations $AnnexinV^+gp38^+EpCAM^+$ and $AnnexinV^+gp38^+EpCAM^+CD133^+$ identified taMPs that allowed the distinction of biliary cancer from non-biliary cancers (here, HCC and NSCLC). In detail, $AnnexinV^+gp38^+EpCAM^+$ taMPs were increased in biliary cancer patients by 4.7-fold as compared to non-biliary cancer patients. AUROC value (0.778), sensitivity (71%), specificity (71%) as well as positive predictive value (77%) indicated their diagnostic value as a novel biomarker for biliary cancer. $AnnexinV^+gp38^+EpCAM^+CD133^+$ taMPs confirmed our differentiation between biliary and non-biliary patients, albeit with slightly better sensitivity (74%) but with lower positive predictive value (71%).
Conclusion: Our results provide evidence that the novel progenitor marker gp38/podoplanin in the combination $AnnexinV^+gp38^+EpCAM^+$ identifies taMPs that serve as a novel biomarker for biliary cancer. Thus, this method represents a minimal-invasive, accurate liquid biopsy screening tool for early and specific detection of biliary cancer.

FRI-149

Recommendations for the management of women with suspected hepatocellular adenoma and childbearing potential

M. Gaspersz[1], J. Klompenhouwer[1], M. Broker[1], F. Willemssen[2], M. Thomeer[2], Türkan Terkivatan[1], R.D. Man[3], J. Ijzermans[1]. [1]*Erasmus MC, Surgery, Rotterdam, Netherlands;* [2]*Erasmus MC, Radiology, Rotterdam, Netherlands;* [3]*Erasmus MC, Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: a.klompenhouwer@erasmusmc.nl

Background and Aims: Hepatocellular adenoma (HCA) is a rare benign liver tumor occurring mostly in females in their reproductive phase. Pregnancy in these women requires special consideration, as hormone induced growth and bleeding can occur. Therefore, pregnancy is often discouraged or surgical resection is performed before pregnancy. However, a definitive diagnosis is not always made due to suboptimal imaging. If conception does take place in these patients with suspected or diagnosed HCA, intensive follow-up with ultrasound to detect lesion growth is recommended. The aim of this study was to assess the accuracy of diagnostics of the liver lesion in women included in a study to monitor change of liver adenoma during pregnancy.
Method: This study was performed in patients included in the Pregnancy And Liver adenoma Management (PALM) study cohort, an ongoing multicenter prospective cohort study investigating the incidence of growth during pregnancy in HCA <5cm. In this study, pregnant patients with suspected HCA on imaging underwent extensive follow-up to assess growth of the liver lesion. Definitive diagnosis was established with state of the art contrast enhanced MRI (CE-MRI) with gadolinium based contrast agents, preferably before pregnancy. Patients who did not have a definitive diagnosis underwent CE-MRI after giving birth. Patients who were still pregnant in October 2017 were excluded.
Results: Between October 2011 and October 2017, a total of 57 patients were included in this study. Median age was 34 years (IQR 32–37) and median HCA size 25 mm (IQR 20.8–41.5). Twenty-nine patients did not undergo CE-MRI before pregnancy. Out of these patients, HCA was suspected based on conventional MRI in 19 (66%), ultrasound in 7 (24%), CT in 2 (7%) and contrast-enhance ultrasound in 1 (4%). CE-MRI confirmed HCA diagnosis in 48 patients (84%), 9 patients (16%) turned out to have Focal Nodular Hyperplasia (FNH). Out of the 9 patients who were diagnosed with FNH, 8 were treated in a non-referral hospital and 1 in a tertiary referral centre ($p = 0.018$). None of the patients who eventually were diagnosed with FNH underwent CE-MRI before pregnancy.
Conclusion: This study indicates that a large proportion of childbearing women suspected of having a HCA are misdiagnosed and have FNH. Misdiagnosis may have major impact on patients as FNH does not require intensive follow-up. Therefore, diagnostic work-up with state of the art imaging of a benign liver lesion in younger fertile women should be performed at the moment of first presentation. This approach may prevent unnecessary anxiety and inconvenience if they present with pregnancy in follow up.

FRI-150

Preoperative van Willebrand factor is a predictor for early recurrence and overall survival in patients undergoing liver resection for oncological entities

D. Pereyra[1], R. Baumgartner[1], A. Padickakudy[1], C. Schuetz[1], S. Haegele[1], P. Jonas[2], C. Brostjan[1], T. Grünberger[2], P. Starlinger[1]. [1]*Medical University of Vienna, Department of Surgery, Vienna, Austria;* [2]*Rudolfstiftung Hospital, Department of Surgery, Vienna, Austria*
Email: N1342352@students.meduniwien.ac.at

Background and Aims: We previously reported on the predictive role of van Willebrand factor–antigen (vWF-Ag) for poor post-operative outcome. Briefly, a preoperative cut-off at 182% vWF-Ag was found to be predictive for prolonged hospitalization and intensive care stay, postoperative liver dysfunction and morbidity. However, vWF-Ag was also implicated as an important factor for tumor metastasis. In addition, levels of vWF-Ag were shown to be higher in patients with metastasized colorectal carcinoma in comparison to patients with only localized disease. Interestingly, levels of vWF-Ag were found to be predictive for overall survival (OS) in this cohort. Thus, within the present study we evaluated oncological outcome in patients undergoing liver resection and aimed to assess a possible association to levels of vWF-Ag.
Method: VWF-Ag was evaluated prior to surgery in 96 patients undergoing liver resection for any malignant entity of the liver. Postoperatively, disease free survival (DFS) and OS were assessed.
Results: Applying the cut-off at 182% vWF-Ag, we were able to identify a group of patients with higher incidences of disease recurrence after 6 months (vWF < 182%=8.6% vs vWF ≥ 182%=19%) and 12 months (vWF < 182%=16.4% vs vWF ≥ 182%=41.2%, $p = 0.031$). Using logistic regression, we observed a significantly increased risk for the development of disease recurrence within 12 postoperative months (Odds ratio = 3.578, $p = 0.038$). Of note, multivariable analysis showed independency of our proposed cut-off from other confounding and baseline characteristics including tumor properties. Interestingly, also OS was found to be reduced in patients with preoperative vWF-Ag levels above 182% (1 year: vWF < 182% = 92.7% vs vWF ≥ 182% = 58.3%, $p < 0.001$; 2 years: vWF < 182% = 68.9% vs vWF ≥ 182% = 38.1%, $p = 0.018$; 3 years: vWF < 182%=58.3% vs vWF ≥ 182%=16.7%, $p = 0.004$), which was also shown in Kaplan-Meier analysis, where median OS of patients in vWF < 182% was 1.2 years, while median OS was not reached after 4.4 years in vWF ≥ 182% ($p < 0.001$).
Conclusion: To our knowledge, this investigation represents the first evidence on the predictive potential of vWF-Ag for oncological short-term outcome after liver resection in patients suffering from malignant liver tumors. Interestingly, the higher incidence of early tumor recurrence in patients with preoperative levels of vWF-Ag above 182%, potentially in synergy with a higher incidence of postoperative complications, seem to ultimately translate into decreased OS.

FRI-151

Treatment and prognosis of hepatic epithelioid hemangioendothelioma based on SEER data analysis from 1973 to 2007

S.S. Kim[1], J.Y. Cheong[1], H.J. Cho[1], S.W. Cho[1], O.K. Noh[2]. *[1]Ajou university school of medicine, Gastroenterology, Suwon; [2]Ajou university school of medicine, Radiation oncology, Suwon*
Email: cocorico99@gmail.com

Background and Aims: Malignant hepatic epithelioid hemangioendothelioma (HEH) is a rare malignant tumor of vascular origin with unknown etiology and a variable natural course. This study evaluated the current management and prognosis of HEH status based on SEER data analysis from 1973 to 2007.
Method: Using SEER database, a total 79 patients with HEH were analyzed from 1973 to 2014. Patient survival was calculated using Kaplan-Meier survival curves with log rank test.
Results: The mean age of patients with HEH was 53.0 years, and the male to female ratio was 1:2.6. About one third (40.8%) of patients were diagnosed at regional metastatic stage followed by local (30.3%) and distant metastatic stage (28.9%). Median tumor size was 3.85cm (IQR, 2.50–7.93cm). Thirty four (43.0%) of patients received no treatment or the treatment information was missing. Of the 45 treated patients, the most common treatment was chemotherapy (48.9%) followed by resection (22.2%). About 22.2% of patients were treated with more than one method. The 1-year and 5-year survival rates were 88% and 88%, respectively in resection or liver transplantation group; 72% and 49%, respectively in other treatment or observation group. Resection or liver transplantation based treatment was only independent predictive factor for survival (hazard ratio 0.17, 95% confidence interval 0.04–0.75, P = 0.020).
Conclusion: Resection or liver transplantation is worth considering for treatment of patients with HEH.

FRI-152

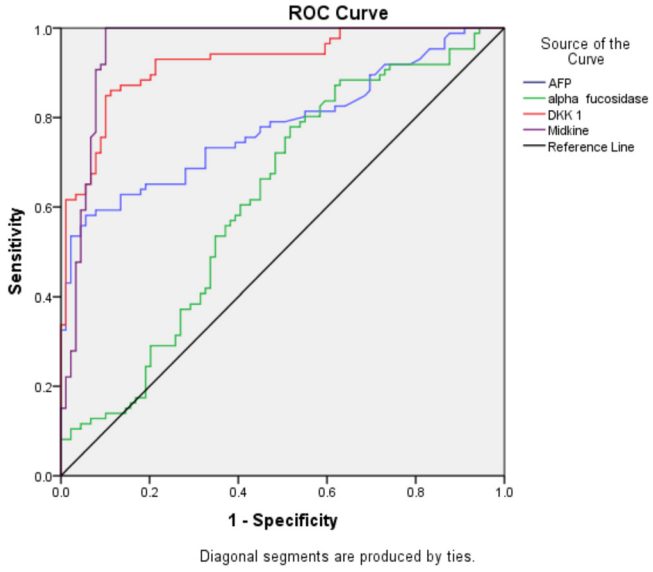
The validity of serum midkine, dickkopf-1 and alpha-L-fucosidase as surrogate biomarkers for the diagnosis of hepatocellular carcinoma

N.A. Habachi[1,2], A. El-Shayeb[2,3], A. Mansour[2,4], M. Zaghloul[2,5]. *[1]Alexandria University, Faculty of Medicine, Physiology department, Alexandria, Egypt; [2]Alexandria University, Faculty of Medicine, Alexandria clinical research center, Alexandria, Egypt; [3]Alexandria University, Faculty of Medicine, Tropical medicine department, Alexandria, Egypt; [4]Alexandria University, Faculty of Medicine, Clinical pathology, Alexandria, Egypt; [5]Kafrelsheikh University, Faculty of Medicine, Hepatology, Gastroenterology and Infectious diseases, Kafr ElSheikh, Egypt*
Email: mariam_zaghloul@med.kfs.edu.eg

Background and Aims: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, particularly in Egypt where hepatitis C (HCV) is highly prevelant. Currently, alpha fetoprotein (AFP) level is the gold standard diagnostic tool for detection and monitoring HCC but with low sensitivity. Thus, the identification of alternative or combined serum markers of HCC is highly needed. Therefore, the aim of this work was to verify the value of serum midkine, dickkopf-1(DKK-1) and alpha-L-fucosidase (AFU) in detection of HCC development in cirrhotic HCV patients.
Method: Serum midkine, DKK1and AFU were investigated in 175 patients (89 cirrhotic HCV patients as group I and 86 cirrhotic HCV patients with HCC as group II). Besides, 69 apparently healthy volunteers as controls were enrolled. Serum AFP, midkine, DKK-1and AFU were measured by ELISA.
Results: Serum AFU was significantly higher in group II than in groups I and III (z = 2.75 and 8.99 respectively) (p = 0.006 and 0.00respectively). Also, serum DKK-1 was significantly higher in group II than in groups I and III (z = 9.66 and 10.55 respectively) (p = 0.00 and 0.00respectively). Moreover, serum midkine was significantly higher in group II than in groups I and III (z = 10.38 and 10.58 respectively) (p = 0.00 and 0.002 respectively). Both serum DKK-1 and midkine were significantly higher in advanced HCC patients than in those with early HCC (z = 2.64 and 3.05 respectively) (p = 0.008 and 0.002 respectively).
ROC curve analysis showed that the diagnostic potential of serum midkine and DKK-1to detect HCC occurrence was superior to that of AFP.

	Cut-off value	Specificity	Sensitivity	Positive predictive value	Negative predictive value	Efficacy	AUC
AFP(ng/ml)	40	64%	82%	77%	70.19%	73.14%	0.78
alpha -L-fucosidase (U/l)	0.37	50%	74%	58.33%	65.67%	61.14%	0.62
DKK-1(ng/ml)	2.32	80%	89%	80.2%	88.6%	84%	0.92
Midkine(ng/ml)	5.1	90%	100%	89%	100%	94%	0.95

Using 40ng/ml as a diagnostic cut-off value for AFP, It was diagnostic in 55/86 HCC patients and missed 31patients (36%). While, serum AFU was positive in 24/31 (77.4%), seum DKK-1 was positive in 28/31 (90%) and serum midkine was positive in 30/31 (96.77%). A logistic regression analysis was performed to ascertain the effects of serum midkine, DKK1and AFU on the likehood that cirrhotic HCV patients would have HCC. The logistic regression model was statistically significant x^2=137.45 and p = 0.000. Among the three variables tested, only serum midkine and DKK-1 significantly predicted HCC development in cirrhotic HCV patients (p = 0.00 and 0.017 respectively).



Conclusion: Serum midkine and DKK-1 are reliable and promising diagnostic as well as prognostic biomarkers for HCC in cirrhotic HCV patients.

FRI-153

The impact of platelets on patients with hepatocellular carcinoma

B. Scheiner[1], S. Popp[1], F. Hucke[1], S. Bota[2], M. Peck[2], N. Rohr-Udilova[1], T. Reiberger[1], C. Müller[1], M. Trauner[3], W. Sieghart[1], M. Pinter[1].
[1]Medical University of Vienna, Department of Internal Medicine III, Div. of Gastroenterology and Hepatology, Vienna, Austria, [2]Klinikum Klagenfurth am Wörthersee, Department of Gastroenterology & Hepatology, Endocrinology and Nephrology, Klagenfurth, Austria; [3]Medical University of Vienna, Div. of Gastroenterology and Hepatology, Wien, Austria
Email: bernhard.scheiner@meduniwien.ac.at

Background and Aims: Platelets have been reported to influence tumor biology and may promote metastasis. Traditionally, thrombocytopenia (TCP) – a hallmark of cirrhosis – was associated with hepatocellular carcinoma (HCC) development. However, the impact of platelet count (PLT) on the outcome in patients with established HCC is not well studied. Therefore the aim of this study was to evaluate the effect of platelet count and function on survival in patients with advanced HCC.
Methods: Outcomes of cirrhotic patients with a diagnosis of HCC between 1995–2013 who were not eligible for surgical treatment and did not receive any anti-platelet therapy were retrospectively studied. TCP was defined as a PLT < 150G/L. Mean platelet volume (MPV) is a surrogate marker of platelet production in the bone marrow.
Results: Among 626 patients with unresectable HCC, TCP was present in 378 (60.4%) and was associated with favourable tumor characteristics: lower diameter of the largest nodule (5.6 ± 3.2 vs. 7.6 ± 4.2 cm), less extrahepatic spread (9.5% vs 20.2%, both $p < 0.001$), less macrovascular invasion (21.2% vs 31.0%, $p = 0.005$), lower BCLC stages (63.0% vs 73.4% BCLC C/D; $p = 0.007$) as compared to patients with normal PLT. On univariate analysis, TCP and a larger MPV ≥ 11fL were associated with longer overall survival (OS) (median OS (95%CI), 11.5 (9.3–13.8) vs. 5.5 (3.8–7.1) months; $p = 0.001$; MPV ≥11fL: 11.7 (9.1–14.2) vs. 6.0 (4.4–7.6) months; $p < 0.001$). In multivariate analysis, the combined variable of TCP and larger MPV was independently associated with longer OS (HR (95%CI), 0.79 (0.64–0.97); $p = 0.026$). This effect was most pronounced in advanced tumor stages (BCLC C/D).

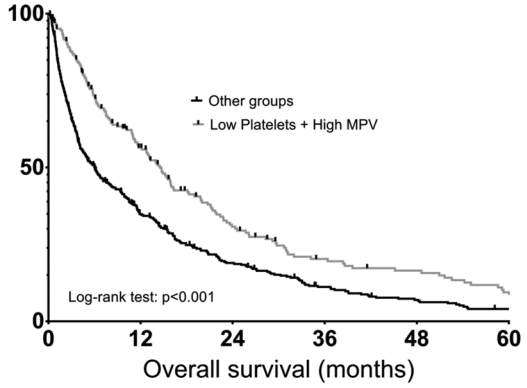


Figure 1: Comparison of overall survival between patients with a platelet count <150 G/L and a MPV ≥11 fL versus patients with other platelet characteristics

Conclusions: Thrombocytopenia and higher MPV are associated with better outcome in patients with advanced HCC. These findings may prompt further clinical research on additive anti-platelet therapy in the management of HCC.

FRI-154

Proton pump inhibitors and risk of hepatocellular carcinoma: a population-based study

W.-Y. Kao[1], C.-W. Su[2], E.C.-H. Tan[3], P.-C. Lee[2], Y.-H. Huang[2], C.-C. Chang[4], M.-C. Hou[2], H.-C. Lin[2], J.-C. Wu[5]. *[1]Taipei Medical University Hospital, Division of Gastroenterology, Department of Medicine, Taipei, Taiwan; [2]Taipei Veterans General Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [3]Ministry of Health and Welfare, National Research Institute of Chinese Medicine, Taipei, Taiwan; [4]Taipei Medical University Hospital, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [5]Taipei Veterans General Hospital, Department of Medical Research, Taiepi, Taiwan*
Email: cwsu2@vghtpe.gov.tw

Background and Aims: The long term use of proton pump inhibitors (PPIs) has been associated with hypergastrinemia. The pro-growth effects of gastrin have been hypothesized to create the potential for increased cancer risk in different organs for all PPIs. The association between PPIs use and hepatocellular carcinoma (HCC) risk are scarce. This study aims to investigate the association between PPIs use and HCC risk in a national population-based cohort.
Method: By analyzing data from the Taiwan National Health Insurance Research Database between year 2003–2013, we identified 35,356 patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) after excluding patients who both diagnosed HBV and HCV, HCC or other cancers within one year before the cohort entry date, follow-up duration less than one year and survival time less than 180 days. PPI use was defined as more than 28 cumulative defined daily doses. After one-to-one propensity score matching by gender, age, follow-up time, comorbidity and medication, 7,517 patients with and without PPIs use, including 11,192 patients with HBV and 3842 patients with HCV, were enrolled for analyses, respectively. The Kaplan-Meier method and Cox proportional hazards models were performed for multivariable and stratified analyses to estimate the association between PPIs use and HCC risk.
Results: Among the HBV cohort, 284 developed HCC during a median follow-up of 51 months. PPIs use was not associated with an increased HCC risk (adjusted hazard ratio, 0.88; 95% confidence interval, 0.70–1.12; $p = 0.306$). Among the HCV cohort, 220 developed HCC during a median follow-up of 50 months. PPIs use was not associated with an increased HCC risk (adjusted hazard ratio, 1.01; 95% confidence interval, 0.77–1.32; $p = 0.942$). We observed no relationship between dose of PPI taken and HCC risk in the HBV and HCV cohorts, respectively. Subgroup analysis also confirmed PPIs use was not associated with an increased HCC risk.
Conclusion: PPIs use in clinical practice was not associated with HCC risk in the present population-based study.

FRI-155

Virologic control increased overall survival after radiofrequency ablation of hepatocellular carcinoma developed on hepatitis related cirrhosis

M. Allaire[1], S. Rekik[2], L. Richard[3], A. Mamana[2], E. Guyot[4], N. Gisèle[2], B. Valerie[2], Véronique Grando[2], M. Ziol[5], P. Nahon[2,6], N. Ganne-Carrié[2,6], O. Sutter[7], E. Audureau[3], O. Seror[7], J. Charles Nault[2,6]. *[1]CHU CAEN, Service d'Hépato-gastroentérologie et nutrition, CAEN, France; [2]CHU Jean Verdier, Service d'Hépatologie, BONDY, France; [3]Université Paris-Est, Unit EA4393, Créteil, France; [4]CHU Jean Verdier, Service de biochimie, Bondy, France; [5]CHU Jean Verdier, Service d'anatomopathologie, BONDY, France; [6]Inserm UMR 1162, PARIS, France; [7]CHU Jean Verdier, Service de radiologie, BONDY, France*
Email: allama5@hotmail.fr

Background and Aims: The effect of virologic suppression on long-term outcomes after radiofrequency ablation (RFA) of hepatocellular carcinoma (HCC) on hepatitis B and C cirrhosis remains to be determined.

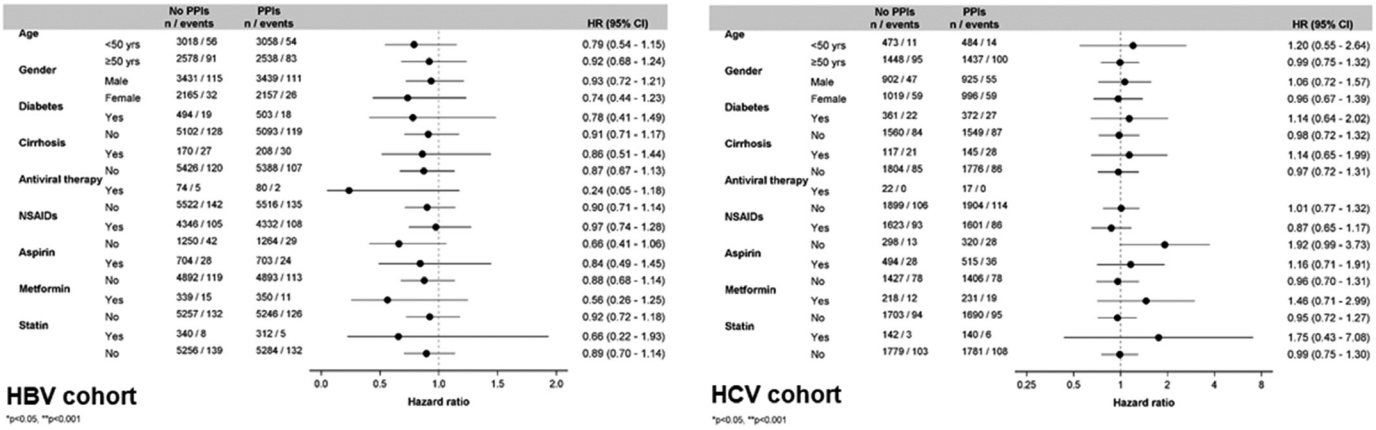


Figure 1: (abstract: FRI-154)

Method: Cirrhotic patients treated by RFA for HCC within Milan criteria and naïve of previous treatment were included. Time-to-events data were estimated by Kaplan-Meier with the log rank test, using Cox uni- and multivariate models and after adjustment using an ITWP propensity score.
Results: 389 patients (Child-Pugh A 86.6%, 473 tumors, median size 25 mm) were included with cirrhosis due to HCV in 166 patients, due to HBV in 43 patients and due to alcohol and/or metabolic syndrome alone in 182 patients. Overall survival (OS) was 79.8%, 42.4% and 16%; overall tumor recurrence 45%, 78% and 88% at 2, 5 and 10 years, respectively. HBV patients have an increased median overall survival (119 vs 51 mths, p = 0.0059) and decreased distant tumor recurrence (52% vs 79% at 5 yrs and 68% vs 88% at 10 yrs, p = 0.02) compared to patients with HCV, alcohol or NASH, even in multivariate analysis (HR = 0.55, p = 0.01 for recurrence and HR = 0.45, p = 0.03 for survival). 39 HBV patients among 43 achieved negative PCR before or after RFA either spontaneously or due to antiviral treatment. Patients with negative PCR obtained before RFA had longer median time to tumor recurrence than patients with a persistent positive at the time of RFA (13 mths vs 90 mths, p = 0.01) with a trend to an increased OS (70 mths for PCR- vs 120 mths for PCR+, p = 0.11).
HCV patients have the same OS or tumor recurrence compared to patients with alcohol or NASH. 54 of 166 HCV patients (33%) obtained sustained virologic response (SVR) before RFA or during follow-up (interferon regimens n = 33, direct antiviral agents (DAA) n = 20, other n = 1). Using time-dependent analysis, no significant difference was noted in tumor recurrence between SVR and non-SVR patients. In contrast, SVR patients had increased median OS (median survival not reached at 120 mths) compared to non-SVR patients (49 mths, p < 0.001), independently of other prognostic factors in multivariate analysis (HR = 0.44, p = 0.026). No increase in tumor recurrence after SVR using DAA was observed before or after adjustment using an ITWP propensity score.
Conclusion: Virologic suppression reduces overall mortality after RFA for HCC developed on HBV and HCV related cirrhosis suggesting that treatment of etiology is crucial for improving survival after efficient percutaneous treatment.

FRI-156

Clinical and biological features according to fibrosis of HBV related HCC in a Western country

M. Allaire[1], E.H. Weam[2], S. Brichler[3], L. Blaise[2], N. Gisèle[2], B. Valerie[2], V. Grando[2], F. Arbadi[2], P. Nahon[2,4], M. Ziol[5], J. Charles Nault[2,4], N. Ganne-Carrié[2,4]. *[1]CHU CAEN, Service d'Hépato-gastroentérologie et nutrition, CAEN, France; [2]CHU Jean Verdier, Service d'Hépatologie, Bondy, France; [3]CH Avicenne, Service de bactériologie et virologie, AVICENNE, France; [4]Inserm UMR 1162, PARIS, France; [5]CHU Jean Verdier, Service d'anatomopathologie, Bondy, France*
Email: allama5@hotmail.fr

Background and Aims: Hepatitis B virus (HBV) is a major cause of hepatocellular carcinoma (HCC). HCC characteristics in HBV patients without cirrhosis have been poorly studied, especially in Western countries. The aim of our study was to compare the characteristics of HCC complicating HBV infection within the presence or absence of underlying liver cirrhosis (LC).
Method: All patients with HBV infection and HCC discussed between 2007 and 2017 in an expert French center multidisciplinary meeting were included retrospectively. The diagnosis of cirrhosis was defined by histological criteria and/or the combination of clinico-biological, ultrasonography and elastometry data. Data were collected at the diagnosis of HCC.
Results: Among the 2,039 HCC discussed, 152 HBV patients were included. Patients (men 93%, mean age 54.8 ± 16 years, BMI > 25 kg/m^2 36%, chronic alcohol intake 40%), from Africa (63%), Europe (18%) and Asia (16%), had HBV viral load >2000IU/l, positive AgHBe and HBsAg titre > 1000IU/l in 39%, 12% and 54% of cases respectively. 53% of them received HBV antiviral treatment at HCC diagnosis.
The majority of HCC (76%) had <3 lesions (median size of the largest lesion 90.1 ± 58.9mm) and 28% were infiltrative. Portal thrombosis and/or metastasis were observed in 18% and 10% of cases respectively; 60% were BCLC B-D. The median AFP level was 13.81 ± 16.37 ng/ml; 55% of patients had AFP level > 100ng/ml and 54% an AFP score > 2.
130 out of 152 patients (86%) had LC (Child-Pugh A/B/C: 77%/18%/5%), among whom 57% had endoscopic signs of portal hypertension. Among the 22 patients without LC (14%), 80% were classified as F0-F1 according to the METAVIR classification.
Compared to patients with LC, non-LC patients had fewer risk factors for HCC (HCV, HDV and NASH) (5 vs 42%, p < 0.001). No difference was observed for alcohol consumption (36 vs 38%, p = 0.91) nor virological parameters. Regarding HCC characteristics, non-LC patients had larger lesions (lesion > 6 cm: 64 vs 30%, p = 0.002) and AFP level > 100ng/ml (68 vs 41%, p = 0.02).

Conclusion: In a French expert center, 14% of HCC complicating HBV infection are diagnosed in a non-cirrhotic liver, are mainly developed in non-fibrotic liver F0–1 (80%), with larger and/or more aggressive tumors (high AFP level) compared with HCC developed in HBV cirrhosis. In addition, non-cirrhotic patients have fewer risk factors for HCC (HCV, HDV and NASH) than patients with cirrhosis suggesting a direct viral mechanism in the process of carcinogenesis.

FRI-157

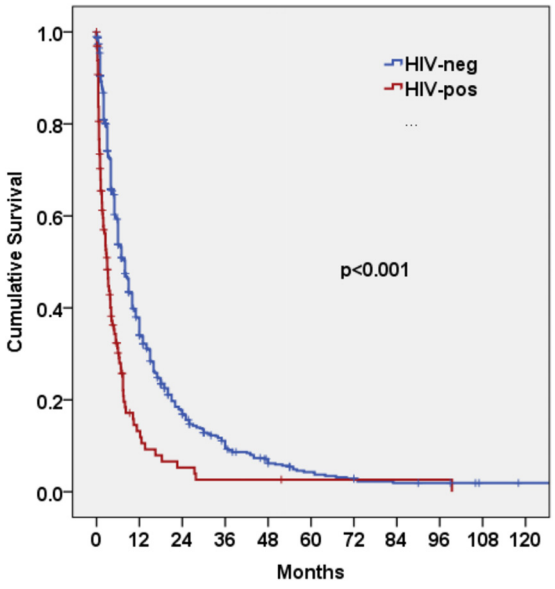
HIV infection adversely influences the natural history of untreated hepatocellular carcinoma (HCC)

D.J. Pinato[1], T.-Y. Chen[2], E. Allara[3], F. Trevisani[4], B. Minguez[5], M. Zoli[6], M. Harris[7], A.D. Pria[8], N. Merchante[9], H. Platt[10], M. Jain[11], E. Caturelli[12], L. Kikuchi[13], J. Pineda[9], M. Nelson[8], F. Farinati[14], G. Ludovico Rapaccini[15], A. Aytaman[16], M. Yin[17], M. Bower[8], E. Giovanni Giannini[18], N. Brau[19]. *[1]Imperial College London, Surgery and Cancer; [2]VA Central Texas HCS; [3]University of Cambridge; [4]University of Bologna; [5]Hospital Universitario Vall d'Hebron; [6]Università di Bologna, Bologna, Italy; [7]St. Paul's Hospital, Vancouver, BC; [8]National Centre for HIV Malignancy, Chelsea & Westminster Hospital & Imperial College; [9]Universidad de Sevilla, Spain; [10]MSD, USA; [11]University of Texas Southwestern Medical Center; [12]ASL Viterbo; [13]Universidade de São Paulo, Brazil; [14]University of Padova; [15]Universita" Cattolica del Sacro Cuore, Rome; [16]VA New York Harbor HCS; [17]Columbia University, NY; [18]University of Genova; [19]Divisions of Infectious Diseases & Liver Diseases, Mount Sinai School of Medicine*
Email: david.pinato09@imperial.ac.uk

Background and Aims: HCC is a leading cause of mortality in people living with HIV. However, studies evaluating whether HIV can affect the natural history of HCC have been inconsistent due to heterogeneity in geographical origin, stage, and treatment status. In this large, multicenter study we aimed to assess the prognostic impact of HIV status in two large cohorts of patients who did not receive active anticancer treatment.

Method: HIV-infected patients with untreated HCC were retrospectively identified from 47 centers in North and South America, Europe, and Australia and compared to 776 HIV-negative subjects with treatment-naïve HCC recruited from the ITALICA consortium. The primary endpoints were overall survival, with HIV status being tested as prognostic factor in uni- and multivariable survival analyses. Secondary endpoints were presentation and staging of HCC at diagnosis.

Results: Among the 132 HIV-positive patients, 56% had undetectable plasma HIV RNA, and the median CD4+ cell count was 256/mm^3. Compared to the 776 HIV-negative patients, they were younger (53 vs. 67 years, $p < 0.001$), more commonly male (95% vs. 80%, $p < 0.001$), hepatitis C virus positive (74% vs. 54%, $p < 0.001$), but had similar Child-Turcotte-Pugh (CTP) scores at diagnosis (7 vs. 7, $p = 0.37$). They presented more commonly with larger tumours (median diameter, 6.0 vs. 4.0 cm, $p < 0.001$), with uni-nodular lesions (62% vs 51%, $p = 0.012$), had higher AFP level (median 714 vs. 77 ng/dl, <0.001) and a higher proportion of portal venous invasion (36% vs 26%, $p = 0.034$) and distant metastases (28% vs. 8%, $p < 0.001$). HIV-positive patients had lower median survival (3.0 vs. 8.0 months HIV [-], Log rank $p < 0.001$) with estimated 1-year survival rates of 13% vs. 24%. Multivariable Cox regression analysis identified HIV infection as an independent predictor of worse survival (H.R., 1.62; 95% C.I., 1.19–2.19, $p = 0.002$) together with age, male sex, living in the Americas vs. Europe, CTP score, AFP level, portal vein invasion and BCLC stage. Among HIV-positive patients, independent predictors of mortality were CTP score, AFP level, and presence of metastases, but not HIV viral load, CD4+ cells or BCLC stage.



	Median Survival	1-yr	2-yr	5-yr	Estimated Survival
HIV-positive	3.0 months		13%	5%	3%
HIV-negative	8.0 months	34%	17%	4%	

Conclusion: HIV infection is independently associated with adverse survival in patients who did not receive treatment for HCC. Mechanistic studies to investigate the biologic foundations of such survival difference are urgently required.

FRI-158

Factors implicated in the risk of developing hepatocellular carcinoma (HCC) in patients with cirrhosis due to HCV. Implications of Sustained Virological Response (SVR)

A. Castaño, A. Gomez, M. Torner, M. Fraile, C. Álvarez-Navascués, V. Cadahía-Rodrigo, M.L.G. Dieguez, M. Varela, M. Rodríguez. *Hospital Universitario Central de Asturias, Liver Unit. Division of Gastroenterology&Hepatology, Oviedo, Spain*
Email: castaogarciacongresos@gmail.com

Background and Aims: One of the goals of the treatment of HCV is the reduction in the risk of developing HCC. With the new DAAs, high rates of SVR are obtained in patients with cirrhosis. Aim: To analyze the factors involved in the development of HCC in a series of patients with HCV cirrhosis and to determine if SVR reduces the risk.

Method: 699 patients with HCV cirrhosis, Child A/B, included in a surveillance program for the early diagnosis of HCC based on semi-annual AFP and US controls. The patients who reached SVR during the follow-up were considered viremic until that moment, censored at that point and included again as patients with SVR, updating the clinical and demographic variables.

Results: 72% male sex, mean age 53 ± 9 years, 89% Child A, 22% with previous decompensation, 60% with varices and 34.6% with SVR (53 with IFN and 189 with DAAs). During a mean follow-up of 44 ± 50 months, 98 patients developed HCC, with a mean annual incidence of 3.7% and a cumulative probability at 5 and 10 years of 17% and 33% respectively. The probability of developing HCC was significantly lower in patients with SVR than in those without SVR (annual incidence: 1.7% vs. 4.3%, $p = 0.013$). The follow-up of patients with SVR was lower than that of those without SVR (26 ± 32 vs. 54 ± 55 months, $p < 0.001$). In the univariate analysis the following other variables were associated with the risk of developing HCC: male gender ($p = 0.051$), age > 55 years ($p < 0.001$), previous

decompensation (p = 0.001), absence of HIV (p = 0.015), alcohol intake (p = 0.050), Child B (p < 0.001), varices (p < 0.001), platelet count < $115\times10^3/mm^3$ (p < 0.001), AFP > 5ng/ml (p = 0.003) and AST > UNL (p = 0.006). There was no association with GT-3 (p = 0.45), diabetes (p = 0.97), ALT > UNL (p = 0.42) or GGT > UNL (p = 0.55). In the multivariate analysis, the variables that were associated independently were: male sex (OR:2.58, 95%CI:1.55–4.30; p < 0,001), age > 55 (OR:3.04, 95%CI:1.93–4.77; p < 0,001), previous decompensation (OR:1.68, 95%CI:1.00–2.79; p = 0.046), Child B (OR:2.26, 95% CI:1.25–4.09, p = 0.007), varices (OR:2.01, 95%CI:1.19–3.38, p = 0.009), platelet <$115\times10^3/mm^3$ (OR:1.60, 95% CI:1.01–2.55, p = 0.044) and AFP > 5 ng/ml (OR:1.75, 95%CI:1, 11–2,75; p = 0.016).

Conclusion: Classical factors, sex, age, advanced disease and AFP levels continue to be the main conditioning factors in the development of HCC in patients with HCV cirrhosis. In this series of patients, SVR, achieved mainly with DAAs, has not been associated independently with a decrease in HCC risk in the short-term.

FRI-159

Increased intestinal permeability and inflammation are associated with hepatocellular carcinoma in patients with NAFLD-related liver cirrhosis

F. Ponziani[1], S. Bhoori[2], V. Petito[1], F.P. Sterbini[3], D. Morelli[4], T.D. Michele[3], M. Sanguinetti[5], A. Gasbarrini[1], V. Mazzaferro[4], M. Pompili[6]. *[1]Policlinico Agostino Gemelli, Internal Medicine, Gastroenterology, Hepatology, Roma, Italy; [2]Istituto Nazionale Tumori, Hepatobiliary and Liver Transplant Surgery, Milano, Italy; [3]Policlinico Agostino Gemelli, Microbiology, Roma; [4]Istituto Nazionale Tumori, Hepatobiliary and Liver Transplant Surgery, Milano; [5]Policlinico Agostino Gemelli, Microbiology, Roma, Italy; [6]Policlinico Agostino Gemelli, Biochemistry, Roma*

Email: francesca.ponziani@yahoo.it

Background and Aims: Increased intestinal permeability (IP) is common in patients with cirrhosis. Leaky gut is associated with the translocation of microbial products and fragments and this process is involved in the pathogenesis of NAFLD.

The aim of this study is to investigate if intestinal permeability and inflammation are associated with HCC in NAFLD patients.

Method: 21 Cirrhotic patients with NAFLD and HCC, 33 liver cirrhotic patients (20 with NAFLD and 13 with chronic hepatitis C) comparable for age, liver function and portal hypertension and 20 age-matched healthy controls were included in the study. Quantification of zonulin-1 (ZO1) and lipopolysaccharide (LPS), as indices of IP, and fecal calprotectin as marker of intestinal inflammation were performed using ELISA and the Liaison® analyzer.

Subjects affected by gastrointestinal or systemic diseases potentially affecting IP and those with documented alcohol intake during the last year or who had taken antibiotics during the last 6 months were excluded from the study.

Results: IP was increased in patients with liver cirrhosis who had higher serum levels of ZO1 and LPS compared to controls (ZO1: 11.33 (1.93) vs. 7.05 IQR 2.41 ng/ml p <0.0001; LPS 13.17 IQR 13.01 vs 2.52 IQR 2.14 EU/ml p = 0.012; Figure 1). There was no significant difference between cirrhotic patients with HCC and those without HCC (ZO1: 11.35 IQR 1.16 vs 11.23 IQR 53.93 ng/ml p = 0.993; LPS 12.82 IQR 12.82 IQR 12.2 p = 0.974 EU/ml Figure 1).

Fecal calprotectin levels were increased in cirrhotic patients with and without HCC compared to controls (75.65 IQR 335.25 vs 10.35 IQR 9.2 mcg/g p < 0.0001 Figure 1). Within the cirrhosis group, patients with HCC showed higher calprotectin levels than patients without HCC (457 IQR 603 vs 59.85 IQR 185 mcg/g, p < 0.005 Figure 1).

Conclusion: IP is increased in cirrhotic patients with and without HCC, but the latter also show higher fecal calprotectin. This could be related to a higher intestinal inflammatory status, which may contribute to exacerbate the inflammatory liver injury contributing to the development of neoplastic lesions in cirrhotic NAFLD patients.

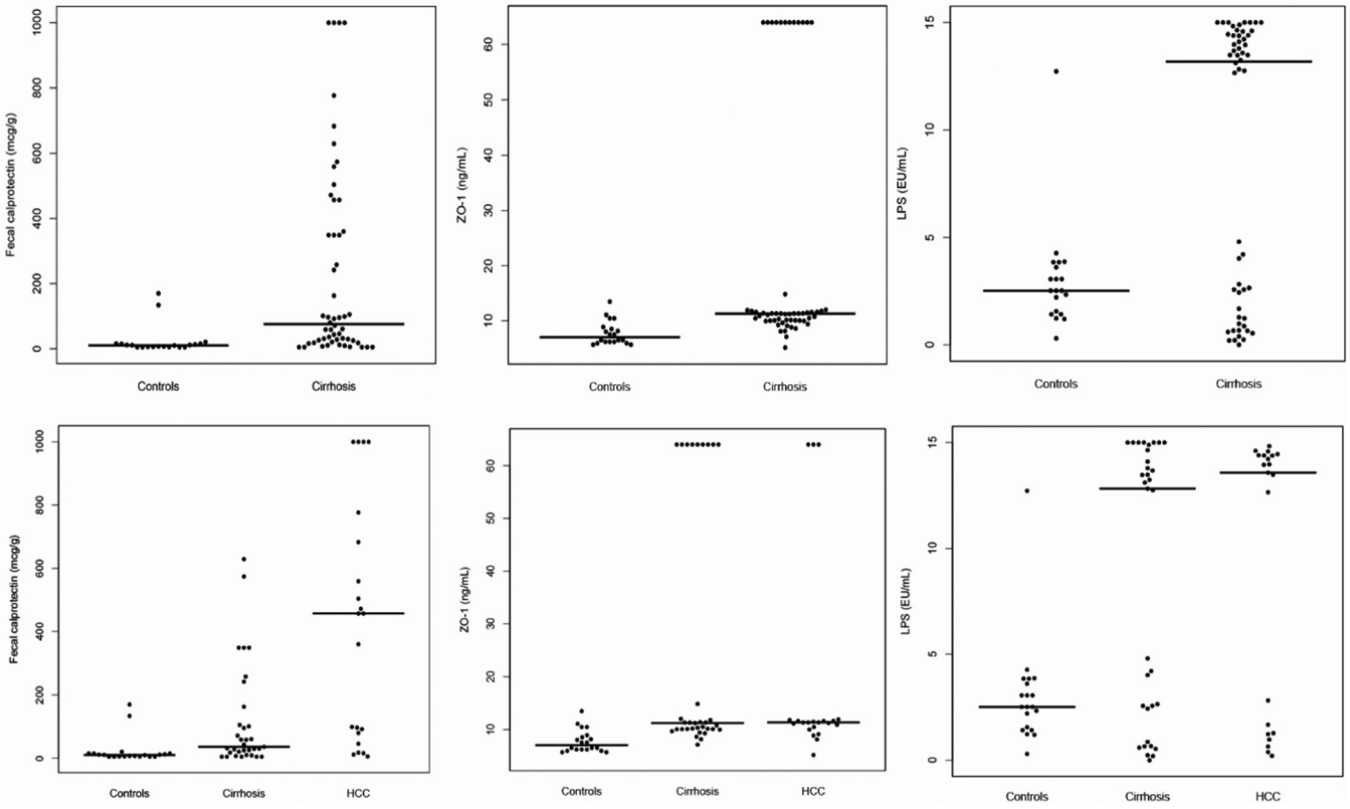


Figure 1: (abstract: FRI-159)

FRI-160

Towards elucidating a universal panel of diagnostic biomarkers for early hepatocellular carcinoma

U. Abellona[1], D.P. Mark[2], O. Oleribe[3], N. Ladep[4], H. Reeves[5], S. Greer[6], M. Prince[6], S. Ryder[7], K. Nash[8], M. Cramp[9], M. Thursz[1], J. Nicholson[1], E. Holmes[1], S. Taylor-Robinson[1], E. Okeke[2], M. Lemoine[1]. [1]*Imperial College London;* [2]*Jos University Teaching Hospital;* [3]*Excellence And Friends Management Care Centre;* [4]*Wirral University Teaching Hospital;* [5]*Newcastle University;* [6]*Manchester University NHS Foundation Trust;* [7]*The University of Nottingham;* [8]*University Hospital Southampton NHS Foundation Trust;* [9]*Plymouth Hospitals NHS Trust*
Email: mei.u11@imperial.ac.uk

Background and Aims: Hepatocellular carcinoma (HCC) is a major contributor to disease burden globally with the majority of cases occurring in resource-limited settings. The current lack of an accurate method for early diagnosis is a major factor limiting treatment outcome in countries like Nigeria, where tumours present late. This work draws upon British populations presenting earlier and Nigerian populations with more advanced disease (with HCC arising from different aetiologies). We aimed to identify discriminatory signals that could be potential universal diagnostic biomarkers using metabolic profiling of both serum and urine.

Methods: Urine and serum samples from European and African populations were collected (United Kingdom: n = 252, 128 HCC, 44 cirrhosis, 80 healthy control; Nigeria: n = 496, 140 HCC, 97 cirrhosis, 133 non-cirrhotic hepatitis B, 126 healthy controls). Un-targeted metabolic profiling using proton nuclear magnetic resonance (NMR) and liquid chromatography-mass spectrometry (LC-MS) were performed. Data were analysed by multivariate statistical analyses.

Results: Unsupervised principal component analysis of both urine and serum data of all datasets show observable differential clustering of HCC and cirrhosis samples from hepatitis B and healthy controls (NMR data - Figure 1). Predictive models of the supervised partial least squares analysis could be built, comparing HCC against non-cirrhotic hepatitis B and healthy controls ($R2 > 0.5$, $Q2 > 0.4$, $p < 0.001$), and also in comparisons to cirrhosis ($R2 > 0.5$, $Q2 > 0.1$, $p < 0.01$), respectively for each dataset. Identified discriminatory signals include metabolites related to gut microbial metabolites (hippurate and p-cresol sulphate) in urine, choline metabolism (choline and betaine) and intermediates of central energy metabolism (succinate and lactate) in serum.

Conclusion: Results of urine data validates previously published results and this is the first comprehensive profiling of serum samples of studies of similar kind. Together, these comprehensively characterised cohorts provide in-depth insights into the metabolic phenotypes of HCC patients, which will inform a shortlist of discriminatory compounds for further investigations for their utility as potential diagnostic biomarkers that are universally applicable irrespective of underlying aetiology, ethnicity and environmental exposure.

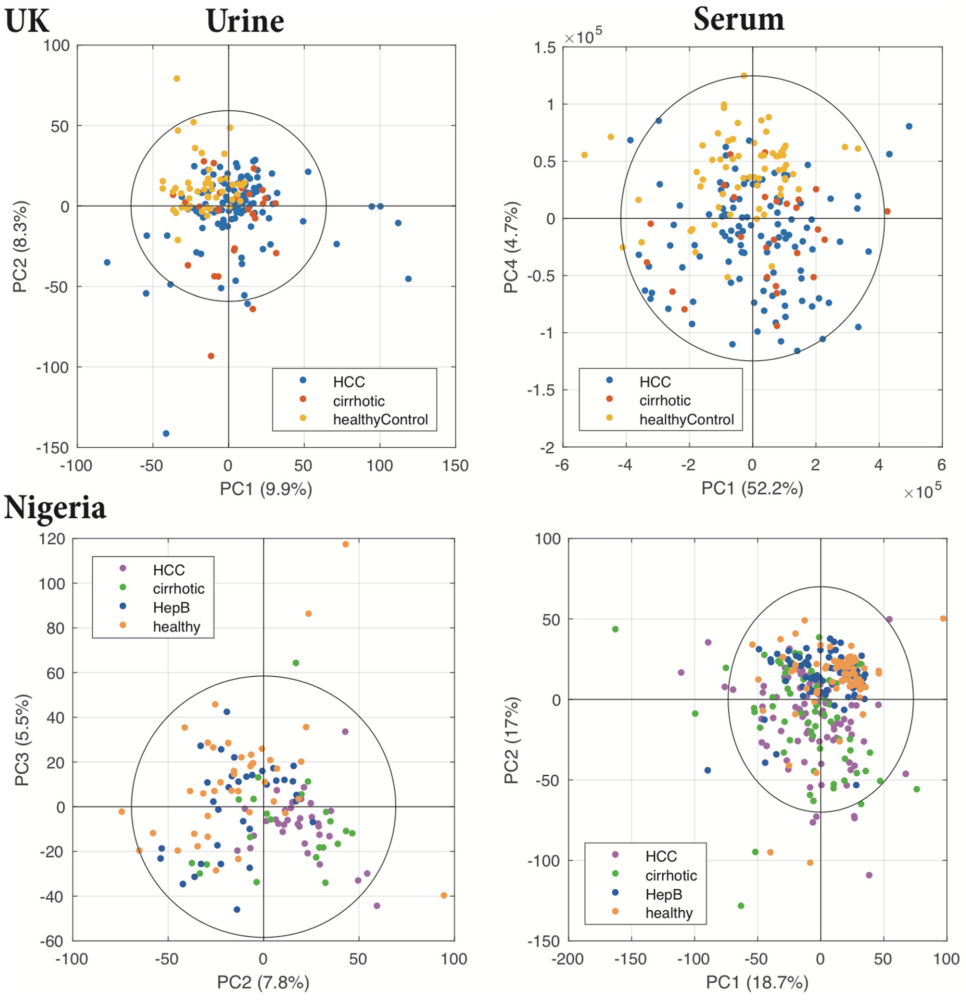


Figure 1: Scores plot of principal component analysis of NMR data.

FRI-161

Presence of steatosis does not increase the risk of Hepatocellular Carcinoma in patients with Chronic Hepatitis B over long follow-up

C.T. Lim[1], B.B.G. Goh[1], K.H.T. Lim[2], W.Q. Leow[2], R. Azhar[2], W.K. Wan[2], R. Kumar[1]. [1]*Singapore General Hospital, Gastroenterology and Hepatology;* [2]*Singapore General Hospital, Pathology, Singapore*
Email: thomson.lim@mohh.com.sg

Background and Aims: Chronic Hepatitis B (CHB) remains an important disease in many parts of the world and with the rising prevalence of metabolic syndrome worldwide; patients with concomitant CHB and hepatic steatosis are increasingly encountered. However the characteristics, interactions and long term follow-up among these patients remain to be elucidated.
The aim of this study is to assess the liver histology, clinical characteristics and progression to hepatocellular carcinoma (HCC) in CHB patients with or without concomitant hepatic steatosis who had liver biopsy performed.
Method: 292 CHB patients with liver biopsy performed between the years 2000–2014 were identified from hospital records. Liver biopsy histology was reviewed again by trained pathologists for presence of >5% steatosis and non-alcoholic steatohepatitis (NASH). The clinical characteristics were analysed and stratified by presence (Group 1) or absence (Group 2) of hepatic steatosis. Patients were prospectively followed-up for progression of development of HCC till 01/06/2017. HCC was confirmed based on contrast enhanced imaging.
Results: Hepatic steatosis was seen in 64% (100/182) of patients with hepatitis B on biopsy. At the time of biopsy, the mean age was 45.3 ± 11.9 years with 72.6% males and predominantly of Chinese ethnicity (94.9%).
On mean follow-up of 10.6 ± 3.8 years, HCC was seen in 26 patients with follow-up of up to 17 years-patient years follow-up. Hepatic steatosis was not a significant risk factor for HCC on cox-regression analysis (p = 0.555), while advanced age and presence of cirrhosis were significant for HCC development (p value = 0.016 and 0.04 respectively). There is also no significant association between types of CHB treatment and HCC development.
In a subgroup analysis of even low HBV DNA defined as HBVDNA < 7 log copies/ml, presence of hepatic steatosis was not associated with increased risk of HCC as well. (p value = 0.471)
Conclusion: In patients with Hepatitis B presence of concomitant steatosis does not increase the risk of hepatocellular cancer development.

FRI-162

Sarcopenia is not a predictor of survival or sorafenib toxicity in advanced hepatocellular carcinoma: A Dutch multicenter study

T. Labeur[1,2], J. van Vugt[3], D.T. Cate[3], B. Takkenberg[1], B.G. Koerkamp[3], R.D. Man[4], O. van Delden[5], J. Ijzermans[3], F. Eskens[6], H.-J. Klümpen[2]. [1]*Academic Medical Center, Gastroenterology & Hepatology, Amsterdam, Netherlands;* [2]*Academic Medical Center, Medical Oncology, Amsterdam, Netherlands;* [3]*Erasmus University Medical Center, Surgery, Rotterdam, Netherlands;* [4]*Erasmus University Medical Center, Gastroenterology & Hepatology, Rotterdam;* [5]*Academic Medical Center, Radiology, Amsterdam, Netherlands;* [6]*Erasmus University Medical Center, Medical Oncology, Rotterdam, Netherlands*
Email: t.a.labeur@amc.uva.nl

Background and Aims: Sorafenib is standard of care for patients with advanced stage hepatocellular carcinoma (HCC), but there is no baseline biomarker to predict treatment outcomes. In several other cancer types, sarcopenia is associated with impaired survival and increased treatment toxicity, but such studies in European patients with advanced stage HCC are lacking.
This study aims to assess the association between sarcopenia and sorafenib outcomes and toxicity in a large European cohort of patients with advanced stage HCC.
Method: A retrospective analysis was performed in a Dutch cohort of 323 patients with HCC treated with sorafenib at two tertiary referral centers between 2007 and 2016. Skeletal muscle mass and density were measured at the third lumbar vertebra level (L3) using computed tomography (≤3 months prior to start) and correlated with overall survival (OS), time-to-progression (TTP), response rate and toxicity.
Results: A total of 273 patients (85%) were included, of which 142 (52%) had sarcopenia and 111 (41%) had a low muscle density. Sarcopenic patients were older (67 vs 62 years, p < 0.01) and slightly more often Child Pugh B (15% vs 8%), although this was not statistically significant (p = 0.06). Skeletal muscle mass showed an independent association with TTP, but not with OS, response rate or toxicity. Sarcopenic patients had more grade 3/4 liver toxicity (31% vs 23%) during treatment, but this was not statistically significant (p = 0.13). In Child-Pugh A patients, there were no significant associations with OS, TTP or sorafenib toxicity.

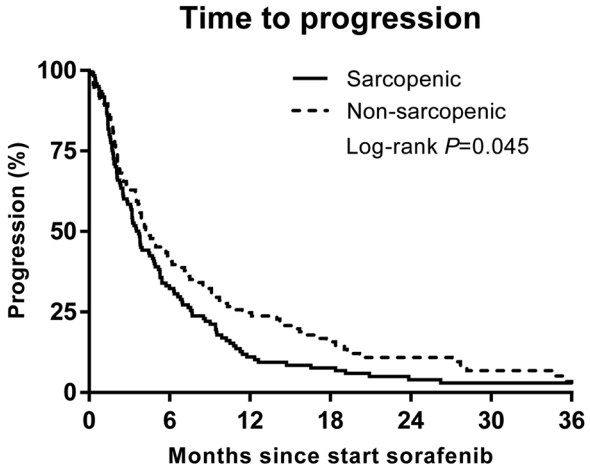


Figure 1: TTP in patients with and without sarcopenia (3.7 vs 4.4 months, p = 0.045).

Conclusion: In Dutch patients receiving sorafenib for advanced stage HCC, sarcopenia is associated with TTP, but is not an independent predictor of survival, response rate or toxicity.

FRI-163

The direct comparison between 7th AJCC staging system and 8th AJCC staging system for prediction of survival with Korean multicenter HCC patients

Y.-S. Lee[1], J.H. Kim[1], C.U. Lee[2], S.J. Suh[3], Y.K. Jung[2], Y.S. Seo[4], H.J. Yim[4], J.E. Yeon[4], K.S. Byun[4]. [1]*Korea University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South;* [2]*Korea University College of Medicine, Department of Internal Medicine, Ansan;* [3]*Korea University Ansan Hospital, Department of Internal Medicine, Ansan-si, Gyeonggi-do, Korea, Rep. of South;* [4]*Korea University College of Medicine, Department of Internal Medicine, Seoul*
Email: kjhhepar@naver.com

Background and Aims: AJCC staging is the most commonly used staging system in most solid tumors, and recent AASLD hepatocellular carcinoma (HCC) guideline also endorsed this AJCC staging system based on status of tumor, node, and metastasis. Recently, 8th edition of AJCC staging system was released in December 2016. This study aimed to compare prediction of survival in HCC patients between 7th AJCC staging system and 8th AJCC staging system.

Method: From 2004 to 2013, 2211 newly diagnosed HCC patients were consecutively enrolled in three Korea University medical centers and the medical records of patients were retrospectively reviewed. Each patients were classified following both of 7th AJCC staging system and 8th AJCC staging system.
Results: Chronic hepatitis B (1523, 68.9%) was main attributable factor in development of HCC, followed by chronic hepatitis C (256, 11.6%) and alcohol consumption (241, 10.9%). 1514 patients (68.5%) died during study period and median overall survival (OS) was 24.7 months. According to 7th AJCC staging system, 894 (40.4%) patients were included into stage I; 459 patients (20.8%) into stage II; 180 patients (8.1%) into stage IIIa; 354 patients (16.0%) into stage IIIb; 3 patients (0.1%) into stage IIIc; 119 patients (5.4%) into stage IVa; and 202 patients (9.1%) into stage IVb. According to 8th AJCC staging system, 400 (18.1%) patients were categorized into stage IA; 498 patients (22.5%) into stage IB; 442 patients (20.2%) into stage II; 193 patients (8.7%) into stage IIIa; 357 patients (16.1%) into stage IIIb; 119 patients (5.4%) into stage IVa; and 202 patients (9.1%) into stage IVb. Both 7th staging system and 8th staging system show distinct survival outcomes according to each stage. Although 7th AJCC staging system significantly well predicted 1 year of survival than 8th AJCC staging system (AUROC; 0.796 vs 0.784, p = 0.013), AUROCs of 3 year and 5 year were similar in 7th and 8th AJCC staging system (0.754 vs 0.752 in 3 year, p = 0.601; 0.744 vs 0.742 in 5 year, p = 0.643).
Conclusion: Both 7th and 8th AJCC staging system show distinct survival outcome according to each stage. Moreover, both 7th and 8th AJCC staging system are similar in prediction of survival outcomes compared to BCLC staging system.

FRI-164

Serum and urine extracellular vesicles contain mRNA biomarkers for primary sclerosing cholangitis (PSC) and cholangiocarcinoma (CCA)

A. Arbelaiz[1], A. Lapitz[2], M. Krawczyk[3,4], Á. Santos-Laso[2], J.L. Lavin[5], M.J. Perugorria[2,6,7], R. Jimenez-Aguero[2], A. Lacasta[2], C. Ibarra[8], A. Sanchez-Campos[8], J.P. Jimeno[9], E. Gonzalez[10], F. Lammert[3], M. Marzioni[11], R. Macias[6,12], J. Marin[6,12], T.H. Karlsen[13,14], J. Falcon-Perez[6,7,10], A. María Aransay[5,6], L. Bujanda[2,6], Jesús Banales[2,6,7]. *[1]Biodonostia Research Institute, Liver Diseases, Donostia, Spain; [2]Biodonostia Research Institute, Donostia University Hospital, Liver Diseases, San Sebastian, Spain; [3]Saarland University Medical Center, Saarland University, Department of Medicine II, Homburg, Germany; [4]Medical University of Warsaw, Department of General, Transplant and Liver Surgery, Warsaw, Poland; [5]CIC bioGUNE, Genome Analysis Platform, Derio, Spain; [6]"Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas" (CIBERehd), Carlos III National Institute of Health, Madrid, Spain; [7]IKERBASQUE, Basque Foundation for Science, Bilbao, Spain; [8]Hospital of Cruces, Bilbao, Spain; [9]"Complejo Hospitalario de Navarra", Pamplona, Spain; [10]CIC bioGUNE, Laboratory of exosomes, Derio, Spain; [11]Università Politecnica delle Marche, Department of Gastroenterology, Ancona, Italy; [12]Biomedical Research Institute of Salamanca (IBSAL), Experimental Hepatology and Drug Targeting (HEVEFARM), Salamanca, Spain; [13]Norwegian PSC Research Center, Oslo University Hospital, Division of Cancer Medicine, Surgery and Transplantation, Oslo, Norway; [14]Research Institute of Internal Medicine, Oslo University Hospital, Oslo, Norway*
Email: jesus.banales@biodonostia.org

Background and Aims: Cholangiocarcinoma (CCA) represents a heterogeneous group of biliary cancers with poor prognosis. The etiology of the majority of CCAs is unknown, but conditions such as primary sclerosing cholangitis (PSC) are risk factors. Simultaneously, PSC patients frequently (80%) present inflammatory bowel disease, mainly ulcerative colitis (UC). To date, there are not available sensitive and specific non-invasive biomarkers for the early diagnosis and monitoring of CCA, PSC and UC. The aim of this study was to investigate the potential value of serum and urine extracellular vesicles (EVs) as carriers of mRNA biomarkers for CCA, PSC and UC.
Method: EVs were isolated from serum and urine of CCA (n = 13 and 28), PSC (n = 8 and 7), UC (n = 8 and 12) and healthy (n = 9 and 5) individuals, using ultracentrifugation/filtration methods. The content of EVs was determined by mRNA microarray-based transcriptomics.
Results: Both serum and urine EVs showed round morphology (by transmission electron microscopy), similar size (~180 nm diameter by nanoparticle tracking analysis) and markers (CD9, CD63 and CD81 by immunoblotting) consistent with exosomes and small-size microvesicles. The mRNA profiles of serum EVs revealed 1,091 mRNA transcripts differentially expressed ($p < 0.01$) in CCA *vs.* controls, 100 in PSC *vs.* controls, 87 in UC *vs.* controls, 1,522 in CCA *vs.* PSC, and 107 in PSC *vs.* UC. Moreover, the mRNA profiles of urine EVs revealed 963 mRNA transcripts differentially expressed ($p < 0.01$) in CCA *vs.* controls, 334 in PSC *vs.* controls, 386 in UC *vs.* controls, 263 in CCA *vs.* PSC, and 98 in PSC *vs.* UC. In serum EVs, *RCN1* and *PON1* transcripts had area under the ROC curve (AUC) values of 0.974 and 0.959 in CCA *vs.* controls, respectively, *MTRF1L* (AUC = 0.947) and *XKR6* (AUC = 0.936) in PSC *vs.* controls, *LOC441376* (AUC = 0.937) and *P4HA1* (AUC = 0.927) in UC *vs.* controls, *CMIP* (AUC = 1.000) and *CCNB1IP1* (AUC = 1.000) in CCA *vs.* PSC, and *SNORA11B* (AUC = 0.941) and *GRM3* (AUC = 0.929) in PSC *vs.* UC. In urine EVs, *ERRFI1* and *SF4* transcripts had AUC values of 0.986 and 0.964 in CCA *vs.* controls, respectively, *FASN* (AUC = 1.000) and *KHNYN* (AUC = 1.000) in PSC *vs.* controls, *SFRS17A* (AUC = 1.000) and *PTPRT* (AUC = 0.983) in UC *vs* control, *LDHA* (AUC = 0.911) and *MT1F* (AUC = 0.893) in CCA *vs.* PSC, and *ROGDI* (AUC = 0.976) and *AOF2* (AUC = 0.964) in PSC *vs.* UC.
Conclusion: Our results underscore the value of serum and urinary EV transcriptomic (mRNA) signatures as diagnostic tools for CCA, PSC and UC.

FRI-165

Age and not comorbidity determines access to liver transplantation of patient with hepatocellular carcinoma

A. Lué[1], S. Lorente[1], F.J. Aranguren[1], L. Cortes Garcia[1], A. García-Gil[2], T. Serrano[1]. *[1]Hospital Clínico Universitario Lozano Blesa, Gastroenterology and Liver Unit; [2]Hospital Clínico Universitario Lozano Blesa, Hepatobiliopancreatic Surgery Unit*
Email: alberto.lue@hotmail.com

Background and Aims: Hepatocellular carcinoma (HCC) is the second most frequent cause of cancer mortality worldwide and the leading cause of mortality in patients with liver cirrhosis (LC). Liver transplantation (LT) is the treatment that increases survival the most in the early stages of this cancer. However, due to the shortage of donors, not all patients can access to LT. Our objective is to evaluate the applicability of this treatment and the factors related to the access to LT with main focus on comorbidity.
Method: Analysis was performed from a prospective registry of patients with HCC attended in our center. Cirrhotic patients with HCC who met Milan criteria were selected. The patients were divided into 3 groups: not evaluated for LT (A); evaluated for LT but not transplanted (B) and transplanted (C). Clinical and analytical variables, related to the tumor and comorbidity were evaluated, Charlson Comorbidity Index (CCI) was performed.
Results: Between February 2008 and February 2017, 338 patients were included in the registry and 150 (44%) of them met the Milan criteria. The 80% were males, with a median age of 62 (IQR: 57–69) years. In almost half of the patients liver transplantation was not considered (group A, n = 72) and therefore only 52% of these patients were evaluated for LT although almost a third of them could not be transplanted (group B, n = 24). Finally, only 36% of the patients who fulfilled the Milan criteria underwent to LT (group C, n = 54). When the different variables were analyzed in the three groups of patients, there were significant differences between the three

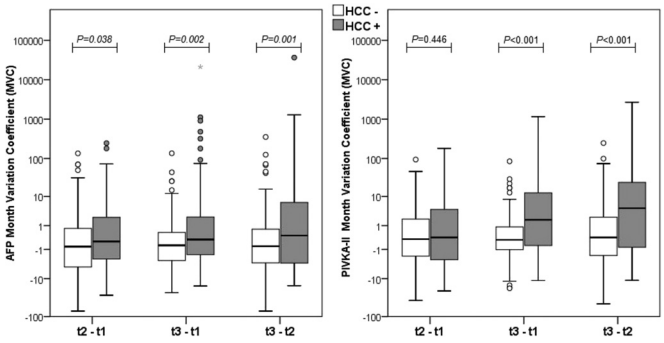
groups in age (p < 0.001), CCI (p = 0.006), creatinine levels (p = 0.037) and bilirubin levels (p = 0.002). No significant differences were observed between the groups in the etiology of LC, diagnosis on screening program, tumor size, number of nodules, Child's stage or alpha-fetoprotein levels. In the multivariate analysis, only age was associated with a lower probability of receiving LT (OR 0.942, 95% CI: 0.908–0.978 per year of age) and no other comorbidity factors.
Conclusion: Only one third of patients with hepatocellular carcinoma who meet Milan criteria can benefit from liver transplantation. Age and not comorbidity is the only factor that significantly determines access to LT.

FRI-166

Clinical significance of time related fluctuations of AFP and PIVKA-II serum levels in single patients with cirrhosis undergoing surveillance for hepatocellular carcinoma

G. Ricco[1], C. Cosma[2], G. Bedogni[3], A. Biasiolo[4], M. Guarino[5], P. Pontisso[4], F. Morisco[5], F. Oliveri[1], D. Cavallone[1], F. Bonino[3,6,7], M. Plebani[2], M.R. Brunetto[1,8]. *[1]University Hospital of Pisa, Hepatology Unit and Laboratory of Molecular Genetics and Pathology of Hepatitis Viruses, Reference Center of the Tuscany Region for Chronic Liver Disease and Cancer, Pisa, Italy; [2]University Hospital of Padua, Department of Laboratory Medicine, Padua, Italy; [3]Italian Liver Foundation (FIF), Trieste, Italy; [4]University of Padua, Department of Internal Medicine, Padua, Italy; [5]University of Naples "Federico II", Department of Clinical Medicine and Surgery, Gastroenterology Unit, Napoli, Italy; [6]National Research Council, Institute of Biostructure and Bioimaging, Napoli, Italy; [7]University of Pittsburgh Medical Center, Institute for Health, Chianciano Terme, Italy; [8]University of Pisa, Department of Clinical and Experimental Medicine, Pisa, Italy*
Email: maurizia.brunetto@unipi.it

Background and Aims: The clinically meaningful variations of circulating HCC biomarkers in the single patient are uncertain. We studied the dynamics of AFP and PIVKA-II in 2–3 consecutive sera obtained at random time points in cirrhotic patients with and without HCC.
Method: AFP and PIVKA-II were measured in 1163 sera of 418 cirrhotics (31.1% HBV, 58.6% HCV, 10.3% Non-viral) undergoing ultrasound HCC surveillance at 3 centres: 124 developed HCC (29 with 1 and 95 with 2 sera before the serum at diagnosis), 294 remained HCC free for at least 12 months after the last specimen (2 sera in 62 and 3 sera in 232). HCC diagnosis was made according to EASL guidelines. Tests were performed in a single laboratory using automated chemiluminescent-enzyme-immunoassays (Fujirebio, Tokyo, Japan): AFP and PIVKA-II dynamic ranges 0.8–22,451 ng/ml and 1.37–75,000 mAU/ml and normality upper limits 7.4 ng/ml and 48 mAU/ml, respectively. Time between time-points (t1, t2, t3) was expressed in months. AFP/PIVKA-II time-related changes were analysed by calculating the month-related variation coefficients ($MVC=\{[(xt_{last}-xt_{first})/xt_{first}]\times 100\}/(xt_{last}-xt_{first})$) and using a random-effect generalized least squares (RE-GLS) regression model.
Results: In figure 1 we report the MVC between groups. Multiple time-related ROC curve analysis of MVC shows 6 months (± 1.5) as best time frame for both biomarkers. Using 10% MVC as cut-off the Sensitivity/Specificity for HCC diagnosis were 17.8/96.3% and 27.7/93.8% for AFP and PIVKA-II, respectively. Log_{10}AFP time-related (1–6 months) changes estimated by RE-GLS ranged between 1.06–1.19 (95%CI 0.72–1.63) and 0.87–1.16 (95% CI 0.92–1.45) for HCC+ and HCC-, whereas the values of log_{10}PIVKA-II were 1.07–1.18 (95%CI 0.75–1.39) and 1.01–1.05 (95%CI 0.93–1.16), respectively. In HCC- patients AFP was influenced by disease activity and showed more variability than PIVKA-II. The gap of median MVC between HCC+ and HCC- was up to six-fold higher for PIVKA-II than AFP.



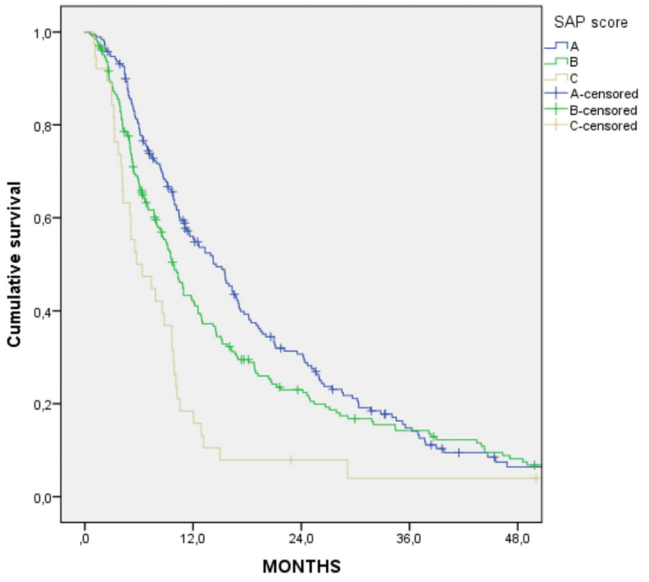
Conclusion: The month-related variation coefficient (MVC) of AFP and PIVKA-II appears a reliable measure for individualized HCC surveillance with an optimal time frame [6 (± 1.5) months] coincident with the suggested timing of ultrasound surveillance. A 10% MVC cut-off for both biomarkers qualifies as a candidate diagnostic tool worth to be tested in prospective studies.

FRI-167

Prognostic scores for sorafenib-treated hepatocellular carcinoma patients: a validation study of the HAP and SAP scores

F. Tovoli[1], G.G.D. Costanzo[2], G. Magini[3], F. Trevisani[1], T. Pressiani[4], R. Sacco[5], S. Marinelli[1], R. Tortora[2], L. Bucci[1], M.G. Lucà[6], L. Bolondi[1], A. Granito[1]. *[1]University of Bologna, Department of Medical and Surgical Sciences, Italy; [2]Cardarelli Hospital, Department of Transplantation – Liver Unit, Italy; [3]Papa Giovanni XXIII Hospital, Gastroenterology and Transplant Hepatology, Italy; [4]Humanitas Clinical and Research Center, Medical Oncology and Hematology Unit, Italy; [5]Pisa University Hospital, Department of Gastroenterology; [6]Papa Giovanni XXIII Hospital, Gastroenterology and Transplant Hepatology*
Email: francesco.tovoli2@unibo.it

Background and Aims: Prognostic classifications for patients treated with sorafenib for hepatocellular carcinoma (HCC) are lacking. Very recently, Edeline and collaborators reported that both the hepatoma arterial embolisation prognostic score (HAP, previously used as a prognositic indicator for patients undergoing trans-arterial che-moembolizatio) and the authors' proposed Sorafenib Advanced HCC Prognosis (SAP) score were able to provide discriminant prognostic information. Aim of our study was to validate these findings in a large cohort of sorafenib-treated patients in Italy.
Method: We analyzed a large retrospective-prospective database gathering the clinical data of 432 patients from 6 Italian centres, who were prescribed with sorafenib between 2008 (date of licence in Italy) and 2016. The HAP score was calculated according to the following criteria: largest tumor nodule > 7 cm (1 point); bilirubin >1 mg/dl (1 point); albumin <36 g/l (1 point); alfa-fetoprotein > 400 mg/dl (1 point). It was subsequently categorized as follows: HAP A (0 points); HAP B (1 point); HAP C (2 points); HAP D (>2 points). The SAP score calculation was very similar, but included a further criterion (PS > 0 = 1 point). This score was categorized as proposed by Edeline et al: SAP A (0–1 points); SAP B (2–3 points); SAP C (>3 points).
Results: The SAP score was significantly associated with the overall survival (OS), with a median OS of 14.6 months for SAP A, 9.8 months for SAP B and 5.7 months for SAP C (p < 0.001, log-rank test). Also the HAP score provided prognostic information, however HAP B and HAP C patients showed similar OS (median OS: HAP A 16.7 months, HAP B 10.9 months, HAP C 10.5 months, HAP D 5.9 months).
Conclusion: Our results validate both the SAP and the HAP score as prognostic indicators for HCC patients undergoing treatement with sorafenib. Differently from the previously published paper on this topic, however, our results suggest that the SAP may be a better prognosticator compared with the HAP score. The use of these simple scores may facilitate stratification in trials and inform clinical decision making.



FRI-168

CD44 rs187115 gene polymorphism in cirrhotic hepatitis C patients with hepatocellular carcinoma

A. El-Shayeb[1], N. Abdeen[1], N. Lewis[2], A. A. Khalifa[1]. *[1]Faculty of Medicine, Alexandria University, Tropical Medicine, Alexandria, Egypt; [2]Faculty of Medicine, Alexandria University, Clinical Pathology, Alexandria, Egypt*
Email: nermodean@gmail.com

Background and Aims: The burden of hepatocellular carcinoma (HCC) has been increasing in Egypt over the past 10 years owing to the high prevalence of HCV. It has been strongly suggested that stepwise, irreversible accumulation of genetic alterations is the responsible driving force to the development and progression of malignancies. CD44 is an extracellular matrix-cell adhesion molecule that regulates tumor cell differentiation, epithelial-mesenchymal transition, p53 stress response, invasion, metastatic deposits, and chemoresistance. The correlation between CD44 rs187115 SNP expression and HCC is not thoroughly established.And hence, we aimed to study the possible contribution of CD44 rs187115 SNP polymorphism regarding HCC development, tumour behaviour and aggressiveness.
Methods: This study was carried out on 120 Egyptian individuals classified into **four groups:**

- **Group I** Twenty patients having metastatic HCC
- **Group II** Twenty patients having non metastatic HCC
- **Group III** Forty patients with HCV related liver cirrhosis
- **Group IV** Forty healthy subjects as control

CD44 rs187115 SNP(C/T) was detected by allelic discrimination using Real-Time PCR after DNA Extraction.
Results: CC/CT genotypes were the most frequent genotypes present in the metastatic HCC group in comparison to the non metastatic HCC, cirrhotic and control groups ($p < 0.001$, 0.006 and 0.033 respectively), HCC patients possessing CT + CC genotypes were more likely to have an aggressive malignancy and thus poor prognosis compared to Wild type (TT) carriers. Significant positive correlation was noted between the presence of CT/CC genotypes and tumor size, multicentricity, Infiltrative behaviour, portal vein thrombosis, portahepatis lymph node metastases and distant metastases. ($p = 0.038$, 0.025, 0.028, 0.010 and 0.001 respectively), Presence of C allele was found to be associated with an increase of 6 folds of the risk of developing portal vein thrombosis and 8 folds of the risk of developing metastases with $p = 0.028$ and 0.010 respectively.
Conclusion: CD44 SNPrs187115 may serve as a novel prognostic biomarker for HCC that identifies patients who are at a risk of faster tumor progression and metastasis.

FRI-169

Hepatocellular carcinoma as second primary malignancy: exposing an overlooked presentation of liver cancer

D. Dandachi[1,2], M. Hassan[3], A. Kaseb[4], G. Angelidakis[1], H. Torres[1,4]. *[1]The University of Texas MD Anderson Cancer Center, Department of Infectious Diseases, Houston, United States; [2]Baylor College of Medicine, Department of Infectious Diseases, Houston, United States; [3]The University of Texas MD Anderson Cancer Center, Department of Epidemiology, Houston, United States; [4]The University of Texas MD Anderson Cancer Center, Department of Gastroenterology, Hepatology, and Nutrition, Houston, United States*
Email: dima.dandachi@bcm.edu

Background and Aims: Hepatitis C (HCV) infection is the leading cause of hepatocellular carcinoma (HCC) in the United States. Antiviral therapy in patients with HCV infection reduces the risk of HCC development by 71 to 75%. HCV-infected patients with different primary cancers are also at risk for HCC development as a second primary malignancy (HCC-SPM). Limited information is available on the characteristics of HCC-SPM. Herein, we determine the prevalence and clinical features of HCV-associated HCC-SPM when compared to primary HCC (HCC-P).
Method: Patients with HCV-associated HCC seen at MD Anderson Cancer Center (2011–2017) were enrolled in a prospective observational study. At enrollment, patients completed a questionnaire on medical history and HCC risk factors. Information on demographics, co-morbidities, HCV treatment, tumor characteristics, virologic and oncologic outcomes were extracted from the medical records. Patients with multiple cancers diagnosed simultaneously or with Hepatitis B, or HIV coinfections were excluded.
Results: Of the 213 enrolled, 193 were included in the final analysis: most patients were ≥ 50 years old (97%); white (64%); and men (78%). Twenty-eight (14%) patients developed HCC-SPMs. The majority of underlying primary cancers were solids tumors (86%), predominantly skin and breast cancers. In 20 (71%) patients, the diagnosis of HCC-SPM was made incidentally. When HCC-SPM and HCC-P were compared, there were no differences between the 2 groups in smoking, alcohol intake, body mass index, diabetes mellitus, and pathology. However, HCC-SPM had better liver function tests and tumor characteristics. The majority of patients with HCC-SPM (76%) and HCC-P (71%) had chronic viremia due to lack of diagnosis, lack of treatment, or prior unsuccessful treatment. Among all patients, those treated with direct-acting antivirals had significantly higher sustained virologic response compared to interferon-based therapy (80% vs.45% $p < 0.01$). Among the 28 patients with HCC-SPM, 22 (79%) had their primary cancer in remission at time of HCC diagnosis; 19 of those had outcome data, 6 (32%) of whom died.
Conclusion: Cancer patients with any type of malignancies must be screened for HCV as HCC-SPM can develop in 14% of infected patients. Regular cancer surveillance on these patients could favor a better outcome, but early HCV treatment to prevent the development of HCC-SPM should decrease the mortality rate observed in one-third of such patients.

FRI-170

Adherence to enhanced post-treatment surveillance is associated with increased detection of early stage recurrence after radiofrequency ablation but not surgical management of hepatocellular carcinoma

Y. Chan[1], S. Maclennan[1], L. Douglas[1], S. Congly[1], C. Coffin[1], E. Dixon[2], J. Wong[3], K. Burak[1]. [1]*University of Calgary Liver Unit, Division of Gastroenterology and Hepatology;* [2]*University of Calgary, Department of Surgery;* [3]*Foothill Medical Center, Department of Diagnostic Imaging*
Email: yingenics@gmail.com

Background and Aims: Little is known about the optimal surveillance schedule after curative intent treatment of hepatocellular carcinoma (HCC). Current guidelines advocate cross-sectional imaging at 3–6 months intervals for the first 2 years, but are not backed by strong evidence of benefit. In Calgary, we perform MRI one month after radiofrequency ablation (RFA) and 3–6 months after surgery. Thereafter we alternate contrast enhanced ultrasound and MRI every 3 months for two years and then every six months for another 3 years. We conducted a retrospective study to investigate the impact of surveillance intensity on clinical outcomes following curative HCC treatment.
Method: From a combined surgery and interventional radiology database in Calgary (2012–2015), 124 unique HCC patients receiving post-treatment surveillance after successful resection (n = 46) or RFA (n = 78) were identified after excluding patients who received transarterial chemoembolization (TACE) (n = 43), failed to achieve radiological remission (n = 38) or died within three months (n = 10). Baseline characteristics, imaging frequency, and clinical outcomes were collected. A surveillance rate defined as sum of actual number of images performed divided by the sum of the expected number of images in the defined surveillance period for each subject was calculated.
Results: Baseline characteristics including age, gender and liver disease were similar in both groups. The surgery group had a higher percent of Barcelona Clinic Liver Cancer (BCLC) staging 0 (p = 0.00052), non-cirrhotic (p = 0.0045), and first HCC (p = 0.00027) then the RFA group. The two-year disease-free survival and five-year mortality rate on Kaplan-Meier analysis, as well as mean surveillance rate (89 ± 15% vs 84 ± 21%) were comparable. Interestingly, BCLC B/C recurrence (n = 8) was significantly associated with a lower surveillance rate as compared to BCLC 0/A (n = 32) recurrence in RFA patients (76 ± 22% vs 92 ± 14%, p = 0.015), but this was not observed in the surgical cohort. Comparison of mean imaging interval (120 ± 47 days vs 82 ± 29 days, p = 0.038) and time to recurrence (591 ± 245 days vs 399 ± 222 days, p = 0.048) between BCLC B/C and 0/A recurrence also differed in the RFA cohort but not in the surgery cohort. Univariant analysis did not identify other predictors of more significant recurrence.
Conclusion: In conclusion, high intensity post-treatment surveillance of HCC patients after locoregional therapy, but not surgical resection, appears to be associated with detection of recurrence at an earlier stage. Ongoing follow-up will determine if this is associated with a survival benefit.

FRI-171

Hepatocellular carcinoma: pretreatment computed tomography texture analysis as an independent predictor of survival after surgical resection

L.B. Defour[1], S. Mulé[2], T. Piardi[3], D. Sommacale[3], C. Hoeffel[2], G. Thiéfin[1]. [1]*Centre Hospitalo-Universitaire de Reims, Service d'Hépatogastroentérologie, Reims, France;* [2]*Centre Hospitalo-Universitaire de Reims, Département de Radiologie, REIMS, France;* [3]*Centre Hospitalo-Universitaire de Reims, Service de Chirurgie Générale, Digestive et Endocrine, REIMS, France*
Email: gthiefin@chu-reims.fr

Background and Aims: Image texture analysis is an emerging method of quantifying tumor heterogeneity that may provide valuable non invasive information about tumor prognosis. The purpose of this study was to determine whether texture parameters analyzed on pre-operative contrast-enhanced CT can predict overall survival and recurrence-free survival in patients with hepatocellular carcinoma treated by resection.
Method: We retrospectively included all patients operated for hepatocellular carcinoma who underwent liver contrast-enhanced CT scan within three months prior to treatment in our center between 2009 and 2015. Tumor texture analysis was performed using TexRad software in a two-step process including image filtration and statistical quantification of tumor CT texture. The following texture parameters were evaluated on both contrast-enhanced arterial and portal phases: mean gray-level kurtosis, standard deviation, kurtosis, skewness and entropy values. Measurements were made before and after spatial filtration at different anatomic scales (SSF) ranging from 2 (fine texture) to 6 (coarse texture). Univariate and multivariate Cox analyses were performed to identify independent predictors of overall survival and recurrence-free survival.
Results: Forty-seven patients were included (37M/10F; median age: 66 years). Median follow-up time was 345 days. Nineteen patients had a recurrence. At arterial CT phase, kurtosis at SSF = 3 hazard ratio (HR = 4.24, p = 0.041), SSF = 4 (HR = 4.07, p = 0.003), SSF = 5 (HR = 1.83, p = 0.027) and skewness at SSF = 6 (HR = 6.66, p = 0.04) were independent predictors of overall survival. At portal-venous phase, skewness without filtration (HR = 76.98, p = 0.025), SSF2 (HR = 178.26, p = 0.009) and SSF3 (HR = 26.26, p = 0.006) were independently associated with overall survival. No textural feature was identified as an independent predictor of recurrence free survival.
Conclusion: In patients with resectable hepatocellular carcinoma, pretreatment CT texture features such as skewness and kurtosis are significantly associated with overall survival and may have the potential to become a useful tool to select the best candidates for resection.

FRI-172

Particularities of hepatocellular carcinoma on chronic hepatitis C in the era of all- oral antiviral treatment

E.L. Iliescu[1], S. Ioanitescu[1], R. Dumitru[2], L. Toma[1], M.B. Ureche[1], A. Mercan-Stanciu[1], C. Iancu[1], M. Dodot[1]. [1]*Fundeni Clinical Institute, Internal Medicine, Bucharest, Romania;* [2]*Fundeni Clinical Institute, Interventional Radiology, Bucharest, Romania*
Email: laura_ate@yahoo.com

Background and Aims: Despite the high efficacy of direct antiviral agents in curing chronic hepatitic C virus (HCV) infection, the risk of complications, including hepatocellular carcinoma (HCC) persists. This study aims to analyze the particularities of HCC in patients who are undergoing or have finished treatment with ombistavir/ paritaprevir/ ritonavir (OMB/PTV/r), dasabuvir (DSV) with or without ribavirin (RBV) in the setting of chronic HCV hepatitis or compensated cirrhosis.
Method: This is a prospective study which included 368 patients admitted who underwent or are undergoing treatment with OMB/PTV/r + DSV +/- RBV, for a duration of 12 weeks, from December 2015 to October 2017. Screening for HCC was based on abdominal ultrasonography and levels of alpha fetoprotein (AFP) at the beginning of the therapy, monthly during therapy and 3 months after the end of treatment (at evaluation of SVR). If abnormalities were detected, contrast-enhanced ultrasongraphy or computer tomography were performed. The patients were categorized as follows, depending of the degree of liver fibrosis determined by Fibromax® or liver biopsy: F4 (compensated cirrhosis), F3 with or without HCV related comorbidities, F2 with HCV related comorbidities.
Results: The mean age in the study group was of 57+/-21.5 years, with a predominance of female sex (57%). Distribution of the degree of fibrosis was F4–53.8%, F3- 29.9%, F2- 16.3%. Initial AFP levels were

above normal in 50.2% of the patients, but CEUS and CT scan showed no signs of HCC. On treatment, HCC was diagnosed in 4 patients. At the end of treatment, other 4 patients were diagnosed, while at SVR 6 patients presented with HCC (total HCC incidence 0.03%). All patients had F4 fibrosis. A particularity was the small increase of AFP levels-up to 50ng/ml, requiring abdominal imaging for further evaluation. Antiviral treatment was continued in all patients, with the achievement of SVR. 2 patients underwent transarterial chemoembolization (TACE) during antiviral treatment, without significant complications. Furthermore, out of the 10 patients diagnosed after treatment, 6 underwent TACE. Abdominal CT in these patients was unable to detect the extent of the tumor (with an infiltrative aspect) and 7 patients required abdominal MRI for a complete evaluation. For the time being, 4 patients required 2 TACE procedures; at the moment only one patient has developed a new HCC nodule.
Conclusion: Patients with chronic HCV hepatitis, especially cirrhosis, are still at risk of developing HCC even after obtaining SVR. Slight changes in AFP levels and dedicated imaging with special consideration to infiltrative tumors are the screening and diagnostic keys in these patients.

FRI-173
Short-term evaluation of hepatocellular carcinoma after locoregional treatment: Usefulness of contrast-enhanced ultrasonography
G. Gibiino, M.E. Ainora, M. Pompili, M. Garcovich, L. Riccardi, E.D. Stasio, F. Ponziani, A.M.D. Gaetano, G. Ludovico Rapaccini, A. Gasbarrini, M. Assunta Zocco. *Policlinico Agostino Gemelli, Internal Medicine, Gastroenterology and Liver Unit*
Email: ainoramariaelena@yahoo.it

Background and Aims: In patients with hepatocellular carcinoma (HCC), an accurate assessment of the therapeutic response is of crucial importance in order to schedule further treatments. Contrast-enhanced ultrasound (CEUS) with second generation contrast agents performed 1 month after treatment is almost as sensitive as CT in depicting the residual tumor. However, the efficacy of CEUS performed early after the procedure is still debated. The aim of our study was to evaluate the diagnostic accuracy of CEUS for the assessment of tumour response shortly after locoregional therapy in patients with unresectable HCC.
Method: Ninety-four patients with 104 HCC lesions who were scheduled to receive percutaneous ethanol injection (PEI), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) or combined treatment (RFA + TACE) were enrolled in this study. With contrast-enhanced computed tomography (CECT) at 1 month as the reference standard, the ability of CEUS performed 48 hours after the procedure in detecting residual disease was evaluated. Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy of the avascular pattern at CEUS were calculated. Patients were followed periodically to look for tumor or disease progression. Survival probability was estimated with the Kaplan-Meier method and relate to CEUS responses.
Results: Based on CECT findings 43/104 lesions (41.3%) were diagnosed as having residual viability after 1 month. CEUS performed 48 hours after treatment detected residual tumor in 34 of the 43 nodules with treatment failure at CECT with a sensitivity, specificity, PPV, NPV and accuracy of 79.1%, 96.7%, 94.4%, 86.8% and 89% respectively. There was a high degree of concordance between CEUS and CECT (kappa coefficient = 0.78). A hyperemic halo was visible in 35 lesions without a statistically significant difference between concordant and discordant cases ($p = 0.2$). Responders according to 48 hours CEUS had a significantly longer mean overall survival and time to progression compared to non-responders (1169 *vs* 887 days, and 453 *vs* 271 days, respectively).
Conclusion: CEUS performed 48 hours after treatment can be considered a reliable modality for the evaluation of the real extent of necrosis and has a prognostic value in the assessment of hepatocellular carcinoma.

FRI-174
Performance of Wisteria floribunda agglutinin-positive Mac2-binding protein as an HCC biomarker in an ethnically diverse cohort of patients with chronic HBV and HCV
T. Jun[1], M.-L. Yu[2], Y.-C. Hsu[3], Y. Tanaka[4], M. Nguyen[1]. [1]*Stanford University Medical Center, Division of Gastroenterology and Hepatology, Stanford, United States;* [2]*Kaohsiung Medical University, Hepatobiliary Division, Kaohsiung, Taiwan;* [3]*E-Da Hospital, Division of Gastroenterology and Hepatology, Kaohsiung, Taiwan;* [4]*Nagoya City University Graduate School of Medical Sciences, Department of Virology and Liver Unit, Nagoya, Japan*
Email: tjun@stanford.edu

Background and Aims: *Wisteria floribunda* agglutinin-positive Mac2-binding protein (M2BPGi) is a novel biomarker which has been shown to correlate with liver fibrosis. M2BPGi has also been investigated as a biomarker for hepatocellular carcinoma (HCC). Single-center studies in East Asian populations with chronic hepatitis B (HBV) or chronic hepatitis C (HCV) infections have shown promising results. We conducted this study to assess M2BPGi as a biomarker for HCC in an ethnically diverse cohort of patients with both HBV and HCV.
Method: This was a prospective cohort study of 947 adult patients with liver disease and serum samples drawn between 2001 and 2016 at three centers in the US and Taiwan. Patients with chronic hepatitis B (HBV, n = 714) or chronic hepatitis C (HCV, n = 233) and at least 1 year of follow-up were included. Patients were excluded if they developed HCC within 6 months of entering the study, had antiviral treatment prior to enrollment, had HBV-HCV coinfection or had non-viral HCC. Cirrhosis was diagnosed based on imaging, clinical and histopathological findings. The primary outcome was development of HCC within 10 years. M2BPGi was measured as a cutoff index (COI).
Results: Median M2BPGi was significantly higher among patients with cirrhosis compared to patients without cirrhosis (2.7, IQR 1.14–6.07 vs. 0.83, IQR 0.51–1.54, $p < 0.001$). Median M2BPGi was also significantly higher among the 85 patients who developed HCC compared to those who did not (3.22, IQR 1.38–7.2 vs. 1.16, IQR 0.62–3.00, $p < 0.001$). M2BPGi had a higher area under the receiver operating curve (AUROC) for predicting HCC for all patients than for cirrhotic patients (0.72 vs 0.58). M2BPGi also had a higher AUROC for HCC among HBV patients than HCV patients (0.84 vs. 0.48). Among cirrhotic patients, the AUROC for HCC was higher for HBV patients than HCV patients (0.68 vs 0.47). M2BPGi was a predictor of HCC in univariate analyses, but it was not an independent predictor of HCC in a multivariate analysis of cirrhotic patients controlling for age, gender, ethnicity, treatment status, etiology and MELD score.
Conclusion: M2BPGi is strongly correlated with cirrhosis, which is a powerful predictor of HCC. In our ethnically diverse cohort, M2BPGi had more discriminatory value among HBV patients than HCV patients. When considering only cirrhotic patients, M2BPGi performed better among HBV patients than HCV patients.

FRI-175
A functional ATG16L1 (T300A) gene variant is associated with increased risk for hepatocellular carcinoma in cirrhosis
P. Reuken[1], P. Lutz[2], M. Casper[3], E. Al-Herwi[1], A. Stallmach[1], F. Lammert[3], H.D. Nischalke[2], T. Bruns[1]. [1]*Jena University Hospital, Dpt. of Internal Medicine IV, Jena;* [2]*Bonn University Hospital, Department of Internal Medicine I, Bonn, Germany;* [3]*Saarland University Medical Center, Department of Medicine II, Homburg*
Email: philipp.reuken@med.uni-jena.de

Background and Aims: Protein and organelle turnover by autophagy is a key component to maintain cellular homeostasis in liver diseases. Loss of the autophagy protein ATG16L1 is associated with reduced intracellular bacterial killing, Paneth cell abnormalities, and aberrant

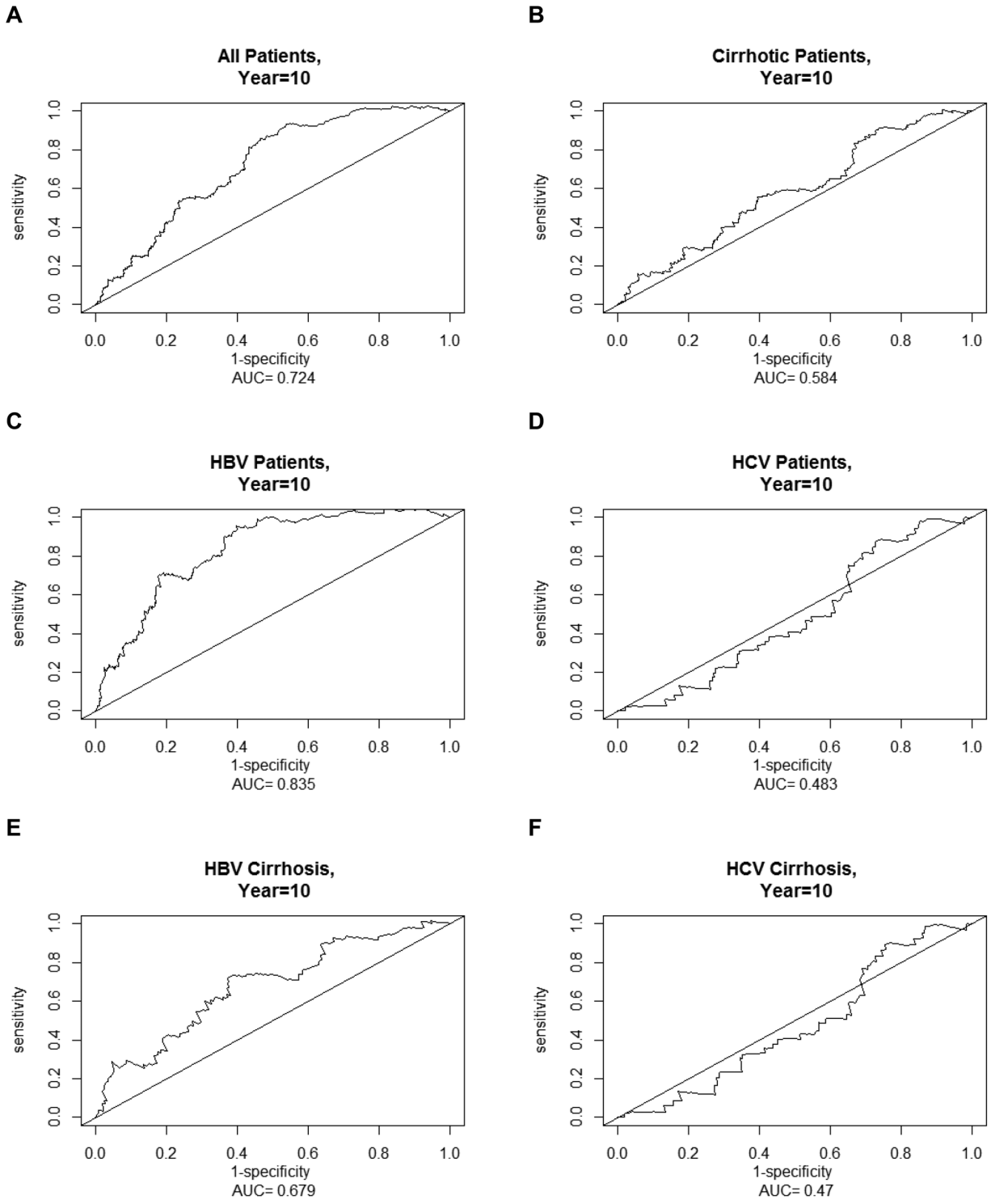


Figure 1: (abstract: FRI-174): Time-dependent receiver operating characteristic (ROC) curves for M2BPGi as a predictor of HCC for (A) All patients (B) Cirrhotic patients (C) HBV patients (D) HCV patients (E) Cirrhotic HBV patients (F) Cirrhotic HCV patients

interleukin-1β production, perpetuating chronic inflammation and carcinogenesis. Here we hypothesized that the functional p.T300A gene variant in *ATG16L1* is associated with an increased risk for hepatocellular carcinoma (HCC) in cirrhosis.

Method: A case control study was performed using a prospective derivation cohort (107 patients with HCC in cirrhosis and 101 controls with cirrhosis) and an independent validation cohort (124 patients with HCC in cirrhosis and 108 controls with cirrhosis) in patients with cirrhosis of any aetiology. The p.T300A variant (rs2241880) was determined by Taqman PCR.

Results: The majority of patients had alcoholic cirrhosis (70%). Patients with HCC were older, more often male and showed higher serum transaminase activities than patients without HCC. The G allele of the variant was found more frequently in patients with HCC in cirrhosis as compared to cirrhotic patients without HCC both in the derivation cohort (62% vs. 51%; odds ratio [OR] 1.58; 95% confidence

interval [CI] 1.07–2.33) and in the validation cohort (59% vs. 50%; OR 1.46; 95% CI 1.01–2.10). Overall, the association of the homozygous p.T300A variant with HCC (univariate OR 1.81; 95% CI 1.19–2.76; p = 0.006) remained significant after adjustment for male sex, older age, and aetiology in multivariate analysis (adjusted OR 2.09; 95% CI 1.28–3.26; p = 0.003). Patients, who had developed HCC, did not show worse survival in presence of the p.T300A variant.
Conclusion: The functional *ATG16L1* gene variant p.T300A is associated with an increased risk of HCC in this cohort study. In addition to clinical features, *ATG16L1* variants may be taken into account when performing risk-based HCC surveillance in cirrhosis.

FRI-176

Serial changes in alpha-fetoprotein, lectin-bound alpha-fetoprotein and Des-r-Carboxy prothrombin in prospectively collected serum samples before the diagnosis of hepatocellular carcinoma

J. Choi[1], S. Young Yi[2], Y.-S. Lim[1], W. Lee[3], S. Chun[3]. [1]*Asan Medical Center, University of Ulsan College of Medicine, Department of Gastroenterology, Seoul, Korea, Rep. of South;* [2]*Asan Medical Center, University of Ulsan College of Medicine, Hepatology, Seoul, Korea, Rep. of South;* [3]*Asan Medical Center, University of Ulsan College of Medicine, Department of Laboratory Medicine, Seoul, Korea, Rep of South*
Email: limys@amc.seoul.kr

Background and Aims: Few biomarker studies using prospectively collected specimens in patients at risk of hepatocellular carcinoma (HCC) has been reported. The aims of our study were to evaluate the performance of alpha-fetoprotein (AFP), Lectin-Bound alpha-fetoprotein (AFP-L3) and Des-r-Carboxy Prothrombin (DCP) and their ability to detect preclinical disease before the clinical diagnosis of HCC.
Method: Samples from a total of 689 patients were collected by previously conducted four randomized trials in patients with compensated cirrhosis or chronic hepatitis B. Forty-two HCC cases and controls (n = 168) were matched for age, gender, etiology of liver disease, cirrhosis, and duration of follow-up in a 1:4 ratio for the analyses. Samples at the time of HCC diagnosis, 6- and 12- months prior to the diagnosis of HCC were tested for AFP, AFP-L3 and DCP for performance in discriminating HCC cases from controls.
Results: Of 42 cases with HCC, 38 (90.5%) had early stage HCC (BCLC stage 0 and A) and median tumor size was 1.6 cm (range: 0.9–11.0). AFP and AFP-L3 started to increase from 6 months before the diagnosis of HCC ($p < 0.05$), while they remained unchanged in the controls. The AUROCs for AFP, AFP-L3, and DCP at month 0 were 0.77, 0.73, and 0.71, respectively. Combination of AFP and AFP-L3 showed the highest AUROC of 0.83. No additional benefit in performance was observed by adding DCP. The sensitivity and specificity for detecting HCC by the combination of AFP and AFP-L3 were 79% and 87%, under optimal cut-off values for AFP and AFP-L3 (4.7 ng/ml and 0.5%, respectively).
Conclusion: Combination of AFP and AFP-L3 showed better performance than any single biomarkers in detecting HCC among patients at risk. AFP and AFP-L3 began to increase from 6 months before the clinical diagnosis of HCC. AFP-L3 may improve the performance of HCC surveillance when used as a supplementary test to AFP.

FRI-177

Sphingolipids: a further step into the detection of early and intermediate hepatocellular carcinoma

I. Nenu[1], C. Hebristean[2], P. Fisher[1], A. Suciu[1], H. Stefanescu[1], B. Procopet[3], D. Liliana[1,4], A. Cavasi[1,4], A. Seicean[1,4], Z. Sparchez[1,4], M. Tantau[5], C. Socaciu[6], M. Grigorescu[1,4]. [1]*Regional Institute of Gastroenterology and Hepatology "Octavian Fodor", Hepatology Department, Cluj-Napoca, Romania;* [2]*Center for Applied Biotechnology BIODIATECH, SC Proplanta, Cluj-Napoca, Romania;* [3]*29348900, Cluj-Napoca, Cluj-Napoca, Romania;* [4]*University of Medicine and Pharmacy "Iuliu Hatieganu", 3rd Medical Clinic, Cluj-Napoca, Romania;* [5]*University of Medicine and Pharmacy "Iuliu Hatieganu" Cluj-Napoca, Gastroenterology and Hepatology, Cluj, Romania;* [6]*Center for Applied Biotechnology BIODIATECH, Applied Biotehnology in Diagnostic and Molecular Therapy, Cluj-Napoca, Romania*
Email: iuliana.nenu@gmail.com

Background and Aims: Throughout the last years metabolomics has played an important role in providing new insights into the detection and progression of hepatocellular carcinoma (HCC). Sphingolipids, a family of membrane lipids, are involved in numerous cell functions, including cell death pathways and have an altered expression in many types of cancer. The aim of the study was to identify a metabolomic biomarker for HCC diagnosis and to compare its diagnostic accuracy with alpha fetoprotein (AFP).
Method: 104 patients (54 HCC BCLC stages 0, A and B developed on compensated cirrhosis and 50 compensated cirrhotic controls) were included. Common workup for the assessment of liver disease and AFP was carried out in each patient. High pressure liquid chromatography (HPLC) coupled with quadruple time of flight electrospray in a positive ionization mode mass spectrometry (QTOF-ESI+-MS) was performed from serum samples of each patient. MetaboAnalysis, performing univariate and multivariate statistical analysis was used to identify candidate biomarkers. Their performance for detection of early/intermediate HCC was evaluated using semi-quantitative assessment and through a leave-one-out cross-validation based on area under the receiver operating characteristics (ROC) curve.
Results: 15 metabolites were identified. Sphingolipids are the most upregulated in HCC patients, particularly C16 sphinganine (C16-SPH) ($p < 0.001$ vs. compensated cirrhosis). The expression of C16-SPH was 4.869 times higher in HCC than in cirrhotic controls ($p < 0.005$). The area under the curve (AUC) of C16-SPH for the diagnosis of HCC was significantly higher compared to AFP [0.969 (95%CI, 0.923–1) vs. 0.544 (95%CI, 0.415–0.673), p (deLong test) <0.001]. For a cutoff value of 0.737, C16-SPH correctly classified 97/104 (93.26%) of patients.

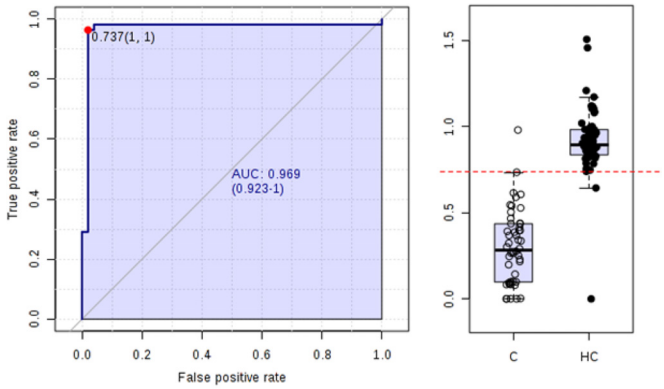


Figure 1- ROC curve for C16-sphinganine

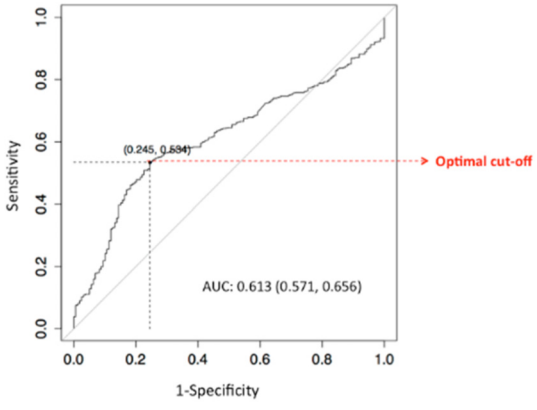
Conclusion: Sphingolipids show a significant upregulation in patients with HCC compared to patients with cirrhosis. Of them, C16-SPH might stand as a novel diagnostic marker for the identification of early and intermediate HCC in patients with chronic liver diseases.

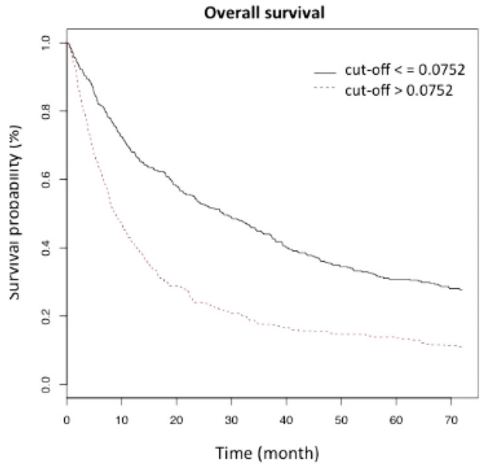
FRI-178

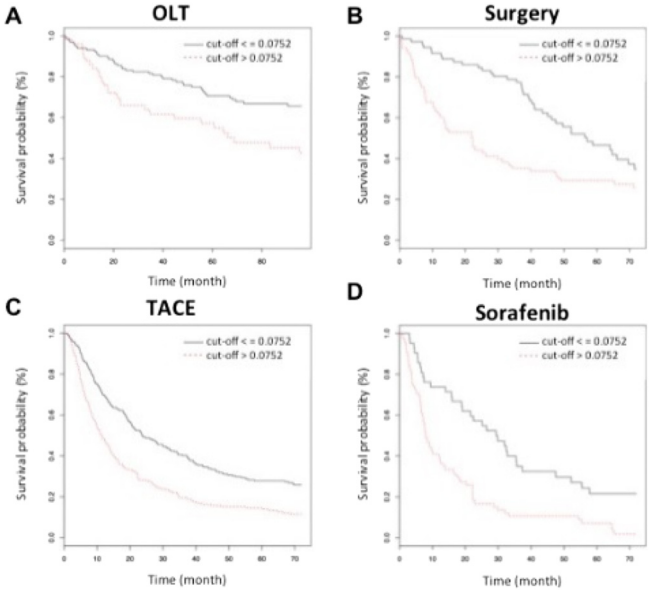
A high alpha-fetoprotein slope prior to therapy correlates with poor prognosis of patients with hepatocellular carcinomas

C. Czauderna[1], S. Koch[1], L. Pilz[1], S. Franck[1], H. Lang[2], R. Klöckner[2], M.-A. Wörns[1], P. Galle[1], J. Marquardt[1], A. Weinmann[3]. [1]*Johannes Gutenberg University, Mainz, Department of Medicine I, Mainz, Germany;* [2]*Johannes Gutenberg University, Mainz, Department of Diagnostic and Interventional Radiology, Mainz;* [3]*Johannes Gutenberg University, Mainz, Department of General, Visceral and Transplant Surgery, Mainz*
Email: carolin.czauderna@unimedizin-mainz.de

Background and Aims: Hepatocellular Carcinoma (HCC) is the second leading cause of cancers death worldwide. Biomarkers for accurate prediction of prognosis are limited and urgently needed to improve patient management. Alpha-fetoprotein (AFP) is a well-established biomarker for HCC and widely used in prognostic score systems. However, diagnostic accuracy of "static" AFP-values is limited and clinical potential as a prognostic and/or predictive marker needs to be more precisely defined. Here we evaluated the prognostic value of pre-treatment serum AFP changes on the overall survival (OS) of HCC-patients in a German cohort.
Method: We retrospectively analyzed patients with confirmed HCC (n = 859) treated at the University Medical Center of the Johannes Gutenberg-University Mainz between 1998 and 2014. Baseline parameters concerning patient status, tumor size and liver function, as well as pre-treatment static and dynamic AFP were investigated. AFP-slope was defined as the delta of two pre-treatment measurements normalized to daily increment/decline. Prognostic impact was assessed using Kaplan-Meier analyses as well as by univariate and multivariate cox regression models. Optimal-cut-off values were defined using receiver operating characteristic curves.







Results: In univariate cox regression analyses, single AFP-value failed to show a prognostic impact (p = 0.81), while pre-treatment AFP-slope showed a strong association to OS (p < 0.001). Besides several known clinical parameters such as Child Pugh B (p < 0.001) and C (p < 0.001), portal vein thrombosis (PVT) (p < 0.001), extra-hepatic spread (p = 0.0001) and tumor size (p < 0.001), pre-treatment AFP-slope (p < 0.001) could be confirmed as an independent factor on OS of HCC-patients in multivariate analyses. Receiver operating characteristic analysis showed that the best discriminant cut-off value was a pre-treatment AFP-slope greater than 0,0752ng/ml/day with an area under the curve of 0.613. At this cut-off sensitivity was 53,4% and specificity reached 75.4%. Patients with an AFP-slope greater than 0,0752ng/ml/day prior to liver transplantation, surgery, local ablation or Sorafenib therapy had a worse overall survival than those with an AFP-slope under the threshold.
Conclusion: AFP changes prior to therapy are predictive for the overall survival of HCC-patients. The addition of an AFP-slope to established prognostic parameters might improve prognostic classification of HCC.

FRI-180

In Moldova, social situation is a primary modulator of survival in a hepatocellular carcinoma

A. Turcanu[1], P. Pineau[2], E. Tcaciuc[1], V.-T. Dumbrava [1]. [1]*State University of Medicine, Gastroenterology and Hepatology, Chisinau, Moldova;* [2]*Institut Pasteur, Unité « Organisation nucléaire et Oncogenèse », INSERM U993, Paris, France*
Email: adela_turcanu@yahoo.com

Background and Aims: Moldova is the country with the highest primary liver cancer incidence in Europe in both sexes. Many factors modulate the risk of developing hepatocellular carcinoma (HCC) in the settings of a chronic viral hepatitis. Especially, individual patients risks that include geographical origin; host-related factors (both genetic and lifestyle); and specific viral determinants are known to be players of unequal importance.
Method: We conducted a retrospective study on 148 HC cases diagnosed in the main University Hospital of Chisinau, to delineate tolls attributable to the different risk factors prevalent in Moldova. HCC diagnosis was based on the presence of a liver mass at imaging, on the clinical context, notably the presence of a chronic liver disease or cirrhosis, on serological markers of viral infections, and on alpha fetoprotein levels. Data about socio-demographic status, clinical

symptoms, clinical biochemistry, blood cell count, tumor number and diameter, lymph nodes involvement, metastases, treatment and survival length were recovered from medical files and stored in a database.

Results: The overall survival of patients was known for 108 of them. The median survival was 12 months (inter-quartile range 7–24). No tumor risk factor was significantly associated with poor survival. Tobacco use and Type 2 Diabetes were risk factors only marginally associated with difference of survival (Log rank test, p = 0.059 and p = 0.073). By contrast, lower education level (primary school) was significantly associated with a poorer survival (p = 0.0169). Self-recognized alcohol intake was a frequent hallmark of lower level of education (p = 0.0017), and low family income (67.1 vs 48.3%, OR = 2.16, 95%CI: 1.00–4.47, p = 0.0330). Habitants from Southern Moldova were more often represented among alcohol drinkers than in non-drinkers (24.6 vs 9.6%, OR = 3.0, 95%CI: 1.05–10.04, p = 0.0255). Other features conditioning survival length were tumor diameter, clinical symptoms (portal thrombosis, hemorrhage, hepatic encephalopathy), biochemical markers (AST, urea) and of course surgical treatment.

Conclusion: In Moldova, social status of the patients greatly influences survival in HCC. Level of education, closely conditioning alcohol consumption, is linked to late stage addressing for medical consultation in HCC when therapy is only palliative. Efforts should now be made to raise the degree of awareness about liver disease in the deprived sections of Moldovan population.

FRI-181

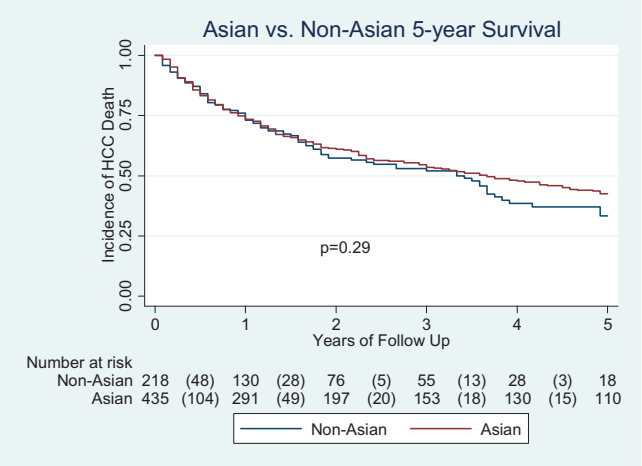
Clinical presentation and survival of Asian and non-Asian patients with HBV-related hepatocellular carcinoma (HBV-HCC): Results of 767 United States patients with long-term follow-up

J. Hoang[1], P. Nguyen[1], J. Leong[2], J. Yang[3], A. Le[1], L. Roberts[3], M. Schwartz[4], M. Nguyen[1]. *[1]Stanford University Medical Center, Division of Gastroenterology and Hepatology; [2]Mt. Sinai Hospital, Recanati/Miller Transplantation Institute; [3]Mayo Clinic, Department of Gastroenterology and Hepatology; [4]Liver Cancer Program, Icahn School of Medicine at Mount Sinai, Department of Surgery*
Email: mindiehn@stanford.edu

Background and Aims: Studies comparing clinical presentation of Asians and Non-Asians with HBV-related HCC are limited. Our goal was to evaluate clinical presentation and long term outcomes for HBV-HCC between Asians and Non-Asians in the United States (US).

Method: We performed a retrospective cohort study of 767 (508 Asian, 259 Non-Asian) consecutive adult patients ≥18 years-old diagnosed with HBV- HCC at three U.S. medical centers from 1993–2016. Patients were identified by ICD-9 diagnosis codes and confirmed to have HBV-HCC by chart review. Structured data extraction was performed for each medical record using the same data frame at each center. Kaplan-Meier analysis was conducted to determine differences in 5-year survival between the two groups.

Results: The cohort was predominantly male (79.7% of Asians vs. 80.7% of Non-Asians). Asians were younger (mean age 60.1 vs. 63.7, p = 0.0002), had lower BMI (mean 24.1 vs. 27.2, p < 0.0001), longer follow-up years (mean 3.0 vs. 2.4, p = 0.04), and were less likely to be decompensated (21.9% vs. 33.4%, p < 0.0001). There were no Asians with HCV infection (0% vs. 10.0%, p < 0.0001) or with HBV-HIV co-infection (0% vs. 6.2%, p < 0.0001). Asians had similar HCC treatment rates (74.0% vs. 76.5%, p = 0.46) and cirrhosis prevalence (60.6% vs. 64.8%, p = 0.25) compared to Non-Asians. Asians presented with lower Child-Pugh Class (B: 27.3% vs. 48.8%, C: 7.9% vs.12.5%, p < 0.0001), MELD score (mean 10.8 vs. 11.6, p = 0.13), and BCLC stage (Stage B: 40.7% vs. 47.2%, Stage C: 14.0% vs. 34.8%, p < 0.0001). Asians were less likely to receive curative HCC treatments (77.4% vs. 81.8%, p < 0.0001) and were less likely to be listed for transplantation (23% vs. 33.5%, p < 0.003) or have transplantation (7.8% vs. 20.7%, p < 0.0001) despite higher rates of meeting the Milan criteria (32.1% vs. 26.6, p < 0.12). HCC death incidence per 1000 person-years was lower in Asians than Non-Asians (101.68 vs. 145.33) with a cumulative five-year incidence of 43.9% vs. 56.1%, respectively, though the overall long-term five-year survival was not significantly different (p = 0.29) (Figure).



Conclusion: There were distinct differences in clinical presentation of Asian and Non-Asian patients with HBV-HCC. Asians are less likely to undergo liver transplantation and have lower HCC treatment rates despite meeting the Milan criteria. Research is needed to determine the cause of the disparity.

FRI-182

Dynamic [18F] FLT-PET is sensitive in detecting hepatocellular carcinoma

R. Sharma, E. Aboagye, T. Barwick. *Imperial College, Medical Oncology, London, United Kingdom*
Email: r.sharma@imperial.ac.uk

Background and Aims: Contrast enhanced multiphase CT and MRI are standards by which the effectiveness of palliative treatments in the management of hepatocellular carcinoma (HCC) is monitored. However, conventional imaging techniques have limited sensitivity in visualising HCC, and in particular, CT/MRI cannot effectively differentiate necrotic or dysplastic nodules from residual tumour. Furthermore, as most tyrosine kinase inhibitors result in a cytostatic rather than cytotoxic response, conventional imaging modalities are not adequate in assessing efficacy.

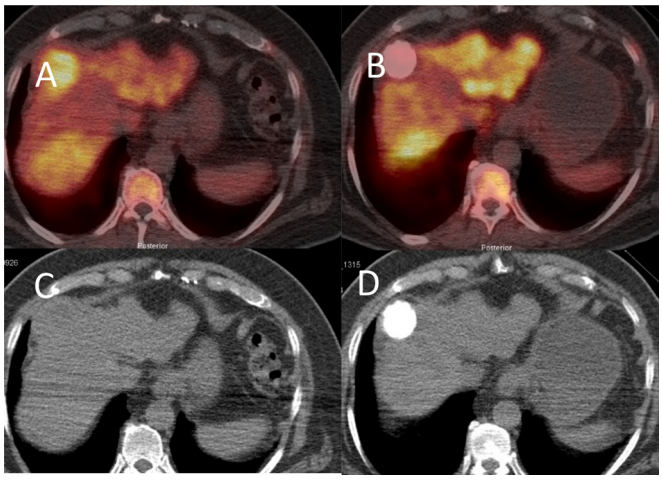
PET imaging not only assesses tumour size but also functional changes at a cellular level. Fluorothymidine (FLT) is a marker of proliferation that is a substrate for the cell cycle regulated enzyme, thymidine kinase-1 (TK-1). FLT is not susceptible to inflammation and has a high specificity for malignancy. Previous studies investigating PET imaging in HCC have been hampered by poor signal to background noise within the liver.

The OVERALL OBJECTIVES of this project are to assess sensitivity of FLT PET/CT in detecting HCC at baseline compared to multiphase contrast-enhanced CT (CECT), and to evaluate response to transterial chemoembolisation (TACE) in patients with advanced stage HCC with [18F]FLT-PET/CT compared to CECT using modified RECIST (mRECIST) and progression free survival.

Method: A tissue microarray (TMA) consisting of HCC and surrounding cirrhotic tissue was constructed (n = 38) and expression of TK-1 assessed. 18 patients with BCLC-C disease suitable for TACE underwent dynamic [18F]FLT-PET/CT imaging 1 week prior to TACE and 6 weeks following, at the time of follow-up imaging. Response was assessed by mRECIST.

Results: A significant increase in TK-1 was observed in HCC compared with surrounding cirrhotic tissue (p < 0.05). [18F]FLT-PET/CT was sensitive in detecting HCC at baseline (A) and following TACE (B)

compared to CECT (C-D). The correlation between [18F]FLT uptake and mRECIST will be assessed and ability to predict hepatic PFS.



Conclusion: Despite a previous study suggesting that [18F]FLT-PET/CT has low sensitivity and specifity in detection HCC due to high liver to background ratio, we found that using dynamic scanning protocol, [18F]FLT-PET/CT is a sensitive imaging modality which should be pursued in larger studies.

FRI-183

Monofocal HCC: Milan Criteria or BCLC staging system? An analysis of the ITA.LI.CA. Database

G. Peserico[1], B. Penzo[2], F. Pelizzaro[1], A. Imondi[1], A. Meneghetti[2], A. Sartori[1], M. D'elia[2], A. Vitale[1], F. Trevisani[3], F. Farinati[1]. *[1]Università degli Studi di Padova, Dip. Scienze Chirurgiche, Oncologiche e Gastroenterologiche, Università di Padova; [2]Università degli Studi di Padova; [3]Università degli studi di Bologna*
Email: giulia88.fish@gmail.com

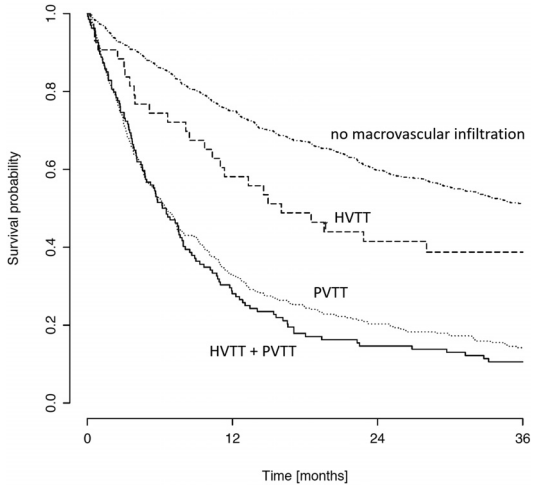
Background and Aims: The Barcelona Clinic Liver Cancer (BCLC) algorithm, adopted by the EASL (European Association for the Study of the Liver) guidelines, predicts prognosis and recommends treatment choices in hepatocellular carcinoma (HCC). This study aimed at evaluating the need of the 5 cm cut-off adopted in the Milan Criteria to correctly stage and treat monofocal HCC.
Method: 1623 monofocal, not "very early", HCCs, recruited in the 2001–2014 Italian Liver Cancer (ITA.LI.CA) database and stratified by diameter (1345 SMALL HCC, >2/≤5cm, and 278 LARGE HCC, >5cm), were analysed. Among them, 1087 were "early" monofocal HCC. The monofocal HCCs were compared to 1048 BCLC B stage HCC and sub-grouped according to the adherence to the guidelines for resection. Statistics included chi-square, Kaplan-Meier (Log-rank) and Cox multivariate analysis.
Results: Overall median survival was 38 months (Confidence Interval – C.I. – 36–41), with 41 months (C.I.: 38–45) in SMALL HCC and 21 in LARGE HCC (C.I.: 17–26) ($p < 0.0001$). At multivariate analysis, the two subgroups presented different predictors of survival and statistically different therapeutic choices; surgery provided the best survival in both groups. BCLC B HCC median survival was similar to that of LARGE HCC (Hazard Ratio – H.R. – 1.103, C.I.: 0.932–1.304). Considering only resection, the survival of BCLC B HCC was significantly shorter than that of the SMALL tumors ($p = 0.0002$). According to the adherence to guidelines, patients resected out of the BCLC criteria were the largest group (57%), especially in LARGE HCC (64%); a multivariate analysis showed that diameter was the only independent predictor of survival ($p < 0.0001$) ("adherence to guidelines", $p = 0.99$). Similar results were obtained analysing the 1087 BCLC A monofocal HCC, sub-grouped according to the 5 cm cut-off (49 months, C.I.: 45–53, in the 924 SMALL HCC and 31 months, C.I.: 25–44, in the 163 LARGE HCC).
Conclusion: The 5 cm cut-off – according to the Milan criteria – stratifies monofocal (early or not) HCC in two categories different in survival, predictors and therapeutic choices. Single HCC >5 cm have a median survival comparable to BCLC B HCC. In monofocal HCC, surgery correlates with the longest survival; although the best survival is reached in SMALL HCC, resection should be recommended even in the large tumours, due to the better survival achievable. In fact, tumour burden has a heavier impact on survival than "adherence to guidelines".

FRI-184

Hepatic vein tumor thrombosis in patients with hepatocellular carcinoma

S. Schotten[1], A. Weinmann[2], V. Steinle[1], S. Koch[3], D. Graafen[1], F. Meyer[1], C. Düber[1], A. Maehringer-Kunz[1], R. Kloeckner[1]. *[1]Medical Center of the Johannes Gutenberg University, Diagnostic and Interventional Radiology, Mainz, Germany; [2]Medical Center of the Johannes Gutenberg University, Internal Medicine I, Mainz, Germany; [3]Medical Center of the Johannes Gutenberg University, Clinical Registry Unit (CRU), Mainz, Germany*
Email: sebastian.schotten@gmail.com

Background and Aims: Portal vein tumor thrombosis (PVTT) significantly impairs the prognosis of patients with hepatocellular carcinoma (HCC) and classifies them as advanced stage (BCLC-C). However, the relevance of hepatic vein tumor thrombosis (HVTT) remains unclear. Aim of this study is to compare the prognosis of patients with different forms of macrovascular infiltration as this might influence the choice of treatment.
Method: 1478 HCC-patients were extracted from the clinical registry of our tertiary referral center treated between 01/2005–01/2017. Macrovascular infiltration was diagnosed by re-evaluation of all available CT- or MRI-studies by two experienced radiologists in consensus reading. Overall survival (OS) was calculated for all subgroups (no infiltration, PVTT, HVTT, HVTT + PVTT).
Results: 1341 patients could finally be included. 807 patients (60.2%) had no infiltration, 358 showed PVTT (26.7%), 43 (3.2%) an isolated HVTT and 133 (9.9%) had HVTT + PVTT. The corresponding overall survival was: 37.3, 6.5, 16.0, and 6.5 months, respectively ($p < 0.001$).



Conclusion: Overall, HVTT was more common than expected (13.1%). Often it occurs in combination with PVTT which leads to dismal prognosis. However, in the subgroup with isolated HVTT, prognosis was significantly better compared to patients with PVTT (16.0 versus 6.5 month). This renders the question if patients with isolated HVTT should be classified as BCLC-C, like patients with PVTT, or whether BCLC-B might be more appropriate.

FRI-185

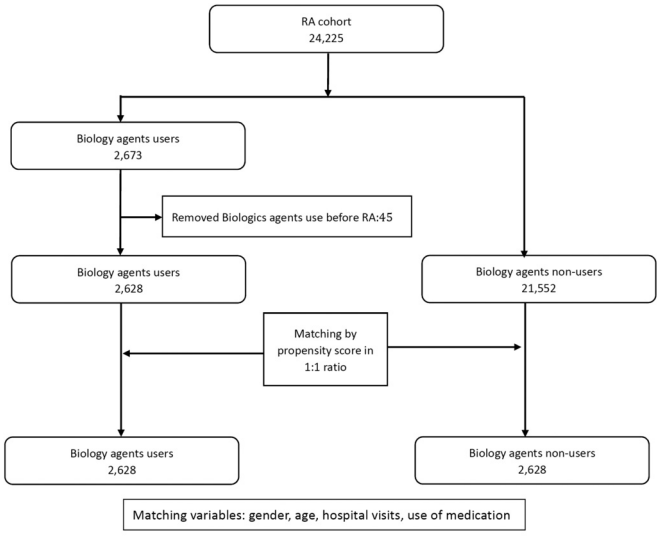
Risks of hepatocellular carcinoma and cirrhosis-associated complications in patients with rheumatoid arthritis receiving biologics: A 10-year population-based propensity-score matched cohort study

C.-S. Hsu[1], H.-C. Lang[2], H.H. Lin[3], Y.-C. Chao[4], C.-L. Chen[5]. *[1]LIver Diseases Research Center, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, New Taipei, Taiwan; [2]Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan; [3]Division of Gastroenterology, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan; [4]Division of Gastroenterology, Department of Internal Medicine, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan; [5]Division of Gastroenterology, Department of Internal Medicine, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan*
Email: hsu.chingsheng@gmail.com

Background and Aims: Using immunomodulatory agents for the management of rheumatoid arthritis (RA) may not only modify the involved immunologic pathways but also alter normal immunosurveillance and the risk of malignancy. Several studies have shown an increased risk of HBV or HCV infection in RA patients, which likely increases the risk of developing hepatocellular carcinoma (HCC) for RA patients. However, few studies have addressed the relationship between the HCC risk and RA. We aimed to examine the risk of HCC and cirrhosis-associated complications in patients with RA who took biologics.

Method: All patients with RA aged ≧ 18 years in the Taiwan National Health Insurance program between January 1, 2000, and December 31, 2009, were enrolled. We matched biologics RA users and non-users by propensity scores in a 1:1 ratio. Our primary outcome was a diagnosis of HCC and cirrhosis-associated complications during a 10-year follow-up period. The risk of outcomes was represented as a hazard ratio (HR) calculated in Cox proportional hazard regression models.

Results: 2,628 biologics users and 2,628 non-users were included in the primary outcome analysis (Figure). 6 biologics users and 15 non-users developed HCC, and 39 biologics users and 54 non-users developed cirrhosis-associated complications (HCC excluded) at the end of 10-year observation. The biologics users had a comparable risk of HCC (HR = 1.01, 95% CI = 0.37–2.77, p = 0.9811) and cirrhosis-associated complications (HR = 1.35, 95% CI = 0.76–2.38, p = 0.30) to the biologics non-users after adjusting for all baseline covariates, including age, sex, the frequency of medical visits, and CCI.



Note:
The index date of biologics users was defined as the date of using biologics; and the index date of biologics non-users was defined as the date of first RA diagnosis.

Conclusion: Although immunomodulatory agents may alter the risk of malignancy, use of biologics does not increase the risk of HCC and cirrhosis-associated complications in RA patients.

FRI-186

Risk assessment of hepatocellular carcinoma in chronic liver disease patients with a combination of liver stiffness measurement and controlled attenuation parameter by FibroScan

K. Morikawa[1], T. Izumi[1], T. Sho[1], K. Suzuki[1], A. Nakamura[1], M. Ohara[1], N. Kawagishi[1], M. Umemura[1], M. Nakai[1], G. Suda[1], K. Ogawa[1], Y. Kudo[2], M. Nishida[2], M. Baba[3], K. Furuya[3], N. Sakamoto[4]. *[1]Hokkaido University, Department of Gastroenterology and Hepatology, Sapporo-shi, Hokkaido, Japan; [2]Hokkaido University Hospital, Division of Laboratory and Transfusion Medicine, Japan; [3]JCHO Hokkaido Hospital, Department of Gastroenterology; [4]Hokkaido University, Department of Gastroenterology and Hepatology, Sapporo-shi, Hokkaido*
Email: kenichi.morikawa@med.hokudai.ac.jp

Background and Aims: Patients with chronic liver disease (CLD) have hepatocellular carcinoma (HCC) causing risk. Recent advantage based on ultrasound technology provide us to evaluate liver stiffness measurement (LSM) and amount of hepatic fat quantitatively. This study aimed to investigate the applicable cutoff values of LSM and controlled attenuation parameter (CAP) for primary HCC development, and evaluate its clinical usefulness for risk assessment of HCC in hepatitis C virus (HCV), hepatitis B virus (HBV), and non-alcoholic fatty liver disease (NAFLD) patients.

Method: 1054 patients (88 with primary HCC and 966 without HCC) with a clinically evident CLD (HCV, 419; HBV, 377; NAFLD, 258) were enrolled in this retrospective and cross-sectional study.

Results: In HCV, LSM of more than 8.0 kPa (OR: 4.06, 95%CI: 1.46–13.19, p = 0.0066) and CAP of less than 221 dB/m (OR: 2.80, 95%CI: 1.07–8.81, p = 0.0355) were independent risk factors for primary HCC development. In HBV, LSM of more than 6.2 kPa was an independent risk factor for primary HCC development (OR: 11.22, 95%CI: 4.10–34.49, $p < 0.0001$). In NAFLD, LSM of more than 5.4 (OR: 7.53, 95%CI: 1.97–49.81, p = 0.0018) and CAP less than 265 dB/m (OR: 4.56, 95%CI: 1.80–12.46, p = 0.0012) were independent risk factors for primary HCC development. Other risk factors for primary HCC development were low albumin and elevated α-fetoprotein for HCV, old age and low platelets for HBV, low albumin and complication with high-blood pressure for NAFLD.

Conclusion: The cutoff values of LSM and CAP for the risk of HCC development were different depending on the etiology. The determining the cutoff values of fibrotic stage and hepatic steatosis for HCC occurrence and its combination use would be useful in daily clinic in assessing HCC risks among CLD patients.

FRI-187

Single-cell mRNA sequencing to characterize circulating tumor cells in hepatocellular carcinoma

D. D'avola[1,2], C. Villacorta[2], S.N. Martins-Filho[2,3], A. Craig[2], I. Labgaa[2,4], J.V. Felden[2,5], A. Kimaada[6], A. Bonaccorso[7], P. Tabrizian[7], B.M. Hartmann[8], R. Sebra[9,10], M. Schwartz[11], A. Villanueva[2,12]. *[1]Liver Unit, Department of Medicine, Clinica Universidad de Navarra and Ciberehd, Liver Unit, Department of Medicine, Pamplona, Spain; [2]Division of Liver Diseases, Department of Medicine, Liver Cancer Program, Tisch Cancer Institute, Graduate School of Biomedical Sciences, Icahn School of Medicine at Mount Sinai, Division of Liver Diseases, Department of Medicine, New York, United States; [3]Departamento de Patologia, Faculdade de Medicina FMUSP, Universidade de Sao Paulo, Departamento de Patologia, Sao Paulo, Brazil; [4]Department of Visceral Surgery, Lausanne University Hospital CHUV, Lausanne University Hospital CHUV Department of Visceral Surgery, Lausanne, Switzerland; [5]Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Department of Internal Medicine, Hamburg, Germany; [6]Department of Genetic and Genomic Science, Ichan School of Medicine at Mount Sinai, New York, United States; [7]Department of Surgery, Icahn*

School of Medicine at Mount Sinai, New York, United States; [8]Department of Neurology, Icahn School of Medicine at Mount Sinai, Department of Neurology, New York, United States; [9]Sema4, a Mount Sinai Venture, Stanford (CT), United States; [10]Department of Genetic and Genomic Science, Ichan School of Medicine at Mount Sinai, Department of Genetic and Genomic Science, New York, United States; [11]Department of Surgery, Icahn School of Medicine at Mount Sinai, Department of Surgery, New York, United States; [12]Division of Hematology and Medical Oncology, Department of Medicine, Icahn School of Medicine at Mount Sinai, Division of Hematology and Medical Oncology, Department of Medicine, New York, United States
Email: ddavola@unav.es

Background and Aims: Hepatocellular carcinomas (HCC) release circulating tumor cells (CTCs) to the bloodstream. Despite that numerous reports found a direct correlation between the number of CTCs and poor clinical outcomes, only few studies have provided a molecular characterization of CTCs. The aim of our study was to develop a method to extensively analyze the transcriptome of CTCs from HCC patients using single-cell mRNA sequencing (scRNAseq).
Method: For this pilot study we included 6 patients with HCC and 1 control (no cancer). Our approach included 3 sequential steps: 1) 8 ml of blood were withdrawn using heparin tubes and CD45 cells were depleted using an immunodensity assay (Rosette depletion kit). The enriched cellular suspension was separated in 2 aliquots. 2) The presence of CTCs was assessed in the first aliquot by flow cytometry imaging (Imagestream, Amnis®). CTCs were defined as: having a compatible shape by bright field morphologic analysis, being CD45 negative, and expressing at least one of the following markers: ASGPR1, pan-CK, EPCAM and GPC3. 3) If candidate CTCs were detected, the second aliquot was subjected to scRNAseq using 10X Chromium Genomics. The analytical pipeline was adjusted to be specifically sensitive to detect outliers and included principal component analysis (PCA), non-linear clustering methods (t-SNE) and differential gene expression.
Results: Most patients had advanced HCC (BCLC-C, 3/6), and in 4/6 we detected candidate CTCs upon Imagestream analysis, while the control patient was negative. From the 2 patients analyzed by scRNAseq, we sequenced a total of 7,381 and 3,560 cells in patient 1 and 2, respectively. Both PCA and differential expression confirmed the presence of 2 cells with hepatic lineage (i.e., overexpression of ADH, HFE, TTR, FABP11, GSTA1, APOH, FGB, APOA2, ALB, ORM1) in the blood of patient 1, and one in patient 2. Also, the 3 CTCs identified in the 2 patients overexpressed genes typically deregulated in HCC tissue samples (e.g., HULC, SPP1, SPINK1). Gene expression profiling of the 2 CTCs found in patient 1 revealed significant differences between them, including the overexpression of the known HCC driver IGF2 in one of these CTCs.
Conclusion: Application of scRNAseq enables the identification of CTCs in HCC patients. Genome-wide transcriptome profiling allows for a dense molecular characterization of CTCs, which underscores its potential role to monitor HCC heterogeneity using a minimally invasive approach.

FRI-188
Validation of the MESH, HKLC and BCLC classification in a large German cohort of hepatocellular carcinoma patients

S. Franck, I. Schmidtmann, E. Heil, S. Koch, C. Czauderna, M.-A. Wörns, M. Sprinzl, R. Klöckner, P. Galle, J. Marquardt, A. Weinmann. *University Medical Center Mainz*
Email: sophia.franck@icloud.com

Background and Aims: The BCLC staging system is most frequently used to classify HCC patients in the US and Europe and is endorsed by guidelines of EASL and AASLD. However, staging systems vary among different countries and a variety of other classification schemes have been proposed, but clinical utility across different cohorts is a matter of ongoing scientific discussion. Here, we evaluate the prognostic accuracy of Hong Kong Liver Staging System (HKLC) and MESH (Model to Estimate Survival for HCC) Score in comparison to BCLC staging in a Western cohort of HCC patients.
Method: We retrospectively analyzed 1102 patients of the HCC cohort treated at the University Medical Center of Mainz between 1998 and 2014 and compared the predictive ability of survival time of three classification systems (BCLC, HKLC, MESH). 903 patients were treated in accordance with all three scoring systems. Predictive ability was tested using integrated Brier score (IBS), a measure for prediction error, and variants of the c-index such as Harrell's C.
Results: From the 903 investigated patients 98% were Caucasian, 82.2% male and 17.8% female. HCC etiology was mainly alcohol abuses (38.3%), chronic hepatis C (22.5%) and hepatitis B infection (10.4%). The majority of patients were CHILD A (52.3%). Patients were classified as HKLC I: 12.8%, II: 31.4%, III: 28.5%, IV: 9.2% and V: 18.1%. MESH 0: 4.5%, 1:15.5%, 2: 24.3%, 3: 21.1%, 4: 11.7%, 5: 5.2%, 6: 0.9%. BCLC A: 22%, B: 16.1%, C: 44.37, D: 17.4%.
Kaplan-Meier analyses showed significant differences in survival between stages defined by BCLC (median survival BCLC A: 51.1, BCLC B: 20.5, BCLC C: 10.1, BCLC D: 3.5 months respectively; $p < 0.0001$), HKLC (HKLC I: 54.6, HKLC II: 31.3, HKLC III: 10.8, HKLC IV: 5.1, HKLC V: 3.1 months respectively; $p < 0.0001$) and MESH (MESH 0:NA, MESH 1: 37.1, MESH 2: 22, MESH 3: 10.6, MESH 4: 5, MESH 5: 3.6, MESH 6: 1.3 months respectively; $p < 0.0001$). However, MESH and HKLC showed more robust classification concordance ($c = 0.701$ and 0.692 respectively) and lower prediction error (IBS 0.166 and 0.161) than BCLC ($c = 0.659$; IBS: 0.177).
Conclusion: Our analyses of different scoring system for HCC confirmed prognostic ability of all three scores. Our comparative analyses and subsequent evaluation by IBS and c-index suggest that MESH and HKLC possesses a high predictive accuracy in Western HCC patients with lower prediction error than BCLC. Prospective head-to-head evaluation of different scoring systems is warranted.

Autoimmune and chronic cholestatic liver disease: Experimental and pathophysiology

FRI-191
Obeticholic acid response in primary biliary cholangitis associated with differential expression of antigen presentation, Wnt signalling and mRNA splicing

M. Seifi[1], J. Jovel[1], K. Siminovitch[2], R. Pencek[3], D. Shapiro[3], A.L. Mason[1]. *[1]University of Alberta, Medicine, Edmonton, Canada; [2]University of Toronto, Toronto, Canada; [3]Intercept Pharmaceuticals, San Diego, United States*
Email: andrew.mason@ualberta.ca

Background and Aims: In the POISE phase III trial, PBC patients unresponsive to UDCA were treated with 5–10mg obeticholic acid (OCA) with a response rate of 47% using the primary endpoint of alkaline phosphatase level <1.67 times the upper limit of normal and 15% reduction. To better understand biomarkers for response, differences in transcriptional activity of whole blood were evaluated in responders versus non-responders using RNA-seq.
Method: 174 samples of whole blood RNA from 86 PBC patients were cloned into TruSeq libraries and processed by Illumina HiSeq to generate 5 GB data per library. After removal of low quality reads, sequences were aligned to the human genome GRCh38.81 using TopHat2 aligner and counted with HTSeq. Differential expression analysis was conducted using the DESeq2 R package and genes deregulated with a false discovery rate < 0.05 were considered differentially expressed. Pathway analyses were conducted using Gene Ontology Consortium and compared to prior databases of PBC "omics" studies.

Results: After OCA therapy, increased expression was observed in 161 genes and decreased expressed in 158 genes with a FDR < 0.05 in responders versus non-responders. The major upregulated genes in the OCA-responsive patients were the genes associated with negative regulation of mRNA splicing via the spliceosome (38 fold enrichment, p < 0.0002) and regulation of alternative mRNA splicing via the spliceosome (30 fold, p < 0.0000003). Non-responders experienced increased expression of genes associated with antigen processing and presentation of exogenous peptide antigen via the major histocompatibility (MHC) class I (14 fold, p < 0.0014), Wnt signaling developmental pathway (11 fold, p < 0.009), negative regulation of mitotic cell cycle (11 fold, p < 0.05), tumor necrosis factor-mediated signaling pathway (11 fold, p < 0.005), Fc receptor signaling pathway (7 fold, p < 0.003) and regulation of endocytosis (6 fold, p < 0.05). Notably RNASE transcripts associated with interferon innate responses were some of the most upregulated genes in the non-responders.
Conclusion: Non-responders displayed a peripheral blood transcriptome of increased antigen presentation, cytokine signaling, with elevated developmental gene and cell cycle gene expression. Whereas the responders experienced increased expression of genes associated with regulation of mRNA splicing that include the ribonucleoprotein targets for autoantibodies in patients with SLE. Wnt signaling and cell cycle genes have been previously linked to PBC in prior microarray studies and pathway-based analysis of PBC genome-wide association studies, whereas differential production of spliceosome proteins have been found in proteomics studies of PBC patients. These studies suggest that OCA non-responders have increased monocyte proliferation, antigen presentation and immune activation.

FRI-192

TGR5 modulates gallbladder function and bile acid pool composition : potential hepatoprotective impact in mice

B.J. Valeska[1], G. Mathilde[1], M. Gregory[1], D. Isabelle[1], B. Raphael[2], C. Ullmer[3], L. Humbert[4], D. Rainteau[4], T. Tordjmann[1]. *[1]INSERM, U1174, Orsay, France; [2]CEA, SHFJ, Orsay, France; [3]Roche Innovation Center, Basel, Switzerland; [4]INSERM, U1057, Paris, France*
Email: thierry.tordjmann@u-psud.fr

Background and Aims: The BA receptor TGR5 protects the liver against BA overload in obstructive context and after partial hepatectomy in mice, although mechanisms are undefined. We explored TGR5 impact on GB function and BA pool composition.
Methods: WT and TGR5-KO mice were submitted to: extended 89% hepatectomies (EH) upon normal (ND) or cholestyramin (CT2%)-enriched diet; bile duct ligation (BDL, 7 and 15 days); cholic acid (CA 1%, 5 days)-enriched diet; cholecystectomies (CCT); TGR5 agonist (RO5527239 10 mg/kg/d, Roche) treatment. Survival, liver injury (H&E, plasma ALT and Bilirubin) and regeneration (liver weight, PH3, Ki67, PCNA), BA pool composition (plasma, liver; LC-MS) were analyzed. GB weight, volume and filing (99Tc Mebrofenin scintigraphy) were measured in WT and TGR5-KO mice, upon vehicle or RO5527239 treatment. GB and hepatic bile pH were analyzed upon vehicle and RO5527239 treatment.
Results: In TGR5-KO as compared with WT mice, post-EH survival was reduced (25 vs 64% at day 9), hepatic necrosis (bile infarcts) and BA overload were exacerbated, while regeneration parameters were similar at both early and late stages. CT treatment (which restrains BA overload), and UDCA (which makes a more hydrophilic BA pool) strikingly improved survival, suggesting that BA overload and composition contributed to post-EH liver failure and mortality in TGR5-KO mice.
In TGR5-KO as compared with WT mice, GB weight and volume were smaller, and GB filling was deeply impaired (mebrofenin scintigraphy). RO5527239 treatment induced rapid GB dilatation in WT but not in TGR5-KO mice, while the BA pool was shifted towards a more hydrophilic (less toxic) composition (less secondary BA) in WT mice. This treatment had no significant effect on BA synthesis enzymes (hepatic CYPs mRNAs). Upon RO5527239 treatment, GB but not hepatic bile pH was strongly acidified in WT but not TGR5-KO mice, greatly facilitating BA passage from GB bile towards the blood, shunting BA route to the intestine (thus reducing secondary BA).
In the BDL and CA-enriched diet models, GB had a protective effect in WT but not TGR5-KO mice, as shown by more body weight loss, liver injury and inflammatory infiltration observed in CCT versus sham operated mice.
Conclusion: TGR5 significantly impacts GB function (filing and pH regulation) and thereby BA pool composition/toxicity, potentially supporting TGR5 hepatoprotective properties in the context of massive liver resection or other BA overload settings.

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NLRP3 deletion leads to decreased inflammation and prevents fibrosis formation in mice after chronic bile duct ligation

M. Frissen[1], L. Lijun[1], V. Bieghs[1], K.M. Schneider[1], A. Mohs[1], E. Latz[2], A. Wree[1], C. Trautwein[1]. *[1]Uniklinik RWTH Aachen, Department of Internal Medicine III, Aachen, Germany; [2]Rheinische Friedrich-Wilhelms-Universität Bonn, Bonn, Germany*
Email: mfrissen@ukaachen.de

Background and Aims: Hepatic toxicity caused by cholestasis triggers different cell death pathways. Caspases activity, one of the main players in apoptotic and pyroptotic cell death initiation, is modulated by the NLRP3 inflammasome. The NLRP3 inflammasome complex hereby modulates liver inflammation, fibrosis and hepatocyte pyroptosis in mice. Thus we studied the role of NLRP3 inflammasome complex formation after cholestatic liver injury.
Method: Bile duct ligation (BDL) was performed on WT, NLRP3 knockout (NLRP3-/-) and ASC-/- mice. Mice were sacrificed after acute (48 hours) or chronic (28 days) BDL injury. Inflammation, fibrosis and cell death were evaluated with histologic quantification, immunostaining, qPCR, western blot and flow cytometry analysis.
Results: Acute cholestatic liver injury in NLRP3-/- mice resulted in a significant increase in serum transaminases compared to WT mice. In addition, severe hepatic inflammation, as evidenced by higher mRNA levels for TNF, IL-1b, MCP-1 and the influx of Ly6G + Cd11b+ cells, was observed in NLRP3-/- mice. The exacerbated liver injury can be explained by an excessive necroptotic response in NLRP3-/- mice, as shown by increased mitochondrial ROS production and RIPK1 and 3 expression. In contrast, during chronic cholestasis, the lack of NLRP3 expression leads to reduced serum transaminases, less inflammation and liver fibrosis. TUNEL, caspase-3 and -8 staining showed decreased cell death in NLRP3-/-mice. Furthermore, clusters of caspase-3 positive cells were observed only in WT mice 28d after BDL, associated with pyroptosis. Since NLRP3-/- mice are unable to activate caspase-1 and cleave IL-1b, pyroptotic cell death was absent in these mice, subsequently leading to ameliorated fibrosis. Moreover, expansion of CK19+ (progenitor/oval) cells was triggered in NLRP3-/- mice which may explain the protective phenotype in knockout mice. ASC-/- mice showed a similar but less severe phenotype than NLRP3-/- mice; after 2d BDL the serum transaminases and hepatic inflammation was slightly elevated compared to WT mice. In the chronic phase ASC-/- mice were comparable to NLRP3-/- mice, since they also lack inflammasome activation and accompanied pyroptotic cell death.
Conclusion: The inability to form NLRP3 inflammasome complex after bile duct ligation leads to an early increase in liver injury, mediated by mitochondrial ROS and RIPK activation. However, in the chronic phase in NLRP3-/- and ASC-/- mice, lack of pyroptosis leads to less inflammation and subsequent fibrosis.

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Activation of pyruvate kinase isoform M2 (PKM2) in myeloid cells protects from Concanavalin A-mediated liver injury

J.P. Weltzsch[1], T. Krech[2], M.G Vander Heiden[3], G. Tiegs[1], A. Horst[1].
[1]*University Medical Center Hamburg-Eppendorf, Inst. Exp.Immunology and Hepatology, Hamburg, Germany;* [2]*University Medicl Center Hamburg-Eppendorf, Department of Pathology, Hamburg, Germany;* [3]*Massachusetts Institute of Technology, Koch Institute for Integrative Cancer Research, Cambridge, MA, United States*
Email: ahorst@uke.de

Background and Aims: Immune-mediated liver injury is a common complication in autoimmune liver disease. Immune cells switch from their steady state to inflammation by a metabolic switch from oxidative phosphorylation to aerobic glycolysis. Pyruvate kinase M2 (PKM2) is a key regulator of the metabolic switch; its poorly active dimeric isoform limits the glycolytic flux. In macrophages, the PKM2 dimer enhances HIF-1α-dependent transcription of glycolytic enzymes and pro-inflammatory cytokines, such as IL-1β, fostering myeloid M1-like polarization. Contrary, the highly active PKM2 tetramer promotes myeloid M2-type polarization and production of anti-inflammatory cytokines, such as IL-10. Tetramerization and activation of PKM2 by the small molecule activator TEPP-46 could bias myeloid cell polarization towards an anti-inflammatory phenotype and elicit liver protection. It is our goal to identify a protective role for PKM2 activation in immune-mediated liver injury.
Method: In Concanavalin A (ConA)-induced liver injury in mice with a myeloid-specific knockdown of PKM2 ($PKM2^{\Delta myel}$), plasma ALT and cytokine levels were measured by enzyme assays/ELISA. Myeloid cells from liver, spleen, bone marrow and peripheral blood were characterized by flow cytometry. Glycolysis enzyme and cytokine profiles in macrophages and liver tissue were analyzed with RT-PCR. Hepatic immune cell influx and necrosis was studied in immune histology. TEPP-46 was applied i.p. prior to i.v. ConA injection.
Results: ConA-induced liver injury was exacerbated in $PKM2^{\Delta myel}$ mice, evident by significant elevation of plasma ALT, IL-1β and IL-6 levels, and increases in hepatic myeloid cell infiltration and necroses. Bone marrow-derived macrophages and hepatic tissue exhibited a pro-inflammatory cytokine profile and increases of glycolytic regulators. We found that the myeloid-specific knockdown of PKM2 produced predominant dimerization of the residual PKM2 protein. Contrary, administration of TEPP-46 and PKM2 tetramerization attenuated liver injury and pro-inflammatory cytokine release.
Conclusion: Lack of PKM2 activity exacerbated ConA-induced hepatitis in $PKM2^{\Delta myel}$ mice. Contrary, activating PKM2 by TEPP-46 prior to ConA challenge conveyed liver protection. PKM2 activation offers a novel therapeutic strategy to ameliorate immune-mediated liver injury.

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Ceacam1 controls IL-2-dependent regulatory T cell induction in immune-mediated hepatitis

A. Horst[1], C. Wegscheid[1], C. Schaefers[1], B. Schiller[1], K. Neumann[1], S. Lunemann[2], A. Langeneckert[2], K. Oldhafer[3], C. Weiler-Normann[4], C. Schramm[4], K.S. Lang[5], B. Singer[6], M. Altfeld[2], L. Diehl[1], G. Tiegs[1].
[1]*Institute for Experimental Immunology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany;* [2]*Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany;* [3]*Department for General and Abdominal Surgery, Asklepios Hospital Barmbek, Hamburg, Germany;* [4]*I. Medical Clinic and Polyclinic, Center for Internal Medicine, Hamburg, Germany;* [5]*Institute for Immunology, University of Duisburg-Essen, Essen, Germany;* [6]*Institute for Anatomy, University of Duisburg-Essen, Essen, Germany*
Email: ahorst@uke.de

Background and Aims: Disturbance in regulatory T cell (Treg) homeostasis, dysbalance between effector T cells (Tconv) and Treg and impaired Treg function can cause autoimmune liver disease. Ceacam1 is an immune co-receptor with dichotomous roles in T cell regulation: its short isoform (Ceacam1S) can activate T cells and induce Tregs, whereas its long isoform (Ceacam1L) with two intracellular immune receptor tyrosine-based inhibitory motifs (ITIMs), inhibits activated T cells, natural killer (NK) a, NKT and myeloid cells. In the liver, Ceacam1 has anti-fibrotic effects in models of non-alcoholic steatohepatitis. However, its role in immune-mediated hepatitis is unknown. Here, we define a Ceacam1 isoform-specific role for Ceacam1 in the regulation of Treg homeostasis.
Method: Immune-mediated liver injury was induced by Concanavalin A (ConA) in wildtype and *Ceacam1*$^{-/-}$ mice. Liver injury was assessed by measurement of plasma ALT activities. Cytokine concentrations/expression was measured by ELISA and qRT-PCR. Treg conversion and Treg markers were analyzed in T cell-hepatocyte cocultures and *in vivo* by flow cytometry. Treg function was analyzed *in vitro* and *in vivo* after adoptive cell transfer. In liver biopsies from patients with AIH and alcoholic hepatitis, Ceacam1 expression by intrahepatic T cells was analyzed by qRT-PCR.
Results: ConA-inudced liver damage was aggravated and persisted in *Ceacam1*$^{-/-}$ mice. Congruently, we observed hyperexpansion of Tconv, but reduction of IL-2 production and hepatic $Foxp3^+$ $CD4^+$ Treg frequencies. Also, IL-2-mediated signal transducer and activator of transcription (STAT)5 phosphorylation was impaired in Ceacam1$^{-/-}$$CD4^+$ T cells, and expression levels of Foxp3, CD25 and Bcl-2 were reduced in Ceacam1$^{-/-}$ Tregs. Lack of IL-2 hampered Treg conversion from naïve Ceacam1$^{-/-}$$CD4^+$ T cells *in vitro*. Adoptive cell transfer experiments revealed that hepatic Treg expansion and suppressive activity required Ceacam1 expression by $CD4^+$ T cells and Tregs. Importantly, we found predominant Ceacam1S expression on $CD4^+CD25^+$ T cells from mice with acute liver injury and expression of both isoforms in liver-derived $CD4^+$ T cell clones from patients with liver injury.
Conclusion: Ceacam1S confers protection from T cell-mediated liver injury by augmenting IL-2 production and phosphorylation of STAT5 in $CD4^+$ T cells, thereby promoting Treg induction and stability.

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The suppressive effect of Interleukin-17-expression in antigen specific CD8+ T cells in acute experimental cholangitis in mice

S. Stein[1], D. Schwinge[1], T. Krech[2], A. Lohse[1], J. Herkel[1], C. Schramm[1].
[1]*University Medical Center Hamburg-, Eppendorf, I. Medical Clinic and Polyclinic, Hamburg, Germany;* [2]*University Medical Center Hamburg-, Eppendorf, Department of Pathology, Hamburg, Germany*
Email: st.stein@uke.de

Background and Aims: Interleukin (IL)-17 has been associated with the pathogenesis of several autoimmune disorders. Increased numbers of Th 17 lymphocytes and IL-17 could be observed in serum and livers of patients with inflammatory liver diseases, including autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). We here investigate the role of IL-17 in disease induction using an inducible mouse model of acute cholangitis.
Method: K14-OVAp recipient mice express an ovalbumin peptide, the SIINFEKL sequence, on biliary epithelial cells. Acute cholangitis was induced by adoptive transfer of transgenic OVA-specific OT-1 $CD8^+$ T cells and OT-1 $CD8^+$ T cells lacking IL-17A/F to investigate the role of IL-17 in the initiation and progression of cholangitis. Liver enzymes, histology, cytokine expression and flow cytometry were used to assess liver inflammation.
Results: Adoptive transfer of antigen specific OT-1 $CD8^+$ T cells led to portal inflammation in K14-OVAp recipient mice with the transferred cells mainly localized around bile ducts. The lack of IL-17A/F in transferred OT-1 CD8+ T cells resulted in enhanced liver inflammation compared to the transfer of IL-17-competent OT-1 cells. Liver infiltrating antigen-specific CD8+ T cells lacking IL-17 were highly activated, secreted large amounts of IFN-gamma and displayed increased proliferative capacity. Since biliary epithelial cells were activated after contact with $CD8^+$ T cells the increased accumulation

of IL-17-deficient transferred OT-1 cells led to the enhanced expression of T cell directed chemokines with subsequent recruitment of endogenous T cells into the liver.
Conclusion: We could here show that the lack of IL-17 in antigen specific $CD8^+$ T cells induces a severe phenotype of experimental cholangitis. Our results indicate an important suppressive function of IL-17 during the onset of antigen dependent cholangitis. Caution should be taken when targeting IL-17 for the treatment of cholangitis.

FRI-197
Batf3-dependent CD103 + CD11b-dendritic cells are crucial for the development of primary biliary cholangitis
D. Reuveni[1], S. Assi[1], P. Leung[2], O. Shibolet[1], E. Gershwin[2], E. Zigmond[1]. *[1]Tel-Aviv Sourasky Medical Center and Sackler School of Medicine, Tel-Aviv University, The Research Center for Digestive Tract and Liver Diseases, Tel Aviv, Israel; [2]University of California at Davis, Division of Rheumatology, Allergy and Clinical Immunology, Davis, United States*
Email: zigmondu@gmail.com

Background and Aims: Primary biliary cholangitis (PBC) is a progressive autoimmune cholestatic liver disease characterized by non-suppurative cholangitis. Dendritic cells (DCs) are professional antigen presenting cells composed of distinct subsets with unique functions and phenotypic characteristics. DCs were identified in liver sections of PBC patients embedded in the damaged bile ducts, however, solid data evaluating their importance and function in the *in-vivo* context is still missing. Conventional type 1 - $CD11b^-CD103^+$ (cDC1s) are unique subset of DCs efficiently perform cross presentation of antigens to $CD8^+$ T cells. Our aim was to assess the role of cDC1s in the pathogenesis of PBC.
Method: We utilized an inducible murine model of PBC by immunization of mice with the xenobiotic 2-octynoic acid conjugated to bovine serum albumin. We took advantage of the reporter mouse $Zbtb46^{gfp/+}$ to identify hepatic DCs by flow cytometry and Immunofluorescence and the Batf3 KO mice that specifically lack the cDC1s subset, to evaluate their role in PBC pathogenesis.
Results: Immunofluorescence of $Zbtb46^{gfp/+}$ reporter mice revealed that $CD103^+$ cDC1s are predominantly located within the portal tracts. Histopathology assessment demonstrated peri-portal infiltration of lymphocytes and mononuclear cells in WT mice, whereas, in Batf3 KO mice only minor abnormalities were observed (histological disease severity score of 6.5 vs. 2.75, $p < 0.05$). Alkaline phosphatase and total bile acid, the biochemical hallmarks of PBC, were decreased in Batf3 KO mice (103 vs. 81 IU/l and 30 vs. 8 μmol/l, respectively, $p < 0.005$). Hepatic expression level of TNFα and IFNγ were both about 2 fold decreased in Batf3 KO mice, $p < 0.05$, further supporting reduced hepatic inflammation in cDC1s-deficient mice. Flow cytometry analysis revealed about 2 fold reduction in hepatic CD4/CD8 T cells ratio in Batf3 KO mice, $p < 0.05$, indicating reduced hepatic $CD8^+$ T cells infiltration. Importantly, Sirius red staining of liver sections exhibit peri-portal collagen deposition only in the control group, a finding that was supported by a statistical significant pro-fibrotic hepatic gene-expression signature in this group.
Conclusion: Overall, these results indicate a role for DCs and specifically the $CD11b^-CD103^+$ DC subset in the pathogenesis of autoimmune cholangitis and improve our understanding concerning break of tolerance mechanisms in PBC. Our findings may pave the road to new immune based cell specific targeted therapeutic endeavours.

FRI-198
FXR agonist obeticholic acid increases gallbladder FGF19 in gallstone patients
S. Al-Dury[1], A. Wahlström[1], P. Katrin[2], T. Anders[3], M. Ståhlman[1], L. Olsson[1], M. Trauner[4], P. Fickert[2], D. Moore[5], F. Backhed[1], L. Fändriks[6], M. Wagner[2], H.-U. Marschall[1]. *[1]Sahlgrenska Academy, University of Gothenburg, Department of Molecular and Clinical Medicine/ Wallenberg Laboratory, Gothenburg, Sweden; [2]Medical University of Graz, Department of Medicine, Graz, Austria; [3]Ersta Hospital, Department of Surgery, Stockholm, Sweden; [4]Medical University of Vienna, Division of Gastroenterology and Hepatology, vienna, Austria; [5]Baylor College of Medicine, Molecular and Cell Biology, Houston, TX, United States; [6]Sahlgrenska Academy, University of Gothenburg, Department of Gastrosurgical Research and Education, Gothenburg, Sweden*
Email: hanns-ulrich.marschall@gu.se

Background and Aims: Obeticholic acid (OCA) is the first in class steroidal agonist of the nuclear farnesoid X receptor (FXR) and was recently approved for the treatment of primary biliary cholangitis (PBC). We aimed to explore the molecular actions of OCA in human liver and gallbladder in patients awaiting laparoscopic gallstone surgery.
Method: As part of the investigator-initiated randomized placebo-controlled OCABSGS trial (NCT01625026) twenty otherwise healthy gallstones patients were randomized to OCA (25mg/day) or matching placebo during three weeks until the day before surgery (study medication kind gift of Intercept). Sampling for serum liver enzymes, lipids, bile acids (BAs), BA synthesis marker C4 (7α-hydroxy-cholest-4-ene-3-one), FGF19 and markers of insulin resistance (HOMA-IR) were obtained before treatment and at the day of surgery. During surgery, biopsies were taken from the liver and the gallbladder, for FXR ChIPSeq, RNASeq, and proteomics. Gallbladder bile acid was investigated for BAs and FGF19.
Results: All patients finished the study per protocol. OCA vs. placebo groups were well matched by gender (female, 80 vs. 80%), age (48.8 ± 8.9 vs. 50.8 ± 13.3 years, all data mean ± SD), BMI (27.9 ± 4.9 vs. 28.7 ± 4.5 kg/m^2), HOMA-IR (2.4 ± 1.5 vs. 2.7 ± 1.8). OCA significantly ($p < 0.05$) increased serum FGF19 (from 95.0 ± 25.2 to 234.4 ± 106.8 ng/L) and decreased serum C4 (from 25.4 ± 22.6 to 1.3 ± 1.7 nmol/L) and endogenous BAs (from 1341 ± 900 to 422 ± 435 nmol/L). FGF19 in gallbladder bile of OCA-treated patients was significantly ($p < 0.005$) higher than in controls (403 ± 165 vs. 135 ± 131 ng/L), whereas biliary BAs were significantly ($p < 0.05$) lower (98.6 ± 76.9 vs. 186.6 ± 100.9 mmol/L). No changes occurred in controls. OCA and its conjugates contributed to total serum and biliary BAs by 45.7 ± 17.3% and 16.9 ± 6.4%, respectively, at the day of surgery. There were no significant correlations between individual serum and gallbladder bile levels of total BAs, OCA and FGF19.
Conclusion: This is the first report describing enriched levels of FGF19 in human bile during treatment of OCA, suggesting that hepatobiliary tree can produce FGF19 in humans. In contrast, the murine homologue FGF15 is not expressed in the hepatobiliary tree.

FRI-199
Loss of BSEP protects MDR2/ABCB4 KO mice from cholestatic liver injury by altering bile acid profile and signaling
C. Fuchs[1], G. Paumgartner[1], V. Mlitz[1], S. Wolfrum[2], A. Wahlström[3], M. Ståhlman[3], T. Stojakovic[4], C. Wolfrum[5], H.-U. Marschall[6], M. Trauner[1]. *[1]Medical University of Vienna, Internal Medicine III, Gastroneterology&Hepatology, Vienna, Austria; [2]ETH Zürich, Laboratorium für Organische Chemie; [3]University of Gothenburg, Department of Molecular and Clinical Medicine; [4]Medical University of Graz, Clinical Institute of Medical and Chemical Laboratory Diagnostics; [5]ETH Zürich, Institute of Food, Nutrition and Health; [6]Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden*
Email: michael.trauner@meduniwien.ac.at

Background and Aims: Cholestasis is characterized as intrahepatic accumulation of potentially cytotoxic bile acids (BAs) subsequently leading to liver injury reflected by disruption of hepatocellular integrity, inflammation, fibrosis, cirrhosis and increased risk for cancer. Bile salt export pump (Bsep/Abcb11) is the main canalicular BA transporter and rate limiting step for hepatobiliary BA secretion. Here we aim to investigate the role of Bsep in development of liver

injury in a mouse model of sclerosing cholangitis - the Mdr2KO mouse.
Method: To explore the consequences of Bsep loss in a mouse model of sclerosing cholangitis, Mdr2/Bsep double knockout (DKO) mice were generated. WT mice subjected to bile duct ligation (BDL) as well as Mdr2KO mice were fed with a tetrahydroxylated bile acid (THBA). Gene expression profile of inflammatory and fibrotic markers, serum biochemistry, liver histology, immunohistochemistry (IHC) and serum BA composition were assessed.
Results: In contrast to Mdr2KO mice, DKO mice were protected against liver and bile duct injury, reflected by serum biochemistry and H&E staining. Gene expression of inflammatory markers F4/80, Tnfα and Mcp1 remained unchanged (compared to WT Ctrls) in DKO mice, while in Mdr2KO mice these markers were increased (4fold, 6fold and 8fold, respectively; $p < 0,05$). Fibrosis markers were increased in Mdr2KO mice (Desmin 9fold, Col1a1 24fold; $p < 0,05$) but remained unchanged in DKO mice. mRNA expression of Cyp3a11 and Cyp2b10, two enzymes involved in BA hydroxylation/detoxification were increased 5fold and 100fold in DKO mice, respectively, while Mdr2 KO mice showed unchanged levels. In line, 67% of serum BAs in DKO mice were polyhydroxylated, with tetrahydroxylated BAs being most prominent. In Mdr2KO mice, polyhydroxylated BAs were completely absent. Notably THBA feeding profoundly reduced expression levels inflammatory markers (IL1b and Cxcl1 by 50%) and fibrotic marker (Col1a2 by 80%) in Mdr2 KO. In line, THBA feeding improved inflammation in WT BDL mice, reflected by reduced number of F4/80 positive cells and improved gene-expression profile (F4/80 by 50%, Cxcl1 by 55% and Cxcl2 by 75%; $p < 0,05$) compared to WT BDL mice.
Conclusion: Loss of Bsep results in increased expression/activity of enzymes involved in BA hydroxylation/detoxification, thus protecting Mdr2 KO mice from development of cholestatic liver disease. Therefore, THBA may be a new potential treatment strategy for cholestatic liver diseases.

FRI-200
The faecal microbiome of patients with primary sclerosing cholangitis has a characteristic signature across different geographic regions
T. Liwinski[1], F.-A. Heinsen[2], M.-C. Rühlemann[2], C. Bang[2], R. Zenouzi[1], J.R. Hov[3], M. Kummen[3], T.H. Karlsen[3], W. Lieb[4], A. Lohse[1], A. Franke[2], C. Schramm[1]. *[1]University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; [2]Christian-Albrechts-University of Kiel, Institute of Clinical Molecular Biology, Kiel, Germany; [3]Oslo University Hospital and University of Oslo, Norwegian PSC Research Center, Oslo, Norway; [4]Christian-Albrechts-University of Kiel, Institute of Epidemiology and Biobank Popgen, Kiel, Germany*
Email: t.liwinski@uke.de

Background and Aims: Characteristic changes in the faecal microbiome of patients with primary sclerosing cholangitis (PSC) have been reported in single centre studies. However, it is unknown whether PSC is associated with a common microbial signature across geographical regions.
Method: Stool samples were collected from two independent cohorts in Norway and Germany. A total of 388 patients at a median age of 47 years (range, 15–78) were included in the analysis: 137 patients with PSC including 75 patients with concurrent inflammatory bowel disease (IBD), 118 patients with ulcerative colitis (UC) and 133 healthy controls (HC). The microbiomes were profiled by sequencing of the 16S ribosomal RNA gene targeting the V1-V2 region, biodiversity analysis, machine learning classification, receiver operating characteristic (ROC) analysis and gene set enrichment analysis of the predicted metagenome.
Results: In both cohorts as well as in a pooled analysis, the global microbiota composition (beta diversity) was significantly different between PSC and HC ($p < 0.001$) and between PSC and UC ($p < 0.001$) measured by the Bray-Curtis-dissimilarity. In contrast, no differences were observed between PSC with and without IBD. We found a common microbial signature of 7 genera distinguishing patients with PSC from HC in both the Norwegian and German cohort. Intra-individual (alpha) diversity was not different between PSC and HC in the German cohort, but a decreased alpha diversity was present in the Norwegian PSC patients. We further assessed whether the faecal microbiota can be used to distinguish between healthy and diseased individuals across geographical regions. A random forest classifier trained on the common microbial signature of 7 genera in the German cohort yielded an area under the curve (AUC) of 0.81 classifying the Norwegian subjects in PSC or HC (accuracy 0.72, sensitivity 0.65, specificity 0.84), suggesting a cross-regional common microbiome profile associated with PSC. Gene set enrichment analyses of the predicted metagenomes of patients with PSC were performed independently in the Norwegian and German patients. In both cohorts, we found overexpression of proinflammatory bacterial pathways and pathways of bacterial invasion of epithelial cells.
Conclusion: The faecal microbiome of patients with PSC has a distinct signature common across different geographic areas, underlining the potential pathogenetic relevance of the identified bacterial genera. The metagenomic profile might be skewed towards bacteria-driven intestinal inflammation and gut barrier disruption. Potential causal relationships between PSC and gut microbiota dysbiosis should be further explored by longitudinal analyses.

FRI-201
The faecal microbiome of patients with autoimmune hepatitis is characterised by reduced diversity and is different from healthy subjects and patients with ulcerative colitis
T. Liwinski[1], C. Casar[1], M.-C. Rühlemann[2], C. Bang[2], F.-A. Heinsen[2], R. Zenouzi[1], D. Gerald[3], W. Lieb[4], A. Lohse[1], A. Franke[2], C. Schramm[1]. *[1]University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; [2]Christian-Albrechts-University of Kiel, Institute of Clinical Molecular Biology, Kiel, Germany; [3]LMU Munich University Hospital, Department of Medicine II, Munich; [4]Christian-Albrechts-University of Kiel, Institute of Epidemiology and Biobank Popgen, Kiel, Germany*
Email: t.liwinski@uke.de

Background and Aims: The intestinal microbiome might affect liver inflammation and hepatic immune regulation via the gut-liver axis. In autoimmune hepatitis (AIH), a disease of unknown aetiology, the intestinal microbiota has not been characterised in detail.
Method: Stool samples were collected from 75 adult patients (58 women and 17 men, median age 62 years) with biopsy-proven diagnosis of AIH, 88 patients with ulcerative colitis (UC) and 95 healthy control (HC) subjects. Seven patients with AIH were excluded because of recent antibiotic use. The microbiomes were analysed by sequencing of the 16S ribosomal RNA gene targeting the V1-V2 region, taxonomic and phylogenetically informed ecological statistics, predictive modelling with random forests, receiver operating characteristic (ROC) analysis and predicted metagenome profiling. All analyses were adjusted for relevant demographic and clinical data and controlled for the false discovery-rate.
Results: The mean intra-individual (alpha) diversity of the stool microbiota in patients with AIH was significantly decreased compared to HC (Faith's phylogenetic diversity (PD), $p = 0.006$), but significantly higher than in patients with UC (PD, $p = 0.001$). The overall microbiota composition (beta diversity) was different in patients with AIH compared to both HC ($p < 0.001$) and UC ($p < 0.001$) as measured by the weighted unique fraction (UniFrac) metric. Biochemical remission was associated with a different microbiome structure in AIH ($p = 0.002$). Several differentially abundant genera were identified comparing AIH to HC (e.g. *Erysipelotrichaceae*, *Lachnospiraceae* and *Streprococcus*) and comparing AIH to UC (e.g. *Lachnospiraceae*, *Clostridia Family XIII* and *Blautia*). The identified

microbial signature was used for predictive modelling of the diagnosis class on patient samples that were randomly split from the whole cohort. In the respective validation cohorts, the classifiers were able to distinguish between AIH or HC (area under the curve (AUC) 0.82, accuracy 0.83, sensitivity 0.75, specificity 0.89) and AIH or UC (AUC 0.89, accuracy 0.8, sensitivity 0.8, specificity 0.81). The predicted metagenome profile showed different expression patterns in several microbial pathways including enrichment of lipopolysaccharide (LPS) synthesis in AIH patients.
Conclusion: The stool microbiome of patients with AIH is characterised by reduced diversity and is different from both healthy subjects and patients with UC. Biochemical remission was associated with changes in faecal microbiota abundance. The predicted metagenome profile hints at an increased exposure of patients with AIH to gut-microbiome derived LPS, which should be confirmed by metagenomic sequencing.

FRI-202
Different bile acids display distinct ability to trigger Nlrp3 inflammasome activation in a cell-dependent manner contributing to cholestatic liver injury and fibrosis
M. Inzaugarat[1], T.M. Holtmann[1], M. Frissen[1], L.J Geisler[1], J. Reissing[1], K. Markus Schneider[1], Z.H. Wolfgang[1], V. Bieghs[1], C. Trautwein[1], A. Wree[1,2]. *[1]RWTH University Hospital Aachen, Department of Internal Medicine III, Aachen, Germany; [2]University of California San Diego, Department of Pediatrics, La Jolla, United States*
Email: minzaugarat@ukaachen.de

Background and Aims: Bile acids are a major component of bile and crucial for the development of liver injury, although the exact mechanisms remained unknown. Thus, our aim was to test the hypothesis that toxic bile acids trigger inflammasome activation, contributing to cholestatic liver fibrosis progression.
Method: Primary hepatocytes, Kupffer Cells (KC) and hepatic stellate cells (HSC) isolated from C57BL/6 WT and Nlrp3 knockout (Nlrp3-/-) mice were stimulated with cholic acid (CA), deoxycholic acid (DA) or lithocholic acid (LCA) for 3 h followed by nigericin or ATP. Additionally, WT and Nlrp3-/- mice were fed with diet supplemented with 0,5% CA, DA or LCA for 7 days. Activation of the NLRP3 inflammasome and inflammatory or fibrotic changes were assessed via histologic quantification, inmunofluorescence, ELISA, gene expression and flow cytometry analysis.
Results: WT HSC displayed increased Nlrp3 and IL1β mRNA levels mature IL1α and Caspase1 activity after treatment with DA or DA + ATP. This Nlrp3 activation was accompanied by an upregulation of connective tissue growth factor (CTGF) and TGF-β mRNA levels, collagen1 and vimentin protein expression after DA or DA + ATP stimulation. On the other hand, LCA or LCA + nigericin treatment increased Nlrp3 and IL1α mRNA levels and mature IL1α by inducing ROS production but not cathepsin B activity in WT KC. Moreover, pyroptosis but not necrosis, mRNA levels of TNF, iNOS, CCR8, Activin A and CCL22, as well as galectin 3 protein expression were found increased in WT KC after LCA or LCA + nigericin treatment. Interestingly, Nlrp3-/- HSC or KC failed to upregulate IL1α expression as well as fibrotic or inflammatory markers after DA or LCA treatment. In contrast, bile acids did not show an effect on Nlrp3 expression or ALT and AST levels in WT hepatocytes. LCA-fed WT mice showed increased ALT, AST, and GLDH serum levels and presence of inflammation; while DA-fed mice displayed augmented ALT, AST, and GLDH serum levels, and signs of fibrosis. Nlrp3-/- mice fed with LCA or DA diet showed an improvement in AST serum levels as well as ameliorated inflammation and fibrosis. WT or Nlrp3-/- mice fed with CA supplemented diet did not show any change in the liver.
Conclusion: Toxic bile acids are able to trigger Nlrp3 inflammasome expression and activation in a cell-specific manner, inducing upregulation of inflammatory and fibrotic markers.

FRI-203
Decreased ratio of Tregs to Th17 cells exacerbates disease progression of autoimmune hepatitis
Y. Liu, W. Yan, W. Yuan, P. Wang, D. Huang, Q. Ning. *Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology*
Email: qning@vip.sina.com

Background and Aims: $CD4^+$ $CD25^+$ $Foxp3^+$ regulatory T cells (Tregs) functions to restrain excessive effector T cell responses, IL-17-producing Th cells (Th17) is a key player in the pathogenesis of autoimmune disorder. In this study, we aimed to explore the role of Treg/Th17 balance in a murine model of autoimmune hepatitis (AIH) induced by human cytochrome P4502D6 (CYP2D6) and patients with AIH.
Method: The AIH murine model was established by delivering adenovirus vector containing CYP2D6 (Ad-2D6) into the liver of C57BL/6 mice intravenously and intraperitoneally. Treg/Th17 balance in the liver of Ad-2D6 mice including their frequencies and production of functional cytokines were evaluated by multi-colour flow cytometric assay and Enzyme-linked immunosorbent assay (ELISA) respectively. An immunotherapy strategy was performed on Ad-2D6 mice by adoptively transferring with $CD4^+CD25^+$ T cells isolated from healthy mice using MACS microbeads at week 3 and week 4 post infection. The peripheral Treg/Th17 balance was also detected in 18 AIH patients.
Results: Compared with control group, Ad-2D6 mice exhibited progressive liver damage including inflammatory cell infiltration and piecemeal necrosis in the portal area and central vein from 2–4 weeks post infection. A significantly higher serum titers of IgG (week 2 and week 4, $P < 0.05$) and detectable autoantibody against CYP2D6 were observed. Interestingly, Ad-2D6 mice showed a significant and sustained decrease in proportion of hepatic Tregs and ratio of Treg/Th17 (week 4 and week 6, $P < 0.05$), and an obvious increase in hepatic IL-17 and IL-22 expression (week 4, $P < 0.05$). Adoptive transfer with $CD4^+CD25^+$ T cells resulted in improved hepatic pathological feature, decreased IgG and autoantibody titers, which might be attributed to the significantly increased Treg/Th17 ratio ($P < 0.05$) and decreased levels of hepatic IL-17 ($P < 0.05$) and IL-22. AIH patients with Child-Pugh class B or C showed significant lower treg proportions ($P < 0.05$) and relative lower ratio of Treg/Th17 than those of patients with Child-Pugh class A.
Conclusion: The decreased ratio of Treg/Th17 was involved in the immunopathogenesis of AIH. Adoptive immunotherapy with $CD4^+CD25^+$T cells could be in favor of correcting Treg/Th17 imbalance and preventing poor prognosis of AIH.

FRI-204
A novel CCL24 blocking monoclonal antibody ameliorates liver injury in experimental models of cholestasis
M. Segal[1], A. Katav[2], S. Hashmueli[3], A. Aharon[1], M. Pinzani[4], J. George[5], A. Hall[4], A. Mor[1]. *[1]Chemomab, Chemomab, Tel Aviv, Israel; [2]Chemomab, Chemomab, Israel; [3]Chemomab, Chemomab, TelAviv, Israel; [4]University College London, University College London, London, United Kingdom; [5]Kaplan medical center, Kaplan medical center, Israel*
Email: adimor@chemomab.com

Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by progressive destruction of bile ducts caused by diffuse inflammation and fibrosis. Chemokines are proteins that share the ability to induce migration and activation of specific subsets of cells and play a critical role in inducing liver inflammation and fibrosis. CCL24, a pro inflammatory and profibrotic chemokine, was recently found to be involved in the progression of inflammatory and fibrotic pathways and tested for its involvement in PSC.
In this study we tested the expression levels of CCL24 and its cognate receptor-CCR3 in liver tissues from PSC patients and explored the effect of CM101, a novel CCL24 blocking monoclonal antibody, on

biliary inflammation and fibrosis progression in two experimental animal models of cholestasis recapitulating features of PSC.
Method: Immunofluorescence was performed to detect CCL24 and CCR3 expression in liver biopsies from PSC patients. The antifibrotic and anti-inflammatory effects of CM101 were evaluated in two animal models: bile duct ligation (BDL) in rats and acute α-naphthylisothiocyanate (ANIT) induced cholestasis in mice. For the BDL model, Sprague Dawley rats underwent bile duct ligation and treated with CM101 at 10mg/kg IV twice weekly for two weeks. ANIT induced cholestasis model was evaluated in mice treated with 60 mg/kg ANIT with or without a single IV dose of 10mg/kg CM101 and scarified on day 3.
Results: Liver samples from PSC patients exhibited a significant overexpression of CCL24 in immune cells and hepatocytes; CCL24's receptor, CCR3, was significantly overexpressed in hepatocytes.
Blockade of CCL24, using CM101, showed significant reduction of liver damage employing the two experimental cholestasis models. In the BDL model 10mg/kg CM101 resulted in 50% reduction in the fibrosis area compared with the control treated group, $p < 0.05$. Additionally, ALT levels were reduced significantly in the CM101 treated group compared to vehicle (154.9 ± 13.8, compare to 119.7 ± 9.5), $P \leq 0.05$. In the ANIT induced cholestasis model, we found that liver enzymes including ALK phosphatase, Bilirubin, AST and ALT were significantly reduced in the CM101 treated mice group as compared to control mice. $P \leq 0.05$, $P \leq 0.01$. Biliary necrosis, biliary neutrophilic infiltration, fibroblast proliferation and Hepatic necrosis were scored using a 1–3 score according to histological findings. CM101 treated animals exhibited significantly reduced scores (4.5 ± 1, n = 8) as compared with vehicle treated group (5.8 ± 0.8, n = 8) in ANIT induced cholestasis model $P \leq 0.05$.
Conclusion: The CCL24-CCR3 is significantly over expressed in patients with PSC. Ablation of CCL24 with the novel monoclonal antibody CM101 resulted in attenuation of experimental cholestasis. Thus, CCL24 appears as an attractive new target for treatment in patients with PSC.

FRI-205
Generation of a novel mouse model for the study of autoimmune liver disease overlap syndrome
S. Fuchs[1], M. Bayer[1], M.P. Manns[2], E. Hintermann[1], U. Christen[1].
[1]Goethe University Hospital Frankfurt, Pharmazentrum Frankfurt, Frankfurt am Main, Germany; [2]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany
Email: christen@med.uni-frankfurt.de

Background and Aims: Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) have in common that an aggressive autoimmune reaction results in liver tissue destruction and development of severe hepatic fibrosis. Patients are classified as having an overlap syndrome (OS) if they display overlapping features within the spectrum of these autoimmune liver diseases (ALD). AIH-PSC OS is characterized by an interface hepatitis with or without plasmacytosis, portal edema or fibrosis, ductopenia, ductal distortion and proliferation, cholate stasis or obliterative fibrous cholangitis. Further the criteria include elevated levels of AST/ALT, γ-globulin, IgG, AP, GGT as well as the absence of AMA. The aim of our study was to generate a mouse model that reflects human AIH-PSC OS and allows for an investigation of the pathogenesis.
Method: We combined two well-established mouse models: First, the CYP2D6 mouse model for AIH, in which wildtype mice are infected with an Adenovirus encoding the human autoantigen cytochrome P450 2D6 (Ad-2D6). Second, the mdr2 KO mouse which develop PSC-like disease spontaneously. Thus, mdr2 KO mice were infected with Ad-2D6 and the obtained data compared to those from mice with solitary AIH or PSC.
Results: Ad-2D6-infection of mdr2 KO mice at week 7 of age resulted in several clinical AIH-PSC OS features.
Serology: ALT and AP levels were strongest in the AIH-PSC OS model group. The kinetic pattern of ALT seems to follow the one found for solitary AIH. Similarly, the kinetic pattern for AP followed the one from the solitary PSC group, indicating that one ALD is exacerbating the serological markers of the other disease.
Histology: Cholangitis, fibrosis, and cellular infiltration was significantly exacerbated in the AIH-PSC OS group as detected and quantified for selected markers, such as CK19 (cholangiocytes), desmin (HSC), collagen III (fibrosis), CD4 T cells, B cells, CD11b+ and CD11c+ cells. Enhanced expansion of cholangiocytes was accompanied by a high number of HSC in the fibrotic periductal region.
Specific immune response: No significant increase in anti-CYP2D6 antibody titer has been observed in the AIH-PSC OS group. In contrast, we found a higher activity of pANCA-like antibodies in the AIH-PSC OS group compared to mice with solitary PSC. However, the frequency of CYP2D6-specific T cells was enhanced in the AIH-PSC OS group.
Conclusion: Our data suggest that infection of mdr2 KO mice with Ad-2D6 indeed results in a model system that reflects many aspects of an AIH-PSC OS as found in patients including elevated serologic liver damage makers, enhanced cholangitis and fibrosis, exacerbated interface hepatitis-like cellular infiltration of the liver, higher levels of pANCA-like antibody reactivity and enhanced CYP2D6-specific T cell immune response.

FRI-206
Anticholestatic mechanisms of ursodeoxycholic acid in inflammatory cholestasis induced by lipopolysacharide
M.V. Razori[1], P.M. Maidagan[1], E.S.S. Silva[2], N. Ciriaci[1], I. Barosso[1], M.L. Ruiz[1], M.G. Roma[1]. *[1]Institute of Experimental Physiology (CONICET-UNR), Faculty of Biochemical & Pharmaceutical Sciences, Rosario; [2]Health Science Department, DCBS, Universidad Autónoma Metropolitana (UAM), D.F., Mexico*
Email: roma@ifise-conicet.gov.ar

Background and Aims: Sepsis-induced cholestatic is causally associated with the release of lipoplysacaride (LPS) from Gram (-) bacteria; LPS stimulates the production of inflammatory cytokines, and the further impairment in expression/localization of transporters involved in bile formation, such as Bsep (bile salt transporter) and Mrp2 (bilirubin/GSH transporter). There is no established therapy for sepsis-induced cholestasis. Ursodeoxycholic acid (UDCA) is the most widely used therapeutic agent for human cholestatic diseases, but its action mechanisms in inflammatory cholestasis are largely unknown. Therefore, we addressed this issue in the rat model of LPS-induced cholestasis.
Method: Male Wistar rats were randomized in 4 experimental groups: Control, UDCA (25 mg/Kg/day, i.p., 5 days), LPS (10 mg/Kg, i.p., over the last 2 days), and UDCA + LPS. On the 6th day, we assessed serum alkaline phosphatase (ALP, a membrane enzyme induced/removed by bile salts accumulated in cholestasis), bile salt output (BSO), total glutathione output (GSHtO), Bsep expression by real-time RT-PCR and Western blotting, and Bsep localization by immunofluorescence staining followed by confocal microscopy, image analysis, and statistical comparison of the densitometric profiles along a line perpendicular to the canaliculus by Mann-Whitney test. Circulating levels of the inflammatory cytokines TNF-α and IL-6 were measured by ELISA.
Results: (expressed as % of control; $^{*}p < 0.05$ *vs.* control; $^{\#}p < 0.05$ *vs.* LPS). Administration of UDCA to LPS-treated rats reduced serum ALP (199 ± 16$^{*\#}$ *vs.* 280 ± 16%*), and increased BSO (85 ± 20%$^{*\#}$ *vs.* 58 ± 10%*), but not GSHtO. This was associated with an improvement in the proportion of Bsep in the apical membrane, assessed by western blot (85 ± 20% *vs.* 66 ± 9*). Improved membrane localization was confirmed by comparing Bsep densitometric profiles in confocal images (see figure); LPS decreased the fluorescence intensity in the canalicular area, associated with an increase in the pericanalicular region ($p < 0.001$ *vs.* control), and this was counteracted by UDCA.

UDCA also normalized Bsep mRNA levels ($119 \pm 40^{\#}$ *vs.* $15 \pm 3^{*}$), without attenuating LPS-induced serum TNF-α and IL-6 elevations.

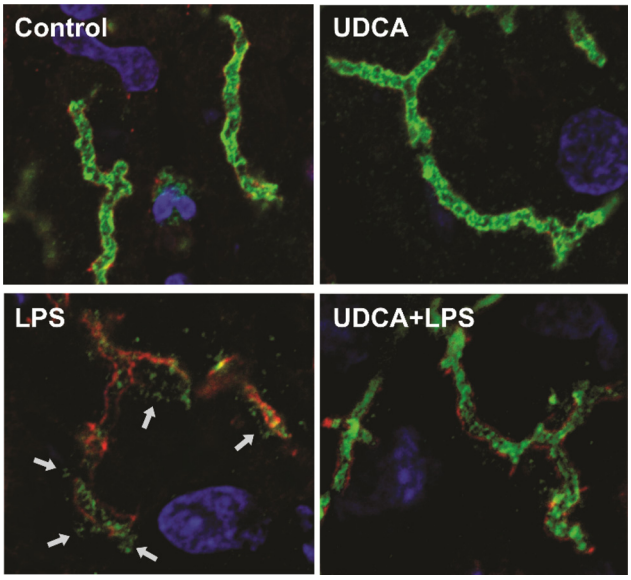


Figure 1: Co-immunostaining of Bsep (green), occludin (red, a canalicular limit marker). LPS relocalized Bsep from the canalicular to the pericanalicular area (arrows), and this effect was prevented by UDCA.

Conclusion: UDCA improves bile salt biliary excretion by mechanisms unrelated to immunosuppressive effects. Its beneficial effects rather involve improvement in gene expression and canalicular membrane localization of Bsep. These effects are likely due to the well-recognized properties of UDCA as a nuclear-receptor ligand and as a stimulator of Bsep canalicular trafficking from its synthesis place, respectively, thus affording proper localization to the newly synthesized transporters.

FRI-207

Fine tuning of SIRT1 expression is essential to protect the liver from cholestasis

B. Blokker[1], M. Maijo[1], M. Philo[1], V. Gutierrez[2], E. Halilbasic[3], C. Fuchs[3], G. Legall[1], M. Milkiewicz[4], P. Milkiewicz[5], Jesús Banales[6], S. Rushbrook[7], José Matos[2], M. Trauner[3], M. Muller[8], MaríaL. Martínez-Chantar[9], M. Varela-Rey[2], N. Beraza[10]. [1]*Quadram Institute, United Kingdom;* [2]*cicbiogune, Spain;* [3]*Medical University Wien, Vienna, Austria;* [4]*Pomeranian Medical University in Szczecin, Szczecin, Poland;* [5]*Medical University of Warsaw, Liver and Internal Medicine Unit, Warsaw, Poland;* [6]*Biodonostia, San Sebastian, Spain;* [7]*Norwich and Norfolk University Hospital, Norwich, United Kingdom;* [8]*University of East Anglia, Norwich, United Kingdom;* [9]*cicbiogune, Derio, Spain;* [10]*Quadram Institute, Norwich, United Kingdom*
Email: naiara.beraza@quadram.ac.uk

Background and Aims: Human cholestasis comprises etiologically heterogeneous conditions characterized by the accumulation of bile acids in the liver that actively contribute to liver injury. We previously described that Sirtuin 1 (SIRT1), a histone deacetylase, controls bile acid (BA) metabolism via the regulation of farnesoid X receptor (FXR). We found that the overexpression of SIRT1 impaired liver regeneration that was associated with the inhibition of FXR and increased BA synthesis. Notably, we found that Nor-Ursodeoxycholic acid (NorUDCA) reduces SIRT1 expression in the liver, overall alleviating the damaging phenotype found in SIRT1 overexpressing mice ($SIRT^{oe}$) after PH. We aim to investigate the implication of SIRT1 during cholestatic liver disease.
Method: SIRT1 expression was determined in livers from patients with cholestatic disease (PSC and PBC), in mice following bile duct ligation (BDL) and in primary hepatocytes in response to bile acid (BA) load. The BDL experimental model was applied to SIRT1 overexpressing mice ($SIRT^{oe}$) to determine the biological relevance of SIRT1 during cholestasis. Additionally, a group of $SIRT^{oe}$ mice were treated with NorUDCA and subjected to BDL.
Results: SIRT1 gene and protein expression were up-regulated in livers from PBC and PSC patients, suggesting the regulation of SIRT1 as a general mechanism occurring during cholestasis regardless of the aetiology. Further studies in mice after BDL and in mouse primary hepatocytes confirmed the up-regulation of SIRT1 in response to BA. To gain understanding on the biological relevance of SIRT1 up-regulation during cholestasis, $SIRT^{oe}$ mice were subjected to BDL and showed aggravated parenchymal injury and increased fibrogenesis when compared to WT/BDL animals. SIRT1 overexpression correlated with lower FXR expression and increased BA synthesis. Increased accumulation of toxic BA in the liver was further associated with higher apoptotic cell death and lower NF-κB activation in hepatocytes from $SIRT^{oe}$ mice compared to WTs, both *in vivo* and *in vitro*. Finally, reduced liver parenchymal damage found in $SIRT^{oe}$/NorUDCA/BDL mice was associated with attenuated SIRT1 expression and restored FXR and NF-κB signalling.
Conclusion: SIRT1 expression is increased during human and murine cholestasis and has a detrimental role in mediating cholestasis-induced liver injury. Attenuation of SIRT1 represents a potential mechanism of action for NorUDCA in attenuating liver injury during cholestasis.

FRI-208

Leukemia inhibitory factor induces cholangiocyte proliferation and corrects the impaired bile duct proliferation in sortilin-deficient mice following cholestatic injury

I. Zvibel[1], E. Hubel[1], R. Avraham[1], E. Lavoie[2], S. Fishman[1], J. Dranoff[2], O. Shibolet[1]. [1]*Ichilov Hospital, Tel Aviv-Yafo, Israel;* [2]*University of Arkansas at Little Rock, Little Rock, United States*
Email: isab@tlvmc.gov.il

Background/Aims: Sortilin, a member of the Vps10 domain receptor family, acts both as a trafficking molecule and as a co-receptor. In its role as co-receptor, sortilin enhances the leukemia inhibitory factor (LIF) receptor/gp130 signal, which may regulate cholangiocyte proliferation, induction of reactive cholangiocytes and bile duct morphogenesis. We have investigated the role of played by sortilin in the induction of reactive cholangiocytes and in bile duct morphogenesis in cholestatic liver injury, and whether it is mediated via LIF signaling.
Methods: Cholestatic liver injury was induced by bile duct ligation (BDL) in WT and *Sortilin1*$^{-/-}$ (*Sort1*$^{-/-}$) mice. LIF (1μg/mouse) was administered daily to WT and *Sort1*$^{-/-}$ mice for 3 and 14 days following BDL. Cholangiocyte proliferation was assessed by Ki67 immunohistochemistry (IHC) and bile duct morphogenesis by IHC for cytokeratin 19 (CK19). Reactive cholangiocytes were characterized by immunofluorescence and immunobloting for integrin β6, connective tissue growth factor and osteopontin.
Results: *Sort1*$^{-/-}$ mice displayed strikingly diminished ductular reaction, demonstrated by reduced cholangiocyte proliferation and attenuated formation of reactive cholangiocytes 3 days after BDL. Notably, 14d after BDL, while WT and *Sort1*$^{-/-}$ had similar numbers of CK19-positive cholangiocytes, *Sort1*$^{-/-}$ mice had significantly less CK19-positive cholangiocytes forming ducts, indicating impaired bile duct morphogenesis. The impaired bile duct morphogenesis was accompanied by attenuated expression of morphogenesis transcription factor Hes1, a target of Notch2-Jagged1 signaling. LIF administration for 3 days to bile duct-ligated WT or *Sort1*$^{-/-}$ mice increased cholangiocyte proliferation, but did not induce expression of reactive cholangiocyte markers. LIF administration for 14 days to bile duct ligated *Sort1*$^{-/-}$ corrected the impaired bile duct morphogenesis, accompanied by increased expression of Hes1.

Conclusion: Sortilin mediates the ductular reaction and ductular morphogenesis in the setting of cholestatic injury at least in part by regulation of LIF signaling.

FRI-209

Relapse of autoimmune hepatitis is associated with a low intrahepatic ratio of regulatory T cells to cytotoxic T cells prior to immunosuppression withdrawal

F. Derben[1], J. Hartl[2], J. Schlue[3], A. Lohse[2], M.P. Manns[4], C. Schramm[2], E. Jaeckel[1], R. Taubert[1]. *[1]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [2]University Medical Centre Hamburg-Eppendorf (UKE), 1st Department of Medicine, Hamburg, Germany; [3]Hannover Medical School, Institute for Pathology, Hannover, Germany; [4]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany*
Email: Finn.C.Derben@stud.mh-hannover.de

Background and Aims: The majority of autoimmune hepatitis (AIH) patients reach biochemical remission (BR) under steroid and azathioprine based therapies. After at least 2 years of BR an immunosuppression withdrawal can be attempted, although a relapse is common. Intrahepatic regulatory T cells (Tregs) decline overproportionally under immunosuppressive therapy and more intrahepatic Tregs are associated with the achievement of BR. In the current study the intrahepatic T cells compartment in pre-weaning biopsies should be assessed with regard to the success of the subsequent immunosuppression withdrawal.
Method: Intrahepatic $CD4^+$ and $CD8^+$ T cells as well as $CD4^+FOXP3^+$Tregs were quantified with immunofluorescence co-staining of CD4, CD8 and FOXP3 in liver biopsies taken from 24 AIH patients at two centers before immunosuppression withdrawal.
Results: All patients had stable BR before pre-weaning liver biopsies were taken. All biopsies exhibited a histological remission (hepatitis activity index (HAI) ≤ 3). AIH relapsed in 12/24 (50%) patients after in median 7 (range: 1–66) months after initiation of weaning. Patients with sustained remission (SR) were followed in median 20 (3–54) months after initiation of weaning.
From all histological parameters of intrahepatic T cell infiltration (portal infiltration densities and portal cell ratios of $CD4^+$, $CD8^+$, and $CD4^+FOXP3^+$ cells; size of portal infiltrates) only the ratio of $CD4^+FOXP3^+$ Tregs to $CD8^+$ cells was significantly higher (SR: 0.15 ± 0.07; relapse (R): 0.10 ± 0.04; p = 0.045) in pre-weaning liver biopsies with subsequent SR. Furthermore, SR was associated with a lower HAI in pre-weaning biopsies (SR: 0.7 ± 0.5; R: 1.6 ± 1.1; p = 0.039). However, T cell infiltration parameters were not significantly associated with the HAI in the pre-weaning biopsy. Time until AIH relapsed was not reliably associated with any T cell infiltration parameters also.
Liver biopsies from the time of AIH diagnosis were only available from 2 patients with relapse and 8 patients with SR. Thus, no reasonable analysis of the initial T cell infiltration was possible, yet.
Conclusion: The local balance of Tregs and cytotoxic T cells in the liver itself seems to be related to the degree of sustained AIH remission. An increased Treg/CD8 ratio in the liver is also associated with liver graft protection in T cell-mediated rejection and with a worse prognosis in hepatocellular carcinoma.

FRI-210

Experimental autoimmune hepatitis in mice is associated with formation of ectopic lymphoid tissue in the liver

M. Preti, A.-L. Mueller, D. Krzikalla, D. Schwinge, A. Lohse, C. Schramm, A. Carambia, J. Herkel. *Uniersitätsklinikum Hamburg Eppendorf, I. Department of Medicine, Hamburg, Germany*
Email: max_preti@yahoo.it

Background and Aims: We have previously described a new autoimmune hepatitis model in mice, which express an MHC class II-restricted immunodominant T cell epitope of the Lymphocytic Choriomeningitis Virus glycoprotein (GP_{61-80}) specifically in hepatocytes, and which are also transgenic for a T cell receptor recognizing the GP_{61-80} peptide (EASL Abstract in: Journal of Hepatology 2017; Vol.66, Issue 1, S74). Using this model, we here investigated the formation of ectopic lymphoid tissue (ELT) in the pathogenesis of autoimmune hepatitis. ELT are inducible centres for generating antigen-specific immune responses, formed in non-lymphoid organs mainly by T and B cell aggregates together with follicular dendritic cells.
Method: ELT formation was characterized by histological analysis of HE-stained paraffin-embedded liver sections taken at various disease stages. ELT encapsulation was confirmed by Sirius red staining. Immune cell aggregates within ELT were characterized by staining of CD4+ T cells, B220+ B cells or follicular dendritic cells.
Results: Already at an age of 4 weeks, almost all mice showed ELT formation exclusively in the liver. At that age, these mice displayed only mild periportal infiltrates and no overt hepatitis. ELTs were encapsulated and showed a high degree of organisation, with T and B cell zones, interspersed with Foxp3+ regulatory T cells and dendritic cells. At an advanced disease stage, at 20–30 weeks of age, these mice spontaneously developed autoimmune liver disease resembling human autoimmune hepatitis, marked by periportal lymphocytic infiltrates, interface hepatitis, elevated serum ALT, and antinuclear autoantibodies, resulting in over 50% mortality by the age of 30 weeks. At that disease stage with overt hepatitis, hepatic ELTs had vanished and the characteristic cell aggregates of T cells, B cells and dendritic cells were dispersed and had merged into the large hepatic infiltrates.
Conclusion: Hepatic ELT formation occurs early in the pathogenesis of autoimmune liver disease. However, the pathogenic drive exerted by hepatic ELTs may be concealed in advanced disease stages, as ELTs merge into the inflammatory liver infiltrates, suggesting that the pathogenic relevance of ELTs for autoimmune liver diseases might have been underestimated.

FRI-211

Cell therapy for acute liver injury- *in vivo* efficacy of mesenchymal stromal cells in toxic and immune-mediated murine hepatitis

M. Alfaifi[1], V. Vigneswara[1], N.-T. Luu[1], C. Baan[3], M. Hoogduijn[3], M. Gargesha[2], D. Roy[2], S. Elliman[4], L. O'flynn[4], G.M. Hirschfield[1], P.N. Newsome[1]. *[1]National Institute for Health Research (NIHR) Birmingham Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, United Kingdom, [2]BioInVision, Cleveland, United States, [3] Erasmus Medical Centre, University of Rotterdam, Rotterdam, Netherlands, [4]Orbsen Therapeutics, Galway, Ireland.*
Email: p.n.newsome@bham.ac.uk

Background and Aims: The ability of umbilical cord-derived mesenchymal stromal cells (MSC) to immunomodulate offers therapeutic potential in liver injury but the inherent heterogeneity of unsorted MSC populations may explain varied/reduced function as well as posing regulatory challenges. Thus, we aimed to evaluate the therapeutic potential and the mechanism of action of purified CD362+ MSC infusion in murine models of acute liver injury.
Method: Umbilical cord (UC) derived MSC were injected intravenously into 8–10 week old male C57Bl/6 injured by single dose of Carbon tetrachloride (CCl4) & Ova-Bil mice (allo-immune liver injury induced by infusion of OT1 and OT2 cells). MSC used were either unsorted or sorted CD362+. The extent of liver damage was determined by liver histology, serum analysis, gene expression and FACS analysis 3 or 5 days after cell infusion. Homing and biodistribution of stem cells was determined by whole mouse cryo-imaging of Q-dot labelled MSC following infusion of UC-MSC into injured mice.
Results: $CD362^+$ MSC were as effective as unsorted MSC in ameliorating liver injury, with reductions in serum ALT seen in both models: CCl_4 - ALT 138 IU vs 50 IU in control (Con) group. Ova-Bil

mice - ALT 345 IU vs 102 IU in Con group. In contrast heat-inactivated MSC had no effect on liver injury. MSC also led to a reduction in CD45+ staining on liver sections in both models of liver injury corroborated by an accompanying reduction in hepatic CD45+ cells in (FACS analysis of liver digest). In addition there was a significant reduction in hepatic CD19+ B cells (75005 cells/g tissue vs 143801/g tissue) in digested liver in CCl_4 injury. Cryo-imaging of three or five days' time-course in both animal models indicated that MSC had migrated to the lung within 1 hour and were then cleared rapidly, although there was a liver-specific increase in MSC 2–3 day in Ova-Bil mice.

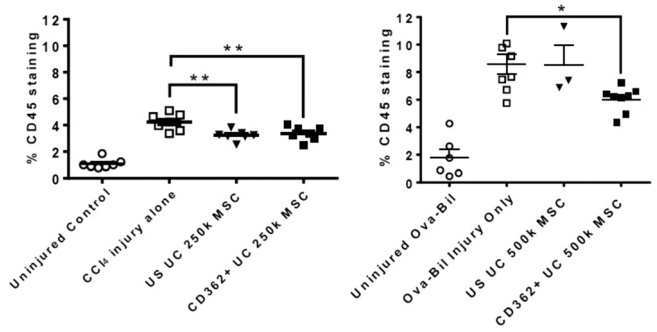


Figure 1: Hepatic CD45 staining following MSC administration

Conclusion: CD362^{+} human MSC exert potent anti-inflammatory activity in toxic and immune-mediated murine liver injury with demonstrable reductions in infiltrating inflammatory leucocytes and B cells.

FRI-212

Cu isotope ratio shifts in common bile duct ligated mice and correlates with the degree of cholestatic-induced liver disease

S.V. Campenhout[1], M. Costas-Rodríguez[2], A.A.M.B. Hastuti[2], S. Raevens[1], A. Geerts[1], X. Verhelst[1], F. Vanhaecke[2], H.V. Vlierberghe[2], L. Devisscher[1]. *[1]Ghent University, Gastroenterology and Hepatology, Ghent, Belgium; [2]Ghent University, Chemistry, Ghent, Belgium*
Email: Sanne.VanCampenhout@UGent.be

Background and Aims: Chronic liver disease covers a range of hepatic disorders which have resulted in liver cirrhosis. Identifying mechanisms which drive disease progression and non-invasive markers that can identify patients at risk are important challenges. We have previously shown that the serum Cu isotope ratio shifts in female cirrhotic patients in favour of the lighter isotope ^{63}Cu compared to ^{65}Cu, and that the magnitude of this shift correlates with disease severity. To date, it is unclear which mechanisms are at the basis of this shift. Here, we used the common bile duct ligation (CBDL) model to investigate the different stages of cholestatic-induced liver disease and its correlation to Cu isotope ratios.
Method: Eight-week-old SV129 mice underwent a CBDL or sham surgery and were analysed 2, 4, 6 and 8 weeks post surgery. Liver disease was determined by serum bilirubin levels, Metavir fibrosis score and hepatic pro-inflammatory cytokine and chemokine levels. Multi-collector inductively coupled plasma-mass spectrometry was applied to determine Cu isotope ratios in serum and tissues. Duodenal explants from CBDL and sham operated mice were used to evaluate the contribution of two metal receptors CTR1 and DMT1 to Cu isotope uptake specificity.
Results: CBDL operated mice gradually developed cholestasis as demonstrated by higher total and direct bilirubin levels 2, 4, 6 and 8 weeks post surgery ($p < 0.05$). This was associated with increased absolute and relative liver and spleen weights ($p < 0.0001$) and a decrease in body weight ($p < 0.001$). Hepatic inflammatory chemokines CXCl1 and CCl2 were increased in CBDL mice compared to sham operated mice, independent of gender or time post surgery ($p < 0.0001$). Mice developed F2 and F3 fibrosis after 6 and 8 weeks of CBDL, respectively. Determination of Cu isotope ratios in different organs and serum revealed an overall shift in favour of the lighter isotope ^{63}Cu (ranged from -0.2 to -1.4 per mille) which correlated with the levels of bilirubin, inflammatory chemokines and fibrosis ($p<0.003$). Duodenal explants from CBDL mice incubated with Fe, Zn and Cu showed a lower ^{65}Cu/^{63}Cu isotope ratio compared to tissue from sham mice whereas this was not observed when DMT1 inhibitor was co-administered.
Conclusion: Cholestasis is associated with a Cu isotope ratio shift in favour of the lighter isotopes in mouse serum and tissue and this might be mediated by a changed preference of DMT1 for Cu isotope uptake in the duodenum.

FRI-213

Sarcopenia induction in a mouse model of chronic cholestatic liver disease: Role of the ubiquitin-proteasome system and oxidative stress

C. Cabello-Verrugio[1], F. Campos[1], J. Abrigo[1], F. Aguirre[1], B. Garces[1], M. Arrese[2], D. Cabrera[3], F. Simon[1]. *[1]Facultad de Ciencias Biológicas & Facultad de Medicina, Universidad Andres Bello, Departamento de Ciencias Biológicas, Santiago, Chile; [2]Facultad de Medicina, Pontificia Universidad Católica de Chile., Departamento de Gastroenterologia, Santiago, Chile; [3]Facultad de Salud, Universidad Bernardo O Higgins., Departamento de Ciencias Químicas y Biológicas, Santiago, Chile*
Email: claudio.cabello.verrugio@gmail.com

Background and Aims: Sarcopenia is defined as decreased muscle mass and strength and has been associated with the progression of chronic liver diseases (CLD). However, the physio pathological mechanisms behind this association remain ill-defined. The most common mechanisms of muscle weakness induction are decreased fiber diameter and myosin heavy chain (MHC) levels and increased activity of ubiquitin-proteasome system (UPS) and reactive oxygen species (ROS). In this study, we aim to characterize the development of sarcopenia secondary to CLD induced by the hepatotoxin 5-diethoxycarbonyl-1,4-dihydrocollidine (DDC), a model of Sclerosing Cholangitis and Biliary Fibrosis.
Method: Six four-months-old male mice (C57BL6) were fed a normal diet or DDC supplemented diet for 6 weeks. Functional tests to evaluate muscle strength, mobility, and motor skills were performed while the mice were alive. The muscle strength in isolated gastrocnemius was also assayed via electrophysiological measurements. Morphometric measures of fibers' diameter and types were determined through immunofluorescence. Total and ubiquitinated protein levels of myosin heavy chain (MHC) and E3 ubiquitin ligases were evaluated by Western Blot and Immunoprecipitation assays. Reactive oxygen species (ROS), and oxidation-dependent modified protein in gastrocnemius tissue were also determined.
Results: Our results showed that DDC fed mice developed sarcopenia as evidenced by a loss of muscle mass and strength (Fig.1A). Likewise, muscle fiber cross sectional area also was decreased in DDC fed mice which also present a different pattern of muscle fibers types and a reduced MHC protein levels (Fig 1B and C, respectively). While muscle UPS activity (Fig. 1D), ROS levels, and oxidation-modified protein levels were increased. Interestingly, these results were correlated with serum bile acids levels and additionally the results observed were not due to changes in food and water intake or mice mobility (Fig. 1E) since we did not find any differences in these parameters. Fig. 1F shows the histological injury and inflammation observed in DDC fed mice evaluated through Hematoxylin/Eosin staining.
Conclusion: Together, our results shows that DDC fed mice develops sarcopenia involving decreased levels of myofibrillar proteins, increased UPS activity, and oxidative stress. These results were correlated with serum bile acids levels but not with food intake or mobility.

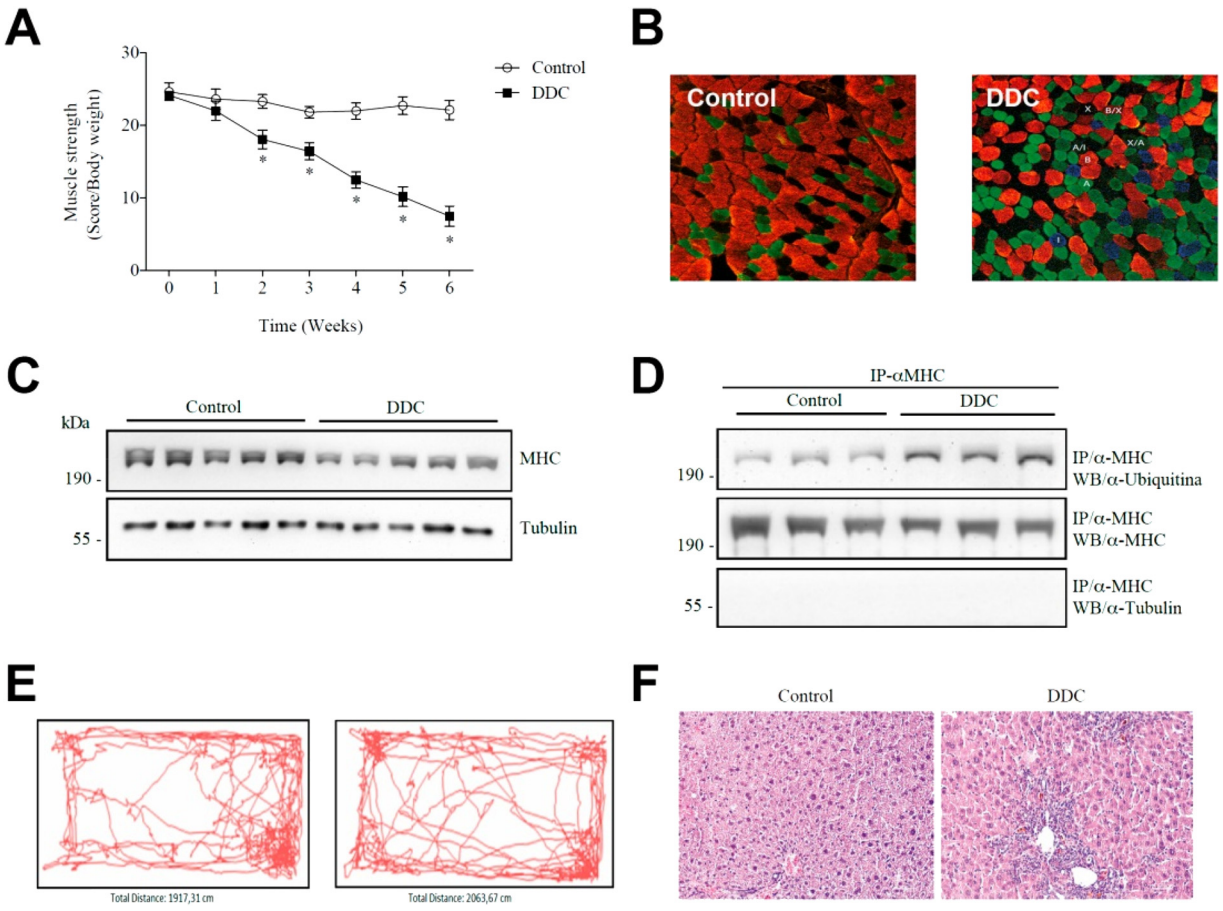


Figure 1: (abstract: FRI-213)

FRI-214

The atypical antidepressant mirtazapine is hepatoprotective in a mouse model of immune-mediated hepatitis

W. Almishri[1], A.A. Shaheen[2], G. Kaplan[3,4], M.G Swain[5,6]. *[1]University of Calgary, Department of Medicine, Snyder Institute for Chronic Diseases; [2]Cumming School of Medicine, Department of Medicine, Division of Gastroenterology and Hepatology; [3]Department of Medicine, Division of Gastroenterology and Hepatology; [4]Cumming School of Medicine; [5]Snyder Institute for Chronic Diseases, Department of Medicine; [6]Division of Gastroenterology and Hepatology*
Email: swain@ucalgary.ca

Background and Aims: Depression is a prevalent comorbidity in many immune-mediated diseases, often requiring antidepressant therapy. Some antidepressants exhibit immunomodulatory activity, including the atypical antidepressant mirtazapine (mitz). Therefore, we performed a series of experiments to determine the impact of mitz treatment on liver injury in a well characterized model of immune-mediated liver damage due to administration of concanavalin A (con A) in mice.

Method: C57BL/6 mice were treated with vehicle (veh), con A (13.5 mg/kg IV) or con A+ mitz (20 mg/kg ip) and liver/ blood samples collected 3 and 16 hrs later. Liver injury was assessed by measuring plasma ALT levels and microscopic hepatic necrosis scores. Hepatic cytokine/ chemokine levels were measured by Luminex® and immune cell infiltration by flow cytometry and immunohistochemistry (IHC). Expression of hepatic adhesion molecules was determined by IHC.

Results: Mitz administration markedly attenuated Con A-induced liver damage, as reflected by decreased ALT levels (ALT IU/L: veh = 39.8 ± 26.0 vs. con A+ veh = 3769 ± 1703 vs. Con A+ mirtz = 416 ± 237; ***p ≤0.001 conA+ veh vs. other groups) and hepatic necrosis scores. Moreover, mitz treatment significantly reduced con A-induced increases in hepatic TNFα and IFNγ levels. IFN-γ pg/mg protein: veh = 0.1 ± 0.02 vs. con A+ veh = 1.4 ± 0.068 vs. con A+ mitz = 0.9 ± 0.13; ***p ≤ 0.001 veh vs. other groups; **p ≤ 0.01 con A+ veh vs. con A+ mitz group; TNFα pg/mg protein: veh = 0.5 ± 0.05 vs. con A+ veh = 1.3 ± 0.07 vs. con A+ mitz = 0.8 ± 0.1; ***p ≤ 0.001 con A+ veh vs. other groups; **p ≤ 0.01 veh vs. con A+ mitz group. Mitz also prevented con A-induced increases in hepatic ICAM-1 expression. Hepatic lymphocyte recruitment was similar in con A vs. con A+ mitz treated groups, however mitz treatment reduced Con A-induced hepatic neutrophil recruitment by ~50% (*p ≤ 0.017) and hepatic expression of the key neutrophil chemoattractants CXCL1 and CXCL2.

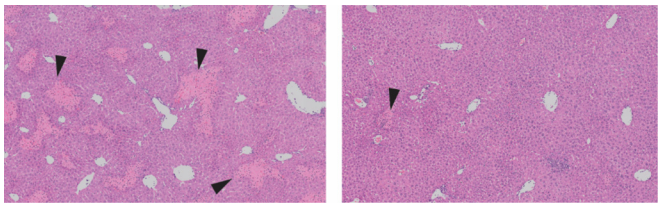


Figure 1: Mirtazapine pretreatment profoundly attenuates ConA-induced immune-mediated hepatitis Administration of mirtazapine leads to a striking reduction in liver damage 16 hrs post-con A treatment, as reflected by degree of histological damage in H&E stained liver sections. This figure shows two representative liver sections from con A treated mice (16 hrs post-con A) that received either PBS vehicle (left panel) or mirtazapine (right panel).

Conclusion: Mitz treatment exhibits robust hepatoprotective effects in the con A hepatitis through a striking attenuation of hepatic proinflammatory cytokine and neutrophil chemokine expression, and a marked reduction in hepatic ICAM-1 expression. Given the growing recognition of neutrophils in the regulation of hepatic immunity, mirtazapine may represent a novel therapy for treating immune-mediated liver diseases.

FRI-215

Fine-mapping and colocalisation analysis of GWAS risk loci in Primary Sclerosing Cholangitis suggests role for proto-oncogene ETS2 in disease pathogenesis

E. Goode[1,2], L. Moutsianas[2], N. Soranzo[2], S. Rushbrook[3], T. Raine[2,4], C. Anderson[2]. [1]*University of Cambridge, Institute of Metabolic Science, Cambridge, United Kingdom;* [2]*Wellcome Trust Sanger Institute, Human Genetics, Cambridge, United Kingdom;* [3]*Norfolk and Norwich University Hospital, Department of Gastroenterology, Norwich, United Kingdom;* [4]*University of Cambridge, Department of Medicine, Cambridge, United Kingdom*
Email: ecg44@cam.ac.uk

Background and Aims: Primary Sclerosing Cholangitis (PSC) is a biliary disease leading to cholestatic cirrhosis and high risk of cholangiocarcinoma. Genome-wide association studies (GWAS) have identified 22 PSC-associated non-HLA risk loci. Attempts to extract disease-relevant biological insights have been hindered by challenges identifying the causal variants driving the signals within each locus, due to linkage disequilibrium. Furthermore, identifying the genes impacted by these variants has proven difficult as the majority lie in non-coding genomic regions. This study aimed to identify the most likely causal variant within each risk locus and assess its impact on gene regulation by assessing the probability that the PSC association signal and functional quantitative trait loci (QTL) are driven by the same causal variant.
Method: Using the software package *Finemap,* we performed Bayesian fine-mapping analysis of PSC risk loci, focusing on 1Mb regions centred on the most associated SNP, to determine the most likely causal variant or credible set that explained >95% of the observed signal within each locus. We then performed colocalisation analyses with QTL for expression (eQTL), methylation and histone modifications in common peripheral blood cell types.
Results: Fine-mapping of the Chr21:rs2836883 region identified rs4817988 as the most likely causal variant (Posterior probability of causality = 0.58), with a credible set of 10 SNPs. Due to its proximity to the most associated SNP, the gene commonly assigned to this region is *PSMG1.* However, the PSC association signal was found to colocalise with an eQTL in peripheral blood monocytes for *ETS Proto-Oncogene 2* (*ETS2*), where the PSC risk allele increased expression of *ETS2* (*Fig 1a*). Furthermore, this signal also colocalised with an H3K27ac histone acetylation marker, associated with higher activation of transcription (Fig 1b). *ETS2* is highly expressed in PSC-relevant tissues, liver and colon, and encodes a transcription factor that regulates human telomerase activity, silencing of which has been implicated in the death of human breast cancer tissue cells. rs4817988 overlaps a promotor flanking region involved in distal transcriptional regulation of *ETS2* in monocytes.
Conclusion: Increased risk of PSC is associated with increased expression of *ETS2* and thus a pro-cancer phenotype. This study suggests that further investigation of the ETS2 pathway as a potential mechanism for PSC-related dysplasia, is warranted.

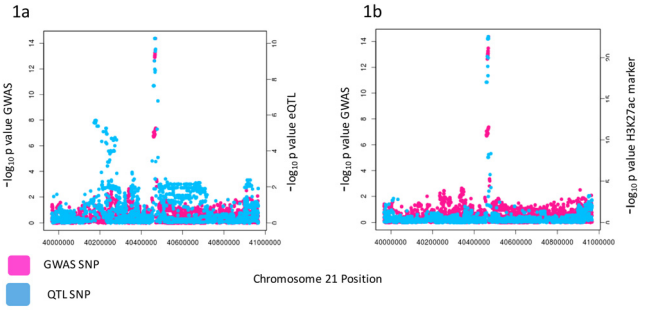


Figure: 1a) Colocalisation plot for PSC-associated regions and eQTL in monocytes with $-\log_{10}$ p-values plotted against chromosomal position; 1b) Colocalisation plot for PSC-associated regions and H3K27ac histone acetylation marker in monocytes with $-\log_{10}$ p-values plotted against chromosomal position

FRI-216

Hypersensitivity and constitutive activation of the IL-12/STAT4 pathway in NK cells in Primary Biliary Cholangitis: A novel mechanism

T. Hydes[1], S. Khakoo[2], J. Naftel[2]. [1]*University Hospital Southampton, Department of Gastroenterology and Hepatology, Southampton, United Kingdom;* [2]*University of Southampton, Faculty of Medicine, Southampton, United Kingdom*
Email: therasa@doctors.org.uk

Background and Aims: Natural Killer (NK) cells are cytotoxic against biliary epithelial cells in Primary Biliary Cholangitis (PBC). GWAS studies have identified IL-12/STAT4 axis polymorphisms as being associated with developing PBC. NK cells express the IL-12 receptor & respond to stimulation via the STAT4 pathway. We recently showed the human liver to be enriched in NK cells expressing the "homing" & "hyperfunctional" markers, CXCR6 & CD49a, & identified IL-12 to be important in the upregulation of these markers on peripheral NK cells. We therefore assessed the IL-12-STAT4 axis in NK cells in PBC.
Method: PBMCs were isolated from patients with PBC (n = 35), the non-inflammatory liver disease haemochromatosis (HFe) (n = 31) & healthy controls (HC) (n = 9). NK cells were analysed for surface markers (CXCR6, CD49a), intracellular pSTAT4 & IFNγ at rest & post purification & stimulation with IL-12/IL-15.
Results: Circulating NK cells, expressed greater levels of CD49a & CXCR6 compared to HFe & HC groups (CD49a: 2.2% vs 1.3% vs 0.9%, p = 0.0013, p = 0.0039 respectively; CXCR6: 3.4% vs 2.4 vs 2.0%: p = 0.0052, p = 0.0014 respectively). Stimulation with a low concentration of IL-12, 0.005ng/ml for 12 hours, led to significant upregulation of CXCR6 on NK cells from patients with PBC (3.1% to 4.8%, p = 0.0005), but not those with HFe (2.7% vs 2.6%, p = ns) (PBC 4.8% vs HFe 2.7%, p = 0.0056). Furthermore NK cells from individuals with PBC produced IFNγ in response to this low dose of IL-12 (1.1% rest, 2.9% IL-12 0.005ng/ml, p = 0.0004) & in greater quantities compared to HFe patients (2.9% vs 1.2%, p = 0.001) & HCs (2.9% vs 0.4, p < 0.0001). CD49a+ NK cells from PBC patients contained the highest frequencies of IFNγ+ NK cells (median 8.6%, range 0–43%) in response to low-dose IL-12 & were more sensitive than CD49a+ NK cells from HFe patients (median 2.6%). To investigate if NK cells from PBC patients are primed *in vivo* by IL-12 we tested STAT4 phosphorylation. A higher percentage of NK cells from PBC patients (4.3%) expressed pSTAT4 at rest compared to HFe patients (2.3%) & HCs (0.5%) (p = 0.0012 & p < 0.0001). No differences were found in T-cells.
Conclusion: Our data provide a functional correlate to the PBC GWAS studies. Circulating NK cells from individuals with PBC are hypersensitive to IL-12, leading to activation & expression of liver homing markers. NK cells in PBC exist in an IL-12 primed state, therefore blocking NK cells downstream of STAT4 may provide a novel therapeutic target.

FRI-217

Deletion of tumor necrosis factor alpha receptor 1 leads to an increased Th17 cell response in the chronically inflamed liver

L. Berkhout[1], B. Schiller[1], G. Ravichandran[1], T. Krech[2], G. Sass[1], G. Tiegs[1], R. Barikbin[1]. [1]*Institute of experimental immunology and hepatology, University medical center Hamburg-Eppendorf, Hamburg;* [2]*Department of Pathology, University medical center Hamburg-Eppendorf, Hamburg, Germany*
Email: l.berkhout@uke.de

Background and Aims: Chronic hepatic inflammation has several major consequences including cirrhosis, liver failure and cancer. Tumour necrosis factor alpha receptor-1 (TNFR1) activation is known to induce cell death, inflammation, and fibrosis but also hepatocyte survival and regeneration. In this study we analysed the role of TNFR1 during chronic liver inflammation.
Method: We ablated TNFR1 in a mouse model of chronic hepatitis and inflammation induced hepatocellular carcinoma (multidrug resistance protein 2 knockout mice; *mdr2*$^{-/-}$) creating *tnfr1*/*mdr2*$^{-/-}$ mice. Liver injury was assessed by plasma levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP). Cytokine concentrations were determined by Legendplex assay. Immune cell composition was analysed by flow cytometry. Hepatic immune cells were stimulated *ex vivo* with PMA & Ionomycin. Fibrosis was analysed via quantification of the hepatic hydroxyproline content and Sirius Red staining. Hepatic expression levels of targets involved in inflammation, fibrosis, and tissue regeneration were analysed via real time RT-PCR.
Results: We observed significantly increased ALT and ALP plasma levels, as well as significantly increased neutrophil and Th17 cell infiltration into the liver of *tnfr1*/*mdr2*$^{-/-}$compared to *mdr2*$^{-/-}$ mice. *Ex vivo* stimulated hepatic immune cells of *tnfr1*/*mdr2*$^{-/-}$ mice produced significantly more IL-17, which directly correlated with tissue injury. *Tnfr1*/*mdr2*$^{-/-}$ mice showed significantly increased hepatic expression of pro-inflammatory cytokines (*il-1beta, il-23, tgf-beta, ccl2, cx3cl1*), mediators of cell death (pycard, rip3), and fibrosis (*alpha-sma, collagens I and III, mmps*) compared to *mdr2*$^{-/-}$ mice. The *tnfr1*/*mdr2*$^{-/-}$ mice further showed increased hepatic hydroxyproline levels and Sirius Red positive areas in stained tissue sections. The expression of proliferation markers (*pcna*, *ccnA2*) was up-regulated in the *tnfr1*/*mdr2*$^{-/-}$.
Conclusion: Constitutive knockout of TNFR1 did not improve the pathological phenotype of *mdr2*$^{-/-}$ mice. It instead caused enhanced Th17 cell and neutrophil infiltration, accompanied by higher IL-17 production and exacerbated tissue damage, which resulted in increased fibrosis. Increased inflammation and fibrosis in combination with active regeneration implies an ideal microenvironment for tumour development in the livers of *tnfr1*/*mdr2*$^{-/-}$ mice. Long term studies will show whether the *tnfr1* knockout alters tumour development and progression in the *mdr2*$^{-/-}$ model.

FRI-218

Lysophosphatidic acid activates peripheral glia cells via LPA receptor 1

K. Wolf[1], L. Gebhardt[2], J. Robering[2], M. Fischer[3], A. Kremer[1]. [1]*Friedrich-Alexander University Erlangen-Nürnberg, Department of Medicine 1, Erlangen;* [2]*Friedrich-Alexander University Erlangen-Nürnberg, Institute of Physiology and Pathophysiology, Erlangen, Germany;* [3]*University of Vienna, Center for Physiology and Pharmacology, Vienna, Austria*
Email: andreas.kremer@uk-erlangen.de

Background and Aims: Pruritus is a frequently observed symptom in hepatobiliary disorders which can dramatically reduce the quality of life of affected patients. Lysophosphatidic acid could be identified as potential pruritogen, however, the molecular mechanisms resulting in neuronal activation remain elusive.
Methods: C57BL/6, TRPV1$^{-/-}$, TRPA1$^{-/-}$ mice as well as Wistar rats served as source for dorsal root ganglia (DRG) cultures. A Schwann cell culture was established from sciatic nerve preparations. Transient receptor potential (TRP) A1 and V1 were cloned from murine and human mRNA. Expression analyses were performed by qPCR. Fura-2 microfluometry was performed to quantify changes in cytosolic free calcium concentrations.
Results: LPA 18:1 elevated cytosolic free calcium concentrations in mouse and rat DRG cultures. Only a minor fraction (1.6%) of sensory neurons were activated by LPA, whereas the majority of activated cells were satellite glial cells (SGC). The magnitude of LPA-responses was inversely correlated with calcium responses to potassium and capsaicin. Besides satellite glial cells also Schwann cells responded to the application of LPA 18:1. Intriguingly, satellite glia cells responding to LPA were also activated by the TGR5 agonist INT-777. A striking cross-desensitization of LPA and established pruritogens could be observed. Heterologously expressed human and murine TRP channels in HEK293T cells showed at best a marginal involvement of TRP channels in cellular responses to LPA. The respective gial cells of TRPV1$^{-/-}$ and TRPA1$^{-/-}$ mice showed not relevant reduction in LPA-induced calcium responses. Various pre-treatments of wildtype DRG cultures using thapsigargin, the phospholipase C inhibitor (PLC) U73122, and the LPA receptor 1 and 3 blocker Ki16425 indicated a G protein-coupled LPA receptor signaling via a PLC-IP3 pathway releasing calcium from intracellular stores. Real-time PCR experiments indicated a high expression of LPAR1 in mouse and rat DRGs and Schwann cells as well as a weak expression of LPAR4, LPAR5, and LPAR6.
Conclusion: LPA 18:1 largely activated satellite glia cells and peripheral Schwann cells via LPAR1. Intriguingly, LPA response SGCs were also activated by a TGR5 agonist, indicating that a cooperative effect of two or more pruritogens may be required for the onset of cholestatic itch.

FRI-219

Intrahepatic type II natural killer T cells switch to a pro-inflammatory cytokine profile in patients with autoimmune hepatitis

M. Sebode[1], C. Schramm[1], L. Fischer[2], A. Lohse[1], P. Arrenberg[1]. [1]*University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany;* [2]*University Medical Center Hamburg-Eppendorf, Department of Hepatobiliary Surgery and Transplantation, Hamburg, Germany*
Email: marcialsebode@web.de

Background and Aims: Natural killer T (NKT) cells are unconventional T cells that recognize lipid antigens presented by the non-classical MHC molecule CD1d. NKT cells have been investigated in murine models of autoimmune hepatitis (AIH), in which type I NKT cells are pathogenic, whereas type II NKT cells protect from liver disease. However, the role of human NKT cells, especially human type II NKT cells, in autoimmune liver diseases is unclear. Here, we have analyzed peripheral and intrahepatic human NKT cells and the intrahepatic expression of CD1d in AIH compared to control groups.
Method: The frequency and cytokine profile of peripheral and intrahepatic type I NKT and type II NKT cells from patients with AIH, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) were analyzed by flow cytometry. Healthy liver tissue of the resection margin of liver adenomas and liver biopsies from patients with drug-induced liver injury (DILI) served as control groups. Type I and type II NKT cells were specifically stained by a-Galactosylceramide- and Sulfatide-loaded human CD1d-tetramers, respectively. CD1d was stained immunohistochemically in liver biopsies.
Results: The frequency of peripheral and intrahepatic type I NKT cells was very low in patients with AIH (0.005% and 0.03% of peripheral and intrahepatic leukocytes) and did not differ significantly in comparison to control groups. In contrast, AIH patients revealed an increased frequency of peripheral type II NKT cells compared to

healthy controls (0.11% of peripheral leukocytes vs. 0.05%, p = 0.02). Furthermore, an increased number of intrahepatic type II NKT cells in patients with AIH (3.78% of intrahepatic leukocytes) compared to healthy controls (1.82%) and patients with DILI (2.07%, p = 0.02) was detected. Intrahepatic, but not peripheral type II NKT cells of AIH patients had a different cytokine profile than healthy controls with an increase of TNFa (77.8% vs. 59.1%, p = 0.03), a decrease of IFNg (32.7% vs. 63.0%, p = 0.02) and suppression of IL-4 (0% vs 2.1%, p = 0.05). Infiltrating immune cells in portal areas of patients with AIH expressed significantly more CD1d compared to control groups.
Conclusion: Intrahepatic Sulfatide-reactive type II NKT cells of AIH patients reveal an increased production of TNFa and show a complete suppression of IL-4. Contrasting with a protective role in their murine counterpart, human type II NKT cells could contribute to the pro-inflammatory mechanisms of AIH. Neither cholangiocytes nor hepatocytes, but infiltrating cells in portal areas of AIH patients show an increased expression of CD1d and could thereby activate type II NKT cells in AIH patients.

FRI-220

Human chorionic-plate-derived mesenchymal stem cells restore hepatic lipid metabolism in a rat model of bile duct ligation

Y.B. Lee[1], J.H. Choi[2,3], E.N. Kim[4], J. Seok[2], H.-J. Lee[2], G.J. Kim[2]. *[1]CHA Bundang Medical Center, CHA University, Department of Internal Medicine, Seongnam, Korea, Rep. of South; [2]CHA University, Department of Biomedical Science, Seongnam, Korea, Rep. of South; [3]The Feinberg School of Medicine, Northwestern University, Department of Dermatology, Chicago, United States; [4]CHA Bundang Medical Center, CHA University, Clinical Research Center, Seongnam, Korea, Rep. of South*
Email: yunbin@hanmail.net

Background and Aims: In cholestatic liver diseases, impaired bile excretion disrupts lipid homoeostasis. We investigated changes of lipid metabolism, including mitochondrial β-oxidation, in a rat model of bile duct ligation (BDL) in which chorionic-plate-derived mesenchymal stem cells (CP-MSCs) were transplanted.
Method: Male 7-week-old Sprague-Dawley rats were used. One week after BDL, rats in the transplanted group were injected with CP-MSCs (2×10^6 cells, 8–10 passages) intravenously via tail vein, whereas rats in the nontransplanted group were injected with culture medium. Liver tissues and blood samples for further analysis were collected 1, 2, 3, and 5 weeks post-transplantation in the transplanted group and 1, 2, 3, and 5 weeks post-BDL in the nontransplanted group.
Results: The concentration of serum cholesterol, which was elevated after BDL, was significantly decreased following transplantation of CP-MSCs. The expression levels of genes involved in intracellular lipid uptake, including long-chain fatty acyl-CoA synthetases and fatty acid transport proteins, were decreased in rats after BDL, however, were not significantly changed by subsequent CP-MSC transplantation. Carnitine palmitoyltransferase 1A (CPT1A), a rate-limiting enzyme in mitochondrial β-oxidation, was upregulated after BDL and then was downregulated after CP-MSC transplantation. CPT1A expression was changed via microRNA-33–a posttranscriptional regulator of CPT1A–in a peroxisome proliferator-activated receptor α-independent manner. Cellular adenosine triphosphate production–an indicator of mitochondrial function–was reduced after BDL and was restored by CP-MSC transplantation. Expression levels of heme oxygenases also were significantly affected following BDL and CP-MSC transplantation.
Conclusion: Lipid metabolism is altered in response to chronic cholestatic liver injury and can be restored by CP-MSC transplantation. Our study findings support the therapeutic potential of CP-MSCs in cholestatic liver diseases and help understanding fundamental mechanism by which CP-MSCs affect energy metabolism.

FRI-221

In vitro rescue of ABCB11 nonsense mutations: Induction of a readthrough of premature stop codons

R. Amzal[1], A. Thebaut[1,2], M. Almes[1,2], M. Lapalus[1], B. Grosse[1], L. Bidou[3,4], O. Namy[3], E. Jacquemin[1,2], E. Gonzales[1,2]. *[1]Inserm, UMR-S1174, Hepatinov, University of Paris-Sud 11, ORSAY; [2]Pediatric Hepatology and Pediatric Liver Transplantation Unit, National Reference Centre for Rare Pediatric Liver Diseases, Bicêtre Universitary Hospital, Assistance Publique-Hôpitaux de Paris, Le Kremlin-Bicêtre, France; [3]Institute for Integrative Biology of the Cell (I2BC), CEA, CNRS, University Paris Sud, University Paris-Saclay, Gif sur Yvette, France; [4]University Pierre et Marie Curie, Paris, France*
Email: emmanuel.gonzales@aphp.fr

Background and Aims: Progressive familial intrahepatic cholestasis type 2 (PFIC2) is due to mutations of *ABCB11*, encoding the canalicular bile salt export pump (BSEP). Nonsense mutations (premature termination codon, PTC) are responsible for severe forms of the disease. The aim of this study was to assess the ability of drugs to induce a readthrough of PTC of *ABCB11*.
Methods: Six PTC identified in PFIC2 patients were studied (p.Y354X, p.R415X, p.R470X, p.R1057X, p.R1090X and p.E1302X). The readthrough levels of the human and rat PTC in their nucleotide environment were first quantified before and after treatment with aminoglycosides (G418 (200µg/mL), gentamicin (800, 1200µg/mL)) and Ataluren® (15µM) using a dual reporter assay (luciferase/galactosidase) in NIH3T3 line. Mutagenesis was used to reproduce non-sense patient mutations in Bsep cDNA. After transfection of these Bsep-GFP plasmids in HEK293, MDCK and Can 10 lines, cells were treated with gentamicin. Expression and cellular localization of the full-length Bsep protein resulting from the readthrough were studied by epifluorescence and confocal microscopies after immunostaining using anti-GFP, anti-Ntcp and anti-ZO-1 antibodies. Stable MDCK clones co-expressing $Bsep^{WT}$ or $Bsep^{R1090X}$ and Ntcp were used to study the vectorial transport of [^{3}H]taurocholate.
Results: In NIH3T3 cells, aminoglycosides significantly increased the readthrough levels of all human and rat mutations while Ataluren® only slightly increased the readthrough level of the human p.E1302X. In HEK293 cells, gentamicin induced a readthrough of 4 PTC (p.R415X, p.R470X, p.R1057X, p.R1090X). The resulting full-length proteins localized within the cytoplasm, except $Bsep^{R1090X}$ that was also detected at the plasma membrane. In Can 10 cells, gentamicin treatment significantly increased readthrough of the R1090X PTC and the resulting full-length protein was detected mainly in the cytoplasm but also at the canalicular membrane. At 27°C, a condition known to mimic the effect of chaperone therapy, the proportion of $Bsep^{R1090X}$ full-length protein localized at the canaliculus significantly increased. In MDCK cells, functional study of $Bsep^{R1090X}$ full-length protein performed after gentamicin-induced readthrough showed a significant increase in the transport of [^{3}H]taurocholate.
Conclusion: This study constitutes a proof of concept for readthrough therapy in selected patients with PFIC2 due to PTC of *ABCB11*, such as p.R1090X and suggests that combination with chaperone therapy might further improve the rescue.

FRI-222

The anti-inflammatory receptor TREM2 protects the liver from cholestatic injury in mice

I. Labiano[1], A. Esparza-Baquer[1], O. Sharif[2,3], P. Milkiewicz[4], M. Milkiewicz[5], E. Hijona[1,6], R. Jimenez-Aguero[1], M. Marzioni[7], D.A. Mann[8], L. Bujanda[1,6], J. Banales[1,6,9], M.J. Perugorria[1,6,9]. *[1]Biodonostia Health Research Institute, Donostia University Hospital, University of the Basque Country (UPV-EHU), Department of Liver and Gastrointestinal diseases, Donostia-San Sebastián, Spain; [2]Austrian Academy of Sciences, Research Center for Molecular Medicine, Vienna, Austria; [3]Medical University of Vienna, Department of Medicine I, Laboratory of Infection Biology, Vienna, Austria; [4]Department of General,*

Transplant and Liver Surgery, Medical University of Warsaw, Liver and Internal Medicine Unit, Warsaw, Poland; [5]Pomeranian Medical University, Department of Medical Biology, Szczecin, Poland; [6]CIBERehd, Centro de Investigación biomédica en Red, Donostia-San Sebastián, Spain; [7]Università Politecnica delle Marche, Department of Gastroenterology and Hepatology, Ancona, Italy; [8]Faculty of Medical Sciences, Newcastle University, Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom; [9]IKERBASQUE, Basque Foundation for Science, Bilbo-Bilbao, Spain
Email: aitor.esparza@biodonostia.org

Background and Aims: Cholestasis is a common feature of different cholangiopathies such as PSC and PBC. Cholestasis causes liver inflammation and injury in epithelial cells, thereby inducing ductular reaction and activation of non-parenchymal liver cells [i.e. kupffer cells (KC) and hepatic stellate cells (HSC)] that ultimately results in biliary fibrosis. Liver injury leads to alterations in the intestine epithelial barrier, enabling the translocation of bacterial components to the liver via the portal vein. In the liver, these bacterial components bind to toll-like receptors (TLRs) expressed in KC and HSC promoting inflammation and progression of the wound-healing response. The triggering receptor expressed on myeloid cells 2 (TREM2) is an anti-inflammatory receptor that inhibits TLR-mediated signaling. This study aims to evaluate the role of TREM2 in cholestasis.
Method: TREM2 expression was analyzed in the liver of PBC and PSC patients and normal controls. Wild type (WT) and *Trem-2* knock out (*Trem2*$^{-/-}$) mice were subjected to bile duct ligation (BDL), or sham, for 7 days. Thereafter, sera were collected for the analysis of biochemical markers and livers were obtained for further histological and gene expression analysis. *In vitro*, KCs were isolated from WT and *Trem2*$^{-/-}$ mice, treated with lipopolysaccharide (LPS) and cytokine and chemokine expression was assessed.
Results: TREM2 expression is upregulated in the liver of PBC and PSC patients as compared to healthy controls; this receptor was also upregulated in a BDL based model of murine cholestasis. After BDL, *Trem2*$^{-/-}$ mice showed exacerbated liver injury with increased hepatocyte necrosis and immune-cell infiltration compared to WT, as assessed by H&E staining. This was accompanied by augmented mRNA levels of cholangiocyte (*Ck-7* and *Ck-19*) and proliferation markers (*Ki67* and *PCNA*), indicating that *Trem-2*$^{-/-}$ animals suffered exacerbated ductular reaction. Likewise, *Col1a1* and α *Sma* mRNA levels revealed enhanced fibrogenesis in *Trem2*$^{-/-}$ livers compared to WT after BDL. In addition, the expression of pro-inflammatory cytokines (*Il-6* and *Tnf-*α) and chemokines (*Mcp-1* and *Cxcl1*) were upregulated in these mice. LPS-treated *Trem2*$^{-/-}$ KC displayed increased expression of pro-inflammatory (*Il-6, Il-1*β and *Tnf-*α) and chemokine (*Cxcl1*) markers, both at mRNA and protein level, as compared to WT-derived KC.
Conclusion: TREM2 is overexpressed in the livers of PBC and PSC patients and during experimental cholestasis in mice. This receptor negatively regulates TLR4-mediated pro-inflammatory cytokine expression in KC, thereby protecting the liver from cholestatic injury in mice.

FRI-223
Elevated plasma levels of FGF19 isassociated with repression of bile salt synthesis in patients with obstructivecholestasis

K. Koelfat[1], E. Neis[1], S. Rensen[1], P. Jansen[1], C. Dejong[1,2], F. Schaap[1,2], S.O. Damink[1,2]. *[1]Maastricht University Medical Center and NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University, Surgery, Netherlands; [2]RWTH University Hospital Aachen, Aachen, Germany, Department of General, Visceral and Transplantation Surgery, Germany*
Email: k.koelfat@maastrichtuniversity.nl

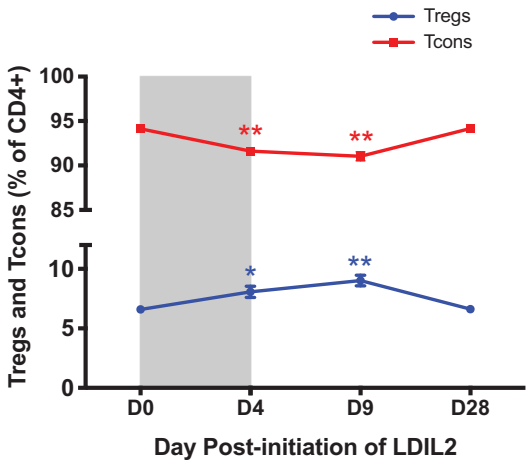
Background and Aims: The enterokine fibroblast growth factor 19 (FGF19) represses bile salt (BS) synthesis in the liver. It is hypothesized that production of FGF19 is shifted to the liver in patients with obstructive cholestasis (viz. lack of luminal BS). To study the orgin of FGF19 under conditions of cholestasis, we studied venous-arterial (VA) differences across major abdominal organs and investigated the relation with BS synthesis under cholestatic conditions.
Method: Plasma levels of BS/FGF19 and C4 (plasma marker of BS synthesis) were determined in arterial blood (RA), and portal (PV), hepatic (HV), superior (SMV) and inferior mesenteric (IMV) veins of cholestatic patients (n = 6) and controls (n = 14), who underwent pancreatic surgery.
Results: Cholestatic patients had higher levels of bilirubin ($P < 0.001$), ALP ($P = 0.009$), γGT ($P = 0.02$), ALT (P 0.02) and AST ($P = 0.02$), reflecting cholestatic injury. FGF19 levels were higher in all blood vessels of cholestatic patients (range 0.37 to 34.0 ng/mL) compared with controls (range 0.03 to 0.37 ng/mL) ($P < 0.001$). Likewise, BS levels were increased in all vessels in the cholestatic group, except for in SMV, (range 11.6 to 536.3 vs 0.4 to 122.7 µmol/L, ($P < 0.05$). Indeed, BS and FGF19 were closely related ($\rho = 0.72$, $P < 0.001$). FGF19 was not significanlty released by the small/large intestine or liver in cholestatic patients and controls. Nonetheless, we observed higher splanchnic release of FGF19 ($P = 0.03$) in cholestatic patients, suggesting increased production across the splanchnic area under conditions of obstructive cholestasis. In controls, BS were released by the small intestine ($P < 0.001$), not by the large intestine ($P = 0.24$), and taken up by the liver ($P < 0.001$). BS and FGF19 levels were positvely correlated with bilirubin levels ($\rho = 0.57$, $P = 0.02$, $\rho = 0.63$, $P = 0.008$, respectively). C4 levels were significantly lower in OC-patients compared with controls ($P < 0.05$). Moreover, BS and FGF19 levels were negatively related to C4 levels ($\rho = 0.74$, $P < 0.001$, $\rho = -0.75$, $P < 0.001$, respectively).
Conclusion: This study reveals that circulating levels of FGF19 are elevated during obstructive cholestasis and this is associated with cholestasis and decreased BS synthesis. Hepatic production is unlikely to contribute to the elevated FGF19 levels in obstructive cholestasis.

FRI-224
Low-dose interleukin-2 expands the number of circulating regulatory T cells in patients with treatment-refractory autoimmune hepatitis

T.Y. Lim[1,2], E. Codela[2], E. Gray[2], M. Heneghan[1], M. Martinez-Llordella[2], A. Sanchez-Fueyo[1]. *[1]King's College Hospital, Institute of Liver Studies, London, United Kingdom; [2]King's College London, MRC Transplant Centre, London, United Kingdom*
Email: llty24@gmail.com

Background and Aims: Low-dose interleukin-2 (LDIL-2) selectively expands regulatory T cells (Tregs) and improves their functional capacity. It has been administered to patients with a variety of autoimmune disorders including type 1 diabetes, systemic lupus erythematosus and graft-versus-host disease. However it has not been used in the setting of autoimmune hepatitis (AIH).
Method: We conducted immunomonitoring experiments on sequential blood samples collected from 2 patients not responding to second line immunosuppression and receiving 6 monthly courses of LDIL-2 (daily subcutaneous of 1 million IU IL-2 for 5 days).
Patient 1 is a 21 years old woman, diagnosed age 13. Although initially stable on azathioprine and prednisolone, she relapsed and was switched to mycophenolate mofetil (MMF) and tacrolimus treatment. However she relapsed again despite high dose steroids. Patient 2 is a 57 years old woman, diagnosed age 53, and was intolerant to azathioprine. She was maintained on MMF and prednisolone but relapsed. Patient 1 was cirrhotic on biopsy and Patient 2 had F3 fibrosis.
Results: There was no significant biochemical response in Patient 1, but Patient 2 achieved biochemical remission after 6 cycles of LDIL-2 therapy (AST from 259 to 44 IU/ml, and IgG from 20.9 to 16.2g/L). Neither patient developed any serious adverse events. Both patients experienced only transient injection-site erythema.

In both patients, LDIL-2 increased circulating Tregs ($CD25^+FOXP3^+$) significantly after each cycle at day 4 and peaked at day 9. However this returned to baseline at day 28. The median relative increase in Tregs was 26% (IQR 18–50%). A more detailed immunophenotypic analysis revealed that the changes in Treg numbers were due to increases in the proportion of resting and effector Tregs ($CD45RA^+FOXP3^{lo}$ and $CD45RA^-FOXP3^{hi}$, respectively), with no significant changes being observed in the non-suppressive $CD45RA^-FOXP3^{lo}$ $CD4^+$ Treg subset. In contrast, the proportion of conventional T cells (Tcons, $CD25^-FOXP3^-$) was reduced significantly following LDIL-2 therapy (Fig.1). In addition, LDIL-2 therapy led to an increase in expression of the proliferation marker Ki-67, as well as the activation markers CD25 and FOXP3, in Tregs, but not in Tcons. LDIL-2 also increased the responsiveness of Tregs to IL-2, as measured by expression intracellular phosphorylated signal transducer and activator of transcription-5 (pSTAT5). LDIL-2 also transiently increased the levels of the immunosuppressive cytokine, IL10, and CXCL-10, which promotes the trafficking into the liver of CXCR3 expressing Tregs.



Conclusion: We report for the first time that LDIL-2 can be safely used in AIH patients. It results in selective expansion of endogenous circulating Tregs and increases their sensitivity to IL-2. Our observations demonstrate the feasibility of improving inflammatory liver damage using this novel immunostrategy.

FRI-225

Intrahepatic recuriment of cytotoxic NK cells contributes to autoimmune hepatitis progression

F. Xiao[1], G. Ai[1], W. Yan[1], X. Luo[2], X. Wan[1], Q. Ning[1]. *[1]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, China; [2]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology*
Email: qning@vip.sina.com

Background and Aims: It is widely accepted that multiple subsets of immune cells are involved in the pathogenesis of autoimmune hepatitis AIH during which the autoimmune response is initiated by self-antigen recognition by the uncommitted CD4 helper T-cells (Th0) leading to Th1/Th2/Th17 differentiation in response to different cytokine stimulation. This is followed by the differentiation and activation of monocyte/Macrophage, natural killer (NK) cells, cytotoxic CD8 T cells, B cells leading to the destruction of liver parenchyma. However, exact contribution of NK cells to AIH remains poorly understood. In this study, we aim to dissect the role of peripheral and liver resident NK cells in AIH progression.
Methods: Peripheral blood mononuclear cells were isolated from AIH at patients at active phase and remission phase and subjected to flow cytometry for NK cells detection. Liver NK cells was isolated from mice of experimental autoimmune hepatitis and analyzed by flow cytometry. $CD56^{dim}$/ $CXCR3^-$ and $CD56^{bright}$/ $CXCR3^+$ NK cells in AIH patients/mice were drafted as cytotoxic and regulatory NK cells, respectively.
Results: Frequency of peripheral NK cells, more accurately CD56dimNK subset, was reduced in AIH patients. The reduction of $CD56^{dim}$NK was negatively correlated with disease progression. In experimental autoimmune hepatitis (EAH), hepatic accumulation of NK cells was observed along with a decrease of NK cells in the periphery. In addition, infiltrated NK cells are almost conventional $CXCR3^-$ NK cells, the counterpart of $CD56^{dim}$NK cells in the human. Both conventional $CXCR3^-$ NK cells of infiltration and liver resident NK cells are activated progressively at active phase as demonstrated by expression of granzyme B, Perforin, and IFN-γ.
Conclusion: Recruitment of peripheral cytotoxic NK cells into the liver, but not liver resident NK cells expansion, accounts for AIH progression.

FRI-226

Deep immunophenotyping of liver infiltrating lymphocytes reveals distinct differences in the T cell compartment of patients with primary sclerosing cholangitis

T. Poch[1], L. Glau[2], A. Langeneckert[3], L. Hess[3], W. Salzberger[3], G. Martrus[3], S. Lunemann[3], D. Schwinge[1], M. Koch[4], L. Fischer[4], K. Oldhafer[5], M. Altfeld[3], A. Lohse[1], E. Tolosa[2], C. Schramm[1].
[1]University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Institute of Immunology, Hamburg, Germany; [3]Heinrich Pette Institute, Virus Immunology Unit, Hamburg, Germany; [4]University Medical Center Hamburg-Eppendorf, Department for Hepatobiliary Surgery and Transplant Surgery, Hamburg, Germany; [5]Asklepios Barmbek Hospital, Department of General and Abdominal Surgery, Hamburg, Germany
Email: t.poch@uke.de

Background and Aims: Although genetic associations point towards immune dysregulation as part of the pathogenesis of Primary Sclerosing Cholangitis (PSC), the contribution of immune cells to the development and progression of PSC remains elusive. Few studies have so far analysed specific cell subsets within PSC livers. We here report on an unbiased investigation of the immunophenotype within liver and peripheral blood of patients with PSC.
Method: In an ongoing study, liver tissue and corresponding peripheral blood of five PSC patients has been obtained at time of liver transplantation. Liver tissue from resection margins of liver tumours and corresponding blood was used as controls. Lymphocytes were stained for surface markers or restimulated for cytokine measurements. More than 70 different antibodies to cell surface markers were used and analysed in a BD LSR Fortessa™. Conventional data analysis was performed using the BD FACSDIVA™ software for guided hierarchical gating. In addition, unsupervised analysis of differentially abundant clusters was conducted using SPADEVizR, and for visualization of high dimensionality data we used t-SNE algorithms.
Results: We provide extensive flow cytometric data on immune cell subsets in blood and livers of patients with PSC. Previously described changes in cellular subsets could be reproduced, such as diminished frequencies of mucosal associated invariant T cells (MAIT) in patients with PSC compared to controls, and a marked increase in MAIT frequencies in liver compared to peripheral blood, which supports the validity of this approach. Our data suggests that, in end stage PSC livers, major T cell populations do not differ in frequency but in expression of specific surface markers. Focusing on the $CD4^+$ T cell compartment, we were able to detect significant differences in the abundance of specific subsets between diseased livers and controls. Potentially exhausted $CD4^+$ T cells ($PD\text{-}1^+BTLA^+CD57^+$) were enriched in PSC livers, whereas presumably regulatory cells ($CD25^+LAG3^+CD44^+$) were significantly less frequent.

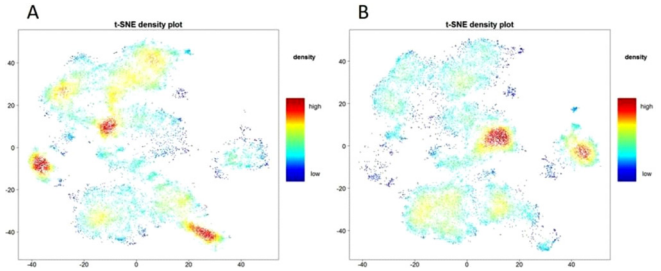


Figure 1: The T cell compartment differs clearly between PSC and control samples. Flow cytometric data of five PSC-LTx and five controls was used for analysis by t-distributed stochastic neighbour embedding (t-SNE). Density maps of the T cell compartments illustrate the different distribution of the respective cells across the clusters. (A) Events of controls are shown. (B) Events of PSC-LTx are displayed.

Conclusion: We show for the first time in-depth data of the hepatic immunophenotype in comparison to peripheral blood in patients with PSC. Significant differences were observed in the intrahepatic $CD4^+$ T cell compartment between PSC and controls, and also between liver and blood. We believe that our data will contribute to unravel the role of immune cells in the pathogenesis of PSC.

FRI-227

Cross-species molecular imaging of bile salts and lipids: Identification of hydroxyl-sulfatides as marker of bile ducts

B. Flinders[1], L. Huizing[1], M. van Heerden[2], F. Cuyckens[2], S. Olde Damink[3], R.M.A. Heeren[1], F. Schaap[4], R. Vreeken[2]. *[1]Maastricht Multimodal Molecular Imaging Institute (M4I), Maastricht University, Maastricht, Netherlands; [2]Janssen Research & Development, Beerse, Belgium; [3]Maastricht University Medical Centre, Maastricht University Medical Center, Maastricht, Netherlands; [4]Maastricht University, Dept of Surgery, Maastricht, Netherlands*
Email: frank.schaap@maastrichtuniversity.nl

Background and Aims: The liver is the primary organ involved in handling of bile salts, a class of amphipathic molecules with beneficial signaling activities as well as detrimental detergent action. To allow in-depth investigation of functions of bile salts in healthy and diseased liver, the spatial distribution of bile salt species within the liver needs to be studied. We furthermore aimed to identify specific lipid markers that define the structural elements of the liver.
Method: Matrix-assisted laser desorption/ionization-mass spectrometry imaging (MALDI-MSI) was used to monitor the spatial distribution of bile salts and lipids in liver sections of rat, dog, and patients with unaffected and cholestatic parenchyma.
Results: MALDI-MSI in negative ion mode showed the local presence and identity of a variety of bile salts, predominantly taurine-conjugates, as localized patches of varying sizes (representing the bile ducts) throughout the liver tissue. Specific molecular markers were identified for the connective tissue (a phosphatidic acid [PA (18:0_18:1)–H]$^-$), the liver parenchyma (a phosphatidylinositide [PI (18:0_20:4)-H]$^-$), and the bile ducts (a hydroxyl-sulfatide [ST-OH (18:1_24:0)-H]$^-$). The sulfatide (m/z 906.6339) was found to be localized in a thin lining on the inside of the bile duct, co-localizing with cytokeratins, and encasing luminal bile salts. In a liver specimen of a patient with primary sclerosing cholangitis (PSC), a similar distribution of aforementioned sulfatide was observed, albeit in constricted ductular structures. PSC-specific lipid markers species were not apparent in connective tissue or the bile ducts.
Conclusion: MALDI-MSI indicates that hepatic bile salts are primarily contained within the biliary network. Lipid markers were identified that define the distinct structural elements of the liver. Of these novel markers, sulfatides are uniquely expressed in the bile duct epithelium.

Cirrhosis and its complications: Experimental and pathophysiology

FRI-228

Necroptosis signalling pathway in hepatic fibrosis; role of receptor-interacting serine-threonine kinase 3 and mixed lineage kinase domain-like in cirrhosis

W. Saeed[1], D.W. Jun[1], E. Kim[1], B.-K. Kang[2], J.Y. Jeong[3], S.B. Ahn[4], M.M. Kim[5], H. Oh[1], K.S. Jang[6], E.C.J. Jang[7], J.H. Sohn[8]. *[1]Hanyang University School of Medicine, Department Internal Medicine, Seoul, Korea, Rep. of South; [2] Hanyang University School of Medicine, Department of Radiology, Seoul, Korea, Rep. of South; [3]Hanyang University, College of Medicine, Guri Hospital, Department of Internal Medicine, Guri-si, Gyeonggi-do; [4]Eulji university college of medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [5]Hanyang University School of Medicine, Department of Radiology, Seoul; [6]Hanyang University School of Medicine, Department of Pathology, Seoul, Korea, Rep. of South; [7]Soonchunhyang University College of Medicine, Department of Occupational and Enviroment Medicine, Cheonan-si, Chungcheongnam-do, Korea, Rep. of South; [8]Hanyang University, College of Medicine, Guri Hospital, Department of Internal Medicine, Guri-si, Gyeonggi-do, Korea, Rep. of South*
Email: noshin@hanyang.ac.kr

Background and Aims: The key necroptosis molecules, receptor-interacting serine-threonine kinase 1 (RIP1) and RIP3, have been recently studied extensively in hepatic pathologies. We evaluated anti-fibrotic properties of RIP3 and mixed lineage kinase domain-like (MLKL) inhibition in hepatic fibrosis models.
Method: Common bile duct (CBD) ligation and thioacetamide (TAA) induced fibrosis models were established in $RIP3^{(-/-)}$ mouse and $MLK^{(-/-)}$ KO *in vivo* model. Serum AST, ALT, bilirubin and tissue analysis for H&E, Sirius Red staining and immunohistochemistry was performed. RIP3 and MLKL inhibitor (GSK-872, and Necrosulfonamide) treated LX-2 cells were analysed for wound healing, and α-SMA, colla1α, p-MLKL, and RIP3 immunostaining. qRT-PCR analysis for RIP3, α-SMA, colla1α, TIMP1, vimentin, Bax, Bcl2, JNK1, JNK2 and MLKL was performed.
Results: Human liver tissue MLKL immunoreactivity (IRS) score increased in NASH patients and IRS score was correlated with fibrosis. In CBD ligation induced fibrosis model extensive fibrosis was observed compared to TAA-induced fibrosis model. Both $RIP3^{(-/-)}$ and $MLKL^{(-/-)}$ KO mice had significantly decreased fibrosis compared to wild type animals, while the serum AST, ALT, and bilirubin were not significantly decreased. Both $RIP3^{(-/-)}$ and $MLKL^{(-/-)}$ KO mice had significantly decreased α-SMA, coll1α, and TIMP-1 expressions. MLKL expressed in activated stellate cell as well as necroptic condition (TNF-α, and pancaspase inhibitor). MLKL inhibitor delayed wound healing, and decreased α-SMA, coll1α, and vimentin expressions in LX-2 cell. MLKL inhibitor increase intracellular lipid accumulation. RIP3 inhibitor increased M2 phenotype marker in RAW cell.
Conclusion: RIP3 and MLKL inhibition protects from CBD ligation and TAA induced hepatic fibrosis via inhibited stellate cell reversion.

FRI-229

Role of Toll-like receptor 4 (TLR4) in regulating severity of hyperammonemia and gene expression of urea cycle enzymes

A. Kerbert[1,2], Y. Sharifi[1], R. Jalan[1], F. Andreola[1]. *[1]UCL Medical School, Royal Free Hospital London, Liver Failure Group, UCL Institute for Liver and Digestive Health, London, United Kingdom; [2]Leiden University Medical Center, Gastroenterology & Hepatology, Leiden, Netherlands*
Email: j.c.kerbert@lumc.nl

Background and Aims: In liver failure, hyperammonemia (HA) is thought to result from reduced urea cycle enzyme (UCE) activity due

to diminished hepatocyte cell mass. However, episodic HA is observed in cirrhotic patients with superimposed sepsis, suggesting that alternative mechanisms may be involved. Deletion of toll like receptor-4 (TLR4) was shown to protect against neuroinflammation in hyperammonemic mice. The present study aimed to determine whether 1) stimulation of TLR4 with lipopolysaccharide (LPS) in cirrhotic animals resulted in HA and 2) to investigate whether TLR4 regulates gene expression of UCEs in HA mice.

Method: Two animal models were performed. 1) in bile duct ligated (BDL) rats (n = 4), 0.03 mg/kg LPS was administered intravenously 4 weeks after surgery. Plasma ammonia levels were assessed. 2) 4 groups of mice were studied: wild type control (WTC, n = 5), WT with hyperammonemia (WTH, n = 5), TLR4 knockout control ($TLR4^{-/-}C$, n = 5) and $TLR4^{-/-}$ with HA ($TLR4^{-/-}H$, n = 5). HA was induced by addition of 0.28 M ammonium chloride to drinking water for 3 days after which mice were sacrificed. qPCR was used to assess gene expression of UCEs in liver tissue. Relative gene expression is presented using the comparative C_T method ($2^{-\Delta CT}$ and $2^{-\Delta\Delta CT}$) using WTC as a calibrator.

Results: Administration of LPS to BDL animals was associated with a significant increase in plasma ammonia concentrations (p = 0.048). In the $TLR4^{-/-}$ mice, the increase in plasma ammonia levels was significantly lower compared to WT animals (p < 0.001). HA resulted in an increase in relative expression levels ($2^{-\Delta CT}$) of Carbamoyl Phosphate Synthetase 1 (CPS1) and Argininosuccinate Syntethase 1 (ASS1) in both WT (not significant) and $TLR4^{-/-}$ animals (CPS1: p = 0.002, ASS1: p = 0.071). Using $TLR4^{-/-}C$ as a calibrator, relative gene expression of CPS1 (figure) and ASS1 was shown to be approximately twice as high in the $TLR4^{-/-}H$ animals [fold changes ($2^{-\Delta\Delta CT}$): 2.6 and 1.9, respectively]. Gene expression of the other UCEs was similar between groups.

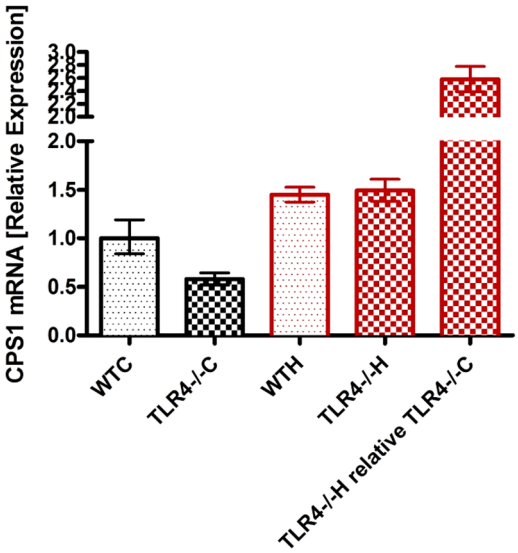


Figure 1: Relative gene expression ($2^{-\Delta\Delta CT}$) of CPS1 in WT and TLR4KO mice with and without hyperammonemia using WTC and $TLR4^{-/-}C$ as calibrators.

Conclusion: The results of this study show for the first time the role of TLR4 in modulating gene expression of UCE and therefore the severity of HA. As CPS1 is a key, rate-limiting UCE, these data point towards a novel pathway of ammonia removal and underline that TLR4 may be a therapeutic target for treating HA.

FRI-230

Regulatory T cells modulate the concentration of short chain fatty acids and the Th function in response to induced bacterial traslocation episodes, and improve the integrity of the gut barrier in an experimental cirrhosis model

O. Juanola[1,2,3], I. Gómez-Hurtado[1,2], P. Piñero[1,2], R. García-Villalba[4], A. Marín[4], E. Caparrós[1,2,3], F.T. Rodrigo[1,5], P. Zapater[2,6,7], J.M. González-Navajas[1,2,8], F.T.-B. Barberán[4], R. Francés[1,2,3,9]. *[1]Instituto ISABIAL, FISABIO, Alicante, Spain; [2]Instituto de Salud Carlos III, CIBERehd, Madrid, Spain; [3]Universidad Miguel Hernández, Medicina Clínica, San Juan de Alicante, Spain; [4]CEBAS-CSIC, Campus de Espinardo, Murcia, Spain; [5]Hospital General Universitario de Alicante, Hematology, Alicante, Spain; [6]Hospital General Universitario de Alicante, Pharmacology; [7]Universidad Miguel Hernández, Pharmacology, Pediatrics and Organic chemestry; [8]Hospital General Universitario de Alicante, Alicante, Spain; [9]Hospital General Universitario de Alicante, Alicante, Spain*
Email: ojuanola@gmail.com

Background and Aims: Regulatory T cells (Tregs) are a key population in keeping a balanced inflammatory response to the intestinal dysbiosis developed during cirrhosis. The short chain fatty acids (SCFAs) produced by the microbiota contribute to achieve a mature host's immune system. Our hypothesis is that Tregs participate in maintaining stable SCFAs levels against induced bacterial traslocation (BT) and improve the integrity of the gut barrier in experimental liver damage.

Method: Rag 1 knockout (KO) mice with oral CCl4 induced cirrhosis during 12 weeks were included (n = 65). A subgroup of animals received *E. coli* 24 hours before laparotomies (n = 38). Naïve T cells and Treg cells were purified from C57Bl/6 WT mice spleens by negative selection and sorted by flow citometry. Recipient Rag KO mice were injected i.p, either with splecnic 2×105 naïve T cells or with 1×105 naïve T cells plus 1×105 Treg cells, from donor WT mice. Laparotomies were performed 48 hours after the adoptive transfer inductions. Intestinal content, ileum, colon, spleen, mesenteric lymph nodes and liver were collected. SCFAs concentration was determined by mass spectroscopy. Th response to *E. coli* was determined by flow cytometry. Gut barrier integrity markers were analized at gene and protein expression levels.

Results: The SCFAs concentrations in the study groups are represented in Figure 1. All SCFAs, but acetic acid, decreased their concentration in response to *E. coli* significantly. However, Treg transferred group showed similar levels in animals treated or untreated with *E. coli*. Th17 and Th1 response in Tnaïve + Treg cotransferred mice was significantly reduced compared with those Rag KO animals transferred just with Tnaïve cells. The gene and protein expression of ZO1, Occludin, Claudin 1, Claudin 2 was significantly increased in Rag KO mice cotransferred with Tnaïve + Tregs.

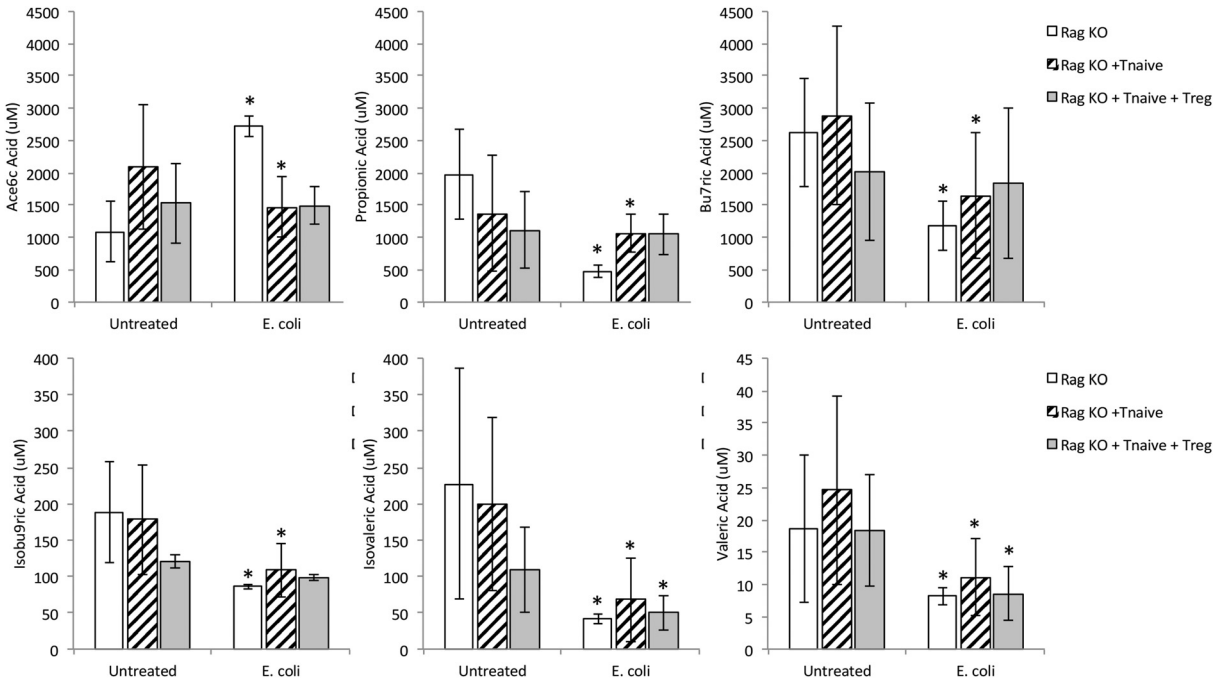
Conclusion: Tregs buffer the intestinal concentration of SCFAs and limit the intensity of Th response to *E. coli*. This association could be mediated by the protective effect of Tregs on gut barrier integrity.

FRI-231

Characterization of the protective effects of yaq-001on organ injury in cirrhosis

F.D. Chiara[1], J. Li[2], H. Lu[1], N. Davies[1], R. Mookerjee[1], R. Jalan[1], J. Macnaughtan[1]. *[1]University College London, ILDH, United Kingdom; [2]Imperial College, Human Development and Microbial Signalling, United Kingdom*
Email: francesco.chiara@ucl.ac.uk

Background and Aims: Bacterial translocation is central to the pathogenesis of complications of cirrhosis. Selective intestinal decontamination with antibiotic therapy is associated with the attendant risk of resistance and superinfection leaving an unmet clinical need. Yaq-001 is a safe, non-absorbable enterosorbant with a high affinity for bacterial toxins which does not exert an antibiotic effect. Previous studies have demonstrated that Yaq-001 reduces ALT,



** p=0.01 comparado con el grupo no tratado*

Figure 1: (abstract: FRI-230)

portal pressure and improves immune function in a rodent model of cirrhosis but the mechanisms by which this occurs are incompletely characterized. The purpose of this study was to evaluate the interorgan effect of Yaq-001.

Method: 4 weeks- BDL Male Sprague-Dawley rats were randomized to receive chow +/- Yaq 001 from week 2. Liver, ileal and colonic tissue RNA was extracted and RNA-Seq libraries were prepared by using Illumina's TruSeq Sample Preparation Kit. Reads were mapped to the rat genome. To identify the pathways that were significantly enriched in samples was performed using Kyoto Encyclopedia of Genes and Genomes (KEGG) and Ingenuity pathway analysis (IPA). The gene sets showing FDR, 0.25, a well-established cutoff for the identification of biologically relevant genes, were considered enriched between the

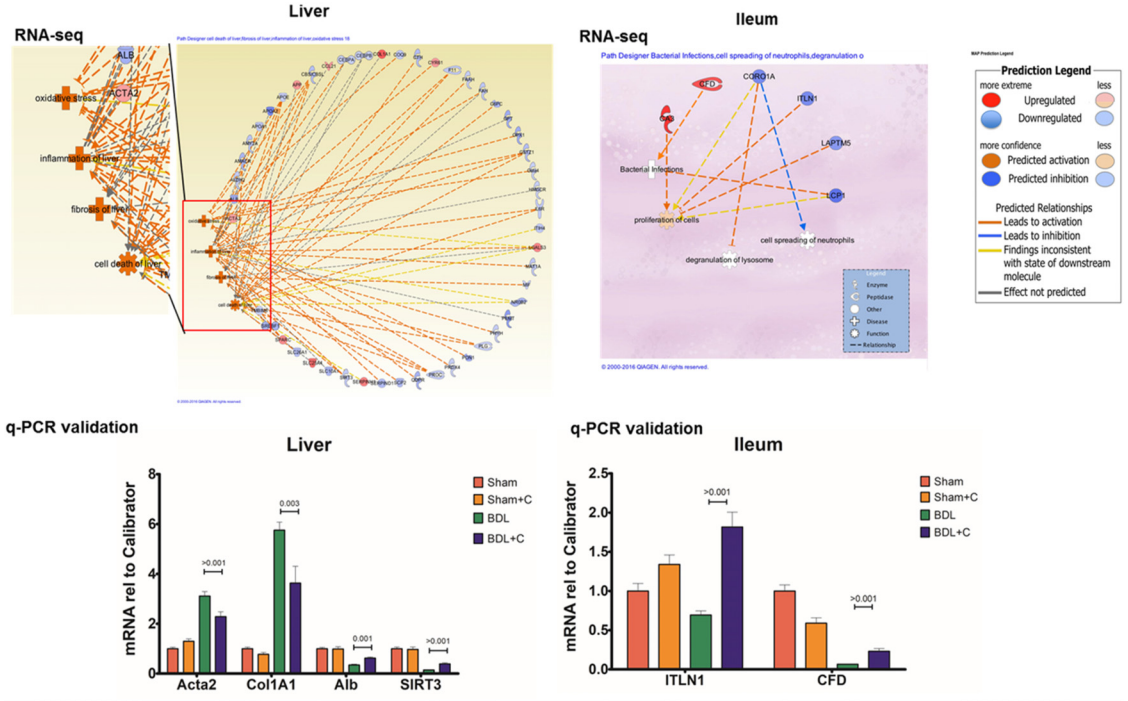


Figure 1: (abstract: FRI-231)

classes under comparison. 1H-NMR spectroscopy was performed on liver ileal and colonic tissue.
Results: In the ileum of BDL rats, RNA-seq analysis showed that bacterial infections (z-score 1.47; P 2×10^{-4}), proliferation of cells (z-score 2.17; 1×10^{-6}) and inhibition of degranulation of lysosomes (z-score –1.49; P 3×10^{-4}) mechanisms are activated. These pathways were inhibited by Carbon treatment. Genes such as ITLN1 and CFD, which play a role in the defense system, were validated by q-PCR. In the liver, Yaq-001 treatment led to regulation of genes involved in the inhibition of oxidative stress (z-score –2.59; P 2×10^{-5}), inflammation (z-score –1.35; P 4×10^{-3}), fibrosis (z-score –1.29; P 1×10^{-4}), and cell death (z-score –1.19; P 1×10^{-3}). Q-PCR analysis confirmed that α-SMA (ACTA2) and Col1a1 were significantly down regulated upon the treatment. Significant shifts in metabolomic profile were observed in lipid and water-soluble fractions on principal component analysis of liver tissue but not ileum or colon. Yaq-001 treatment did not significantly alter metabolomic profile of BDL or sham liver, ileal or colonic tissue.
Conclusion: Yaq-001 attenuates organ injury in cirrhosis by effects on inflammation, fibrosis and cell death pathways. No deleterious effects on the small or large intestine were observed at a gene expression or metabolomic level. Yaq-001 is therefore a safe, efficacious intervention to reduce organ injury in cirrhosis.

FRI-232
Systemic inflammation and portal vein thrombosis in gastroesophageal varices
X. Huang, S. Chen. *Zhongshan Hospital, Fudan University, Department of Gastroenterology, Shanghai, China*
Email: huangxiaoquan1010@aliyun.com

Background and Aims: Patients combined with portal vein thrombosis (PVT) have the higher risk of re-bleeding and the poor prognosis. Growing evidence showed that cirrhosis is associated with the ongoing pro-thrombotic state and systemic inflammation, that possible originating from gut microbiome. However, the correlation between systemic inflammation and PVT is unknown.
Method: We prospectively enrolled cirrhotic patients with gastroesophageal varices between Dec 1st, 2016 and Aug 31st 2017. Patients were divided into PVT group (n = 107) and non-PVT group (n = 139) according to computer tomography angiography. Peripheral blood levels of IL-2R, IL-6, IL-8, IL-10, TNF-α, IFN-γ, ICAM-1, VCAM-1 were quantified by ELISA and cytometric bead array. Furthermore, stool microbiota was quantified to investigate the role of the gut microbiota in the formation of PVT.
Results: Among groups, characteristics were similar including age (55.1 ± 11.9 v.s. 55.1 ± 11.9, p = 0.957) and hepatic venous pressure gradient (HVPG, 16.5 ± 6.7 v.s. 17.0 v.s. 4.8, p = 0.673). Comparing to the control, cirrhotic patients with PVT displayed significant higher serum levels of IL-6 [4.85 (3.15–6.99) v.s. 3.09 (2.06–5.20) pg/ml, p < 0.001], TNF-α [10.75 (7.77–17.75) v.s. 9.16 (7.01–12.40 pg/ml, p = 0.029), IFN-γ (2.27 ± 1.48 v.s. 1.29 ± 1.01, p = 0.018), ICAM-1 (53615.70 ± 25264.07 v.s. 41890.56 ± 21283.02 pg/ml, p = 0.124), VCAM-1 (20210.62 ± 1556.62 v.s. 19245.87 ± 1778.75 pg/ml, p = 0.092). In addition, IL-2R correlated with HVPG (r = 0.3072, p = 0.0114). Fecal microbiota analysis showed that Bacteroides, Prevotella, Enterobacter, Faecalibacterium and Alistipes are the most abundance genera in these patients. The diversity of gut microbiome in PVT group were significant reduced, and Eggerthella was notably increased in PVT group (p = 0.032), while Barnesiella (p = 0.053), Phascolarctobacterium (p = 0.070) and Clostridium XI (p = 0.086) were increased in PVT group.
Conclusion: The study provides the first evidence that systemic inflammation plays the important role in portal vein thrombosis. The changes in gut microbiota might be underlying mechanism in the formation of thrombus.

FRI-233
Pharmacokinetics study of 2 investigational rifaximin soluble solid dispersion formulations (immediate release and sustained extended release) in healthy volunteers
J. Vittitow, Z. Heimanson, R. Israel, E. Lowe. *Salix Pharmaceuticals, Bridgewater, United States*
Email: Jason.Vittitow@bausch.com

Background and Aims: Rifaximin, a nonsystemic antibiotic with low aqueous solubility, is administered as a 550-mg tablet twice daily for prevention of overt hepatic encephalopathy recurrence in adults. To improve gastrointestinal (GI) luminal solubility while minimizing systemic exposure, a new investigational formulation, rifaximin soluble solid dispersion (SSD), was developed. The oral rifaximin SSD tablet was designed to target the small (immediate release [IR]) or large (sustained extended release [SER]) intestine. This phase 1 trial evaluated single-dose pharmacokinetics (PK).
Method: A 2-stage, open-label, randomized, crossover study evaluated the PK of single doses of 80-mg rifaximin SSD IR or 80-mg rifaximin SSD SER tablets in volunteers (fasted [stage 1] or fed state [stage 2]). In stage 2, volunteers were randomly assigned to receive IR or SER after a high-fat meal. Blood samples were collected at baseline and through 48 hours postdose.
Results: 48 adults (mean age, 31.9 y) entered stage 1; 39 entered and completed stage 2. As expected, based on drug release criteria, exposure parameters were different between IR and SER tablets (Table). In the fasted state, rifaximin systemic exposure was greater after a dose of rifaximin SSD IR vs SER (Table). Based on bioequivalence acceptance criteria, exposure in the fasted state, measured by AUC and C_{max}, was statistically different between IR and SER tablets. In stage 2 (fed state), rifaximin systemic exposure (C_{max} and AUC) with IR and SER tablets was not clinically significantly impacted when administered with food, with only small changes in mean values vs fasted state. Median T_{max} was delayed in fed state for IR (3.0 h) and SER (4.0 h) tablets but differences vs fasted state were not significant. A single dose of rifaximin SSD IR and SER tablets was well tolerated.

Table 1: Single-dose PK (fasted state)

	Rifaximin SSD IR tablet (n = 48)*	Rifaximin SSD SER tablet (n = 46)*
C_{max}, mean, ng/ml (SD)	5.2 (4.4)	1.4 (0.8)
T_{max}, median, h (range)	1.5 (0.5–6.0)	2.0 (0.5–6.0)
AUC_{0-last}, h·ng/ml	22.7 (16.3)	8.5 (5.4)
AUC_{0-inf}, h·ng/ml	24.9 (16.6)	10.2 (5.7)
$t_{1/2}$, mean, h (SD)	8.7 (4.1)	6.6 (3.4)

*Patients with sufficient samples. AUC_{0-inf} = area under the plasma concentration–time curve from time zero to infinity; AUC_{0-last} = area under the plasma concentration–time curve from time zero to the last measurable concentration; C_{max} = maximum observed plasma concentration; SD = standard deviation; $t_{½}$ = terminal half-life; T_{max} = time to maximum observed plasma concentration.

Conclusion: Data suggest progressive decreases in systemic exposure as a function of increasing delay in GI release (eg, IR vs SER) and show minimal effects of food. Also, 80-mg rifaximin SSD IR and SER tablets exhibit half-lives that may indicate increased GI residence times and the feasibility of a once-daily dosing regimen.

FRI-234

Simvastatin-loaded polymeric micelles are a new, safe and effective drug delivery system targeting liver sinusoidal endothelial cells

D. Hide[1,2], I. Raurell[1,2], D.F. de So Rafael[3], F.D.S. Andrade[3], S. Schwartz[3], S. Augustin[2,4], J. Genesca[4], M. Martell[1,2]. *[1]VHIR - Vall d'Hebron Institut de Recerca, Liver Unit, Barcelona; [2]CIBERehd, Madrid, Spain; [3]VHIR - Vall d'Hebron Institut de Recerca, CIBBIM - Nanomedicina, Barcelona; [4]Hospital Universitario Vall d'Hebron, Liver Unit, Barcelona, Spain*
Email: diana.hide@vhir.org

Background and Aims: Self-assembled polymeric micelles (PM) are versatile nanocarriers that can load hydrophobic or hydrophilic drugs and can be functionalized in its surface potentially reaching any cell type. Simvastatin has been tested in many models of acute and chronic liver injury showing promising results, but also some adverse effects such as muscular and hepatic toxicity. Thus, the main aim of this study is to characterize the effect of two types of PM loaded with simvastatin targeting liver sinusoidal endothelial cells (LSEC) as a new drug delivery system to improve the treatment of liver diseases
Method: PM with two different polymers (F108 and F127) were produced and analyzed in parallel. Physicochemical characterization included drug encapsulation, size, and polydispersion index. Functional characterization performed in HUVEC and LSEC comprise internalization, cytotoxicity, gene expression assays and phenotype examination by scanning electronic microscopy (SEM). *In vivo* administration of simvastatin-loaded PM was performed for biodistribution and maximum tolerated dose (MTD) assays.
Results: Entrapment efficiency of 20mg/ml simvastatin with a 50:1 polymer: drug ratio was >96%. Size of the produced PM was 22.4 ± 0.23nm and polydispersity index 0.192 ± 0.009nm. Internalization of PM both in HUVEC and LSEC endothelial cells was over 90% in the first hour of incubation regardless the detection method employed. Toxicity assay of PM + SIMVA revealed a 100% cell viability up to 1mM simvastatin concentration in HUVEC and 50 μM in LSEC. In HUVEC, PM + SIMVA were less toxic that the non-encapsulated drug. In LSEC, toxicity values were similar for PM + SIMVA and free simvastatin, indicating no increased toxicity by PM formulation. Functionally, the effects of PM + SIMVA were similar to free simvastatin in HUVEC and LSEC cultures. In summary, a significant increase in KLF2 and eNOS compared to vehicle treated cells was observed, and in both cases simvastatin (free or encapsulated) caused a significant increase in fenestrae frequency and endothelial porosity. Intravenously administered PM were mainly found in the liver. After PM + SIMVA in vivo administration 3 days a week during two weeks, survival was 100% in all concentrations (0.5, 1 or 2 mg/kg) tested and no adverse effects were observed.
Conclusion: PM loaded with simvastatin are less toxic for endothelial cells than the free drug and are effective improving endothelial phenotype. In vivo administration of PM + SIMVA at high concentrations is possible and mainly targets the liver.
Project code: PI15/00066. ISCIII-FEDER CO-FUNDING

FRI-235

Transcriptome analysis of human and murine cirrhotic livers identifies shared molecular pathways as potential targets to enhance cirrhosis regression

E. Lafoz, M.V. Barceló, Héctor García-Calderó, M. Vila-Casadesús, D. Tripathi, M. Ruart, J. Lozano, J. Gracia-Sancho, V. Hernandez-Gea, J.-C. Garcia-Pagan. *Barcelona Hepatic Hemodynamic Laboratory. Hospital Clínic. IDIBAPS, University of Barcelona. CIBEREHD, Barcelona, Spain*
Email: jcgarcia@clinic.ub.es

Background and Aims: In patients with advanced liver disease, etiological treatment partially improves liver fibrosis and portal hypertension. This pattern is replicated in preclinical models of advanced cirrhosis after 8 weeks of etiological agent discontinuation. The aim of our study was to unravel core molecular pathways involved in cirrhosis regression to identify potential new targets to enhance it.
Method: Microarray analysis was done in livers from 1) cirrhotic patients 2) healthy control patients 3) TAA or CCl_4 cirrhotic rats 4) cirrhotic rats after 8-week of CCl_4 or TAA discontinuation 5) control rats. RNA was hybridized to GeneChips (Affimetrix). Differentially expressed genes were analysed in human and rat cirrhosis in relation to their control counterparts (gene list enrichment analysis: Kyoto Encyclopedia of Genes and Genomes and reactome). Enriched pathways shared in human and both models or rat cirrhosis were identified. From those, pathways that did not normalize during cirrhosis regression in rat models were selected.
Results: 6885 genes were upregulated in cirrhotic patients and 1052 genes in rat models. Gene list enrichment analysis revealed 10 shared pathways enriched in rats and human including: ECM (ECM organization, elastic fibre formation), immune system (cytokine signaling, signaling by interleukins, hematopoietic cell lineage), developmental biology, muscle contraction (striated muscle contraction, dilated cardiomiopathy), cancer (pathways in cancer) or hypertrophic cardiomyopathy. Of these, only 2 (hematopoetic cell lineage and striated muscle contraction) normalized during regression while the other 8 remained upregulated.
On the other hand, 7734 genes were downregulated in patients with cirrhosis and 628 in cirrhotic rat livers. Gene list enrichment analysis revealed 5 shared pathways including: metabolism (metabolic pathways, metabolism of lipids and lipoproteins, biological oxidations, peroxisomal lipid metabolism) and transport and catabolism (peroxisome). Three of these pathways (lipid and lipoproteins metabolism, peroxisomal lipid metabolism and peroxisome) did not normalize during regression.
Conclusion: The current study identifies molecular pathways commonly altered both in human and rat cirrhotic livers that do not normalize during cirrhosis regression. Characterization and identification of druggable pathways may reveal innovative and translational therapeutic strategies able to promote cirrhosis regression.

FRI-236

In cirrhotic rats, mitochondria-targeted antioxidant mitoquinone attenuates liver inflammation and fibrosis by modulating oxidative stress and mitophagy

S. Turkseven[1,2], M. Bolognesi[1], A. Brocca[1], P. Angeli[3], M.D. Pascoli[1]. *[1]University and General Hospital of Padova, Unit of Internal Medicine and Hepatology, Department of Medicine (DIMED), Padova, Italy; [2]Ege University, Department of Pharmacology, Izmir, Turkey; [3]Unit of Internal Medicine and Hepatology, University and General Hospital of Padova, Padova, Italy*
Email: m.dipascoli@tin.it

Background and Aims: Mitochondrial dysregulation is responsible for excessive reactive oxygen species production. Selective removal of dysfunctional mitochondria from the mitochondrial network by mitophagy is a crucial step for maintaining mitochondrial quality control. Since in liver cirrhosis oxidative stress plays a major role in triggering liver inflammation and fibrosis, in an experimental model of cirrhosis, we investigated the effect of mitochondria-targeted antioxidant mitoquinone on these processes.
Method: Liver cirrhosis was induced in Spraque-Dawley rats by common bile duct ligation. Mitoquinone (10 mg/kg/day, oral gavage) or vehicle were administered from 3rd to 28th day after common bile duct ligation. The day of the last administration animals were sacrificed. Liver oxidative stress, inflammation, fibrosis and parkin dependent mitophagy was evaluated.
Results: In cirrhotic rats, histological examination showed that mitoquinone prevented liver inflammation, hepatocyte necrosis and fibrosis. Mitoquinone administration was associated with a decreased gene expression of transforming growth factor beta, collagen1A1 and tumor necrosis factor alpha. Moreover, mitoquinone

reduced hepatic oxidative stress, as shown by reduced oxidative carbonylation of the proteins, by modulating antioxidants such as catalase, Mn superoxide dismutase and Cu/Zn superoxide dismutase. Parkin-dependent mitochondrial quality control was improved by mitoquinone, as shown by the increase in Parkin translocation to mitochondria, suggesting an increased selective removal of dysfunctional mitochondria. Furthermore, mitoquinone attenuated apoptosis by reducing hepatic protein expression of cleaved caspase-3.
Conclusion: Mitochondria-targeted antioxidant mitoquinone improves liver inflammation and fibrosis in cirrhotic rats by reducing hepatic oxidative stress, preventing apoptosis and promoting removal of dysfunctional mitochondria. Therefore, it may represent a promising strategy for prevention and treatment of liver cirrhosis.

FRI-237

Ascites NK cells are phenotypically distinct from blood and liver NK cells in patients with liver cirrhosis and become activated by bacterial stimulation in-vitro and during spontaneous bacterial peritonitis

P. Lutz[1,2,3], H.C. Jeffery[3], N. Jones[4], B. Krämer[1,2], J. Birtwistle[5], J. Nattermann[1,2], U. Spengler[1,2], C.P. Strassburg[1,2], D. Adams[3,6], Y.H. Oo[3,6]. *[1]Department of Internal Medicine I, University of Bonn; [2]DZIF, University of Bonn; [3]Centre for Liver Research and National Institute of Health Research Liver Biomedical Research Unit Birmingham, University of Birmingham; [4]Institute of Life Science, Swansea University; [5]Human Biomaterial Resource Centre, University of Birmingham; [6]University Hospital of Birmingham NHS Foundation Trust*
Email: philuweltweit@web.de

Background and Aims: Ascites is frequent in liver cirrhosis and further complicated by bacterial translocation and spontaneous bacterial peritonitis (SBP). Despite the clinical impact of SBP, little is known about ascites as an immune cell compartment. Therefore, we analysed lymphocytes in different human tissues to compare their phenotype and function.
Method: Mononuclear cells from blood, ascites and liver explants of patients with advanced liver disease were extracted by density centrifugation. Phenotyping and analysis of functional responses were carried out using flow cytometry. Migration and cell metabolism were assessed by transwell assays and using Seahorse technology, respectively.
Results: At first, ascites, blood and liver explants from 43 patients without SBP were studied (74% male; median age 53 years; alcoholic cirrhosis in 51%). In contrast to B-, CD4-, CD8-, regulatory T-, MAIT- and γδ T-cells, NK cell frequency was increased in ascites compared to blood (median 27% vs 7%; $p < 0.001$), but not to liver. Most ascites NK cells were $CD16^{positive}$ (73% vs 83% in blood and 41% in liver; $p < 0.01$). Expression of the activating receptor NKG2D was decreased on ascites and liver $CD16^{positive}$ NK cells ($p = 0.009$), while expression of the inhibitory receptor NKG2A was comparable on blood (64%) and ascites (57%) $CD16^{positive}$ NK cells, but decreased in liver (45%; $p = 0.02$). As demonstrated by HLA-DR expression, ascites and liver $CD56^{dim}$ NK cells were more activated compared to blood ($p = 0.03$). Consistently, a significantly increased maximal respiration of ascites versus blood NK cells indicated a greater capacity to respond to activation. Ascites $CD16^{positive}$ NK cells expressed higher levels of CXCR3 than blood or liver NK cells, corresponding to increased ascites levels of CXCL10 secreted by $CD14^{positive}$ monocytes/macrophages. Stimulation of mononuclear cells with Escherichia coli (E. coli) led to downregulation of NKG2D-, upregulation of HLA-DR-expression and secretin of Interferon-gamma (IFNg) mediated by IL-12 and IL-18 in NK cells from ascites, but not from blood. Blocking IFNg modulated the inflammatory response of E. Coli stimulated ascites $CD14^{positive}$ monocytes/macrophages. Similarly, ascites NK cells were more activated and expressed less NKG2D in SBP compared to uninfected ascites in a second cohort of patients.
Conclusion: Ascites NK cells may be implicated in local immune defense against translocating bacteria by interacting with monocytes/macrophages.

FRI-238

Protective role of VEGF-A165b in liver cirrhosis with portal hypertension

R. Schierwagen[1], C.-E. Ruiner[1], J. Lehmann[1], A. Pohlmann[1], S. Klein[2], F. Uschner[1], F. Magdaleno[1], C. Jansen[1], R. Pe[3], J. Trebicka[1,4,5,6]. *[1]University of Bonn, Department of Internal Medicine I, Bonn, Germany; [2]Newcastle University, Fibrosis Research Group, Newcastle; [3]Paris Cardiovascular Research Center, INSERM U970, Paris, France; [4]European Foundation for the Study of Chronic Liver Failure - EF Clif, Barcelona, Spain; [5]Institute for Bioengineering of Catalonia, Barcelona, Spain; [6]Odense University Hospital, Department of Medical Gastroenterology and Hepatology, Odense, Denmark*
Email: robert.schierwagen@ukbonn.de

Background and Aims: Chronic liver damage and vascular diseases may lead to the development of portal hypertension. The vascular endothelial growth factor A (VEGF-A) plays a central role in this context by regulating vascular angiogenesis. However, it is still uncertain in which way VEGF-A contributes to the development of portal hypertension. Several alternative splice variants of VEGF-A may explain the opposing results gathered so far. This study investigates the role of the splice variant $VEGF\text{-}A^{b}_{165}$ for the development of portal hypertension.
Method: Blood from cirrhotic patients was gathered at transjugular portosystemic shunt insertion. Levels of total VEGF-A and $VEGF\text{-}A^{b}_{165}$ were measured using ELISA-kits. miRNAs were assessed by RT-PCR. Hepatic and vascular contractile, as well as endothelial cells were *in vitro* incubated with $VEGF\text{-}A^{b}_{165}$ and effects on contraction, fibrogenesis and angiogenesis were measured by gene expression and protein synthesis.
Results: Total levels of VEGF-A showed an increased gradient over the liver in cirrhotic patients and are packed in microparticles of endothelial origin to a large extent. Furthermore, high levels of total VEGF-A in the portal vein are associated with an unexpected improvement of survival, which seems to be affiliated to the splice variant $VEGF\text{-}A^{b}_{165}$. Along with increasing $VEGF\text{-}A^{b}_{165}$ levels over the liver, higher levels of miRNAs 125b and 126 were measured post-hepatic, which may act as regulators of the VEGF-A production. Only levels of $VEGF\text{-}A^{b}_{165}$, but not total VEGF-A levels, reflect disease progression with highest values in patients without ascites and decreasing levels with developing ascites. Incubation with $VEGF\text{-}A^{b}_{165}$ decreased vascular angiogenesis and contractility. However, intrahepatic $VEGF\text{-}A^{b}_{165}$ increases contraction of hepatic stellate cells and tends to increase proliferation.
Conclusion: Circulating $VEGF\text{-}A^{b}_{165}$ turns out to be a marker of complication severity in cirrhotic patients with portal hypertension. Higher levels of $VEGF\text{-}A^{b}_{165}$, representing no/less severe complications, explain the benefit in survival. If the decreased vascular angiogenesis and contractility in patients accounts for this benefit has to be investigated extensively in regard to treatment approaches for portal hypertension and its complications in cirrhotic patients. Care needs to be taken to the possible unfavorable effects on hepatic cells, especially hepatic stellate cells.

FRI-239

Real world experience of lusutrombopag for thrombocytopenia in patients with liver cirrhosis

H. Takada, N. Izumi, M. Kurosaki, J. Itakura, K. Tsuchiya, H. Nakanishi, Y. Yasui, T. Nobuharu. *Musashino Red Cross Hospital*
Email: takadahi@musashino.jrc.or.jp

Background and Aims: Lusutrombopag is an oral thrombopoietin receptor agonist which have been approved for use to improve thrombocytopenia in cirrhotic patients before invasive procedures. We herein report the efficacy and safety of administration of lusutrombopag for thrombocytopenia in real-world setting.
Method: A total of 1606 consecutive cirrhotic patients who were scheduled to undergo invasive procedures from January 2014 to September 2017 in our hospital was studied. Platelet counts and the

frequency of platelet transfusion were monitored. From November 2013 to September 2017, lusutrombopag was administered in 16 patients with liver cirrhosis whose platelet count <50.000/microl. Lusutrombopag administration was stopped at day 5 if the patients achieved platelet counts ≥50.000/microl or increase of ≥20.000/microl within day 5, and was continued for a total of 7 days in other patients.

Results: The median platelet counts with radio-frequency ablation (RFA, n = 686), transarterial chemoembolization (TACE, n = 770) and endoscopic injection sclerotherapy/endoscopic variceal ligation (EIS/EVL, n = 150) was 123.000, 116.000, and 116.000/ microl, respectively. The proportion of patients with platelet count <50.000/microl were 6.0%, 6.4%, and 6.0%, respectively. For these patients with low platelet counts, platelet transfusion was given in 67%, 42%, and 60%, respectively. Lusutrombopag was administered in 16 patients, the platelet counts before administration of lusutrombopag was 39.000 ± 11.000/microl which increased to 78.000 ± 29.000/microl before the invasive procedure ($p < 0.05$). Platelet transfusion was necessary in only one patient (6%). There was no adverse events such as bleeding and thrombosis.

We developed a scoring system where each of the following was scored as 1 (platelet counts 30.000–50.000/microl, Child-Pugh grade A, Spleen index 20–35, and alcohol drinkers), and each of the following was scored as 2 (platelet count less than 30.000/microl, Child - Pugh grade B, and Spleen index over 35). Among lusutrombopag administered patients, 10 patients had total scores of 4, and 6 patients had scores of 5. In patients of score 4, a significant increase in platelet count was observed compared with the patients of score 5 (52.000 ± 22.000 vs. 26.000 ± 16.000/microl, $p = 0.023$). The platelet counts reached to plateau at day 10 in patients with baseline platelet counts 30000–50000/microl (n = 13) and at day 12 in patients with <30000 /micro (n = 3).

Conclusion: The administration of lusutrombopag for thrombocytopenia in cirrhotic patients was effective and safe in the real-world setting, and reduced the need for platelet transfusion in 94% of patients.

FRI-240

Chronic liver damage causes a reduction in the number and a dysfunction of the activity of liver resident macrophages

E. Pose[1,2,3,4], M. Coll[2,3,4], B. Surewaard[5], Z. Zeng[5], D. Blaya[3,4], L. Perea[3,4], B. Aguilar-Bravo[3,4], J. Vallverdú[3,4], I. Graupera[1,2,4], P. Sancho-Bru[3,4], P. Kubes[5], P. Ginès[1,2,4]. *[1]Hospital Clinic de Barcelona, Liver Unit, Barcelona, Spain; [2]University of Barcelona, Faculty of Medicine and Health Sciences, Barcelona, Spain; [3]IDIBAPS, Barcelona, Spain; [4]CIBEReHD, Barcelona, Spain; [5]The Calvin, Phoebe & Joan Snyder Institute for Chronic Diseases, University of Calgary, Calgary, Canada*
Email: pgines@clinic.ub.es

Background and Aim: Patients with decompensated cirrhosis have high risk of infections, which are the main cause of death in this population. Liver resident macrophages or Kupffer cells (KCs) play an essential role in the immune system given their high capacity of eliminating bacteria from the circulation. Although immune function of the liver is thought to be impaired in cirrhosis and contribute to the risk of infections, there is lack of information about KCs population and function. Our aim was to evaluate the number, function and role in the predisposition to infections of KCs in patients with cirrhosis.

Methods: KCs were quantified by CD68+ area in liver biopsies from patients with compensated (n = 22) and decompensated cirrhosis (n = 19), acute liver failure (n = 9) or controls (n = 9). KCs isolated from explants of patients with cirrhosis and from a control group were stimulated with LPS; response was evaluated by inflammatory cytokines expression. In vivo KCs phagocytic capacity in patients with cirrhosis was evaluated by hepatic SPECT with 99mTc-phytate. In vivo KC function was studied in a mouse model of chronic liver injury (DDC diet) infected with bacteria over-expressing GFP (*MRSA*, $5{\cdot}10^7$ cfus, *iv*). Bacterial catching capacity was determined by spinning-disc intravital microscopy. Bacterial dissemination to extra-hepatic organs and survival were evaluated.

Results: The area occupied by KCs in liver biopsies from patients with cirrhosis was significantly lower compared to the other groups ($p < 0.01$). KCs from patients with cirrhosis showed a decreased response to inflammatory stimulus compared to controls. Patients with decompensated cirrhosis showed a lower uptake of 99mTc-phytate by the liver. In DDC mice, bacterial catching capacity by KCs was reduced compared to that in controls ($p < 0.05$). Bacterial dissemination and bacteremia were markedly increased in chronic liver injured mice. Moreover, survival after infection was reduced in DDC mice compared to controls ($p < 0.05$).

Conclusion: Patients with cirrhosis have a reduction in liver resident macrophages. This cell population exhibits an impaired phagocytic capacity and response to inflammation. KCs from mice with chronic liver injury show a reduced capacity of capturing bacteria from the circulation, leading to a major susceptibility to infections. Therefore, increasing the number and promoting phagocytic capacity of KCs might be a good strategy to reduce the risk of infections in patients with cirrhosis.

FRI-241

An immuno-metabolic phenotype of acute-on-chronic liver failure predicts early mortality

R. Zia[1], U.-K. Umlai[1], K.L Leary[1], V. Patel[2], I.D Wilson[1], J. Wendon[2], M. Coen[1], M.J.W. Mcphail[2]. *[1]Imperial College London, Computational and Systems Medicine, London, United Kingdom; [2]Kings College Hospital, Institute of Liver Studies, London, United Kingdom*
Email: rabiya.zia08@imperial.ac.uk

Background and Aims: Mortality rates for acute-on-chronic liver failure (ACLF) remain high and immune dysfunction is a key accelerator of disease progression in ACLF patients. More accurate prognostic biomarkers are needed and changes in phospholipid (PC) metabolism accurately predict survival in acutely decompensated (AD) cirrhosis. We expand on this by profiling ACLF patients and quantifying downstream inflammatory mediators: eicosanoids (ECs). We aim to characterize immune-metabolic changes that explain progression to ACLF and aid prognostic scoring.

Method: Metabotyping of lipids in human serum was performed by untargeted ultra-performance liquid chromatography-mass spectrometry (UPLC-MS) in positive (LPOS) and negative (LNEG) ionisation modes, and targeted UPLC-MS to quantify EC in the following patients: ACLF (n = 49), AD (n = 50), stable cirrhosis (n = 13) and HC (n = 38). Univariate analysis using the Kruskal-Wallis (KW) with a post-hoc Dunns test and multivariate analysis using principal component analysis (PCA) and orthogonal projections to latent structures discriminant analysis (OPLS-DA), were used for analyses. External validation was performed on LNEG and LPOS datasets by calculating area under the receiver operating curve (AUROC). Tentative metabolite identification (metID) from LPOS and LNEG data was performed using online metabolite databases.

Results: Multivariate analysis of the LNEG and LPOS data generated models which show separation between all groups in PCA in PC1 – (LPOS: $R2 = 0.56$ $Q2 = 0.52$ and LNEG: $R2 = 0.60$ $Q2 = 0.56$). Tentative metID of LPOS and LNEG data revealed that most discriminant endogenous metabolites for AD vs ACLF were PCs. OPLSDA models of survival (30 days) were computed from LNEG ($R2Y = 0.50$, $Q2Y = 0.29$, CV-ANOVA p-value = $1{\times}10^{-6}$) with AUROC of 0.92, sensitivity = 90%, specificity = 79%, $p < 0.001$, LPOS ($R2Y = 0.56$, $Q2Y = 0.35$, CV-ANOVA p-value = $5{\times}10^{-8}$) with AUROC of 0.96, sensitivity = 90%, specificity = 88%, $p < 0.001$ and EC ($R2Y = 0.43$, $Q2Y = 0.32$, CV-ANOVA p-value = $4{\times}10^{-6}$) data. Univariate analysis of ECs showed that anti-inflammatory ECs were raised in survivors: Lipoxin-A4($p = 0.005$), 5,6-DHET($p = 0.0001$), Lipoxin-B4($p = 0.007$), 5(S)-HETE($p = 0.007$), PGE2($p = 0.001$) and PGD2($p = 0.002$).

Conclusion: We demonstrate that changes in lipid and EC metabolism are discriminant between AD and ACLF. Furthermore, greater

circulating levels of anti-inflammatory ECs may be involved in resolution of the inflammatory response and are characteristic of survival in AD and ACLF.

FRI-242

Etiology-specific hemostatic profiles in cirrhosis

S. Bos, J. Adelmeijer, H. Blokzijl, P.W. Kamphuisen, S. Tim, T. Lisman.
University medical center Groningen, Groningen,
Email: s.bos01@umcg.nl

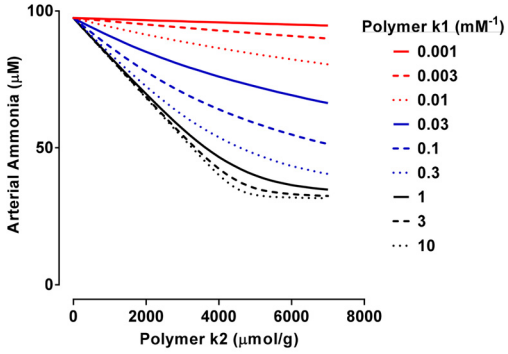
Background and Aims: Patients with cirrhosis may acquire profound changes in their hemostatic system. Although hemostatic changes have been extensively studied, most studies were performed in groups of patients with mixed etiology. We hypothesized that hemostatic changes might be different across etiologies.
Methods: 41 healthy controls and 79 patients with cirrhosis (21 alcoholic liver disease (ALD), 16 non-alcoholic steatohepatitis (NASH), 28 cholestatic liver disease (17 primary sclerosing cholangitis, 11 primary biliary cholangitis), 14 viral hepatitis (7 hepatitis C, 7 hepatitis B)) were studied. Patients with malignancy were excluded. Routine diagnostic tests of hemostasis, thrombin generation assays, and a plasma-based fibrinolytic assay were performed. In addition, plasma levels of individual hemostatic factors were determined.
Results: All cirrhotic patients had comparable severity of disease according to their MELD-score (9 [7–11]). Prothrombin time was significantly prolonged for all etiologies and highest in ALD. The platelet adhesive protein VWF was elevated in all groups, but substantially lower in viral hepatitis than in other etiologies. The VWF-cleaving protease ADAMTS13 was decreased in cholestatic disease and viral hepatitis but not in ALD and NASH. The endogenous thrombin potential was significantly increased compared to controls in all patient samples with the highest values in NASH. Plasma levels of factor VIII were elevated in all groups except viral hepatitis, FVII was similarly decreased in all groups and prothrombin levels were decreased in all groups except in viral hepatitis. Protein C and antithrombin were similarly decreased in all groups. Fibrinogen levels were elevated in all groups and highest in the cholestatic group. Fibrinolytic potential was similar in all groups, with a small decrease in fibrinolytic potential in the cholestatic group.
Conclusion: There are notable differences in the hemostatic profile in cirrhotic patients of different etiologies. For example, the hemostatic status of patients with cholestatic liver disease has notable hypercoagulable features, but also decreased thrombin generation compared to the other groups. In line with our previously published data, patients with NASH do not appear particularly hypercoagulable, although TGA was highest in this group. These distinct differences necessitate further research focussing on individualized management of bleeding and thrombosis in patients with cirrhosis.

FRI-243

Prediction of blood ammonia levels in modeled human liver dysfunction and application to gut-restricted ammonia lowering therapeutics

C. Brew[1], S. Smith[1], L. Noiret[2], E. Labonté[1], C. Rose[3], S. Harrison[1].
[1]Relypsa, Research Biology, Redwood City, United States; [2]Universite Pierre et Marie Curie, bioinformatique, Paris, France; [3]Université de Montréal, CRCHUM, Tour Viger, Dept. Medicine, Montreal, Canada
Email: christinebrew@yahoo.com

Background and Aims: Hepatic encephalopathy (HE) is a debilitating complication of cirrhosis which is defined as an array of neuropsychiatric abnormalities. Patients with HE suffer from a poor quality of life including impaired driving skills, inability to work, and susceptibility to frequent falls. A primary cause of HE is the accumulation of ammonia in the systemic circulation which leads to toxic levels of ammonia in the brain. Because a majority of ammonia is generated in the gut, one therapeutic strategy is to bind ammonia in the lumen using a gut-restricted polymer, preventing ammonia absorption into the systemic circulation. To understand the optimal binding properties required to efficiently lower blood ammonia, it is imperative to understand inter-organ ammonia metabolism in cirrhosis.
Method: We have developed a dynamic *in silico* model of ammonia distribution using Berkeley Madonna PK/PD modeling software. Physiological parameters were defined to describe the flux of ammonia in healthy and cirrhotic states, and were obtained from reported inter-organ fluxes of ammonia in fasted individuals with and without cirrhosis. Key physiological changes in cirrhosis include an increase of splanchnic blood flow, porto-systemic shunting and a loss of hepatic functions. The model was validated by assessing how it predicts blood ammonia levels at baseline and following an oral ammonia challenge, as well as its prediction of ammonia concentrations in the portal vein and feces under various degrees of portal-systemic shunting and liver impairment.
Results: Arterial ammonia levels were very sensitive to factors such as ammonia production in the gut, hepatic and muscle ammonia extraction, degree of porto-systemic shunting, and portal blood flow. Other parameters, such as the GI absorption rate constant for ammonia and gut volume had less impact on arterial ammonia levels. We assessed the impact of various theoretical, gut-restricted ammonia binding therapeutics, and found it is feasible to significantly reduce blood ammonia levels by removing ammonia from the gut. The model has been used to evaluate how a change in affinity and/or capacity of the binding agent impacts systemic ammonia levels (Figure).



Theoretical impact of polymer on arterial ammonia levels in a model of human cirrhosis; evaluation of the sensitivity to polymer capacity (k2) and affinity (k1)

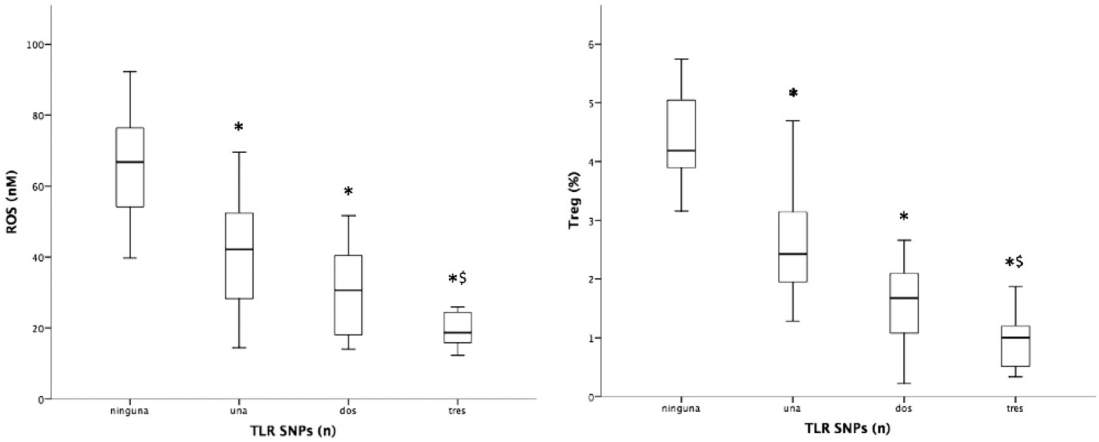
Conclusion: In summary, we developed the first dynamic model of interorgan ammonia metabolism in cirrhosis. The model demonstrates that binding ammonia in the gut should meaningfully lower arterial blood ammonia levels in cirrhosis.

FRI-244

Polymorphisms in toll-like receptors identify a defective oxidative response and a reduction in the regulatory T cell population in patients with cirrhosis and non-infected ascites

P. Piñero[1], O. Juanola[2], I. Gómez-Hurtado[3], P. Zapater[3], E. Caparrós[2], José Such[2,4], J.M. González-Navajas[5], Rubén Francés[2,3,5]. *[1]Fundación Isabial-Fisabio, Hospital General Universitario de Alicante, CIBERehd, Alicante, Spain; [2]Universidad Miguel Hernández, Dpto. Medicina Clínica, Alicante, Spain; [3]CIBERehd, Instituto de Salud Carlos III, Madrid, Spain; [4]Cleveland Clinic Abu Dhabi, Digestive Disease Institute, Abu Dhabi, United Arab Emirates; [5]Fundación Isabial-Fisabio, Hospital General Universitario de Alicante, Alicante, Spain*
Email: paupinrom@gmail.com

Background and Aims: Patients with cirrhosis are frecuently exposed to the translocation of bacterial antigens that complicate the course of the disease. Toll-like receptors (TLRs) are a fundamental part of the innate immune response in the resolution of these episodes, which requires the production of reactive oxygen species (ROS) for clearance. This response is controlled by regulatory T



** p=0.01 comparado con la ausencia de SNPs; $ p=0,01 comparado con la presencia de 1 ó 2 SNPs*

Figure (abstract FRI-244)

lymphocytes (T reg), which balance the response and favor immunological tolerance.
We aim to evaluate if the accumulation of polymorphisms in the TLR genes decreases the oxidative response and the proportion of Treg cells in patients with cirrhosis.
Method: Prospective observational study in patients with cirrhosis and non-infected ascites. Serum ROS concentration was determined by ELISA and the blood Treg cell population was quantified by flow cytometry using a CD3+ CD4+ CD25+ CD127-FoxP3+ panel.
Results: We included 71 patients with a mean age of 60 ± 10 years. The main etiology was alcohol and the mean Child-Pugh was 9.2 ± 1.8. Twenty-two patients (30.9%) were taking β-blockers and 25 (35.2%) PPIs. Seven patients did not show SNPs (9.9%), 33 showed 1 SNP (46.5%), 26 patients the combination of 2 SNPs (36.5) and 5 carried the 3 SNPs studied (7.1%). The concentration of ROS and the percentage of Treg cells in blood are shown in Figure 1. Patients without SNPs showed significantly higher ROS and Treg levels than those observed in patients with one or more SNPs. In addition, patients with 3 SNPs showed significantly lower levels in both variables compared with patients with 1 or 2. A positive correlation was observed between ROS concentrations and the percentage of Tregs in the sample studied (r = 0.615, p = 0.001).
Conclusion: Polymorphisms in TLR genes limit the immune response and its modulation. Therefore, they could hinder the clearance of translocated bacterial antigens in patients with cirrhosis and non-infected ascites.

FRI-245
Bacterial translocation during experimental cirrhosis coincidences with the infiltration of inflammatory monocytes in the gut
L. Meelberghs[1], S. van der Merwe[1,2], F. Nevens[1,2], L. Verbeke[1,2], H. Korf[1], P. Windmolders[1], I.V. Elst[1]. *[1]KU Leuven, Laboratory of Hepatology, Leuven, Belgium; [2]UZ Leuven, Gastroenterology and Hepatology, Leuven, Belgium*
Email: lore.meelberghs@kuleuven.be

Background and Aims: Patients with advanced cirrhosis are susceptible to bacterial infections. The majority of infections originate from the gut due to a failure of the intestinal barrier function and the local innate immune system to dampen the response towards translocated bacteria. Indeed, we have previously demonstrated that intestinal myeloid cells from decompensated cirrhosis patients feature elevated levels of inflammatory parameters that may aggravate intestinal barrier dysfunction. However, the mechanisms governing the intricate cross talk between host and microbe, remain incompletely understood. Here we aim to elucidate the role and dynamics of inflammatory monocytes and macrophages during cirrhosis pathogenesis.
Method: C57BL/6J mice received subcutaneous carbon tetrachloride (CCl_4) injections (2ml/kg of CCl_4 50% (v/v)) (n = 5–8) or vehicle only (n = 3–4) twice a week. Mice were sacrificed after 4-, 9-, 14-, or 19 weeks and the extent of liver fibrosis/cirrhosis was assessed histologically following Picrosirius Red staining. Additionally, intestinal samples (proximal- distal small intestine, and colon) were collected for flow cytometry and mesenteric lymph nodes (MLNs) and plasma were collected for bacterial culture and liver function tests respectively.
Results: Histological analysis confirmed advanced fibrosis and cirrhosis development at week 14 and 19 respectively. Bacterial translocation as evaluated by culture positive MLN's, occurred at week 19, although elevated levels of bacterial products such as LPS, were detected both at week 14 and week 19 of CCl_4 exposure. Flow cytometric analyses of lamina propria cells isolated from the small bowel and colon revealed a gradual decrease in the frequencies of $MHC^{high}CD11b^{high}CX3CR1^{pos}CD64^{pos}$ resident macrophages. Conversely, intestinal samples from cirrhotic mice were enriched with $MHCII^{int}CD11b^{int}CX3CR1^{pos}Ly6C^{pos}$ inflammatory monocytes and the latter observation coincided with the presence of bacterial products in the circulation. Moreover, infiltrating inflammatory monocytes expressed high levels of CCR2 implicating their responsiveness towards the chemokine microenvironment.
Conclusion: These studies reinforce the pathogenic role of monocytes in dysregulated responses to intestinal bacteria during cirrhosis. Further understanding of their importance during intestinal barrier dysfunction are ongoing and may lead to strategies aimed at interrupting cirrhosis-driven pathology.

FRI-246
Effectiveness of a practical nutritional intervention in advanced liver disease: A prospective study
D. Costa[1], H. Silva[2], A.Célia Caetano[1], Luís Meira-Machado[3], C. Rolanda[1], R. Gonçalves[1], D. Fernandes[1]. *[1]Braga Hospital, Gastroenterology; [2]School of Medicine; University of Minho; [3]University of Minho, Centre of Mathematics and Department of Mathematics and Applications*
Email: dc.dalilacosta@gmail.com

Background and Aims: Malnutrition is one of the most prevalent complications of advanced liver disease and is associated with poor clinical outcome. In mixed populations of malnourished patients, the benefits of nutrition therapy are evidenced by reduction in mortality, infections and hospital length of stay. However, cirrhosis-specific studies are limited. The aim of the present study was to evaluate the

impact of an adequate oral diet on nutritional status of patients with advanced liver disease (ALD) during a period of 3 months.
Methods: A prospective, interventional and single-center study was performed. Nutritional assessment was achieved in 75 consecutive patients with ALD (Child-Pugh B and C) evaluated between January and May 2017. 24 patients diagnosed with protein-caloric malnutrition according with Bioelectrical impedance analysis (BIA) measures were introduced to an appropriate nutritional plan (energy intake of 35–40 kcal/kgBW/d and a protein intake of 1.5 g/kgBW/d) developed and implemented (verbal and written) by the Department of Nutrition. Patients were divided into two equal groups according with diet compliance (DC v non-DC). Clinical, anthropometrical and biochemical data were assessed at a 3-month follow-up.
Results: Patients in both groups did not differ significantly. Most were male (21; 87.5%), Child-Pugh B (21; 87.5%) with a mean age of 57.6 years. According to BIA, the controlled diet significantly improved nutritional status in DC group (p = 0.003), since 8 patients were no longer malnourished at 3-month follow-up. At paired analysis, all nutritional parameters improved in DC group, though only dry-weight body mass index (BMI) (p = 0.010), triceps skinfold (TSF) (p = 0.019) and arm circumference (AC) (p= 0.006) were significant. When compared to non-DC, mid-arm muscle circumference (MAMC) also improved (p = 0.01). At biochemical analyses, leucocyte count significantly decreased (p = 0.029) in DC and no significant differences were identified between the groups.
Conclusion: We showed that a rational and practical nutritional approach is effective in improving nutrition status in ALD during a short-term follow-up.

FRI-247
Udenafil decreases portal pressure and improves erectile dysfunction in liver cirrhosis

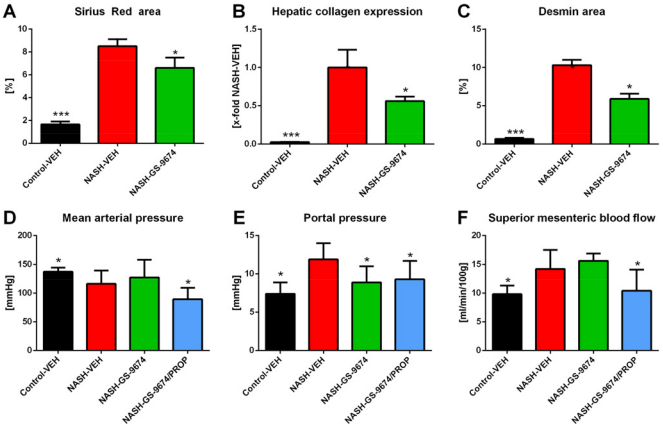
F.E. Uschner[1], K. Glückert[1], S. Klein[2], F. Magdaleno[1], R. Schierwagen[1], J. Trebicka[1,3,4,5]. *[1]University Hospital Bonn, Internal Medicine I, Bonn, Germany; [2]Newcastle University, Institute of Cellular Medicine, Newcastle upon Tyne; [3]European Foundation for the Study of Chronic Liver Failure - EF Clif, Barcelona, Spain; [4]Odense University Hospital, Department of Medical Gastroenterology and Hepatology, Odense, Denmark; [5]Institute for Bioengineering of Catalonia, Barcelona, Spain*
Email: frank.uschner@ukb.uni-bonn.de

Background and Aims: In liver cirrhosis contraction of myofibroblasts leads to increased hepatic resistance and portal hypertension. As a consequence, patients develop varices and gastrointestinal bleeding. Even though the prophylaxis with non-selective ß-blockers (NSBB) reduces bleeding risk, it may induce or augment erectile dysfunction, which impairs quality of life in these patients. Udenafil has been shown to reduce portal pressure (PP) and as a phosphodiesterase-5 (PDE-5) inhibitor it might improve erectile dysfunction. Therefore, the present study investigated the effects of udenafil and NSBB on portal hypertension and erectile function in cirrhotic rats.
Method: Erectile function in male cirrhotic patients was investigated by standard questionnaire (International Index of Erectile Function). Liver cirrhosis was induced by bile duct ligation (BDL) or CCl_4 intoxication. The portal pressure (PP) was measured invasively *in vivo* before and after i.v. bolus-injection of udenafil and was compared to placebo. The portal and systemic hemodynamics were investigated using the coloured microsphere technique. Isolated *in situ* liver perfusion in BDL and CCl4 intoxicated rats investigated the relaxation of the hepatic vascular bed by udenafil. Erectile function was assessed *in vivo* by cavernous nerve stimulation and simultaneous corpus cavernosum pressure (CCP) measurement before and after treatment with propranolol and udenafil in sham operated and BDL rats.
Results: 8 out of 13 male cirrhotic patients (61%) report erectile dysfunction and 5 out of them (62%) are under NSBB. Udenafil decreased the PP *in vivo* and consequently the hepatic vascular resistance in experimental liver cirrhosis. Furthermore, udenafil reduced the perfusion pressure dose-dependently during *in situ* liver perfusion. Interestingly, erection related increase in CCP was significantly lower in BDL compared to sham operated rats at baseline and propranolol treatment even worsened the erection in these animals. Remarkably, udenafil treatment significantly increased CCP in untreated, as well as in propranolol pre-treated cirrhotic rats.
Conclusion: Udenafil treatment ameliorated portal hypertension and improved erectile dysfunction in experimental liver cirrhosis. Therefore, udenafil could be a treatment option for portal hypertension with particularly improving quality of life in male cirrhotic patients.

FRI-248
The FXR agonist GS-9674 reduces fibrosis and portal hypertension in a rat model of NASH

P. Schwabl[1,2], G. Budas[3], E. Hambruch[4], P. Supper[1,2], M. Burnet[5], J. Liles[3], T. Sullivan[3], E. Huntzicker[3], M. Birkel[4], D. French[3], D. Tumas[3], M. Peck-Radosavljevic[1,6], W. Watkins[3], M. Trauner[1], D. Breckenridge[3], C. Kremoser[4], T. Reiberger[1,2]. *[1]Medical University of Vienna, Div. of Gastroenterology and Hepatology, Dept. of Internal Medicine III, Vienna, Austria; [2]Medical University of Vienna, Vienna Hepatic Hemodynamic Lab, Vienna, Austria; [3]Gilead Sciences, Inc., Foster City, United States; [4]Phenex Pharmaceuticals AG, Heidelberg, Germany; [5]Synovo GmbH, Tübingen, Germany; [6]Klinikum Klagenfurt, Abteilung für Innere Medizin, Klagenfurt, Austria*
Email: philipp.schwabl@meduniwien.ac.at

Background and Aims: FXR agonists reduce fibrosis and portal pressure (PP) in rat models of toxic and cholestatic cirrhosis. Moreover, FXR agonists improve histological features of NASH in patients. We studied the effects of FXR agonism on hepatic fibrosis and hemodynamics in a rat model of advanced NASH with or without non-selective betablockade as medical standard treatment of portal hypertension.
Methods: Male Wistar rats received a choline-deficient high fat diet (CDHFD) for 14 weeks with repeated $NaNO_2$ injections (25mg/kg i.p., 3x/week) from weeks 4–14 to induce NASH. Vehicle (VEH) or FXR agonist GS-9674 (30mg/kg) were gavaged daily from weeks 4–14. In each group a subset also received the beta-blocker propranolol (PROP, 25mg/kg). Mean arterial pressure (MAP), heart rate (HR), portal pressure (PP) and superior mesenteric artery blood flow (SMABF) were measured. Fibrosis was assessed by Sirius Red area (SR) and collagen expression. As indicator of hepatic stellate cell (HSC) activation desmin area (DA) was quantified by immunofluorescence. Target engagement was assessed by qRT-PCR profiling of FXR downstream signaling in hepatic and ileal tissue.



Results: NASH rats had significant steatosis, fibrosis and portal hypertension compared to healthy controls. GS-9674 significantly increased *Fgf15* expression in the ileum (+282%; p = 0.045) and decreased *Cyp7a1* in the liver (–63%; p = 0.005). In GS-9674 treated NASH rats, liver fibrosis (SR: 6.6 ± 0.9 vs. 8.5 ± 0.6%; p = 0.047) and hepatic collagen expression (–43.7%; p = 0.032) were significantly

reduced, compared to VEH treated controls. In line, GS-9674 also significantly reduced HSC activation (DA: 5.9 ± 0.7 vs. 10.3 ± 0.8%; p = 0.004). Treatment with GS-9674 significantly decreased PP (8.9 ± 2.2 vs. 11.9 ± 2.1 mmHg; p = 0.020), without affecting systemic hemodynamics (MAP, HR). GS-9674 seemed to non-significantly increase SMABF by 10%. Interestingly, the combination of FXR agonism with beta-blockade (GS-9674 + PROP) significantly reduced SMABF (10.5 ± 3.7 vs. 14.2 ± 3.3 mL/min/100g; p = 0.032) without further decrease in PP. However, in PROP treated groups significant lower MAP (−23%) and HR (−37%) were noted.

Conclusion: The non-steroidal FXR agonist GS-9674 reduces liver fibrosis and HSC activation in NASH rats, and decreases portal pressure without deteriorating systemic hemodynamics. The combination of GS-9674 with propranolol additionally decreases mesenteric hyperperfusion, yet also affects mean arterial pressure and heart rate.

FRI-249

Genetic factors of hepatic encephalopathy on patients with cirrhosis: candidate gene study

A. Gil-Gomez[1], J. Ampuero[1], Ángela Rojas[1], Rocío Gallego-Durán[1], R.M. Hernandez[1], J.-R. Garcia-Lozano[2], M.R. Gomez[1]. *[1]Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla. CIBERehd., SeLiver Group, Sevilla, Spain; [2]Departamento de Inmunología, Hospital Universitario Virgen del Rocío, Sevilla, Spain*
Email: agil-ibis@us.es

Background and Aims: To determine the impact of genetic factors on the development of hepatic encephalopathy (HE) in patients with cirrhosis.

Method: Two-hundred and ninety-four cirrhotic patients followed-up for 4.7 ± 3.6 years were included. Up to 62 SNPs in candidate genes involved in the pathophysiology of HE: inflammation, hyperammonemia, intestinal barrier integrity or oxidative stress were selected. Samples were genotyped by using OpenArray custom plates. Likewise, a haplotype formed by four SNPs within *GLS* plus the length of a microsatellite in the promoter region of *GLS* were determined and all together considered as a single factor (GLS mutations).

Results: GLS mutations, together with in *FUT2*-rs601338, *TLR9*-rs5743836, *SLC1A3*-rs2562582 and *SLC1A5*-rs313853 SNPs, encoding for proteins involved in maintenance of intestinal barrier integrity by host-microbial interactions, pro-inflammatory response triggered by pathogens and glutamine transport, respectively, were associated to HE development. Multivariate analysis by Cox Regression showed that MELD, sodium, albumin, previous episodes of HE, *GLS mutations* and SNPs risk-genotypes were independently associated to HE risk (Fig. 1). Further, 4 groups were segregated according to presence of risk mutations within these five genes: 0–1, 2, 3 and 4–5. Finally, the cumulative survival free of HE after 10 years was 74.5%, 60.6%, 57.2% and 19.5% respectively (Log Rank 39.55; p = 0.000).

Conclusion: The presence of unfavorable genotypes in risk variants could explain the differences in the appearance of HE. This genetic fingerprint could be implemented in clinical practice for decision making in the management of cirrhotic patients.

FRI-250

LSECtin and CD206 participate in the regulation of the hepatic inflammatory response to E coli in a model of cirrhosis

E. Caparrós[1,2], P. Piñero[2], O. Juanola[2,3], I. Gómez-Hurtado[2], P. Zapater[4], J.M. González-Navajas[2], Rubén Francés[2,4,5]. *[1]universidad Miguel Hernandez, Medicina Clínica, San Juan de Alicante, Spain; [2]Fundación ISABIAL-FISABIO, Hospital General Universitario de Alicante, Spain; [3]universidad Miguel Hernandez, Farmacología; [4]Universidad Miguel Hernandez, Medicina Clínica, Spain; [5]CIBERehd, Hospital General Universitario de Alicante, Spain*
Email: ecaparros@umh.es

Background and Aims: The function of the hepatic immune system in the clearance of bacterial products is essential to maintain tissue homeostasis. Antigen presenting cells (APCs) play an important role in this regulation through different pathogen receptors.

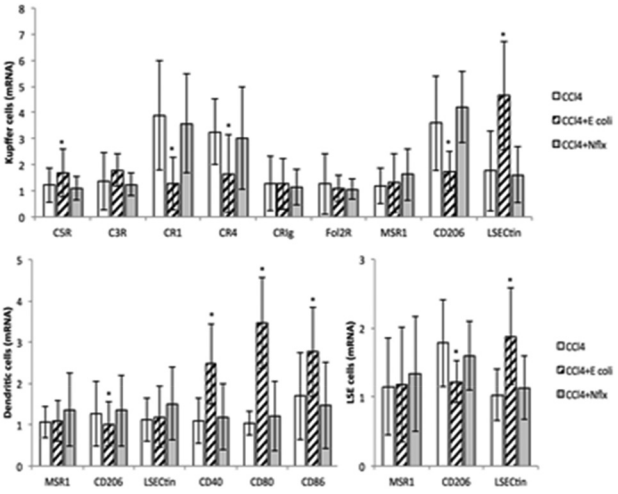
Method: Sprague-Dawley rats were treated with oral CCl_4 for 12 weeks (Group 1). In addition, one subgroup received intraperitoneal *E. coli* 24h before laparotomy (Group 2) and another subgroup received oral norfloxacin during the week prior to laparotomy (Group 3). The perfused livers were harvested and Kupffer cells (KCs), dendritic cells (DCs) and endothelial sinusoidal cells (LSECs) were purified using labelled microbeads. The gene expression and phenotypic profile of different receptors of innate immunity were analyzed.

Results: Gene expression of different markers in hepatic APCs is shown in figure 1. After administration of *E. coli* in cirrhotic rats, the response of the innate immune system is polarized towards the induction of local inflammation, represented by a significant reduction of the complement inhibitors (CR1 and CR4) in KCs and an increase in costimulatory molecules in DCs. Transcription of CD206, indicator of anti-inflammatory response, decreases significantly in all populations. On the other hand, the LSECtin receptor, involved in the inhibition of sustained T cell response, increases

Table (abstract: FRI-249).

Variable	No-HE (n = 198)	HE (n = 96)	Univariate	Multivariate (HR, CI95%)
Sex; male	70.7% (140/198)	71.9% (69/96)	.919	
age ± SD	57.0 ± 9.6	59.4 ± 10.1	.044	
MELD	10.0 ± 3.3	12.6 ± 4.4	.000	1.102 (1.034–1.174) p = 0.003
Previous HE	13.6% (27/198)	31.3% (30/96)	.000	1.958 (1.139–3.366) p = 0.015
MHE				
PHES (<-4)	26.5%	31.3%	0.109	
CFF (<39Hz)	36.8%	45.9%	0.008	
Albumin (g/dL)	3.99 ± 0.67	3.55 ± 0.68	.000	0.999 (0.998–0.999) p = .000
Bilirubin (mg/dL)	1.51 ± 1.35	2.18 ± 1.65	.001	
Platelets (× 10^9/L)	130.9 ± 74.6	104.6 ± 59.7	.004	
AST (IU/L)	49.8 ± 39.1	60.07 ± 43.68	.062	
Sodium (mmol/L)	139.8 ± 3.3	137.7 ± 5.0	.000	0.886 (0.839–0.935) p = .000
Basal ammonia	70.2 ± 40.4	87.34 ± 48.5	.003	
rs601338 (AG/AA vs GG)	69.7% (138/196)	83.2% (79/96)	.014	1.356 (1.010–1.858) p = .043
rs5743836 (GA/GG vs AA)	28.8% (57/198)	42.7% (41/96)	.019	1.499 (1.178–1.196) p = .001
rs2562582 (CT/CC vs TT)	23.7% (47/198)	36.5% (35/96)	.005	1.555 (1.216–1.984) p = .000
rs313853 (CT/CC vs TT)	51.8% (100/196)	64.1% (60/96)	.013	1.462 (1.137–1.876) p = .003
GLS mutations	67.4% (132/198)	82.8% (78/96)	.003	1.809 (0.987–3.313) p = .055
Exitus	19.2% (38/198)	40.6% (39/96)	.000	
Liver Transplantation	10.6% (21/198)	21.9% (21/96)	.000	

significantly in KCs and LSECs. The profile analysis of these molecules by flow cytometry correlates with the genetic findings.



Conclusion: The expression of LSECtin in KCs and LSECs could compensate the hepatic proinflammatory response induced by E. coli, thus collaborating in the prevention of hepatic damage mediated by the immune system.

FRI-251

Changes of bile acids profile in different etiologies of liver cirrhosis and its association with neutrophil response

I. Komarova[1], A. Horvath[1], E. Krones[1], B. Leber[1], B. Schmerboeck[1], F. Durchschein[1], G. Zollner[1], R.E. Stauber[1], W. Spindelböck[1], P. Douschan[2], P. Stiegler[3], D. Kniepeiss[3], T. Stojakovic[4], Günter Fauler[4], V. Stadlbauer[5]. [1]*Medical University of Graz, Department of Gastroenterology and Hepatology, Graz, Austria;* [2]*Medical University of Graz, Department of Pulmonology, Austria;* [3]*Medical University of Graz, Department of Surgery, Division of Transplant Surgery, Austria;* [4]*Medical University of Graz, Clinical Institute of Medical and Chemical Laboratory Diagnostics, Austria;* [5]*Medical University of Graz, Department of Gastroenterology and Hepatology, Austria*
Email: irina.komarova@medunigraz.at

Background and Aims: Liver cirrhosis is associated with high risk of bacterial infections. Impaired neutrophil function can contribute to the development of this complication. Bile acids are important signaling molecules and immune modulators, but their influence on the immune response in liver cirrhosis is not yet fully understood. Our aim was to analyze the changes in bile acids profile in liver cirrhosis depending on its etiology and severity and their role in neutrophil functional response.

Method: Unconjugated, glycine and taurine conjugated cholic (CA), chenodeoxycholic (CDCA), deoxycholic (DCA), lithocholic (LCA), ursodeoxycholic (UDCA) bile acids concentration in serum of 109 liver cirrhotic patients (mean age = 56.9 ± 8.9) and 21 healthy volunteers (mean age = 58.0 ± 6.9) was measured by high-resolution mass spectrometry. Respiratory burst and phagocytic ability of neutrophils were assessed by flow cytometry (Phagoburst and Phagotest, Glycotope, Germany). Patients were grouped by cirrhosis etiology (alcoholic etiology – n = 54, viral etiology – n = 32, other etiology – n = 23) and liver function (Child-Pugh A – n = 79, Child-Pugh B + C – n = 30).

Results: All bile acids were increased in liver cirrhosis and their composition significantly changed. This was reflected in decreased proportions of secondary, unconjugated, glycine conjugated, 12-alpha-hydroxylated bile acids, as well as decreased CDCA, DCA and UDCA relative abundances compared to healthy volunteers. These changes increased with deterioration of the liver function. Within the cohort of patients with Child A cirrhosis, there were significantly higher levels of glycocholic acid (p = 0.005), total UDCA (p = 0.055), total unconjugated (p = 0.006), 12-alpha-hydroxylated (p = 0.007) bile acids in alcoholic cirrhosis compared to viral cirrhosis. Elevated total UDCA levels were associated with increased neutrophil priming, indicating an increased readiness of neutrophils to respond to a stimulus and glycocholic acid levels were associated with decreased oxidative burst in response to E.coli bacteria (Figure 1).

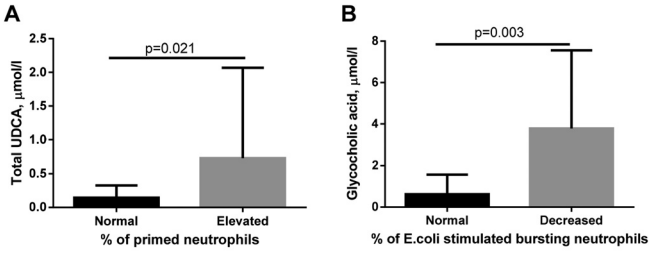


Figure 1. UDCA and glycocholic acid serum levels in 79 patients with Child A cirrhosis according to neutrophil priming and E.coli stimulated burst function.

Conclusion: Bile acids profile in liver cirrhosis depends on etiology and disease severity. The changes in bile acids composition are associated with changes in neutrophil functionality. In order to investigate the direct influence of bile acids on neutrophils and to understand the underlying mechanisms further studies are required.

FRI-252

Assessment of conjugated, primary and secondary bile acids in the portal venous system across the spectrum of chronic HCV associated liver disease; link to inflammation and microbial products

R. Ali, G. Zhang, E. Townsend, C. Koh, E. Levy, D.E. Kleiner, O. Etzion, T. Heller. *National Institutes of Health, Translational Hepatology Section, NIDDK, Bethesda, United States*
Email: rabab.ali@nih.gov

Background and Aims: There is growing evidence of the critical role bile acids (BA) play in chronic liver disease, particularly in the cross-talk between the diseased liver and gut microbiome. Altered BA conjugation and hydroxylation are potential mechanisms modulating the gut-liver axis and may contribute to disease progression. The relative proportions of BA metabolites in the portal vein have not been well explored. The aim of this study was to characterize BA in association with liver injury and immune markers in the portal vein of HCV patients across the spectrum of liver disease severity.

Method: HCV-infected patients underwent liver biopsy with portal vein cannulation (LBPVC) and portal serum was obtained. Ultrahigh Performance Liquid Chromatography-Tandem Mass Spectroscopy and ELISAs were used to assess 28 BA and microbial products and cytokines, respectively.

Results: 29 patients had LBPVC; 16 were non-cirrhotic {Ishak Fibrosis (IF) 0–4} and 13 compensated cirrhotic (IF 5–6). Conjugated/unconjugated ratio (CR), and primary/secondary ratio (P/S) was calculated for each BA. For all reported correlations Spearman r > 0.35, and p < 0.05. CR of chenodeoxycholate (CDCA), cholate (CA), and deoxycholate (DCA) was associated with higher ALP, and CR of Ursodeoxycholate (UDCA) with higher ALT and AST. Conjugated CDCA, not CA, positively correlated with portal zonulin; a gut epithelial integrity marker. CR for CDCA, not CA, positively correlated with sCD14 and sCD163. CR for DCA and UDCA was associated with elevated sCD14, and sCD163 and zonulin, respectively. In primary BA, conjugated CDCA/CA ratio was higher in cirrhotics (Mann-Whitney p < 0.05) and positively correlated with hepatic activity index, portal CXCL9, IL12p40, IL16, E-selectin, Thrombomodulin, and HMGB-1. Increased P/S correlated with higher ALT, increased portal LPS (gram negative marker), decreased lipoteichoic acid (gram positive marker), and higher tauro-beta-muricholate (TBMCA).

TBMCA was higher in cirrhotics (Mann-Whitney $p < 0.05$) and associated with higher ALT, ALP, Bilirubin, AFP, and PT.
Conclusion: Higher conjugation of portal BA is linked to liver injury, macrophage activation and loss of gut epithelial integrity. In cirrhotics, a greater CDCA/CA ratio not only suggests a shift from classic to alternative BA pathway, but an association with inflammatory markers in the portal vein. Increased P/S is related to hepatic injury, microbial products, and emergence of a hydrophilic BA; TBMCA, which in turn, is strongly associated with cirrhosis. These changes in BA have biological and therapeutic implications that are worthy of further study.

Viral hepatitis B/D: Clinical aspects except therapy

FRI-254
Occult hepatitis B infection in hepatocellular carcinoma patients with negative HBsAg

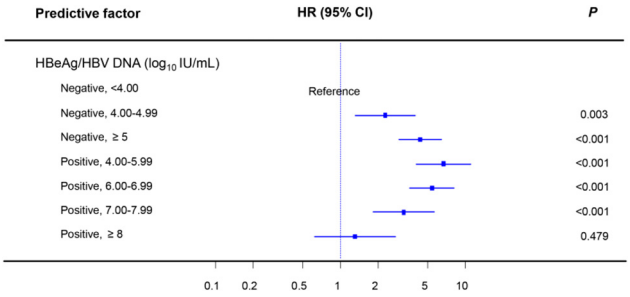
D. Wong[1,2], L.-Y. Mak[1], W.P. To[1], T.-t. Cheung[2,3], W.-K. Seto[1,2], Y.Y.J. Fung[1,2], K. Man[2,3], C.L. Lai[2,4], M.-F. Yuen[2,4]. *[1]The University of Hong Kong, Medicine, Hong Kong, Hong Kong; [2]The University of Hong Kong, State Key Laboratory for Liver Research, Hong Kong, Hong Kong; [3]The University of Hong Kong, Surgery, Hong Kong; [4]The University of Hong Kong, Medicine, Hong Kong*
Email: dannykhwong@gmail.com

Background and Aims: Chronic hepatitis B and C infections are the two major causes of hepatocellular carcinoma (HCC) worldwide. However, HCC can also be caused by non-viral etiologies such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis (AIH), and primary biliary cholangitis (PBC). It is not known whether patients with non-viral causes of HCC may have superimposed occult hepatitis B infection (OBI) as an additional risk factor causing HCC. We aimed to investigate the incidence of OBI in HCC patients with undetectable hepatitis B surface antigen (HBsAg).
Method: Tumor and adjacent non-tumor liver tissues were obtained from 90 patients with non-viral causes of HCC. Eighty-four patients had paired tumor and non-tumor tissues available, while three patients had only non-tumor tissues and three had only tumor tissues available. Total liver DNA was extracted from the non-tumor tissues and from the tumor tissues if non-tumor tissues were not available. OBI was detected by 4 sets of independent nested PCR, using primers targeting the S, precore, polymerase, and X regions of the hepatitis B virus (HBV) genome. OBI was diagnosed when positive PCR detection was identified in two or more HBV genomic regions.
Results: All 90 patients had undetectable serum HBsAg and anti-HCV. Of these, 18 (21%) had ALD, 14 (16%) had either NASH or NAFLD (denoted by mild histological fatty changes), two had PBC, two had recurrent pyogenic cholangitis (RPC), one patient had AIH, and the remaining 53 patients (60%) had no cause identified i.e. cryptogenic HCC. Histological analysis of the non-tumor tissues identified that 19 (21%) patients had liver cirrhosis. Overall, OBI was detected in 45/90 (50%) of HCC patients. Specifically, OBI was detected in 7/18 (39%) HCC patients with ALD, 7/14 (50%) patients with NAFLD/NASH, and 1/2 (50%) patient with PBC, and 30/53 (57%) patients with cryptogenic HCC.
Conclusion: Half of the HCC patients with no serum marker for HBV had underlying OBI. Nearly 60% of patients with cryptogenic HCC had viral hepatitis B disease in the form of OBI. This suggests that the significance of HBV infection causing HCC is likely to be underestimated. In patients with ALD or NAFLD/NASH, around 40–50% HCC patients had OBI, suggesting that OBI may be a common synergistic factor (with ALD or NAFLD/NASH) for hepatocarcinogenesis in these patients.

FRI-255
Non-linear association between serum hepatitis B virus DNA levels and hepatocellular carcinoma risk in treatment-naive, non-cirrhotic chronic hepatitis B patients

G.-A. Kim[1], S. Han[2], G.H. Choi[3], J. Choi[3], Y.-S. Lim[3]. *[1]Asan Medical Center, University of Ulsan College of Medicine, Health Screening and Promotion Center, Seoul, [2]Gachon University, Department of Applied Statistics, Gyeonggi-do, Korea, Rep. of South; [3]Asan Medical Center, University of Ulsan College of Medicine, Department of Gastroenterology, Seoul, Korea, Rep. of South*
Email: limys@amc.seoul.kr

Background and Aims: The REVEAL-HBV studies on the natural history of chronic hepatitis B showed a linear correlation between serum hepatitis B virus (HBV) levels and the risk of hepatocellular carcinoma (HCC). However, virus titers above 10^6 copies/ml were not quantified, and most of the patients were HBeAg-negative (85%). The progression of these HBeAg-negative patients would not be identical to that of young HBeAg-positive immune-tolerant phase patients with very high HBV DNA levels.
Method: The study subjects were recruited from a historical cohort of 4367 treatment-naïve, non-cirrhotic CHB patients (1240 HBeAg-positive and 3127 HBeAg-negative) with serum ALT levels lower than 2 × upper limit of normal (females, <19IU/ml; males, <30IU/ml) at a tertiary referral hospital in Korea. Cox proportional hazards regression model predicted HCC risk considering sex, age, HBeAg status, serum HBV DNA levels, ALT levels, and platelet counts.
Results: During the total follow-up of 23,690 person-years, 221 patients (5.1%) developed HCC. Old age, male gender, and lower platelet counts were found to be associated with an increased risk of HCC. Among HBeAg-negative patients, HBV DNA levels were linearly associated with increasing risk of HCC. In contrast, among HBeAg-positive patients, HBV DNA levels were inversely associated with the risk of HCC. The risk of HCC was the lowest in HBeAg negative patients with HBV DNA level below 4 $\log_{10}$IU/ml (reference group), and was the highest in HBeAg positive patients with HBV DNA levels between 4 $\log_{10}$IU/ml and 6 $\log_{10}$IU/ml (hazard ratio [HR] 6.89; 95% confidence interval [CI] 4.20–11.29). HBeAg-positive patients with HBV DNA levels above 8 $\log_{10}$IU/ml showed similar risk of HCC compared with the reference group (HR 1.36; 95% CI 0.65–2.84).



Conclusion: In our large cohort of treatment-naïve, non-cirrhotic chronic hepatitis B patients, the association between HBV DNA levels and HCC risk was not linear, but was parabolic. HCC risk was the highest in patients with HBV DNA levels between 4 $\log_{10}$IU/mL and 6 $\log_{10}$IU/ml. These data may help assess the HCC risk among the patients who are not subject to antiviral treatment which consequently call attention to the necessity of developing a new treatment indication.

FRI-256
Hepatitis B splice variants are strongly associated with and are indeed predictive of hepatocellular carcinoma

M.-H. Pan[1], H.-H. Hu[1], H. Mason[2], J. Bayliss[2], M. Littlejohn[2], Y.-L. Lin[3], C.-Y. Su[1], C.-T. Chiang[1], C.-J. Chen[1], S. Locarnini[2], H.-I Yang[1], P. Revill[2]. *[1]Genomics Research Center, Academia Sinica, Taipei 115, Taiwan;*

[2]*Peter Doherty Institute of Infection and Immunity, VIDRL Royal Melbourne Hospital, Melbourne, Australia;* [3]*Genomics Research Center, Academia Sinica, Melbourne, Australia*
Email: peter.revill@mh.org.au

Background and Aims: Over 257 million people live with chronic hepatitis B, resulting in up to 880,000 deaths annually due to cirrhosis and liver cancer (hepatocellular carcinoma, HCC). Chronic HBV (CHB) is incurable, and infected persons have a life-long risk of developing liver cancer, the 5th most common cancer and 3rd leading cause of cancer-related mortality. Identifying mechanisms by which HBV causes liver cancer is of paramount importance. We have previously shown that HBV splice variants were strongly associated with liver cancer[1]. The purpose of the current study was to validate these findings using a large international cohort of patients with HBV-mediated liver cancer, from the REVEAL[2] study in Taiwan.
Method: HBV DNA in serum was purified from over 150 patients with liver cancer and 370 control patients who had chronic HBV but had not developed liver cancer. The ratio of splice variant to wild-type HBV was quantified by real time PCR and associations between the relative abundance of splice variants and liver cancer was determined by univariate and multivariate analysis.
Results: Quantitative real time PCR was performed for splice (spHBV) and wild-type HBV DNA on over 600 samples. After adjustment for known HCC-related risk factors (serum HBV DNA, α-fetoprotein, HBV genotype), subjects with spliced HBV DNA level >10% were at least 3 times more likely to develop HCC than patients with lower levels of splice variants. For patients with secreted spHBV of >20%, the adjusted OR (95% CI) of HCC development was 23.3, $p < 0.0001$). In most HCC patients with elevated spHBV levels, this occurred up to 5 years prior to HCC diagnosis.
Conclusion: Our previous pilot study of Australian patients suggested that the secretion of splice HBV variants into the blood compartment was strongly associated with liver cancer. We have now validated this finding utilising the highly characterised REVEAL Taiwanese cohort. The striking finding that HBV infected subjects were more likely to develop liver cancer if splice variants formed at least 20% of the secreted viral pool suggests we have identified a novel biomarker of HCC in this setting.

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FRI-257

Lower baseline quantitative HBcAb may help predict response to sequential combination therapy with IFN, rhIL-2 and HBV therapeutic vaccine in entecavir-suppressed CHB patients

W. Yan[1], Q. Yuan[2], D. Wu[1], M. Han[1], G. Chen[1], K. Ma[1], N. Xia[3], Q. Ning[1]. [1]*Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Institute and Department of Infectious Disease, Wuhan, China;* [2]*School of Public Health, Xiamen University, Diagnostics and Vaccine Development in Infectious Diseases, Xiamen, China;* [3]*National Institute of Diagnostics and Vaccine Development in Infectious Diseases, School of Public Health, Xiamen University, State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics, Xiamen, China*
Email: qning@vip.sina.com

Background and Aims: HBcAb has been revealed to be closely correlated with hepatic inflammatory activities and treatment response in HBeAg positive chronic hepatitis B (CHB) patients recently. The aim of this study was to investigate the relationship of quantitative serum HBcAb levels and antiviral efficacy in 94CHB patients undergoing a multi-center, randomized trial (Endeavor Study, ClinicalTrials.gov: NCT02360592).
Method: HBeAg positive CHB patients who had received entecavir (ETV) for 1–5 years, with HBeAg loss and HBVDNA ≤ 1000 copies/ml, were randomized to continue with ETV therapy for 48 weeks (Group I) or switch to conventional interferon (IFN)-α-2bfor 48 weeks (Group II) or IFN-α-2b for 48 weeks in combination with recombinant human interleukin-2 (rhIL-2) for 12 weeks plus HBV therapeutic vaccine for 48 weeks (Group III). Treatment response was defined as HBsAg loss and/or HBeAg seroconversion at week 48. Serum HBcAb was quantified in a blinded fashion by using a newly developed double-antigen sandwich immune-assay calibrated by WHO standards.
Results: Compared with the patients continuing with monotherapy (Group I), patients switching to combined therapy (Group II and III) exhibited a significant higher rate of response (7.41% vs. 23.88%, $p = 0.048$). A positive correlation between baseline HBcAb levels and HBsAg levels was observed in all patients included ($r = 0.364$, $p = 0.001$), while positive correlation between the two variables during treatment only existed among patients undergoing combined therapy ($r = 0.446$, 0.315, 0.315, $p = 0.000$, 0.014, 0.026 at week 0, week 12, week 48, respectively). In contrast to monotherapy which had no obvious influence on serum HBcAb levels, combined therapy resulted in a significant decline in HBcAb levels (week 12 VS. week 0, $p = 0.038$, week 36 VS. week 0, $p = 0.034$). Compared with non-responders within combined therapy group, responders showed significantly lower HBcAb levels during early phase of treatment ($p = 0.017$, 0.016, 0.012 at week 0, week 4, and week 12, respectively). Furthermore, baseline HBcAb level appeared to be an ideal predictor for response to combined therapy, including having a larger AUROC curve (0.714, 95% CI 0.588–0.840, $p = 0.003$). We defined 2.695 $\log_{10}$IU/ml as the optimal cut-off value of baseline HBcAb level to predict response (sensitivity 80.8%, specificity 60.1%, PPV 56.76%, NPV 83.33%). Patients with baseline HBcAb ≤ 2.695 $\log_{10}$IU/ml had significantly more chances to achieve response than those with baseline HBcAb > 2.695 $\log_{10}$IU/ml (56.76% [21/37] VS. 16.67% [5/30]).
Conclusion: For CHB patients with HBeAg loss post ETV treatment, baseline quantitative HBcAb titer might be a novel non-invasive biomarker for predicting treatment response to sequential combination therapy with IFN, rhIL-2 and HBV therapeutic vaccine.

FRI-258

Antiviral therapy can be avoided in most HBeAg-negative Caucasian patients in the Gray Zone

M. Bonacci, S. Lens, Z. Mariño, M.C. Londoño, S. Rodriguez-Tajes, A. Mas, M. García-López, Sofía Pérez del Pulgar, J.M. Sanchez-Tapias, X. Forns. *IDIBAPS, CIBERehd, Liver Unit, Barcelona, Spain*
Email: bonacci@clinic.cat

Background and Aims: Gray zone (GZ) is an ill-defined situation including patients not accomplishing criteria of Inactive Carrier [(IC) HBV-DNA < 2,000IU/ml/ALT < 40U/l] or HBeAg-negative chronic hepatitis B [(CHB) ALT > 80U/l, HBV-DNA > 2,000IU/ml and fibrosis (≥2) or ALT > 80U/l and HBV-DNA > 20,000IU/ml]. We aim to investigate long-term outcomes of untreated GZ patients compared to IC.
Method: Non-cirrhotic, HBeAg-negative patients with HBV-DNA ≤ 20,000IU/ml and ALT ≤ 80U/l were retrospectively studied. At baseline patients were grouped into: 1) ICs; 2) GZ-1 (HBV-DNA < 2,000IU/ml and ALT 40–80U/l); 3) GZ-2 (HBV-DNA 2,000–20,000IU/ml and ALT < 40U/l), and GZ-3 (HBV-DNA 2,000–20,000IU/ml ALT 40–80U/l). Data were also analyzed using the AASLD threshold for ALT normality.
Results: In total 287 subjects were studied, including 137 ICs and 150 GZ patients (60 GZ-1, 54 GZ-2 and 36 GZ-3). Baseline features were similar across groups and 84% were Caucasian. APRI, FIB-4 and GPR excluded advanced fibrosis in all patients. Genotype (GT) was available in 185 (64%) patients and similarly distributed across Groups. Prevalence of GT A, D, F, B/C and E/H was 48%, 36%, 6.5%, 6.5% and 3%, respectively. After a median FU of 8.2 (5–19) years ALT elevations >40U/l occurred in 30% of IC, and >80U/l in 6.6% of IC and 28% of GZ patients. HBV-DNA elevations >2,000 IU/ml occurred in 23% of IC and >20,000IU/ml in 3% of IC and in 40% of GZ. Overall, HBsAg loss rate was 18% in IC and 13% in GZ (p = ns) and occurred only in GT A/D patients. Excluding patients who lost HBsAg, transition into IC occurred in 60/131 (45%) GZ patients. Indeed, GT A was associated with higher HBsAg loss [HR = 2.6 (1.1–6); 0.01]. whereas HBV-DNA fluctuation >2,000IU/ml negatively predicted this outcome [HR = 0.54 (0.4–0.8); 0.01] and transition into IC [HR = 0.31 (0.16–0.62); 0.01].

Progression to CHB occurred in only 18 (6,3%) GZ patients and was more frequent in GT B/C (33%) than in GT A/D (8%). At last FU, markers of hepatic fibrosis and liver stiffness excluded advanced fibrosis in all patients. One non-cirrhotic GT C patient developed HCC. Using AASLD diagnostic criteria, 77 (227/287) more subjects fell into the GZ at baseline, but its long-term outcome was equally favorable.
Conclusion: The prognosis of untreated Caucasian GZ patients is excellent, with high rate of HBsAg loss and low rate of CHB. Based on these observations antivirals may safely be avoided in most GZ patients, particularly in GT A/D. Genotyping may help to predict outcomes in GZ.

FRI-259

Basal values and on treatment decline of hepatitis B core-related antigen are predictive of response to interferon therapy in chronic hepatitis D

A. Olivero[1], G.P. Caviglia[1], A. Ciancio[1], C. Bosco[1], R. Fontana[2], G. Niro[2], M. Rizzetto[1], G. Maria Saracco[1], A. Smedile[1]. *[1]University of Turin, Department of Medical Sciences; [2]IRCCS Casa Sollievo della Sofferenza, Gastroenterology Unit*
Email: caviglia.giampi@libero.it

Background and Aims: Therapy with pegylated interferon-alpha-2a (Peg-IFN) is considered the standard of care for patients with chronic active HDV infection (CHD). Since reliable predictors of treatment response are still debating, we investigated the role of hepatitis B core-related antigen (HBcrAg) for the prediction of response in CHD patients treated with Peg-IFN.
Method: A total of 65 sequential serum samples from 13 CHD patients (8M/5F; median age 54 years) who underwent Peg-IFN treatment between 2010 and 2015 were analyzed. All patients were HBV genotype D and HDV genotype 1; 11 were anti-HBe+. Serum HBcrAg and HBsAg levels were determined by CLEIA (Lumipulse®, Fujirebio, Japan). HBV DNA and HDV RNA were detected by real-time quantitative PCR. All markers were measured at baseline, 6, 12, 18 and 12 months after end of therapy (12MFU). HBcrAg kinetics were analyzed by repeated measures ANOVA.
Results: Overall, 8 out of 13 patients cleared HDV RNA and were still negative at 12MFU (responders, R). Among them, 2 patients cleared HBsAg and 1 became anti-HBs+. Five patients were nonresponders (NR). Mean baseline HBcrAg, HBsAg, HBV DNA and HDV RNA levels were 3.6 ± 1.4logU/ml, 3.17 ± 1.33LogIU/ml, 2.02 ± 1.67logIU/ml and 4.79 ± 1.21logIU/ml, respectively. We observed a significant correlation between HBcrAg and HBsAg ($r = 0.763$, $p < 0.001$), HBV DNA ($r = 0.844$, $p < 0.001$) and HDV RNA ($r = 0.761$, $p < 0.001$). Baseline HBcrAg levels were slightly higher in NR compared to R patients (4.6 ± 1.3 vs. 3.1 ± 1.1logU/ml, $p = 0.052$). Optimal baseline HBcrAg threshold to discriminate Rs from NRs was 3logU/ml; this cut-off was associated to an area under the curve (AUC) of 0.787, with a sensitivity (Se) of 63% and specificity (Sp) of 80%. On-treatment HBcrAg kinetics showed a significant ($p = 0.026$) linear decline in R patients from baseline to 12MFU; conversely, no decline was observed in NRs ($p = 0.256$). A 6M on treatment HBcrAg redsuction >0.1 LogU/mL showed a AUC = 0.737 (Se = 88% and Sp = 60%). By combining baseline HBcrAg levels and reduction values at 6 months this accuracy improved (AUC = 0.925, Se = 100% and Sp = 80%).
Conclusion: Serum levels of HBcrAg, at baseline and at month 6 on therapy, are predictors of treatment response to Peg-IFN in patients with CHD.

FRI-260

Soluble cytotoxic T-lymphocyte-associated antigen-4 and soluble programmed cell death protein-1 are predictive immune checkpoint seromarkers for spontaneous functional cure of chronic hepatitis B with opposite effects

H.-I. Yang[1], H.-H. Hu[1], M.-H. Pan[1], W.-S. Luo[1], R.W.-J. Jeng[2], C.-Y. Su[1], C.-T. Chiang[1], C.-L. Jen[1], S.-N. Lu[3], L.-Y. Wang[4], M.-H. Lee[5], J. Liu[6], M. Nguyen[7], C.-J. Chen[8]. *[1]Academia Sinica, Genomics Research Center, Taipei, Taiwan; [2]Chang Gung University, Taoyuan, Taiwan; [3]Chang-Gung Memorial Hospital, Department of Gastroenterology, Kaohsiung, Taiwan; [4]MacKay College of Medicine, Taipei, Taiwan; [5]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan; [6]Stanford University School of Medicine and Lucile Packard Children's Hospital, Perinatal Epidemiology and Health Outcomes Research Unit, Division of Neonatology, Department of Pediatrics, Palo Alto, CA, United States; [7]Stanford University Medical Center, Division of Gastroenterology and Hepatology, Palo Alto, CA, Taiwan; [8]Academia Sinica, Taipei, Taiwan*
Email: hwaii.yang@gmail.com

Background and Aims: The seroclearance of hepatitis B surface antigen (HBsAg) is regarded as a functional cure for patients with chronic hepatitis B, who often show an immune inhibitory checkpoint-associated T cell exhaustion. We aim to assess soluble cytotoxic T-lymphocyte-associated antigen-4 (sCTLA-4) and programmed cell death protein-1 (sPD-1) as novel seromarkers for spontaneous HBsAg seroclearance.
Method: Serum levels of sPD-1 and sCTLA-4 were evaluated in all 1,046 patients from the REVEAL-HBV study who were hepatitis B e antigen-seronegative with serum HBV DNA undetectability. Multivariate Cox regression analyses were used to assess associations of baseline sPD-1 and sCTLA-4 level with subsequent spontaneous HBsAg seroclearance, and to estimate rate ratio (RR) with 95% confidence interval (95% CI).
Results: A total of 390 patients achieved spontaneous HBsAg seroclearance during a mean 5.4 years of follow-up. Baseline sPD-1 levels were positively correlated with baseline sCTLA-4 levels ($p < 0.0001$). Incidence rates of spontaneous HBsAg seroclearance increased with decreasing levels of baseline sPD-1 ($p_{trend}<0.0001$), but with increasing sCTLA-4 levels ($p_{trend}<0.0001$). After adjustment for gender, age, serum levels of alanine aminotransferase, sPD-1 and sCTLA-4, the RR (95%CI) of HBsAg seroclearance was 3.6 (2.2–6.0), 4.5 (2.8–7.4), and 11.6 (6.9–19.6), respectively, for baseline sPD-1 levels of 536–3999, 125–535, and <125pg/ml compared to sPD-1 levels of ≥4000pg/ml; and were 1.2 (0.8–1.9), 1.7 (1.1–2.7), and 2.1 (1.3–3.4), respectively, for baseline sCTLA-4 levels of 0.5–1.2, 1.3–2.5, and 2.6–16ng/ml compared to sCTLA-4 levels of <0.5ng/ml as the referent. Using patients who had sPD-1 levels ≥536pg/ml and sCTLA-4 < 0.5ng/ml as the referent, the RR (95% CI) of HBsAg seroclearance was 0.9 (0.4–1.8), 1.0 (0.5–2.0), and 2.5 (1.4–4.5), respectively, for patients had the same levels of sPD-1 and sCTLA-4 levels of 0.5–1.2, 1.3–2.5, and 2.6–16ng/ml; the RR (95%CI) was 3.9 (1.7–9.2), 3.9 (1.7–8.9), 5.3 (2.3–12.0), and 4.6 (1.9–10.7) respectively, for those who had sPD-1 levels <536pg/ml and sCTLA-4 levels of <0.5, 0.5–1.2, 1.3–2.5, and 2.6–16ng/ml.
Conclusion: Reduced sPD-1 levels while increased sCTLA-4 levels predict greater chance of spontaneous HBsAg seroclearance in HBeAg-seronegative CHB patients with HBV DNA undetectability. Serum sCTLA-4 levels offer addition predictability on HBsAg seroclearance in patients with high sPD-1 levels.

FRI-261

The levels of middle surface HBV antigen increase in patients with HBV-driven liver cancer despite prolonged virological suppression: implications for a novel marker of HBV-driven hepatocarcinogenesis

G. Brancaccio[1], R. Salpini[2], L. Colagrossi[2], V. Fini[2], M. Cantone[1], A. Battisti[2], L. Piermatteo[2], Y. Oda[2], C.F. Perno[2], G.B. Gaeta[1], V. Svicher[1]. *[1]Infectious Diseases Naples Italy; [2]Department of Experimental Medicine and Surgery, Rome Italy*
Email: p.brancaccio@alice.it

Background and Aims: HBV ORF S is composed by 3 regions: preS1, preS2 and S, encoding the Large-HBs (L-HBs), Middle-HBs (M-HBs), and Small-HBs (S-HBs). Here, we investigate the still unknown kinetics of HBs forms in virologically suppressed patients (pts) developing HCC.
Method: This study enrolled 30 cirrhotic HBV chronically infected pts on HBV-DNA suppression by potent antiviral therapy. Among them,

13 developed HCC after a median [IQR] time of15 [8–18] months and 17did not develop HCC despite a median [IQR] observation time of 41 [30–48] months. For each patient, 2 plasma samples under virological suppression were collected at enrolment (T0) and at HCC diagnosis or at last control for not-HCC pts (T1). Ad hoc ELISAs were designed to quantify L-HBs, M-HBs and total-HBs at T0 and T1 (Beacle Inc). Each sample was processed at least in duplicate. Spearman and Bland-Altman tests were used to verify the concordance in total-HBs quantification between Beacle and COBAS HbsAg II assays (Roche Diagnostics).

Results: Total-HBs quantification by Beacle and Cobas assays showed high concordance (Rho = 0.82, p < 0.001). At T0, median (IQR) levels of total-HBs, M-HBs and L-HBs were 3.5 (2.6–4.0)log ng/ml, 2.3 (1.4–2.6)log ng/ml and 0.7(0.1–1.9)ng/ml(with no significant differences between HCC- and not-HCC pts). By analysing the kinetics of HBs forms, total-HBs showed >10% reduction in most pts (53.8% [7/13] of HCC- vs 47.1% [8/17] of not-HCC pts). Similarly, in HCC- and not-HCC pts, total-HBs remained stable (30.8% [4/13]vs 29.4% [5/17]) or showed >10% increase (15.4% [2/13] vs 23.5% [4/17], p = 0.67). Regarding M-HBs,>10% reduction of this form was observed in a similar proportion of HCC- and not-HCC pts (30.8% [4/13] vs 29.4% [5/17]). Conversely and notably, the proportion of patients undergoing > 10% increase in M-HBs was significantly higher in HCC- than in not-HCC group (46.2% [6/13] vs 11.8% [2/17], p = 0.049) suggesting an enhanced M-HBs production in the setting of HBV-driven hepatocarcinogenesis. Finally, no difference in L-HBs kinetics is was observed in HCC- and not-HCC pts.

Conclusion: An increase in M-HBs levels characterizes a conspicuous proportion of HCC-pts despite prolonged suppression and stable/reduced total-HBs. This suggests the contribution of M-HBs in mechanisms underlying HBV-driven hepatocarcinogenesis, presumably driven by an enhanced transcriptional activity of pre-S2 promoter from cccDNA and/or HBV-DNA integrated into the host genome. The role of M-HBs as marker predictive of HCC deserves further investigation.

FRI-262

Identifying epigenetic markers for characterization of host response to hepatitis B virus infection during the development of hepatocellular carcinoma

W.-J. Wu[1], S.-H. Yang[1], W.-J. Liu[1], W.-Y. Kao[1], Y.-C. Kuo[1], C.-L. Lin[2], C.-J. Liu[3], Y.-W. Huang[4], C.-F. Wu[1], M.-W. Yu[1]. *[1]National Taiwan University, College of Public Health; [2]Ren-Ai Branch, Taipei City Hospital, Department of Gastroenterology; [3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Cathay General Hospital Medical Center, Liver Center*
Email: yumw@ntu.edu.tw

Background and Aims: High viremia is a strong risk factor of hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC). There is increasing evidence that HBV has mechanisms to alter immunity via epigenetic control. We used microarray and pyrosequencing to assess methylation sites related to viral load, and determine the effect of such epigenetic changes on the risk of HBV-related HCC.

Method: We first conducted epigenome mapping of leukocyte DNA with the Infinium HumanMethylation450 array in a case-control study (n = 96) nested in a cohort of men with chronic HBV infection. For identified signals, we then conducted an extended analysis with pyrosequencing in a case-cohort sample with longitudinal viremia data from the cohort (n = 561). CpG sites that remained significant in the extended analysis were tested in a case-sibling study (n = 444).

Results: After adjustment for age and blood cell composition, epigenome-wide analysis indicated 3.38-fold (p = 2.61·e-49) enrichment of viremia-related CpGs in HCC-related CpGs compared to HCC-unrelated CpGs. The strongest association signal of viremia among HCC-related CpGs was in the promoter of the *IFI44L* gene (p = 5.69·e-6), involved in type I/II interferon pathways. Co-methylation analysis identified functional link of 191 genes located on different chromosomes (absolute correlation > 0.5; p < 1·e-6) with *IFI44L*, which were significantly enriched for specific immune pathways relevant to HBV infection. The association between *IFI44L* methylation intensity and HCC was independent from alanine aminotransferase and was confirmed in both the case-cohort study (p = 0.0030) and case-sibling study (p < 0.0001), showing a multivariate odds ratio of 1.69 (95% CI = 1.19–2.38) and 4.97 (95% CI = 3.18–7.78), respectively, for every 0.1 decrease in methylation beta value. In addition, we found negative effects of *IFI44L* methylation on viremia levels (p = 0.0039) and HBeAg positivity (p = 0.0018) in cross-sectional analyses, and a negative effect of *IFI44L* methylation on viremia levels in longitudinal analysis (p = 0.0220). Mediation analysis showed that viral load and HBeAg explained part of the effect of *IFI44L* methylation on HCC.

Conclusion: Our data provide new insights into the virus-host interaction, and decreased *IFI44L* methylation is predictive of viremia levels, linking hepatitis B progression to HCC.

FRI-263

External validation of clinical scoring system for the prediction of hepatocellular carcinoma in chronic hepatitis B treated by nucleotide/nucleoside analogue

M. Kurosaki, J. Itakura, T. Nobuharu, Y. Yasui, K. Tsuchiya, H. Nakanishi, K. Takaura, N. Izumi. *Musashino Red Cross Hospital, Department of Gastroenterology and Hepatology*
Email: kurosaki@musashino.jrc.or.jp

Background and Aims: The PAGE-B score using age, platelet counts, and gender, is a simple risk scoring system that predict risk of hepatocellular carcinoma (HCC) in Caucasian hepatitis B patients treated with nucleotide/nucleoside analogue (NUC). This study validated the reliability of PAGE-B score in Asian patients treated with NUCs. The role of NUC therapy for HCC risk reduction was also evaluated by using by this score to adjust for the baseline HCC risk.

Method: The PAGE-B score was calculated in 300 chronic hepatitis B patients treated by NUCs for an average of 8.2 years, and in 431 patients not treated with NUCs and observed for average of 6.3 years. The accuracy of this score to predict HCC development was evaluated. The cumulative incidence of HCC was compared between NUC treated and not treated patients after stratification by PAGE-B score to evaluate the role of NUC therapy for HCC risk reduction.

Results: The 3-, 5-, and 7-year cumulative HCC incidence in NUC treated vs. not treated patients was 2.5% vs. 6.2%, 3.7% vs. 8.3%, and 5.1% vs. 10.4%, respectively (p = 0.009). The proportion of NUC treated patients with PAGE-B ≤9, 10–17, ≥18 was 27%, 48%, and 25%, respectively, and their 5-year cumulative HCC incidence rates was 0%, 3.2%, and 9.5%, respectively (p < 0.0001). The area under the receiver operating characteristic curve of PAGE-B score for the prediction of HCC at 5-year in NUC treated patients was 0.829. The hazard ratio (HR) of PAGE-B ≥ 18 for HCC development during NUC treatment was 6.9 (95% confidence interval (CI) 4.3–11.0, p < 0.0001). Similarly, in patients not treated by NUC, area under the receiver operating characteristic curve of PAGE-B score for the prediction of HCC at 5-year was 0.834, and the HR of PAGE-B ≥18 for HCC development during NUC treatment was 7.7 (95% CI 4.4–13.7, p < 0.0001). NUC treated and not treated patients were stratified by PAGE-B score to adjust for the baseline HCC risk and the role of NUC therapy for HCC risk reduction was evaluated. The 5-year cumulative HCC incidence was significantly lower in NUC treated patients

compared to not treated patients if PAGE-B ≥18 (9.5% vs. 33.7%, p = 0.002), lower with borderline significance if PAGE-B 10–17 (3.2% vs. 5.8%, p = 0.059), and did not differ if PAGE-B ≤9 (0% vs. 1.3%, p = 0.13). In multivariable analysis including all patients, PAGE-B ≥18 (HR 7.4, 95%CI 4.6–11.8, p < 0.0001) and no NUC treatment (HR 1.5, 95%CI 1.2–1.9, p = 0.002) was an independent risk of HCC development.
Conclusion: The PAGE-B score which was originally developed based on data of Caucasian hepatitis B patients treated with NUC was also a reliable predictor for HCC development in Asian patients treated by NUCs. Adjustment of the baseline HCC risk by this score revealed that long term NUC therapy significantly reduced the incidence of HCC in patients with high PAGE score but not in those with low score.

FRI-264
Monitoring patients with a resolved hepatitis B virus infection for HBV reactivation
A. Tamori, R. Kozuka, H. Motoyama, H. Fujii, A. Hagihara, S. Uchida-Kobayashi, H. Morikawa, M. Enomoto, Y. Murakami, N. Kawada. *Osaka City University, Hepatology, Osaka, Japan*
Email: atamori@med.osaka-cu.ac.jp

Background and Aims: Hepatitis B virus reactivation (HBV-R) can occur in various conditions, such as in patients taking immunosuppressive or immuno-modified agents. It is speculated that the incidence rate of HBV-R depends on the drug used and the treatment duration. However, few reports are available about HBV-R in patients undergoing short-duration immunosuppressive therapy, particularly in HBV resolved patients. In the present study, we prospectively examined the incidence rate of HBV-R in patients with resolved HBV infection receiving various treatments.
Patients and Method: HBV DNA was prospectively examined by polymerase chain reaction analysis in 437 HBsAg-negative and anti-HBc positive patients who received cytotoxic or immunosuppressive therapy. The present cohorts consisted of 155 patients receiving long-duration immunosuppressive therapy; 113 with rheumatoid arthritis (RA), 15 with psoriasis, 14 who underwent renal transplantation, and 13 with inflammatory bowel disease, as well as 60 patients receiving short-duration immunosuppressive therapy. There were also 49 with sudden deafness and 11 with Bell's palsy. In addition, HBV-R was examined in 763 patients with chronic hepatitis C virus treated with direct acting anti-viral (DAA).
Results: The observation period for long-duration immunosuppressive therapy was a median of 41 months (range, 2–110 months). HBV-R occurred in five (4.4%) of 113 patients with RA and three (21%) of 14 patients who underwent renal transplantation. Rituximab was administered to two of three HBV-R patients who underwent renal transplantation. HBV reactivated at 2–27 months from the start of immunosuppressive therapy. Pre-emptive therapy with entecavir prevented hepatitis related to HBV-R. HBV-R did not occur in patients who received short-duration immunosuppressive therapy with prednisolone; the observation period was a median of 5 months (range, 1–14 months). HBV reactivated without hepatitis flare in one patient treated with sofsbuvir + ledipasvir.
Conclusion: HBV-R rarely occurred in HBV resolved patients treated with short-duration prednisolone or DAA. In contrast, continuous HBV monitoring was necessary in patients with RA and those who underwent renal transplantation.

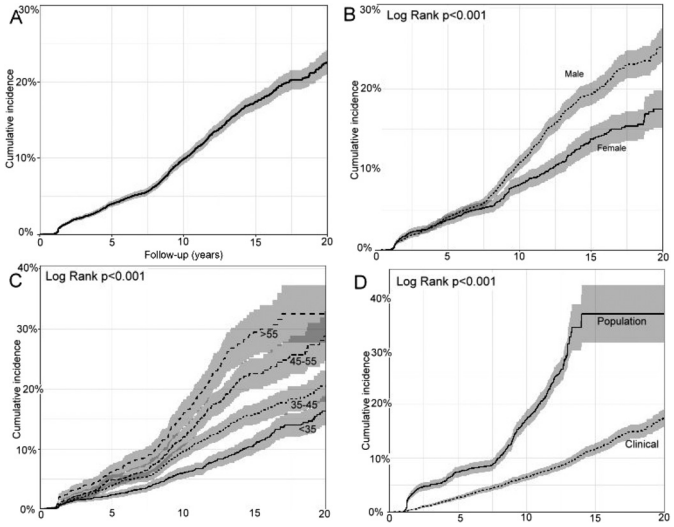
FRI-265
Relationship between hepatitis B core-related antigen and chronic hepatitis B outcome in HBeAg negative patients: a 10-year longitudinal study
W. Pan To[1], D. Wong[1,2], L.-Y. Mak[1], W.-K. Seto[1,2], K.-S. Cheung[1], Y. Yue, J. Fung[1,2], C. Lung Lai[1,2], M.-F. Yuen[1,2]. *[1]Queen Mary Hospital, Medicine, Hong Kong, Hong Kong; [2]The University of Hong Kong, State Key Laboratory of Liver Research, Hong Kong, Hong Kong*
Email: mfyuen@hku.hk

Background and Aims: Hepatitis B core-related antigen (HBcrAg) is a novel serological marker of HBV. It correlates well with serum HBsAg, HBV DNA and intrahepatic cccDNA levels. However, long-term data regarding the predictive value of HBcrAg is limited. We aim to determine the relationship between HBcrAg levels after spontaneous HBeAg seroconversion and hepatocellular carcinoma (HCC).
Method: We recruited chronic HBV patients with a documented time of spontaneously HBeAg seroconversion. Blood tests including liver function test and alpha-fetoprotein were performed. Cirrhosis was defined as the presence of cirrhotic features in the ultrasonography. HBcrAg and HBsAg were checked at three time points: within 3 years (the baseline), at 5 years and 10 years after HBeAg seroconversion. HBcrAg were measured by the Lumipulse G HBcrAg assays in a Lumipulse G1200 analyzer (Fujirebio Inc, Tokyo, Japan). HBV DNA was measured at the baseline. Multivariate logistic regression was used to investigate the predictors for the development of HCC.
Results: We recruited 209 patients. There were 120 (57.4%) male and the median age was 40 year-old (interquartile range [IQR]: 34–45 years). The median duration for follow-up was 13.1 years (IQR: 11.8–15.5 years). Cirrhosis was present at baseline in 9 patients (4.3%). HCC developed in 16 patients (7.7%) during the follow-up period. The median level of HBcrAg at baseline was 68.0kU/ml (IQR: 14.2–363.0kU/ml) while the median level of HBV DNA at baseline was 4.02 log IU/ml (IQR: 3.05–5.38logIU/ml). Patients who developed HCC had a significantly older age of HBeAg seroconversion compared with those without HCC (median age 50.1 vs 39.3 respectively, p = 0.002). More patients in the HCC group than in patients without HCC had baseline cirrhosis (31.3% vs 2.1%, p < 0.001). The median level of HBcrAg at baseline was significantly higher in HCC patients when compared with patients without HCC (518.6 vs 59.6kU/ml respectively, p = 0.003), while there were no differences in the levels of HBsAg and HBV DNA (3.24 vs 3.47logIU/ml and 4.61 vs 4.01logIU/ml, respectively; all p > 0.05). Independent risk factors for development of HCC included age of HBeAg seroconversion older than 50 years (odds ratio [OR]: 10.84, 95% confidence interval [95%CI]: 3.04–38.66), presence of baseline cirrhosis (OR: 6.29, 95%CI: 1.06–37.50) and a higher baseline HBcrAg (OR: 1.77, 95%CI 1.01–3.12). HBcrAg levels at 5 years and 10 years after HBeAg seroconversion were found to have no association with HCC, probably due to the limited number of patients with HCC after 5 years of HBeAg seroconversion (n = 9).
Conclusion: High HBcrAg level within 3 years after HBeAg seroconversion was independently associated with the development of HCC in chronic hepatitis B patients, while other independent risk factors included older age (>50 years) at HBeAg seroconversion and presence of baseline cirrhosis.

FRI-266
Real-world rates of hepatitis B surface antigen seroclearance in patients with chronic hepatitis B: a systematic review, conventional aggregated data meta-analysis and individual patient data meta-analysis
Y.H. Yeo[1], H.J Ho[2], H.-I Yang[3], T.-C. Tseng[4], M.-S. Kwak[5], Y.M. Park[6], Y.Y.J. Fung[7], M.B. Ferret[8], M. Rodríguez[9], C.M. Preda[10], T. Ungtrakul[11], P. Charatcharoenwitthaya[12], X. Li[13], M. Huan Le[1], B. Wei[1], B. Zou[1], A. Le[1], D. Jeong[1], N. Chien[14], L. Kam[14], T. Hosaka[15], M.R. Barciela[16], F. Suzuki[15], M. Kobayashi[17], T. Sriprayoon[18], Y. Chong[13], T. Tanwandee[18], M.-F. Yuen[19], H.-S. Lee[5], J.-H. Kao[20], A. Lok[21], C.-Y. Wu[22,23], M. Nguyen[1]. *[1]Stanford University Medical Center, Department of Medicine, Palo Alto, United States; [2]Taichung Veterans General Hospital, Division of Gastroenterology & Hepatology, Taichung, Taiwan; [3]Academia Sinica, Genomics Research Center; [4]National Taiwan University Hospital, Department of Internal Medicine, Taiwan; [5]Seoul National University Hospital, Department of Internal Medicine and Liver Research Institute, Seoul, Korea, Rep. of South; [6]Bundang Jesaeng General Hospital, Department of Internal Medicine and Biomedical Research Center, Korea, Rep. of South; [7]The University of Hong Kong, Queen Mary Hospital, Department of Medicine, Hong Kong, China; [8]Valle d'Hebron University Hospital, Liver Unit, Spain; [9]Hospital Universitario Central de*

Asturias, Liver Unit; [10]Fundeni Clinical Hospital, Gastroenterology and Hepatology Department, Bucharest, Romania; [11]HRH Princess Chulabhorn College of Medical Science, Faculty of Medicine and Public Health, Thailand; [12]Siriraj Hospital, Department of Internal Medicine; [13]The Third Affiliated Hospital, Sun Yat-sen University, Department of Infectious Diseases, China; [14]Kaohsiung Medical University, School of Medicine; [15]Toranomon Hospital, Department of Hepatology, Japan; [16]Hospital Universitario Vall d'Hebron, Liver Unit, Internal Medicine Department, Barcelona, Spain; [17]Toranomon Hospital, Research Institute for Hepatology, Japan; [18]Siriraj Hospital, Faculty of Medicine, Thailand; [19]The University of Hong Kong, Li Ka Shing Faculty of Medicine, Hong Kong; [20]National Taiwan University Hospital, Department of Internal Medicine, Taipei, Taiwan; [21]University of Michigan, Division of Gastroenterology and Hepatology, United States; [22]Taipei Veterans General Hospital, Medical Research Department, Taipei City, Taiwan; [23]Taipei Veterans General Hospital, Division of Gastroenterology & Hepatology, Taipei City, Taiwan
Email: mindiehn@stanford.edu

Background and Aims: Hepatitis B surface antigen (HBsAg) loss is a rare but important marker of chronic hepatitis B (CHB) functional control. However, there is considerable heterogeneity across published datasets with variable HBsAg clearance rates. Our goal was to perform aggregated data meta-analysis (ADMA) and individual patient data meta-analysis (IPDMA) to estimate pooled annual and cumulative HBsAg seroclearance rates and to identify their predictors.
Method: Two researchers independently searched PubMed and Embase from inception to July 5, 2017 for relevant studies and extracted data. Authors of all included studies were contacted for original individual participant level data. We estimated pooled rates of HBsAg loss using random effects model in ADMA and Cox proportional-hazard models with a cluster statement in IPDMA. This study with pre-planned subgroup analyses has been registered in PROSPERO.
Results: Out of the 4,469 abstracts and articles reviewed, 26 full-article studies (n = 39,661) were included. ADMA showed a pooled annual HBsAg seroclearance rate of 1.11% (95%CI 0.84–1.37%). In IPDMA of original data from 9 cohorts from the US, Europe and Asia (n = 12,317), 1,196 patients had HBsAg loss over 100,393.9 person-years of follow-up, yielding an annual incidence rate of 1.13% (95%CI: 1.08–1.20%) (Fig 1A). The 5-, 10-, 15-, and 20-year pooled cumulative rates were 4.03%, 9.90%, 17.40%, 22.51%, respectively. In subgroup analysis, older patients, males, and population-based community participants (vs. clinical cohorts) had significantly higher rates of HBsAg seroclearance (Figs. 1B-D). Multivariate Cox regression showed that males (adjusted hazard ratio [aHR]:1.17, 95% CI:1.02–1.34) and age >55 years (aHR:1.77, 95%CI:1.45–2.15) were significant independent predictors for higher rates of HBsAg loss, while positive HBeAg (aHR:0.33, 95%CI:0.26–0.42), antiviral therapy (aHR:0.52, 95% CI:0.31–0.86), cirrhosis at entry (aHR:0.58, 95%CI:0.34–0.97), HBV DNA > 20,000IU/ml (aHR:0.31, 95%CI:0.25–0.39) and quantitative HBsAg (qHBsAg) > 1200IU/ml (aHR:0.2, 95%CI:0.17–0.24) were independently associated with lack of HBsAg seroclearance. However, Asian (vs. non-Asian) ethnicity and population-based community (vs. clinical center) study setting were not.
Conclusion: The pooled annual HBsAg seroclearance rate was approximately 1.1% from both ADMA and IPDMA. Male sex, older age, antiviral treatment, HBeAg negativity, non-cirrhosis, lower HBV DNA and qHBsAg were independent predictors of HBsAg loss, but not ethnicity or study setting (population-based community vs. clinical cohorts).



FRI-267
Association of common polymorphism in the Interleukin 1 beta gene with Hepatitis B virus-related hepatocellular carcinoma in Caucasians

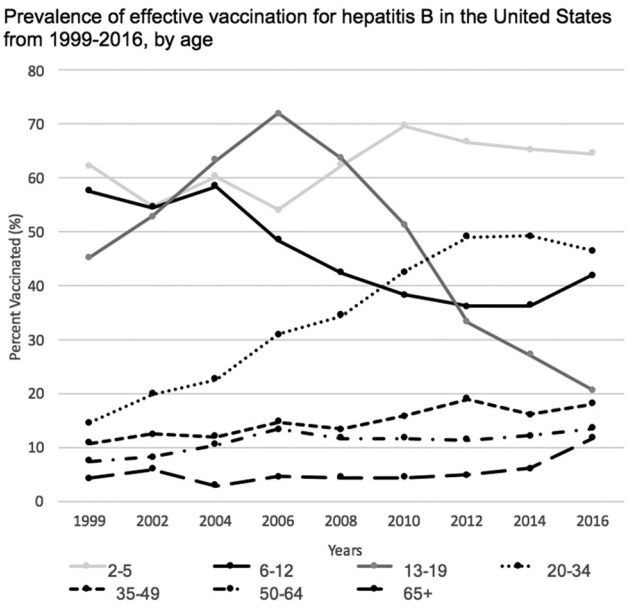
J. Fischer[1], L. Shuang[2], K. Eleni[3], E. Schott[4], F. Balazs[5], H. Renate[6], T. Berg[7], F. van Boemmel[3]. *[1]University Hospital Leipzig, Section of Hepatology, Division of Gastroenterology and Rheumatology, Leipzig, Germany; [2]University Hospital Leipzig, Section of Hepatology, Division of Gastroenterogy and Rheumatology, Leipzig, Germany; [3]University Hospital Leipzig, Section of Hepatology, Division of Gastroenterogy and Rheumatology, Leipzig, Germany; [4]HELIOS Klinikum Emil von Behring, Klink für Innere Medizin ll, Berlin, Germany; [5]HELIOS Klinikum Berlin-Buch, Department of Internal Medicine and Gastroenterology, Berlin, Germany; [6]Liver and Study Center Checkpoint, Berlin, Germany; [7]University Hospital Leipzig, Section of Hepatology, Division of Gastroenterogy and Rheumatology, Leipzig, Germany*
Email: janett.fischer@medizin.uni-leipzig.de

Background and Aims: Chronic hepatitis B (CHB) is a major risk for the development of liver cirrhosis and hepatocellular carcinoma (HCC). Pro-inflammatory cytokines such as interleukin 1 beta (IL1beta) mediate several immune responses and promote liver disease progression. Genetic variations within the promotor of IL1beta might alter cytokine expression and affect the progression to cirrhosis and HCC. We aimed to investigate the association of polymorphisms within the promotor of the IL1beta gene with CHB progression in Caucasian patients.
Method: 609 Caucasian patients with CHB and 235 individuals with spontaneous HBs-antigen sero-clearance (SC) were retrospectively enrolled. In the CHB group, 83% were HBe-antigen negative and 49% of patients were inactive carriers. 89 patients had developed liver cirrhosis and 41 were diagnosed with HCC and cirrhosis. Host genomic DNA was extracted from peripheral blood samples. Genotyping of the IL1beta rs1143623, rs1143627 and rs16944 was performed by polymerase chain reaction and melting curve analysis.
Results: Between the CHB and SC groups gender distribution (61% vs. 54% males; p = 0.042) and mean age (53.7 ± 13.8 vs. 65.1 ± 14.4 years; p < 0.0001) were significantly different. There were no differences in genotype distribution of all three IL1beta SNPs between the CHB and SC groups and stages during CHB. The C allele of rs1143623 was more frequent in patients with liver cirrhosis (62% vs. 49%, p = 0.030) and multivariate analysis revealed an association with an increased likelihood for cirrhosis development (OR = 1.63 [95%CI: 1.01–2.61] p = 0.044). The C alleles of rs11463623 and of rs1143627 were more frequent in patients with HCC (73% vs. 49%, p = 0.003; 80% vs. 64%, p = 0.028). In contrast, carriers of the C allele of rs16944 had fewer HCC

(71% vs. 86%, p = 0.013). In multivariate analyses the C allele of rs1143623 remained independently associated with HCC (OR = 2.81 [95% CI: 1.24–6.39] p = 0.014).
Conclusion: We identified for the first time an association of a common polymorphism within the interleukin 1 beta gene with the development of HBV-related liver cirrhosis and HCC in Caucasian patients. The risk conferred by this polymorphism is independent from the CHB disease stages which are currently regarded as important HCC risk factor. Further studies in larger cohorts and functional analysis are needed to confirm these results and elucidate the impact of these genetic variants in liver fibrogenesis and carcinogenesis.

FRI-268
Effective hepatitis B vaccination by serologic results in the United States: a population-based study from 1999–2016
M. Huan Le[1], D.H. Lee[1], M.-H. Lee[2], E. Gane[3], S. So[4], M. Nguyen[1].
[1]Stanford University Medical Center, Department of Gastroenterology and Hepatology, Palo Alto; [2]National Yang Ming University, Taipei, Taiwan; [3]The University of Auckland, Auckland, New Zealand; [4]Stanford University School of Medicine, Asian Liver Center, Palo Alto, United States
Email: mindiehn@stanford.edu

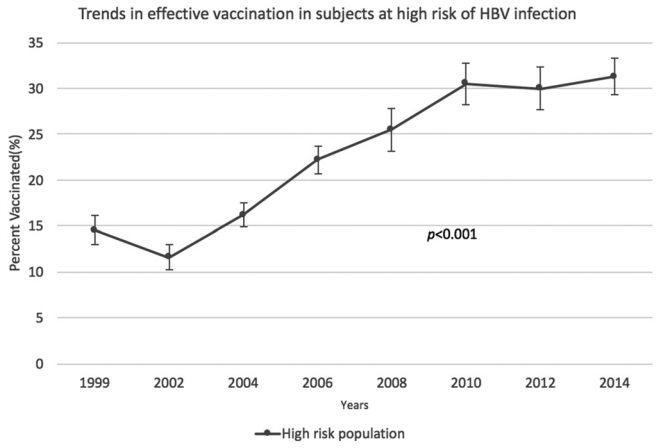
Background and Aims: In the United States (USA), the Centers for Disease Control and Prevention have estimated vaccine coverage to be greater than 90% in all children and teens and 24.6% in adults aged 19 and older in 2015. However, these results were obtained through survey questionnaire and have not yet been confirmed through serologic results. The aim of this study was to determine the trends in vaccination in the general USA population from 1999–2016 based on serologic results.
Method: Of the 92,062 participating in the National Health and Nutrition Examination Survey from 1999–2016, 71,777 subjects age 2 years and older who completed HBV serology tests were included in this analysis. Subjects age 2–5 years were defined as having effective vaccination if they were HBV surface antibody positive, as this group did not undergo HBV core antibody testing. Subjects age 6 years and older were defined as having effective vaccination if they were HBV core antibody negative and HBV surface antibody positive. Analyses were weighted to represent the USA population.
Results: From 1999 to 2016, overall effective vaccination increased significantly from 19.3% to 25.9% (p < 0.001). Across various demographic and socioeconomic groups, significant increases in vaccination were seen in male (18.8–23.3%, p = 0.001), female (19.8–28.4%, p < 0.001), USA born (20.5–26.4%, p < 0.001), foreign born (12.7–23.4%, p < 0.001), non-Hispanic White (18.2–25.0%, p = 0.001), non-Hispanic Black (21.8–26.8%, p = 0.002), Other-multiracial (20.2–31.0%, p = 0.004), uninsured (13.5–19.9%, p < 0.001), insured (20.7–26.8%, p < 0.001) and in higher income individuals (19.4–26.2%, p < 0.001). No significant changes in effective vaccination were seen in Mexican American/Hispanic and low income individuals. There was a significant increase in effective vaccination in subjects age 2–5 years old (p for trend = 0.003) and in age 20 years and older (p for trend < 0.001). Surprisingly, there was a significant decrease in effective in subjects age 6–12 years and 13–19 years (p for trend < 0.001) from 1999–2016 (Figure). Based on population estimates from 2011–2014, 79.6 million Americans (25.9%) have effective vaccination while 221.7 million Americans remain at risk of infection.
Conclusion: Despite significant improvements in vaccination from 1999 to 2016, hundreds of millions of Americans remain at risk of HBV infection. Further efforts must be made to educate and immunize all subjects that may be at risk of infection and to understand factors associated with the decreasing rate of effective vaccination for the school-age group in the more recent period (6–19 years old).



FRI-269
Suboptimal rates of effective hepatitis B vaccination in adults at high risk of infection in the United States from 1999–2014
M. Huan Le[1], D.H. Lee[1], M.-H. Lee[2], E. Gane[3], S. So[4], M. Nguyen[1].
[1]Stanford University Medical Center, Department of Gastroenterology and Hepatology, Palo Alto, United States; [2]National Yang Ming University, Taipei, Taiwan; [3]The University of Auckland, Auckland, New Zealand; [4]Stanford University School of Medicine, Asian Liver Center, Palo Alto, United States
Email: mindiehn@stanford.edu

Background and Aims: In the United States, hepatitis B vaccination in adults at high risk of infection has been recommended by the Centers for Disease Control and Prevention (CDC) since 1982. In 2006, the CDC updated their immunization guidelines to call for increased vaccination of high risk populations. However, the effectiveness of these guidelines are unclear since the high risk group remains understudied. Therefore, using objective serologic results, the aims of this study were to determine the trends and predictors of vaccination in those at high risk of infection.
Method: A total of 42,364 adults age 18 and over who completed HBV serologic tests from 1999–2014 were included in this study. Subjects were defined as having effective vaccination if they were HBV surface antibody positive and HBV core antibody negative. High risk populations were defined by CDC and US Preventive Services Task Force recommendations (intravenous (IV) drug use, high risk sexual behavior, risk of exposure to blood borne diseases). Analyses were weighted to represent the USA population.
Results: 6,465 adults (34.8%, 95%CI: 33.5–36.1) were identified as persons that engaged in behaviors that put them at high risk for HBV infection. In this high risk group, effective vaccination increased significantly from 14.5% in 1999 to 31.3% in 2014 (Figure). In those at high risk of infection, significant increases in vaccination from 1999–2004 to 2011–2014 were observed in those who were evaluated for a sexually transmitted disease (16.3–29.6%, p < 0.001) and those with multiple sex partners (14.2–36.9%, p < 0.001). No statistically significant changes in vaccination were observed in IV drug users (7.36–14.5%, p = 0.109), HCV positive individuals (6.41–8.34%, p = 0.556), homosexual men (11.8–24.0%, p = 0.051), and hemodialysis patients (50.1–37.2%, p = 0.450). Independent predictors of vaccination include younger age (OR: 4.13 95%CI: 2.35–7.23, p < 0.001), female (OR:1.7 95%CI: 1.45–2.05, p < 0.001), other-multiracial ethnicity (OR: 1.58 95%CI: 1.09–2.28, p = 0.016), college educated (OR = 2.54 95%CI:

2.81–3.56, p < 0.001), being single (OR: 1.46 95%CI: 1.20–1.78, p < 0.001), and having health insurance (OR: 1.56 95%CI: 1.29–1.89, p < 0.001).



Conclusion: Significant increases in vaccination have been observed in subjects at high risk of infection from 1999–2014. However, approximately 70% of this group remains unvaccinated, especially in HCV positive individuals and IV drug users. Further efforts must be made to educate and immunize subjects that are at high risk of HBV infection.

FRI-270

Droplet digital PCR quantitation of HBV cccDNA pool and transcriptional activity in long-term nucleos(t)ide analogue treated patients

A. Inchauspé[1,2,3], Maëlle Locatelli[1,3], F. Lebosse[3,4], A. Diederichs[1], A. Freydier-Berthet[2], A. Alam[2], K. Carter[2], L. Fraisse[2], M. Bourliere[5], K. Hamed[6], Cécile Challier[2], B. Testoni[1], F. Zoulim[1,3,7]. *[1]CRCL, INSERM U1052, Lyon, France; [2]Sanofi, TA-ID, Marcy l'étoile, France; [3]Université de Lyon 1, Lyon, France; [4]Hospices Civiles de Lyon, Lyon, France; [5]Hopital Saint-Joseph, Marseille, France; [6]Novartis, East Hanover, United States; [7]Hospices Civiles de Lyon, Lyon, France*
Email: fabien.zoulim@inserm.fr

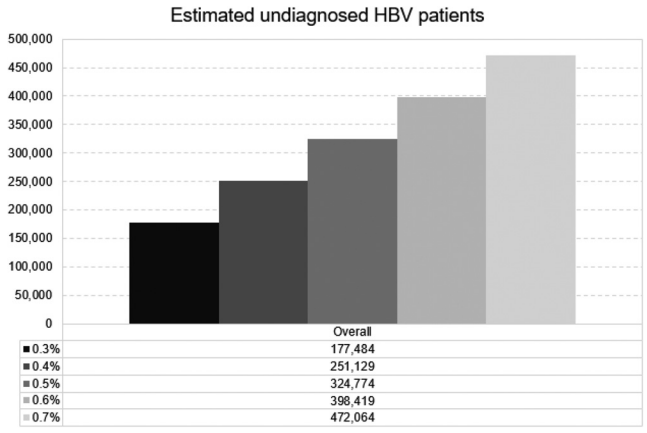
Background and Aims: Nucleos(t)ide anssalogue (NA) therapy for chronic hepatitis B leads to viral suppression in the majority of patients. However, no significant effect on the established pool of covalently closed circular (ccc)DNA has yet been described. cccDNA stably resides in the nucleus of infected hepatocytes and serves as a unique template for pre-genomic RNA (pgRNA), the essential intermediate for full viral replication. Robust data on the effect of long-term (>2 years) NA therapy on intrahepatic cccDNA pool levels are lacking because of technical limitations associated with the sensitivity of cccDNA quantitation in small liver biopsy samples.
Method: To address this issue, a droplet digital PCR (ddPCR) assay to absolutely quantify both cccDNA and transcriptional activity (calculated as pgRNA/cccDNA ratio) was set up and applied to 64 liver biopsy samples. Fifty-six samples were obtained from patients treated with telbivudine for 3–5 years, and 8 samples from 4 patients who received mixed NA therapy in the PEGAN study with paired biopsy samples before and after the administration (or not) of add-on 48-week peg-IFN.
Results: ddPCR was ten times more sensitive than classic qPCR for cccDNA detection in HepG2-NTCP infected cells. A duplex ddPCR protocol was designed for absolute quantification of pgRNA content and internal normalization using the *gusb* housekeeping transcript. Among the samples from the 56 telbivudine-treated patients, 70% were negative for cccDNA quantification by classic qPCR. However, ddPCR analysis detected cccDNA in 89% of these qPCR-negative samples. In total, only 11% of NA-treated patient samples had undetectable intrahepatic cccDNA by ddPCR, a percentage comparable to a matched control group of non-treated patients (12%). Notably, absolute quantitation by ddPCR showed that both cccDNA amount and pgRNA/cccDNA ratio were significantly decreased in samples from NA-treated patients as compared to non-treated patient samples. All of the 8 biopsies derived from the PEGAN patients had undetectable cccDNA levels by qPCR, but ddPCR detected cccDNA in 7 of them. Analysis of cccDNA and pgRNA in matched samples revealed no significant effect of the peg-IFN add-on on both cccDNA amount and activity.
Conclusion: This ddPCR protocol extended the limits and precision of cccDNA and pgRNA detection in vivo and demonstrated that liver samples from most long-term NA-treated patients still harbour transcriptionally active cccDNA.

FRI-271

Estimated the number of undiagnosed patients and antiviral treatment rate of chronic hepatitis B in the U.S. based on the Truven Health MarketScan Database

E. Ogawa[1,2], D. Jeong[1], Y.H. Yeo[1], M. Nguyen[1]. *[1]Stanford University Medical Center, Department of Gastroenterology and Hepatology, Palo Alto, United States; [2]Kyushu University Hospital, Department of General Internal Medicine, Fukuoka, Japan*
Email: mindiehn@stanford.edu

Background and Aims: Prior studies suggest that only one-third of chronic hepatitis B (CHB) in the U.S. are aware of their diagnosis and only 10–20% or less of diagnosed patients are treated with antiviral therapy. Our goal is to estimate total number of undiagnosed CHB and treatment rate of CHB patients in a large nationwide sample of U.S. population.
Method: We used the commercial U.S. Truven Health MarketScan Database (n = 73,644,921; 1/1/2007-12/31/2014) to identify the number of patients with CHB diagnosis (≥1 inpatient or ≥2 outpatient ICD-9-CM codes for CHB). Other study inclusion criteria include continuous insurance and prescription coverage for 6 months prior to the first CHB diagnosis and 6 months after. Then, using the National Health and Nutrition Examination Survey (NHANES) prevalence estimates of HBV infection of 0.3%–0.7%, we estimated the number of undiagnosed CHB patients by subtracting the number of estimated CHB patients by NHANES prevalence in this population of approximately 73 million people with the number of patients who were identified as having CHB in this population sample. We also estimated the proportion of diagnosed CHB patients who received a prescription of any of the FDA-approved anti-HBV medications.
Results: In total, we identified 43,765 CHB in this cohort of 73,644,921 during the study period, yielding a prevalence of known or diagnosed CHB of 0.059% (95%CI: 0.059–0.060). The prevalence of diagnosed CHB increased with age and were 0.036% (95%CI: 0.036–0.037) for the 18–34 age group, 0.069% (95%CI: 0.068–0.070) for the 35–44 group, 0.072% (95%CI: 0.071–0.073) for the 45–54 group, and 0.077% (95%CI: 0.076–0.079) for the 55–64 group. Notably, diagnosed CHB prevalence was higher among HMO insured patients vs. other insurance types: 0.088% (95%CI: 0.086–0.090) vs. 0.056% (95%CI: 0.055–0.057). Based on the NHANES prevalence rate with 0.3–0.7% in HBV infection, the estimated number of undiagnosed patients by sensitivity analysis was shown in Figure. The overall treatment rate with anti-HBV drugs was 11.5% (95%CI: 11.2–11.8) (5,033/43,765). HBV treatment rate among aged 55–64 (10.7%, 95%CI: 10.1–11.3) group was lower than the aged 35–44 (12.9%, 95%CI: 12.2–13.5) and 45–54 (13.2%, 95%CI: 12.6–13.9) groups. HBV treatment for insured patients with HMO (14.3%, 95%CI: 13.6–15.0) was also higher than those with other insurance type (11.0%, 95%CI: 10.6–11.3).



Conclusion: In this large U.S. nationwide sample of over 73 million people with insurance coverage, the prevalence of diagnosed CHB was only 0.059%, 5–12 times lower than the NHANES estimates. In this sample alone, there were an estimated total of 177,484–472,064 people with CHB but have not been diagnosed. Treatment rate was also dismally low. Further efforts are needed to improve the current poor linkage to care for CHB patients.

FRI-272

Combination of HBV serological markers to predict the burden and productivity of intrahepatic HBV reservoir and disease progression in HBeAg negative Chronic Hepatitis B

V. Svicher[1], R. Salpini[1], L. Colagrossi[1], D.D. Carlo[1], A. Battisti[1], L. Piermatteo[1], N. Hansi[2], F.C. Silberstein[1], C.F. Perno[3], U.S. Gill[2], P. Kennedy[2]. *[1]Tor Vergata University, Experimental Medicine and Surgery, Italy; [2]Blizard Institute, Barts and The London SMD, QMUL, Hepatology, Centre for Immunobiology, London, United Kingdom; [3]University of Milan*
Email: valentina.svicher@uniroma2.it

Background and Aims: The persistence of HBsAg and ongoing viral replication is associated with an increased risk for the development of hepatocellular carcinoma in chronic hepatitis B (CHB). At present serological markers measured in the peripheral compartment alone are used to risk stratify patients for disease progression and treatment candidacy. Limited data exist on the intrahepatic (it) compartment and how serum markers reflect the intrahepatic HBV reservoir and its transcriptional activity. We investigated if improved virological characterisation could better inform treatment decisions particularly in those patients with HBV DNA <20,000 IU/ml.
Method: The peripheral and intrahepatic compartments of HBeAg negative CHB patients (n = 84) were compared between disease cohorts with different virological characteristics. Patients were classified as follows: Group 1 (HBV DNA <2,000 IU/ml; n = 12), Group 2 (HBV DNA 2,000–20,000 IU.ml; n = 25), Group 3 (HBV DNA >20,000 IU/ml; n = 47). cccDNA, itHBV DNA and pgRNA were assayed by qPCR and serum HBcrAg measured by Lumipulse (Fujirebio). Correlations between peripheral and intrahepatic compartments were assessed with Spearman rank. AUROC was used to define the threshold ability of peripheral parameters to predict the intrahepatic reservoir.
Results: Overall serum HBV DNA and HBcrAg positively correlated with cccDNA (Rho = 0.56 & 0.48; p = <0.001), itHBV DNA (Rho = 0.49 & 0.59; p = <0.001) and pgRNA (Rho = 0.74 & 0.45; p = <0.001 & 0.004). Conversely weaker correlations were noted for quantitative HBsAg (qHBsAg) with cccDNA (Rho = 0.31, p = 0.007), itHBV DNA (Rho = 0.39 p = 0.001) and pgRNA (Rho = 0.13, p = 0.43). On sub-group analysis groups 1 and 2 demonstrated a comparable intrahepatic reservoir. In contrast, compared to group 2, patients in group 3 were characterised by higher levels of cccDNA (p = 0.004), itHBV DNA (p = 0.004) and pgRNA (0.002). By AUROC, the combination of: serum HBV DNA <20,000 IU/ml, HBcrAg <2.0 log IU/ml and qHBsAg <3.2 log IU/ml identified a limited HBV reservoir with a 75% positive predicted value and 95% specificity.
Conclusion: Serum HBcrAg correlates with the burden and productivity of the intrahepatic HBV reservoir in HBeAg negative CHB patients. This parameter combined with serum HBV DNA and qHBsAg can enhance disease stratification and identify those patients at low risk of disease progression. The combination of these serological parameters could be utilised to inform treatment decisions particularly in those patients with HBV DNA <20,000 IU/ml.

FRI-273

Comparison of the risks of hepatocellular carcinoma in patients with chronic hepatitis B virus infection: estimation of direct carcinogenic effect of hepatitis B virus

Y. Chang, J.-H. Lee, J.Y. Nam, H.Y. Lee, H. Cho, Y.Y. Cho, E.J. Cho, S. Yu, Y.J. Kim, J.-H. Yoon. *Department of Internal Medicine and Liver Research Institute, Seoul National University College of Medicine*
Email: pindra@empas.com

Background and Aims: Chronic hepatitis B virus (HBV) infection is one of the major risk factors for hepatocellular carcinoma (HCC) development. The major mechanism of HBV-induced hepatocarcinogenesis is an indirect pathway through the process of inflammation and fibrosis, but a direct oncogenic effect of HBV also contributes. It remains still unknown the impact of direct carcinogenic effect of HBV.
Method: This study included consecutive patients diagnosed as chronic HBV infection with normal alanine aminotransferase (ALT) levels and without evidence of cirrhosis at a tertiary referral hospital in Korea. Study participants were classified according to the presence of HBeAg, serum HBV DNA levels, and antiviral treatment: HBeAg-positive chronic infection (HBeAg-positive and HBV DNA >20,000 IU/ml), untreated HBeAg-negative chronic infection (HBeAg-negative and HBV DNA <2,000 IU/ml without antiviral treatment), or treated HBeAg-negative chronic infection (HBeAg-negative and HBV DNA <2,000 IU/ml with antiviral treatment). Primary endpoint was an HCC development. Cox proportional hazard model and inverse-probability weighting (IPW) were utilized to adjust baseline characteristics.
Results: A total of 1,197 patients were included: 373 HBeAg-positive, 308 untreated HBeAg-negative, and 516 treated HBeAg-negative chronic infection. Age and baseline liver function were significantly more favorable for HBeAg-positive group than HBeAg-negative groups. In multivariate analyses to adjust confounding factors, HBeAg-positive group showed significantly higher risks of HCC than both untreated HBeAg-negative group (adjusted hazard ratio [aHR] = 7.93, 95% confidential interval [CI] = 2.87–21.91, p < 0.001) and treated HBeAg-negative group (aHR = 8.51, 95%CI = 3.32–21.5, p < 0.001). After balancing baseline characteristics with IPW, HBeAg-positive group consistently showed significantly higher risks of HCC than both untreated (HR = 4.44, 95%CI = 2.22–8.88, log-rank p < 0.001) and treated HBeAg-negative group (HR = 3.03, 95%CI = 2.14–4.29, log-rank p < 0.001).
Conclusion: Even with normal ALT level, HBeAg-positive chronic infection phase had 4.4–7.9-fold and 3.0–8.5-fold higher risk of HCC than untreated and treated HBeAg-negative chronic infection, respectively. These results might suggest the considerable impact of direct oncogenic effect of HBV in HCC development.

FRI-274

Modified PAGE-B score predicts the risk of hepatocellular carcinoma in Asians with chronic hepatitis B on antiviral therapy

M. Lee[1], J.H. Kim[1], B.G. Jun[2], T.S. Kim[1], E.-H. Cho[1], D.H. Choi[1], K.T. Suk[3], S. Kang[4], M.Y. Kim[4], Y.D. Kim[2], G.J. Cheon[2], D.J. Kim[3], S.K. Baik[4]. *[1]Kangwon National University Hospital, Department of Internal Medicine, Korea, Rep. of South; [2]Gangneung Asan Hospital, Department of Internal Medicine, Korea, Rep. of South; [3]Chuncheon Sacred Heart Hospital, Department of Internal Medicine, Korea, Rep. of South;*

[4]*Wonju Severance Christian Hospital, Department of Internal Medicine, Korea, Rep. of South*
Email: minjonglee2@naver.com

Background and Aims: Recently, PAGE-B score has been developed to predict the risk of hepatocellular carcinoma (HCC) in Caucasian patients with chronic hepatitis B (CHB). We aimed to validate PAGE-B scores in Asian patients with CHB and suggested modified PAGE-B scores to potentiate the predictive performance.
Method: From 2007 to 2017, we examined 2,844 Asian patients with CHB receiving entecavir/tenofovir therapy. We assessed the performances of PAGE-B and three conventional risk prediction models (CU-HCC, GAG-HCC, and REACH-B) for HCC development. A modified PAGE-B score (mPAGE-B) was developed (derivation set from three centers, n = 1,896) based on multivariable Cox models. Bootstrap for internal validation and external validation (validation set from one center, n = 948) were performed.
Results: The 5-year cumulative HCC incidence rates were 5.6% and 5.0% in the derivation and validation datasets, respectively. In the derivation dataset, age, gender, serum albumin levels, and platelet counts were independently associated with HCC. The mPAGE-B score was developed based on age, gender, platelet counts, and albumin levels (time-dependent area under receiver operating characteristic curves [AUROC] = 0.81, 0.80 after bootstrap validation). In the validation set, the original PAGE- B showed similar AUROCs to CU-HCC, GAG-HCC, and REACH-B at 5 years (0.73 vs 0.67, 0.69, and 0.68 respectively; all p > 0.05), whereas the AUROCs of mPAGE-B at 5 years were significantly higher than those of the PAGE-B and the three other models (0.82, all p < 0.001). HCC incidence rates within 5 years of antiviral therapy initiation in CHB patients were significantly lower compared with rates beyond year 5.

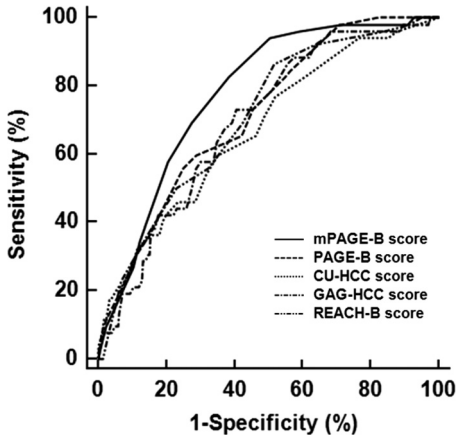


Figure 1: Time-dependent AUROCs of mPAGE-B scores and other prediction models for the prediction of HCC development within 5 years.

Conclusion: Although PAGE-B is applicable in Asian CHB patients receiving entecavir/tenofovir therapy, mPAGE-B scores including additional albumin levels showed better predictive performance than the original PAGE-B score.

FRI-275

Role of hepatitis B core-related antigen and antibodies to hepatitis B core antigen level in the natural history of chronic HBV infection

G.P. Caviglia[1], A. Olivero[1], A. Ciancio[1], F. Tandoi[2], G. Troshina[1], C. Bosco[1], L. Boglione[1], M. Rizzetto[1], R. Romagnoli[2], G.M. Saracco[1], A. Smedile[1]. [1]*University of Turin, Department of Medical Sciences, Turin, Italy;* [2]*University of Turin, Department of Surgical Sciences*
Email: caviglia.giampi@libero.it

Background and Aims: The natural history of chronic hepatitis B (CHB) is characterized by different dynamic phases which are not necessary sequential. Antiviral therapy is recommended only in patients with chronic hepatitis (CH) or cirrhosis, whereas patients with chronic infection (CI) should be periodically monitored. However, a reliable identification of CHB patients requiring treatment could be challenging when hepatitis is in a biochemical remission simulating a CI profile. We assessed the added value of hepatitis B core-related antigen (HBcrAg) and anti-hepatitis B core antibody class IgG (anti-HBc IgG) levels for the discrimination between the different CHB phases.
Method: Serum samples of 132 CHB patients (13 CH-HBeAg+, 64 CH-HBeAg- 21 low viremic CI-HBeAg- [fluctuating HBV DNA between 2000 and 20,000 IU/mL] and 34 true CI-HBeAg- [HBV DNA persistently <2,000 IU/ml]) and 97 HBsAg-/anti-HBc+ subjects (51 occult HBV infection [OBI]+ and 46 OBI-) were analyzed. HBsAg, HBcrAg and anti-HBc IgG level were assessed by CLEIA (Lumipulse®, Fujirebio, Japan). Biomarkers levels were reported in logIU/ml, logU/ml and Log cut-off index (COI), respectively. OBI+ was defined according to consensus statements.
Results: Mean HBsAg, HBcrAg and anti-HBc IgG levels were different among CHB phases (one-way ANOVA, p < 0.001), with higher values in CH-HBeAg+ (4.47 ± 0.79 log IU/ml, 6.9 ± 0.3 log U/ml and 4.07 ± 0.69 logCOI, respectively) and lower in true CI-HBeAg- (2.25 ± 1.26 log IU/ml, 2.2 ± 0.4 log U/ml and 3.29 ± 0.52 logCOI, respectively). We observed a correlation between HBV DNA and HBsAg (r = 0.642, p < 0.001), HBcrAg (r = 0.875, p < 0.001) and anti-HBc IgG (r = 0.515, p < 0.001). Area under the curve (AUC) for the discrimination between low viremic and true CI-HBeAg- was 0.736 for HBsAg, 0.749 for HBcrAg and 0.648 for anti-HBc IgG; a higher accuracy (AUC = 0.812) was obtained combining HBcrAg and anti-HBc IgG. Among HBsAg-/anti-HBc+ subjects, anti-HBc IgG levels were different between OBI+ and OBI- (1.16 ± 0.60 vs. 0.78 ± 0.64 logCOI, p = 0.004) with AUC = 0.671.
Conclusion: The combination of HBcrAg and anti-HBc IgG levels may improve the correct identification of true CI-HBeAg- patients (HBV DNA persistently <2,000 IU/ml) that do not require antiviral therapy. Anti-HBc IgG is the only circulating HBV marker detectable and quantifiable in HBsAg- subjects with previous HBV exposure and may help clinicians to predict HBV reactivation in OBI+ subjects undergoing pharmacological immunosuppression.

FRI-276

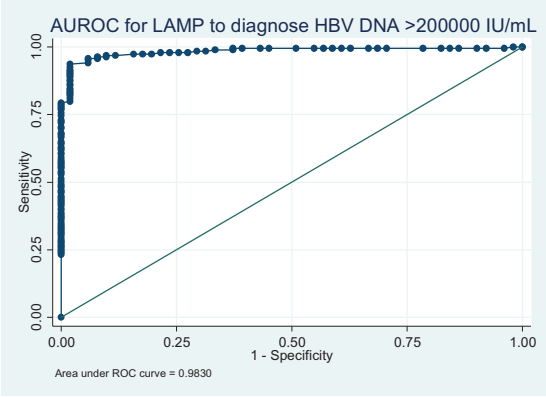
Pan-genotypic loop-mediated isothermal amplification assay for HBV: a simple, rapid and affordable point-of-care test to semi-quantify HBV DNA

J. Vanhomwegen[1], A. Kwasiborski[1], V. Sauvage[2], L. Boizeau[2], D. Hoinard[1], D. Candotti[2], S. Laperche[2], Y. Shimakawa[3]. [1]*Institut Pasteur, Unité de recherche et d'expertise Environnement et risques infectieux;* [2]*Laboratoire associé aux centre Nationaux de Référence des Hépatites B et C, et du VIH, Institut National de la Transfusion Sanguine (CNR-INTS), Département des agents transmissibles par le sang;* [3]*Institut Pasteur, Unité d'Epidémiologie des Maladies Emergentes*
Email: yusuke.shimakawa@pasteur.fr

Background and Aims: To achieve the global elimination of HBV, it is essential to scale up antiviral therapy through decentralized services in low- and middle-income countries (LMIC). However, the access to nucleic acid amplification test to quantify HBV DNA, a key marker to determine treatment eligibility, is limited and non-affordable in LMIC. Loop-mediated isothermal amplification assay (LAMP) is a simple, rapid and inexpensive technique to efficiently amplify DNA at a constant temperature. We designed a pan-genotypic LAMP assay to semi-quantify HBV viral load (VL) and evaluated its performance.
Method: Pan-genotypic primers sets were designed on conserved HBV gene regions using the LAMP Explorer software. The ability of LAMP to discriminate two clinically important HBV DNA levels (2,000 and 200,000 IU/mL), determined by the reference PCR assay (Roche COBAS®), was evaluated using well-characterized plasma samples from 240 French blood donors with positive HBV DNA (genotype A (n = 67), B (31), C (37), D (45), E (51) and F (9)) and 50 HBV-negative controls. HBV DNA was extracted from plasma using a simple

bead-based extraction method (Dynabeads™ SILANE), and amplified at 65°C for 60 minutes using real-time fluorescence reader (Genie III, OptiGene, UK) and real-time turbidmeter (Loopamp EXIA, Eiken Chemicals, Japan).

Results: The broadness of the LAMP was confirmed through a successful detection of synthetic DNAs from 8 major HBV sub-genotypes (A1/2/3, B, C, D, E, and F) with detection limits ranging from 10 to 100 genome copies/µL. Results obtained from donor samples showed a linear correlation between time-to-result (minutes) using LAMP and HBV DNA level. The AUROC was 0.91 (95%CI: 0.87–0.94) with 75.7% sensitivity and 92.0% specificity to diagnose high VL (2,000 IU/ml) and 0.98 (0.97–1.00) with 98.0% sensitivity and 92.6% specificity to diagnose very high VL (200,000 IU/ml) (Figure). The performance did not vary according to genotypes. No cross-reactivity was observed with HCV, HIV, or CMV in 37 tested samples. The cost per assay was <10€, and the completion time (extraction and amplification) was 90 minutes.



Conclusion: We developed a pan-genotypic LAMP assay to semi-quantify HBV VL. High accuracy to diagnose VL >200,000 IU/ml support its use as a rapid point-of-care test to identify women at elevated risk of mother-to-child transmission at peripheral antenatal clinics in LMICs. Real-life field evaluation of HBV-LAMP is ongoing in Africa.

FRI-277

Basal core promoter mutations as potential predictors of an enlarged intrahepatic HBV reservoir and enhanced cccDNA transcriptional activity in HBeAg negative chronic hepatitis B infection

L. Colagrossi[1], R. Salpini[1], U.S. Gill[2], A. Battisti[1], L. Piermatteo[3], D.D. Carlo[1], N. Hansi[2], F.C. Silberstein[3], C.F. Perno[4], P. Kennedy[5], V. Svicher[3]. *[1]Tor Vergata University, Department of Experimental Medicine and Surgery, Rome, Italy; [2]Blizard Institute, Queen Mary University of London, Centre for Immunobiology, London, United Kingdom; [3]Tor Vergata University, Department of Experimental Medicine and Surgery, Roma, Italy; [4]University of Milan, Milan, Italy; [5]Blizard Institute & Barts and the London School of Medicine & Dentistry QMUL, Hepatology Unit, Centre for Immunobiology, London, United Kingdom*
Email: luna_colagrossi@yahoo.it

Background and Aims: The basal core promoter (BCP) mutations 1766T, 1764A + 1762T are known to cause HBeAg-negativity. However, their impact on modulating the burden and productivity of intrahepatic HBV reservoir in vivo is still controversial.

Method: This study includes 72 drug-naïve patients (pts) with HBeAg negative chronic HBV infection (D:45.8%, C:19.4%, E:18.1%, A:9.7%, B:7%), with a BCP sequence (nucleotide:1742–1814) obtained from liver biopsy. Intrahepatic cccDNA and pregenomic RNA (pgRNA) are assessed by qPCR. Serum HBcrAg is measured by Lumipulse (Fujirebio). BCP mutations are defined according to the reference sequence of each specific genotype. Mann-Whitney test is used to compared levels of intrahepatic and serum parameters in presence of each BCP mutation and in its absence (referred as wt). AIggen algorithm is used to estimate BCP binding affinity for transcription factors (TF) (a decreased dissimilarity score [DS] indicates an increased binding affinity in presence of a mutation).

Results: 1766T and 1764A + 1762T (occurring in 9.7% and 29.2% of pts) are the only BCP mutations tightly correlated with increased cccDNA (median [IQR]:2.6[2.2–3.2] and 2.0[1.0–2.5] vs 1.8[0.9–2.2]logcps/1000cells for wt, p = 0.001 and 0.01) and serum HBV-DNA (median [IQR]:4.9[3.8–5.4] and 5.0[4.7–5.4] vs 3.4[2.2–4.5] IU/ml for wt, p = 0.003 and 0.001). Multivariable analysis confirms that the presence of ≥1 of these mutations independently correlates with higher cccDNA and serum HBV-DNA after correcting for patients' demographics, HBV genotypes, virological parameters (OR[95%CI]:2.9[1–8.2] p = 0.05 and 3.3[1.1–9.7] p = 0.03). 1766T and 1764A + 1762T also determine a higher burden of pgRNA (median [IQR]:20[13–32] and 460[5–1077] vs 2[1–10]cps/1000cells for wt, p = 0.02 and 0.006) and HBcrAg (median [IQR]:4.3[3–5.1] and 4.0[3–4.9] vs 2.6[2–3.3]logU/ml for wt, p = 0.03 and 0.002), supporting their contribution to an enlarged and more productive HBV reservoir. Moreover, 1762T + 1764A increases binding affinity for HNF-1alfa TF (DS:1.8 vs 4.6 for wt) and introduces TF binding site HNF-1beta (absent in wt). Finally, all patients with 1766T present a Ishak score ≥2 (p = 0.001), suggesting its role in liver damage.

Conclusion: 1766T and 1764A + 1762T tightly correlate with an enriched intrahepatic HBV reservoir endowed by enhanced productivity. These mutations should be considered in therapeutic strategies aimed at silencing cccDNA and could act as markers to identify patients at higher risk of disease progression.

FRI-278

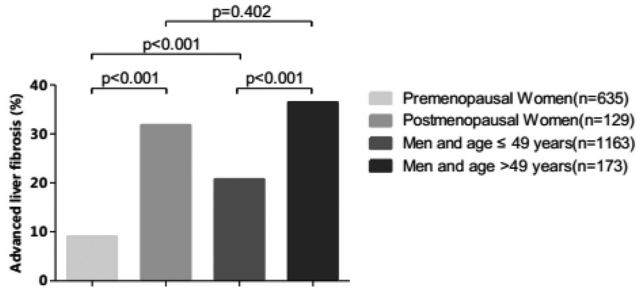
Impact of gender, menopause status and age at menarche on severity of liver fibrosis among patients with chronic hepatitis B

M. Xiong[1], Y. Shuling, F. Zeng[2], J. Li[2], J. Liu[2], Q. Wu[2], J. Chen[2], J. Hou[2]. *[1]Guangzhou; [2]Guangzhou, China*
Email: chjj@smu.edu.cn

Background and Aims: The role of menopause status and age at menarche in the development of chronic hepatitis B(CHB) remain poorly understood. We performed a cross-sectional study to assess the role of menopause status and age at menarche in relationship to advanced liver fibrosis in CHB cases prior to antiviral therapy.

Method: Seven hundred and sixty-four consecutive female and one thousand three hundred and thirty-six age-matched male patients during the same period of time were prospectively evaluated, which all had positive serum HBsAg over 6 months and without antiviral therapy. Liver fibrosis was assessed by Liver stiffness measurement (LSM) using transient elastography (Fibroscan®502). Menopause status and age at menarche were collected and documented from all female patients using a standardized questionnaire.

Results: 129 (16.9%) patients were postmenopausal, 98 (12.8%) had advanced fibrosis in females. The median age of overall, menopause and menarche was 35, 49 and 14 years among women, respectively. Prevalence of advanced liver fibrosis increased from premenopausal to postmenopausal women (9.0 vs. 31.8%, p < 0.001, figure 1). Moreover, the menarche age was positively associated with liver fibrosis, the frequency of advanced fibrosis in groups of menarche age < 13, 13 or 14, and >14 years were 5.9%, 10.7% and 18.8% (p < 0.001, figure 2), respectively. Menopause status (postmenopausal vs. premenopausal, OR = 2.12–4.02, p < 0.05) and age at menarche (>14 vs. <13 years, OR = 2.38–3.83, p < 0.05) were consistently independent risk factors of advanced liver fibrosis across all four multivariate logistic regression models in female patients (table 1). Compared to premenopausal women, men and age < 50 (OR = 1.84–2.86, p < 0.05) had higher odds of advanced liver fibrosis. However, compared to postmenopausal women, men and age > 49 (p = 0.402) had a similar prevalence of advanced liver fibrosis (figure 1).



1B. Relationship of advanced liver Fibrosis to menarche age.

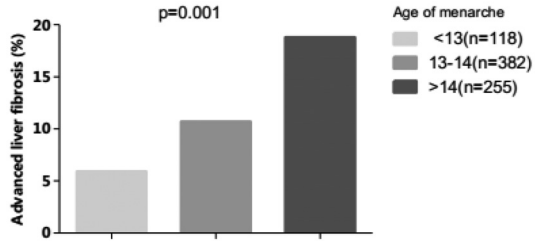


Table 1: Associations between the advanced liver fibrosis and menopause or age at menarche

	N	OR	95% CI	P value
Menopause				
Model 1	764	2.22	1.10–4.49	0.027
Model 2	763	2.12	1.04–4.33	0.040
Model 3	694	2.91	1.31–6.46	0.009
Model 4	605	4.02	1.59–10.16	0.003
Age at menarche				
Model 1	755			
13 or 14		1.89	0.81–4.41	0.139
>14		2.38	1.01–5.57	0.047
Model 2	754			
13 or 14		2.08	0.88–4.95	0.096
>14		2.67	1.11–6.39	0.028
Model 3	687			
13 or 14		2.13	0.85–5.33	0.106
>14		2.61	1.02–6.65	0.045
Model 4	599			
13 or 14		2.73	0.90–8.30	0.076
>14		3.83	1.25–11.78	0.019

model 1 was adjusted for age; model 2: model 1 plus adjustment for BMI, Diabetes and Hypertension. model 3:model 2 plus adjustment for ALT. model 4: model 3 plus adjustment for HBeAg status and HBV DNA level.

Conclusion: Menopause status and age at menarche were associated with advanced liver fibrosis in antiviral treatment naive female patients with CHB. The protective effect of female gender against severity of liver fibrosis was lost for postmenopausal women.

FRI-279

Early on-treatment alanine aminotransferase normalization reduces risk of hepatic events in patients with chronic hepatitis B

L.-H. Grace Wong[1,2,3], Y.-K. Tse[2], H. Chan[4], T.C. Yip[2], W. Sun, V. Wong[2,3]. *[1]The Chinese University of Hong Kong, Institute of Digestive Disease, Hong Kong; [2]The Chinese University of Hong Kong, Department of Medicine and Therapeutics, Hong Kong; [3]The Chinese University of Hong Kong, State Key Laboratory of Digestive Disease, Hong Kong; [4]The Chinese University of Hong Kong, Hong Kong, Hong Kong, Hong Kong*
Email: wonglaihung@cuhk.edu.hk

Background and Aims: Alanine aminotransferase (ALT) normalization is regarded as biochemical response to antiviral treatment. Recent studies showed that patients receiving tenofovir alafenamide (TAF) were more likely to achieve ALT normalization than those receiving tenofovir disoproxil fumarate (TDF), despite a similar rate of viral suppression. We aimed to evaluate the impact of ALT normalization during antiviral treatment with entecavir or TDF in patients with chronic hepatitis B (CHB).

Method: A territory-wide cohort of CHB patients who received entecavir and/or TDF from January 1, 2005 to December 31, 2016 in Hong Kong was identified. Serial on-treatment ALT levels were collected and analyzed. ALT normalization (ALT-N) was defined as ALT <30 U/l in males and <19 U/l in females. The primary and secondary outcome were composite hepatic events (including hepatocellular carcinoma [HCC]) based on ICD-9-CM diagnosis codes. Patients with pre-existing hepatics or during the first year of antiviral treatment, follow-up and survival <1 year were excluded.

Results: 21,182 CHB patients (10,437 with and 10,745 without ALT-N at 12 months after antiviral treatment) were identified and followed for 4.0 ± 1.7 years. Patients with and without ALT-N differed in gender distribution (76.9% *vs.* 58.4% male), baseline ALT (58 *vs* 61 U/l), rate of positive hepatitis B e antigen (31.5% *vs.* 37.1%), baseline serum HBV DNA (4.9 *vs.* 5.1 $\log_{10}$ IU/ml), less cirrhosis (8.8% *vs.* 10.5%) and prevalence of diabetes mellitus (8.1% *vs.* 9.1%). 627 (3.0%) patients developed hepatic events (509 HCC and 172 other cirrhotic complications). Compared to no ALT-N, ALT-N at 3, 6, 9 and 12 months reduced the risk of hepatic events, after adjustment for baseline ALT and other important co-variates, with adjusted hazard ratios (95%CI) 0.61 (0.48–0.76), 0.54 (0.44–0.66), 0.53 (0.44–0.64) and 0.50 (0.42–0.61) respectively (all $p < 0.001$). The cumulative incidence (95%CI) of hepatic events at 6 years was 3.51% (3.06%–4.02%) in ALT-N and 5.70% (5.15%-6.32%) in no ALT-N group ($p < 0.001$).

Cumulative incidence of composite endpoint at 6 years (%) (95% CI)	3 months	6 months	9 months	12 months
Without ALT normalization	4.76 (4.34–5.21)	5.24 (4.76–5.77)	5.57 (5.04–6.16)	5.70 (5.15–6.32)
With ALT normalization	4.27 (3.54–5.15)	3.60 (3.07–4.21)	3.44 (2.98–3.97)	3.51 (3.06–4.02)

Conclusion: Early on-treatment ALT normalization can be translated into improved clinical outcomes in CHB patients receiving NA treatment.

FRI-280

Occult Hepatitis B infection is frequent and a risk factor of advanced liver disease in The Gambia, West Africa

G. Ndow[1,2], D. Cohen[3], Y. Shimakawa[4], M.L Gore[5], R. Njie[2,6], P. Suso[2], B. Sanneh[7], I. Baldeh[7], M. Mendy[6], U. D'alessandro[8], M. Thursz[1], I. Chemin[9], M. Lemoine[1]. *[1]Imperial College London, Division of Integrative Systems Medicine & Digestive Diseases, Department of Surgery & Cancer, London; [2]MRC Unit The Gambia, Hepatitis Department, Disease Control & Elimination, Fajara, Gambia; [3]INSERM, Cancer Research Center of Lyon (CRCL), Lyon, France; [4]Institut Pasteur, Paris, Unité d'épidémiologie des maladies émergentes, Paris, France; [5]Imperial College London, Faculty of Medicine, London, United Kingdom; [6]International Agency for Research on Cancer (IARC), Lyon, France; [7]National Public Health Laboratories, Ministry of Health, The Gambia, Kotu, Gambia; [8]MRC Unit The Gambia, Fajara, Gambia; [9]INSERM, Lyon, France*
Email: g.ndow@imperial.ac.uk

Background and Aims: Occult hepatitis B infection (OBI) has been poorly documented in Africa. Yet, its prevalence and clinical implication may impact the objectives and strategies currently recommended by the World Health Organization to achieve hepatitis B virus (HBV) control and elimination. We aimed to estimate the prevalence and its clinical outcomes on liver disease in The Gambia, West Africa.

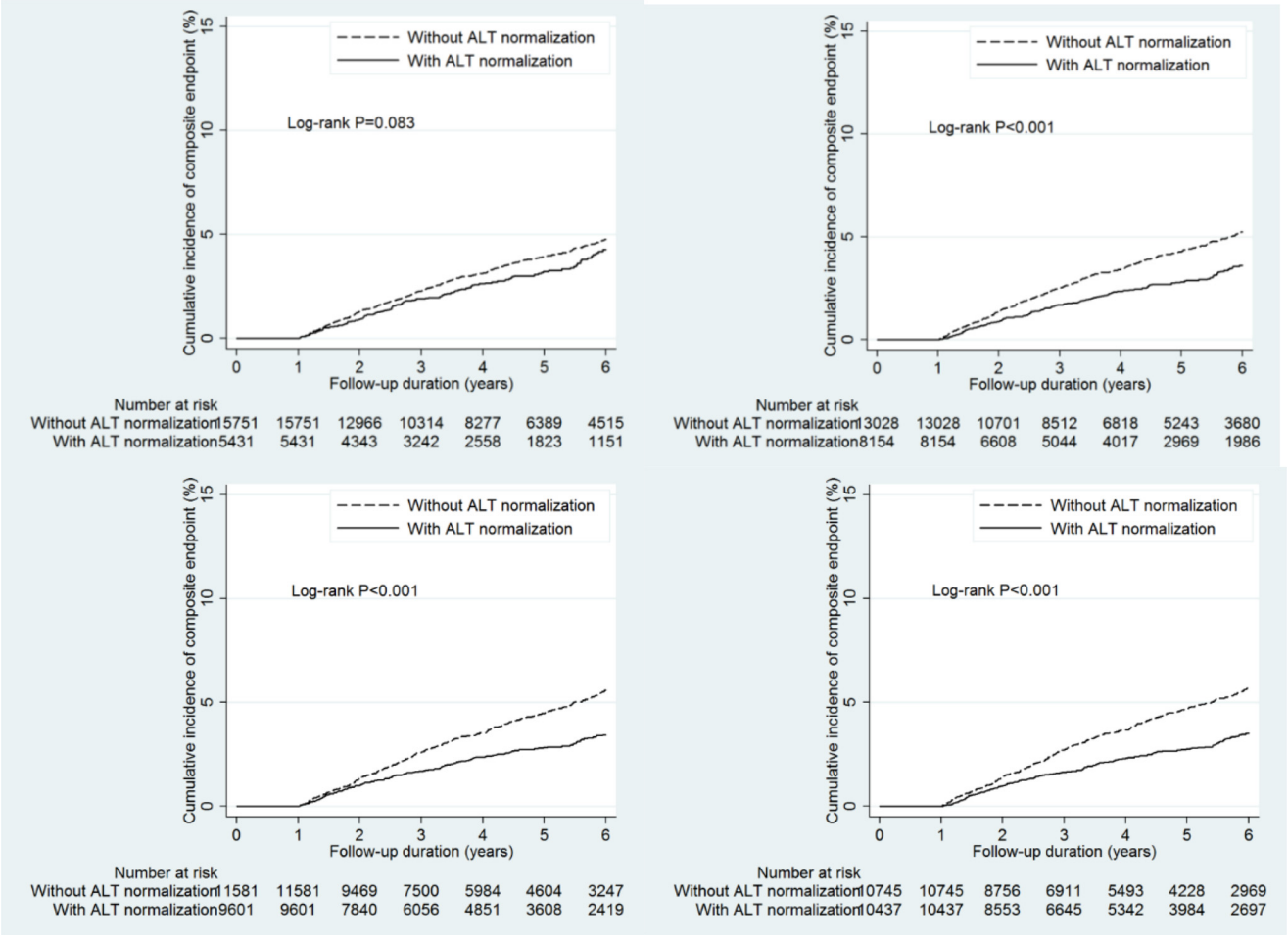


Figure 1: (abstract: FRI-279): Kaplan-Meier analysis of the cumulative incidence of hepatic events according to normalization of alanine aminotransferase (ALT) [AASLD criteria] after antiviral treatment: (A) 3 months, (B) 6 months, (C) 9 months and (D) 12 months

Method: A case-control analysis to assess the association between OBI and advanced liver disease [cirrhosis and/or hepatocellular carcinoma (HCC)] was nested in the PROLIFICA programme. This consisted of a large community and hospital-based screening for hepatitis B surface antigen (HBsAg) using a rapid point-of-care test. Those negative for HBsAg were invited for further virological and liver assessment. Negative HBsAg was serologically confirmed using the chemiluminescent microparticle immunoassay (Architect, Abbott) and HBV DNA was measured using nested PCR and DNA quantified using an in-house PCR with limit of detection of 10 IU/l (Ghosh et al., 2016). OBI was defined as negative HBsAg serology with a detectable HBV DNA in the serum.

Results: Of 4,838 people screened negative for HBsAg in the community between December 2011 and January 2014, we randomly selected 330 subjects as control group. The hospital screening enrolled 107 consecutive HBsAg negative patients with suspected advanced liver disease. The prevalence of OBI was significantly higher ($p < 0.001$) among patients with advanced liver disease (18.3%, 95%CI 9.7–26.8) than in community-screened controls (9.4%, 95%CI 6.2–12.6). Patients with cirrhosis (n = 29) had the highest prevalence of OBI (37.9%, 95%CI 19.1–56.7). OBI patients were mainly males (68%) with median age 46yrs (37–62) and median HBV DNA 138IU/ml. PreS2 mutations were observed in 14% (5/57) of patients with OBI. Hepatitis C virus infection, present in 18.3% of patients with advanced liver disease and 2.7% of community-screened controls, was associated with both OBI and advanced liver disease [OR: 10.8 (4.0–29.2), $p < 0.001$]. After adjusting for confounding factors (age, sex, HCV), OBI was significantly associated with advanced liver disease [OR: 2.8 (1.3–6.0), $p = 0.006$].

Conclusion: OBI is common in West Africa where HBV is still endemic. It is an independent risk factor for advanced liver disease in Gambian adults, particularly for liver cirrhosis. In light of HBV elimination, screening strategies based on HBsAg testing alone may not be adequate for sub-Saharan Africa.

FRI-282

Long-term outcomes and significance of HBeAg Seroclearance in Chronic Hepatitis B: Novel Predictive Scores for HCC and HBsAg seroclearance

Y.Y.J. Fung, K.-S. Cheung, D. Wong, L.-Y. Mak, W.P. To, W.-K. Seto, C.L. Lai, M.-F. Yuen. *The University of Hong Kong, Medicine, Hong Kong, Hong Kong*
Email: jfung@gastro.hk

Background and Aims: We aimed to determine the clinical outcomes, the factors and predictive scores for hepatocellular carcinoma (HCC) and hepatitis B surface antigen (HBsAg) seroclearance of a large cohort of patients undergoing HBeAg seroclearance (ESC).

Method: Patients with documented ESC were followed up 3–6 monthly. Baseline characteristics and longitudinal laboratory results were recorded. Predictive scores for HCC (HCC-ESC) and HBsAg seroclearance (HBsAg-ESC) were derived from multivariate Cox regression models.

Results: A total of 723 patients underwent ESC with a median ESC age and follow-up of 36.0 and 18.3 years respectively. Only 3.5% and 3.0% had persistently normal ALT and HBV DNA <2logsIU/ml respectively after ESC. For patients with 100%, 100–90%, 90–50%, 50–10%, 10–0%, and 0% normal ALT after HBeAg seroclearance, the rate of HCC was 4.3%, 2.2%, 3.6%, 3.9%, 17.3%, and 37.2% at 20 years after ESC respectively ($p < 0.001$). At 20 years after ESC, the cumulative incidence of HCC and HBsAg seroclearance was 7.9% and 13.5% respectively, with an overall survival of 91.5%. ESC age, male sex, cirrhosis, hypoalbuminemia, viral load, and ALT were significant factors for HCC, whereas ESC age, male sex, viral load, and antiviral therapy were significant factors for HBsAg seroclearance. The HCC-ESC score to predict the HCC risk for up to 20 years after ESC was calculated using age (years) + 20*sex (male = 1; female = 0) + 29*cirrhosis (presence = 1; absence = 0) + 5*DNA (logIU/ml) + 31*ALT group (flares or persistently abnormal ALT = 1; otherwise = 0) + 23*hypoalbuminemia (<39 g/l, presence = 1; absence = 0). With an optimal cut-off of 129, 121, and 114, the AUROC for predicting development of HCC at 5, 10 and 20 years after HBeAg seroclearance was 0.95, 0.91, and 0.92 respectively. The HBsAg-ESC score to predict HBsAg seroclearance up to 20 years was calculated using age (years) + 15*sex (male = 1; female = 0)–6*DNA (logIU/ml)–40*history of treatment (presence = 1; absence = 0). Using optimal cut-offs of 19, 17, and 12 to predict HBsAg seroclearance at 5, 10, and 20 years after HBeAg seroclearance were associated with an AUROC of 0.88, 0.84, and 0.74 respectively.

Conclusion: Male gender, older age at ESC, ALT, and higher level of HBV DNA were associated with higher rates of HCC after ESC. HCC-ESC and HBsAg-ESC predictive scores can determine the likelihood of developing HCC and achieving HBsAg seroclearance.

FRI-283

Serum WFA+–M2BP level as a diagnostic marker of HBV-related HCC: A case-control study

N. Chuaypen[1], Y. Tanaka[2], P. Tangkijvanich[1]. [1]*Faculty of Medicine, Chulalongkorn University, Department of Biochemistry, Bangkok, Thailand;* [2]*Nagoya City University Graduate School of Medical Sciences, Department of Virology and Liver Unit, Nagoya, Japan*
Email: pisittkvn@yahoo.com

Background and Aims: Serum glycosylated Wisteria floribunda agglutinin-positive Mac-2 binding protein (WFA +– M2BP) is a novel marker for staging liver fibrosis and predicting hepatocellular carcinoma (HCC) occurrence. This study aimed at evaluating the performance of WFA +– M2BP in the diagnosis of HCC in patients with chronic hepatitis B virus (HBV) infection.

Method: WFA+–M2BP levels were measured in stored samples collected at initial diagnosis of 150 patients with HBV-related HCC and 150 age- and gender-matched patients with non-malignant chronic HBV infection.

Results: Patients with HCC had higher levels of WFA+–M2BP than those without HCC [(5.3 ± 3.9 vs 1.8 ± 0.9 cutoff index (COI), $p < 0.001$]. In the HCC group, WFA +– M2BP levels correlated with Child-Pugh classification but did not correlate with HBV markers, alpha-fetoprotein (AFP) and BCLC stage. The areas under the curve (AUROC) for differentiating HCC from non-HCC were 0.92 (95%CI; 0.89–0.95, $p < 0.001$) for WFA +– M2BP, 0.90 (95%CI; 0.87–0.94, $p < 0.001$) for AFP and 0.97 (95%CI; 0.95–0.98, $p < 0.001$) for the combined tests. At the optimal cut-off (2.4 COI), WFA +– M2BP had sensitivity, specificity and accuracy of 79.3%, 91.3% and 85.3%, respectively. WFA+–M2BP was superior to AFP in differentiating early-stage HCC (BCLC stages 0 and A) from cirrhosis with AUROC of 0.80 (95%CI; 0.68–0.91, $p < 0.001$) and 0.73 (95%CI; 0.60–0.86, $p = 0.002$), respectively. By

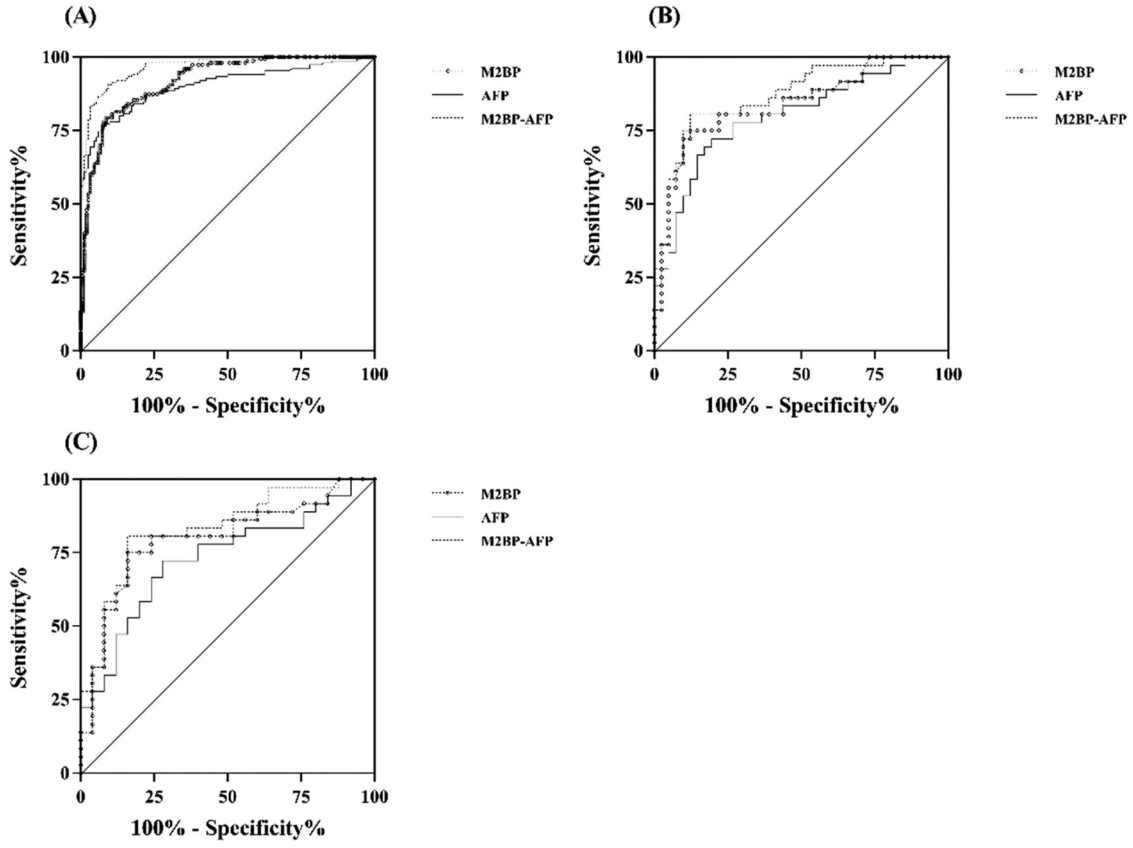


Figure 1: (abstract: FRI-283): ROC curves of serum WFA +– M2BP, AFP and combined markers in differentiating HCC and non-HCC (A) All patients (B) Early HCC vs non-HCC (only F3-F4) (C) Early HCC vs non-HCC (only F4)

univariate analysis, elevated WFA+–M2BP (≥4.0 COI) was correlated with poor overall survival in patients with HCC.
Conclusion: WFA +– M2BP exhibited a better diagnostic performance than AFP in detecting early-stage HCC. Thus, WFA +– M2BP level could represent a promising marker for early diagnosis of HCC in patients with chronic HBV infection.

FRI-284
The incidence of hepatocellular carcinoma in hepatitis B virus infected persons of different origins, living in Sweden
A.-S. Duberg[1], C. Lybeck[1], A. Fält[2], H. Wedemeyer[3], S. Montgomery[2,4,5], S. Aleman[6]. *[1]Örebro University, Infectious Diseases, Faculty of Medicine and Health, Örebro, Sweden; [2]Örebro University, Department of Clinical Epidemiology and Biostatistics, Örebro, [3]Hannover Medical School, Dept. of Gastroenterology and Hepatology, Hannover, Germany; [4]Karolinska Institutet, Clinical Epidemiology Unit, Stockholm, Sweden; [5]University College London, Department of Epidemiology and Public Health, London, United Kingdom; [6]Karolinska Institutet, Department of Infectious Diseases, Stockholm, Sweden*
Email: ann-sofi.duberg@orebroll.se

Background and Aims: Chronic hepatitis B (CHB) is associated with an increased risk of hepatocellular carcinoma (HCC) in both cirrhotic and non-cirrhotic persons. CHB patients with high risk for HCC are therefore recommended to undergo surveillance for HCC, with an estimated cut-off for surveillance in non-cirrhotic patients at incidence rate (IR) of 0.2% per year. People originating from Asia and men from Africa are estimated to have particularly high risks, but the IR for HCC when living in the Western world has not been fully estimated. Therefore, our aim was to study the incidence of HCC by age and origin in persons with CHB who are living in Sweden.
Method: In this national population-based study all persons diagnosed with CHB in Sweden during 1990–2015, their country of birth, co-infections, antiviral therapy, liver cancer or death/emigration were identified retrospectively, using the national HBV-surveillance register and other national registers. Those co-infected with hepatitis C were excluded. Observation time started at date of reported CHB diagnosis. The IR was calculated for different age groups and by region of birth.
Results: In total 16,410 persons (47% women) with CHB were studied. The number of persons and observation time (person-years) by origin were: Western Europe 2,316 (25,415); Eastern Europe 2,349 (26,237); Middle East/North Africa 4,402 (47,320); Sub-Saharan Africa 3,677 (30,565), Asia 3,537 (35,358) and other 129 (1,277). Those from Sub-Saharan Africa were youngest and had the shortest mean time in Sweden, 11.6 years. There were in total 232 diagnosed HCCs (82% in men); 23, 54 and 58 in people from Sub-Saharan Africa, Asia and Middle East/North Africa, respectively. The corresponding mean ages at HCC diagnoses were 45, 51 and 59 years, respectively. The IR exceeded 0.2% for men from Asia from age-group ≥40–49 years (IR 0.63, 95%CI 0.39–1.00), and for men of all other origins from age-group ≥50–59 years. Among African men aged <40 years there were 7 HCC, with incidence rate 0.05 and 0.11 in age groups 20–29 and 30–39 years, respectively. In women, HCC was rare but exceeded 0.2% among those aged ≥60 years with origins from East Europe, Asia and Middle East/North Africa.
Conclusion: In this study only men of Asian origin exceeded the cut-off for HCC surveillance by ages 40–49 years. African men had a few HCCs at younger ages, but did not exceed the cut-off before age 50–59 years. This study confirms the high risk for HCC in especially Asian men living in the Western world, but questions the benefit of surveillance at younger ages for men with African origin who live in a Northern European country.

FRI-285
The efficacy of a computer alert programme for increasing hepatitis B screening rates before starting immunosuppressive therapy
A. Koksal[1], B. Toka[2], A.T. Eminler[2], İlhan Hacibekiroglu[3], C. Sunu[4], M.I. Uslan[2], O. Karabay[5], E. Parlak[2]. *[1]Sakarya University, Department of Gastroenterology, Sakarya, Turkey; [2]Sakarya University Faculty of Medicine, Department of Gastroenterology, Sakarya, Turkey; [3]Sakarya University Faculty of Medicine, Department of Medical Oncology, Sakarya, Turkey; [4]Sakarya University Faculty of Medicine, Department of Hematology, Sakarya, Turkey; [5]Sakarya University Faculty of Medicine, Department of Infectious Diseases, Sakarya, Turkey*
Email: koksalas@yahoo.com

Background and Aims: Hepatitis B Virus (HBV) screening before starting immunosuppressive treatment is of vital importance in order to prevent HBV reactivation and its associated clinical consequences. Despite all recommendations by international organizations, screening rates are far below desired. The aim of this study was to assess the efficacy of a computer alert programme "HBVision" for increasing HBV screening rates.
Method: "HBVision" identifies patients at risk of HBV reactivation by specific ICD-10 codes and immunosuppressive medication reports and sends sequential alert messages to screen for HBsag, anti-HBc IgG and consult a specialist if one of them is positive. The demographic variables, treatment protocols, HBV screening and consultation rates of oncology and hematology patients who received immunosuppressive treatments one year before (control group) and after "HBVision" (study group) were retrospectively compared. Patients <18 years of age and with a prior diagnosis of chronic HBV infection or hepatitis were excluded.
Results: HBsag and anti-HBc IgG screening rates (68.6% and 13.1%, respectively) were significantly higher in the study group (n = 602) compared to control group (n = 815) (55% and 4.3%, respectively) ($p < 0.001$, for both). Subgroup analysis revealed significant improvements in the screening rates of HBsag (65.8%) and anti-HBc IgG (5.1%) in oncology patients ($p < 0.001$), anti-HBc IgG (89.1%) in hematology patients ($p < 0.001$), HBsag (67.2%) and anti-HBc IgG (9.6%) in patients receiving moderately immunosuppressive agents ($p < 0.001$, for both) and anti-HBc IgG (82.8%) in those receiving highly immunosuppressive agents ($p < 0.001$) (Table).The consultation rates in patients with a positive HBV serology increased from 52% to 75% after the alert system ($p = 0.6$).
Conclusion: The computer alert programme significantly increased HBV screening rates before starting immunosuppressive treatments, however the results were still below ideal. Additional efforts, such as modifying the computer programme according to feedback, and seeking other methods to increase awareness and remove concerns of clinicans are probably needed.

FRI-286
First clinical evaluation in chronic hepatitis B patients of the synthetic farnesoid X receptor agonist EYP001
R. Erken[1], F. Stelma[1], E. Roy[2], S. Diane[2], P. Andre[3], J. Vonderscher[2], M. Eric[2], S. Tim[4], P. Philippe[5], L. Christian[5], P. Scalfaro[6], H. Reesink[1], C.M. Sousa[7], E. Jacob[7]. *[1]Academic Medical Center, Hepatology; [2]ENYOPHARMA SA, Lyon; [3]CIRI, Inserm U1111, Lyon, France; [4]UMCG, Department of Gastroenterology & Hepatology, Groningen, Netherlands; [5]CALVAGONE, Pharmacometrics, Liergues, France; [6]ENYOPHARMA SA, Lyon, [7]Nova discovery*
Email: ps@enyopharma.com

Background and Aims: The nuclear farnesoid X receptor (FXR) is an investigational target for non-alcoholic steatohepatitis therapy, while its clinical relevance for inhibition of hepatitis B virus (HBV) replication remains to be established. In a recent study on hepatocytes from fransgenic mice receptive to primary human liver cells infected with HBV for 35 days, the at sacrifice isolated cells were cultured. Treatment with Entecavir of these cells produced a dose

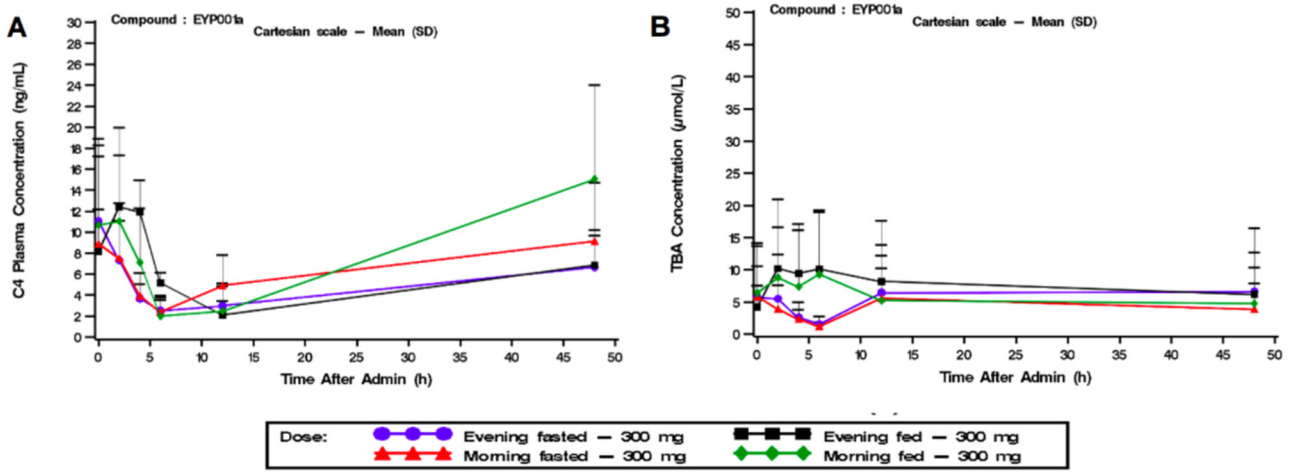


Figure 1: (abstract: FRI-286)

dependant inhibition of HBV DNA secretion (Emax: 80%) with no effect on HBeAg or HBsAg, whereas FXR agonist inhibited in a dose dependant manner both HBV DNA (Emax: 60%) and viral protein secretion (HBeAg, HBsAg: Emax 80% and 60% respectively). We aimed to explore in chronic hepatitis B (CHB) patients the safety and bile acid related pharmacology of FXR agonist EYP001.

Method: CHB patients were randomized to 4 crossover single dose oral treatment periods receiving 300 mg EYP001 administered fasted or fed, either in the morning or evening. Relative EYP001 bioavailability, safety, tolerability, FXR related pharmacodynamic and HBV markers were assessed.

Results: 11 CHB patients (3 females, 8 males, mean age 39.8 years) with a low HBV DNA viral load (mean+/-SD 1266+/-1862IU/ml) were included. All completed the 4 periods and 6 patients had mild, short lasting gastrointestinal adverse effects possibly related to EYP001, one reported mild pruritus resolving spontaneously after few hours. No clinically significant changes in liver enzymes nor lipids occurred. EYP001 reached similar Cmax with all 4 dosing conditions, whereas Tmax tended to increase with food. Exposure was not impacted by food with similar area under the curve (0-last (ng*h/mL), mean (90% CI), $p > 0.05$): morning fasted (8073 (5044–14413)) versus fed 9456 (7203–15272) and evening fasted 8157 (4386–12976) versus fed 8459 (5916–12218). Also in all periods despite similar rapid EYP001 elimination kinetics, FGF19 and C4 showed a prolonged FXR target engagement over at least 12 hours (Figure A). Total bile acids (TBA) decreased in fasted condition and increased with food (Figure B). HBV markers did not change significantly.

Conclusion: Our preliminary results show that oral doses of EYP001 are well tolerated by CHB patients and induce prolonged FXR engagement. Further clinical testing to assess the HBV effect with repeated dosing is in progress. An in silico and an in vivo model further explore the relationship between FXR and HBV (Monteiro Sousa C. and Fusil F. submitted).

FRI-287
Quantification of hepatitis B virus covalently closed circular DNA by a peptide nucleic acid-clamping PCR method

C.-T. Yeh, C.-W. Hsu, M.-W. Lai. *Liver Research Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan*
Email: chautingy@gmail.com

Background and Aims: Recently, new antivirals against hepatitis B virus (HBV) have been vigorously developed. As current antiviral treatments can already persistently suppress HBV replication to an undetectable level, the next reasonable goal of treatment should be to eliminate cccDNA. Assessment of cccDNA requires liver biopsy, where qPCR is unavoidable. However, the traditional cccDNA specific qPCR method has a very limited range of concentrations for accurate quantification. Here, we developed a peptide nucleic acid (PNA)-clamping PCR method to provide a wider range of specific cccDNA quantification.

Method: Two PNA fragments complementary to the minus-strand of HBV DNA were designed. Two sets of PCR primers were synthesized. Set-one: the traditional cccDNA specific primers, flanking the rcDNA gap. Set-two: the UPNA and DPNA primers were up- and down-stream of the two PNA fragments. Serum-derived rcDNA and plasmid-derived cccDNA mimics were serially diluted to examine the specific detection/quantification ranges. HBV-DNA was clamped with PNA fragments before subjected to qPCR using the two sets of primers. Paraneoplastic liver tissues (n = 222) from HBV-related HCCs were included for actual cccDNA quantification.

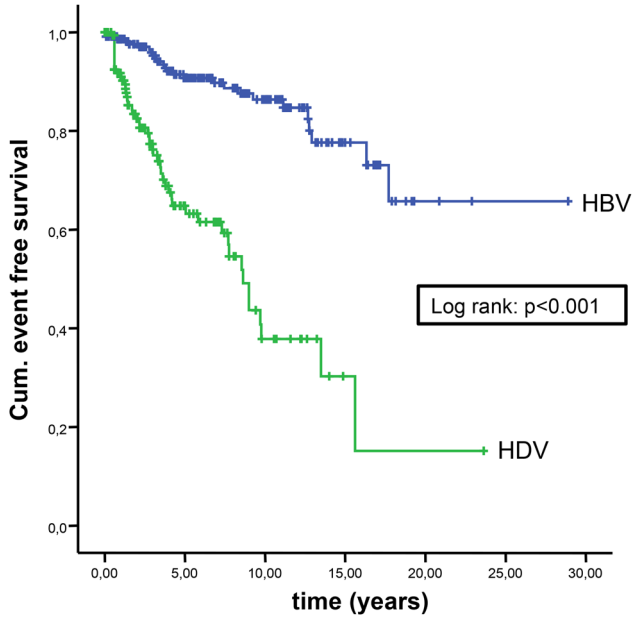
Results: Following PNA clamping, the Set-one primers can detect and quantify cccDNA specifically within the range of 10(1) to 10(4) copies in the PCR reaction, whereas the Set-two primers can quantify cccDNA specifically within the range of 10(3) to 10(5) copies. Together, cccDNA can be quantified in the range of 10(1) to 10(5) copies. If PNA clamping was not performed, Set-one primers can only detect cccDNA specifically within the range of 10(1) to 10(3) copies. With the PNA clamping method, of 222 paraneoplastic liver tissues subjected for cccDNA quantification, 6 required further dilution to make the sample fall into the effective quantification range. The amount of cccDNA was not associated with postoperative recurrence, metastasis, or survival. Multivariate linear regression analysis showed that cccDNA levels were associated with liver cirrhosis and prothrombin time.

Conclusion: A PNA-clamping PCR method was devised for cccDNA quantification. A wider range of specific cccDNA detection, 10(1) to 10(5) copies, could be achieved. 6/222 liver tissue sample required pre-dilution to avoid out-of-range measurement.

FRI-288
Long-term outcome of hepatitis delta compared to HBV monoinfection

A. Wranke[1], K. Deterding[2], B. Heidrich[2,3,4], B.C. Serrano[2], J. Kirschner[2], B. Bremer[2], C. Mix[2], K. Port[2], M. Cornberg[2], M.P. Manns[5], H. Wedemeyer[6]. *[1]Department of Gastroenterology, Hepatology and Endocrinology, Hanover Medical school; [2]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School; [3]German Center for Infection Research (DZIF), Partner Side HepNet Study-House; [4]Microbial Interactions and Processes Research Group, Centre for Infection Research; [5]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [6]Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany*
Email: wranke.anika@mh-hannover.de

Background and Aims: Hepatitis D-virus (HDV) infection causes the most severe form of chronic viral hepatitis. Studies suggested that the underlying hepatitis B-virus (HBV) infection may contribute to disease progression. However, the importance of HBV and HDV replication for the development of hepatic complications in patients with hepatitis delta is a matter of debate. Moreover, the introduction of potent nucleos(t)ide analogous (NA) may have altered the course of liver disease. The aim of this study was to compare the clinical long-term outcome of hepatitis delta versus HBV monoinfection in a single center cohort of patients with access to HBV NA according to HBV guidelines.
Method: We retrospectively studied 177 patients with chronic hepatitis D who were followed for at least 6 months. In addition, we selected 225 patients with HBV monoinfection from a large cohort of hepatitis B patients who were matched for gender, age, region of origin, HBeAg status and MELD score. Endpoints were defined as hepatic decompensation (ascites, encephalopathy, variceal bleeding), liver transplantation, HCC, or liver-related death. NA therapy was administered to 64 HDV and 112 HBV patients. 67 HDV and 23 HBV patients had received IFNa-based therapies.
Results: Patients infected with HDV or HBV alone had similar baseline characteristics (male:68% vs. 69%; mean age 39 vs. 37 years; country of birth: eastern Mediterranean 34% vs. 36%; median HBV DNA 4.4 vs. 2.4 logIU/ml and were followed for a median of 6.2 (0.6–23.6) and 7.6 years (0.6–22.9) years, respectively. The incidence of cirrhosis at the first visit was higher in patients with HDV infection (44.6%) than in HBV monoinfection (13.8%) ($p < 0.001$). Clinical complications developed earlier (first episode after a median of 3.6. vs. 6.0 years; $p = 0.04$) and more frequently (29% vs. 12%, $p < 0.001$) in HDV patients. In addition, HDV was significantly associated with the development of endpoints in Kaplan Meier analysis ($p < 0.001$). Even after excluding cirrhotic patients, HDV infected patients showed a worse outcome (Kaplan Meier $p < 0.001$). In a multivariate Cox-regression HDV infection was an independent factor associated with the development of endpoints ($p = 0.04$; HR:2.0;95%CI:1.0–4.1). In addition, albumin levels, platelet counts, age, gamma GT, alkaline phosphatase and INR values were associated with the clinical long-term outcome while HBV DNA levels and NA therapy could not be linked to progression to clinical complications.



Conclusion: HDV infected patients had a higher risk to develop liver-related clinical endpoints compared to HBV monoinfected patients even after the introduction of potent NA against HBV.

FRI-289
The WHO guidelines for chronic hepatitis B fails to detect half of the patients in need of treatment
H. Aberra[1], H. Desalegn[1], N. Berhe[2], G. Medhin[2], S.G. Gundersen[3], A. Johannessen[4]. [1]*St Paul Hospital Millennium Medical College, Addis Ababa, Ethiopia;* [2]*Addis Ababa University, Addis Ababa, Ethiopia;* [3]*University of Agder, Kristiansand, Norway;* [4]*Oslo University Hospital Ullevål, Oslo, Norway*
Email: johannessen.asgeir@gmail.com

Background and Aims: Patients with chronic hepatitis B (CHB) who have liver fibrosis and/or ongoing necroinflammation of the liver are at increased risk of disease progression. Antiviral treatment can stop the progression to cirrhosis and reduce the risk of hepatocellular carcinoma. In 2015, the World Health Organization (WHO) issued guidelines for the management of CHB in low- and middle-income countries Antiviral treatment was recommended based on 3 criteria: (i) clinically diagnosed cirrhosis, (ii) aspartate aminotransferase to platelet ratio index (APRI) >2.0, or (iii) age ≥30 years with abnormal ALT and viral load >20,000 IU/ml. The aim of this study was to evaluate the performance of the WHO guidelines in a large cohort of CHB patients in Ethiopia.
Method: Out of 1303 HIV-negative CHB patients enrolled at St. Paul's Hospital Millennium Medical College in Addis Ababa, 1213 treatment-naïve patients aged 18 years and older were included in this study. All patients underwent a standardized evaluation at baseline, including blood tests and transient elastography (Fibroscan 402, Echosense, France). A Fibroscan threshold of 7.9 kPa was used to define significant fibrosis and 9.9 kPa to define cirrhosis. Treatment eligibility was assessed using the most recent guidelines from the European Association for the Study of the Liver (EASL) as the "gold standard".
Results: Out of 1213 patients with CHB, 317 (26.1%) were eligible for treatment according to the EASL 2017 guidelines. For comparison, only 159 (13.1%) were eligible according to the WHO 2015 guidelines. Most patients (112 of 159, 70.4%) who fulfilled the WHO criteria were patients with decompensated cirrhosis, who might have a dismal prognosis even with therapy. Only 23 of 105 patients (21.9%) with compensated cirrhosis, who are likely to benefit the most from therapy, were eligible for treatment according to the WHO criteria. APRI lacked sensitivity in this setting: only 23 of 317 (7.3%) in need of treatment had an APRI value >2.0.
Conclusion: The WHO guidelines for CHB fails to detect a considerable proportion of patients in need of treatment. A revision of the WHO treatment criteria should be based on local data.

FRI-290
A new utility of HBcrAg – a pan-genotypic predictor of mother to child HBV transmission
I. Carey[1], M. Bruce[1], M.-A. Mcleod[1], T. Bowyer[2], M. Horner[1], R. Byrne[1], B. Wang[1], G. Dusheiko[1], K. Agarwal[1]. [1]*King's College Hospital, Institute of Liver Studies, London, United Kingdom;* [2]*King's College Hospital, Denmark Hill Campus, London, United Kingdom*
Email: ivana.kraslova@kcl.ac.uk

Background: The EASL 2017 guidelines advise commencing antiviral therapy to prevent mother to child (MCTC) transmission of hepatitis B virus (HBV) in all patients with HBsAg >10,000 IU/ml. HBsAg levels vary between HBeAg positive and negative patients and between genotypes as well as stage of disease. In our centre all pregnant mothers with HBV DNA >200,000 IU/ml at 2nd trimester, irrespective

of HBsAg levels are offered antiviral therapy to prevent MTCT, together with infant vaccination and HBIg at birth. Hepatitis B core-related antigen (HBcrAg) is a new serological marker and its clinical importance is emerging. However, its utility for assessing the risk of HBV MTCT has not been evaluated.

Aims: To assess whether HBcrAg plasma concentrations can predict the risk of HBV MTCT (HBV DNA >200,000 IU/ml) more efficiently than HBsAg levels at the 2nd trimester.

Methods: Plasma samples were collected at 2nd trimester (median gestation 25 weeks) from 514 HBsAg+ pregnant women with chronic hepatitis B. All had post-delivery follow-up >1 year and their infants' HBV infection status was assessed. HBV DNA was measured by TaqMan PCR [IU/ml], HBV genotyping was tested by direct sequencing, HBsAg plasma levels were measured on Abbot Architect® [IU/ml] and HBcrAg concentrations were quantified [$\log_{10}$ U/ml] by Luminex G® (Fujirebio) assay. The results were stratified for comparison according to the risk of HBV MTCT (HBV DNA >200,000 IU/ml = high risk vs. HBV DNA <200,000 IU/ml = low risk).

Results: In single centre cross-sectional study 514 patients (median age 31 yrs) were enrolled; 62/514 (12%) patients were HBeAg positive. HBV DNA >200,000 IU/ml was found in 72/514 (14%) patients (50 of these 72 were HBeAg positive). 163/514 (32%) patients had high HBsAg (>10,000 IU/ml): 48 of these 163 patients had both high HBsAg and HBV DNA >200,000 IU/ml and were predominantly infected with genotypes B & C. In contrast 115/163 patients had HBsAg concentrations >10,000 IU/ml, but a HBV DNA < 200,000 IU/ml (mainly genotypes A, D & E). Only mothers with HBV DNA > 200,000 IU/ml were treated with prophylactic nucleoside analogues. There were no cases of MTCT in our cohort. We observed that median HBcrAg concentrations were higher in high risk group patients (7.0 vs. 2.4, $p < 0.01$). All patients with high MTCT risk, defined as HBV DNA >200,000 IU/ml had HBcrAg levels greater than 6 $\log_{10}$U/ml and this did not differ between genotypes or HBeAg status. ROC analysis confirmed that HBcrAg is a more accurate predictor of high risk MCTC than HBsAg (HBcrAg AUROC = 1.0 vs. HBsAg AUROC = 0.78, both $p < 0.01$).

Conclusions: Pregnancy plasma HBcrAg concentrations represent a more accurate tool than HBsAg levels to assess the risk of HBV MTCT, is applicable in both HBeAg positive and negative mothers and is not influenced by HBV genotypes. HBcrAg levels greater than 6 $\log_{10}$U/ml predict a high risk of MTCT and offer a non nucleic acid based alternative for maternal testing.

FRI-291

Virological heterogenity of hepatitis delta among Vietnamese populations

T.B. Mai[1,2,3], X.H. Nghiem[3,4,4], T.S. Bui[3,5], M.H. Nguyen[6], P.G. Dao[3,5], L.T. Nguyen[3,7], H.S. Le[3,4], C.-T. Bock[8], H. Wedemeyer[9], T.P. Velavan[3,10].

[1]University of Tuebingen, Institute of Clinical Infectious Diseases, Tuebingen, Germany; [2]108 Military Central Hospital, Department of Gastroenterology, Hanoi, Viet Nam; [3]108 Military Central Hospital, Vietnamese – German Center of Excellence in Medical Research (VG-CARE), Hanoi, Viet Nam; [4]108 Military Central Hospital, Institute of Clinical Infectious Diseases, Hanoi, Viet Nam; [5]108 Military Central Hospital, Institute of Clinical Infectious Diseases, Hanoi, Viet Nam; [6]Duy Tan University, Center for Molecular Biology, Da Nang, Viet Nam; [7]Vietnam Military Medical University, Department of Pathophysiology, Hanoi, Viet Nam; [8]Robert Kock Institute, Viral Gastroenteritis and Hepatitis Pathogens and Enteroviruses, Berlin, Germany; [9]Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany; [10]University of Tuebingen, Institute of Tropical medicine, Tuebingen, Germany

Email: maibinhtieuhoa108@gmail.com

Background and Aims: Hepatitis delta virus (HDV) is an underestimated pathogen in Vietnam, where HBV is endemic with an estimated prevalence of >10%. HBsAg-positive patients (n = 1062) recruited for three cross sectional studies (2009, Northern Vietnam; 2015, Central Vietnam; and 2015, Northern Vietnam) were utilized. Hepatitis delta virus infections were investigated and the circulating HDV genotypes were subjected to molecular characterization.

Methods: The study cohort comprises of clinically characterized HBV patients, including acute hepatitis (AHB; n = 30), chronic hepatitis

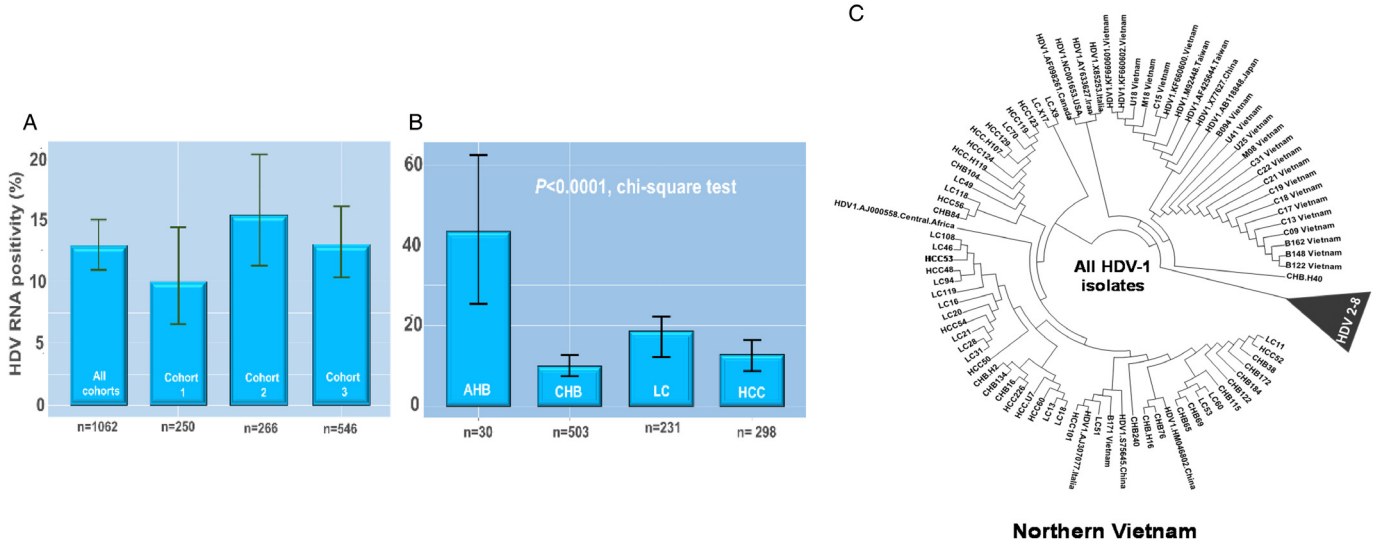


Figure 1: (abstract: FRI-291): Phylogenetic tree was constructed based on the alignment of 235bp of 103 nucleotide sequences isolated from HDV/HBV co-infected patients. Full-length HDV genomes through HDV1-8 retrieved from NCBI database along with GenBank accession numbers were included for the analysis. A neighbor-joining tree was constructed with a bootstrap of 1000 replicates. The bar at the base of the tree indicates the scale for nucleotide substitutions per position. (**A**) Phylogenetic tree of 25 HDV strains isolated from the Central cohort. (**B**) Phylogenetic analysis of 78 HDV strains isolated from 2 cohorts in Northern Vietnam. (**C**) Phylogenetic clade reconstructed with all available HDV genotypes but visualize only HDV1 isolates from 2 cohorts in Northern Vietnam.

(CHB; n = 503), liver cirrhosis (LC; n = 231), and hepatocellular carcinoma (HCC; n = 298). RNA were isolated from serum of HBV patients and were subsequently reverse transcribed to cDNA. HDV specific nested PCR assays were employed. HDV isolates, positive by nested PCR were subsequently sequenced for L-HDAg region and HDV genotypes were determined.

Results: Among all HBV patients investigated, 13% (137/1062) were HDV RNA positive. The distribution of HDV positivity varied between 14% (Northern region) and 10% (Central region). The HDV positivity were significantly distributed among the clinical sub groups (p < 0.0001). Patients with acute hepatitis revealed a high HDV positivity (AHB: 43%), followed by liver cirrhosis (LC: 17%), hepatocellular carcinoma (HCC: 12%) and in chronic hepatitis B patients (CHB: 10%). Both HDV-1 and –2 genotypes were identified with HDV-1 being the predominant genotype in Northern Vietnam (91%) and HDV-2 being detectable mainly in Central Vietnam (80%). Liver enzymes were significantly elevated among patients with HBV and HDV coinfection and were associated with worse clinical outcomes and liver diseases progression compared to HBV mono infection.

Conclusions: HDV is equally endemic to HBV mono infections, with a prevalence of up to 13% in Vietnamese populations. HDV genotypes are differentially distributed among Northern and Central regions. Patients with HBV infections are recommended to undergo screening for HDV.

FRI-292

Comorbidities in chronic hepatitis B patients currently treated with nucleos(t)ide analogues

S.(S.) Siakavellas[1], I. Goulis[2], S. Manolakopoulos[3], C. Triantos[4], Z. Kalliopi[5], E. Tsentemidou[2], H. Kranidioti[3], K. Zisimopoulos[4], C. Tsoulas[6], G. Dalekos[5], G. Papatheodoridis[1]. *[1]Medical School of National and Kapodistrian University of Athens, Laiko General Hospital, Academic Department of Gastroenterology, Athens, Greece; [2]Medical School of Aristotle University of Thessaloniki, 4th Department of Internal Medicine, Thessaloniki, Greece; [3]Medical School of National and Kapodistrian University of Athens, Hippokratio General Hospital, 2nd Department of Internal Medicine, Athens, Greece; [4]University Hospital of Patras, Department of Gastroenterology, Patras, Greece; [5]Thessaly University Medical School, Department of Medicine and Research Laboratory of Internal Medicine, Larissa, Greece; [6]Gilead Sciences Hellas, Medical Department, Greece*
Email: s.siakavellas@gmail.com

Background and Aims: Long-term monotherapy with a high genetic barrier NA represents the treatment option for the majority of chronic hepatitis B (CHB) patients, who are becoming older having increased likelihood for comorbidities and comedications and raising potential safety risks. We assessed the presence of concurrent non-hepatic diseases and drug use in a large cohort of CHB patients receiving nucleos(t)ide analogues (NAs) and their potential impact on the disease course and outcomes of these patients.

Method: We included 500 consecutive CHB patients, who were receiving long-term therapy with a NA in 2016 at the outpatients liver clinics of 5 major tertiary Greek centers (100 patients from each center). HDV, HCV and HIV coinfected patients were excluded. Epidemiological/clinical characteristics and data for concomitant disease, drug use and investigations ordered were collected from the patients' records.

Results: Their mean age was 58 ± 18 years (>60 years: 46%) and 66% were males. The majority of patients (81%) were from Greece and a considerable minority from Albania (12%). Most patients were receiving tenofovir disoproxil fumarate (TDF, 60%) or entecavir (ETV, 37%) monotherapy. Decompensated cirrhosis at baseline was present in 10%, while HCC under therapy developed in 21 (4.2%) patients. Mean duration of total NA(s) therapy was 72 ± 58 (range 1–212) and of the latest therapy 45 ± 31 (range 1–186) months. LFTs and renal tests were determined every 6 ± 3, HBV DNA every 16 ± 9 and liver stiffness every 17 ± 7 months. The most common (prevalence > 2%) comorbidities were hypertension (28%), non-HCC cancer(s) (12%), diabetes (11%), rheumatologic diseases (10%), thyroid diseases (9%), obesity (9%), metabolic bone disease (8%), hyperlipidaemia (6%), organ transplantation (3%) and renal failure (3%). Patients with a longer duration of latest therapy (≥4 vs <4 years) were older (mean age: 58 vs 56 years, p = 0.004) and had more frequent history of prior use of NA(s) (53% vs 35%, p < 0.001) and of pre-treatment liver biopsy (39% vs 14%, p < 0.001) and less frequently liver decompensation (5% vs 13%, p = 0.008) and non-HCC cancers (8% vs 15%, p = 0.020). Liver decompensation was relatively more frequent in obese than non-obese patients (17% vs 9%, p = 0.068) and HCC developed more frequently in patients with than without diabetes (11% vs 3%, p = 0.022).

Conclusion: CHB patients currently treated with NAs, almost exclusively ETV or TDF, are often older than 60 years having several comorbidities and thus requiring careful management.

FRI-293

Key mutational patterns in HBsAg C-terminus profoundly affect HBsAg levels in HBeAg-negative chronic HBV genotype D infection

R. Salpini[1], A. Battisti[1], L. Carioti[1], D.D. Carlo[1], O. Anastasiou[2], U.S. Gill[3], L. Colagrossi[1], A. Bertoli[1], M. Aragri[1], L. Fabeni[4], V. Fini[1], L. Piermatteo[1], A. Iuvara[5], V. Malagnino[6], C. Cerva[6], M. Lichtner[7], C.M. Mastroianni[7], G.M.D. Sanctis[8], P. Maurizio[9], M. Marignani[10], C. Pasquazzi[10], N. Iapadre[11], T. Mari[12], G. Parruti[13], J. Vecchiet[14], L. Sarmati[6], M. Andreoni[6], M. Angelico[5], S. Grelli[1,5], P. Kennedy[3], J. Verheyen[2], F.C. Silberstein[1], C.F. Perno[15], V. Svicher[1]. *[1]Tor Vergata University, Department of Experimental Medicine and Surgery, Rome, Italy; [2]Institute of Virology, University of Duisburg-Essen, Essen, Germany; [3]Blizard Institute, Barts and The London School of Medicine & Dentistry, QMUL, Hepatology, Centre for Immunobiology, London, United Kingdom; [4]National Institute for Infectious Diseases L. Spallanzani-IRCCS, Antiretroviral drug monitoring laboratory, Rome, Italy; [5]Tor Vergata University Hospital, Microbiology and Virology Unit, Rome; [6]Tor Vergata University Hospital, Infectious Diseases Unit, Rome, Italy; [7]"Sapienza" University, Department of Public Health and Infectious Disease, Rome, Italy; [8]"Umberto I" University Hospital, Department of Gastroenterology, Rome, Italy; [9]"S.S. Filippo e Nicola" Hospital, Infectious Disease Unit, Rome, Italy; [10]"S.Andrea" Hospital, Department of Gastroenterology, Rome, Italy; [11]"San Salvatore" Hospital, Infectious Diseases Unit, Rome, Italy; [12]"Nuovo Regina Margherita" Hospital, Department of Gastroenterology, Rome, Italy; [13]Pescara General Hospital, Infectious Diseases Unit, Pescara, Italy; [14]University "G. d'Annunzio" Chieti-Pescara, Clinic of Infectious Diseases, Department of Medicine and Science of Aging, Rome, Italy; [15]University of Milan, Milan, Italy*
Email: battisti.arianna@gmail.com

Background and Aims: HBV genotype D is characterized by lower HBsAg levels than other genotypes. The goal of this study is to investigate the role of specific mutations in HBsAg C-terminus (known to be critical for proper HBsAg release) on HBsAg levels in HBeAg-negative patients with chronic HBV genotype D infection.

Method: This study includes 310 consecutive drug-naïve patients (pts) stratified according to HBsAg levels (≤ or >1,000 IU/ml). Correlation of mutations with HBsAg ≤ 1,000 IU/ml is determined by Fisher exact test. Association among mutations in C-terminus is assessed by binomial correlation coefficient (phi). I-Tasser is used to predict three-dimensional HBsAg structures (aa:1–226) and their stability (ΔΔG[wt-mutated] < 0 indicating reduced stability in presence of mutation based on Quan, 2016).

Results: Median (IQR) serum HBV-DNA and HBsAg is 3.6(2.9–4.5) log IU/ml and 2,144(729–6,524)IU/ml, respectively. Specific mutations in HBsAg C-terminus tightly correlate with HBsAg ≤ 1,000IU/ml

(p from <0.001 to 0.04). ≥1 of these mutations occurs in 58.4% of pts with HBsAg ≤ 1,000 IU/ml (range prevalence:6.5–33.4%), while they are present in ≤3.3% (V190A, Y206F, S210N), 7.3% (Y206C) and 12.3% (S204N) of pts with HBsAg > 1,000 IU/ml. These mutations lie on divergent pathways involving other mutations in HBsAg C-terminus: V190A with F220L (Phi = 0.41, p = 0.003), S204N with L205P (Phi = 0.36, p = 0.005), Y206F with S210R (Phi = 0.47, p < 0.001) and S210N with F220L (Phi = 0.40, p = 0.006). Notably, each of these pairs of mutations drastically decreases HBsAg levels compared to wt (250 [15–339]IU/ml for V190A + F220L, 226[123–394]IU/ml for S204N + L205P, 451[81–571]IU/ml for Y206F + S210R and 335[209–417]IU/ml for S210N + F220L vs 2,791[1,009–8,212]IU/ml for wt, P = 0.003–0.02). Some of them also decrease serum HBV-DNA levels (2.2[1.6–2.7]logIU/ml for V190A + F220L and 2.3[1.9–2.9]logIU/ml for S204N + L205P vs 3.4[2.7–4.1]logIU/ml for wt, p = 0.01–0.04), suggesting a detrimental impact also on the release of viral particles. By structural analysis, all the pairs of mutations associated with low HBsAg determine a reduced stability of HBsAg C-terminus (ΔΔG[mut-wt] from −0.52 to −1.92), supporting their role in impairing HBsAg release.

Conclusion: Specific clusters of mutations in HBsAg C-terminus correlate with lower HBsAg levels and determine an impaired stability of HBsAg, supporting their detrimental role on HBsAg release. The knowledge of these mutations can help in optimizing the clinical interpretation of HBsAg levels in HBV genotype D.

FRI-294

Patients with genotype 5 hepatitis delta infection have a favourable outcome of disease and better treatment response to pegylated interferon therapy compared to genotype 1 patients

M. Spaan, M. Bruce, D. Shang, M. Horner, G. Dusheiko, I. Carey, K. Agarwal. *King's College Hospital, Institute of Liver Studies, London, United Kingdom*
Email: m.spaan@erasmusmc.nl

Background and Aims: Co-infection with hepatitis delta virus (HDV) causes rapid progression to liver cirrhosis and hepatic decompensation. HDV has 8 different genotypes and while genotype 1 is the most prevalent in Europe and frequently studied, genotype 5 is found in patients of predominantly African origin. In this study we aim to compare differences in disease progression and treatment response between genotype 1 and 5 patients.

Methods: 46 patients with HBV/HDV co-infection (HBsAg+, anti-HDV antibodies positive, HDV RNA positive) who attended our center between January 2005 and December 2016 were enrolled; none of the patients had an acute HBV or HDV infection or were co-infected with HIV and/or HCV. 39 patients had samples available for HDV genotyping by direct sequencing: 20 patients were found to have genotype 1, and 19 patients were infected with genotype 5.

Results: For 46 patients median age was 34.1 years, median follow-up time was 4.6 yrs and patients were predominantly males (58.7%). 56.6% were of African vs 21.7% of European origin. 50% of patients were cirrhotic upon first presentation. For genotyped patients, most patients with HDV genotype 5 were of African origin (95%) and had HBV genotype E (60%) in contrast to HDV genotype 1 patients who were primarily of European origin (47%) and were infected with HBV genotype D (53%). Age, gender and median follow-up time did not differ between both groups. HBV DNA viral loads were low and similar in both groups. No differences were observed in HDV RNA viral load and HBsAg concentrations. Genotype 1 patients were more often cirrhotic at diagnosis (63% GT1 vs 30% GT5, p = 0.05) and cirrhotic HDV genotype 1 patients were more likely to develop an episode of hepatic decompensation compared to cirrhotic patients with HDV genotype 5 (37% GT1 vs 0% GT5, p = 0.003). 24 patients were treated with pegylated interferon and median follow-up time after treatment was 48 weeks (28–80 weeks). Post-treatment response (>24 weeks) was more favorable in patients infected with genotype 5 (18% GT1 vs 62% GT5, p = 0.047)

Conclusions: Patients infected with hepatitis delta genotype 5 seem to have a better prognosis with fewer episodes of hepatic decompensation and more favorable response to pegylated interferon therapy.

FRI-295

Prevalence and clinical outcome of hepatitis Delta infection in patients with HIV/HBV coinfection

G.B. Gaeta[1,2], S. Milensu[3], G. Brancaccio[4], M. Puoti[5], A. D'arminio Monforte[6], A.D. Luca[7], A. Vergori[8], S. Rusconi[5], A. Mazzarelli[9], A. Castagna[5], A. Antinori[10], A. Cozzi-Lepri[3]. *[1]Infectious Diseases, Specialistic and Internal Medicine, Naples, Italy; [2]Infectious Diseases, Naples, Italy; [3]University College, London, United Kingdom; [4]Infectious Diseases, Internal and Specialistic Medicine, Naples, Italy; [5]Infectious Diseases, Milan, Italy; [6]Clinic of Infectious Diseases, Milan, Italy; [7]Infectious Diseases, Siena, Italy; [8]Clinical Division, Rome, Italy; [9]Banca Biologica, Rome, Italy; [10]Clinical Department, Rome, Italy*
Email: giovannibattista.gaeta@unicampania.it

Background and Aims: Hepatitis Delta virus (HDV) co-infects about 20 million HBsAg+ individuals worldwide. HIV infected persons with HBV coinfection are at risk for HDV. We explored the prevalence of HDV infection and its clinical impactin the ICONA cohort.

Method: Anti-HDV status was assessed among HBsAg + patients enrolled in1997–2015. We performed a cross-sectional analysis to comparebaseline (the date of first HBV test) characteristics of HBV+/HDV+ vs. HBV+/HDV-patients. The proportion of patients HDV+ amongst patients who were HBV+ per year of enrolment was alsocalculated. Composite clinical outcome (CCO) was defined as the occurrence of any of the following events: Fib4 score > 3.25; clinical diagnosis of cirrhosis; decompensation; hepato-carcinoma (HCC) or death. Kaplan Meier method was used to plot the time to develop the CCO, stratified by anti-HDV status. Univariable and multivariable Cox regression models adjusted forage, gender, nationality, region, education, CD4 count, HIV-RNA viral load, smoking status, alcohol consumption, mode of HIV transmission and HCV infection status, were fitted and relative hazards (RH) shown.

Results: Among 13,558 HIV positive patients enrolled as of September 2015, 10,988 were HBsAg-negative, 1,953 were nottested for HBsAg and 617 patients were HBsAg-positive; of these, 115 (18.6%) wereanti-HDVpositive, 403 (65.3%) anti-HDV negative and 99 (16.0%) not tested for HDV. Proportions of anti-HDV positive cases tended to decrease from the year 1997 to 2011 (from 28% to 4%) then appear to increase to 8% in the period 2012–2015. Overall, 171 patients (28%) developed the CCO over time of whom 55/115 (48%) HDV positive, 98/403 (24%) HDV negative and 18/99 (18%) HDV unknown (p < 0.001). In unadjusted Cox regression analysis, RH was 2.34 95%CI:1.68–3.26; the association was attenuated after controlling for HCV coinfection (RH = 1.46; 95%CI:0.98, 2.17). Other factors independently associated with higher risk of CCO were: male gender, older age, lower CD4 count, alcohol use and smoking. In the subset of people who received anti-HBV therapy, 43/79 (54%) HDV+ patients and 84/320 (26%) HDV-neg patients developed CCO (OR = 3.36; 95% CI:1.95–5.78).

Conclusion: Presence of anti-HDV antibodies in HIV-coinfected individuals is a marker of faster progression to severe liver disease and death even in participants who received anti-HBV therapy.

FRI-296

Clinical features of HDV infection in Mongolian patients

A. Enkhbat[1], O. Lkhagva-Ochir[2], D. Boldbaatar[2], B. Dashtseren[2], A. Bungert[3], Z. Genden[2], D. Yagaanbuyant[2], N. Dashdorj[3], N. Dashdorj[2,3]. [1]*Liver Center, Laboratory, Ulaanbaatar, Mongolia;* [2]*Liver Center, Hospital, Ulaanbaatar, Mongolia;* [3]*Onom Foundation, Ulaanbaatar, Mongolia*
Email: anir@livercenter.mn

Background and Aims: It is estimated that 7.14% of Mongolian population having double infection with hepatitis B (HBV) and D (HDV) viruses. By current study our goal was to take an inquiry into the clinical features of delta viral infection in Mongolia.
Method: A total of 445 chronic HDV patients at the Liver Center, Mongolia were randomly chosen, and their clinical parameters were determined.
Results: Majority of patients were female 56% with mean age of 44.87 ± 10.7, ranging from 18–82 years. 409 patients (92%) were HDV-RNA positive, 85 (19.1%) HBV-DNA negative and 68 (15.2%) had positive hepatitis C (HCV) RNA. Mean values of clinical biochemical markers were 82.59 ± 84.2 for ALT and 58.46 ± 53.0 for AST while mean platelet count was 185.4 ± 64.7. Liver fibrosis were staged by elastography (Fibroscan). There were F0-F1–143 (32.13%), F2–44 (9.89%), F2-F3–87 (19.55%), F3 – 17 (3.82%), F3-4 – 96 (21.57%), F4 – 58 (13%) patients, respectively. Clinical immunological markers were determined in 363 patients for HBsAg and 206 for HBeAg out which 23 (11.2%) were positive for HBeAg. Antiviral therapy was administered to 161 patients out of which 154 received with anti HBV nucleos/tide analogues, 6 patients received anti-HCV nucleos/tide analogues and one patient receiving both antivirals.
Conclusion: HDV represent more severe outcomes in male patients compared to females with elevated levels of clinical biochemical markers, viral loads, liver fibrosis as well and may reduce life expectancy as well.
Biochemical markers are not significantly altered and cannot be sufficiently predict HDV clinical course. There is moderate positive correlation (0.42) between AST/Platelet index ratio and liver elastography (Fibroscan) scoring. Notable differences in platelet counts were observed in three cohorts grouped by liver elastography scores: <10 kpa, 10–15 kpa and >15 kpa. HBsAg level had weak correlation (0.14) with HDV viral load. Overall the current clinical tests done for chronic HBV management are largely ineffective for monitoring, diagnosing and predicting future outcome of chronic HDV patients, except maybe for platelet count and liver fibrosis.

FRI-297

Monitoring of subjects with previous hepatitis B exposure on Rituximab for hepatitis B reactivation and on demand treatment for hepatitis B reactivation is safe and reduces cost

V. Ekstrom[1], T. Tang[2], A. Chan[3], F. Mohamad[2], M. Tao[2], W.C. Chow[4], R. Kumar[1]. [1]*Singapore General Hospital, Gastroenterology & Hepatology, Singapore, Singapore;* [2]*National Cancer Centre, Oncology, Singapore, Singapore;* [3]*National Cancer Centre, Pharmacy, Singapore, Singapore;* [4]*Gastroenterology and Hepatology, Singapore, Singapore*
Email: vekstrom@gmail.com

Background and Aims: Hepatitis B reactivation (HBVr) is known to occur in patients with Hepatitis B virus (HBV) exposure on treatment with Rituximab. On demand treatment remains controversial due to concerns of HBV-related acute liver failure while anti-viral prophylaxis increases cost and potentially induces drug resistance. This study aims to determine prospectively the rate of HBVr in patients with HBV exposure who receive Rituximab and to determine the safety of on demand treatment if they require treatment with nucleoside analogs (NA).

Method: Ongoing single centre, prospective observational study at National Cancer Centre Singapore and Singapore General Hospital. All patients with B-cell lymphoma requiring rituximab were screened for Hepatitis B serology markers. Those who had positive Hepatitis B core total antibody (HBcAb) and negative Hepatitis B surface antigen (HBsAg) and HBV DNA levels were recruited. HBsAg, HBV DNA and Alanine aminotransferase (ALT) were monitored at 4–6 weekly intervals during therapy, 6 weekly intervals after the last dose of rituximab for 52 weeks and 12 weekly intervals for another 52 weeks. Whilst on rituximab, NA would be started if they had 2 readings more than 4 weeks apart of either HBV DNA >100 IU/ml irrespective of ALT, or ALT more than upper limit of normal (ULN) and HBV DNA >20 IU/ml. Following completion of the planned rituximab treatment, NA would be started if they had 2 readings of ALT > ULN and HBV >200 IU/ml at least 4 weeks apart, or ALT > ULN and HBV DNA increasing by >1 log in past 8 weeks or relapse of underlying lymphoma and HBV DNA was detectable.
Results: To date, 27 patients (77.8% Chinese/14.8% Malay/7.4% others) were recruited in the study. Mean age was 70.6 ± 9.9 years and 55.6% were males. 8 developed detectable HBV DNA. Only 3 required treatment with NA while on rituximab due to rising HBV DNA which occurred at a mean duration of 59.7 days after starting Rituximab. All the patients who had increased HBV DNA did not have elevated ALT. None of the patients with Hepatitis B surface antibody (anti-Hbs) >100 IU/ml had HBVr while anti-Hbs >10 IU/ml was not protective for HBVr. The 5 who did not require treatment had a detectable HBV DNA < 20 IU/ml which returned to undetectable levels spontaneously. None developed HBV-related acute hepatitis flare or jaundice. 2 patients passed away (1 from fungaemia, 1 from metastatic cervical cancer).
Conclusion: Close observation without primary antiviral prophylaxis was safe for HBV-exposed patients who were on Rituximab based-chemotherapy. This helped reduce cost of medication that can be avoided. Patients with anti-Hbs >100 IU/ml have very low chance of reactivation.

FRI-298

Prevalence and impact of hepatitis E virus infection in the Hepatitis B Research Network cohort

D. Mcgivern[1], T. Benzine[2], S.H.-H. Lin[3], J. Wang[4], R. Fontana[4], S. Belle[3], M. Fried[5]. [1]*University of North Carolina at Chapel Hill, UNC Lineberger Cancer Center;* [2]*University of North Carolina, UNC Lineberger Cancer Center;* [3]*University of Pittsburgh, Department of Epidemiology, Pittsburgh, United States;* [4]*University of Michigan, Division of GI and Hepatology, Ann Arbor, United States;* [5]*University of North Carolina at Chapel Hill, UNC Liver Center, Chapel Hill, United States*
Email: mfried@med.unc.edu

Background and Aims: Patients with chronic HBV may experience spontaneous biochemical flares of liver disease activity. This study aimed to determine (i) the prevalence of prior HEV infection and possible acute HEV infection among persons with chronic HBV and (ii) whether HEV infection is associated with liver disease flares among persons with chronic HBV.
Method: To obtain prevalence estimates, serum from a random sample of 600 of the 1,991 participants in the Hepatitis B Research Network (HBRN) adult cohort were tested for anti-HEV IgM and IgG (Wantai assay). HEV RNA was measured by qRT-PCR. At or after enrollment, 72 participants (none treated with peg-IFN) experienced biochemical flares [ALT ≥10 × ULN (female = 200, male = 300 U/l)] of select etiologies, adjudicated by hepatologists. Serum samples of flare cases [49 pre-flare (>6 weeks prior to flare), 72 at-flare (–6–12 weeks), and 51 post-flare (>12–48 weeks)] were analyzed for anti-HEV (IgM or IgG) seroprevalence. Sera from flare cases at-flare were matched (1:4) to sera from non-flare controls by propensity scores accounting for sex, age, place of birth, and HBeAg status. Post-flare

samples were matched (1:4) by propensity score and time between samples.
Results: In the prevalence study, mean age was 43 years, 51% were female and 72% were Asian. Anti-HEV IgG and IgM seroprevalence was 28.5% and 1.7%, respectively. None of the 10 anti-HEV IgM + participants had detectable HEV RNA. Their median ALT was 27.5 (range: 9-76)U/l. Characteristics independently associated with anti-HEV (IgG+ or IgM+) included older age, males, not US/Canada-born, less education, and higher HBV DNA. The flare etiology was unknown for 7/72 (10%). Of the others, the most common of the selected causes were spontaneous viral reactivation (49%) and unsuccessful or spontaneous immune clearance (32%). Using at flare matched samples, the odds of flaring was not significantly different between anti-HEV positive (IgG+ or IgM+) and anti-HEV negative (IgG- and IgM-) participants (OR: 1.3, 95%CI: 0.7 to 2.5). Similar results were found using post-flare matched samples (OR: 1.2, 95%CI: 0.6 to 2.6). For the flare cases, seroprevalence of HEV was similar pre- (29%), at- (36%), and post-flare (31%). HEV RNA was not detected in any samples.
Conclusion: Seroprevalence of anti-HEV IgG is high among individuals with chronic HBV in the US and Canada, but acute HEV infection does not appear to account for ALT flares of disease in patients followed in the HBRN cohort.

FRI-299

Red blood cell distribution width to albumin ratio is a potential index for predicting long-term prognosis for hepatitis B virus-related liver cirrhosis

C. Wu[1], J. Wang[2], R. Huang[1], W. Ding[2], J. Xia[1], X. Yan[1], Y. Liu[3], Y. Chen[3].
[1]*Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Department of Infectious Diseases, Nanjing, China;* [2]*Huai'an No. 4 People's Hospital, Department of Hepatology, China;* [3]*Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Department of Experimental Medicine*
Email: dr.wu@nju.edu.cn

Background and Aims: It is essential to identify the severity of HBV-related liver diseases and predict long-term prognosis. We aimed to evaluate a novel index, the red blood cell distributionwidth(RDW)-to-albumin ratio(RAR), for the prediction of liver-related mortality in HBV-related liver cirrhosis.
Method: 223 patients with HBV-related liver cirrhosis, 318 chronic hepatitis B(CHB) patients and 197 healthy controls(HC) were recruited as a training cohort. 265 patients with cirrhosis, 194 CHB patients and 167 HC from another center were recruited as an external validation cohort. The diagnostic values of RAR for the severity of HBV-related liver cirrhosis were calculated by ROC curves and compared with other noninvasive methods. The prognostic value of baseline RAR were assessed using Kaplan–Meier analysis.
Results: In the training set, median RAR values were significantly higher in patients with HBV-related liver cirrhosis as compared with CHB patients ($p < 0.001$) and HC ($p < 0.001$). RAR was positively correlated with Child–Pugh scores ($r = 0.569$, $p < 0.001$) and MELD scores ($r = 0.139$, $p = 0.038$). The AUCs of RAR were significantly higher than that of AST-to-platelet(PLT) ratio index (APRI), fibrosis-4 index (FIB-4), gamma-glutamyl transpeptidase (GGT) to PLT ratio (GPR), RDW-to-PLT ratio (RPR), AST-to-ALT ratio (AAR) and neutrophil-to-lymphocyte ratio (NLR) in predicting HBV-related liver cirrhosis and decompensated cirrhosis. The performance of RAR in identifying the severity of HBV-related liver cirrhosis was similar in the validation cohort. The mean follow-up duration was 34.9 (IQR, 25.0–49.5) months in cirrhosis patients in the training cohort, during which 21 patients died. The cirrhosis patients were followed for 33.2 (IQR,16.6–45.9) month in the validation cohort. RAR was an independent predictor of mortality by Cox Regression models (HR 30.6; 95%CI 2.3–409.6; $p = 0.01$). The patients with HBV-related liver cirrhosis were divided into two group by the median (0.48) of RAR value with an incidence rate for liver-related death of 5.9%, 19.0% in the training cohort, and 5.6%, 26.4% in the validation cohort, respectively. Kaplan-Meier analysis showed high RAR values was significantly associated with higher cumulative incidence of death throughout follow-up both in the training cohort ($p = 0.005$) and validation cohort ($p < 0.001$).
Conclusion: RAR can be used as a novel index for the prediction of severity in HBV-related liver diseases. More importantly, RAR is a useful prognostic index for HBV-related liver cirrhosis.

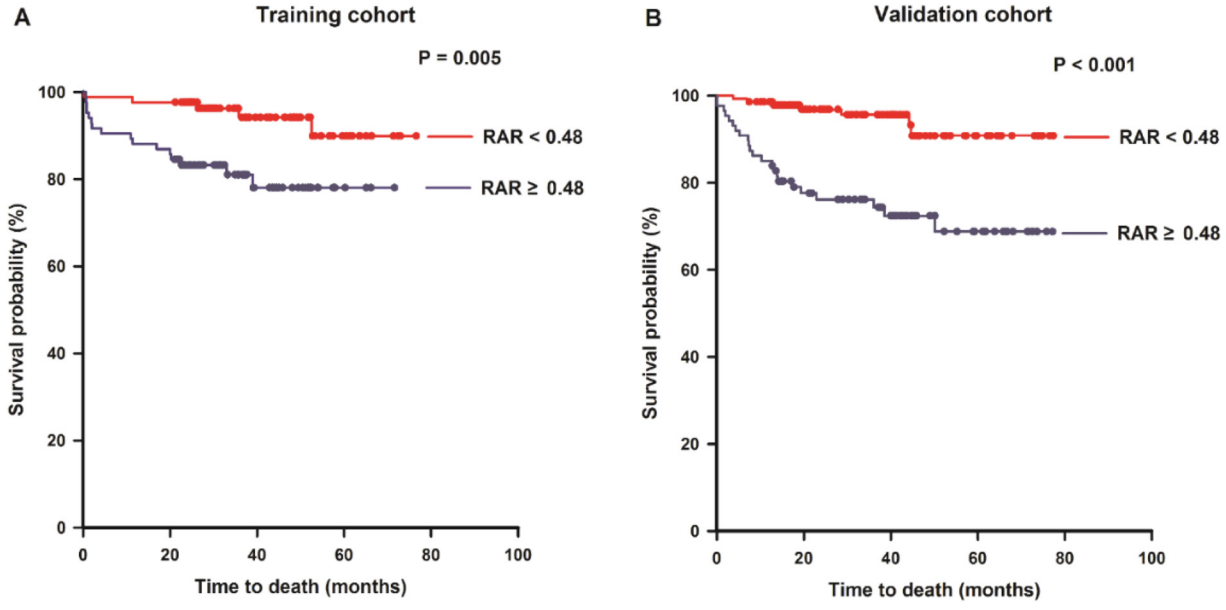


Figure 1: (abstract: FRI-299)

FRI-300

Disease progression is affected by pattern of serum alanine aminotransferase dynamics in a cohort of patients with hepatitis B e antigen-negative chronic infection: 4 years follow-up of a prospective longitudinal study (ALBATROS study)

V. Knop[1], J. Vermehren[1], Jörg Petersen[2], P. Buggisch[2], H. Wedemeyer[3], M. Cornberg[3], S. Mauss[4], M. Sprinzl[5], T. Berg[6], F. van Boemmel[6], H. Klinker[7], D. Hüppe[8], J.-P. Bronowicki[9], M. Bickel[10], T. Welzel[1], S. Susser[1], S. Zeuzem[1], C. Sarrazin[1,11]. *[1]J.W.Goethe Universität, Medizinische Klinik 1, Frankfurt, Germany; [2]Asklepiosklinik St.Georg, Hamburg, Germany; [3]Medizinische Hochschule, Hannover, Germany; [4]Gastroenterologische Schwerpunktpraxis, Düsseldorf, Germany; [5]I. Medizinische Klinik und Poliklinik, Mainz, Germany; [6]Universitätsklinikum Leipzig, Germany; [7]Universitätsklinikum Würzburg, Germany; [8]Hepatologische Schwerpunktpraxis Herne, Germany; [9]Centre Hospitalier Universitaire de Nancy, France; [10]Infektiologikum Frankfurt, Germany; [11]St. Josefs-Hospital Wiesbaden, Germany*
Email: viola.knop@kgu.de

Background and Aims: During the natural course of chronic HBV infection little is known about the effect of alanine aminotransferase (ALT) dynamics for the outcome of long-time follow-up.
The aim of the present study was to investigate the clinical significance of ALT changes between baseline (BL) and 4 years follow-up (FU4) for hepatitis B e antigen (HBsAg) seroconversion as well as for disease progression in a cohort of European untreated HBeAg-negative infected patients.
Method: Patients with HBeAg-negative low-replicative chronic HBV were enrolled for long-term follow-up over 10 years. Definition of low-replicative HBV without indication for antiviral therapy at study inclusion was based on EASL guidelines. Biochemical and virological parameters as well as transient elastography (TE) were performed at BL and 1x/year.
Results: Data of FU4 were available in 227 patients, mainly infected with HBV genotype A and D. Patients were classified according to ALT levels into the following groups: patients with constantly normal ALT ≤ 0.5 × ULN [group A; 18/227 (7.9%)], constantly normal ALT > 0.5 × ULN [group B; 151/227 (66.5%)], transient ALT elevation [group C; 51/227 (22.5%)] and persistent ALT increase [group D; 7/227 (3.1%)]. Overall, HBsAg seroconversion and reactivation with start of antiviral therapy was observed in 12/227 (5.3%) and 14/227 (6.2%) patients, respectively. HBsAg seroconversion was not significantly affected by ALT dynamics during 4 years FU [2/18 (11.1%), group A; 9/151 (6%), group B; 1/51 (2%), group C; 0/7, group D]. Patients with transient or persistent ALT elevation (group C and D) had a significant higher risk of disease progression with parallel increase of HBV DNA (>2000 IU/ml) and started with antiviral treatment compared to group A and B patients [6/51 (11.8%) and 4/7 (57.1%) in groups C and D versus 0/18 and 4/151 (2.6%) in groups A and B, respectively; $p < 0.0001$]. Single-point measurement of ALT showed significant correlations with liver stiffness by TE ($r = 0.34$; $p < 0.0001$), BMI ($r = 0.269$; $p < 0.0001$), triglycerides ($r = 0.229$; $p = 0.001$), quantitative HBsAg ($r = 0.207$; $p = 0.004$) and LDL cholesterol ($r = 0.145$; $p = 0.045$).
Conclusion: In our study cohort with 4-year period of follow-up patients with transient or persistent ALT elevation were shown to have a higher risk of disease progression. ALT levels ≤ 0.5xULN appeared to be no further advantage for the long-term outcome. Beside viral factors transaminase levels were also correlated to metabolic parameters, such as LDL cholesterol and BMI.

FRI-301

Serum Mac-2-binding protein glycosylation isomer in assessing liver fibrosis in chronic hepatitis B infection

L.-Y. Mak[1], W.-K. Seto[1,2], K.-S. Cheung[1], Y.Y.J. Fung[1,2], D. Wong[1,2], C.L. Lai[1,2], M.-F. Yuen[1,2]. *[1]The University of Hong Kong, Li Ka Shing Faculty of Medicine, Hong Kong; [2]State Key Laboratory for Liver Research, Hong Kong, China*
Email: mfyuen@hku.hk

Background and Aims: Mac-2-binding protein glycosylation isomer (M2BPGi) is a novel serum marker for diagnosis of liver fibrosis in various liver diseases, while data in chronic hepatitis B (CHB), especially longitudinal data, is limited. We aimed to evaluate the role of M2BPGi in diagnosing advanced fibrosis (F3) and cirrhosis (F4) in HBeAg-ve CHB using liver stiffness measurement (LSM) as the reference.
Method: We performed transient elastography for HBeAg-ve CHB patients who were managed in Queen Mary Hospital, Hong Kong. LSM was performed by Fibroscan® (Echosens, Paris, France) and presence of no/minimal fibrosis (F0/F1), grey area and F3/F4 was defined using the alanine-aminotransferase-based EASL-ALEH criteria. Serum M2BPGi were measured using the HISCL-800 immunoanalyzer (Sysmex Corporation, Hyogo, Japan).
Results: 240 HBeAg-ve CHB patients (M:F = 116:124) of median age 47.5 years were recruited. The majority were treatment-experienced (85.8%). The median ALT was 26 U/l (range: 10–180 U/l). The median liver stiffness was 6.9 kPa (IQR 4.9–11.7 kPa) and 78 of them (32.5%) had F3/F4 by transient elastography at baseline. The corresponding median M2BPGi values for F0/1/2, F3 and F4 progressively increased in parallel with more advanced stages of liver fibrosis: 0.39, 0.46 and 0.82 COI, respectively ($p < 0.01$) (Figure 1A). The AUROC for diagnosing ≥ F3 by serum M2BPGi was 0.754. Using a cut-off value of 0.605, the sensitivity, specificity, PPV and NPV for ≥ F3 was 62.5%, 79.4%, 60.3% and 80.9%, respectively. In a subgroup of 86 patients who had repeated LSM 10 years after the initial LSM, the proportion of patients with F3/4 was reduced from 36.7% to 16.3% ($p < 0.001$). The median serum M2BPGi levels were significantly different between patients with F3/4 compared to those with F0/1/2 at baseline (0.67 COI vs. 0.41 COI, $p < 0.05$) and also at 10-year (0.62 COI vs. 0.48 COI, $p = 0.039$). 21 (24.4%) showed significant fibrosis regression (i.e. F3 or F4 → F0 or F1). The median change in serum M2BPGi level was -0.11 compared to + 0.03 COI in the other patients who did not showed significant fibrosis regression ($p = 0.011$). (Figures 1C-1D)
Conclusion: Serum M2BPGi was an accurate serum marker for liver fibrosis in HBeAg-ve CHB patients. Using a cut-off level of 0.605 COI, 80.9% patients without ≥ F3 can be excluded. Serum M2BPGi levels remained significantly higher for patients with ≥ F3 compared to those with F0/1/2 even after 10 years. Serum M2BPGi levels also decreased significantly in patients who had fibrosis regression after 10 years.

FRI-302

Changes in serum levels of the novel mac-2 binding protein glycosylation isomer and risk of hepatocellular carcinoma among chronic hepatitis B patients treated with nucleos(t)ide analogues

Y.-C. Hsu[1], T. Jun[2], M.-L. Yeh[3], Y.-T. Huang[4], M.-L. Yu[3], M. Nguyen[2], Y. Tanaka[5]. *[1]Fu-Jen Catholic University Hospital, Department of Medical Research; [2]Stanford University Medical Center, Department of Medicine, Palo Alto, United States; [3]Kaohsiung Medical University Hospital, Division of Hepatology Department of Internal Medicine; [4]Academia Sinica, Institute of Statistical Science; [5]Nagoya City University Graduate School of Medical Sciences, Department of Virology & Liver unit*
Email: holdenhsu@gmail.com

Background and Aims: Current data is limited in how mac-2 binding protein glycosylation isomer (M2BPGi) would change and whether it can predict hepatocellular carcinoma (HCC) development in nucleos (t)ide analogues (NA)-treated chronic hepatitis B (CHB) patients. We

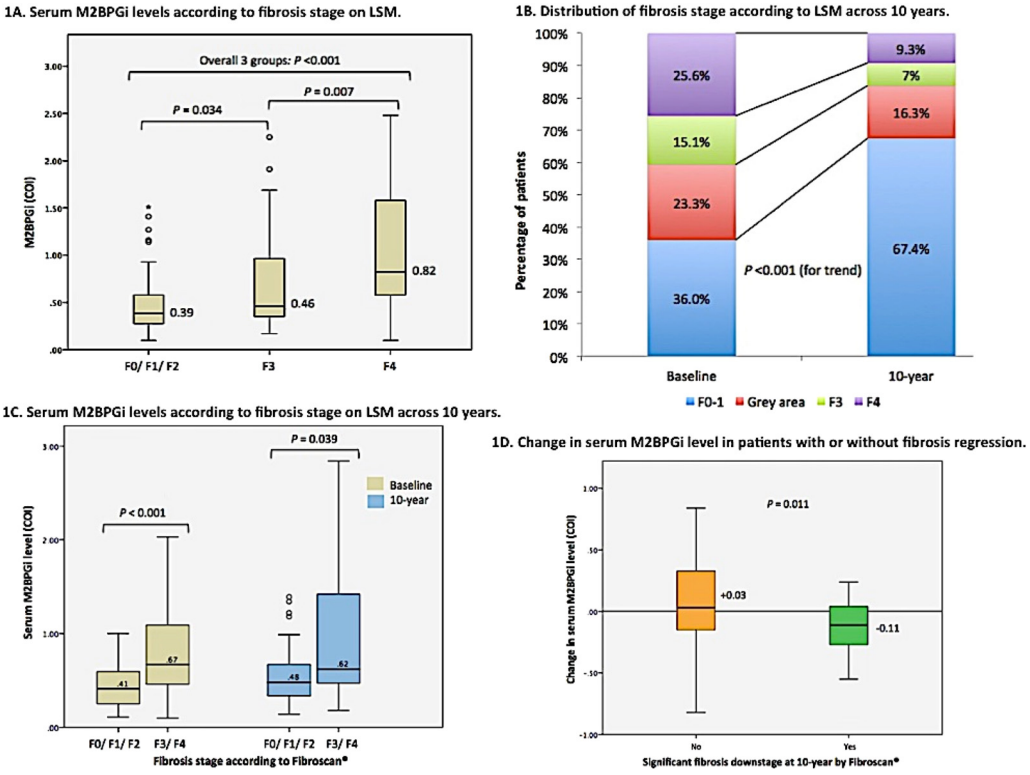
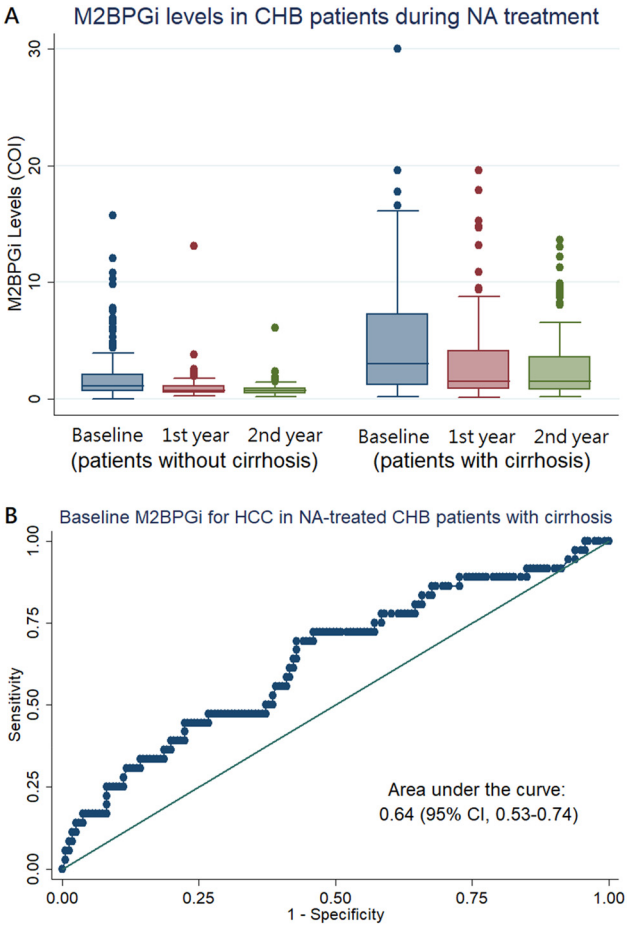


Figure 1: (abstract: FRI-301)

aimed to clarify the dynamic change of M2BPGi and its association with HCC in CHB patients during NA treatment.

Method: Previously untreated CHB (without co-infection) patients were prospectively enrolled at 3 centers in the US and Asia. Sera were serially collected at the time (but prior to) of NA initiation, then at 1 year and at 2 years after therapy. Those with baseline HCC or who developed HCC within one year of therapy were excluded. We used multivariable Cox proportional hazard model to evaluate the association between serial serum M2BPGi levels (cut off index; C.O.I) measured at different time points and subsequent occurrence of HCC.

Results: The analysis included 387 eligible patients: 73.6% male, 50.9% with cirrhosis, and median age of 48 years. Median M2BPGi levels significantly decreased from baseline (1.7; interquartile range [IQR], 0.78–4.4), to 1.0 (IQR, 0.61–1.83) at 1 year, and to 0.88 (IQR, 0.58–1.75) at 2 years after treatment initiation. This trend was consistent with or without cirrhosis (Figure, panel A). In paired analysis of the 275 patients who had M2BPGi measurements at all 3 time points confirmed that the decline during the first year (median, 0.56; IQR, 0.07–2.07) was significantly more pronounced than those during the second year following therapy initiation (median, 0.08; IQR, −0.18–0.40) ($p < 0.0001$, Wilcoxon signed-rank test). During a median follow-up of 72.7 (IQR, 44.2–103.4) months, HCC occurred in 37 patients, almost all of whom (n = 36) had cirrhosis at baseline. On multivariate Cox regression analysis of the 197 patients with cirrhosis, HCC risk was independently and significantly associated with pretreatment M2BPGi (adjusted hazard ratio [aHR], 1.10 per COI; 95%CI, 1.04–1.16) in addition to age (aHR, 1.07 per year; 95%CI, 1.02–1.13) and diabetes mellitus (aHR, 2.21; 95%CI, 1.04–4.70), but serum M2BPGi measured at one year or two years after treatment was not. The concordance rate of baseline M2BPGi for HCC occurrence in NA-treated CHB patients with cirrhosis was 0.64 (95%CI, 0.53–0.74) (Figure, panel B).



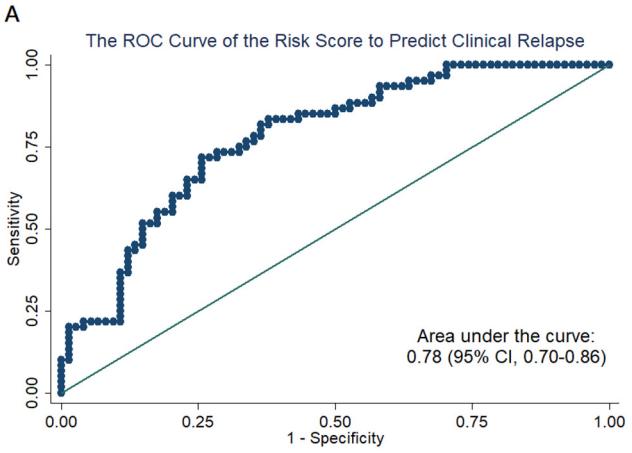
Conclusion: Serum M2BPGi levels decreased in CHB patients during oral antiviral therapy, with the most pronounced decline occurring in the first year of therapy. Baseline M2BPGi levels were independently associated with the risk of HCC among patients with cirrhosis. Further studies with large sample size of treated non-cirrhotic patients are needed to investigate the role of M2BPGi as a predictor of HCC in this population.

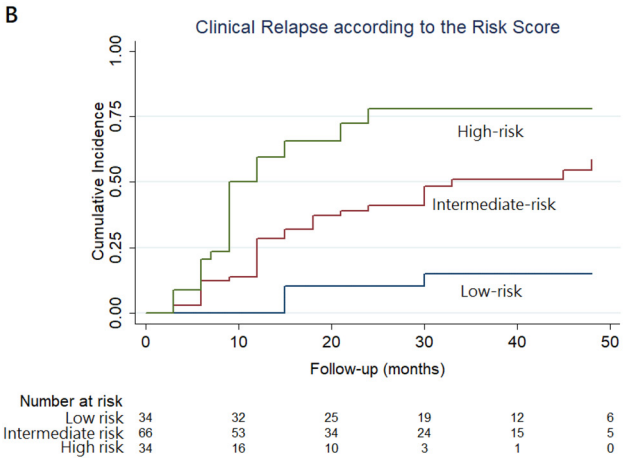
FRI-303

A risk score combining quantitative hepatitis B surface antigen and core-related antigen levels to predict off-therapy relapse after cessation of nucleos(t)ide analogues in patients with chronic hepatitis B

Y.-C. Hsu[1], Y. Tanaka[2], M. Nguyen[3], C.-Y. Chang[1], C.-M. Tai[4], C.-H. Tseng[4], C.-C. Chen[5], M.-S. Wu[5], J.-T. Lin[1]. *[1]Fu-Jen Catholic University, School of Medicine College of Medicine, New Taipei; [2]Nagoya City University Graduate School of Medical Sciences, Department of Virology & Liver unit, Nagoya, Japan; [3]Stanford University Medical Center, Department of Medicine, Palo Alto, United States; [4]E-Da Hospital, Department of Medicine, Kaohsiung; [5]National Taiwan University Hospital, Department of Internal Medicine, Taipei, Taiwan*
Email: holdenhsu@gmail.com

Background and Aims: Clinical relapse frequently follows cessation of nucleos(t)ide analogues (NAs) in patients with CHB; however, there are currently no accurate prediction tools to identify patients who would relapse. We aimed to develop a risk score to predict clinical relapse in CHB patients who discontinue NA therapy.
Method: This prospective study enrolled 134 CHB patients (79.1% male; median age, 49.3 years) without cirrhosis who discontinued NAs after a minimum of 3 years on therapy. Serum HBeAg was negative and hepatitis B virus (HBV) DNA undetectable at the end of treatment (EOT) in all patients, whereas HBeAg was positive in 35 patients prior to treatment). Clinical relapse was defined as serum HBV DNA > 2,000 IU/ml plus alanine aminotransferase (ALT) > 80 U/l. Predictors of clinical relapse were determined by the multivariable Cox proportional hazard model. The regression coefficients in the model were weighted to build a risk score.
Results: During a median follow-up of 21 (range, 3~60) months, 60 patients experienced a clinical relapse with the cumulative incidence of 54.1% (95%CI, 44.9–63.9%) at 4 years. The Cox model identified ALT (adjusted hazard ratio [aHR], 1.02 per U/l; 95%CI, 1.01–1.03), age (aHR, 1.04 per year; 95% CI, 1.02–1.07), HBsAg (adjusted HR, 1.94 per logIU/ml; 95% CI, 1.21–3.11), and HBcrAg (aHR, 1.39; 95% CI, 1.06–1.82) as the independent EOT factors associated with subsequent clinical relapse, and lead to a risk score with the formula of ALT (U/l) + 2*Age (years) + 32*HBsAg (logIU/ml) + 16*HBcrAg (logIU/ml). The score achieved a Harrel's c statistic of 0.78 (95%CI, 0.70–0.86). A score <235 (n = 31) and >285 (n = 35) points distinguished low- and high-risk groups with the 4-year cumulative incidences of 15.6% (95%CI, 6.0–37.1%) and 79.9% (95%CI, 62.7–92.7%), respectively. Moreover, all of the 7 patients who cleared HBsAg during the follow-up had a score <235 points.
Conclusion: The current score based on age, ALT, qHBsAg, and HBcrAg may predict the risk of clinical relapse after cessation of NA therapy in CHB patients and calls for external validation to help identify those who can safely discontinue NAs.





FRI-304

Acute hepatitis B in adulthood: not such a benign disease

J. Llaneras[1], M. Riveiro-Barciela[2,3], P. Suanzes[1], E. Mena[1], S. Romero[1], M. Ventura-Cots[1], F. Sanpedro[1], R. Esteban[2,3], M.B. Ferret[2,3]. *[1]Hospital Universitari Vall d'Hebron, Emergency Department, Barcelona, Spain; [2]Hospital Universitari Vall d'Hebron, Liver Unit, Barcelona, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos III, Madrid, Spain*
Email: jllanera@vhebron.net

Background and Aims: Acute hepatitis B (AHB) remains a common cause of acute viral hepatitis though series concerning its outcome date back to the 80s [Tassopoulos NC, Gastroenterology 1987; McMahon BJ, J Infect Dis 1985]. The aim of this study was to analyze the characteristics and prognosis of AHB in adulthood within the last 3 years.
Method: Prospective study including all consecutive AHB in subjects aged over 16 years attended at our hospital from October 2014 to October 2017. Diagnosis of AHB was based on the presence of positive antiHBc IgM.
Results: 239 cases of acute hepatitis were recorded during the 3 years period. 33 (14%) were AHB: 85% male, median age 49 years (IQR: 38–56). Baseline ALT value was 1431 IU/mL (IQR: 412–2211) and bilirubin 5.8 mg/dL (IQR: 1.8–9.9). 64% of patients presented jaundice at diagnosis. Four (12%) subjects had undergone immunosuppressant drugs within the previous year, 2 for oncological malignancies and 2 for transplantation, and all of them were antiHBc positive/HBsAg negative prior to immunosuppression and HBeAg positive with HBV DNA >10E8 at diagnosis of AHB. Prognosis: Twelve (36%) developed chronic hepatitis B and 3 acute liver failure (ALF), the latter treated

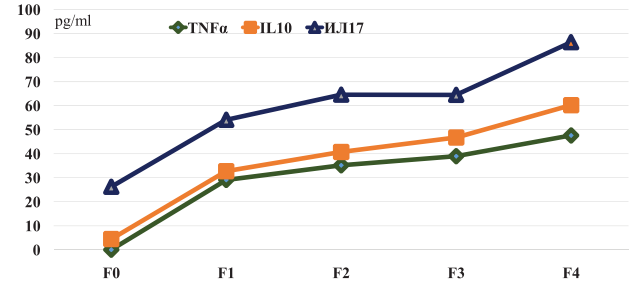
with nucleos(t)ids analogs. Three (9%) out of the 12 AHB that developed chronic infection, presented histological evidence of cirrhosis one year after AHB. Overall, 11 (33%) required hospital admission and 2 (6%) out of 3 ALF died and the other survived after liver transplant. Multivariate analysis showed that jaundice was the only independent factor associated with AHB cure (OD 1.7, p = 0.02).
Conclusion: A high rate of chronification was observed in adults with acute hepatitis B. Jaundice was the only protetive factor against the development of chronic infection.

FRI-305
The first results of genotyping of virus hepatitis D and virus hepatitis B in Kazakhstan
B. Ilyassova[1], B. Baymakhanov[1], Y. Bakhytkali[2], A. Kyzdarbekov[3], V. Ayupova[4]. *[1]National Scient Center of Surgery Named A.Syzganova, of Hepatopancreatobiliary Surgery and Liver Transplantation, Almaty, Kazakhstan; [2]Hospital of Infection Deseases of Shymkent, Shymkent, Kazakhstan; [3]Hospital of Infection Deseases of Taraz, Taraz, Kazakhstan; [4]Hepatological Center of Almaty, Almaty, Kazakhstan*
Email: bs-immunolog@mail.ru

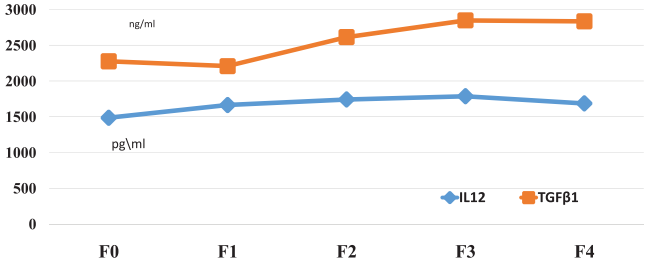
Background and Aims: The 5-year experience of the transplant center in Almaty has shown that out of 100 recipients, 30 patients had cirrhosis and/or HCC in the outcome of chronic hepatitis D (CHD), 19 patient had PBC, 15 had billiary athresia, 15 – chronic hepatitis B (CHB), 10 had chronic hepatitis C, 4- AIH. Cirrhosis in the outcome of CHD is the most common cause of liver transplantation in Kazakhstan.
CHD is associated with the most severe form of hepatotropic-induced viral hepatitis [Rizzetto M et al., 1983]. The severity of the course of CHD may be dependent on host and viral factors. Multivariate analysis identified age, HBV genotype C, and HDV genotype I as independent factors for poor outcomes [Su CW, Huang YH, Huo TI et al., 2006].
The National Scientific Center of Surgery named A. Syzganov in 2017 has started the scientific project to study the factors of progression of liver cirrhosis in the Kazakh population. One of the factors of progression of liver cirrhosis in Kazakhstan are genotypes of HBV and HDV.
Method: Blood samples of patients were examined for the determination of genotypes of HBV and genotypes of HBV by the PCR method. Isolation of HDV RNA and HBV DNA was performed using the GeneJETViral DNA and RNA Purification Kit, ThermoScientific, according to the manufacturer's instructions. PCR was performed using specific primers. Purified PCR products were sequenced in two directions, using a forward and reverse primer (BigDye™ Terminator v3.1 CycleSequencingKit).
Results: 144 patients in chronic hepatitis B and D were examined, including 56 men, 89 women. The average age was 40.9 ± 8,6 years. In 102 patients diagnosed with chronic viral hepatitis D, 42 patients with CHB. Among patients with CHD, 79,4% (82 patients) had a positive PCR result of HDV RNA in the absence of HBV DNA in the blood. 20,6% (21) patients with CHD were HBV DNA-positive and HDV RNA-positive at the same time. In patients with CHD the stage of liver fibrosis F0 (Metavir) had 24 (23,5%) patients, F1–4 (3,9%), F2–5 (4,9%), F3-32 patients (31,3%), F4 had 37 (36,2%) patients.
In patients with CHB, 41 patients were HBeAg-negative, i.e. mutant strain of the virus and only 1 patient (2,3%) was HbeAg-positive. In patients with CHD 6 patients had a viral load of less than 2000 IU. The stage of liver fibrosis F0 (Metavir) had 8 (33,3%) patients with CHB, F1-4 (16%), F2–5 (11,9%), F3-7 patients (17,1%), F4 had 14 (33,3%) patients.
The PCR analysis has showed that in all patients (100%) with CHD have 1 genotype of HDV. In 92.9% (39 patients) of CHB, genotype D was found, in 4.7% (2)-genotype A of HBV and in 2,4% (1)-genotype B. Genotype B has HbeAg-positive patient. The 21 patients with positive PCR of HBV DNA and HDV RNA has genotype D of HBV.
Conclusion: The severe course of chronic viral hepatitis D is due to the prevalence of the 1 genotype of HDV. For chronic hepatitis B, the most common genotype is D.

FRI-306
The levels of cytokines in progression of chronic hepatitis D
B. Ilyassova[1], B. Abzhaparova[2], N. Ibrayeva[3], A. Abdraimova[4]. *[1]National Scient Center of Surgery Named A.Syzganova, of Hepatopancreatobiliary Surgery and Liver Transplantation, Almaty, Kazakhstan; [2]National Scient Center of Surgery Named A.Syzganova, of Multidisciplinary Department 1, Almaty, Kazakhstan; [3]National Scient Center of Surgery Named A. Syzganova, Laboratory, Almaty, Kazakhstan; [4]National Scient Center of Surgery Named A.Syzganova, Laboratory, Almaty, Kazakhstan*
Email: bs-immunolog@mail.ru

Background and Aims: The viral hepatitis D is very important problem in Kazakhstan. Cirrhosis in the outcome of chronic hepatitis D (CHD) is the most common cause of liver transplantation in Kazakhstan. The severity of the course of CHD may be dependent on host and viral factors, as CHD is an immune-mediated disease [Grabowski J, Wedemeyer H., 2010].
The aim of the study was to determine the role of cytokines in the progression of liver fibrosis in chronic hepatitis D.
Method: A total of 105 patients with chronic viral hepatitis D and liver cirrhosis in the outcome of viral hepatitis D were examined, 29 men, 76 women in the age 39,1 ± 7,4 years. Patients were examined by blood test, TNF-α, IL-12, IL-17, IL -10, TGFβ1 concentrations in the serum by ELISA (IBL (Germany). The fibrosis stage was determined by Fibroscan-502.
Results: The results showed significant increase of bilirubin depending on the stage of fibrosis ($p = 0.004$), as well as a significant decrease of platelets ($p = 0.0001$), a significant increase of ALT ($p = 0.40$), AST ($p = 0.004$). The results of the level of signaling fibrogenesis molecules showed increase of TNF-α ($p = 0.009$), IL-10 ($p = 0.002$), depending on the stage of fibrosis. Levels of IL17, IL12/23, and TGFβ1 also appeared to be elevated in F3-F4 compared to patients with F0-F2, however, there is no significant. The TNFα has a positive correlation with the level of ALT ($r = 0.358$, $p < 0.0001$), AST ($r = 0.452$, $p < 0.0001$) and negative with creatinine ($r = –0.396$, $p = 0.002$), urea ($r = –0.280$, $p = 0.019$), platelets ($r = –0.290$, $p = 0.005$); and leukocytes ($r = –0.342$, $p = 0.001$). IL-10 has a positive correlation with ALT level ($r = 0.256$, $p = 0.004$), AST ($r = 0.380$, $p < 0.0001$), bilirubin ($r = 0.194$, $p = 0.037$), and negative with albumin ($r = –0.586$, $p = 0.005$), creatinine ($r = –0.389$, $p = 0.003$), urea ($r = –0.267$, $p = 0.026$), platelets ($r = –0.379$, $p < 0.0001$); and leukocytes ($r = –0.382$, $p < 0.0001$). IL-17 has negative significant relationship with ALT and AST ($r = –0.209$, $p = 0.021$ and $r = –0.249$, $p = 0.006$). The level of TGFβ1 in the blood of patients has a positive statistically significant relationship with ALT indices ($r = 0,263$, $p = 0,014$), AST ($r = 0,263$, $p = 0,004$), albumin ($r = 0,600$, $p = 0,004$), total plasma protein ($r = 0,296$, $p = 0,027$), TNF levels α ($r = 0,897$, $p < 0.0001$), IL-10 ($r = 0.665$, $p < 0.0001$), and negative with IL-17 level ($r = –0.677$, $p < 0.0001$) and creatinine ($r = –0.354$, $p = 0.014$).
Conclusion: Progression of fibrosis in chronic HDV infection is associated with the activity of the level of TNF-α and of IL-10, which have a negative relationship with IL-17 and positive association with TGFβ1. An increase in IL12/23 and the presence of a negative correlation of IL-17 with TGFβ1 indicates that the initiation of autoimmune inflammation occurs in the initial stages of fibrosis and during the progression of fibrosis in cirrhosis occurs decrese of severity autoimmune inflammation



Picture 1. The cytokines levels in patients with CHD on the different stages of fibrosis



Picture 2. The IL12 and TGFβ1 levels in patients with CHD on the different stages of fibrosis

FRI-307

Assessment of hospitalizations and comorbidities in 2138 hepatitis B patients followed in diverse specialist care clinics based on administrative data analysis: The Canadian hepatitis B network

C. Coffin[1], A.-A. Shaheen[2], R. Bailey[2], K. Doucette[3], M. Ma[4]. [1]*University of Calgary, Cumming School of Medicine, Calgary, Canada;* [2]*Bailey Health Clinic, Edmonton, Canada;* [3]*University of Alberta, Division of Infectious Diseases;* [4]*University of Alberta, Division of Gastroenterology*
Email: cscoffin@ucalgary.ca

Background: Epidemiological data on chronic hepatitis B (CHB) patients in North American suggest that due to increasing age and adoption of "Western" lifestyle and dietary habits, CHB patients may have significant comorbidities affecting CHB natural history.
Aim: To evaluate the effect of demographics and specific comorbidities on hepatitis B patient ambulatory visits and hospitalization outcomes and to associate these outcomes to type of specialist care.
Methods: We used ambulatory care, hospitalization discharges, and laboratory databases in Alberta, Canada from 2012–2016, to identify CHB patients (HBsAg + ve) who were followed by a specialist. Specialist practice cohorts included community gastroenterology, academic hepatology, liver transplant and infectious diseases. We compared demographics (age, sex), HBV status (HBV DNA, HBeAg serology, ALT), diabetes control (HBA1C ≥6.5%), lipid profile, and CKD (i.e., eGFR <60) between different practices. We evaluated percentage of liver related vs. non-liver related ambulatory care presentations and hospitalizations. We used appropriate statistical methods with two tailed tests in our analyses.
Results: In 2,138 hepatitis B patients (median age 41 y [IQR 33–53], 53% male), the median ALT was 27 (in 93% tested), median HBV DNA 2.4 log IU/ml (in 83% tested), and the majority of those with available HBeAg status (737/2,138) tested HBeAg negative (83%). Overall 5.5% had elevated HBA1C, 2.6% had eGFR <60, and most showed normal lipid profile (median TC, LDL, HDL, TGL was 4.5, 2.6, 1.3, 1.0mmol/l respectively). During the 4-year period, 27% (584/2138) were hospitalized (median length of stay 3 days) but only 10% of hospitalizations were liver related (51/584). Only 13% of ambulatory care visits were liver related (4,710/31,659). Compared to non-liver related admission, CHB patients admitted with liver related causes were older (53 vs 36, $p < 0.01$), male (77% vs. 27%) and had lower eGFR (74 vs. 99, $p < 0.01$) but similar HBA1C and Lipid profile. The rates of liver related admission and ambulatory visits varied per type of specialist care ($p = 0.03$).
Conclusions: In our large cohort of CHB patients, only a small proportion had liver related ambulatory visits or hospitalizations. Older age, male gender and lower kidney function was more common in those with liver related admissions. Additional long-term prospective cohort data is important to determine disease trends for hepatitis B patients in Canada.

FRI-308

Can pre-core region mutations distinguish between HBeAg negative genotype A1 and A2 patients with similar HBV DNA viral load levels?

N. Bolton, M. Bruce, M. Horner, E. Gonsalkorala, G. Dusheiko, K. Agarwal, I. Carey. *Institute of Liver Studies, King's College Hospital, London, United Kingdom*
Email: ivana.kraslova@kcl.ac.uk

Background: A pilot study assessing HBcrAg and HBsAg plasma concentrations in HBeAg negative genotype A patients demonstrated that genotype A2 patients have higher HBcrAg and HBsAg levels than A1 patients despite similar HBV DNA levels. While HBsAg originates from cccDNA and integrated DNA and is encoded by pre-S/S gene, HBcrAg is a new serological marker and combines antigenic reactivity against HBeAg, HBV core antigen and core-related protein (p22cr), and is encoded by pre-core/core gene and can be detected by commercially available assay (Luminex G®, Fujirebio). It is not clear whether mutations within pre-core region (basal core promoter = BCP and pre-core stop codon = PC) can explain this difference in HBcrAg and HBsAg levels between genotypes A1 and A2.
Aims: We aimed to compare the frequency of BCP (A1762T/G1764A) and PC (G1896A) mutations between genotype A1 and A2 HBeAg negative patients matched by HBV DNA.
Method: Plasma samples from 40 HBeAg negative genotype A HBV infected patients (20 patients with genotype A1 vs. 20 patients with genotype A2) (median age 38 years) matched according to HBV DNA (20 patients with HBV DNA <2,000 IU/ml vs. 20 patients with HBV DNA > 20,000 IU/ml) were quantified for HBsAg levels by Abbott Architect® [IU/ml], and HBcrAg by Luminex G® assay [$\log_{10}$U/ml]. The detection of BCP and PC variants was carried out using the INNO-LiPA® line probe assay and confirmed by the direct population sequencing.
Results: Median HBV DNA levels were similar between A1 and A2 (5,400 IU/ml vs. 2,590 IU/ml, $p > 0.05$), in contrast median HBsAg levels were lower in genotype A1 than genotype A2 patients (4,614IU/ml vs. 11,422.5 IU/m, $p = 0.02$) and median HBcrAg concentrations tended to be lower in A1 patients (2.05 $\log_{10}$U/ml vs. 2.8 $\log_{10}$ U/ml, $p = 0.08$). Eight genotype A1 patients (40%) and 4 patients with genotype A2 (20%) possessed the BCP dual variant A1762T/G1764A, while more A2 patients (6 = 30%) than A1 patients (2 = 10%) had the G1896A PC variant. There was no significant association with presence of PC and/or BCP variants with high HBsAg, HBcrAg or HBV DNA levels.
Conclusion: BCP variants (A1762T/G1764A) were more prevalent in A1 patients, whereas PC variants (G1896A) were more frequent in A2 genotype HBeAg negative patients. HBsAg level was significantly higher in A2 patients, although this did not associate considerably with presence of PC and/or BCP variants. Further studies focussing on the pre-S/S region might add more clarity to the dissociation in HBsAg levels between genotype A1 and A2.

FRI-309

Switching immunoglobulin base therapy to nucleoside/nucleotide analogues monotherapy is safe and effective as preventive therapy of reccurent HBV in liver transplanted patients- single centre experience

O. Sneh[1,2], M. Cohen-Naftaly[2,3], Y. Harif[3], A. Issachar[2,3], E. Mor[2,4], R. Tur-Kaspa[1,5], M. Brown[1,6]. *[1]Liver Institute, Rabin medical center, Beilinson hospital, petach tikva, Israel; [2]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, Israel; [3]Liver Institute, Rabin medical center Beilinson hospital, Petach-Tikva, Israel; [4]Rabin medical center beilinson hospital, organ transplantation department; [5]Bar Ilan unviersity, Israel; [6]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel*
Email: orlysneh@gmail.com

Background and Aims: Hepatitis B is common indication for liver transplantation. The recurrence rate of HBV after transplantation decreased dramatically during the 80s due to prophylactic therapy including hepatitis B immunoglobulin(HBIg), and in the introduction of nucleoside/nucleotide (Nuc) analogues reduced the recurrence rates even further. Several studies from Asia demonstrated the effectiveness of 3rd generation Nuc analogues at preventing HBV reactivation after liver transplantation when used as monotherapy. Published data on cessation of HBIg from western world are rather scarce. We aimed to determine the long-term efficacy of nucleot(s)ide monotherapy after cessation of HBIg prophylaxis in patients transplanted due to complications of HBV infection with regard to recurrence of hepatitis, viral replication, and survival.
Method: This is a retrospective study on a prospectively maintained data base. In 2013 we established criteria for interruption of HBIg in liver transplant patients as following- good compliance, at least 2 y post liver transplantation, normal liver function tests, HBeAg negative, viral load less than 2,000 IU/ml at transplantation, undetectable HBV DNA in serum during follow up. The anti-viral therapy had been switched in patients who have been on lamivudine to entecavir or tenofovir.
Results: More than 600 patients were transplanted in our centre, 84 due to HBV. 19 patients were eligible for monotherapy according to the predefined criteria. Six patients were Anti HDV positive and five were transplanted due to HCC. The patients were treated with dual therapy for an average of 8.3+/−4.5y. Twelve patients were treated with lamivudine with negative serum HBV DNA before switching to the newer Nucs. At the time of HBIg cessation, 15 patients treated with entecavir and 4 with tenofovir. During a mean follow up of 3.3+/−1.4 years after HBIG discontinuation there were no hepatitis flares, none of the patients had HBV DNA in serum during follow up, but one of the patients has detectable HBsAg. Two patients had detectable HBsAb, two years after the HBIG was discontinued.
Conclusion: Switching to monotherapy with Nuc analogous in a selected Caucasian population is feasible and is associated with excellent clinical results in liver transplant population including HCC patients and HBV/HDV co-infected patients.

FRI-310

Use of noninvasive biomarkers to assess fibrosis regression in cirrhotic patients during nucleos(t)ide therapy

C. Pan[1], N. Izumi[2], P. Angus[3], A. Duseja[4], E. Nurmukhametova[5], R. Balabanska[6], T. Nguyen[7], J. Yang[8], L. Lin[8], A. Gaggar[8], J.F. Flaherty[8], M. Subramanian[8], S. Ryder[9], W.-L. Chuang[10], P. Marcellin[11]. *[1]NYU Langone Medical Center, NYU School of Medicine, New York, NY, USA; [2]Japanese Red Cross Musashino Hospital, Tokyo, Japan; [3]Austin Health, Heidelberg, Victoria, Australia; [4]Postgraduate Institute of Medical Education and Research, Chandigarh, India; [5]Infectious Clinical Hospital #1 of Moscow Healthcare Department, Moscow, Russia; [6]Tokuda Hospital, Sofia, Sofiya, Bulgaria; [7]Research and Education, Inc., San Diego, CA, USA; [8]Gilead Sciences, Inc., Foster City, CA, USA; [9]Nottingham University Hospital, Nottingham, England, UK; [10]Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [11]Université Paris Diderot, Hôpital Beaujon, Clichy, France*
Email: cpan100@gmail.com

Background and Aims: Noninvasive serum biomarkers for the assessment of liver fibrosis are used in monitoring fibrosis progression in CHB patients. However, limited data is available on the usefulness of these biomarkers in evaluating regression of fibrosis in CHB patients with advanced fibrosis or cirrhosis. The aim of this study is to evaluate commonly used and novel serum biomarkers as a tool in monitoring regression of fibrosis in CHB patients with advanced fibrosis on NUC therapy.
Method: Data from patients with baseline FibroTest score ≥0.75 were pooled across 2 Phase 3 studies evaluating TAF and TDF (GS-US-320–0108 and GS-US-320-0110). Differences in noninvasive biomarkers were evaluated using descriptive statistics of absolute and change from baseline at Weeks 48 and 96 in all patients. Effect of liver inflammation on the noninvasive biomarkers was evaluated in a subgroup analysis between patients with normal and abnormal ALT per AASLD criteria at Week 48. Noninvasive biomarkers evaluated include: FibroTest®, AST-to-platelet ratio index (APRI), fibrosis index based on four factors (FIB-4). Additional analysis using enhanced liver fibrosis panel (ELF), and plasma collagen type III (Pro-C3) will be presented.
Results: 118 patients had FibroTest score ≥0.75 at baseline. The mean (SD) absolute values for FibroTest, APRI, and FIB-4 at Weeks 48 and 96 are shown in the Table. All biomarkers showed an improvement (decline) from baseline at Weeks 48 and 96, with the greatest decline occurring during the first 48 weeks. At week 48, 49 patients had normal ALT and 59 patients had abnormal ALT. Patients with normal ALT had numerically lower FibroTest, FIB-4, and APRI at Week 48 compared to those with abnormal ALT. Patients with abnormal ALT at Week 48 had a greater improvement in fibrosis biomarkers from Week 48 to Week 96 compared to those with normal ALT with mean (SD) FIB-4 of -0.22 (0.81) and APRI of −0.08 (0.60).
Conclusion: Improvement observed with FibroTest, FIB-4, and APRI during the first 48 weeks of initial therapy may over estimate improvement of fibrosis and instead show the impact of liver inflammation. Assessment of these biomarkers compared to ELF and Pro-C3 will be presented.

Table: Serum Marker for Fibrosis in Overall Population and Subset of Patients Stratified by ALT Levels at Weeks 48 and 96

Mean (SD) Absolute Value	FibroTest	FIB-4	APRI
Overall	n = 118	n = 111	n = 111
Baseline	0.84 (0.06)	3.71 (2.31)	2.40 (1.95)
Week 48	0.70 (0.17)	2.23 (1.32)	0.71 (0.55)
Week 96	0.70 (0.17)	2.02 (1.28)	0.63 (0.73)
Normal ALT at Week 48	n = 49	n = 48	n = 48
Week 48	0.63 (0.18)	1.86 (0.95)	0.44 (0.27)
Week 96	0.63 (0.19)	1.79 (1.16)	0.41 (0.28)
Abnormal ALT at Week 48	n = 58	n = 56	n = 58
Week 48	0.76 (0.13)	2.55 (1.50)	0.94 (0.61)
Week 96	0.75 (0.12)	2.15 (1.24)	0.80 (0.91)

FRI-311

HLA-G 3′UTR polymorphism are associated with different patterns of tissue expression and severity of liver injury in chronic hepatitis B infection

S. Ferreira[1], S.G.F. Chachá[1,2], F.C. Dias[3], R.d.C. Santana[4], J.C. de Oliveira Crispim[5], M.O. Brunaldi[6], C. Mendes-Junior[7], L.N.Z. Ramalho[8], E. Donadi[3], A.d.L.C. Martinelli[1]. *[1]School of Medicine of Ribeirão Preto, University of São Paulo (FMRP-USP), Division of Gastroenterology, Department of Medicine, Ribeirão Preto, Brazil; [2]University Federal of São Carlos (UFSCAR), Department of Medicine, São Carlos, Brazil; [3]School of Medicine of Ribeirão Preto, University of São Paulo (FMRP-USP), Division of Clinical Immunology, Department of*

Medicine, Ribeirão Preto, Brazil; [4]School of Medicine of Ribeirão Preto, University of São Paulo (FMRP-USP), Division of Infectious Diseases, Department of Medicine, Ribeirão Preto, Brazil; [5]School of Pharmaceutical Sciences, Federal University of Rio Grande do Norte (UFRN), Department of Clinical and Toxicology Analysis, Natal, Brazil; [6]School of Medicine of Ribeirão Preto, University of São Paulo (FMRP-USP), Department of Pathology, Ribeirão Preto, Brazil; [7]Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto (FFCLRP - USP), Departamento de Química, Ribeirão Preto, Brazil; [8]School of Medicine of Ribeirão Preto, University of São Paulo (FMRP-USP), Division of Gastroenterology, Department of Medicine, Ribeirão Preto
Email: sandrocferreira@terra.com.br

Background and Aims: HLA-G is a non-classical class I histocompatibility molecule with well-recognized immunomodulatory properties, frequently expressed in the livers of hepatitis B virus (HBV)-infected patients. We evaluated the genetic diversity of *HLA-G* 3′ untranslated region (3′UTR) and associated polymorphic sites and its association with the expression of HLA-G in liver biopsies and the severity of liver injury in patients with chronic hepatitis B.
Method: Polymorphic sites at 3′UTR (14bp DEL/INS, +3001C/T, +3003C/T, +3010C/G, +3027A/C, +3032G/C, +3035C/T, +3142C/G, +3187A/G, +3196C/G and +3227G/A) were characterized by sequencing analyses in blood samples of 106 chronic HBV-infected patients and 157 healthy individuals. The immunohistochemistry expression of HLA-G was performed on 106 liver biopsies in patients with chronic hepatitis and classified as mild, moderate or intense according to the pattern of HLA-G tissue expression.
Results: The frequencies of the +303 T allele (p = 0.022) and the +303 TT genotype (p = 0.042) were overrepresented and the +3187 A allele (p < 0.001) and +3187 AA genotype (p < 0.001) were underrepresented in HBV-infected patients when compared to healthy controls. The frequencies of UTR-1 (p = 0.001) and UTR-4 (p = 0.034) haplotypes were respectively over and underrepresented in in HBV-infected patients. The frequencies of the 14 bp DEL/DEL (p = 0.046) and the +3010 GG genotypes (p = 0.026) were significantly increased in the group of patients with mild fibrosis when compared to patients with severe fibrosis/cirrhosis. The +3003 T allele (p = 0.034) and +3003 TT genotype (p = 0.028) were overrepresented in patients with severe liver fibrosis. The frequencies of the 14bp DEL allele (p = 0.047) and the 14bp DEL/DEL genotype (p = 0.034) were significantly increased in liver samples with mild HLA-G expression when compared to those with intense HLA-G expression. On the other hand, the allele +3142 G (p = 0.007), genotype +3142 GG (p = 0.034), allele +3010C (p = 0.004) and genotype +3010 CC (p = 0.015) were significantly associated with intense HLA-G expression. The UTR-4 haplotype (p = 0.034) was significantly associated with mild HLA-G expression.
Conclusion: *HLA-G* 3′UTR polymorphisms were associated with the magnitude of HLA-G expression in the liver and with severity of liver injury in HBV-infected patients.

FRI-312
Prophylactic antiviral therapy for the prevention of mother-to-child transmission of hepatitis B virus can be stopped at delivery
Q.-L. Zeng[1], G.-H. Xu[2], B. Wang[3], Z.-Q. Li[1], Z.-J. Yu[1]. *[1]Department of Infectious Diseases and Hepatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China; [2]Department of Infectious Diseases, The Affiliated Hospital of Yan'an University, Yan'an 716000, Shaanxi Province, China; [3]Department of Gynaecology and Obstetrics, Beijing Tsinghua Changgung Hospital, School of Clinical Medicine, Tsinghua University, Beijing 102218, China*
Email: 15838120512@163.com

Background and Aims: Many studies have demonstrated that antiviral therapy has an important role in the prevention of mother-to-child transmission of hepatitis B virus (HBV). However, three Regional HBV Guidelines recommend various stopping time points of therapy.
Method: In our observational retrospective study, 35 immune-tolerant pregnant women received telbivudine at week 28 of gestation, and discontinued at delivery, month 1, and month 3 postpartum, respectively (Table 1). All the newborns received 200 IU of hepatitis B immune globulin and 10 μg of the HBV vaccine

Table 1 (abstract: FRI-312): Characteristics of the mothers and infants

Characteristic	Group 1 (n = 12)	Group 2 (n = 12)	Group 3 (n = 11)
Age (years)	25.3 ± 4.7	24.8 ± 5.3	26.2 ± 4.0
Maternal HBV DNA levels (log_{10}IU/ml)			
Gestational week 28	7.8 ± 0.7	8.0 ± 0.7	7.9 ± 0.7
At delivery	5.6 ± 0.7	5.7 ± 0.6	5.5 ± 0.7
Postpartum month 1	n.d.	4.7 ± 0.3	4.9 ± 0.6
Postpartum month 3	n.d.	n.d.	3.8 ± 0.5
Postpartum month 7	8.0 ± 0.7	8.0 ± 0.6	7.9 ± 0.4
HBV DNA reduction at delivery	2.3 ± 0.5	2.4 ± 0.6	2.4 ± 0.7
<200,000IU/ml at delivery, n (%)	4 (33.3)	4 (33.3)	3 (27.3)
Maternal ALT levels (U/l)			
Gestational week 28	22.9 ± 7.4	24.9 ± 9.8	27.1 ± 7.7
At delivery	20.7 ± 8.5	17.6 ± 7.3	22.1 ± 9.4
Postpartum month 1	n.d.	23.2 ± 10.7	26.5 ± 10.1
Postpartum month 3	n.d.	n.d.	17.0 (12.0–37.0)
Postpartum month 7	20.0 (14.8–38.3)	24.1 ± 11.1	26.6 ± 13.5
Infant characteristics at birth			
Number of infants	12	12	11
Gestational age (weeks)	38.2 ± 1.4	38.8 ± 1.2	38.9 ± 1.3
Delivery by means of C-section, n (%)	7 (58.3)	6 (50.0)	6 (54.5)
Breast feeding for the first six months, n (%)			
Exclusive breast feeding	8 (66.7)	9 (75.0)	8 (72.7)
Mixed feeding	3 (25.0)	1 (8.3)	2 (18.2)
Artificial feeding	1 (8.3)	2 (16.7)	1 (9.1)
Infant characteristics at month 7			
Detectable HBV DNA, n (%)	0 (0)	0 (0)	0 (0)
Positive HBsAg, n (%)	0 (0)	0 (0)	0 (0)
ALT (U/l)	18.0 (12.3–29.5)	20.1 ± 7.4	19.9 ± 5.3

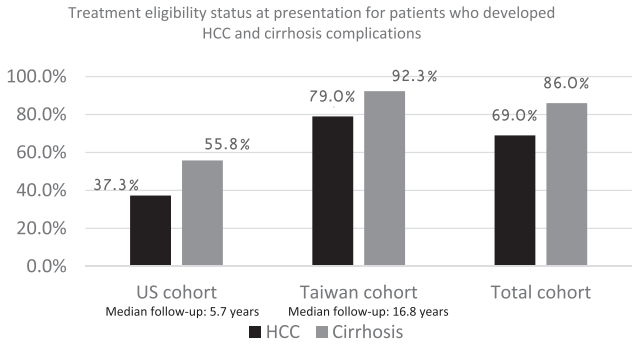
ALT, alanine aminotransferase; C-section, cesarean section; HBsAg, Hepatitis B surface antigen; HBV, hepatitis B virus; n.d., no data. When the data had normal distributions, they were presented as mean ± standard deviation; and for abnormal distributions, median (inter-quartile range) was used.

intramuscularly within 12 hours after birth, and 10 μg of HBV vaccine at months 1 and 6, respectively. The primary outcome was the rate of mother-to-child transmission at 7 months old.
Results: The durations of telbivudine treatment before delivery were 10.2 ± 1.4, 10.8 ± 1.2, and 10.9 ± 1.3 weeks in groups 1, 2, and 3, respectively (Table). The overall percentage of mothers who had an HBV DNA level of <200,000 IU/ml at delivery was 31.4% (11/35). At month 7, no infants had HBV viremia or were hepatitis B surface antigen-positive.
Conclusion: Conclusively, antiviral prophylaxis in immune-tolerant pregnant women can be stopped at delivery based not only on current study but also at least in part on the pharmacoeconomic concerns; and future validation studies are needed.

FRI-313
Validation of AASLD treatment guideline eligibility based on disease outcomes of large community and clinical cohorts of chronic hepatitis B patients

D.H. Lee[1,2], A. Le[2], M. Chung[2,3], V.H. Nguyen[2,4], T. Johnson[2,4], F. Ji[2,5], E. Ogawa[2,6], H.N. Trinh[7], J. Zhang[8], C. Wong[9], C. Wong[9], J. Li[10], H.-I Yang[11], M. Nguyen[12]. *[1]Good Gang-An Hospital, Internal Medicine, Korea, Rep. of South; [2]Stanford University, Division of Gastroenterology and Hepatology, United States; [3]Princeton University, United States; [4]University of California, Berkeley, United States; [5]The Second Affiliated Hospital of Xi' an Jiaotong University, Infectious Disease, China; [6]General Internal Medicine, Japan; [7]San Jose Gastroenterology, United States; [8]Chinese Hosiptal, United States; [9]Wong Clinic, United States; [10]Palo Alto Medical Foundation, United States; [11]Academia Sinica, Genomics Research Center, Taiwan; [12]Stanford University, Division of Gastroenterology and Hepatology, United States*
Email: mindiehn@stanford.edu

Background and Aims: The ultimate goal of treatment in chronic hepatitis B patients (CHB) patients is to improve quality of life and survival by preventing progression of the disease. However, treatment decision by current guidelines is based on surrogate tests, such as ALT and HBV DNA. Therefore, it remains unclear whether current guidelines can adequately identify patients who will benefit from treatment to avoid adverse outcomes in the long term.
Method: A total of 5,030 CHB patients from a US cohort of 6 academic and community clinical centers and 3,653 patients from the community-based Taiwanese REVEAL-HBV cohort were included. Exclusion criteria were age <18years, HCV/HIV/HDV co-infection, <1year of follow-up and prior treatment. We initially captured patients who developed adverse outcomes. In the US cohort, these were defined as HCC, cirrhosis and/or liver-related death and in the Taiwan cohort, HCC and/or liver cirrhosis were captured. Utilizing AASLD 2015 CHB treatment guideline, we evaluated patient eligibility for antiviral treatment at baseline and during follow-up.
Results: In the US cohort, a total of 202 patients developed adverse outcomes. Among these patients, 39.6% (80/202) were treatment ineligible at baseline (Figure). Of these, 63.8% (51/80) remained ineligible on median follow-up time of 5.7 years. In total, 25.2% (51/202) never met treatment criteria prior to development of adverse events. In the Taiwan cohort, with a longer median follow-up of 16.8 years, 476 patients or 13.1% developed adverse outcomes. In these patients, 86.3% (411/476) were treatment ineligible at baseline and 24.1% (99/411) of these patients remained ineligible on follow-up. A total of 20.8% (99/476) never met treatment criteria.
Conclusion: We found that close to half of patients who developed adverse outcomes did not meet guideline treatment criteria at presentation and one quarter never met guideline criteria prior to development of adverse events among patients at US clinical centers. In the population based community cohort from Asia, we found even higher rates of baseline treatment eligibility and one-fifth never met guideline criteria on follow-up. Current treatment guidelines should thus address patients who progress to serious liver related complications.



FRI-314
Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B

Y.B. Lee, Y. Ha, Y.E. Chon, M.N. Kim, J.H. Lee, H. Park, K.S. Rim, S.G. Hwang. *CHA Bundang Medical Center, CHA University, Department of Internal Medicine, Seongnam, Korea, Rep. of South*
Email: yunbin@hanmail.net

Background and Aims: As nonalcoholic fatty liver disease becomes a worldwide epidemic, hepatic steatosis has been frequently demonstrated in chronic hepatitis B patients without excessive alcohol intake. Whether presence of hepatic steatosis in these patients is associated with higher risk of developing hepatocellular carcinoma (HCC) has not been well established. We investigated the impact of histologically proven hepatic steatosis on the risk of HCC development.
Method: Chronically hepatitis B virus-infected patients without significant alcohol consumption, who underwent liver biopsy from January 2007 to December 2015 in a single centre, were consecutively included. Patients were categorised into two groups according to the presence or absence of hepatic steatosis ≥ 5%, and the association of steatosis with subsequent HCC risk was analysed. To adjust for differences in patient characteristics including metabolic features, inverse probability weighting (IPW) using propensity scores was used.
Results: Hepatic steatosis was histologically proven in 70 patients (21.8%) among a total of 321 patients. During the median (interquartile range) follow-up of 5.3 (2.9–8.3) years, 17 of 321 patients (5.3%) developed HCC: 9 of 251 patients (3.6%) without steatosis and 8 of 70 patients (11.4%) with steatosis. The 5-year cumulative incidences of HCC were 1.9% and 8.2% among patients without steatosis and with steatosis, respectively (p = 0.004) (Figure A). Steatosis was associated with higher risk of HCC development (adjusted hazards ratio [HR], 3.005; 95% confidence interval [CI], 1.122–8.051; p = 0.029). After balancing with IPW, the incidences of HCC were not significantly different between the groups (p = 0.187) (Figure B), and the association between steatosis and HCC development was not significant (adjusted HR, 2.292; 95%CI, 0.693–7.587; p = 0.17).
Conclusion: Hepatic steatosis was associated with higher risk of developing HCC in patients with chronic hepatitis B. However, the association of steatosis per se with HCC development was not evident after adjustment for metabolic characteristics.

FRI-315
Quantitative Hepatitis B surface antigen in different phases of Vietnamese chronic HBV infected patients

H. Nguyen, H. Pham. *University of Medicine and pharmacy at Ho chi Minh city, Infectious diseases, Ho Chi Minh, Viet Nam*
Email: camhuong37@yahoo.com

Background and Aims: Quantitative serum HBsAg has been considered as a marker that reflects the effect of immune clearance on HBV in chronic hepatitis B patients (CHB). Serum HBsAg level

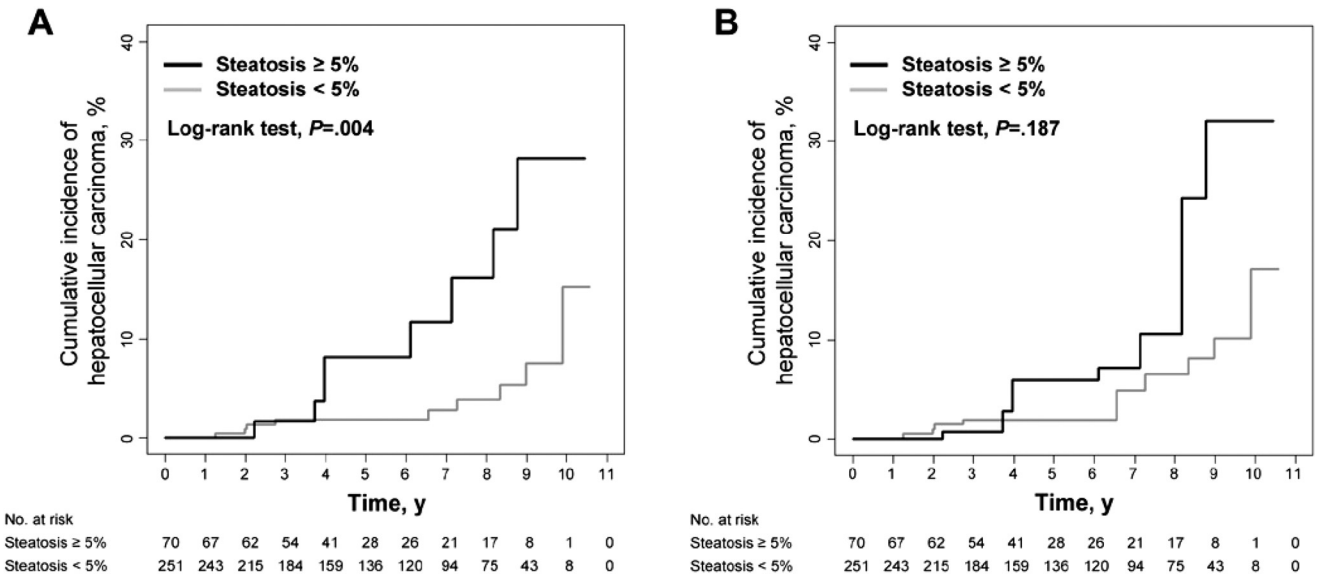


Figure 1: FRI-314

varies in different phases of infection and by genotypes. We aimed to investigate serum HBsAg levels and its correlations with HBVDNA in different phases of Vietnamese CHB.

Method: 450 CHB treatment naïve patients (187 genotype B and 113 genotype C) were recruited in this cross-sectional study. Patients were categorized into 6 groups: Chronic HBV infection HBeAg positive (HBIe+, n = 48), Chronic hepatitis B HBeAg positive (CHBe+, n = 66), Chronic HBV infection HBeAg negative (HBIe- n = 98), Chronic hepatitis B HBeAg negative (CHBe- n = 103), Cirrhosis (n = 63) and HCC (n = 72). The serum HBsAg was measured by ECLIA, using Elecsys HBsAgII kit (Roche). Correlations between HBsAg and HBVDNA were analyzed by Spearman's Rho correlation.

Results: There was no difference of HBsAg levels between genotype B and C. The median HBsAg titers were different between phases of CHB ($p < 0.001$) and significantly higher in HBeAg (+) than that in HBeAg (-) patients. The highest HBsAg level and the narrowest distribution was found in HBIe+ (4.6 log 10 IU/ml), lower in CHBe+ (3.83 log 10 IU/ml), HBIe- (2.8 log 10 IU/ml) and in CHBe- (3.11 log 10 IU/ml), cirrhosis (2.96log10IU/ml) and HCC (3.01log10IU/ml). There were significant correlations between HBsAg and HBVDNA levels in the overall population ($r = 0.572$, $p < 0.001$); The moderate correlations were found in CHBe+ ($r = 0.434$, $p < 0.001$), CHBe- ($r = 0.417$, $p < 0.001$) and HBIe- ($r = 0.393$, $p = 0.002$); The weak correlation was found in HBIe+ ($r = 0.299$, $p = 0.039$) and in the HCC groups ($r = 0.277$, $p = 0.049$). There was not significant correlation between HBsAg and HBVDNA in the cirrhosis group. The ratios of HBsAg/HBVDNA were all distributed around 0.5. Interestingly, the HBIe- group had a widest distribution of HBsAg values and had more cases with high HBsAg values that contributed for the highest ratio of HBsAg/HBVDNA (0.86).

Conclusion: Our study demonstrated that serum HBsAg levels were significantly different in natural phases of chronic HBV infection and was a helpful marker for immune activation; HBsAg were significantly correlated with HBVDNA in all CHB phases but not well correlated in the CHB patients with HCC and cirrhosis. The wide distribution of HBsAg in the HBIe- group suggested the existence of non cccDNA source of HBsAg (the integration source) in this phase.

FRI-316

HBeAg negative chronic hepatitis B patients with HBV-DNA levels between 2,000–20,000IU/ml and normal aminotransferases are really inactive?

B. Ergül[1], Özlem Gül Utku[1], Barış Yılmaz[2], Hüseyin Köseoğlu[2], D. Oğuz[1]. *[1]Kırıkkale University Faculty of Medicine, Gastroenterology, Kırıkkale, Turkey; [2]Hitit University Faculty of Medicine, Gastroenterology, Çorum, Turkey*
Email: bilalergul@gmail.com

Background and Aims: Hepatitis B virus is one of the most important causes of chronic hepatitis, cirrhosis and liver cancer. It is estimated that more than 350 million people are infected worldwide. International guidelines recommend performing biopsy and beginning antiviral therapy to HBeAg negative chronic hepatitis B with HBV-DNA ≥ 2,000 IU/ml and elevated ALT levels. But, datas are limited about HBeAg negative chronic hepatitis B patients with HBV DNA between 2,000 and 20,000 IU/ml and persistently normal ALT levels.

Method: In this study, files of patients who were biopsied due to chronic hepatitis B in Kırıkkale University Faculty of Medicine, Hitit University Faculty of Medicine, Ahi Evran University Training and Research Hospital and Çankırı State Hospital Gastroenterology Clinics between January 2014 and May 2017 were retrospectively evaluated. *Patients were included* in the *study* according to the following criteria: HBeAg negative chronic hepatitis B patients with HBV DNA between 2,000–20,000 IU/ml and persistently normal ALT levels. Persistently normal ALT was defined as 4 consecutive ALT values within a period of 12 months. Exclusion criterias are as follows: history of antiviral therapy, HCV or HDV coinfection, history of cirrhosis or hepatocellular carcinoma and pregnancy. Liver biopsy specimens were evaluated according to Ishak scoring system. Antiviral therapy was started if fibrosis stage ≥2 and/or HAI ≥6.

Results: A total 130 patients were enrolled. The mean age of the study population (72 female, 58 male) was 45.98 (21–73). These patients had a mean ALT: 24.7 (7–40) IU/l, AST: 22.5 (10–38)IU/l, HBsAg: 6342 (1789–10600), HBV-DNA: 8061 (2186–20000)IU/ml. Ninety-seven patients (74.6%) had fibrosis stage ≥ 2 and/or HA ≥6. Of the 33 patients whose treatment could not be started, 21 were over 40 years old (21/91) and 12 were under 40 years old (12/39). There was no significant difference between the rates of treatment initiation of patients older than 40 or under 40 years ($p = 0.35$). HBV-DNA was

found to be 8458 (± 579) IU/ml in the treatment group and 6892 (± 793)IU/ml in the untreated group, and no significant difference was detected between the groups in terms of HBV-DNA (p = 0.11).
Conclusion: Pathological examination of liver biopsies revealed that 74.6% of the patients had significant liver damage and treatment was started. Liver biopsy which is the gold standard method in evaluating chronic hepatitis and fibrosis should be performed for HBeAg negative chronic hepatitis B patients with HBV-DNA levels between 2,000–20,000 IU/ml even though transaminase levels were within normal limits.

FRI-317

Which pregnancy biomarkers predict post-delivery ALT flares in mothers with chronic hepatitis B?

S. Imbert[1], M. Bruce[2], S. Montague[2], M.-A. Mcleod[2], T. Bowyer[2], M. Horner[2], G. Dusheiko[2], K. Agarwal[2], I. Carey[2]. *[1]King's College London, Institute of Liver Studies, London, United Kingdom; [2]King's College Hospital, Institute of Liver Studies, London, United Kingdom*
Email: salome.imbert@kcl.ac.uk

Background: Chronic Hepatitis B (CHB) is an immune mediated disease and the interaction of the virus with the immune system determines its outcome. While pregnancy induces immune tolerance, post-delivery phase is characterised by the immune system reconstitution and ALT flares in 30% of CHB patients. There are no clear in-pregnancy non-invasive markers to predict post-delivery ALT flares. CXCL10 (IP-10) is a chemokine produced by innate immune system within the liver and high plasma levels reflect liver necroinflammation and predict HBeAg seroconversion or HBsAg decline/loss. Hepatitis B core-related antigen (HBcrAg) is a novel serological marker combining antigenic reactivity against HBeAg, HBV core Ag and core-related protein (p22cr) and reflects cccDNA transcriptional activity.
Aims: In this single centre cross-sectional study we explored whether non-invasive markers at 2nd pregnancy trimester including IP-10 and HBcrAg can predict post-delivery ALT flares.
Methods: 201 pregnant CHB patients with plasma samples at 2nd pregnancy trimester (median gestation 26 weeks) and known ALT levels after delivery (median 75 days) were enrolled: 74 patients required therapy with tenofovir (34 due to liver disease & 40 to prevent transmission); 127 patients were therapy naïve. Plasma levels of IP-10 by ELISA [pg/ml], HBV DNA by TaqMan PCR [IU/ml], HBeAg status and HBsAg by Abbott Architect® [IU/ml] and HBcrAg on Luminex G [$\log_{10}$U/ml] were quantified and HBV genotypes were determined by direct sequencing.
Results: 54/201 (27%) patients had post-delivery ALT flares (ALT > 38I U/l and 2-fold increase from pregnancy level) and these were predominant in genotype B & C patients (genotype B&C: 60% = 31/52 vs. genotype A, D & E: 15% = 23/149, p < 0.01). 54 patients were HBeAg positive and had more flares than HBeAg negative (44% = 24/54 vs. 20% = 30/147, p < 0.05, OR 6.12). Pregnancy ALT, HBV DNA and HBsAg did not differ between flare and no flare patients, but flare patients had higher IP-10 and HBcrAg concentrations (medians IP-10: 66.6 vs. 16.7 pg/ml, p < 0.01; HBcrAg: 4.2 vs. 2.65 $\log_{10}$U/ml p < 0.01). When untreated and treated patients were assessed separately; HBV genotypes, HBeAg status, IP-10 and HBcrAg levels differed between no flare and flare patients. For those treated: 36 patients had HBV DNA >200,000 IU/ml; this was associated with more flares (44% = 16/36) than patients with low HBV DNA (23% = 38/165), p < 0.01, OR 2.63. ROC analysis confirmed that plasma IP-10 pregnancy levels were a good predictor (AUROC = 0.82, p < 0.01) and HBcrAg levels were a fair predictor (AUROC = 0.69, p < 0.01).
Conclusions: Pregnancy HBcrAg levels > 5$\log_{10}$ U/ml (OR 3.43, p < 0.01) and IP-10 levels >80 pg/ml predicted post-delivery flares (OR 100.69, p < 0.01) and can act as good non-invasive biomarkers allowing tailored management of CHB in the context of pregnancy. Larger validation studies to confirm the utility of these markers are required.

FRI-318

Adherence to AASLD treatment guidelines on treatment initiation among treatment-eligible patients with chronic hepatitis B: Experiences from primary care and referral practices

V.H. Nguyen[1,2], A. Le[1], M. Chung[1], T. Johnson[1,2], B. Levitt[3], H. Nguyen[3], K. Nguyen[3], H. Trinh[3], C. Wong[4], C. Wong[4], J. Zhang[5], J. Li[6], G. Garcia[1], M. Nguyen[1]. *[1]Stanford University Medical Center, Division of Hepatology and Gastroenterology, Palo Alto, United States; [2]University of California, Berkeley; [3]San Jose Gastroenterology, San Jose, United States; [4]Wong Clinics, San Francisco, United States; [5]Chinese Hospital, San Francisco, United States; [6]Palo Alto Medical Foundation, Gastroenterology, Mountain View, United States*
Email: mindiehn@stanford.edu

Background and Aims: The American Association for the Study of Liver Diseases (AASLD) treatment guidelines for chronic hepatitis B (CHB) patients have changed over time. We aimed to assess the rate of optimal evaluation, treatment eligibility, and treatment initiation for CHB patients in various practice settings in the United States (US).
Method: This was a retrospective cohort study of 4,130 consecutive, treatment-naïve patients with CHB by community primary care physicians (PCP) (n = 616), community gastroenterologists (GI) (n = 2,251), and university hepatologists (n = 1,263) from January 2002 to December 2016. Eligibility was defined by the AASLD criteria and adjusted based on changes over time of the criteria for three lab tests: alanine aminotransferase (ALT), hepatitis B e antigen (HBeAg), and hepatitis B virus (HBV) DNA. Eligibility was assessed in the first 6 months of follow-up. Eligible patients was treated if they were on treatment by 12-month follow-up. The follow-up period was up to 5 years.
Results: By 6-month follow-up, 36.69% of patients had all three lab tests in PCP group, 59.80% in GI, and 79.97% in hepatology (p < 0.0001). All three groups had low eligibility rates:12.76% in PCP group, 24.96% in GI, and 29.43% in hepatology (p < 0.0001). Treatment rates were 38.71% in PCP group, 55.65% in GI, and 57.90% in hepatology (p < 0.0001). Being male (OR: 1.40, 95% CI: 1.09–1.79, p = 0.008); referral to hepatologists (OR: 2.58, 95%CI: 1.45–4.59, p = 0.001); and having positive HBeAg (OR: 1.87, 95%CI: 1.14–3.05, p = 0.013) were the strongest predictors for treatment initiation. Of 3,018 CHB patients who were initially treatment-ineligible, 8.98% became eligible in PCP group, 22.95% in GI, and 14.14% in hepatology (p < 0.0001). Of these patients, hepatology had the highest treatment rate of 81.97%, followed by GI with 61.54%, and lowest in PCP group with 23.91% (p < 0.0001). The strongest predictors for treatment initiation were male gender (HR:1.42, 95%CI 1.06–1.90, p = 0.017); referral to community GI (HR: 3.03, 95%CI: 1.11–8.24, p = 0.03); and having an elevated HBV DNA level (HR: 1.17, 95%CI: 1.04–1.20, p = 0.004). Cumulative incidence of treatment initiation via Kaplan-Meier methods showed higher treatment initiation in GI and hepatology group compared to PCP group in follow-up period (p = 0.006).
Conclusion: The overall treatment rates by 12-month follow-up after diagnosis and in long-term follow-up were significantly low especially for treatment-eligible patients seen by primary care physicians.

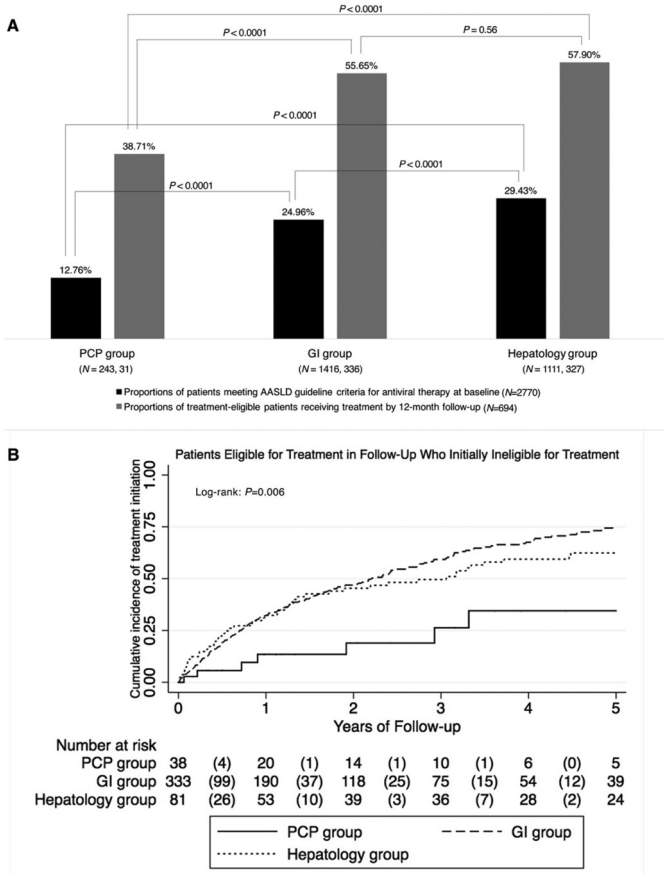


Figure (A) Proportions of eligible patients by 6-month follow-up (n = 2770) and proportions of eligible patients receiving treatment by 12-month follow-up (n = 694); (B) Cumulative incidence of treatment initiation during follow-up by practice settings(n = 452)

Viral hepatitis B/D: Therapy

FRI-319

Durability of HBsAg loss during or after antiviral treatment in a predominantly middle European collective

G. Teuber[1], M. Sprinzl[2], D. Hüppe[3], R. Heyne[4], W.P. Hofmann[5], M. Cornberg[6], S. Arne[7], J. Petersen[8]. *[1]Praxis PD Dr. med. G: Teuber, Frankfurt/M, Germany; [2]UNI-Klinikum, I. Medizinische Klinik, Mainz, Germany; [3]Center of Gastroenterology, Center of Gastroenterology, Herne, Germany; [4]Leberzentrum am Checkpoint, Leberzentrum am Checkpoint, Berlin, Germany; [5]Praxis Wolf Peter Hofmann, Berlin, Germany; [6]Department of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [7]Diabetes Zentrum Mergentheim, Diabetes Zentrum Mergentheim, Bad Mergentheim, Germany; [8]IFI-institute for interdisciplinary medicine, Hamburg, Germany*
Email: gerlinde.teuber@t-online.de

Background and Aims: Concerning the durability of HBsAg loss during or after antiviral treatment only a few data are available indicating a high rate of reactivation with reccurance of HBsAg and/or HBV-DNA of up to 16% in Asian patients. This may be due to the high percentage of patients with perinatal infection in these countries. There are no data from european patients available concerning the durability of HBsAg loss during or after antiviral treatment and the impact on further clinical outcome.

Method: In this retrospective german multicentre study, 143 patients with chronic hepatitis B (mean age: 43 ± 13.8 years, 93 males, 50 females) who lost HBsAg during or after antiviral treatment with peginterferon-α and/or nucleos(t)ides between april 2008 and july 2014 were included. Before antiviral treatment, 15 patients had established liver cirrhosis and 2/15 hepatocellular carcinoma, receiving partial liver resection. Primary end points were reactivation with reccurrence of HBsAg Further endpoints were clinical progressive liver disease, liver transplantation and death.

Results: During the follow-up period (mean: 3.0 ± 2.1 years) a recurrence of HBsAg was observed in only 3/143 patients (2.1%), none with previous seroconversion to Anti-HBs. The HBV reactivation in these patients was not associated with detectable HBV-DNA levels or a rise in ALT-levels. 2/3 patients had baseline cirrhosis and 1/2 subsequently died due to recurrent multifocal hepatocellular carcinoma. Among the 140 patients with persisting HBsAg loss, two initially cirrhotic patients died and one received liver transplantation all due to hepatocellular carcinoma.

Conclusion: In a predominantly caucasian patient population HBsAg loss during and/or after antiviral treatment seems to be durable with low rates of reactivation. Cirrhotic patients, however, have a high risk for developing hepatocellular carcinoma even after HBsAg loss and regular surveillance in these patients seems to be mandatory.

FRI-320

The effect of PEG-IFN add on or switch to on HBsAg clearance in HBeAg- CHB patients recieving entecavir treatment

L. Yan, Y. Xu, L. Chen, Y. Ding, Q. Xie, H. Wang. *Shanghai Jiaotong University School, Department of Infectious Diseases and Hepatology, Shanghai, China*
Email: wanghuirj@163.com

Background and Aims: Chronic hepatitis B (CHB) patients rarely achieve HBsAg loss with nucleoside/nucleotide analogue (NA) therapy. It was evaluated HBsAg loss in HBeAg$^-$ patients with entecavir switched to or added on pegylated interferon (PEG-IFN) in a retrospective study.

Method: Totally 87 HBeAg$^-$ CHB patients treated with entecavir for 24 weeks were studied, 21 switched to PEG-IFN, 13 added on PEG-IFN and 53 continued entecavir therapy (ETV group).

Results: HBsAg clearance at week 48 was reported in 2/21 (10%) patients in switch-to group, 2/13 (15%) patients in add-on group; whereas none was in ETV group. HBsAg reduction at week 48 was 1.055logIU/ml, 0.6452 logIU/ml or 0.014 logIU/ml respectively in switch-to, add-on, or ETV group. The response rate of switch-to, add-on and ETV monotherapy was, 44%, 38% or 2%, respectively. It was analysed that age, BMI, ALT, AST, PLT, liver stiffness, HBsAg titer at baseline, or HBsAg reduction at 24-week, showing that HBsAg titers at baseline and HBsAg reduction at week 24 were associated with HBsAg reduction and clearance. HBsAg reduction was associated with the response rate at week 24, showing that ROC Curve analyse the response versus HBsAg at week 48, the AUROC was 0.865. The PPV for response was 70% and NPV was 100% with the cut-off value 0.2logIU/ml.

Conclusion: In summary, we demonstrated that PEG-IFN enhanced HBsAg loss in HBeAg$^-$CHB population. Patients with HBsAg titers at baseline less than 1000 IU/ml and HBsAg reduction more than 0.2logIU/ml achieved HBsAg loss with a higher chance.

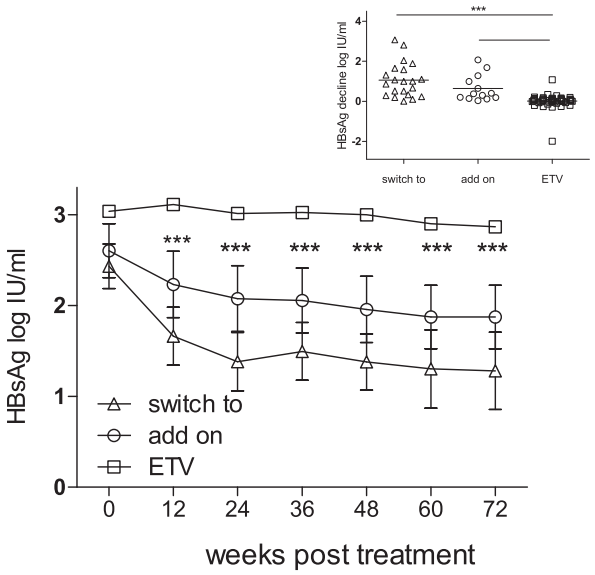


Figure1 HBsAg dynamic change from week to 72
figure inset HBsAg decline in week 48 from baseline

FRI-321

A virological response to PEG-IFNa treatment of hepatitis delta is associated with an improved clinical long-term outcome: 10 years follow-up of the HIDIT-1 study

A. Wranke[1], C. Yurdaydin[2], B. Heidrich[1], Z. Kalliopi[3], K. Yalcin[4], T. Fehmi[5], U. Akarca[6], F. Lammert[7], D. Häussinger[8], T. Müller[9], M. Wöbse[1], M.P. Manns[10], H. Wedemeyer[11], S. Hardtke[1,12]. *[1]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology; [2]Ankara University School of Medicine, Department of Gastroenterology, Ankara, Turkey; [3]University of Thessaly, Department of Medicine and Research Laboratory of Internal Medicine, Larissa, Greece; [4]Dicle University, Medical Faculty, Diyarbaki, Turkey; [5]Cerrahpasa School of Medicine, Istanbul University, Department of Infectious Diseases, Istanbul, Turkey; [6]Ege University School of Medicine, Department of Gastroenterology, Izmir, Turkey; [7]Saarland University Medical Center, Department of Medicine Ii, Homburg, Germany; [8]Heinrich Heine University, Department of Gastroenterology, Hepatology and Infectious Diseases, Düsseldorf, Germany; [9]Charite- Universitätsmedizin, Medizinische Klinik m. S. Hepatologie und Gastroenterologie, Berlin, Germany; [10]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [11]Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany; [12]German Center for Infection Research (DZIF), Partner Site HepNet Study-House, Hannover, Germany*
Email: hardtke.svenja@mh-hannover.de

Background and Aims: Hepatitis delta virus (HDV) infection causes the most severe form of chronic viral hepatitis associated with accelerated fibrosis progression and an increased risk for developing liver-related clinical complications. PEG-interferon alpha results in HDV RNA suppression in 25–30% of patients but late HDV RNA relapses occur and the impact on the development of clinical endpoints is unclear. The aim of this study was to investigate the long-term outcome after a 48 weeks course of PEG-IFNa therapy.
Method: We performed a retrospective follow-up study of patients included in the HIDIT1 trial (Wedemeyer H. et al., NEJM 2011). Patients received 48 weeks of treatment with either peginterferon alfa-2a plus adefovir dipivoxil (Group I), peginterferon alfa-2a alone (Group II), or adefovir dipivoxil alone (Group III). Liver related complications were defined as liver-related death, liver transplantation, HCC and hepatic decompensation (Child Pugh B,C or an increase in MELD of five or more points in relation to baseline values). Patients were censored for further analysis when patients were (re-) treated with PEG-IFNa.
Results: Follow-up data (at least 1 visit beyond post-treatment week 24) were available for 61 patients of the HIDIT 1 trial (Group I (n = 20), Group II (n = 20), Group III (n = 21)). The median time of follow-up was 6.0 (1.1–13.3) years. During follow up 25 patients were (re-) treated with IFN-based therapy (57.1% in PEG-IFNa arms and 64.7% in the adefovir only arm). At the last available visit, 13 (21.3%) patients were HDV RNA negative. Late-HDV RNA relapses of patients being negative at post-treatment week 24 were observed in 6/14 individuals. HBsAg was negative in 2 patients at post-treatment week 24 and in 6 patients (9.8%) at the last available visit (all after PEG-IFNa therapy). 11 patients (18.0%) developed clinical endpoints after a median time of 3.6 (1.4–9.9) years. Most of the patients developed a hepatic decompensation (n = 7) and four patients underwent liver transplantation (including three subjects with an HCC). No significant differences in clinical outcome could be observed between the three treatment arms in Kaplan Meier analyses. Interestingly, only one of the patients who were HDV RNA negative at post-treatment week 24 developed a clinical endpoint and all patients who had undetectable HDV RNA results throughout follow-up (n = 8) remained free of hepatic events. None of the patients who were HBsAg negative at posttreatment week 24 developed a clinical endpoint and but one patient who lost HBsAg later during follow-up still experienced an episode of hepatic decompensation.
Conclusion: This long-term follow-up study of a large randomized clinical trial suggests that an off-treatment HDV RNA response to PEG-IFNa treatment is associated with an improved clinical long-term outcome of hepatitis delta.

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Novel markers predict HBs-antigen seroclearance in chronic hepatitis B patients from the SWAP clinical trial

W.W. Phyo[1], G. Cloherty[2], E. Butler[2], M. Kuhns[2], A. Mcnamara[2], V. Holzmayer[2], J. Gersch[2], W.L. Yang[3], P.E.J. Chang[4], J. Tan[5], A. Taufique[6], Y.Y. Dan[1], Y.M. Lee[1], G.H. Lee[1], P.S. Tan[1], C.Y. Tan[1], Y.W.C. Lee[1], Y.L.A. Tay[1], E. Chan[7], S.G. Lim[1]. *[1]National University Health System Singapore; [2]Abbott diagnostics; [3]Tan Tock Seng Hospital Singapore; [4]Singapore General Hospital; [5]Changi General Hospital Singapore; [6]Khoo Teck Puat Hospital Singapore; [7]Singapore Clinical Research Institute*
Email: mdclimsg@nus.edu.sg

Background and Aims: The utility of novel markers to predict HBsAg loss in Chronic Hepatitis B (CHB) patients have not been compared. In this study, quantitative(q) measurements of HBsAg, HBeAg, HBV core-related antigen (crAg) and HBV RNA were evaluated in a clinical trial of CHB patients.
Method: 111 patients from a randomised control trial of continuing nucleos(t)ide analogues (NA) were compared to add-on or switch-to peginterferon alpha 2b for 48 weeks (wk) 1:2:2 (clinicaltrial.gov NCT01928511), with primary endpoint evaluation after 24 wk follow-up (wk 72). Serum samples were tested with a research HBV RNA assay (log U/ml); qHBeAg, qHBsAg(logIU/ml), and an ultrasensitive HBsAg research assay (sensitivity 0.005IU/ml) (m2000 and ARCHITECT, Abbott Laboratories); and crag (log U/ml; Lumipulse, Fujirebio; HBeAg(-) samples only). Analysis of results was performed with SPSS v20.
Results: 42 patients were in add-on, 46 in switch and 23 in control arms respectively at study completion (wk 72). Baseline (bsl) demographics: mean age 50 years, males 85%, HBV DNA(-) 100%, and HBeAg(+) 31.5%. At end of study, 13(11.7%) patients achieved HBsAg loss (only interferon-treated); 12/13 were HBeAg(-) at bsl. HBsAg loss patients had lower levels of qHBsAg at bsl [1.3 ± 1.1 vs 3.0 ± 0.7 (p < 0.001)], wk 12 [0.3 ± 0.9 vs 2.9 ± 0.8 (p < 0.001)] and wk 24 [0.1 ± 0.6 vs 2.8 ± 0.9 (p < 0.001)]. Patients with HBsAg loss who were bsl HBeAg(-) had lower crAg levels at bsl [3.2 ± 0.3 vs 3.9 ± 0.9 (p = 0.005)], wk 12 [3.2 ± 0.4 vs 3.9 ± 0.9 (p = 0.007)], and wk 24 [3.1 ± 0.2

vs 3.9 ± 0.9 (p = 0.003)]. HBV RNA(-) at wk 24 was also associated with HBsAg loss (61.5% vs 14.3%, p < 0.001). In multivariate analysis adjusted for age, gender, duration of prior NUC treatment and bsl qHBsAg, qHBsAg < 2.0logIU/ml at wk 12 was an independent predictor of HBsAg loss(OR 39.1, 95% CI 1.7–901.5, p = 0.022), with AUROC of 0.96 (96% CI 0.9–1.0, p < 0.001). Other independent predictors were HBV RNA(-) at wk 24[OR 10.6,95% CI 2.8–40.9, p = 0.001] and crAg(-) (<3logU/ml) at wk 12 [OR 6.8 95% CI 1.3–35.5, p = 0.022, AUROC 0.75 (95%CI 0.6–0.9)]. Overall, 24/48 HBsAg(-) samples tested with the ultrasensitive HBsAg research assay were HBsAg(+). None of the specific treatment arms were associated with significant changes in qHBsAg, crAg or HBV RNA that were related to HBsAg loss.
Conclusion: QHBsAg and undetectable crAg at wk 12 and undetectable HBV RNA at wk 24 are important predictors of HBsAg seroclearance.

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Pharmacokinetics and pharmacodynamics modeling of ritonavir boosted lonafarnib therapy in HDV patients: A phase 2 LOWR HDV-3 study

P. Dubey[1], C. Koh[2], P. Surana[2], S. Uprichard[1], M.A.T. Han[2], N. Fryzek[2], G. Subramanya[1], D. Kapuria[2], O. Etzion[3], V. Takyar[2], Y. Rotman[2], C. Yurdaydin[4], J. Glenn[5], S. Cotler[5], T. Heller[2], H. Dahari[1]. *[1]Loyola University Medical Center, United States; [2]Liver Diseases Branch, NIDDK, NIH, United States; [3]Soroka University Medical Center, Israel; [4]University of Ankara Medical School, Turkey; [5]Stanford University School of Medicine, United States*
Email: harel.dahari@gmail.com

Background & Aim: The prenylation inhibitor lonafarnib (LNF) has proven anti-hepatitis D virus (HDV) activity in recent phase 2 clinical trials. The phase 2 LOWR HDV-3 study conducted with an all-oral combination of once-daily ritonavir (RTV) boosted LNF was reported safe and tolerable in patients for up to 6 months of therapy. In the current study, we sought to model RTV-boosted LNF pharmacokinetics (PK) and pharmacodynamics (PD) parameters using data from the LOWR HDV-3 study.
Methods: HDV-infected patients were randomized in LOWR HDV-3 into one of six groups: LNF 50/75/100 mg + RTV 100 mg once daily for 24 weeks (n = 12) or 12 weeks of placebo followed by LNF 50/75/100 mg + RTV 100 mg once daily for 12 weeks (n = 9). Since frequent hepatitis B surface antigen (HBsAg), RTV, LNF and HDV RNA kinetics (0, 6, 12, 18, 24, 36 hrs, 2, 3, 7, 14, 21, 28, 56, 84, 112, 140, 168 days) were available in the 24 week arm of LNF 50/75/100 mg + RTV 100 mg, 12 patients in this arm were included in the modeling analysis. All patients were treated with hepatitis B nucleotide analogues. A modeling framework that includes proliferation of uninfected and infected cells and accounts for LNF concentration, HDV RNA, alanine aminotransferase (ALT) and HBsAg kinetics was used to estimate the LNF PK and PD parameters. The standard Emax model was used to account for the time-dependent LNF effectiveness in blocking HDV production.
Results: While HBsAg levels did not change on therapy, four patterns of HDV RNA response were seen in each dosing group: responders (triphasic (n = 3), flat-partial responders (n = 3), rebound (n = 3)) and non-responders (n = 3). ALT normalization was observed in all triphasic and 2 (out of 3) flat-partial responders. In all 12 patients, a transient increase in RTV concentration was observed with median (interquartile range, IQR) peak C_{max_RTV} = 880 (993)ng/ml during the first week after initiation of therapy followed by a set point of 257 (297)ng/ml from week 2 onwards. Interestingly, C_{max_RTV} >1200 ng/ml was associated with the triphasic response (1 in each LNF dosing group) in which there was a continuous HDV decline on treatment. Based on all 12 patients, the LNF-PK model predicted a median LNF elimination rate k_e = 0.7 (0.3)/day, absorption rate k_a = 9.2 (23.7) /day, and bioavailable fraction F = 1012.7 (682.7) ng/ml. There was no association between PK parameters and response to therapy (p ≥ 0.145). LNF-PD modeling in the 9 responders suggests a median LNF EC_{50} of 289 (422) ng/ml, at which LNF's effectiveness in blocking viral production reaches to half of its maximum, with Hill coefficient n = 1.48.
Conclusions: Modeling daily ritonavir boosted lonafarnib indicates a lower average LNF elimination rate (0.76/day) compared to twice a day unboosted LNF (1.08/day – Hepatology Communications 2017; 1:288–292), which confirms the role of ritonavir to maintain high LNF efficacy under low and daily LNF dosing with minimal side effects.

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Modeling serum HBsAg, HBV DNA and transaminase kinetics during REP 2139 monotherapy in chronic HBeAg+ HBV infection

L. Shekhtman[1,2], N. Borochov[1], S. Cotler[1], L. Hershkovich[1], S. Uprichard[1], M. Al-Mahtab[3], M. Bazinet[4], A. Vaillant[4], H. Dahari[1]. *[1]Loyola University Medical Center, United States; [2]Bar-Ilan University, Israel; [3]Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh; [4]Replicor Inc., Canada*
Email: harel.dahari@gmail.com

Background and Aims: Nucleic acid polymers (NAPs) block the secretion of HBV subviral particles (SVPs) without affecting secretion of Dane particles or intracellular levels of HBsAg (Blanchet et al. J Hepatol.2017;66:S257). In HBeAg+ chronic HBV infection, NAP monotherapy is associated with almost complete removal of circulating HBsAg and substantial reductions in serum HBV DNA (Al-Mahtab et al., PLOS One 2016;11:e0156667). Here we provide a mathematical model that predicts HBV DNA, HBsAg and transaminase kinetic parameters against HBV during REP 2139 monotherapy in the REP 102 protocol (NCT02646189).
Methods: Twelve HBeAg+ chronically infected HBV patients received weekly 500 mg IV infusions of REP 2139 for 20–40 weeks (Al-Mahtab et al., *idem*). HBV DNA (viral load, VL), HBsAg and alanine aminotransferase (ALT(levels were measured every 1–2 weeks during treatment. A model that includes proliferation of uninfected and infected cells and accounts for HBV DNA, HBsAg and ALT dynamics was developed.
Results: Mean baseline VL, ALT and HBsAg were 7.9 ± 1.3Log copies/ml, 79 ± 36IU/l and 4.5 ± 0.7 logIU/ml, respectively. Three non-responders with no decline in VL or HBsAg were excluded. VL and HBsAg significantly declined from baseline levels during therapy. At the end of NAP monotherapy, mean ALT was lower than baseline (61 ± 29 IU/l) however ALT flares (>3-fold increase) were observed in 4 patients between 4 and 9 weeks after initiation of therapy. Model fits indicate that HBsAg and VL declines started 36 ± 32 days after introduction of REP 2139 and estimate a mean REP 2139 efficacy of 96.7% ± 4.4% in blocking HBsAg secretion. Assuming that REP 2139-mediated reductions in HBsAg allow for restoration of immune function, modeling projects a mean increase in the rate of viral clearance of 541-fold per day (range increase of 0.2–4544 fold per day) with mean maximum fold enhancement of 3.2. ± 1.2 logs within 110 ± 35 days post therapy initiation. The model reproduces the observed ALT kinetics in the 5 patients without an ALT flare.
Conclusions: Modeling fits indicated a potent efficacy/enhancement in blocking HBsAg secretion and associated viral clearance. The delay observed before HBsAg and VL decline after introduction of REP 2139 was variable among patients and in some cases was decoupled, suggesting a variable state of immune function participating in the clearance of HBsAg versus HBV DNA. Further modeling efforts to refine the understanding of the modes of action of NAPs against HBV and the nature of ALT flares are ongoing.

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Efficacy and safety of combination therapy with interferon and immunomodulators in entecavir-suppressed chronic hepatitis B patients (the endeavor study)

D. Wu[1], P. Wang[1], M. Han[1], Y. Chen[2], X.-Y. Chen[3], Q. Xia[4], C. Zhu[5], Q. Xie[6], J. Jiang[7], L. Wei[8], D. Tan[9], X. Dou[10], Y.-Y. Yu[11], J. Hou[11], Q. Ning[1]. *[1]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department and Institute of Infectious Disease; [2]The First Affiliated Hospital of Wenzhou Medical University, China; [3]Beijing You'an Hospital, Capital Medical University, China; [4]The First Affiliated Hospital, School of Medicine, Zhejiang University; [5]Jiangsu Province Hospital; [6]Shanghai Ruijin Hospital, Jiaotong University School of Medicine; [7]First Affiliated Hospital of Fujian Medical University; [8]Peking University People's Hospital, China; [9]Xiangya Hospital, Central South University; [10]Shengjing Hospital of China Medical University, China; [11]Nanfang Hospital, Southern Medical University, China*
Email: qning@vip.sina.com

Background and Aims: The ideal endpoint for anti-HBV therapy is the loss of hepatitis B surface antigen (HBsAg). The purpose of the study was to determine the efficacy and safety of sequential combination therapy with interferon (IFN), recombinant human IL-2 (rhIL-2) and therapeutic vaccine in patients treated with long-term entecavir (ETV).

Method: In this pilot and proof of concept, multicentre and randomized trial, 94 HBeAg positive chronic hepatitis B patients who had received ETV for at least 1 years, with HBV DNA ≤ 1000 copies/ml and hepatitis B e antigen (HBeAg) loss, were randomly assigned (1:1:1) to receive ETV (0.5 mg/day, oral) for 48 weeks (Group I) or IFN-α-2b (600 wIU every other day, subcutaneous) for 48 weeks (Group II) or IFN-α-2b for 48 weeks in combination with rhIL-2 (25 wIU every other day, subcutaneous) for 12 weeks plus vaccine (60ug/month, intramuscular) for 48 weeks (Group III). The primary endpoint was HBsAg loss at week 48 (ClinicalTrials.gov: NCT02360592). Peripheral immune cells were evaluated dynamically.

Results: 94 patients were randomized; 93 received ≧1 study drug dose. One patient who were HBeAg-positive at baseline was excluded from the modified intention-to-treat population (group I, n = 27; group II, n = 33; group III, n = 32). At week 48, 3.70% of subjects in group I, 3.03% of subjects in group II and 9.38% of subjects in group III achieved HBsAg loss. Mean HBsAg decline from baseline to week 48 was significantly greater in group III (0.85 log10IU/ml) and group II (0.74log10 IU/ml) than in groups I (0.13log10IU/ml, respectively, $p < 0.05$ for all comparisons vs group I). Among the patients with 100IU/ml < HBsAg < 1500 IU/ml at randomisation, 25% achieved HBsAg loss and mean HBsAg declined 1.65log10 IU/ml from baseline to week 48 in group III, displaying a significant benefit comparing with group I (0% and 0.04log10IU/ml, respectively), while no significant difference was found between group III and group II (6.67% and 0.61 log10IU/ml, respectively). Besides, patients receiving combination treatment showed a significantly higher increase in the $CD56^{bright}$ $CD16^{-}$NK cells proportions at week 4, patients with good response to combination treatment exhibited a significant decline in Treg proportions from week 12 to week 24.

Conclusion: For ETV suppressed patients, particularly those with low serum HBsAg level, sequential combination therapy with IFN and immunomodulators may enhance HBsAg loss and led to partial immune restoration.

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Establishment of persistent functional remission of HBV and HDV infection following REP 2139 and pegylated interferon alpha 2a therapy in patients with chronic HBV/HDV co-infection: 18 month follow-up results from the REP 301-LTF study

M. Bazinet[1], V. Pantea[2], V. Cebotarescu[2], L. Cojuhari[2], P. Jimbei[3], A. Vaillant[1]. *[1]Replicor Inc., Montreal, Canada; [2]Nicolae Testemitanu State University of Medicine and Pharmacy, Chisinau, Moldova; [3]Toma Ciorba Infectious Clinical Hospital, Chisinau, Moldova*
Email: availlant@replicor.com

Background and Aims: HBV/HDV co-infection represents a significant unmet medical need, causes rapid progression of liver disease and has no approved therapy. The previous REP 301 study (NCT02233075) demonstrated the safety and tolerability of REP 2139 in combination with pegylated interferon alpha 2a (pegIFN) and the establishment of functional control of HBV (in 5/12 patients) and HDV (in 9/12 patients) which persisted after the removal of all antiviral therapy (functional remission) in 7 patients (HDV RNA target not detected), 5 of whom also maintained functional remission of HBV (HBsAg < LLOQ, HBV DNA < LLOQ). A three-year supplemental follow-up study (REP 301-LTF, NCT02876419) is currently examining the long-term stability of the functional remissions of HBV and HDV infection achieved in the REP 301 protocol.

Method: All patients completing the proscribed therapy in the REP 301 study were eligible to participate in this study. Supplemental follow up safety and efficacy evaluations are scheduled every 6 months (for a period of three years) following the original 24-week follow-up in the REP 301 study. Virologic status was verified using Architect (HBV) and Robogene MKII (HDV) test platforms. Hepatic stiffness was monitored by Fibroscan.

Results: Of the seven patients which achieved functional remission of their HDV infection at the end of the 24-week follow-up in REP 301 study, all are still maintaining HDV RNA target not detected at 1.5 years of follow-up. Five of these patients also had functional remission of their HBV infection, which is still persisting in 4 patients. In the fifth of these patients, HBV infection is still well controlled (HBV DNA < LLOQ). In all seven patients with functional remission of HDV at 1.5 years of follow-up, liver function is normal and is accompanied by continual reductions in median hepatic stiffness, now below pre-treatment levels in 6 of 7 patients.

Of the remaining five patients who did not achieve functional remission of HBV or HDV infection, new HDV RNA setpoints >1log below baseline are persistent in 2 patients and are accompanied by normal liver function or reduced/stable median hepatitis stiffness.

Conclusion: Functional remission of HDV and HBV infection achieved with REP 2139 and pegIFN is stable at 1.5 years follow-up and is associated with persistently normal liver function and progressive reduction in median hepatic stiffness.

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Dose response and safety of the daily, oral RIG-I agonist Inarigivir (SB 9200) in treatment naïve patients with chronic hepatitis B: results from the 25mg and 50mg cohorts in the ACHIEVE trial

M.-F. Yuen[1], M. Elkashab[2], C.-Y. Chen[3], C. Coffin[4], S. Fung[5], S. Greenbloom[6], J.W. Jang[7], R.W.-J. Jeng[8], D.J. Kim[9], Y.J. Kim[10], W. Kim[11], K.S. Lee[12], Y.-S. Lim[13], A. Ramji[14], R. Iyer[15], C. Macfarlane[15], K. Jackson[16], S. Locarnini[16], N. Afdhal[15], H. Chan[17]. *[1]University of Hong Kong; [2]Toronto Liver Centre; [3]Chia-Yi Christian Hospital; [4]University of Calgary; [5]University of Toronto; [6]Toronto Disgestive Disease Associates Inc; [7]The Catholic University of Korea; [8]Chang-Gung University; [9]Hallym University College of Medicine; [10]Seoul National University Hospital; [11]Borame Medical Center; [12]Yonsei University; [13]Asan Medical Center; [14]University of BC; [15]Spring Bank Pharmaceuticals; [16]VIDRL; [17]Chinese University of Hong Kong*
Email: cmacfarlane@springbankpharm.com

Background and Aims: Inarigivir (previously SB 9200) is an oral HBV antiviral with both direct acting activity and immune-modulation

through activation of the pattern recognition receptor retinoic acid-inducible gene 1 (RIG-I). The ACHIEVE trial is a placebo controlled trial of ascending doses of inarigivir daily or placebo for 12 weeks, followed by a switch to 300mg tenofovir for 12 weeks. We report here the dose response at 25 mg (cohort 1) and 50 mg (cohort 2) daily of Inarigivir on HBV DNA, HBsAg and HBV RNA.

Method: All patients were treatment naïve, non-cirrhotic with elevated ALT. 20 patients per cohort were randomized 4:1 to inarigivir or placebo. Two patients in cohort 2 dropped out secondary to patient preference at day 1 and week 2 and are not in the analysis. 38 of 40 patients were Asian and genotypes B/C predominated.

Results: No clinical or biochemical > grade 3 AE's, no SAE's and no interferon like side effects reported. Overall 5 ALT flares > 200 IU/ml were seen, 2 on placebo and three on Inarigivir. One inarigivir 50 mg patient had an ALT of 487 IU/ml at week 4 and was switched to tenofovir. Week 12 anti-viral response is shown in the Table. Compared to placebo both HBV DNA (t-test, $p < 0.001$) and HBV RNA (t-test, $p = 0.008$) declined in combined inarigivir 25 and 50 mg cohorts. Overall HBeAg -ve patients had a greater anti-viral response than HBeAg + ve patients. HBV DNA response was superior in those with baseline HBV DNA < $6\log_{10}$ and HBsAg < $4\log_{10}$ irrespective of HBeAg status indicating effect of viral burden on response. HBV RNA was undetectable at week 12 in 2 of 7 patients with HBeAg –ve disease in cohort 1 and all 4 patients in cohort 2. Overall 4 of 30 inarigivir treated patients had a > 0.5 log reduction in HBsAg.

	Placebo	Inarigivir 25mgHBeAg + ve	Inarigivir 25 mgHBeAg –ve	Inarigivir 50 mgHBeAg + ve	Inarigivir 50 mgHBeAg –ve
Number	8	9	7	11	5
Age	38	37	43	36	47
Gender M:F	6 : 2	5 : 4	3 : 4	9 : 2	5
Baseline ALT	74	82	75	75	65
Baseline HBV DNA $\log_{10}$	6.36	7.86	5.69	7.79	4.55
Change in DNA (BL to week 12) $\log_{10}$	+0.33	–0.37	–0.86	–0.61	–1.05
Baseline HBsAg $\log_{10}$	3.75	4.31	3.17	4.12	2.96
Change in HBsAg (BL to week 12) $\log_{10}$	–0.18	–0.08	–0.34	–0.07	0
Baseline HBV RNA $\log_{10}$	4.23	6.36	4.20	6.58	3.15
Change in HBV RNA (BL to week 12) $\log_{10}$	+0.99	–0.32	–1.84	–0.46	–3.15

Conclusion: Low dose Inarigivir is well tolerated and associated with reduction in HBV DNA and HBV RNA. This effect is seen without a fully activated immune response and consistent with a direct anti-viral effect which may reflect targeting HBV RNA encapsidation.

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Every-two-week ropegienterferon alfa-2b is safe with higher hepatitis B e antigen seroconversion rate in interferon naive patients with chronic hepatitis B infection: A phase 2, open label, randomized, active control, dose finding study

Y.-W. Huang[1], P.-J. Chen[2], C.-W. Hsu[3], S.-N. Lu[4], M.-L. Yu[5], C.-W. Su[6], W.-W. Su[7], R.-N. Chien[8], C.-S. Hsu[9], S.-J. Hsu[10], H.-C. Lai[11], K. Tseng[12].
[1]Cathay General Hospital Medical Center, Liver Center, Taipei, Taiwan; [2]Department of Medical Research, National Taiwan University, Taiwan; [3]Linkou Chang Gung Memorial Hospital, Division of Hepatogastroenterology, Department of Internal Medicine, Taipei; [4]Kaohsiung Chang Gung Memorial Hospital, Divsion of Hepatogastroenterology; [5]Kaohsiung Medical University Hospital, Hepatobiliary Section, Department of Internal Medicine, and Hepatitis Center, Kaohsiung, Taiwan; [6]Taipei Veterans General Hospital, Division of Hepatogastroenterology, Department of Internal Medicine, Taipei, Taiwan; [7]Changhua Christian Hospital, Department of Internal Medicine, Changhua, Taiwan; [8]Keelung Chang Gung Memorial Hospital, Division of Hepatogastroenterology, Department of Internal Medicine, Keelung; [9]Taipei Tzu Chi General Hospital, Division of Gastroenterology and Hepatology, Department of Internal Medicine, New Taipei City, Taiwan; [10]National Taiwan University Hospital Yun-Lin Branch, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Yunlin, Taiwan; [11]China Medical University Hospital, Division of Hepatogastroenterology, Department of Internal Medicine, Taichung, Taiwan; [12]PharmaEssentia Corp, Medical Research, Taipei, Taiwan
Email: peijerchen@ntu.edu.tw

Background and Aims: Ropeginterferon alfa-2b (P1101) is a novel mono-pegylated interferon alfa-2b with longer duration of action, allowing every-two-week (q2w) injection with high tolerability shown from previous studies. This study aims to find the optimal dose of P1101 by comparing antiviral activity, and safety across treatment groups in interferon naïve patients with chronic hepatitis B virus (HBV) infection.

Method: Thirty-one hepatitis B e antigen (HBeAg)-positive subjects with baseline HBV DNA > 20,000IU/ml and 31 HBeAg-negative subjects with baseline HBV DNA > 2,000IU/ml were randomized at 1:1:1 ratio to subcutaneous treatment of q2w P1101 350 μg (Group 1), q2w P1101 450 μg (Group 2), or weekly (q1w) peginterferon alfa-2a 180 μg (Group 3, control) respectively. Every patient received 48-week treatment (TW48) and 24-week post-treatment follow-up (FW24).

Results: In HBeAg (+) subjects, cumulative HBeAg seroconversion rate was 27% (3/11), 36% (4/11), 11% (1/9) ($p = 0.21$) with median time to HBeAg seroconversion of 24, 24, and 48 weeks ($p = 0.28$), in Group 1, 2, 3 respectively. At FW24, HBV DNA < 2,000 IU/ml was 27% (3/11), 0% (0/11), and 22% (2/9) ($p = 0.22$), hepatitis B surface antigen (HBsAg) < 1,500 IU/ml was 46% (5/11), 18% (2/11), 11% (1/9) ($p = 0.27$), anti-HBe positive rate was 46% (5/11), 46% (5/11), 18% (2/9) ($p = 0.59$) in Group 1, 2, 3 respectively. In HBeAg (-) subjects at FW24, HBV DNA < 2,000 IU/ml was 10% (1/10), 36% (4/11), 50% (5/10) ($p = 0.17$) and HBsAg < 1,500 IU/ml was 80% (8/10), 91% (10/11), 90% (9/10) ($p = 0.83$), in Group 1, 2, 3 respectively. HBeAg (+) and (–) patients pooled together, 10% (2/21), 5% (1/22), 11% (2/19) discontinued treatment due to adverse events (AEs) in Group 1, 2, 3 respectively. The AEs for discontinuation were Grade 3 myocardial infarction (MI) and Grade 4 alanine aminotransferase (ALT) increased in Group 1, multiple Grade 1 AEs in 1 subject of Group 2, and Grade 3 ALT increased in 2 subjects of Group 3. The subject with MI has risk factors of smoking, and hyperlipidemia. About 14% (3/21), 14% (3/22), 11% (2/19) reduced dose in Group 1, 2, 3 respectively. All were due to Grade 3 neutropenia or ALT increased.

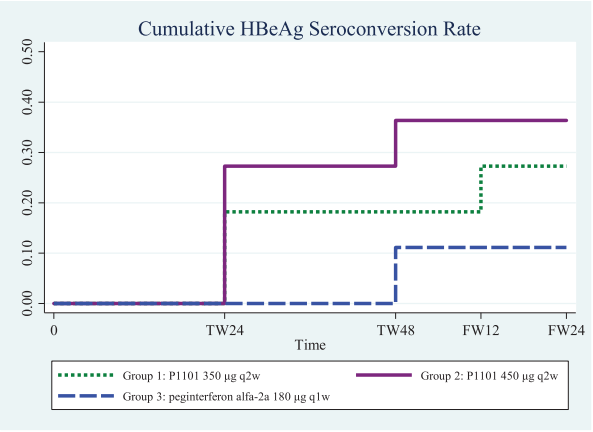


Figure 1: Cumulative HBeAg Seroconversion Rate Over Time in HBeAg-positive Patients

Conclusion: P1101 is safe for chronic HBV infection. P1101 450 µg q2w yielded the highest HBeAg seroconversion rate. Shorter time to HBeAg seronconversion was observed in both P1101 groups. P1101 450µg q2w is selected for a Phase 3 study to confirm efficacy and safety on HBeAg-positive patients.

FRI-329

HBV RNA in serum is an early predictor for sustained immune control following treatment with pegylated interferon alfa in patients with HBeAg negative chronic hepatitis B

M. Farag[1,2], M.V. Campenhout[3], F. van Boemmel[4], V. Rijckborst[3], Y. Cakaloglu[5], P. Ferenci[6], F. Tabak[7], J. Feld[2], B. Hansen[2,3,8], H. Janssen[2]. *[1]University of Toronto, Institute of Medical Sciences, Faculty of Medicine, Toronto, Canada; [2]Toronto General Hospital, University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; [3]Erasmus Medical Centre Rotterdam, Department of Gastroenterology & Hepatology, Rotterdam, Netherlands; [4]University Hospital Leipzig, Department of Gastroenterology and Rheumatology, Section of Hepatology, Leipzig, Germany; [5]Istanbul University Medical School, Department of Gastroenterohepatology, Istanbul, Turkey; [6]Medical University of Vienna, Department of Internal Medicine 3, Gastroenterology and Hepatology, Vienna, Austria; [7]Istanbul University Cerrahpasa Medical School, Department of Infectious Diseases, Istanbul, Turkey; [8]University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada*
Email: mi.farag@mail.utoronto.ca

Background and Aims: Hepatitis B RNA (HBV RNA) is a novel serum biomarker that is a transcriptional product of HBV covalently closed circular DNA. In recent studies in HBeAg negative patients, kinetics of serum HBV RNA were shown to be associated with serologic response following treatment with nucleos(t)ide analogues or PEG-IFN.
We aimed to study the kinetics of HBV RNA during PEG-IFN treatment in HBeAg negative patients and its potential role as response predictor.
Method: HBV RNA levels were retrospectively measured in stored serum samples of 133 HBeAg-negative chronic HBV patients who were treated in an international randomized controlled multicenter trial (PARC study). Patients received PEG-IFN α-2a 180 mcg/week +/- ribavirin 1000–1200 mg daily for 48 weeks. All patients were followed until week 72. HBV RNA was measured at week 0 (baseline), 12, 24 and 48 and week 72 using a RACE-PCR technique (lower limit of quantification (LLQ) 800c/ml). Response was defined as a combined endpoint HBV DNA level below 2,000 IU/ml and normalization of ALT at week 72.
Results: The mean age was 42.2 (SD 11) years, 98 (74%) were male, and distribution of HBV genotypes was 17/1/3/80% for A/B/C/D. The mean (SD; range) HBV RNA at baseline was 4.0 (1.4; 1.7–7.7) $\log_{10}$ c/ml and HBV RNA was < LLQ in 28 (23%) patients. No difference in response was found between patients with or without ribavirin and patients were thus pooled for further analyses.
At 12 and 24 weeks mean HBV RNA declined by 1.7 and 1.8 log c/ml and HBV RNA was < LLQ in 95 (83%) and 99 (84%) patients at these time points, respectively. At week 72, 24 patients (23%) had achieved response. HBV RNA in the responders showed a marked decline (2.1 and 2.2 log c/ml) compared to the non-responders (1.6 and 1.6) at weeks 12 and 2 4, respectively. None of the patients at week 12 (n = 18) and week 24 (n = 17) who exhibited an HBV RNA level above 1500c/ml (3.2 $\log_{10}$ c/ml) had a response at week 72 with a negative predicative value of 100% (p = 0.01 and 0.02 respectively). However, the positive predictive value of patients who had HBV RNA levels below 1500c/ml (3.2 $\log_{10}$ c/ml) at week 12 and 24 was 28% and 27% respectively.
Conclusion: In HBeAg-negative patients with chronic hepatitis B, serum HBV RNA declined during PEG-IFN treatment. An HBV RNA value above 1,500 c/ml (3.2 $\log_{10}$ c/mL) at week 12 was strongly associated with nonresponse to PegIFN treatment.

FRI-330

Determination of the optimum timing of the start of nucleoside analogue by FIB-4 index for hepatitis B patients from the viewpoint of suppressing hepatocarcinogenesis

S. Hige, I. Ozeki, R. Tatsumi, M. Yamaguchi, M. Kimura, T. Arakawa, T. Nakajima, Y. Kuwata, T. Ohmura, J. Toyota, Y. Karino. *Sapporo Kosei General Hospital, Hepatology, Sapporo, Japan*
Email: shuhei.hige@ja-hokkaidoukouseiren.or.jp

Background and Aims: Nucleotide or nucleoside analogue (NA) treatment to hepatitis B patients has been reported to be useful for suppressing the occurrence of hepatocellular carcinoma (HCC). However, not a few patients progress to HCC after the start of NA treatment. On the other hand, early treatment initiation for young patients should be carefully considered since the treatment may last for a long time. Therefore, it is important to find an optimum timing to suppress HCC occurrence effectively. In this study, we evaluated the meaningfulness of annual average of integral FIB-4 index for determining an adequate timing for the start of NA treatment.
Method: A total of 543 HBs antigen-positive patients who did not have a history of HCC were followed from the start of NA administration [entecavir (ETV) 334, lamivudine (Lam) to ETV 80, Lam 30, Lam or ETV plus adefovir (ADV) 99 cases]. FIB-4 was calculated by the following formula: (age [years]×AST [IU/l] / platelet count [10^9/l]×ALT [IU/l]$^{1/2}$). An annual average value of FIB-4 index (FIB-4aa) which was calculated from the integral value of each FIB-4 index during the same year was used for the investigation of this study.
Results: During an average follow-up of 5.3 years, HCC was confirmed in 70 patients. Overall cumulative 3/5/10 year HCC occurrence rate was 8.4/11.2/20.7%. The cumulative 5/10 year rates of patients whose FIB-4aa before the start of NA administration was <1.0, 1.0–2.0, 2.0–3.0, 3.0–4.0, 4.0 ≤ were 0/0, 3.6/5.2, 1.9/1.9, 16.3/32.3, 30.7/40.5%, respectively. The expected HCC risk of those whose FIB-4aa ≥ 3.0 (high FIB-4aa group) was 10 times greater than those whose FIB-4aa < 3.0 (low FIB-4aa group), (cumulative 5/10 year rates: 25.0/36.9 vs 2.2/3.4, p < 0.001). The cumulative 5-year risk in their 30's/40's/50's/60's/70's was 0/3.6/6.1/0/0% for lowFIB-4aa group and 12.5/12.0/28.2/26.3/37.8% for high FIB-4aa group. Among FIB-4aa high group cases, those whose FIB-4aa declined below 3.0 during NA treatment tended to lower the risk of HCC occurrence. 5-year HCC risk of those cases was 19.2%. The risk of those who did not show FIB-4aa decrease was 29.9% (p = 0.08).
Conclusion: FIB-4 index at the start of NA administration was highly correlated with HCC occurrence afterwards. This tendency was the same in any age group over 30's. NA administration should be started before an annual average value of integral FIB-4 index reaches 3.0.

FRI-331

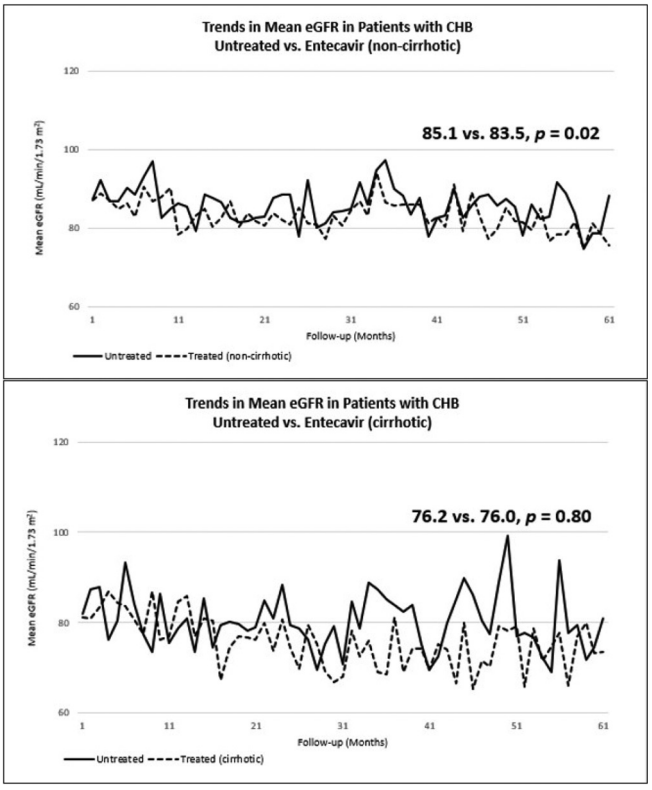
Treatment of chronic hepatitis B and renal impairment in patients with and without cirrhosis

V. Vu, S. Trinh, A. Le, T. Johnson, J. Hoang, D. Jeong, L. Henry, M. Nguyen. *Stanford University Medical Center, Division of Gastroenterology and Hepatology*
Email: mindiehn@stanford.edu

Background and Aims: Recent studies have shown that renal impairment in chronic hepatitis B (CHB) patients may result from treatment with oral nucleos(t)ide analogue medications. However, treatment with entecavir (ETV) has been associated with less renal toxicity, though data on this is limited. It is also unclear whether ETV therapy is more associated with development of poorer renal function compared to untreated CHB patients. The study aim was to determine renal outcomes among CHB patients who are untreated and treated with ETV with and without cirrhosis over time.
Method: Patients infected with CHB who were untreated or treated with ETV were recruited from a retrospective cohort of consecutive adult patients at a U.S. tertiary center between 1996 and 2017. Patients were not recruited if coinfected with hepatitis D, hepatitis C,

or human immunodeficiency virus, or had prior history of treatment with adefovir or tenofovir. Patients were included if they had =>12 months of serial creatinine labs and baseline estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet in Renal Disease Study equation) =>60ml/min/1.73 m^2 (n = 522). Propensity score matching (PSM) for age, sex, race, diabetes (DM), hypertension (HTN), and baseline eGFR was performed to compare untreated patients versus ETV-treated patients without cirrhosis (non-cirrhotic cohort) and with cirrhosis (cirrhotic cohort). Generalized linear regression modeling (GLM) controlling for sex, race, DM, and HTN was performed to generate mean eGFR over time.

Results: The non-cirrhotic cohort (n = 314) had a mean age of 48 ± 12 years. Most were male (58%) and Asian (91%). Twenty patients had DM (6%) and 74 had HTN (24%). Patients had a median eGFR of 85.1 (IQR = 61.5–139.6) and median follow-up of 70 months (IQR = 12–199). The cirrhotic cohort (n = 150) had a mean age of 55 ± 12 years. The majority were male (73%) and Asian (89%), with 27% having DM and 51% having HTN. Median eGFR was 79.1 (IQR = 61.0–118.4) and median follow-up was 69 months (IQR = 13–166). On GLM for the non-cirrhotic cohort, there was a significant difference in the eGFR between untreated patients and ETV-treated patients (85.1 vs. 83.5, p = 0.02). For the cirrhotic cohort, GLM showed no significant difference in the eGFR of untreated patients and ETV-treated patients (76.2 vs. 76.0, p = 0.80) (Figure).



Conclusion: In this PSM study comparing untreated patients and ETV-treated patients with and without cirrhosis, no significant differences in renal function was noted for the cirrhotic group. Mean eGFR was slightly lower in ETV-treated patients than untreated non-cirrhotic patients, but remained at or close to normal range in both groups at 5-year follow-up. These findings suggest that ETV treatment does not have major influence on renal function of CHB patients; but since CHB therapy is often long-term, further studies with longer follow-up is needed.

FRI-332

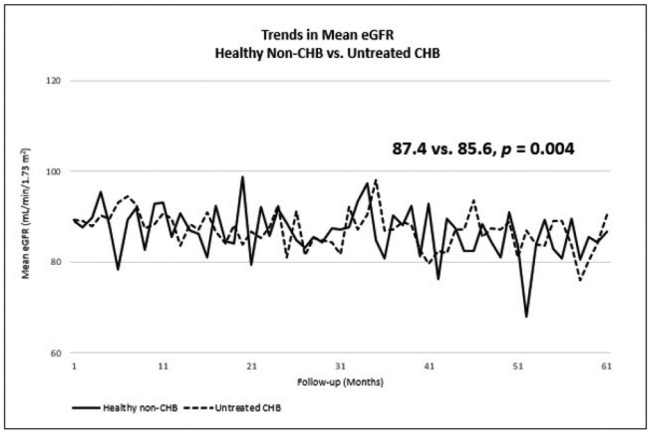
Is renal impairment associated with chronic hepatitis B - a propensity score matched study of healthy non-hepatitis B patients compared to patients with untreated chronic hepatitis B

V. Vu, S. Trinh, A. Le, T. Johnson, J. Hoang, D. Jeong, L. Henry, M. Nguyen.
Stanford University Medical Center, Division of Gastroenterology and Hepatology
Email: mindiehn@stanford.edu

Background and Aims: Renal impairment has been suggested to occur at higher rate in patients with chronic hepatitis B (CHB). However, questions have been raised as to whether the prevalence of renal impairment is a result of the virus itself, a result of HBV treatment, or other factors. The study aim was to explore and compare renal function over time between healthy non-CHB patients and untreated CHB patients.

Method: Healthy non-CHB patients and patients infected with HBV were recruited from a retrospective cohort of consecutive adult patients at one U.S. tertiary center and 3 community gastroenterology and primary care clinic between 1996 and 2017. Healthy non-CHB patients were recruited if they had no history of liver disease, congestive heart failure, human immunodeficiency virus (HIV), or cancer. CHB patients were recruited if they had no hepatitis D virus, hepatitis C virus, or HIV coinfections. Patients were included in the study if they had never received HBV treatment, had =>12months of serial creatinine labs, and had a baseline estimated glomerular filtration rate (eGFR, calculated using the Modification of Diet in Renal Disease Study equation) =>60 ml/min/1.73 m^2 (healthy n = 26, 519; CHB n = 290). Propensity score matching (PSM) for age, sex, race (Asian vs. non-Asian), diabetes (DM), hypertension (HTN), and baseline eGFR was performed to balance the two groups. Generalized linear regression modeling (GLM) adjusting for sex, race, DM and HTN was performed to generate mean eGFR over time.

Results: The PSM groups included 290 healthy non-CHB patients and 290 untreated CHB patients (n = 580). Mean age was 42 ± 12 years. More than half were male (51%) and a majority were Asian (88%). Forty-nine patients had DM (9%) and 143 patients had HTN (25%). Patients had a median baseline eGFR of 88.3 (IQR = 61.0–143.9) and a median follow-up of 82 months (IQR = 12–217). On GLM, the mean eGFR was significantly higher for healthy non-CHB patients compared to untreated CHB patients (87.4 vs. 85.6, p = 0.004) (Figure).



	0	10	20	30	40	50	60
Healthy non-CHB	290	290	248	212	195	182	169
Untreated CHB	290	290	270	250	228	207	189

Conclusion: In this PSM study, untreated CHB patients' eGFR over time decreased significantly more than the healthy non-CHB patients; however, the change in eGFR may not be clinically significant, at least in short-to-medium term follow-up. Therefore,

further research is needed to determine which factors may have contributed to renal impairment in patients with CHB.

FRI-333

Comparison of fibrosis-adjusted long-term clinical outcomes in patients with minimally active chronic hepatitis B who did not undergo antiviral therapy vs. those with complete virological response by antiviral therapy

H.W. Lee, B.K. Kim, S.U. Kim, J.Y. Park, D.Y. Kim, S.H. Ahn, K.-H. Han. *Institute of Gastroenterology, Department of Internal Medicine, Seoul, Korea, Rep. of South*
Email: beomkkim@yuhs.ac

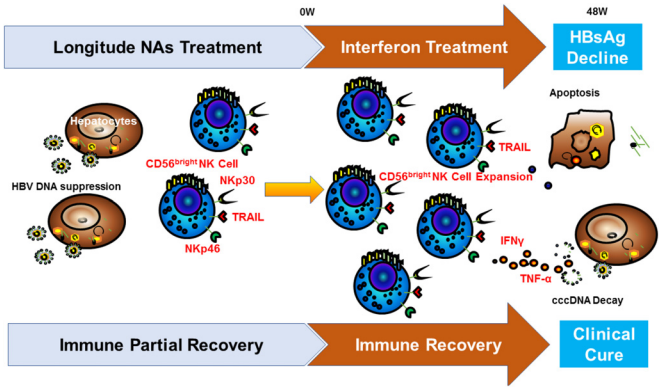
Backgrounds and Aims: The optimal criteria for commencement of antiviral therapy in patients with chronic hepatitis B (CHB) remain to be determined yet. Here, we aimed to compare the risk of hepatocellular carcinoma (HCC) and liver-related event (LRE) between patients with minimally active CHB who did not undergo nucleos(t)ide analog (NUC) therapy according to the current treatment guidelines (MA group) and those with complete virological response by NUCs (VR group).
Methods: We enrolled consecutive patients with CHB who underwent liver stiffness (LS) values by transient elastography between 2006 and 2015. Patients with a history of cirrhosis or hepatocellular carcinoma at the enrollment were excluded. To adjust for imbalances between the MA and VR groups, propensity-score matching (PSM) models with 1:1 ratio were performed based on age, gender, HBeAg, presence of diabetes, and LS value. Cumulative risks of HCC or LRE development were assessed using Kaplan-Meier method.
Results: A total of 915 patients were enrolled. The mean age was 54.2 years old, and 61.2% were male. MA group (n = 209) had higher serum HBV DNA level, alanine aminotransferase (ALT), total bilirubin, LS value and the lower proportion of positive HBeAg compared to VR group (n = 706). Regarding HCC development, MA group had the trend toward the higher risk compared to VR group (p = 0.087). Regarding LRE development, MA group was at the significantly higher risk than VR group (p = 0.003). On the contrary, after PSM, 206 pairs were generated, showing the similar risks between two groups in terms of the cumulative risk of both HCC (p = 0.782) and LRE (p = 0.796) development.
Conclusion: After adjusting the fibrosis degree, the potential prognostic factor for HCC and LE development, MA group also showed similar, cumulative risks compared to VR group, supporting the appropriateness of the current treatment guidelines in patients with CHB.

FRI-334

CD56 bright natural killer cell induces HBsAg clearance via cytolysis and non-cytolysis: Analysis of the OSST patient dataset

A. Shi, X. Zhang, F. Xiao, L. Zhu, W. Yan, M. Han, T. Chen, Q. Ning. *Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department and Institute of Infectious Disease*
Email: qning@vip.sina.com

Background and Aims: HBV surface antigen (HBsAg) reduction is well observed in chronic hepatitis B (CHB) patients treated with pegylate interferon-alpha-2a (Peg-IFNα). However, the mechanism of HBsAg suppression has not been fully elucidated.
Method: Twenty-seven of 55 Entecavir-treated CHB e antigen positive patients were switched to Peg-IFNα treatment (Group A) whereas 28 patients continued entecavir treatment (Group B). The percentage or absolute number of $CD56^{bright}$/$CD56^{dim}$ NK cells, expression of receptors and cytokines were evaluated by flow cytometry for 48 weeks and correlated with treatment efficacy. In Vitro, purified NK cells were co-cultured with HepAD38 cells for measurement of HBsAg, apoptosis and covalently closed circular DNA (cccDNA).
Results: In association with a reduction of HBsAg, the percentage and absolute number of $CD56^{bright}$ NK cell was significantly elevated in patients in group A, especially in Virologic Responders (VRs, HBsAg decreased). Furthermore, percentage of $NKp30^{+}$, $NKp46^{+}$, $TRAIL^{+}$, $TNF\text{-}\alpha^{+}$ and $IFN\gamma^{+}CD56^{bright}$ NK cells were significantly expanded in Group A, which were positively correlated with the decline of HBsAg at week 48. In Vitro, peripheral NK cells from Group A induced decline of HBsAg in comparison with NK cells from Group B which was significantly inhibited by anti-TRAIL, anti-TNF-α and anti-IFNγ antibodies. Furthermore, apoptosis of HepAD38 cells and levels of cccDNA, were significantly reduced by $TRAIL^{+}$ and $TNF\text{-}\alpha^{+}$/$IFN\gamma^{+}$NK cells from Group A respectively.



Conclusion: A functional restoration of $CD56^{bright}$ NK cells in Entecavir-treated patients who were switched to Peg-IFNα contributes to HBsAg and cccDNA clearance through TRAIL-induced cytolysis and TNF-α/IFNγ-mediated noncytolytic pathways.

FRI-335

Loss of HbsAg is enough to discontinue long-term therapy with Nucleos(T)ide analogues in HbeAg negative CHB patients in real clinical practice?

A. Kapatais, P. Labropoulos, E. Ouranou, M. Pavlou, T. Karaoulani. *West Attica-Nikaias Hospital, 1st Pathological clinic, Agia Varvara-Egaleo, Greece*
Email: andreaskapatais@yahoo.gr

Background and Aims: The oral Nucleos(T)ide analogues (Nucs) are the most common therapeutic strategy for treatment of CHB patients. The loss of HbsAg is the endpoint of therapy, but it is still not clear whether the clearance of HbsAg alone is enough to stop long –term therapy with Nucs. The evaluation in clinical practice of the outcome in HbeAg-negative CHB patients who discontinued Nucs therapy after loss of HbsAg.
Method: CHB patients -HbeAg-negative with HbsAg clearance during long –term therapy with Nucs followed for at least 24 weeks, after Nucs discontinuation were examined. HbsAg, anti-Hbs, HBV-DNA levels and ALT/AST were monitored every 3 months after Nucs discontinuation in the first year and every six months thereafter.
Results: Among 420 HbeAg-negative CHB patients who received Nucs therapy between 1999–2014, 24 (5,71%) lost HbsAg after a median duration of therapy about 96 months (range 22–180) were included in our study, median age was 56 years, 15 were males, 16% cirrhotics. 22 patients received monotherapy Nucs (11 lamivudine, 5 entecavir, 4 tenofovir) and 2 patients received lamivudine and adenofovir combination therapy. Only 11 from the 24 patients (46%) developed anti-Hbs (level anti-Hbs <100 IU/ml in 5 and 100–500 IU/ml in 6) whereas 13 patients remained persistantly anti-Hbs negative during follow-up. All the patients stopped Nucs therapy after a median duration of consolidation therapy of 12 months (range 0–70). No case of biochemical and virological breakthrough were reported during 24 months (range 06–180) of post treatment follow.

Conclusion: Loss of HbsAg is a rare event in HbeAg-negative CHB patients who were treated with Nucs. However regardless of anti-Hbs seroconversion and duration of consolidation long –term therapy with Nucs, therapy can be safely discontinued in clinical practice in patients with HbsAg loss, in those with advanced liver disease.

FRI-336

Evaluation of renal and bone safety in post liver transplant patients with chronic kidney disease receiving Tenofovir Alafenamide for HBV prophylaxis

E. Gane[1], B. George[1], S. Munn[1], H. Wang[2], V. Suri[2], J.F. Flaherty[2], A. Gaggar[2]. *[1]NZLTU, Auckland City Hospital, Auckland, NZ; [2]Gilead Sciences, Inc, Foster City, California, USA*
Email: vithika.suri@gilead.com

Background and Aims: Chronic Hepatitis B (CHB) remains a leading indication for orthotopic liver transplantation (OLT) worldwide. Common complications following OLT include renal dysfunction secondary to perioperative renal injury and post-operative nephrotoxicity from calcineurin inhibitors; osteoporosis is also observed secondary to preoperative malnutrition and post-operative corticosteroids. In this setting, antiviral prophylaxis to prevent recurrent HBV infection with tenofovir alafenamide (TAF) may have advantages over tenofovir disoproxil fumurate (TDF) due to its improved renal and bone safety profile.

Method: In this Phase 2 study (NCT02862548), liver transplant recipients with stage 2 or greater chronic kidney disease and receiving antiviral prophylaxis with TDF were randomized 1:1 to either receive TAF 25 mg QD or continue their TDF containing regimen. The primary efficacy analysis was the percent of patients who maintained viral suppression at Week 24. Key pre-specified secondary safety endpoints were changes in hip and spine bone mineral density (BMD), changes in serum creatinine (sCr), estimated GFR by CKD-EPI formula and direct GFR assessment (Chromium-EDTA Renal Scan; Cr-EDTA) over 48 weeks.

Results: 51 patients were randomized and treated at a single site in New Zealand. Baseline characteristics included: mean age 60 years, 75% males, 53% Pacific Islander and mean baseline $eGFR_{CKD-EPI}$ 52 ml/min/1.73 m^2 with 53% of patients with <50 ml/min/1.73m^2. The median baseline surface area corrected $GFR_{Cr-EDTA}$ was 58 ml/min/1.73 m^2. The median interval since transplantation was approximately 9 years. Seventy-six percent of patients were maintained on tacrolimus and 29% remained on long-term prednisone. Of the 47 patients that have reached Week 12 to date, all patients (25 in TAF; 22 in TDF arm) maintained viral suppression. There were no treatment discontinuations and serious adverse events were numerically lower in TAF arm compared to the TDF arm. Switching to TAF treatment resulted in a trend toward improved sCr levels (median change in mg/dl: –0.07 for TAF vs. –0.02 for TDF; p = 0.09) and improved $eGFR_{CKD-EPI}$ (median change in ml/min/1.73 m^2: 2.7 for TAF vs. 0.8 for TDF; p = 0.14) as early as week 12 (Figure). Complete data including changes in bone parameters at week 24 will be available at the time of the presentation.

Conclusion: Early after switching from TDF to TAF in a liver transplant recipient population with high rate of renal dysfunction, viral suppression is maintained while smaller changes in renal function were observed.

FRI-337

RO7020531, a novel prodrug of a toll-like receptor 7 agonist, is safe, well tolerated and activates TLR signaling in healthy volunteers

E. Gane[1], I. Folitar[2], C. Schwabe[1], I. Rodriguez[3], L. Gao[4], E. Calleja[5], R. Upmanyu[6], T. Racek[2], E. Coakley[4], J. Grippo[3]. *[1]Auckland Clinical Studies, Auckland, New Zealand; [2]Roche Innovation Center Basel, Basel, Switzerland; [3]Roche Innovation Center New York, New York, United States; [4]Roche Innovation Center Shanghai, Shanghai, China; [5]Roche Innovation Center New York (former employee); [6]Roche Products Ltd, Welwyn Garden City, United Kingdom*
Email: ilia.folitar@roche.com

Background and Aims: RO7020531 is a double prodrug of RO7011785, a selective toll-like receptor (TLR) 7 agonist with lower potency to activate TLR8. It is being developed as a component of a regimen to cure chronic hepatitis B virus (HBV) infection. TLR7 agonism can drive anti-HBV effects through augmented host immune activity via T- and B- cell activation and cytokine production. The aim of this first-in-human clinical study was to evaluate safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of this immune enhancer in healthy volunteers.

Method: Single oral doses of RO7020531, ranging 3–170 mg, were administered to 80 healthy volunteers in 8 dosing cohorts. Each cohort enrolled 10 subjects randomized 8:2 to RO7020531 or placebo, respectively. Safety and tolerability evaluations included adverse

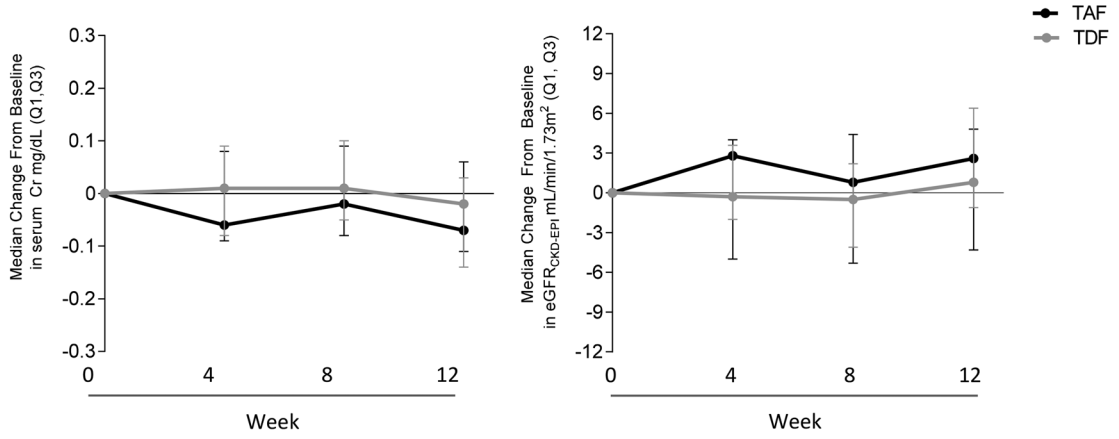


Figure 1: (abstract: FRI-336)

events (AEs), vital signs, ECGs, and laboratory assessments. Plasma PK of RO7020531 and RO7011785, and PD markers of TLR7 response were measured at regular time intervals to 96 hrs post dose.

Results: A blinded safety evaluation demonstrated that all single doses including the highest dose evaluated (170mg) were considered safe and well tolerated. There were few AEs per cohort, the most frequent (>2 subjects) being headache and nausea. All AEs were mild in intensity, and only 3 subjects (10 mg (n = 2) and 170 mg (n = 1)) reported AEs that were considered related to study drug. No serious AEs or discontinuations due to AE were reported.

Across all cohorts, the active TLR7 agonist, RO7011785 appeared rapidly in plasma with a median Tmax of ~0.5 hrs and was eliminated with mean terminal half-life of 3 hrs. Mean plasma RO7011785 AUC increased proportionally from 3 mg to 170 mg doses with relatively low intersubject variability.

Single 100 mg and 140 mg doses activated a cascade of TLR7 responses with initial increases of interferon-alpha within the first 6hrs followed by increased transcription of TLR7, ISG15, MX1 and OAS1 and appearance of plasma IP10 at 12hrs and neopterin 48hrs post dose. The proportion of subjects responding increased from 3/8 (100 mg) to 5/8 (140 mg) with increasing dose. PD data for the 170 mg cohort are pending.

Conclusion: RO7020531, a double prodrug TLR7 agonist, was considered safe and well tolerated with a favorable PK profile in single doses up to 170 mg. The demonstration of TLR7 signaling supports exploring the further development of RO7020531 as a key component of an HBV cure regimen.

FRI-338

Ledipasvir/Sofosbuvir for 12 weeks is safe and effective in adolescents with chronic hepatitis C virus infection and hematological malignancies undergoing chemotherapy

M.H. El-Sayed[1], F.S.E.S. Ebeid[1], A.R. Zekri[2], B. Massetto[3], K. Kersey[3], A. Osinusi[3], F. Zhang[3], D. Brainard[3], W. Elsayed[4], A. El-Haddad[4].
[1]Children's Hospital, Ain Shams University, Pediatric Department, Hematology/Oncology Division, Cairo, Egypt; [2]National Cancer Institute, Virology Department, Cairo, Egypt; [3]Gilead Sciences, Foster City, United States; [4]National Cancer Institute, Pediatric Oncology Department, Cairo, Egypt
Email: manalhelsayed@yahoo.co.uk

Background and Aims: The prevalence of chronic active HCV infection among children in Egypt ranges from 0.2% to 0.8% and among children with haematological malignancies, rates of up to 24% have been reported. While the natural history of HCV infection in children is benign compared to that of adults, ALT flares during chemotherapy in HCV-infected children with hematological malignancies have been associated with more rapid liver disease progression and higher risk of malignancy relapse due to chemotherapy interruption.

Method: Patients 12 to <18 years old with chronic HCV genotype (GT) 1 or 4 infection and undergoing maintenance chemotherapy for hematological malignancies were enrolled into this ongoing open-label, Phase 2 study at 1 site in Egypt, to receive Ledipasvir/Sofosbuvir (LDV/SOF) (90 mg/400 mg) fixed dose combination tablet once daily for 12 weeks. The key efficacy endpoint is sustained virologic response 12 weeks after treatment (SVR12). Safety was assessed by adverse events (AEs) and clinical/laboratory data, including HCV flares defined as an increase in ALT ≥ 3 x baseline and HCV RNA elevation $\geq 1 \times \log_{10}$ from baseline. An interim analysis on the first 13 patients enrolled is presented.

Results: 13 adolescents with a diagnosis of leukemia receiving maintenance chemotherapy were treated with LDV/SOF. 85% were males, 54% had IL28B non CC genotype, and all were infected with HCV GT4 and were HCV treatment naïve. The mean age was 15 years (range 12–17), mean weight was 56 kg (range 46–91) and mean BMI was 21 kg/m^2 (19–32). All patients completed HCV treatment and all 12 patients who have reached 12 weeks post treatment achieved SVR12. The most common AEs reported were diarrhea (3, 23%), vomiting (3, 23%), headache (3, 23%) and pyrexia (4, 31%). 4 patients experienced mild to moderate AEs considered by the investigator related to study drug: headache (3 patients) or generalized pruritus (1 patient); none required chemotherapy interruption. 2 patients had 1 serious AE each (both pneumonia), assessed by the investigator as not related to study drug in both cases. There were no deaths, and no patient experienced HCV flares.

Conclusion: In adolescents with HCV GT4 and leukemia undergoing maintenance chemotherapy, LDV/SOF daily for 12 weeks was well tolerated and resulted in a 100% SVR12 rate in the 12 patients who have reached that timepoint. These data support the use of this all-oral, interferon-and ribavirin-free regimen in adolescents with hematological malignancies.

FRI-339

Clinical and virological predictors of response after antiviral therapy interruption in HBeAg-negative chronic hepatitits B

S. Lens[1], M. García-López[1], Z. Mariño[1], M. Bonacci[1], S. Rodríguez-Tajes[1], E. Perpiñan[1], F. Rodríguez-Frías[2], B. Testoni[3], G. Koutsoudakis[1], M.B. Ferret[2], F. Zoulim[3], Sofía Pérez del Pulgar[1], X. Forns[1]. *[1]Hospital Clinic, IDIBAPS, CIBERehd. University of Barcelona, Liver Unit, Barcelona, Spain; [2]Hospital Vall Hebron, CIBERehd., Internal Medicine, Hepatology Section, Barcelona, Spain; [3]Cancer Research Center of Lyon (CRCL), University of Lyon, UMR_S1052, UCBL, INSERM, U1052, Lyon, France*
Email: slens@clinic.ub.es

Background and Aims: The possibility of stopping nucleos(t)ide analog (NA) therapy in virologically suppressed HBeAg-negative (HBeAg-) patients has been considered in the recent European clinical guidelines. However, the variables predicting a successful discontinuation of NA in this population have not been defined yet. Aim: To investigate the epidemiological, virological and clinical factors associated to a successful NA therapy discontinuation in HBeAg- patients.

Method: Prospective study including non-cirrhotic patients with HBeAg- chronic hepatitis B with viral suppression for more than 3 years under NA therapy. Patients underwent a liver biopsy at inclusion to exclude the presence of advanced fibrosis and to analyze total intrahepatic HBV-DNA(iHBV-DNA) and cccDNA. Standard liver tests with viral serum markers (HBV-DNA, qHBsAg, HBcrAg) were performed at 1-month intervals after NA discontinuation.

Results: Twenty patients have been included so far. Most (85%) were male; median age was 52 years-old. The median duration of NA therapy was 9 years, 16 (80%) received tenofovir. Median (IQR) qHBsAg levels at baseline were 1439 IU/mL (558–3379) and correlated significantly with iHBV-DNA levels (rho = 0.7, $p < 0.01$) and HBcrAg (rho = 0.5, $p < 0.05$) but not with cccDNA levels. After a median follow-up of 43 weeks, 16 patients (80%) remained off-therapy and 5 (25%) presented HBsAg loss. ALT (>3UNL) and DNA peaks (>20,000 IU/ml) were frequently observed during follow-up in 40% and 50% of patients, respectively. Patients with HBsAg loss had significantly lower baseline qHBsAg (63 vs 2122 IU/ml, $p < 0.01$) and iHBV-DNA levels (0.04 vs 0.98 copies/cell, $p < 0.01$). There were no adverse events related to therapy discontinuation.

Conclusion: Antiviral therapy discontinuation is feasible in a high proportion of HBeAg- Caucasian patiens under NA therapy. Interestingly, low qHBsAg levels are associated with a high chance of HBsAg loss, particularly if associated with low iHBV-DNA (but not cccDNA) levels.

FRI-340

Five years follow-up of chronic hepatitis B patients immunized by nasal route with the therapeutic vaccine HeberNasvac

A. Julio, J. Aguiar, G. Guillen, E. Penton, G. Fernandez. *Center for Genetic Engineering and Biotechnology, Vaccines, Havana, Cuba*
Email: julio.aguilar@cigb.edu.cu

Background and Aims: A novel therapeutic vaccine for chronic hepatitis B (CHB) treatment comprising the recombinant hepatitis B surface (HBsAg) and nucleocapsid (HBcAg) antigens has been developed in the last two decades. Preclinical and clinical trials (CT) evidenced safety and immunogenicity in animal models as well as in phase I and I-II CT. Recently, a phase III CT evidenced the superiority of therapeutic vaccination in terms of safety and efficacy compared to PegIFN. These studies were conducted in healthy volunteers and treatment-naïve CHB patients vaccinated by both IN and SC routes. However, pharmacological studies have shown that the nasal route *per se* deserve further attention. The aim of the present study is to evaluate the long term efficacy results in the first 6 patients treated with the therapeutic vaccine HeberNasvac and immunized by the IN route in order to preliminarily understand the effect of the route after five years follow-up.
Method: The phase I clinical trial was conducted in 6 CHB patients previously treated with α-IFN, 3 of them HBeAg positive. Patients were immunized with 100 μg HBsAg and 100 μg HBcAg (HeberNasvac), via nasal spray in ten administrations, every two weeks. Samples from these patients were preserved for a period of five years after the end of treatment to retrospectively analyze the serological and virological variables. Clinical efficacy was monitored by assessing the levels of HBV DNA, ALT, HBeAg to anti-HBeAg seroconversion as well as by qualitative/ quantitative HBsAg serology during this period of time.
Results: After five year follow-up HBeAg loss was verified in the three HBeAg (+) patients, in two cases with seroconversion to anti-HBeAg. A reduction to undetectable viral load was observed in 5 out of 6 patients and in two cases there were HBsAg seroconversion. ALT increases above 2X ULN were only detected in HBeAg (+) patients and associated to HBe antigen loss. All patients were negative for cirrhosis or moderate fibrosis (<7.8 KPa by Fibroscan assessment) at the end of this period. It was not required any alternative medication due to sustainedly normal LFTs and absence of treatment criteria.
Conclusion: In conclusion, HeberNasvac administration was not associated to any safety concern 5 years after the end of treatment. Virological, biochemical, serological variables evidenced the efficacy of this product in this difficult to treat group of patients as well as the absence of disease progression. The use of the intranasal route deserves further evaluation as most of the patients with CHB lives in countries where unsafe injections are frequent and, in addition, the nasal route may further potentiate the immune response in the liver.

FRI-341

Association of metabolic adipokines with persistence of fibrosis in chronic hepatitis B during long-term nucleoside analogue therapy

K.-S. Cheung[1], L.-Y. Mak[1], W.-K. Seto[2,3], D. Wong[2,3], F. Liu[2], Y.Y. James Fung[2,3], C.L. Lai[2,3], M.-F. Yuen[2,3]. *[1]The University of Hong Kong, Queen Mary Hospital, Medicine, Hong Kong; [2]The University of Hong Kong, Medicine, Hong Kong; [3]State Key Laboratory for Liver Research, The University of Hong Kong, Hong Kong*
Email: wkseto@hku.hk

Background and Aims: Liver fibrosis regression during nucleoside analogue (NA) treatment in chronic hepatitis B (CHB) is not guaranteed. There is emerging evidence on metabolic factors being associated with persistence of fibrosis in on-treatment CHB. There are emerging interests in metabolic biomarkers that reflect adipokine dysregulation, e.g. adiponectin, fatty acid-binding protein 4 (FABP4), fibroblast growth factor (FGF-21) and homeostatic model assessment-insulin resistance (HOMA-IR). Their role in CHB-related liver injury has not been well investigated.
Method: We recruited 414 on-treatment CHB patients and performed transient elastography for liver stiffness and controlled attenuation parameter (CAP). Significant fibrosis was defined based on the alanine aminotransferase (ALT)-based EASL-ALEH criteria, while severe steatosis was defined as the presence of CAP ≥ 280 dB/m. Logistic regression was used to investigate the risk factors associated with the development of severe steatosis and significant fibrosis. Apart from the above four variables of interest, we also considered clinical, metabolic, biochemical and virologic parameters.
Results: There were 296 (71.5%) male patients, and the median age of the cohort was 60.2 years (interquartile range [IQR]: 54.2–65.3 years). The median duration of NA treatment was 73.6 months (IQR: 43.0–93.4 months); 378 (91.3%) patients had undetectable HBV DNA (<20IU/ml) at assessment. Severe steatosis and significant fibrosis were found in 89 (21.5%) and 167 (56.4%) patients, respectively. The median adiponectin level was significantly lower among patient severe steatosis than those without severe steatosis (7.6 vs 11.4 ug/ml, $p < 0.001$), while there were no statistically significant differences for

Table: (abstract: FRI-341)

Table 1. Comparison of the median levels of various adipokines between (a) patients with and without severe steatosis; (b) patients with and without significant fibrosis

a	Severe steatosis	Absence of severe steatosis	p-value
FGF-21 (pg/mL)	182.0	231.0	> 0.05
FABP4 (pg/mL)	138.8	93.6	> 0.05
Adiponectin (ug/mL)	7.6	11.4	**< 0.001**
HOMA-IR (mU/L)	6.4	5.7	> 0.05
b	**Significant fibrosis**	**Absence of significant fibrosis**	**p-value**
FGF-21 (pg/mL)	220.0	218.0	> 0.05
FABP4 (pg/mL)	126.8	73.7	**< 0.001**
Adiponectin (ug/mL)	10.2	10.5	> 0.05
HOMA-IR (mU/L)	6.6	5.1	**0.006**

other adipokines (Table 1a). The median FABP4 level was significantly higher among patients with significant fibrosis than those without significant fibrosis (126.8 vs 73.7 pg/ml, p < 0.001), and the median HOMA-IR level was significantly higher (6.6 vs 5.1 mU/l, p = 0.006), while there were no statistically significant differences for other adipokines (Table 1b). Independent risk factors for significant fibrosis included severe steatosis (OR: 2.22, 95% CI: 1.45–4.34), DM (OR: 1.90, 95% CI: 1.03–3.53), thrombocytopenia (OR: 3.78, 95% CI: 2.19–6.65), a lower albumin level (OR 0.90, 95% CI: 0.82–0.98), a higher AST level (OR: 1.05, 95% CI: 1.01–1.10), a higher GGT level (OR: 1.02, 95% CI: 1.01–1.03) and a higher FABP4 level (OR: 1.0016, 95% CI: 1.0003–1.0032).

Conclusion: Both a higher FABP4 level and severe steatosis were independently associated with the presence of severe fibrosis in NA-treated CHB. FABP4 is a marker of fatty acid uptake, transport and metabolism; its role in the fibrogenesis process of CHB requires further investigation.

FRI-342

Tenofovir Disoproxil Fumarate use during pregnancy and infant bone health and growth: the Tenofovir in pregnancy study

A. Kourtis[1], J. Wiener[2], L. Wang[3], B. Fan[4], J. Shepherd[4], L. Chen[5], W. Liu[6], C. Shepard[7], L. Wang[8], A. Wang[8], M. Bulterys[9]. [1]*CDC, dRH;* [2]*CDC, DRH;* [3]*GAP, CDC;* [4]*UCSF, Radiology;* [5]*Guangxi REgion Health and Family Planning Commission, Health and Family Planning Commission;* [6]*Guangxi Center for Disease Control and Prevention, Guangxi Cdc;* [7]*CDC, CGH Gap;* [8]*China Cdc;* [9]*WHO, Dept of HIV and Hepatitis*
Email: apk3@cdc.gov

Background and Aims: There is limited information on bone mineral density and content (BMD, BMC) of infants exposed *in utero* to tenofovir.

Method: The Tenofovir in Pregnancy (TiP) study was a phase II randomized controlled trial of the safety of a regimen containing vs. one not containing tenofovir disoproxil fumarate (TDF), starting as early as 14 weeks gestation, in HIV/HBV co-infected pregnant women and their infants in Guangxi, China (ClinicalTrials.gov, number NCT01125696). Our objective was to assess the effects of TDF exposure *in utero* on infant BMD and BMC, assessed by DXA scans at birth and at 6 months of life, and to assess effects on infant growth, by comparing TDF-exposed and unexposed infants, unadjusted and adjusted for covariates.

Results: Fourteen TDF-exposed and 13 tenofovir-unexposed infants had evaluable BMD and BMC measurements at birth. Tenofovir exposed infants were similar to unexposed infants on mean gestational age (38.1 vs 38.4 weeks) and birth weight (2695 vs 2861 g). The mean difference in BMC between TDF-exposed infants and unexposed infants was −6.4 g (95% confidence interval =−19.9, 7.1) at birth and −5.7 g (95% confidence interval =−26.0, 14.7) at 6 months. The mean difference in BMD at both birth and 6 months between TDF-exposed infants and unexposed infants was −0.01 g/cm^2 (95% confidence interval =−0.02, 0.01). Similar results were obtained when the mean difference in BMC was estimated using a linear mixed model to account for repeated measurements and adjust for relevant covariates (−6.6 g, 95% confidence interval =−16.6, 3.5). Infant weight and height were also similar in the two groups at 6 and 12 months of age.

Conclusion: Maternal TDF use during the second and third trimester of gestation led to non-significant mild decreases in infant BMC and BMD ranging from 10% to 4% and 6% to 3%, respectively, from birth to 6 months of age, that are of uncertain clinical significance. No effects on infant growth were observed through the first year of life.

FRI-343

Updated follow-up analysis in the REP 401 protocol: Treatment HBeAg negative chronic hepatitis B infection with REP 2139 or REP 2165, tenofovir disoproxil fumarate and pegylated interferon alfa-2a

A. Vaillant[1], M. Bazinet[1], V. Pantea[2], G. Placinta[2], I. Moscalu[3], V. Cebotarescu[2], L. Cojuhari[2], P. Jimbei[4], L. Iarovoi[2], V. Smesnoi[4], T. Musteata[4], A. Jucov[3], A. Krawczyk[5]. [1]*Replicor Inc, Montreal, Canada;* [2]*Nicolae Testemitanu State University of Medicine and Pharmacy, Department of Infectious Diseases, Faculty of Postgraduate Education, Chisinau, Moldova;* [3]*ARENSIA Exploratory Medicine, Phase I Unit, Republican Clinical Hospital, Chisinau, Moldova;* [4]*Toma Ciorba Infectious Clinical Hospital, Chisinau, Moldova;* [5]*Universitätsklinikum Essen, Institute for Virology, Essen, Germany*

Background and Aims: The REP 401 study (NCT02565719) is assessing the safety and efficacy of REP 2139 (clinical lead) or REP 2165 combined with tenofovir disoproxil fumarate (TDF) and pegylated interferon α-2a (peg-IFN) in Caucasian patients with chronic HBeAg negative HBV infection.

Method: Lead-in TDF therapy in 40 patients was followed by randomization into an experimental group (48 weeks of TDF, peg-IFN and REP 2139 or REP 2165) or a control group (24 weeks of TDF + peg-IFN) who crossed over to 48 weeks of experimental therapy. Viremia is monitored on the Abbott Architect and Realtime platforms.

Results: Therapy was well tolerated except for one withdrawal due to pegIFN-related depression. Follow-up has been extended to 24 weeks in 18/20 experimental patients and 4–12 weeks in 17/20 crossover patients.

HBV DNA was controlled in all patients during TF lead-in and throughout therapy. Following randomization, experimental patients had HBsAg reductions as follows: 17/20 > 1 log from baseline, 14/20 < 1IU/ml and 13/20 < 0.01 IU/ml. Following crossover in control patients HBsAg reductions were as follows: 19/20 > 1 log from baseline, 14/20 < 1IU/ml and 10/20 < 0.01 IU/ml.

HBsAg < 1 IU/ml in experimental patients was accompanied by increases in anti-HBs (range 25–223,055 mIU/ml) in 13/14 patients and therapeutic liver flares (ALT/AST > 5x ULN with normal synthetic liver function) in 12/14 patients. In control patients, transaminase flares in patients with HBsAg < 1 IU/ml were attenuated but anti-HBsAg elevations were comparable to the experimental group.

Functional control of HBV infection (HBsAg < LLOQ, HBV DNA < LLOQ) is persisting 24 weeks after removal of therapy in 12/14 experimental patients achieving HBsAg <1 IU/ml (REP 2139: 7/10, REP 2165: 5/10) and is stable in the remaining 2 patients. In control patients, functional control of HBV infection is persisting 4-12 weeks in 11/12 patients achieving HBsAg < 1 IU/ml (REP 2139: 4/10, REP 2165 7/10) with available follow-up data and is stable in the remaining patient. Functional control of HBV infection in both groups is accompanied by normalization of ALT/AST in all but 5 patients.

Conclusion: NAPs are effective and well tolerated in combination with peg-IFN and TDF in HBeAg negative chronic HBV infection and elicit the establishment of functional control of HBV infection persisting after removal of therapy and normalization of liver function in a majority of patients.

FRI-344

A randomized, double-blind, double-dummy, controlled, multicenter study of entecavir maleate versus entecavir for treatment of Chinese chronic hepatitis B predominantly genotype B or C: results at week 240

J.-H. Xu[1], C.-D. Jing[1], X.-F. Chen[1], S. Wang[2], Z. Zeng[1], C.-W. Si[1], J. LI[3], Q. Mao[4], D.-Z. Zhang[5], H. Tang[6], J.-F. Sheng[7], X.-Y. Chen[8], Q. Ning[9], G.-F. Shi[10], Q. Xie[11], J. Dai[12], X.-Q. Zhang[12], Z.-N. Xu[12], Y.-Y. Yu[1]. [1]*Dept. of Infectious Diseases, Peking University First Hospital, Peking University, Beijing, China;* [2]*Peking University First Hospital, Beijing, China;* [3]*Jiangsu Province Hospital, Dept. of Infectious Diseases, Nanjing, China;* [4]*The First Affiliated Hospital of The Third Military Medical University, Dept. of*

Infectious Diseases, Chongqing, China; [5]The Second Affiliated Hospital of Chongqing Medical University, Dept. of Infectious Diseases, Chongqing, China; [6]Dept. of Infectious Diseases, West China Hospital, Sichuan University, Chengdu, China; [7]Department of Infectious Diseases, The First Affiliated Hospital, Zhejiang University, Hangzhou, China; [8]Beijing You'An Hospital, Capital Medical University, Beijing, China; [9]Dept. of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [10]Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China; [11]Dept. Infectious Disease, Rui Jin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China; [12]Institute of Drug Research, Jiangsu Chia-tai Tianqing Pharmaceutical Co., Ltd, Nanjing, China
Email: yyy@bjmu.edu.cn

Background and Aims: The efficacy and safety of long-term entecavir (ETV) treatment in chronic hepatitis B (CHB) has been reported previously. But the limitations in those reports undermined the credibility of the results, including the dosage change of entecavir, exposure to drugs other than entecavir during study, lower percentage of patients completing follow-up, insufficient sample size and lower percentage of patients infected by genotype B and C hepatitis B virus (HBV). The present, randomized, double-blind, double-dummy, controlled, multicenter study was designed to evaluate the efficacy and safety of ETV maleate versus ETV in Chinese patients with CHB predominantly genotype B or C. The results at week 144 have been reported before (2016 AASLD liver meeting). Here we present the results at week 240.
Method: Patients were randomly assigned to receive 48 weeks of treatment with either 0.5 mg/day ETV or 0.5 mg/day ETV maleate, then all patients received the treatment with 0.5 mg/day ETV maleate through week 240. HBV DNA levels were measured by the Roche Cobas Ampliprep/Cobas Taqman PCR assay. Adverse events (AE) were recorded.
Results: Two hundred and eighteen (110 in group A) patients with HBeAg-positive CHB and 57 (26 in group A) patients with HBeAg-negative CHB were enrolled. Baseline characteristics were well balanced between the two groups, predominantly (98.5%) genotype B or C. One hundred and thirty-seven (71 in group A) patients with HBeAg- positive CHB and 46 (21 in group A) patients with HBeAg-negative CHB completed the 240-week treatment and follow-up. For the patients with HBeAg-positive CHB, the mean HBV DNA level had similarly decreased from baseline in both groups (A: by 6.67$\log_{10}$IU/ml vs. B: by 6.74$\log_{10}$IU/ml; $p > 0.05$) at week 240. Patients who achieved undetectable levels of serum HBV DNA (<20 IU/ml) at week 240 were similar in the two groups (A: 91.55% vs. B: 87.88%; $p > 0.05$). Both groups achieved similar HBeAg seroconversion rates at week 240 (A: 26.98% vs. B: 20.97%; $p > 0.05$). Both groups achieved similar normalization of ALT at week 240 ($p > 0.05$). For the patients with HBeAg- negative CHB, the mean HBV DNA level had similarly decreased from baseline in both groups (A: by 6.05$\log_{10}$ IU/ml vs. B: by 6.10 $\log_{10}$IU/ml; $p > 0.05$) at week 240. Patients who achieved undetectable levels of serum HBV DNA (<20 IU/ml) at week 240 were similar in the two groups (A: 100% vs. B: 100%). Both groups achieved similar normalization rates of ALT at week 240 ($p > 0.05$). The overall incidence of AE was similar in the two groups.
Conclusion: ETV maleate and ETV showed similar efficacy and safety in Chinese patients with CHB predominantly genotype B or C.

FRI-345
Sustained virological suppression and improved renal function with reduced dose tenofovir disoproxil fumarate in renally compromised patients with chronic hepatitis B

S. Liem[1,2], D. Wong[1], S. Fung[1], A. Zahirieh[3], C. Yim[1], H.A Shah[1], J. Feld[1,4], B. Hansen[1,2,5], H. Janssen[1]. *[1]University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; [2]Erasmus University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [3]Sunnybrook Health Sciences Centre, Toronto, Canada; [4]University of Toronto, McLaughlin-Rotman Centre for Global Health, Toronto, Canada; [5]University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada*
Email: k.s.liem@erasmusmc.nl

Background and Aims: Tenofovir disoproxil fumarate (TDF) therapy effectively suppresses viral replication in patients with chronic hepatitis B (CHB), but occasionally leads to renal impairment. We studied prevalence of viral breakthrough (VBT) and renal function in renally impaired CHB patients on reduced dose TDF, and in patients on full dose TDF.
Method: CHB patients with full and reduced dose TDF (due to eGFR (Cockcroft-Gault) <50 ml/min/1.73 m^2 ± serum phosphate <0.8 mmol/l) were identified at Toronto Centre for Liver Disease. VBT (confirmed HBV DNA > 1logIU/ml above nadir on-therapy (AASLD)), and biochemical breakthrough (confirmed ALT > 1.5xULN) were assessed from 1 month after start of (reduced) TDF dose (baseline) until end of follow-up (EOF). Renal function was assessed by Modification of Diet in Renal Disease (MDRD) and categorized into chronic kidney disease stages 1–5. Outcome was compared between full and reduced dose TDF, and between before and after dose reduction within patients who started on full dose TDF.
Results: Out of 750 patients on TDF, 78 (10%) had reduced dose vs. 672 (90%) full dose. At baseline the mean (SD) age was 69 (10) vs. 45 (13) years, 69% vs.70% was male, mean duration on TDF was 3.4 (2.4) vs. 4.7 (3.1) years for reduced vs. full dose of TDF. Of patients on reduced TDF dose 71% had undetectable HBV DNA (mean 1.4logIU/ml), 82% received TDF 300mg Q48hr (range 75 mg – 300 mg Q48hr), mean MDRD was 52 (19) ml, 42% had chronic kidney disease stage G3b or higher and 12% had decompensated cirrhosis. Mean follow-up was 2.6 (2.3) years. VBT occurred in 1 cirrhotic patient on dialysis using TDF 300 mg weekly (HBV DNA peak 3.6 log) that resolved 4 months after dose increase to biweekly without signs of decompensation, and in 1 patient on full dose TDF (resolved spontaneously). Viral blips (HBVDNA between 1 and 2 logs on 1 occasion) occurred in 2.6% before vs. 5.4% after dose reduction ($p = 0.53$), and in 2.8% of patients on continuous full dose TDF. One biochemical breakthrough occurred in a reduced dose patient (ALT peak 2xULN) and resolved spontaneously without VBT. During dose reduction the MDRD increased from baseline to EOF (+6.0 (21) ml; $p = 0.04$) and 50 (64%) patients reached eGFR > 50ml.
Conclusion: In CHB renal dose adjustment of TDF did not lead to significant VBT while renal function improved. This implies that renal dosing of TDF in CHB is effective and safe, and should be considered a viable option in renally compromised patients.

FRI-346
Low serum HBsAg and HBV DNA predict response of peg-interferon addition to entecavir in HBeAg positive chronic hepatitis B

S. Liem[1,2], B. Hansen[1,3,4], Q. Xie[5], C. Liang[6], W.P. Brouwer[3], H. Chi[3], S. Guo[6], X. Qi[6], N.-P. Zhang[7], T. Fehmi[8], M.V. Campenhout[3], H. Janssen[1]. *[1]University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; [2]Erasmus University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Toronto, Canada; [3]Erasmus University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [4]University of Toronto, Institute of Health Policy, Management and Evaluation, Toronto, Canada; [5]Jiaotong University, Department of Infectious Diseases, Ruijin Hospital, Shanghai, China; [6]Fudan University, Department of Hepatitis Disease, Shanghai Public Health Clinical Center, Shanghai, China; [7]Zhongshan Hospital, Department of Gastroenterology and Hepatology, Shanghai, China; [8]Cerrahpasa Medical Faculty, Istanbul, Turkey*
Email: k.s.liem@erasmusmc.nl

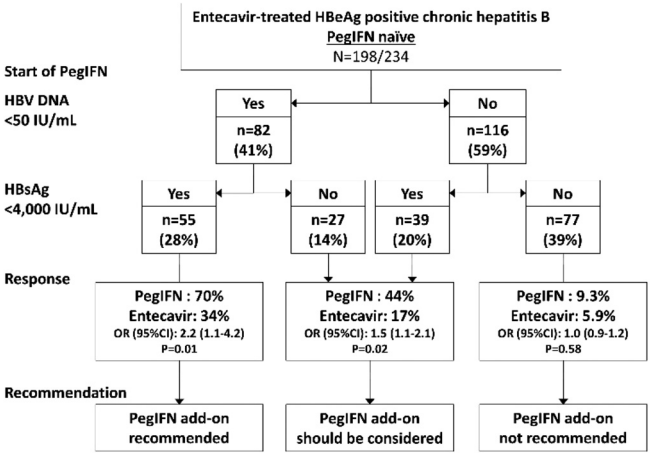
Background and Aims: Addition of peg-interferon (PegIFN add-on) to nucleos(t)ide analogues is effective in a select group of patients with chronic hepatitis B (CHB), but the optimal candidates for PegIFN add-on remain are yet to be identified. To establish clinical starting

rules for PegIFN add-on, we studied the relationship between cut-off values of serum Hepatitis B surface Antigen (HBsAg) and hepatitis B virus (HBV) DNA at start of PegIFN and response at off-treatment follow-up in 234 HBeAg positive CHB patients treated with PegIFN add-on to entecavir (ETV) or continued ETV monotherapy.

Method: HBeAg positive patients from two investigator-initiated, randomized controlled trials were included. Patients received ETV pretreatment for at least 24 weeks and were then (baseline) allocated to 24–48 weeks of ETV + PegIFN alpha add-on, or 24–48 weeks of continued ETV monotherapy. Response was defined as a combination of HBeAg loss with HBV DNA < 200 IU/ml 48 weeks after PegIFN cessation. Cut-off values for HBV DNA and HBsAg at baseline were based on a minimum response difference of 15% between PEG-IFN add-on and ETV monotherapy, and a significant difference between add-on vs. monotherapy below the HBV DNA cut-off, but not above. Receiver Operating Characteristic curves were constructed for each threshold and the Area Under the Curve (AUC) of the thresholds was calculated.

Results: Of 234 patients, 118 started on PegIFN add-on and 116 continued ETV monotherapy. Baseline characteristics of both groups were comparable. Mean baseline HBV DNA was 2.2 (SD 2.4) log IU/mL, median ALT 0.5 (IQR 0.4–0.8) × ULN, and mean HBsAg 3.6 (0.8) logIU/ml. Response was achieved by 38/118 (32%) patients with add-on therapy and 23/116 (23%) on ETV monotherapy ($p = 0.03$). The highest probability of response to PEG-IFN add-on compared to ETV monotherapy (70% vs. 34%, $p = 0.01$) was found in PEG-IFN naïve patients with an HBsAg level below 4,000 IU/ml and HBV DNA level below 50 IU/ml at baseline. The AUC of the combined cut-off values was 0.79 (95%CI: 0.72–0.86). Above these cut-off levels, response rates were very low and not significantly different between treatment groups (9.3% vs. 5.9%, $p = 0.58$).

Algorithm. Probability of response at end-of-follow-up based on HBsAg and HBV DNA



Conclusion: PegIFN add-on to ETV therapy was associated with higher response rates compared to ETV monotherapy in patients with CHB. Based on our study, PegIFN add-on may be recommended in PegIFN naïve patients with serum HBsAg <4,000 IU/ml and HBV DNA <50 IU/ml as off-treatment response was 70%.

FRI-347

Renal outcomes in chronic hepatitis b patients treated with tenofovir disoproxil fumarate or entecavir: a propensity score matched study

S. Trinh[1], A. Le[1], J. Hoang[1], D. Jeong[1], M. Chung[1,2], M.-H. Lee[3], U. Wang[1], M. Nguyen[1]. *[1]Stanford University Medical Center, Division of Gastroenterology and Hepatology, Palo Alto; [2]Princeton University, Princeton, [3]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan*
Email: mindiehn@stanford.edu

Background and Aims: Studies on the use of tenofovir disoproxil fumarate (TDF) causing nephrotoxicity or impaired renal function remain undetermined. Entecavir (ETV) has been shown to not cause any renal dysfunction. Thus, we aim to further compare renal outcomes of patients with chronic hepatitis b (CHB) who were treated with either TDF or unexposed to TDF, ETV.

Method: This is a matched cohort study with adult CHB patients consecutively identified via ICD-9 query at a tertiary medical center in the United States from 2000 to 2016. Data were collected via individual chart review by standardized procedure. Overall, we identified 240 ETV and 172 TDF patients with serial creatinine labs who were treated for at least 12 months. Patients with prior adefovir treatment, hepatitis C, hepatitis D, or human immunodeficiency virus co-infection, were excluded. Patients with baseline estimated glomerular filtration rate (eGFR) <60 was excluded for one of the analyses (eGFR calculated via the modification of diet in renal disease study formula). Propensity score matching (PSM) (for age, sex, baseline eGFR, hypertension, diabetes mellitus, and follow-up duration) was performed to adjust for background risks and differences in length of follow-up. Generalized linear regression modelling (GLM) was used to determine renal outcomes as measured by mean eGFR.

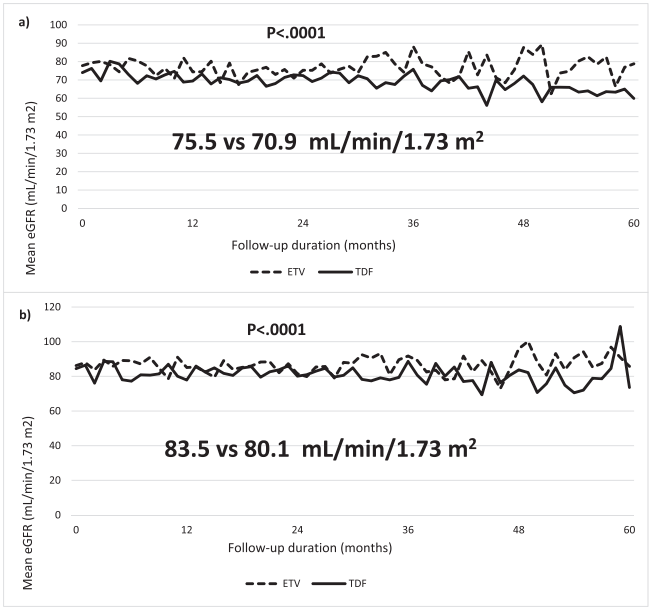


Figure 1: Generalized linear model for trends in mean eGFR in propensity score matched (a) overall, (b) exclusion of eGFR < 60, entecavir and tenofovir treated patients over a long-term follow-up.

Results: After PSM, the overall cohort for both treatment groups (n = 145, 145) were well matched on age, male sex, baseline eGFR, follow-up duration, diabetes mellitus, and hypertension without significant differences between the 2 groups ($p > 0.05$ for all comparisons). On GLM, adjusting for hypertension, diabetes mellitus and cirrhosis, TDF patients had a significantly lower mean eGFR (70.9 vs. 75.5ml/min/1.73 m^2) during follow-up when compared to ETV patients (Figure a). After excluding already renally impaired patients (eGFR < 60ml/min/1.73 m^2) at baseline, we performed another PSM with the same variables above, and found that both groups (n = 124, 124) were also well matched, with no significant differences except for baseline cirrhosis (10.6% in ETV and 22.0% in TDF group, ($p = 0.02$). On GLM, adjusting for the same covariates as above, we again found that TDF patients had a significantly lower mean eGFR (80.1 vs. 83.5 ml/min/1.73 m^2) during follow-up when compared to ETV patients (Figure b).

Conclusion: TDF-treated patients consistently had lower mean eGFR values when compared to ETV overall including patients without renal impairment at baseline and after appropriate matching for

background risks. Thus, renal function should be monitored in CHB patients treated with TDF.

FRI-348

Peginterferon is superior to nucleos(t)ide analogues for reduction ofchronic hepatitis B-related hepatocellular carcinoma in patients with high-riskscore

P. Ren, Z. Cao, R. Mo, Y. Liu, C. Lichang, Z. Tianhui, Z. LI, J. Lu, Y. Liu, Q. Guo, R. Chen, H. Zhou, W. Cai, H. Wang, H. Gui, Q. Xie. *Ruijin Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Department of Infective Diseases, Shanghai, China*
Email: renpeipei1014@163.com

Background and Aims: Although a few studies indicated that pegylated interferon (PEG-IFN) was preferable to nucleos(t)ide analogues (NAs) in reducing hepatocellular carcinoma (HCC) incidence, clinical evidence needs to be strengthened. This study was designed to compare the long-term outcomes of PEG-IFN vs NAs therapy in chronic HBV infection (CHB) patients and further evaluated the treatment type effect on the HCC incidence in patients stratified by previously validated HCC risk scores.

Method: Cumulative HCC incidence rates were calculated using the Kaplan-Meier curve and compared with the log-rank test. To reduce the selection bias, propensity score matching (PSM) was utilized. Area under receiver operating characteristic curves (AUROCs) was used for the predictive performance of different HCC risk scores.

Results: 1,112 CHB patients (755 naïve case) were enrolled to form the main cohort. During the follow-up (median 5.41 years), we finally observed 31, 21 HCC cases respectively in the entire and naïve cohort. The PEG-IFN group had a lower HCC incidence when compared to the NAs group whether in the entire or naïve cohort (8.0% vs 2.3%, p < 0.0001; 8.9% vs 0.0%, p = 0.0002; respectively) (Figure 1 A-B). The result was further confirmed in the baseline PSM subgroup analyses of the entire and naïve cohort (6.8% vs 0.0%, p = 0.0197; 9.9% vs 0.00%, p = 0.0415; respectively) (Figure 1 C-D). Univariate/multivariate cox analysis in the entire cohort manifested older age (hazard ratio [HR] = 2.873, 95% CI 1.093–7.554, p = 0.0323), male (HR = 5.670, 95% CI 1.720–18.696, p = 0.0044), cirrhosis (HR = 5.426, 95% CI 2.487–11.970, p < 0.0001) and treatment type (HR = 0.154, 95% CI 0.036–0.660, p = 0.0117) were associated with HCC occurrence.

In the entire cohort, PAGE-B showed similar AUROCs to GAG-HCC at 3 years (0.884 vs 0.887, respectively; p = 0.9487), 5 years (0.859 vs 0.841, respectively; p = 0.6304) and 10 years (0.822 vs 0.833, respectively; p = 0.7784), whereas AUROCs of PAGE-B or GAG-HCC were significantly higher than REACH-B (0.809, 0.769, 0.758 at 3, 5, 10 years, respectively; all p < 0.05) or CU-HCC (0.787, 0.767, 0.757 at 3, 5, 10 years, respectively; all p < 0.05). The mentioned above HCC scores accuracy analyses in the naïve cohort concurred with the entire cohort. Subgroup analyses in the entire population stratified by PAGE-B or GAG-HCC indicated there was no difference between the PEG-IFN and NAs group in the low-risk patients (PAGE-B <10; GAG-HCC <82) (1.08% vs 0.00%, p = 0.3199; 0.42% vs 3.28%, p = 0.0848; respectively). However, the PEG-IFN group had a lower HCC incidence than the NAs

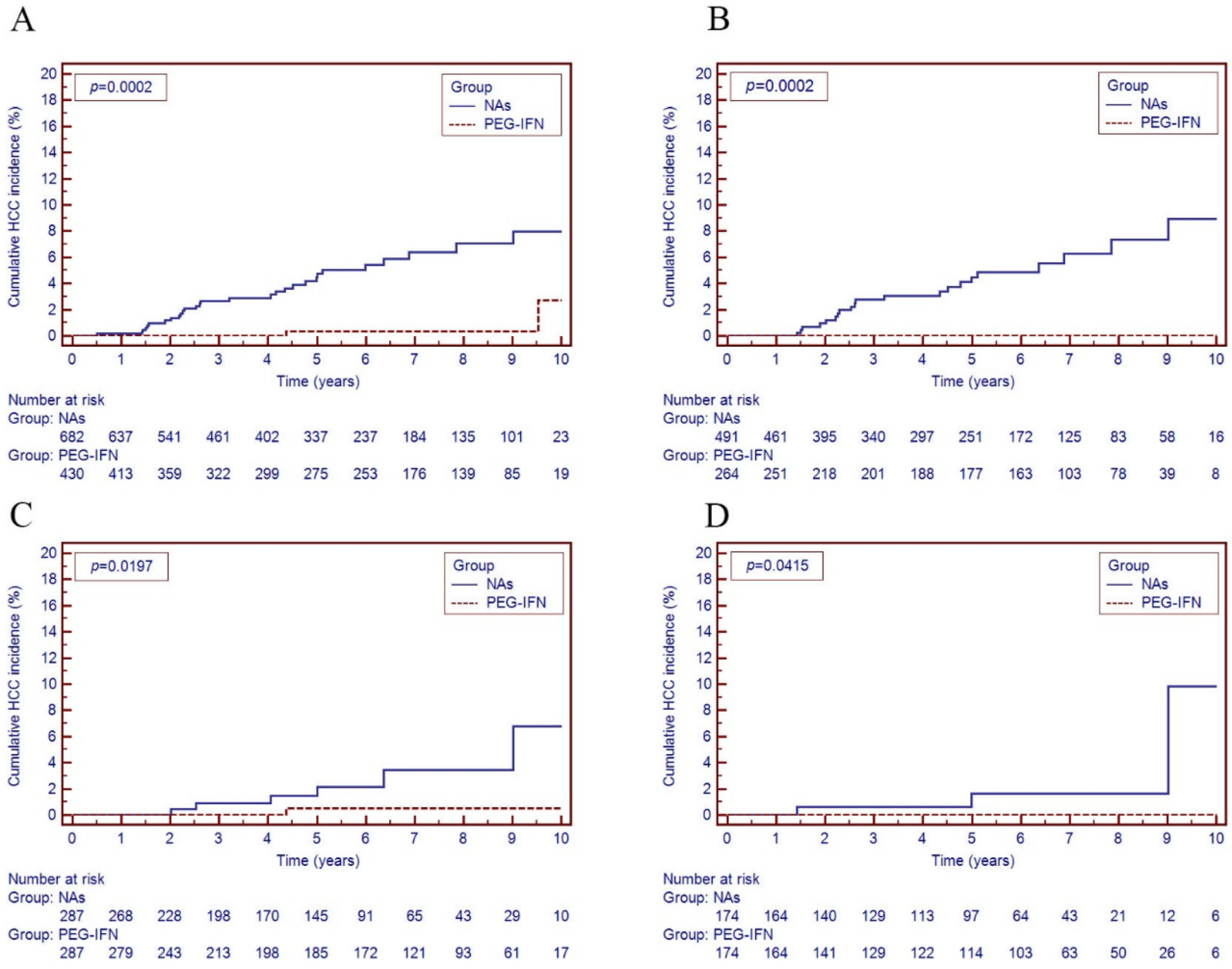


Figure: (abstract: FRI-348)

group in the high-risk score (PAGE-B ≥ 10; GAG-HCC ≥ 82) patients (3.13% vs 10.39%, p < 0.0001; 11.11% vs 13.29%, p = 0.0311; respectively).
Conclusion: Peginterferon is superior to nucleos(t)ide analogues for reduction of chronic hepatitis B-related HCC in patients with high-risk score.

FRI-349
Validation of the EASL 2017 HBV clinical practice guidelines criteria for switching patients long-term treated with Tenofovir difumarate to Entecavir or Tenofovir alafenamide in a real life setting
A. Loglio[1], G. Grossi[1], R. Soffredini[1], M. Borghi[1], F. Facchetti[1], E. Galmozzi[1], G. Lunghi[2], P. Lampertico[1]. *[1]Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, Microbiology and Virology Unit, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: The 2017 EASL HBV CPG recommend to switch TDF treated patients to TAF (if NUC naïve or NUC experienced) or ETV (only if NUC naïve) if they have one of the following risk factors: (1) age >60 years, (2) bone disease [history of fragility fracture, osteoporosis, chronic use of steroids or of any other drugs that worsen Bone Mass Density], (3) renal alterations [eGFR <60 ml/min, albuminuria >30 mg/24h or moderate dipstick proteinuria, low serum phosphate (<2.5 mg/dl), or hemodialysis]. This study was aimed to assess these risk factors in a large cohort of TDF-treated patients to estimate the number of patients who could benefit from this switch.
Method: All consecutive CHB subjects already on TDF before 31 Dec 2016 were enrolled in a cross-sectional real-life study at the control blood sample, between Jan and 31 Jun 2017. GFR was assessed by CG formula; renal safety by UBCR and TmPO4/GFR ratio were also recorded, as last spine DEXA scans, Vit D, PTH levels, steroid use.
Results: 414 patients were enrolled: 63 (22–88) yr, 95% Caucasian, 79% HBeAg negative, 76% males, 44% cirrhotics, treated by TDF for 93 (9–133) months, 34% on a reduced dose, 95% undetectable HBV DNA, 94% normal ALT, 53% NUCs previously treated, 39% arterial hypertension, 10% diabetes, BMI 25 (16–42)kg/m^2. In terms of bone safety, 6% Vit D <15 ng/ml, 20% elevated PTH, 54% osteopenia and 12% osteoporosis at spine (86% of patients had an available DEXA). In terms of renal alterations, 23% had GFR <60 ml/min (70% already on a reduced TDF dose), 21% low serum phosphate, 17% increased albuminuria, 5% moderate dipstick proteinuria, 58% had increased UBCR (>300 ug/g), 66% hyperphosphaturia (<0.80 TmPO4/GFR ratio). By applying EASL criteria, 57% were >60 years (1), 13% had osteoporosis or were steroid-treated (2), and 41% had reduced GFR, hypophosphatemia or albuminuria/proteinuria (3). Overall, 69% had at least one criterion, 6% all criteria (1 + 2+3), 8% age and bone criteria (1 + 2) and 8% bone and renal criteria (2 + 3). 33% met both the age and renal criteria (1 + 3): in this population UBCR was elevated in 86%, reduced TmPO4/GFR ratio in 81%, both tubular markers altered in 66%, 59% already on reduced TDF dose, 79% LMV/ADV previously exposed.
Conclusion: Based on EASL 2017 HBV CPG recommendations, approximately 2/3 of CHB patients long-term treated with TDF in a real life setting are candidates to a ETV or TAF switch.

FRI-350
The long-term risk and outcome of non-neoplastic portal vein thrombosis developing in compesated caucasian HBV cirrhotics treated with Tenofovir or Entecavir
A. Loglio[1], G. Tosetti[1], G. Grossi[1], M. Iavarone[1], M. Viganò[2], F. Facchetti[1], M.G. Rumi[2], A. Sangiovanni[1], M. Primignani[1], P. Lampertico[1]. *[1]Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Ospedale San Giuseppe, Università degli Studi di Milano, Division of Hepatology, Milan, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: The risk of portal vein thrombosis (PVT) in long-term NUCs-treated HBV compensated cirrhotics is not established. We therefore assessed its incidence and predictors in a real-life cohort.
Method: 260 Caucasian HBV-monoinfected compensated HCC-free cirrhotics starting TDF or ETV were consecutively enrolled in a longitudinal cohort study: median age 61 (21–83) years, 81% males, 88% HBeAg negative, 68% with normal ALT, 59% NUCs-experienced, PLT 153 (32–304) x10^9/l, spleen diameter 11 (7–20) cm, liver stiffness 8.8 (3–75) kPa, 13% with esophageal varices (EV) and 4 previously decompensated (1.5%). Patients were followed with blood tests and 6-month abdominal imaging until PVT onset or Nov 2017. PVT was graded with Yerdel classification.
Results: During 103 (16–138) months of study period, 12 (5%) patients developed PVT. Three cases developed a tumoral PVT and were thereby excluded from the analysis. The remaining 9 patients developed non-neoplastic PVT after 58 (23–92) months, with an 8-year cumulative probability of 4.1%. Eight PVT were Yerdel grade 1 (partial thrombosis, without extension into the Superior Mesenteric Vein) while one was grade 2 (partial, with extension into SMV). At multivariable analysis, only previous decompensation (HR 16, 95%CI 2–113, p = 0.005) and EV at baseline (HR 27, 95%CI 5–136, p < 0.001) predicted PVT. The 8-year cumulative incidence of PVT was 28% and 1% among patients with and without baseline EV (p < 0.001) and 50% and 3.4% among those with or without previous decompensation (p < 0.001). PVT was associated with "de novo" ascites in only one patient and with HCC development in 5 patients (56%), but it did not never display any radiological features of neoplastic thrombosis throughout the entire follow-up. Patients underwent anticoagulant therapy (AT) for 8 (2–20) months till PVT resolution (5 patients) or side effects (anemia, variceal bleeding) or events (OLT, end-of-follow-up). Out of 5 resolved PVT, two Yerdel grade 1 recurred 6 and 14 months after AT discontinuation. Out of 9 patients with PVT, 3 died (hepatorenal syndrome, myocardial infarction, gastric ulcer bleeding), 2 were liver transplanted for HCC, 4 are still alive (2 with HCC).
Conclusion: In HBV NUC-suppressed compensated cirrhotics, non-neoplastic PVT is a rare complication, partial in most cases and asymptomatic, but strongly associated with severity of liver disease at baseline and the development of HCC.

FRI-351
Clinical and genetic predictors of HCC occuring in caucasian compensated HBV cirrhotics treated by Entecavir or Tenofovir for 8 years
A. Loglio[1], E. Galmozzi[1], M. Iavarone[1], G. Grossi[1], M. Viganò[2], F. Facchetti[1], M.G. Rumi[2], A. Sangiovanni[1], P. Lampertico[1]. *[1]Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Ospedale San Giuseppe, Università degli Studi di Milano, Division of Hepatology, Milan, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: HCC development remains the leading complication in HBV-related compensated cirrhotics long-term treated by TDF or ETV but the clinical and genetic predictors are poorly known. We therefore looked for baseline predictors of HCC,

including the tolloid like 1 gene (*TLL1*) rs17047200 polymorphism which has been recently shown to predict HCC in HCV patients cured by IFN therapy.

Method: 258 Caucasian HBV-monoinfected HCC-free CPT-A cirrhotics were consecutively enrolled in a longitudinal cohort study when starting TDF or ETV. Age was 61 (21–83) yr, 82% males, 88% HBeAg negative, 69% with normal ALT, BMI 25 (17–40) kg/m^2, 12% diabetics, 60% NUCs-experienced, 5% with previously treated HCCs, PLT 153 (48–304)x10^9/l, spleen diameter 11 (7–20) cm, liver stiffness 9 (3–60) kPa, 14% with esophageal varices (EV). Liver stiffness based model (LSPS) 0.62 (0.12–7.57), 14% PAGE-B score ≥ 18. Patients were regularly followed with blood tests and 6-month abdominal imaging until HCC development or Nov 2017.

Results: Over 102 (18–126) months of study period, 36 (14%) patients developed an HCC after 52 (18–100) months. The 8-year cumulative HCC incidence was 15% (yearly rate 1.9%). HCC developed in 10 (15%) out of 66 AT/TT (26%) patients compared to 26 (13.5%) among 192 AA (74%) subjects, with a 5-year cumulative HCC incidence of 13.5% vs 8.8%, respectively (p = 0.642). At univariate analysis, among several baseline genetic, clinical, demographic and virological features, the presence of EV, HCC history, spleen diameter, baseline Fibroscan, PLT count, age, LSPS and PAGE-B score predicted HCC. At multivariate analysis, previous HCC (HR 7.5, 95%CI 3.4–16, p < 0.001), EV (HR 3.3, 95%CI 1.5–7, p = 0.002), diabetes (HR 2.4, 95%CI 1.1–5.5, p = 0.03), age (HR 1.1, 95%CI 1.0–1.1, p < 0.001) and PLT (HR 0.99, 95%CI 0.98–0,99, p = 0.01) independently predicted de-novo HCC. Among the 244 patients without previous HCC, baseline EV (HR 3.6, 95%CI 1.4–9.1, p = 0.008), spleen diameter (HR 1.6, 95%CI 1.1–1.5, p = 0.005) and age (HR 1.3, 95%CI 1.0–1.1, p = 0.001) were independent predictors of HCC. The 8-year incidence of HCC was 43% and 7% among patients with and without baseline EV (p < 0.001), 20% and 9% among those with spleen diameter >12 or ≤12 cm (p = 0.02), and 17% and 6% among those >60 or ≤60 years (p = 0.007).

Conclusion: In HBV compensated cirrhotics NUC-treated for 8 years, older age and severity of portal hypertension at baseline strongly predict HCC, independently from *TLL1* variants.

FRI-352

Pharmacokinetic-pharmacodynamic modeling of Tenofovir Exalidex in HBV subjects

R. Foster[1], M. Conover[1], C. Canizres[1], D. Trepanier[1], D. Ure[1], T. Matkovits[1], P. Mayo[2]. [1]*ContraVir Pharmaceuticals, Inc., Drug Development, Edison, United States;* [2]*University of Alberta, Pharmacy and Pharmaceutical Sciences, Edmonton, Canada*
Email: ccanizares@contravir.com

Background and Aims: Tenofovir Exalidex (TXL), a lipid conjugate of tenofovir (TFV), is designed to mimic lysophosphatidylcholine to take advantage of natural lipid uptake pathways and achieve high intrahepatic concentrations of TFV diphosphate (TFV-PP) while reducing the peripheral TFV concentrations associated with kidney and bone toxicities. As it is not routinely feasible to measure intrahepatic TFV-PP concentrations in patients, a pharmacokinetic-pharmacodynamic (PK-PD) model was developed to aid and optimize further clinical development of TXL.

Method: TXL was administered to 50 HBV subjects (fasted) at doses ranging from 10–100 mg/day orally. The 50 mg cohort (n = 10) was used to derive PK-PD modeling, as this dose resulted in viral load (VL) reductions (log_{10}) that were not statistically different from Standard-of-Care (SOC, 300 mg, tenofovir disoproxil fumarate). Steady-state PK modeling was generated using linear trapezoidal, linear interpolation, Non-Compartmental Analysis for a 24 hour dosing interval (NCA, Phoenix WinNonLin Ver. 7.0). A linked PK-PD non-linear mixed effects (NLME, Monolix 3.2) model was employed, using an inhibitory Emax model. PK data were also examined using model-dependent analyses. Data after 28 days dosing was used for the current model.

Results: Maximum VL reductions of up to 3.9 log_{10} were observed with 50 mg/day TXL dosing for 28 days. The prodrug, TXL, rapidly disappeared from plasma, with mean (SD) Cmax, Tmax, AUC_{last}, and $t_{1/2}$ values of 51.28 (39.9) ng/ml, 1.60 (0.7) h, 109.44 (84.9) ng.h/ml, and 2.10 (2.0) h, respectively, at day 28. TFV mean (SD) values for Cmax, Tmax, AUClast, and $t_{1/2}$ were 8.51 (2.0) ng/ml, 4.95 (2.2) h, 136.35 (33.5) ng.h/ml, and 23.3 (3.4) hours, respectively. The VL IC_{50} on Day 29 was 2.92 ng/ml. Additionally, TXL could be described using a one-compartment model, whereas for TFV the model of best-fit was multi-exponential.

Conclusion: TXL 50 mg VL reductions were not statistically different (p = 0.19) from SOC, TDF. The PK-PD relationship after dosing on Day 28 was described using a NCA and inhibitory Emax model for TFV. TXL was rapidly cleared compared with TFV, and the clinical antiviral reduction IC_{50} approximated 3 ng/ml. Modeling promises to be a useful tool for the further clinical development and optimization of TXL.

FRI-353

Bile acid monitoring to support safety and efficacy of Myrcludex B in combination with Tenofovir in patients with chronic HBV/HDV co-infection

M. Haag[1,2], U. Hofmann[2], T.E. Mürdter[2], G. Heinkele[2], A. Blank[3,4], W.-E. Haefeli[3,4], H. Wedemeyer[5], P. Bogomolov[6], A. Alexandrov[7], K. Schöneweis[8], S. Urban[8], M. Schwab[1,2,9]. [1]*University of Tübingen, German Center for Infection Research (DZIF), Tübingen, Germany;* [2]*Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology (IKP), Analytics & Synthesis;* [3]*Heidelberg University Hospital, Department of Clinical Pharmacology and Pharmacoepidemiology, Heidelberg, Germany;* [4]*Heidelberg University, German Center for Infection Research (DZIF), Heidelberg, Germany;* [5]*Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany;* [6]*Moscow Regional Research Clinical Institute, Hepatology Department;* [7]*Myr GmbH, Bad Homburg, Germany;* [8]*University Hospital Heidelberg, Department of Infectious Diseases, Molecular Virology, Heidelberg, Germany;* [9]*University Hospital Tübingen, Department of Clinical Pharmacology, Institute of Experimental and Clinical Pharmacology and Toxicology, Tübingen, Germany*
Email: mathias.haag@ikp-stuttgart.de

Background and Aims: Metabolomic monitoring of endogenous biomarkers is of increasing importance for the assessment of drug safety and efficacy. Myrcludex B (MyrB), a novel entry inhibitor for the treatment of HBV/HDV infection, exerts its function through inhibition of the hepatic bile acid (BA) transporter Na^+-taurocholate cotransporting polypeptide (NTCP). We report preliminary results of BA monitoring in a subset of plasma samples from HBV/HDV co-infected individuals participating in a Phase 2b clinical trial (Myr-202 study) receiving 2, 5, and 10 mg MyrB daily in combination with TDF or TDF alone.

Method: Quantification of BA species was carried out in plasma samples before (BL) and during treatment (week 4 and week 12) by a validated LC/MS assay. A subset of samples from the treatment arms TDF alone (n = 12), 2 mg (n = 11), 5mg (n = 14) and 10 mg (n = 11) MyrB/TDF were analyzed to assess dose-dependent alterations. Statistical analysis (Dunn's multiple comparison) was done for cholic acid (CA), taurocholic acid (TCA) and glycocholic acid (GCA) in order to assess effects within the group of unconjugated (CA) and conjugated BAs (TCA, GCA).

Results: Median level at BL ranged between 62–255 nM (CA), 199–511 nM (TCA) and 394–897 nM (GCA) and did not show any significant differences between the treatment groups. At week 4, a dose-dependent elevation of CA was evident compared to TDF alone reaching median fold-changes (FC) of 1.8 (2 mg) and 3.8 (5 mg), respectively. CA amounts in the 10mg group leveled off at a FC of 2.8. Notably, at week 12 the highest rise (FC: 10.3) was evident in the 10mg group while in the 5mg group CA exhibited only a moderate increase (FC: 1.2). In contrast to unconjugated CA, which showed modest increase, circulating levels of the conjugated BAs exhibited more pronounced changes. Here, plasma exposure of TCA and GCA

was highest in the 5mg group (FCs > 20, w4 and w12), followed by lower amounts in the 10 mg group (FCs > 8) and the 2 mg treatment resulted in the least pronounced elevation without reaching significance.
Conclusion: In accordance with the high binding specificity of MyrB for NTCP, a significant and sustained elevation of systemic glycine- and taurine-conjugated BAs after 4 and 12 weeks of treatment was observed. In accordance with a lower transporter specificity of unconjugated BAs, CA was affected to a lesser extent. To substantiate these preliminary results, further analysis on the basis of the complete study cohort is required.

FRI-354
HeberNasvac: Novel therapeutic vaccine against chronic hepatitis B
G. Guillen[1], A. Julio[2], E. Penton[3], Y. Lobaina[3], V. Muzio[4], M. Al-Mahtab, S.M. Akbar[6]. [1]*Center for Genetic Engineering and Biotechnology, Vaccine Department, La Habana, Cuba;* [2]*Center for Genetic Engineering and Biotechnology, Vaccine, La Habana, Cuba;* [3]*Center for Genetic Engineering and Biotechnology, Vaccine, Cuba;* [4]*Center for Genetic Engineering and Biotechnology, Clinical Trial, Cuba;* [6]*Toshiba General Hospital, Japan*
Email: gerardo.guillen@cigb.edu.cu

Background and Aims: Despite the existence of effective prophylactic vaccines, hepatitis B virus (HBV) infections remain a major public health problem. About 370 million people are chronically infected worldwide.
As HBV persistence has been associated with a defect in the development of HBV-specific cellular immunity, therapeutic vaccination has been extensively studied in CHB.
HBsAg-based vaccines, including formulations with novel adjuvants have been used with unclear or negative results. New strategies should be taken into account in the improvement of cell-based immune responses in order to prevent and control the infections and eventually clear the virus.
The aim of this work is to develop a therapeutic vaccine against CHB with the capacity to subvert the tolerance.
Method: HeberNasvac include the use of a novel immunization route (intranasal-IN) and a HBcAg expressed in *E. coli*, used in a combination with HBsAg expressed in *Pichia pastoris*, both antigens expressed as virus like particles. The formulation is a simple mixture of proteins in phosphate buffer. The immunogenicity in Balb/C and transgenic mice was measured using ELISA, LPA and IFNg ELISPOT assays.
The clinical trials with human volunteers where approved by the Research Ethics Board of the Hospitals. The clinical regimen with HeberNasvac (100 µg of each antigen per dose) were five to ten IN inoculations only, every 14 days or 5 SC inoculations in addition to the last five IN inoculations in the same days. In the case of the efficacy trial pegIFNα was administered to the control group for a total of 48 weeks vs 24 weeks for HeberNasvac.
Results: The evaluation in mouse support the rationality of the vaccine targeting the stimulation of CD4(+) and CD8(+) T-cell responses and the induction of pro-inflammatory cytokines capable of controlling viral replication. HeberNasvac proved to be immunogenic and able to stimulate mucosal as well as systemic immunity biased in a Th1 sense.
Phase I, II and Phase III, randomized, double blinded and placebo controlled clinical trials were developed in healthy volunteers and CHB patients. In Phase III trial at week 72 (24 weeks after the end of pegIFNα treatment and 48 weeks after the end of HeberNasvac treatment), the HBV DNA levels were significantly lower in the vaccine group than in the pegIFNα group ($p = 0.03$), with almost 80% of vaccine treated patients remaining under 10,000 c/ml. A delayed rebound was observed in the vaccine group suggesting a sustained antiviral effect.
Conclusion: Preclinical and clinical results with HeberNasvac evidenced the induction of functional immune response and antiviral effect. HeberNasvac was safe and well tolerated inducing reactions similar to those caused by pegIFNα but less frequently and less severe, and more sustained antiviral effect. These results support further development to evaluate HeberNasvac in different schedules and therapeutic combinations.

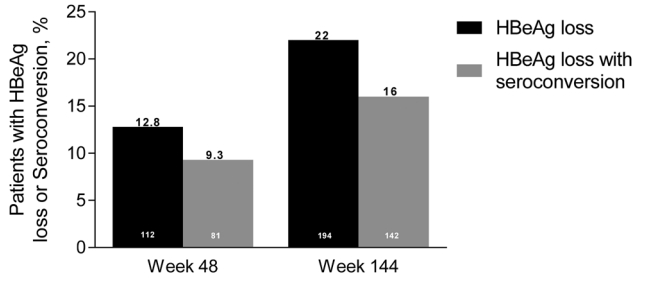
FRI-355
At least 90% long-term adherence is required to lower mortality in patients with chronic hepatitis B taking entecavir
Y.-S. Lim[1], M. Jung Ko[2]. [1]*Asan Medical Center, University of Ulsan College of Medicine, Gastroenterology, Seoul, Korea, Rep. of South;* [2]*National Evidence-based Healthcare Collaborating Agency, Division for Healthcare Technology Assessment Research, Seoul, Korea, Rep. of South*
Email: limys@amc.seoul.kr

Background and Aims: Eradication of hepatitis B virus (HBV) is very rarely achieved, necessitating long-term oral antiviral therapy in patients with chronic hepatitis B (CHB). Medication non-adherence can result in poor virologic suppression and virologic breakthrough in the patients. However, the contribution of non-adherence to the clinical outcomes, such as mortality and hepatocellular carcinoma (HCC), is uncertain. Moreover, there is no consensual standard for the optimal level of drug adherence in the patients.
Method: This was a population-based, observational, longitudinal study of adult CHB patients who initiated treatment with entecavir (0.5 mg/day). The data were obtained from national health insurance service claims database, which covers >99% of the entire population, between 2007 and 2015 in a HBV-endemic country. Patient adherence was subdivided into 3 categories – high (proportion of days covered [PDC], ≥90%), intermediate (PDC, 80%–89%), and low (PDC, <80%) – and compared with incidence of mortality/transplantation and HCC during median 4.4 years of follow-up using multivariable survival models and inverse probability treatment weighting analysis adjusted for sociodemographic factors, cirrhosis, and comorbidities.
Results: Among 51,975 CHB patients treated with entecavir, compared with their high-adherence counterparts, the risk of mortality/transplantation was significantly greater for low-adherers (adjusted hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.27–1.50; $p < 0.001$) and intermediate-adherers (adjusted HR, 1.44; 95% CI, 1.33–1.56; $p < 0.001$). The risk of HCC was not associated with adherence. The higher risk of mortality and similar risk of HCC for low- and intermediate-adherers, compared with high-adherers, were consistently observed in cirrhosis- and non-cirrhosis subcohorts.
Conclusion: Being fully adherent to entecavir (≥90%) was associated with a lower rate of mortality compared with partial adherence. There seemed to be a threshold effect for this benefit in the CHB population; ≥90% adherence may need to be maintained in the long-term to continue to accrue benefit.

FRI-356
Predictors of HBeAg loss and seroconversion by baseline clinical features and viral deep sequencing after 144 weeks of treatment with Tenofovir Alafenamide or Tenofovir Disoproxil Fumarate
Y.-S. Lim[1], Shalimar[2], X. MA[3], A. Shukla[4], H.N. Trinh[5], P. Andreone[6], J.-S. Hwang[7], V. Suri[8], G. Wu[8], A. Gaggar[8], J.F. Flaherty[8], W.-C. Chow[9], P. Marcellin[10], N. Izumi[11]. [1]*Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Songpa, Seoul, Korea the Republic of;* [2]*Gastroenterology, All India Institute of Medical Sciences, New Delhi, India;* [3]*Xiaoli Ma, PC, Bryn Mawr, Bryn Mawr, PA, United States;* [4]*Seth GS Medical College and KEM Hospital, Parel, India;* [5]*Silicon Valley Research Institute, San Jose, CA, United States;* [6]*Center for Research and Studies on Hepatitis, University of Bologna, Bologna, Italy;* [7]*Keimyung University Dongsan Medical Center, Daegu, Korea the Republic of;* [8]*Gilead Sciences, Foster City, CA, United States;*

[9]*Singapore General Hospital, Singapore;* [10]*Service d'Hépatologie, Hopital Beaujon, University of Paris, Clichy, France;* [11]*Department of Gastroenterology and Hepatology, Japan Red Cross Musashino Hospital, Tokyo, Japan*
Email: vithika.suri@gilead.com

Background and Aims: HBeAg seroconversion remains an important serological endpoint for antiviral therapy. We previously reported on HBeAg loss following 48 weeks of oral antiviral therapy in the ongoing phase 3 study described below. Here we present an updated evaluation of factors associated with HBeAg loss with and without anti-HBe seroconversion following 3 years of antiviral therapy.
Method: The study included adults with HBeAg-positive CHB enrolled in a Phase 3 trial (Study GS-US-320–0110) comparing TAF 25 mg QD vs. TDF 300 mg QD. At Week 144, 340 (39%; TAF 226; TDF 114) patients had received 1 year of open label TAF 25 mg QD after switching from double blind (DB) treatment. The associations between HBeAg loss at Week 144 with host, viral, and treatment-related factors, including on-treatment virologic suppression (Roche COBAS Taqman; lower limit of detection 29 IU/ml), were determined using logistic regression analyses.
Results: Among 873 included patients, the median age was 36 yrs, 82% were Asian, and median baseline (BL) ALT and HBV DNA were 85U/l (IQR 60–138) and 7.9 $\log_{10}$IU/ml (IQR 6.9–8.6), respectively. At Week 144, a total of 194 patients (22%) experienced HBeAg loss and 142 patients (16%) underwent HBeAg seroconversion (Figure). Compared with subjects with persistent HBeAg-positivity, those with HBeAg loss were older (median age, 35 vs. 40 yrs), were infected with non-genotype D HBV (75% vs 86%), had lower median HBsAg levels (4.3 vs 3.8 $\log_{10}$IU/ml), a higher median BL ALT (83 vs. 101U/l), a higher prevalence of presumed cirrhosis (FibroTest ≥0.75: 6.4% vs. 13.2%), and lower median BL serum HBV DNA (8.1 vs. 7.7 $\log_{10}$IU/ml) (all $p \leq 0.005$). In multivariate analysis, baseline HBV DNA <8 $\log_{10}$ was an independent viral predictor of both HBeAg loss (OR: 1.816 [1.174–2.808]; $p = 0.007$) and seroconversion (OR: 2.512 [1.684–3.746]; $p < 0.001$); treatment with TAF in the DB period was a predictor of seroconversion (OR: 1.596 [1.044–2.439]; $p = 0.031$) but not loss. Evaluation of baseline viral diversity as assessed by deep sequencing across the genome did not show strong associations of variants with subsequent HBeAg loss.



Conclusion: Following 144 weeks of treatment, HBeAg loss/seroconversion rates remains low in subjects treated with TAF or TDF with lower baseline HBV DNA levels associated with higher rates of response.

FRI-357
Serum hepatitis B virus DNA and pregenomic RNA levels and kinetics in nucleos(t)ide analogue treated and untreated subjects

E. Butler, J. Gersch, A. Mcnamara, M. Kuhns, G. Cloherty. *Abbott Diagnostics, Infectious Disease Research, Abbott Park, United States*
Email: emily.butler@abbott.com

Background and Aims: HBV pregenomic RNA (pgRNA) is detectable in serum from chronic HBV (CHB) patients on nucleos(t)ide analogue (NA) therapy. In untreated CHB patients, serum pgRNA has been observed at lower levels relative to HBV DNA. We compared the serum nucleic acid levels and kinetics in HBV positive populations, including acute infections, HBsAg-positive blood donors, and CHB patients receiving NA therapy.
Method: Samples included the following: on-therapy CHB patient samples (n = 16, Boca Biolistics or DLS), HBsAg-positive donor samples (n = 102, American Red Cross) and 3 seroconversion series (n = 79 samples). HBV DNA was quantified using the Abbott RealTi*m*e HBV viral load assay. HBV pgRNA was quantified with a dual-target research assay developed on the Abbott *m*2000 instrument.
Results: In CHB patients on NA therapy, HBV pgRNA was observed at concentrations greater than HBV DNA in 13/14 quantifiable samples. Differences between pgRNA and DNA were highly variable, ranging from 0.53–5 log, and the correlation of DNA level to pgRNA levels was low ($R^2 = 0.5$). In 102 HBsAg-positive blood donor samples, HBV DNA was elevated relative to pgRNA. The mean difference between DNA and pgRNA was 1.70 ± 0.71 log and correlation of DNA to pgRNA was higher relative to NA treated samples ($R^2 = 0.8$). Among the blood donor samples, both DNA and pgRNA levels were lower in HBeAg-nonreactive samples compared to HBeAg-reactive samples. In seroconversion series from 2 acutely infected plasmapheresis donors that spontaneously resolved HBV infection, the peak DNA levels were 5.53 and 9.23 logIU/ml. HBV DNA correlated with pgRNA levels over time; the mean differences between DNA and pgRNA for the respective series were 2.33 ± 0.53 and 2.58 ± 0.30 log, with DNA being higher. This trend was also observed in an acute case who progressed to chronicity where the maximum DNA level was 9.38 logIU/ml and the mean difference between DNA and pgRNA was 1.85 ± 0.31 log.
Conclusion: In untreated HBV infections, we observed a trend wherein serum pgRNA levels are approximately 2 log lower than HBV DNA throughout acute infection whether the virus is cleared or persists and in individual HBsAg-positive blood donor samples. Consistent relative detection in the serum is suggestive of a linked mechanism for egress for both HBV DNA and pgRNA containing virions.

FRI-358
On-treatmant serum wisteria fioribunda agglutinin-positive Mac-2 binding protein level and risk of hepatocellular carcinoma development in patients with chronic hepatitis B during nucleot(s)ide analog therapy

A. Murata[1,2], T. Genda[1], S. Sato[1]. [1]*Shizuoka, Izunokuni, Japan;* [2]*Hepatology and gastroenteology, 1129, Izunokuni, Japan*
Email: perseverance3@hotmail.co.jp

Background and Aims: Histological analysis of hepatic fibrosis is an important predictive factor for hepatocellular carcinoma (HCC) development in patients with chronic hepatitis B (CHB). Of late, Wisteria floribunda agglutinin (WFA)-positive Mac-2-binding protein (WFA+–M2BP) was has been developed as a noninvasive glycobiomarker of liver fibrosis, and its predictive value for HCC development was is reported in several chronic liver diseases. However, change of in the serum WFA+–M2BP levels during antiviral treatment and its association with HCC development have not been fully assessed in patients with CHB. The present study aimed to analyze the pre- and on-treatment serum WFA+–M2BP levels and its their association with HCC development in CHB patients with CHB who received receiving nucleot(s)ide analog therapy.
Method: This study included 160 CHB patients with CHB who received nucleot(s)ide analog therapy between 2003 and 2015. WFA+–M2BP level was estimated immediately before treatment and at 48 weeks after treatment initiation. Multivariate Cox proportional hazards analysis was used to estimate the hazard ratios (HRs) of variables for HCC development. Cumulative incidences of HCC development were evaluated using the Kaplan–Meier plot analysis and the log-rank test.
Results: During the median follow-up time of 6.9 years (range: 1.1–13.0 years), 14 of the 160 patients developed HCC. On-treatment

serum WFA+–M2BP levels were significantly decreased significantly comparing compared with pre-treatment levels (median, 0.77 COI vs. 1.05 COI, p < 0.001). Multivariate Cox proportional hazards analysis revealed that on-treatment WFA+–M2BP level was an independent risk factor for HCC development (HR: 2.22, 95% confidence interval: 1.47–3.35, p < 0.001). The areas under the receiver operating characteristic curves indicated that the on-treatment WFA+–M2BP level predicted HCC development with high diagnostic accuracy (0.830). The cut-off value of on-treatment serum WFA+–M2BP level was identified as 1.17 COI. The 5-year cumulative incidences of HCC development were 25.5% and 4.5% in patients with high and low on-treatment serum WFA+–M2BP levels, respectively (p < 0.001).
Conclusion: On-treatment serum WFA+–M2BP level was is a useful predictive biomarker for HCC development in patients with CHB receiving nucleot(s)ide analog therapy.

FRI-359

Hepatitis B surface antigen reduction by switching from long-term preceding nucleoside/nucleotide analog administration to pegylated interferon or tenofovir

T. Nobuharu, M. Kurosaki, Y. Yasui, K. Tsuchiya, H. Nakanishi, J. Itakura, N. Izumi. *Musashino Red Cross Hospital, Department of Gastroenterology and Hepatology, Japan*
Email: tamaki@musashino.jrc.or.jp

Background and Aims: Hepatitis B surface antigen (HBsAg) reduction during nucleoside/nucleotide analog (NA) therapy is slow and an alternative strategy for patients receiving ongoing NA to facilitate HBsAg reduction is required. We investigated whether switching to pegylated interferon (PEG-IFN) or tenofovir (TDF) after long-term NA administration enhances HBsAg reduction.
Method: Forty-nine patients who switched from long-term NA (entecavir or lamivudine + adefovir) to 48 weeks of PEG-IFN alfa-2a (PEG-IFN group) and 53 patients who switched to TDF (TDF group) were studied. A total of 147 patients who continued NA and matched for baseline characteristics of PEG-IFN group were analyzed for comparison (NA continuation group). HBsAg reduction at week 48 was investigated.
Results: In comparing the PEG-IFN group and the NA group, HBsAg reduction at week 48 was 0.81 ± 1.1 logIU/ml in the PEG-IFN group, which was significantly higher than that in the NA continuation group (0.11 ± 0.3 logIU/ml, p < 0.001). In patients positive for hepatitis B e-Antigen (HBeAg), HBeAg seroconversion was higher in the PEG-IFN group (44% vs. 8%, p < 0.001). In HBeAg negative patients, only patients in the PEG-IFN group achieved HBsAg loss. HBsAg reduction was 0.18 ± 0.3 logIU/ml in the TDF group, which did not differ from the NA continuation group. However, in subgroup of patients with no reduction of HBsAg during preceding NA (0.05 logIU/ml/year increase), significant reduction of HBsAg was obtained after switching to TDF (0.24 logIU/ml, p = 0.02).
Conclusion: Switching to PEG-IFN after long-term NA enhances the reduction of HBsAg, and switching to TDF was effective in the subgroup of case where HBs reduction was not obtained during preceding NA. These switch strategy would be a treatment option to promote HBsAg loss.

FRI-360

Clinical predictors for relapse after cessation of nucleoside analogues by stopping rule in chronic hepatitis B patients

D.S. Song, UI. Chang, J.M. Yang, S.H. Yoo, J.H. Kwon, J.W. Jang, S.H. Bae, S.K. Yoon. *The Catholic University of Korea, Internal Medicine, Seoul, Korea, Rep. of South*
Email: garden@catholic.ac.kr

Background and Aims: The stopping rule of international guidelines in chronic hepatitis B (CHB) patients treated with nucleoside analogues (NA) has not been verified. We assessed the usefulness of stopping rule of Asia-Pacific Association for the Study of Liver (APASL), and investigated predictors of post-treatment relapse, including HBsAg/HBeAg, clinico-biochemical, and fibrosis parameters.
Method: Patients who stopped NA were included regardless of meeting stopping rule of APASL guideline. Virologic relapse was defined as HBV DNA > 2,000 IU/ml, while clinical relapse was defined as HBV DNA > 2,000 IU/ml and ALT > 2xULN.
Results: A total of 359 CHB patients (172 HBeAg-positive and 187 HBeAg-negative) were recruited for the study: 246 entecavir (ETV)-treated and 113 lamivudine (LAM)-treated patients. Patients who met the stopping rule showed lower one-year virologic and clinical relapse rates than those not. There was no difference in virologic and clinical relapse rates between cessation of ETV and LAM. For the entire patients, higher baseline HBV DNA levels and shorter consolidation were significantly associated with clinical relapse. When stopped NA according to APASL guideline, older age (over 30), lower serum albumin and shorter consolidation were significant risk factors for virologic and clinical relapse. Relapse rate was similar between HBeAg-positive and –negative patients (one-year clinical relapse rates of 29.8% and 21.1%, respectively). In HBeAg-positive patients, higher baseline HBV DNA and shorter consolidation were significant predictors for virologic relapse, and Older age (over 30) and lower serum albumin were significant predictors for clinical relapse. However, in HBeAg-negative patients, there were no significant predictors for virologic and clinical relapse. Low HBsAg titers and non-invasive fibrosis markers, such as fibrosis-4 (FIB-4) score and AST to platelet ratio index (APRI) at cessation of NA were not significant predictors for virologic and clinical relapse.
Conclusion: Stopping rule of APASL guideline is generally acceptable and useful as a guide in decision-making when cost and long-term safety of NA is doubted. Younger patients and good synthetic function who met the stopping rule is best considered for NA discontinuation.

FRI-361

Virological response and safety in a cohort of immigrant patients affected by chronic hepatitis delta treated with PEG-IFN

L. Boglione, G. Cariti, T. Lupia, S.M. Pinna, V. Ghisetti, G. DI Perri. *Amedeo di Savoia Hospital, Medical Sciences, Turin, Italy*
Email: lucio.boglione@unito.it

Background and Aims: Chronic hepatitis due to hepatitis delta virus (HDV) represents the most difficult-to-treat viral hepatitis, because the only available treatment is the pegylated (PEG) interferon alfa (IFN), with limited virological response. Recent migration of young people from Africa and East-Europe brought the attention of the clinicians on this issue. In this retrospective study we reported our experience of treatment with PEG-IFN in a cohort of young immigrant patients affected by chronic HDV infection.
Method: Retrospective analysis of all immigrants affected by HDV and treated with PEG-IFN at our centre of Infectious Disease. Virological response was defined as: “complete virological response” (CR) with HBsAg and HDV-RNA negative at 1 year of follow-up; “partial virological response” (PR) with HBsAg positive and HDV-RNA negative; “null virological response” (NR) with HBsAg and HDV-RNA positive.
Results: The enrolment period was 2007–2014; 46 patients were included in this analysis. Geographical origin was: Central Africa 20 (43.5%), East-Europe 24 (52.1%), Pakistan 2 (3.6%). Median age was 34.5 years; males were 40 (86.9%) HBV genotypes: A, 20 (43.5%); D, 6 (13%); E, 20 (43.5%). Median qHBsAg at baseline was 3.7 logIU/ml HBV-DNA 3.5 logIU/ml, HDV-RNA 5.7 logcp/ml, alanine amino transferase (ALT) 75IU. Liver stiffness was 9.2 kPa. Median time of treatment was 11.5 months, with 4.5 years of follow-up. CR was observed in 11 patients (23.9%), PR in 13 (28.2%), NR in 16 (34.8%). Six subjects (13%) interrupted the treatment for side-effects or drop-out. Dose-reduction from 180 μg/weekly to 135 μg/weekly was reported in 23 patients (50%). Predictive factors of CR were: HBV A genotype (OR = 4.605; 95%IC: 1.090–6.709; p < 0.001), absence of cirrhosis (OR = 1.802; 95%IC: 1.003–3.209; p = 0.018), treatment

duration >1 year (OR = 3.906; 95%IC: 1.440–19.667; p < 0.001). Among NR patients, 4 died (3 due to hepatocellular carcinoma and 1 for hepatic decompesation) and 1 received a liver transplantation.
Conclusion: The only available treatment for hepatitis delta is the PEG-IFN; in this cohort of immigrant patients the CR was 23.9% and the NR 34.8%. The patients with NR and cirrhosis presented a high risk of adverse events after treatment interruption such as hepatocellular carcinoma or hepatic decompesation. Favorable outcome was prevalent in patients with HBV A genotype, without cirrhosis and treated with a PEG-IFN course >1 year.

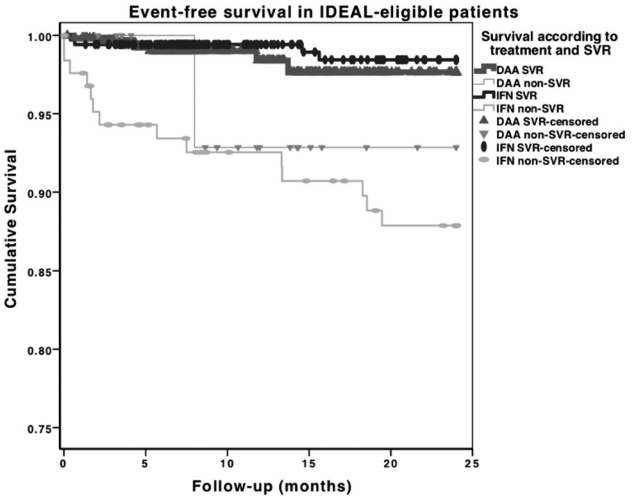
FRI-362
RNA interference therapy with ARC-520 Injection results in long term off-therapy antigen reductions in treatment naïve, HBeAg positive and negative patients with chronic HBV
M.-F. Yuen[1], K. Liu[1], B. Given[2], T. Schluep[2], J. Hamilton[2], C.L. Lai[1], S. Locarnini[3], K. Jackson[3], J.Y. Lau[4,5], C. Ferrari[6], R.G. Gish[7,8].
[1]The University of Hong Kong, Queen Mary Hospital, Hong Kong, Hong Kong; [2]Arrowhead Pharmaceuticals, Pasadena, United States; [3]Victorian Infectious Diseases Reference Laboratory, Victoria, Australia; [4]The University of Hong Kong, Hong Kong, Hong Kong; [5]Hong Kong Polytechnic University, Hong Kong, Hong Kong; [6]University of Parma, Parma, Italy; [7]Stanford University, Palo Alto, United States; [8]Hepatitis B Foundation, Doylestown, United States
Email: tschluep@charter.net

Background and Aims: ARC-520 Injection (ARC), a RNA interference drug, targets cccDNA-derived mRNA in chronic hepatitis B patients (CHB). We previously reported HBsAg reduction and safety in a multi-dose extension study. Here we report additional antigen reductions observed off-therapy during a 6-month follow-up period.
Method: 8 CHB (5 HBeAg-neg, 3 HBeAg-pos) received up to 9 doses of 4 mg/kg ARC once every 4 weeks with daily entecavir (ETV). Treatment naïve CHB who previously received a single IV dose of 4 mg/kg ARC and started daily ETV on the same day were eligible. Viral DNA and antigen knockdown (KD) were measured at regular intervals [qHBsAg, HB core-related antigen (qHBcrAg) in all, qHBeAg in HBeAg-pos]. Patients continued their daily ETV post ARC and were followed for an additional 6 months.
Results: Patients received ETV for 34 to 44 weeks after a single dose of ARC before receiving the first ARC dose of the multi-dose extension. After a single dose of ARC, qHBsAg in 3 of 3 HBeAg-pos and 1 of 5 HBeAg-neg remained below baseline. Multi-dose re-challenge resulted in additional qHBsAg KD in all CHB. Two of three HBeAg-pos and one of five HBeAg-neg had mild ALT elevations post ARC which coincided with additional antigen reductions. In the HBeAg-pos, mean HBsAg reduction was 3.0 log and max reduction 4.6log with one patient achieving an HBsAg level of 1 IU/ml. This patient seroconverted for HBeAg post ARC with mean HBeAg reduction of 2.8 log and max reduction of 4.2 log to LLOQ. Mean HBcrAg reduction was 3.4 log with max reduction of 6.1log in HBeAg-pos. In HBeAg-neg, mean HBsAg KD was 1.0 log and maximum was 2.1 log, HBcrAg reduction was 0.7 log in the only patient positive for this marker.
Conclusion: (1) Consistent with our previous reports, ARC was more active in HBeAg-pos, presumably due to more cccDNA-driven antigen production in treatment naïve HBeAg-pos and a higher fraction of qHBsAg from integrated DNA in HBeAg-neg. (2) Mild ALT elevations off ARC therapy coincided with additional antigen reductions in 2/3 HBeAg-pos and 1/5 HBeAg-neg. (3) Antigen reduction through RNAi in combination with oral ETV may lead to sustained control of CHB off-therapy.

Viral Hepatitis C: Post SVR and long term follow up

FRI-363
Comparison of event-free survival between DAA and IFN-based antiviral therapy for HCV, adjusted for disease severity
L. Krassenburg[1,2], W.R. Zanjir[1], F. Georgie[1], K. Munawar[1], O. Cerocchi[1], E. Stotland[1], J. Lau[1], H. Janssen[1], B. Hansen[1,2,3], J. Feld[1]. *[1]Toronto General Hospital, University Health Network, Toronto Centre for Liver Disease, Toronto, Canada; [2]Erasmus University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [3]Management and Evaluation, University of Toronto, Institute of Health Policy, Toronto, Canada*
Email: lisettekrassenburg@gmail.com

Background and Aims: Long-term follow-up studies have shown that sustained virological response (SVR) is associated with improved clinical outcomes with interferon (IFN)-based therapy. However, the causal link of SVR with outcome has been challenged with the argument that SVR may simply be a component of a "good prognosis" in the natural history of HCV. With markedly improved SVR rates with direct-acting antivirals (DAAs), the benefit of SVR would be expected to diminish if the association of SVR with outcome is not causal. To evaluate this question, we compared liver-related outcomes in IFN-eligible patients treated with DAAs vs. IFN.
Methods: Retrospective data were collected for patients treated with IFN-based therapy or DAAs at the Toronto Centre for Liver Disease from Jun/06 to Dec/16. To control for disease severity, patients were categorized as IFN-eligible (IDEAL) based on meeting criteria for the IDEAL trial comparing PegIFNa2a vs PegIFNa2b. Clinical events, defined as decompensation, hepatocellular carcinoma, liver transplantation and all-cause death, were collected from end of treatment to two years.
Results: Of 1110 IDEAL-eligible patients, 58% received DAAs and 42% IFN, median (IQR) age 55 (48–61) years and genotype (G) distribution 71%/12%/18% for G1/2/3. Cirrhosis was present in 34% DAAs vs 14% IFN (p < 0.001). SVR was 97% with DAAs vs 74% with IFN (p < 0.0001). The 2-year cumulative event-free survival with SVR was 98% for both DAAs and IFN (p = 0.47) and 93% and 88% for non-SVR (p = 0.68). Achieving SVR was associated with improved event-free survival with an adjusted Hazard Ratio (aHR) of 7.69 (95% CI 3–20, p < 0.0001) after controlling for age, sex, genotype, cirrhosis and treatment.



After matching IFN non-responders with DAA patients using inverse probability treatment weighting, the overall event rate was 1.1% in DAA patients compared to 17.9% in IFN non-responders at 2 years underlining the clinical benefit of higher SVR rates.

Conclusion: In IFN-eligible patients, SVR is more commonly achieved with DAAs and confers a similar clinical benefit as in those treated with IFN. The markedly higher SVR rate but reduced overall event rate with DAAs compared to IFN, despite similar disease severity, unequivocally shows that SVR cannot be due to a "good prognosis", but rather SVR is a relevant endpoint leading to improved clinical outcomes.

FRI-364

The number needed to treat to prevent one clinical event at 2 years after antiviral treatment for HCV with DAAs compared to IFN-based therapy

L. Krassenburg[1,2], B. Hansen[1,2,3], W.R. Zanjir[1], F. Georgie[1], O. Cerocchi[1], J. Lau[1], A. Van der Meer[2], H. Janssen[1], J. Feld[1]. [1]*Toronto General Hospital, University Health Network, Toronto Centre for Liver Disease, Toronto, Canada;* [2]*Erasmus University Medical Center Rotterdam, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands;* [3]*Management and Evaluation, University of Toronto, Institute of Health Policy, Toronto, Canada*
Email: lisettekrassenburg@gmail.com

Background and Aims: Sustained virological response (SVR) has been shown to be associated with improved clinical outcomes with interferon (IFN)-based antiviral therapy. The development of direct acting antivirals (DAAs) has markedly increased SVR rates, however there are limited data on the clinical benefits of the improved response rates. We evaluated the number needed to treat (NNT) to prevent one clinical event by using DAAs compared to IFN at 2 years after treatment completion.
Method: Retrospective data were collected on all patients with hepatitis C (HCV) who visited the Toronto Centre for Liver Disease between June 2006 and January 2017. Baseline characteristics and disease severity were evaluated at start of treatment and patients were followed from end-of-treatment until a clinical event (hepatocellular carcinoma, decompensation, liver transplantation or death). The NNT to prevent 1 clinical event at 2 years, was calculated using the estimated survival (Surv) in those with SVR and non-SVR for each treatment group. $NNT = 1/(((Surv_{DAA\text{-}SVR}{}^{*}SVR_{DAA}) + (Surv_{DAA\text{-}nonSVR}{}^{*}(1\text{-}SVR_{DAA}))) - ((Surv_{IFN\text{-}SVR}{}^{*}SVR_{IFN}) + (Surv_{IFN\text{-}nonSVR}{}^{*}(1\text{-}SVR_{IFN}))))$.
Results: Of 1492 patients, 841 (56%) received DAAs and 651 (44%) IFN. SVR was attained by 96% of DAA-treated patients, compared to 69% of IFN-treated patients. Achieving SVR was associated with improved event-free survival compared to non-SVR with an adjusted Hazard Ratio (aHR) of 8.4 (95% CI 5–14, $p < 0.001$), after controlling for age, sex, genotype, cirrhosis and treatment-type. The NNT to prevent 1 clinical event in 2 years with DAA compared to IFN treatment was 21. For patients with compensated cirrhosis at baseline the NNT was 4 and for those with decompensated cirrhosis, the NNT was 6. By HCV genotype (G), the NNT was 21 for G1 and 14 for G3.
Conclusion: The high SVR rates of DAA therapy compared to IFN therapy translate to tangible clinical benefits at two years across patient groups. Although the benefit of DAAs over IFN is greatest in those with cirrhosis at baseline, the NNT is low across patient groups, confirming the broad clinical benefits of DAA therapy.

FRI-365

TLL1 variants do not predict the development of de-novo hepatocellular carcinoma in HCV cirrhotics treated with IFN-free DAA-based regimens

E. Galmozzi[1], F. Facchetti[1], R. D'ambrosio[1], E. Degasperi[1], A. Aghemo[2], R. Soffredini[1], M. Borghi[1], R. Perbellini[1], M. Iavarone[1], A. Sangiovanni[1], P. Lampertico[1]. [1]*Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy;* [2]*Humanitas University, Department of Biomedical Sciences, Rozzano, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: A genome wide association study (GWAS) has recently demonstrated an association between the Tolloid Like 1 (TLL1) *rs*17047200 polymorphism and the development of hepatocellular carcinoma (HCC) among hepatitis C virus (HCV) patients with a sustained virological response (SVR) to Interferon, but whether this holds true for direct-acting antivirals (DAA)-treated patients remains unknown. Aim of our study was to assess the association of TLL1 *rs*17047200 with HCC development in a cohort of HCC-free HCV cirrhotics who were treated with a DAA-based regimen.
Method: 278 consecutive HCC-free HCV cirrhotics [aged 66, 57% males, 49% HCV-1b, 86% CPT-A, LSM 17.6 (12.1–75) kPa, αFP 9.5 (0.8–537) ng/mL, 19% with diabetes] treated with DAA between January 2015 and December 2016 were enrolled in a single Center real-life study. Cirrhosis was defined clinically, histologically (METAVIR F4) or by liver stiffness measurement (LSM >11.9 kPa). HCC was diagnosed according to International recommendations. TLL1 *rs*17047200 A/T variant was analyzed using Taq-Man SNP genotyping assay.
Results: The genotype distribution of TLL1 variant was AA in 202 (73%), AT in 71 (25.5%) and TT in 5 (1.5%) patients. Patients carrying the AA or the AT/TT genotypes were similar according to the most important demographic features such as male gender (56% *vs.* 62%), age (63 *vs.* 62) and BMI (25 *vs.* 25). They were also similar in terms of HCV genotype distribution, baseline LSM (18 *vs.* 16 kPa), diabetes prevalence (19% *vs.* 21%) and platelets count (108 *vs.* 121 x 10^3/mm^3). Similar SVR rates were reported in patients carrying the AA or the AT/TT genotypes (96% *vs.* 96%). De-novo HCC occurred in 25 (9%) patients after 3–28 (median 10) months from DAA start, with a 3-year cumulative probability of 6%. The 3-year cumulative incidence of HCC was 9.1% in patients with TLL1 AA and 9.5% in those carrying the AT/TT variants ($p = 0.67$). No differences were found between AA and AT/TT patients according to HCC characteristics; in fact, they were similar in terms of time to HCC development (10 *vs.*12 months), nodules number (single node in 80% *vs.* 50%), αFP values (6 *vs.* 21, $p = 0.50$), BCLC O/A stage (89% *vs.* 66%), Milan-in criteria (89% *vs.* 67%) and severity of liver disease (CPT-A in 90% *vs.*100%).
Conclusion: In a large cohort of HCC-free HCV cirrhotics treated with DAA, TLL1 variants failed to predict the de-novo development of HCC.

FRI-366

Long-term follow up of patients with chronic HCV and F2 or F3 fibrosis after achieving SVR with DAA-based therapy: results from the Gilead SVR registry

S. Zeuzem[1], M.B. Ferret[2,3], E. Gane[4], I. Jacobson[5], S.C Gordon[6], M. Sulkowski[7], B. Mcnabb[8], F. Chen[8], H. Dvory-Sobol[8], A. Osinusi[8], D. Brainard[8], M. Subramanian[8], A. Ramji[9], K. Agarwal[10], R. Reddy[11], M. Bourliere[12]. [1]*Johann Wolfgang Goethe-Universität, Frankfurt am Main, Germany;* [2]*Hospital Universitario Vall d'Hebron, Barcelona, Spain;* [3]*CIBERehd;* [4]*New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand;* [5]*Department of Medicine, New York University Medical Center, New York, United States;* [6]*Henry Ford Health System, Detroit, United States;* [7]*Johns Hopkins University School of Medicine, Baltimore, United States;* [8]*Gilead Sciences, Inc., Foster City, United States;* [9]*Division of Gastroenterology, University of British Columbia, Vancouver, Canada;* [10]*Kings College Hospital NHS Trust Foundation, London, United Kingdom;* [11]*University of Pennsylvania, Philadelphia, United States;* [12]*Department of Hepato-Gastroenterology, Hôpital Saint-Joseph Marseille, Marseille*
Email: brian.mcnabb@gilead.com

Background: HCV infected patients with F0-F1 fibrosis experienced minimal liver-related morbidity and mortality following sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy. Less is known about the clinical progression of liver disease among HCV-infected patients with F2 or F3 fibrosis who have achieved SVR with DAA regimens.
Methods: Patients enrolled in the Gilead SVR Registry were included in this analysis if they were deemed to have F2 or F3 fibrosis pre-DAA treatment as measured by FibroTest (0.32–0.58 or 0.59–0.72, respectively). Patients could be enrolled up to 60 weeks after initiating DAA-treatment that lead to SVR, and study visits occurred every 24

weeks for up to 144 weeks. Assessments for signs of jaundice, ascites, hepatic encephalopathy (HE), varices, and hepatocellular carcinoma (HCC) and measurement of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (Bili), albumin (ALB), prothrombin time (PT), and platelets (PLT), occurred at each visit.

Results: A total of 1,489 and 857 patients with F2 and F3 fibrosis were enrolled, with median (range) registry follow up times of 1.9 (0–3.3) and 1.8 (0–3.2) years, respectively. Of these, 57% and 72% were male and the mean (range) ages were 55 (19–80) and 57 (19–82) years for F2 and F3 patients, respectively. There were 2 and 4 cases of HCC reported in 2509 and 1371 person-years of follow-up time for patients with F2 and F3 fibrosis, respectively. Overall, the prevalence of liver-related events was low at all visits, remaining stable for F2 and numerically decreasing over time for F3 patients (Table). At Week 144, 1 (0.1%) patient with F2 fibrosis had evidence of varices reported and 1 (0.3%) patient with F3 fibrosis had evidence of jaundice reported. Mean week 144 ALT, AST, Bili, ALB, PT, and PLT were within normal limits and comparable to baseline values. Three patients with F2 and 3 patients with F3 fibrosis died, with no causes of death due to liver disease. No liver transplants were reported. There were 4 patients with F2 and 3 patients with F3 fibrosis who experienced virologic failure during follow up; all but one of these patients had clear virologic evidence for reinfection by sequencing.

	Registry Baseline		Week 48		Week 96		Week 144	
Liver-Related Event, n (%)	F2 n = 1,489	F3 n = 857	F2 n = 1159	F3 n = 640	F2 n = 916	F3 n = 484	F2 n = 677	F3 n = 367
Jaundice	0	1 (0.1)	0	0	0	0	0	1 (0.3)
Ascites	1 (<0.1)	4 (0.5)	0	1 (0.2)	1 (0.1)	0	0	0
Hepatic Encephalopathy	0	1 (0.1)	0	1 (0.2)	0	0	0	0
Varices	0	3 (0.4)	0	2 (0.3)	3 (0.3)	1 (0.2)	1 (0.1)	0

Conclusion: In HCV-infected patients with F2 or F3 fibrosis who achieve SVR with DAA therapy, events including liver-related complications, HCC, death and HCV relapse are rare in the first 144 weeks of follow-up. These data support early treatment of HCV infection and may be useful in guiding monitoring strategies for HCC and other liver-related events following SVR.

FRI-367
Serum immune signatures predict HCC development in DAA-treated HCV patients

J. Debes[1], M. van Tilborg[2], A. Grooshuismink[2], B. Hansen[2], J.S.Z. Wiesch[3], J. von Felden[3], R. de Knegt[4], A. Boonstra[2]. *[1]University of Minnesota; [2]Erasmus Mc; [3]UMC hamburg-Eppendorf; [4]Erasmus Mc, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: debes003@umn.edu

Background and Aims: Concern has arisen about development of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) infection treated with direct-acting antivirals (DAAs). As treatment with DAAs will continue it is imperative to understand which patients might be at risk for HCC following treatment. In this study we aimed to evaluate an immune-signature and its association with development of HCC following DAA treatment.

Method: We evaluated serum levels of 67 immune mediators before, during, and after DAA treatment of HCV infection. Our cohort included 13 patients who developed HCC within 18 months of treatment (3 with HCC recurrence and 10 with *de novo* HCC) and 10 patients who did not develop HCC (controls), within a follow up period of 24 months post treatment, matched for age, HCV genotype and liver fibrosis. All patients had liver ultrasound performed within 3 months of starting DAA treatment and all responded to HCV treatment. Data was analyzed using SAS 9.3 and SPSS version 24. All markers were log transformed to achieve near to normal distributed values. One-way analysis of variance with Bonferroni correction was used to compare the groups.

Results: We identified a set of 12 immune mediators (cytokines, growth factors, and apoptosis markers) whose levels were significantly higher in serum before DAA treatment of patients who eventually developed de novo HCC compared to controls. A panel of 9 of these markers (MIG, IL22, sTRAIL, sAPRIL, VEGF, IL-3, sTWEAK, SCF, IL-21) identified patients who developed *de novo* HCC with an area under the receiver operating characteristic curve (AUROC) value higher than 0.8 and 4 of them showed an AUROC above 0.9. Further analyses in a subset of 7 patients beyond baseline showed modifications of TNF-alpha, sTRAIL and IL-6 levels at 4 and 12 weeks of treatment in those that developed HCC. Moreover, there was a differential modulation of IL-6 in those that developed *de novo* HCC compared to recurrence of HCC.

Conclusion: Our study identified a group of immune mediators that showed significantly higher serum levels before DAA treatment in patients that later developed HCC and could potentially serve as markers for screening. We also provide important input in the potential mechanisms underlying HCC development in patients treated with DAAs.

FRI-368
Long-term immunological and clinical impact of HCV eradication with direct acting antivirals in patients with HCV-associated cryoglobulinemia vasculitis

M. Bonacci, S. Lens, Z. Mariño, S. Rodriguez-Tajes, Concepció Bartres, M. Ramos-Casals, José Hernández-Rodríguez, X. Forns. *IDIBAPS, CIBERehd, Liver Unit, Barcelona, Spain*
Email: bonacci@clinic.cat

Background and Aims: Several reports on patients with HCV-associated vasculitis showed high rates of clinical remission 12–24 weeks after treatment with direct acting antivirals (DAAs). However, cryoglobulins(CRYO) persisted in up to 50% of patients. We aim to assess the long-term clinical/immunological impact of DAA therapy in patients with HCV-related symptomatic or asymptomatic cryoglobulinemia

Method: Patients with circulating CRYO treated with DAA were prospectively followed. Patients were grouped into HCV-vasculitis (CV) or CRYO-asymptomatic (ACC). Complete immunological response (CIR) was defined as CRYO negativization with complement normalization. Among CV, clinical response was complete if BVAS.v3 score = 0 or all affected organs improved; clinical response was partial if BVAS.v3 < 50% of entry score.

Results: 94 patients were included, 50 CV and 44 ACC. Baseline characteristics were similar between groups except for female gender (74% in CV vs. 28% in ACC). CV patients had higher cryocrit (3.2 vs 2.3%; $p < 0.01$), rheumatoid factor (80 vs 10 IU/mL; $p < 0.01$), and lower C4 fraction (0.04 vs 0.09 g/L; $p < 0.01$) than ACC. Main clinical manifestations in CV patients were purpura (56%), polyneuropathy (40%) and nephropathy (16%). SVR rate was 95% (CV:95% vs ACC:93%). Post-treatment follow-up (FU) was 24 (18–27) months and similar between groups. CRYO persisted in 42% and 56% at SVR12, and in only 22% and 18% at last FU in CV and ACC patients, respectively. Overall CIR increased from 38% at SVR12 to 62% [CV (56%) vs ACC (67%), p = ns] at last FU. Complete clinical response increased from 66% at SVR12 to 74% at last FU. Overall, BVAS.v3 decreased from 7 (2–31) at baseline to 3 (0–11) at SVR12 ($p < 0.05$) and to 0 (0–8) at last FU ($p < 0.05$). A BVAS.v3 > 9 and a cryocrit >3% at entry were associated with null clinical response [HR = 0.4 (0.2–0.8), p = 0.01] and non-CIR HR = 0.3 (0.1–0.5), p = 0.01], respectively. Of note, despite viral cure, three cirrhotic CV-patients experienced vasculitis relapse (2 purpura/1 intestinal) associated with reappearance of CRYO during FU. Moreover, one patient experienced non-Hodgkin Lymphoma relapse. No patient with ACC developed an overt CV during FU.

Conclusion: Clinical and particularly immunological response improves significantly overtime after HCV cure in CV and ACC

patients. However, 2 years after HCV elimination CRYO may persist in more than 20% of patients and clinical relapse may occur in a small proportion of CV-patients (even with CRYO reappearance), suggesting that a longer monitoring of these patients is still warranted.

FRI-369

Incidence and predictors of de novo hepatocellular carcinoma in HCV cirrhotic patients treated with direct-acting antivirals: a single-center prospective 3 year study

R. D'ambrosio[1], E. Degasperi[1], M. Iavarone[1], A. Sangiovanni[1], A. Aghemo[2], R. Soffredini[1], M. Borghi[1], R. Perbellini[1], G. Lunghi[3], P. Lampertico[1]. [1]*Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy;* [2]*Humanitas University, Department of Biomedical Sciences, Rozzano, Italy;* [3]*Fondazione Irccs Cà Granda Ospedale Maggiore Policlinico, Microbiology and Virology Unit, Milano, Italy*
Email: pietro.lampertico@unimi.it

Background and Aims: Incidence of hepatocellular carcinoma (HCC) in cirrhotic patients treated with direct-acting antivirals (DAAs) for hepatitis C (HCV) virus infection is still controversial. Aim of the study was to evaluate incidence and predictors of de novo HCC in HCV cirrhotics treated with DAAs.
Methods: Consecutive HCV cirrhotics starting DAAs between November 2014 and December 2016 at a single Center were enrolled. Exclusion criteria were HIV infection, previous HCC history, active HCC or undefined liver nodules at baseline and Child-Pugh-Turcotte (CPT) score C. Cirrhosis was defined clinically, histologically or by liver stiffness measurement (LSM > 11.9 kPa). HCC was diagnosed and staged according to EASL recommendations. Baseline clinical features, biochemistry and non-invasive markers of liver fibrosis (LSM, APRI, Fib-4, LSPS) were assessed.
Results: 510 HCV cirrhotics were enrolled: age was 63 (28–87) years, 60% males, 47% HCV-1b, 82% CPT A, 31% with baseline esophageal varices (EV). Median LSM was 17.3 (12.1–75.0) kPa, APRI 2.0 (0.2–30.5), Fib-4 4.6 (0.3–46.3), LSPS 1.7 (0.3–29.0). A sustained virological response was achieved by 491 (96%). After 22 (1–36) months, de novo HCC occurred in 24 (4.9%) patients, with a 3-year cumulative probability of 6% (95% CI 4%-9%). At diagnosis, median HCC size was 18 (10–100) mm, monofocal in 71%, BCLC 0-A in 83%; CPT was A in 79% patients and median alpha-fetoprotein (AFP) was 6 (1–57) ng/ml. At univariate analysis, de novo HCC was associated with male gender (p = 0.013), diabetes (p = 0.001), baseline LSM (<0.0001) and LSPS (<0.0001). At multivariate analysis, in patients without available LSM (n = 489), male gender [HR 4.42 (95% CI 1.26–15.5), p = 0.02], diabetes [HR 3.59 (95% CI 1.57–8.23), p = 0.002] and baseline Fib-4 [HR 1.08 (95% CI 1.01–1.15), p = 0.018] were independently associated with HCC development. In those with available LSM (n = 404), male gender [HR 10.0 (95% CI 1.33–75.7), p = 0.025], diabetes [HR 2.7 (95% CI 1.06–6.91), p = 0.037] and LSM [HR 1.03 (95% CI 1.01–1.06), p = 0.004] predicted the occurrence of HCC. The 3-year cumulative probability of HCC was 8.7% in males *vs.* 1.6% in females (p = 0.005), 18.0% in diabetics *vs.* 3.2% non-diabetics (p = 0.0003), and 3.4% *vs.* 23% in patients with LSM < or ≥30 kPa (p < 0.0001).
Conclusion: In a large, single-center prospective study of DAA-treated HCV cirrhotics, male gender, diabetes and noninvasive markers of fibrosis independently predicted the development of HCC.

FRI-370

The impact of HCV eradication by IFN-free regimens on the transition of precancerous hepatic nodules to HCC: a prospective observational study

H. Toyoda[1], T. Kumada[1], T. Tada[1], T. Yama[1], K. Mizuno[1], T. Akita[2], J. Tanaka[2]. [1]*Ogaki Municipal Hospital, Gastroenterology, Ogaki, Japan;* [2]*Hiroshima University Institute of Biomedical and Health Sciences, Epidemiology, Infectious Disease Control, and Prevention, Hiroshima, Japan*
Email: hmtoyoda@spice.ocn.ne.jp

Background and Aims: It is controversial whether the eradication of hepatitis C virus (HCV) by interferon (IFN)-free anti-HCV therapy using direct-acting antivirals (DAAs) suppresses or promotes hepatocarcinogenesis in patients with chronic hepatitis C. We investigated the influence of HCV eradication by DAA therapy on hepatocarcinogenesis, observing non-hypervascular hypointense nodules (NHHNs) by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI).
Methods: A total of 401 patients treated with DAA therapy who did not have a history of hepatocellular carcinoma (HCC) were enrolled in this prospective cohort study. All study patients underwent Gd-EOB-DTPA-enhanced MRI just before the start of DAA therapy and were followed up by repeated Gd-EOB-DTPA-enhanced MRI periodically after therapy. The incidence of the hypervascularization of NHHNs detected at baseline to typical HCC and the incidence of new emergence of NHHNs were analyzed.
Results: Low platelet counts, low serum albumin levels, high alpha-fetoprotein levels, and cirrhosis were associated with the presence of NHHNs at baseline by multivariate analysis. In comparison of patients who achieved sustained virologic response (SVR) with propensity score-matched patients with persistent HCV infection, there was no difference in the incidence of hypervascularization of NHHNs to typical HCC among patients who had NHHNs at baseline (2-year incidence: patients with SVR vs. patients with persistent HCV infection, 24.4% vs. 24.9%, p = 0.6170). Among patients who did not have NHHNs at baseline, the incidence of the new emergence of NHHNs did not differ between study patients and propensity score-matched patients with persistent HCV infection (1-year incidence: patients with SVR vs. patients with persistent HCV infection, 3.4% vs. 5.2%, p = 0.7282).
Conclusions: During a 2-year observation period after SVR, the eradication of HCV by IFN-free DAA therapy did not influence hepatocarcinogenesis. HCV eradication did not suppress or enhance the development of typical hypervascular HCC from precancerous NHHNs. (umin.ac.jp/ctr/index.htm, number UMIN000017020)

FRI-371

Impact of curative HCC history on the development of HCC after the eradication of HCV by DAA therapy in patients with HCV infection

H. Toyoda[1], T. Kumada[2], T. Tada[2,3], K. Mizuno[2]. [1]*Ogaki Municipal Hospital, Gastroenterology, Japan;* [2]*Ogaki Municipal Hospital, Gastroenterology, Ogaki, Japan;* [3]*Ogaki Municipal Hospital, Gastroenterology, Ogaki, Japan*
Email: hmtoyoda@spice.ocn.ne.jp

Background and Aims: The incidence of hepatocellular carcinoma (HCC) development in patients with a history of curatively treated HCC is higher than in patients without a history of HCC even after the eradication of hepatitis C virus (HCV) by anti-HCV therapy, i.e., sustained virologic response (SVR). We investigated the differences in the patterns of HCC development after the eradication of HCV between patients with a history of curative HCC and those without it, based on the findings by gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced magnetic resonance imaging (MRI).
Method: Gd-EOB-DTPA-enhanced MRI was examined in 454 patients who achieved sustained virologic response (SVR) by interferon-free

direct-acting antiviral regimens just before the start of the therapy and the changes in Gd-EOB-DTPA-enhanced MRI findings after SVR were compared between patients with a history of HCC (n = 71) and without it (n = 383).
Results: The prevalence of patients with non-hypervascular hypointense nodules (NHHNs) during hepatobiliary phase of Gd-EOB-DTPA-enhanced MRI was significantly higher in patients with a history of HCC at baseline than those without HCC (patients with a history of HCC vs. without HCC, 29.6% vs. 8.6%, p < 0.0001). The incidence of typical hypervsacular HCC after SVR was higher in patients with a history of HCC (40.8%) than patients without (1.3%, p < 0.0001). Among patients with NHHNs at baseline, the hypervascularization of NHHNs to typical hypervascular HCC was more frequently observed in patients with a history of HCC (61.9%) than those without (15.2%, p < 0.0001). In addition, direct emergence of hypervascular HCC was observed in 32.0% of patients with a history of HCC despite the absence of NHHNs at baseline, whereas no hypervascular HCC developed in non-HCC-history patients without NHHNs at baseline (p < 0.0001).
Conclusion: In patients with a history of HCC, non-hypervascular hypointense nodules are more likely to show hypervascularization. In addition, direct emergence of hypervascular HCC not through NHHNs enhances the incidence of HCC development after SVR.

FRI-372
Impact of direct-acting antiviral agents on liver function in patients with chronic hepatitis C virus infection

H. Toyoda[1], S. Berhane[2], E. de Groot[3], T. Tada[1], T. Kumada[1], W. Irving[4], P. Johnson[2]. *[1]Ogaki Municipal Hospital, Gastroenterology, Japan; [2]University of Liverpool, Molecular and Clinical Cancer Medicine, Liverpool, United Kingdom; [3]University of St Andrews, St Andrews, United Kingdom; [4]University of Nottingham, NIHR Biomedical Research Unit in Gastroenterology and the Liver, Nottingham, United Kingdom*
Email: philip.johnson@liverpool.ac.uk

Background and Aims: Whilst the benefit of direct-acting antiviral agents (DAAs) in achieving SVR is now well-accepted, the impact of DAAs on survival is difficult to demonstrate because of the long term follow-up that is required. An alternative, shorter term approach is to assess the efficacy of DAAs on liver function.
Methods: We studied 2,653 patients with chronic hepatitis C virus (HCV) infection, 1,535 receiving DAAs and 1,118 interferon-based therapy. Those receiving DAAs came from the UK [n = 752, median follow-up = 23.9 months (95%CI 23.6, 24.0), mainly patients with decompensated cirrhosis] and Japan [n = 783, median follow-up = 20.2 months (95%CI 18.4, 20.7), mainly with compensated disease]. Median follow-up was 11.1 years (95%C.I. 10.3, 11.8) in the Interferon cohort. Liver function was assessed by the ALBI score.
Results: Among the patients receiving DAAs, 87% achieved SVR (Japan = 95%, UK = 79%). A higher rate of SVR achievement was independently associated with Genotype 1 (vs. other, p < 0.0001), better liver function (lower ALBI score p < 0.0001) and Japanese ethnicity (p < 0.0001). The Japanese patients (receiving DAAs) had virtually normal liver function at the time of treatment and there was therefore no scope to demonstrate improvement. However, among the UK patients receiving DAAs who had predominantly decompensated disease, improvement of liver function was clearly evident over the two years after start of treatment, especially in those achieving SVR [Figure]. These early changes in liver function were very similar to those observed in the first 2–3 years after interferon-based therapy [Figure] suggesting that, over the longer term, patients achieving SVR have improvement and subsequent stabilisation of liver function whilst among those not achieving SVR there is progressive deterioration.
Conclusion: DAAs improve liver function especially in those with decompensated disease who achieve SVR. Experience with interferon-based therapy suggests that failure to achieve SVR is associated with long-term decline in liver function, and in contrast, patients who do achieve SVR can expect long-term disease improvement and subsequent stabilisation of liver function. Our initial analysis suggests that those receiving DAAs are likely, in the long term, to follow a similar course. Liver function is an important factor influencing achievement of SVR in patients receiving DAAs.

FRI-373
Sustainable improvement of patient-reported outcomes in cirrhotic patients with hepatitis C who achieved sustained virologic response

Z. Younossi[1], M. Stepanova[2], A. Racila[2], I. Younossi[2], F. Nader[2], A. Muir[3], M. Bourliere[4], A. Mangia[5]. *[1]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States; [2]Center for Outcomes Research in Liver Disease; [3]Duke University Medical Center; [4]Hôpital Saint Joseph; [5]IRCCS "CSS"*
Email: zobair.younossi@inova.org

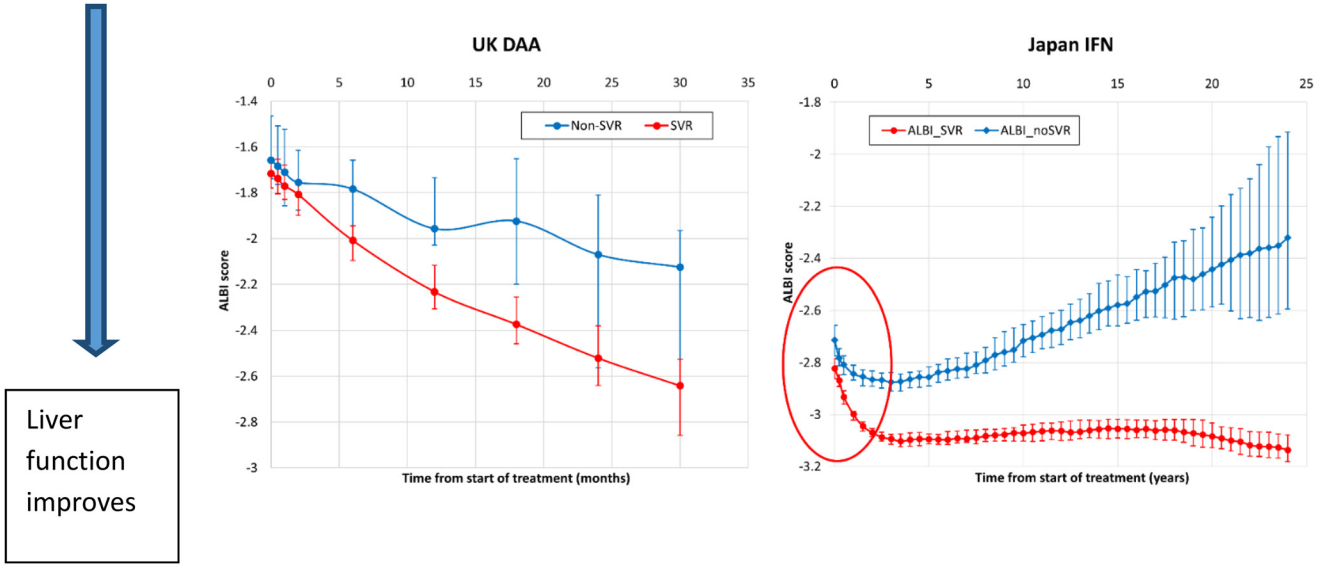
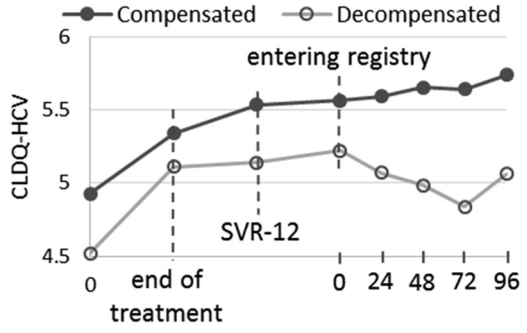


Figure: (abstract: FRI-372): Changes in liver function (ALBI score) over 2.5 years after DAA therapy (left) according to SVR status. Note the similarity of changes in the interferon based-therapy cohort (at the same time of follow-up, red oval). The absolute ALBI score at initiation of therapy is, as expected, much worse in this UK-based cohort of decompensated patients. Note also the difference in scale – months on the left, years on the right.

Background and Aims: HCV infection impairs patient-reported outcomes (PROs). Development of cirrhosis further worsens this PRO impairment. Although achieving sustained virologic response (SVR) can lead to PRO improvement, the long-term sustainability of this improvement in hepatitis C (HCV) cirrhotics has not been established. To assess long-term trends in PROs of patients with cirrhosis who have achieved SVR.
Method: Patients with HCV and cirrhosis who were treated in 12 clinical trials and had achieved SVR-12 were prospectively enrolled in a long-term registry. PROs were collected every 24 weeks using Short Form-36v2 (SF-36), CLDQ-HCV, and WPAI-HCV (20 PRO domains).
Results: Baseline data was available for 786 HCV cirrhotics with SVR-12. Of these, 650 had compensated and 136 decompensated cirrhosis before treatment [age 59.0 ± 7.4 years, 69% male, 22% with pre-treatment type 2 diabetes, 50% employed at enrollment]. Prior to their initial treatment, decompensated patients experienced severe impairment in their PROs in comparison to compensated cirrhotics (by 5.0% to 13.6% of a PRO range size; $p < 0.05$ for 15/20 PROs). After achieving SVR and enrollment into the registry, significant PRO improvements from the pre-treatment levels ($p < 0.05$) were noted in 11/20 PRO domains in decompensated (+4.1%–+19.6%) and in 19/20 PRO domains in compensated patients (+2.1%–17.0%). These PRO gains persisted or improved over time up to 96 weeks of follow-up in the registry (Figure). In multivariate regression analysis, younger age, the absence of baseline decompensation and type 2 diabetes, as well as baseline history of depression and fatigue were independent predictors of greater PRO improvements in the long term ($p < 0.05$).



Conclusion: HCV-infected patients with cirrhosis experience severe PRO impairment which improves after SVR in a sustainable and durable manner. There is some residual PRO impairment post-SVR in decompensated patients which is most likely related to the severity of their liver disease.

FRI-374
The impact of sustained virologic response on severe fatigue in patients with chronic hepatitis C: The role of HCV viremia and co-morbidities

Z. Younossi[1], M. Stepanova[2], L. Deavila[3], L. Gerber[3], E. Lawitz[4], S. Flamm[5], B. Willems[6]. *[1]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States; [2]Center for Outcomes Research in Liver Disease, Washington Dc; [3]Inova Fairfax Hospital, Department of Medicine, Falls Curch, United States; [4]Texas Liver Institute, United States; [5]Northwestern University Medical Center; [6]Centre Hospitalier de l' Université de Montreal, Canada*
Email: zobair.younossi@inova.org

Background and Aims: Fatigue is a major extrahepatic manifestation of chronic hepatitis C infection. Studies suggest that fatigue may improve after HCV clearance. The aim is to assess the impact of SVR on fatigue in HCV patients who suffered from severe fatigue before treatment.
Methods: Participants of phase 2 and 3 clinical trials of sofosbuvir-based regimens completed FACIT-F instrument on the first day of treatment and at post-treatment week 12 visit; the Fatigue Scale score (FS, range 0–52) was used to assess baseline and post-treatment fatigue in patients with SVR.
Results: There were 6,113 patients with HCV who achieved SVR after treatment and had FS calculated prior to treatment and at post-treatment week 12 visit. Patients with FS scores in the lowest quartile (FS < 30; n = 1,467) were considered to have severe fatigue [age: 53.4 ± 9.5 years, 56% male, 40.0% employed, 34.6% cirrhotic, 27.5% reported history of anxiety, 43.4% history of depression, 14.5% had type 2 diabetes, and 6.7% coinfection with HIV]. By SVR-12, 42.4% of patients with pre-treatment severe fatigue (FS < 30) continued to experience severe fatigue (FS < 30) while 45.0% of patients with pretreatment severe fatigue improved to moderate fatigue (FS = 30–47), and 12.6% improved to minimal-or-no fatigue (FS ≥ 48). Patients with improved fatigue scores were younger and less likely to have cirrhosis (24.9% in those who improved to FS ≥ 48 vs. 33.9% in patients improved to moderate fatigue vs. 38.3% in patients without fatigue improvement). Similarly, these patients had lower rates of comorbidities (depression, anxiety, sleep disorders, diabetes, HIV co-infection) (all $p < 0.005$). No association of fatigue improvement with baseline demographic data (sex, race), HCV treatment history, baseline HCV viral load, and baseline BMI was found (all $p > 0.05$). In multivariate analysis, independent predictors of remaining severely fatigued after achieving SVR included the presence of cirrhosis (odds ratio (OR) (95%CI) = 1.38 (1.10–1.73)), having history of depression (OR = 2.07 (1.66–2.58)), sleep disorders (OR = 1.52 (1.20–1.92)), and coinfection with HIV (OR = 1.63 (1.06–2.51)) (all $p < 0.03$).
Conclusions: After SVR-12, more than half (57%) of HCV patients with pre-treatment severe fatigue improved their fatigue scores. Patients who continued to experience severe fatigue post-SVR were more likely to have cirrhosis and other co-morbidities. This suggests that post-SVR fatigue management should focus on managing these comorbidities which also contribute to fatigue.

FRI-375
De novo hepatocellular carcinoma in patients with cirrhosis due hepatitis C virus infection after treatment with direct antiviral agents

P. Ruiz[1], L. Deiss[1], L. Buendía[1], I. Erdozain[1], C. Álvarez[1], P. Gutiérrez[1], J.José Pascual[2], A. Baranda[1], S. Blanco[1], F. Menéndez[1], ÁngelJosé Calderón[3], A. Esain[3]. *[1]Basurto Universitary Hospital, Digestive and Liver Diseases, Bilbao, Spain; [2]Basurto Universitary Hospital, Computer Science, Bilbao; [3]Basurto Universitary Hospital, Digestive and Liver Diseases, Bilbao*
Email: andrea.esainurricelqui@sakidetza.eus

Background and Aims: The risk of developing *de novo* hepatocellular carcinoma (HCC) persists after achieving sustained virological response (SVR) in patients infected with hepatitis C virus (HCV). It has been suggested that risk increases in patients treated with the new direct antiviral agents (DAA). In this prospective study we present our results of incidence and prevalence of *de novo* HCC in cirrhotic patients treated with DAA who achieved SVR, and also, the risk factors involved.
Method: We included all cirrhotic patients due HCV infection without previous HCC who reached SVR after DAA treatment in our hospital from February 2014 until July 2017 (n = 226, median follow up 17 months). We evaluated with the chi-square test the following qualitative variables: Child-Pugh class, pre-treatment alcohol and tobacco consumption, pre-treatment diabetes mellitus (DM), HCV genotype, pre-treatment radiologic and endoscopic portal hypertension features. The quantitative variables were evaluated with the Student's test: age, pre-treatment n° of platelets, pre-treatment fibroscan value.
Results: During follow up, 12 patients were diagnosed of HCC (5.3% prevalence, 3.7% annual incidence). Among all qualitative variables evaluated, Child-Pugh class B vs class A ($p = 0.001$), pre-treatment DM ($p = 0.009$), and pre-treatment presence of radiologic features of portal hypertension ($p = 0.001$) were associated with developing *de*

novo HCC. Among quantitative variables, we evidenced statistically significant differences in the mean value of platelets (p = 0.015). The diagnosis of HCC was made in an average of 8.6 months after the start of treatment with DAA. 75% (9/12) was diagnosed in a stage 0 or A of the BCLC classification. At the end of the follow-up, 92% were alive (11/12).

Conclusion: In our group of patients, a worse hepatic function evaluated with the Child-Pugh classification, indirect markers of portal hypertension (platelets and radiological features) and DM are associated statistically significant with the development of *de novo* HCC.

No aggressive evolution has been observed in patients diagnosed with HCC, although the sample and the time of follow-up are scarce. The incidence (>1.5%) of de novo HCC justifies the screening of HCC in this group of patients.

FRI-376

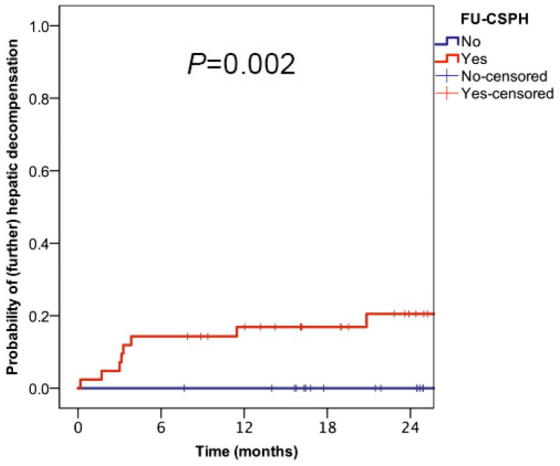
Resolution of clinically significant portal hypertension after sustained virologic response to interferon-free regimens prevents hepatic decompensation

M. Mandorfer[1], K. Kozbial[1], P. Schwabl[1], D. Chromy[1], B. Scheiner[1], R. Paternostro[1], A. Stättermayer[1], P. Munda[1], A. Ferlitsch[1], M. Trauner[1], M. Peck-Radosavljevic[2], P. Ferenci[1], T. Reiberger[1]. [1]*Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Vienna, Austria;* [2]*Klinikum Klagenfurt am Woerthersee, Department of Gastroenterology and Hepatology, Endocrinology, and Nephrology, Klagenfurt, Austria*
Email: mattias.mandorfer@meduniwien.ac.at

Background and Aims: Sustained virologic response (SVR) to interferon (IFN)-free therapies ameliorates portal hypertension. However, the impact of the hemodynamic response on hepatic decompensation has yet to be investigated in this setting.

Methods: Seventy-seven patients with portal hypertension (HVPG ≥6 mmHg) who underwent hepatic venous pressure gradient (HVPG) and liver stiffness (LS) measurement before (baseline [BL]) and after (follow-up [FU]) IFN-free therapy were retrospectively studied.

(Further) hepatic decompensation was defined by variceal (re-) bleeding, incident ascites/worsening of ascites (requirement of paracentesis), incident hepatic encephalopathy (HE)/worsening of HE (admission for grade 3/4 HE).



Results: Patient characteristics at BL: Child-Pugh A: 81%, B: 19%; MELD: 8 (interquartile range [IQR]: 2) points; HVPG: 13 (IQR: 8) mmHg. In the subgroup of patients with a BL-HVPG of 6–9 mmHg (n = 22), no patient progressed to clinically significant portal hypertension (CSPH; HVPG ≥10 mmHg). Among patients with BL-CSPH, a HVPG-decrease ≥10% was observed in 65% (36/55), while 24% (13/55) had a FU-HVPG <10 mmHg (i.e., resolved CSPH). During a median FU of 24.9 (IQR: 15.1) months after the end of HCV treatment, 10 patients developed (further) hepatic decompensation, with variceal bleeding (n = 1), ascites (n = 4), or HE (n = 5) being the first events. Two patients underwent liver transplantation (both had further decompensation) and one patient died (non-liver-related). In patients with BL-CSPH, a HVPG-decrease ≥10% tended to decrease the risk of (further) hepatic decompensation at 2 years (10% vs.27%, p = 0.072). Overall, the absence of FU-CSPH was fully protective of the development of (further) hepatic decompensation (0% vs. 21%, overall p = 0.002; Figure). This was confirmed in the subgroup of patients with BL-CSPH (p = 0.004). The area under the receiver operating characteristic curve (AUROC) of FU-LS for diagnosing FU-CSPH/predicting (further) hepatic decompensation was 0.923/0.887. None of the patients with FU-LS values <12 kPa or <18.9 kPa had FU-CSPH or (further) hepatic decompensation, respectively.

Conclusions: The resolution of CSPH after SVR to IFN-free regimens is associated with a negligible risk of (further) hepatic decompensation, while a HVPG-decrease ≥10% is not fully protective. Moreover, FU-LS seems to provide prognostic information.

FRI-377

Long-term changes of liver elasticity in HVC-infected patients with SVR after treatment with direct-acting antivirals

V. Pietsch[1], K. Deterding[1], D. Attia[1], K. Ringe[2], M. Cornberg[2], M. Gebel[1], M.P. Manns[3], H. Wedemeyer[4], A. Potthoff[1]. [1]*Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany;* [2]*Hannover Medical School, Department of Diagnostic and Interventional Radiology, Hannover, Germany;* [3]*Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany;* [4]*Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany*
Email: veronika-pietsch@gmx.de

Background and Aims: Interferon-free antiviral therapy is associated with high rates of sustained virologic response (SVR). SVR has been associated with a significantly decreased liver stiffness; however, follow-up was mostly limited to 24 weeks after end of treatment (FU24). The aim of this work is to investigate long term liver stiffness changes in SVR patients using both, transient elastography (TE) and ARFI.

Methods: 171 patients (mean age 59 years, 54% male, 81% HCV genotype 1) with chronic HCV infection who achieved a SVR with IFN-free therapies were examined prospectively. 96 patients (56%) had liver cirrhosis (F4) at start of treatment. The duration of therapy was 8 to 24 weeks. All patients underwent liver elastography using TE at baseline and FU96. ARFI was performed at baseline in 169 patients, at FU24 in 126 patients and at FU96 in 92 patients.

Results: TE correlated with ARFI elastography at baseline, FU24 and FU96 (r = 0.779; r = 0.768; r = 0.629, respectively). TE and ARFI values decreased significantly from baseline to FU24 (20.7 ± 16.5 kPa to 14.2 ± 11.4 kPa, p < 0.001; 1.95 ± 0.64 m/s to 1.75 ± 0.64 m/s, p = 0.001). Importantly, neither mean TE nor mean ARFI values showed significant changes from FU24 to FU96 (14.2 ± 11.4 kPa to 13.3 ± 11.5 kPa, p = 0.08; 1.80 ± 0.73 m/s to 1.88 ± 0.88 m/s, p = 0.40). However, between FU24 and FU96 TE decreased in 43% and increased in 23%. ALT levels at baseline were significantly different in patients with and without liver stiffness regression from baseline to FU96 (93 ± 63U/l vs. 57 ± 33U/l, respectively, p = 0.036). Albumin, bilirubin and INR revealed no significant differences between FU24 and FU96. In cirrhotic patients TE changed only significantly from baseline to FU24 and not from FU24 to FU96 (31.3 ± 15.7 kPa to 20.2 ± 12.4 kPa, p > 0.001; 20.2 ± 12.4 kPa to 18.8 ± 12.6 kPa, p = 0.11). At treatment start 16% of patients suffered from Child B/C cirrhosis. 81% of these patients improved to Child A cirrhosis at FU96. Cirrhotic patients at baseline improved to TE values <14.5 kPa in 34% at FU24 and in 48% at FU96.

Conclusions: Using TE and ARFI, we identified a bi-phasic decline in liver stiffness with a more rapid decline observed in almost all patients until FU24 probably driven by decreased inflammation

followed by rather flat phased during further follow-up. TE values may even increase during follow-up in up to 25% of patients.

FRI-378

Wisteria floribunda agglutinin-positive Mac-2 binding protein predicts early occurrence of hepatocellular carcinoma in SVR achieved hepatitis C patients with interferon-free treatment

Y. Yasui, M. Kurosaki, T. Nobuharu, Y. Komiyama, H. Takada, K. Watakabe, M. Okada, W. Wan, T. Shimizu, Y. Kubota, M. Higuchi, K. Takaura, K. Tsuchiya, H. Nakanishi, J. Itakura, N. Izumi. *Musashino Red Cross Hospital, Department of Gastroenterology and Hepatology, Tokyo, Japan*
Email: izumi012@musashino.jrc.or.jp

Background and Aims: The aim of this study is to clarify the predictability of post-treatment WFA+–M2BP for the development and recurrence of hepatocellular carcinoma (HCC) in chronic hepatitis C patients who underwent interferon-free, DAAs antiviral therapy.
Method: This is a retrospective cohort study which included 571 patients who underwent antiviral therapy with interferon free DAAs regimen. Serum WFA+–M2BP was measured after antiviral therapy. HCC occurrence and recurrence were analyzed in patients stratified by previous treatment history of HCC.
Results: In 519 patients who had no history of HCC, 14 patients developed HCC. Patients whose post-DAA treatment WFA+–M2BP ≥ 1.75 cut off index (C.O.I.) showed significantly higher incidences of HCC development ($p < 0.001$). Post-DAA treatment alpha-fetoprotein (AFP) level ≥6 ng/ml was also a predictive factor for the development of HCC ($p = 0.02$). Multivariate analysis showed that post-treatment WFA+–M2BP ≥ 1.75 C.O.I. was an independent factor which significantly associated with the development of HCC. In 52 patients who had previous history of HCC, 25 patients had recurrence after SVR. Patients with post-DAA treatment AFP ≥ 6 ng/ml showed significantly lower recurrence free survival than those with AFP < 6 ng/ml ($p = 0.01$), and AFP ≥ 6 ng/ml at SVR was an only factor associated with recurrence free survival.
Conclusions: Post-treatment WFA+–M2BP is a predictive factor for the development of HCC in DAAs-treated patients with no previous HCC history. In contrast, AFP was predictive for the HCC recurrence after DAAs.

FRI-379

Lack of reduction of serum alphafetoprotein during treatment with direct antiviral agents predicts hepatocellular carcinoma development in a large cohort of patients with HCV-related cirrhosis

C. Masetti[1], R. Lionetti[2], M. Lupo[3], M. Siciliano[4], V. Giannelli[5], F. Ponziani[6], E. Teti[7], C. Dell'unto[8], S. Francioso[7], A. Brega[7], M. Montalbano[9], U.V. Comandini[9], C. Taibi[9], G. Galati[8], U.V. Gentilucci[8], A. Picardi[8], M. Andreoni[10], M. Pompili[11], A. Pellicelli[12], G. D'offizi[9], A. Gasbarrini[4], A. De Santis[13], A. Mario[14]. *[1]Policlinico Tor Vergata, Liver and Transplant Unit, Rome, Italy; [2]National Institute for Infectious Disease Spallanzani, Infectious Diseases-Hepatology; [3]Sapienza University of Rome, Department of Clinical Medicine; [4]Catholic University of Rome, Gastroenterology Unit; [5]San Camillo Forlanini Hospital, Liver Transplantation; [6]A. Gemelli Hospital, Gastroenterology and Hepatology; [7]Tor Vergata University Hospital, Department of Infectious Disease; [8]University Campus Biomedico, Internal Medicine and Hepatology Unit; [9]National Institute for Infectious Diseases Spallanzani, Infectious Diseases-Hepatology; [10]Policlinico Tor Vergata, Department of Infectious Disease; [11]A. Gemelli Hospital, Internal Medicine, Gastroenterology and Hepatology; [12]San Camillo Forlanini Hospital, Department of Liver Transplantation; [13]Sapienza University of Rome, Gastroenterology Unit; [14]Tor Vergata University Hospital, Liver and Transplant Unit*
Email: chiara.masetti12@gmail.com

Background and Aims: Residual risk of hepatocellular carcinoma (HCC) in HCV-infected cirrhotic patients treated with oral direct antiviral agents (DAA) is still a matter of debate. We investigated this issue in a large prospective cohort of cirrhotic patients treated in 7 third-level hospitals in Rome.
Methods: The cohort comprised 1045 cirrhotic consecutive patients who completed a full treatment course with DAA, with a median follow up of 17.3 months after the end of treatment (EOT), including 943 patients without a previous history of HCC and 102 successfully treated for HCC before starting DAA. The majority of patients were males (59.9%), genotype 1b (44.6%), with Child-Pugh A cirrhosis (88.8%); mean age was 63 years.
Univariate and multivariate analysis were performed to detect significant predictors of HCC development after DAA treatment. Kaplan Meier curves were used to predict incidence of HCC in patients with and without reduction in alphafetoprotein (AFP) levels during treatment.
Results: SVR was achieved in 95.3% of patients. HCC developed in 95 (9.9%), including 54/943 (5.7%) *de-novo a*nd 41/102 (39%) recurrent tumors. *De-novo* tumors were more often unifocal ($p = 0.01$) and susceptible to curative treatments ($p = 0.029$). Mean AFP levels decreased from 16.9 ± 36.2 mg/dl at baseline to 11.4 ± 55 mg/dl at EOT. At univariate analysis, predictors of HCC were a previously treated HCC, older age, higher bilirubin levels, higher MELD score, prolonged INR, baseline and EOT AFP levels, virological failure and lack of reduction of AFP levels during treatment. Gender, HCV genotype and treatment schedule were unrelated to HCC development. Kaplan Meier curves showed a lower incidence of HCC in patients showing any reduction of AFP levels during treatment ($p = 0.006$). Those in whom AFP dropped to <6ng/ml had the lowest risk of HCC ($p = 0.0001$). At Cox regression analysis, MELD score (HR 1.14, c.l. 1.04–1.25, $p = 0.0002$), history of previously treated HCC (HR 6.57, c.l. 3.30–13.06, $p < 0.00001$,) and lack of reduction of AFP (HR 3.02, c.l. 1.51–6.01, $p = 0.001$,) were confirmed as independent predictors of HCC.
Conclusions: The residual risk of HCC after DAA treatment remains substantial. The risk is remarkably higher among patients with a previously treated HCC, high MELD score and without reduction of AFP levels during treatment. These findings support the need of a strict surveillance for HCC in these patients, especially if AFP remains >6 ng/ml at EOT.

FRI-380

The course of oesophagogastric varices in patients with cirrhosis after DAA-induced HCV clearance

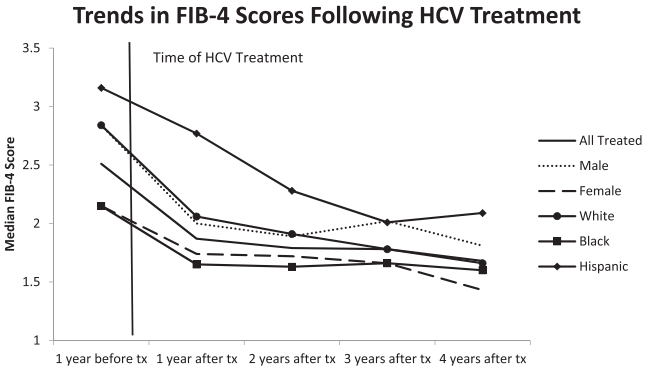
V. Calvaruso[1], I. Cacciola[2], S. Petta[1], G. Caccamo[2], E. Conte[3], M. Licata[1], F. Simone[1], G. Squadrito[2], G. Raimondo[2], A. Craxi[1], V. DI Marco[1]. *[1]University of Palermo, Gastroenterology & Hepatology, Di.Bi.M.I.S., Palermo; [2]University of Messina, Internal Medicin and Hepatology Unit, Messina; [3]University of Palermo, Gastroenterology and Hepatology Unit, DIBIMIS, Palermo*
Email: vincenza.calvaruso@unipa.it

Background and Aims: Use of direct acting antivirals (DAAs) has allowed to clear HCV in almost all patients even in the presence of advanced cirrhosis. Although it has been suggested that cirrhotic portal hypertension may regress after SVR, the ultimate effect of HCV clearance on the development and progression of oesophagogastric varices (OV) is still unexplored. We assessed in a prospective cohort of patients with cirrhosis the evolution of endoscopic features of portal hypertension induced by SVR obtained with DAAs.
Method: 263 consecutive patients (mean age 65.0 ± 10.6, males 56%) with HCV Child-Pugh A cirrhosis treated with DAAs were enrolled between January 2015 and May 2016. All patients underwent esophagogastroscopy (EGS), liver ultrasound (US), liver stiffness measurement (LSM) by Transient Elastography and laboratory tests before the starting DAAs and after achieving SVR. LS * spleen diameter/platelet ratio (LSPS) was calculated as previously described (1).

Results: Twenty-nine patients were excluded from the analysis, 20 (7.6%) since they had F2/F3 OV at baseline and were treated with beta-blockers (BB), and 9 (3.7%) since they did not achieve SVR. Overall, 234 SVR patients were analysed. At baseline, 83 patients (35.5%) did not have OV and 151 (64.5%) had small OV. None received beta-blockers. After a median time of 24.5 months EGS showed *de novo* development of OV in 17/83 (20.5%) patients and progression from F1 to F2/F3 OV in 27/151 patients (17.9%), p = 0.58 by Kaplan Meier. By Cox regression analysis, LSPS as continuum variable (HR:1.05, CI95%:1.01–1.10, p = 0.046) or at a cut off ≥3 (HR:2.87, CI95%:1.44–5.72, p = 0.003) was associated with OV progression. Age (p = 0.15), gender (p = 0.93), BMI (p = 0.84) and SVR did not correlate with progression of OV.
Conclusion: Progression of clinically significant portal hypertension, as assessed by the evolution of oesophagogastric varices, is not uncommon among patients with HCV cirrhosis after HCV clearance. Non-invasive evaluation using combined data of LS, spleen diameter, and platelet count can assist in identifying patients in whom portal hypertension is likely to progress notwithstanding SVR.
1. Berzigotti A. Elastography, Spleen Size, and Platelet Count Identify Portal Hypertension in Patients With Compensated Cirrhosis. Gastroenterology 2013;144:102–111.

FRI-381
Sustained and continued improvement in hepatic fibrosis beyond the first year following hepatitis C virus treatment
R. Wong[1], M. Jain[2], G. Therapondos[3,3], M. Shiffman[4], O. Kshirsagar[5], C. Clark[6], M. Thamer[5]. [1]*Alameda Health System – Highland Hospital, Gastroenterology and Hepatology, Oakland, United States;* [2]*University of Texas Southwestern, Dallas, United States;* [3]*Ochsner Health System, New Orleans;* [4]*Liver Institute of Virginia, Bon Secours Health System, Richmond;* [5]*Medical Technology and Practice Patterns Institute, Bethesda;* [6]*Parkland Health and Hospital System, Dallas*
Email: rowong@alamedahealthsystem.org

Background and Aims: Achieving sustained virologic response following hepatitis C (HCV) treatment reduces risks of disease progression and hepatocellular carcinoma. It is not clear to what degree and how quickly hepatic fibrosis improves following HCV treatment and whether this improvement is sustained beyond the first year after therapy.
Methods: Adults treated for chronic HCV at four large U.S. healthcare systems from 1/1/2011 to 2/28/2017 were retrospectively evaluated to determine changes in fibrosis-4 (FIB-4) scores following HCV therapy. Baseline pre-treatment FIB-4 (calculated at 1 year prior to therapy) was compared to 1 year post-treatment FIB-4 using Student's t-test. To evaluate whether improvements in FIB-4 were sustained beyond the first year following treatment, we additionally evaluated changes in FIB-4 from 1 year post-treatment to 4 years post-treatment.
Results: Among 2,697 patients treated for HCV, overall baseline pre-treatment median FIB-4 was 2.51 (IQR 1.51–4.39). Baseline median FIB-4 was significantly higher in men compared to women (2.84 vs. 2.15, p < 0.001), significantly higher in whites compared to African Americans (2.84 vs. 2.15, p < 0.001), and significantly higher in the oldest age group (2.73 in age >65 vs. 1.32 in age <45, p < 0.001). In the first year following treatment, median FIB-4 score improved by 25.5% (2.51–1.87); in the subsequent 3 years, FIB-4 continued to improve 3.4%/year. While males had greater improvement in FIB-4 during the first year following treatment (29.6% vs. 19.1% in females, p < 0.001), in the subsequent 3 years, the rate of continued FIB-4 improvement trended higher in females compared to males (10.3%/year improvement vs. 3.2%/year, p = 0.062). When stratified by race/ethnicity, whites had the greatest improvement in FIB-4 during the first year following treatment (27.5% improvement), followed by African Americans (23.2% improvement) and Hispanics (12.3% improvement). However, in the subsequent 3 years, the rate of continued FIB-4 improvement was greatest among Hispanics (8.2%/year improvement), followed by whites (6.5%/year), and African Americans (1.7%/year).



Conclusion: While the greatest improvements in FIB-4 scores were observed in the first year following HCV therapy, these improvements were sustained and fibrosis continued to improve beyond the first year. Sex-specific and race/ethnicity-specific differences in rates of fibrosis improvement following HCV therapy were observed.

FRI-382
The role of hepatitis C virus eradication with DAA on insulin resistence regulation
I. Bortoluzzi[1], M. Gambato[2], E. Franceschet[2], A. Zanetto[2], A. Floreani[2], F. Farinati[2], P. Burra[2], A. Mega[3], F.P. Russo[2]. [1]*Mirano Hospital, Gastroenterology Unit;* [2]*Padua University Hospital, Department of Surgery, Oncology and Gastroenterology, Italy;* [3]*Bozen Hospital, Gastroenterology Unit*
Email: francescopaolo.russo@unipd.it

Background and Aims: Insulin resistance (IR) is a common extrahepatic manifestation of Hepatitis C virus (HCV) infection. The aim of this research was to evaluate if viral eradication obtained with DAA plays a role in the development and/or improvement of IR; we also evaluate if IR improvement reduces hepatic complications incidence.
Method: All HCV patients treated with DAA from May 2015 to December 2016 were prospectively included in the study. For each patient, we analyzed blood test and HOMA score before therapy and at 3, 6 and 12 months after its completion. Liver fibrosis was quantified by stiffness with Transient Elastography before treatment, 6 and 12 months after antiviral therapy. IR has been defined as HOMA score ≥2.5. All patients were treated with DAA drugs.
Results: 161 patients were included in the study, between these 117/161 (72.7%) had IR and 44/161 (27.3%) not. Before receiving antiviral therapy patients with IR had higher BMI (p0.0094) and liver stiffness (p < 0.0001) levels compared to those without IR. 158/161 (98.1%) patients obtained viral eradication. We observed a significant IR improvement both at 6 months (p = 0.0412) and 12 months (p = 0.0045) after therapy completion. 4 diabetic patients before therapy obtained resolution of diabetes. High BMI before antiviral therapy was the only predictive factor related to failure of IR improvement. All patients obtained significant liver stiffness reduction after DAA therapy (p < 0.0001), significant improvement in serum albumin levels and platelets count and transaminases normalization. 8/161 (3.9%) patients had hepatocellular carcinoma (HCC) after the end of therapy (4/8 de novo HCC, 4/8 HCC recurrence); 7/8 of these patients had IR.
Conclusion: Viral eradication with DAA leads to IR improvement. High BMI is a risk factor for IR and a negative predictive factor for IR improvement. Persistence of IR after DAA therapy is a risk factor for liver disease complications, such as HCC.

FRI-383

Therapy with oral directly acting agents in hepatitis C infection is associated with reduction in fibrosis and increase in hepatic steatosis

Shalimar, G. Rout, S. Gupta, D. Gunjan, S. Kedia, B. Nayak. *All India Institute of Medical Sciences, New Delhi, India, Department of Gastroenterology, New Delhi, India*
Email: drshalimar@yahoo.com

Background and Aims: Novel directly-acting antivirals (DAAs) are now the standard of care for hepatitis C (HCV) infection and are associated with high sustained viral response at 12 weeks (SVR12). The aim of this study was to evaluate the change in liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) by transient elastography (FibroScan®) post DAA therapy.
Method: LSM and CAP were measured serially (baseline, 12 weeks post completion of therapy and at one year after completion of therapy) in a prospective cohort of 372 chronic hepatitis C (CHC) treated with DAAs. Patients with at least two FibroScan measurements were included. Linear regression was used to assess for factors predictive of dynamic change in LSM and CAP values.
Results: A total of 372 patients were included; mean ± SD age 38.3 ± 12.6 years; 58.3% were males. Cirrhosis- defined by biopsy or fibroscan measurement (≥12.5) kPa- was present in 25.5%. Overall, on paired analysis (n = 317), the LSM (IQR) decreased from baseline value 7.1 (5.3–13.8) kPa to 12 weeks post therapy 6.2 (4.8–11.2) kPa; median decline 0.7 (−0.6–2.6) kPa, p < 0.001. On paired analysis (n = 105), the LSM value decreased from 12 weeks post therapy 6.8 (4.9–11.8) kPa to 1 year LSM 6.6 (4.9–8.7) kPa; median decline 0.6 (−0.5–2.6) kPa, p = 0.002. Similarly, on paired analysis (n = 160), LSM decreased from baseline value 6.9 (5.1–12.7) kPa to 1 year, 6.1 (4.8–9.4) kPa; median decline 0.9 (−0.6–3.2) kPa, p < 0.001. In contrast, on paired analysis (n = 317), CAP value increased from baseline 213.0 (180.0–254.5) dB/m to 12 weeks post therapy 225.0 (190.0–269.0) dB/m; median increase 7.0 (−23.5–45.5) dB/m, p = 0.001. On paired analysis (n = 105), CAP value increased from 12 weeks post therapy 234.0 (182.5–268.5) dB/m to 1 year 244.0 (206.0–286.0) dB/m; median increase 15.0 (−17.0–43.5) dB/m, p = 0.003. Similarly, on paired analysis (n = 160), CAP value increased from baseline value 210.0 (180.3–260.8) dB/m to 1 year 234.0 (204.0–282.0) dB/m; median increase 25.0 (−12.5–61.5) dB/m, p < 0.001. On multivariate linear regression analysis, higher baseline LSM value, low platelet count and BMI were independently associated with reduction of LSM. On multivariate linear regression analysis, low baseline CAP value and low albumin were significantly associated with increase in CAP values.
Conclusion: Treatment with DAAs reduces liver stiffness, but is associated with increase in hepatic steatosis. Future studies are needed to evaluate the factors associated with increase in hepatic steatosis.

FRI-384

Recurrence of hepatocellular carcinoma in patients with a history of HCC after SVR to DAA for chronic hepatitis C

I. Ozeki, H. Suii, R. Tatsumi, M. Yamaguchi, M. Kimura, T. Arakawa, Y. Kuwata, T. Ohmura, S. Hige, Y. Karino, J. Toyota. *Sapporo-kousei general hospital, Hepatology, Sapporo, Japan*
Email: 3767759101@jcom.home.ne.jp

Background and Aims: In patients with previous treatment for hepatocellular carcinoma (HCC) even after SVR achieved by direct-acting antivirals (DAAs), the subsequent recurrence rate of HCC is high. A high AFP level after the end of DAAs is a potential contributing factor for HCC recurrence. Here, we investigated contributing factors for early HCC recurrence with a focus on the AFP-L3 before and after treatment.
Method: Of 542 patients who had started DAAs for chronic hepatitis C at our hospital and achieved SVR24, 84 patients with previous curative treatment for HCC were included in this study. Median age at the start of DAA therapy was 74 (52–88) years; men, 44 (52%); cirrhosis, 55 cases (66%); age at initial HCC treatment, 70 (48–87) years. HCC recurrence rate and contributing factors for recurrence were investigated. ROC analysis was also performed to determine AFP and AFP-L3 before and after DAAs, allowing the prediction of early recurrence (≤1 year after treatment completion). Before the start of DAAs, the final HCC Stage was I /II/III in 51/29/4 patients. The maximal tumor diameter was 14 (6–15)mm. The number of HCC treatment sessions was 1/2/3/4/5/8 in 43/2/3/4/5/2 patients. The last HCC treatment was RFA/ surgery in 57/27 patients. The time between the last HCC treatment and the start of DAAs was <6/6–11/12-23/24-35/≥36months in 27/12/23/5/17 patients. To investigate contributing factors for HCC recurrence, Cox proportional hazards model was used with the following variables: HCC stage, the number of HCC treatment sessions, the time between the last HCC treatment and the start of DAAs, age at the start of DAAs, sex, AST, ALT, γ-GT, FIB-4, M2BPGi, AFP, and AFP-L3. Moreover, FIB-4, M2BPGi, AFP, and AFP-L3 levels at the time of treatment completion were also assessed as posttreatment variables.
Results: (1) HCC recurred in 28 of the 84 patients (33%; mean follow-up period, 17 months). The cumulative recurrence rates were 18/26/32/39% at 6/12/18/24 months. (2) Among the variables before the start of DAAs, an AFP-L3 of ≥ 0.5% was identified as a contributing factor for recurrence (HR 3.8; 95%CI, 1.6–10.2; p = 0.009). AFP-L3 was also identified as a posttreatment contributing factor (HR, 5.7; 95%CI, 2.4–13.3; p < 0.001). (3) The cut-off values of AFP and AFP-L3 for predicting early recurrence within one year after completion of DAAs were, respectively, ≥11.6 ng/ml (AUC 0.62) and 6.1% (AUC 0.80) before treatment and 4.9 ng/mL (AUC 0.65) and 0.5% (AUC 0.78) after treatment. The rate of early recurrence within one year was 86% in patients with an AFP-L3 of ≥ 6.1% at the time of treatment initiation and ≥ 0.5% at the time of treatment completion, which was significantly higher than the corresponding percentage of 17% in patients with the respective AFP-L3 of <6.1% and <0.5%.
Conclusion: AFP-L3 before and after treatment appear to be useful for predicting early recurrence.

FRI-385

In hepatitis C patients with cirrhosis who achieve SVR with treatment, reduction in transient elastography measures does not translate to reduced risk of hepatocellular carcinoma: A prospective cohort study

J. Howell[1,2,3], T. Papaluca[1,3], S. Glasgow[1], K. New[1], T. Hong[1], J. Snell[1], D. Iser[1], M. Ryan[1], S. Bell[1,3], P. Desmond[1,3], S.L.C.Y. Mei[1], C. Croagh[1], T. Nguyen[1], Z. Valaydon[1], G. Shaw[1], B. Demediuk[1], L. Mcdonald[1], A. Craigie[1], L. Stothers[1], M. Lust[1], C. Jeremiah[1], K. Visvanathan[1,3], A. Thompson[1,3]. *[1]St Vincent's Hospital Melbourne, Gastroenterology, Fitzroy, Australia; [2]Burnet Institute, Disease Elimination, Melbourne, Australia; [3]University of Melbourne, Medicine, Parkville, Australia*
Email: jessica.howell@svha.org.au

Background and Aims: Achieving sustained virological response (SVR) with interferon-based therapy in hepatitis C (HCV) reduces risk of hepatocellular carcinoma (HCC). However, in the era of direct-acting antivirals, real-world risk of HCC post SVR is unknown, particularly in patients with reductions in transient elastography (TE) readings post SVR.
Method: In this prospective cohort study conducted between January 1st 2001 and November 8th 2017, HCV patients with cirrhosis (confirmed by TE, ultrasound and/ or liver biopsy) who achieved SVR post treatment underwent HCC surveillance with 6 monthly ultrasounds and clinic review. Patients with previous HCC (including <6 months post SVR) were excluded. A subset of participants had TE performed 6–12 months post SVR. HCC diagnosis per international guidelines was recorded.
Results: 281 patients with cirrhosis who achieved SVR were prospectively followed with a total follow-up time of 8892 person-months at risk (median 15, IQR 12–26 months). Mean age was 58

years (+/–9.4 years), 216 (70%) were male and 266 (87%) were Caucasian. The majority were genotypes 1 (154, 51%) and 3 (120, 39.5%). 146 (48%) had significant alcohol intake and 25 (8.1%) were decompensated. 227 (74.2%) had received direct-acting antiviral therapy, the remainder having received pegylated interferon-based regimens. 15 (5%) developed new HCC post SVR (incidence rate 2.0 cases per 1,000 months person-time at risk (95% CI 1.22–3.35), median time to diagnosis 22 months (IQR 15–86 months). 5/ 15 (33%) had received DAAs (30%). 77 patients had TE performed post SVR (follow-up time of 1,970 person-months at risk). 55 (71.4%) had post-SVR readings <12.5 kPa and 13 (17%) had readings <7.1 kPa. 36/55 (66%) had cirrhosis on imaging despite fall in TE to <12.5 kPa. 5/ 77 patients (6.5%) developed HCC, incidence rate 2.5 per 1,000 person-months at risk (95%CI 1.1–6.1). 3/5 cases had TE readings <12.5 kPa: liver biopsy revealed two cases (TE 10.1 kPa and 12.4 kPa) had cirrhosis and one case (TE 6.5 kPa) had NASH without cirrhosis. None had clinical evidence of portal hypertension, or significant alcohol intake.

Conclusion: In a real-world population with universal access to DAA therapy, HCC risk diminishes, but persists in patients with HCV cirrhosis after SVR. Importantly, HCC can occur in patients whose post-SVR TE readings fall below <12.5 kPa post SVR. Therefore, HCC surveillance should continue irrespective of improvements in post-SVR TE readings.

FRI-386

Risk of de novo hepatocellular carcinoma after DAA treatment within two years following treatment with Ombitasvir/ Paritaprevir/ritonavir ± Dasabuvir ± Ribavirin in the AMBER – real world experience study

R. Flisiak[1], M. Łucejko[1], D. Zarębska-Michaluk[2], K. Tomasiewicz[3], K. Rostkowska[4], M. Tudrujek[3], M. Grzegorz[5], S. Krzysztof[4], J. Białkowska[6], M. Jablkowski[6]. *[1]Medical University of Białystok, Poland; Department of Infectious Diseases and Hepatology, Białystok, Poland; [2]Voivodship Hospital and Jan Kochanowski University, Department of Infectious Diseases, Kielce, Poland; [3]Medical University of Lublin, Poland; Department of Infectious Diseases and Hepatology, Lublin, Poland; [4]Wrocław Medical University, Division of Infectious Diseases and Hepatology, Wrocław, Poland; [5]Voivodship Specialistic Hospital, 2nd Department of Infectious Diseases, Wrocław, Poland; [6]Medical University of Łódź, Department of Infectious and Liver Diseases, Łódź, Poland*
Email: robert.flisiak@umb.edu.pl

Background and Aims: AMBER was an investigators initiated, real world experience study carried-out in 2014–2015, that included one of the first in the world group of patients treated with Ombitasvir/ Paritaprevir/ritonavir ± Dasabuvir ± Ribavirin (OPrDR) in real world setting. Aim of the current analysis is two years follow-up focusing on risk of hepatocellur carcinoma (HCC) development.

Method: 209 patients included in the AMBER study were scheduled for a 2 years follow-up (2yFU) visit. Medical history, physical and ultrasonography examination focused on HCC de-novo development were analysed. Additionaly changes in hepatic stiffness with elastography and laboratory measures of hepatic function were compared between patients with and without de novo HCC within 2yFU, to find out possible predictors of post treatment HCC.

Results: At the moment of abstract submission 2yFU data were available from 202 patients (97%). They were mostly cirrhotics (60%), infected with genotype 1b (86%). HCC history before OPrDR was noticed in 10 patients (5%) and HCC recurrence happen in 2. De novo HCC was diagnosed after OPrDR treatment in 5 patients, between 10 and 24 month of 2yFU. Four of them were cirrhotics, so the risk of HCC within 2yFU after OPrDR treatment was 3.3% in cirrhotics (4/121) and 1.2% in non-cirrhotics (1/81). All 5 de novo HCC has no hepatic lesions at the end of treatment and cirrhotics were screened every 6 months during 2yFU. Among 4 deaths noticed within 2yFU one was due to recurrent HCC and none due to de novo HCC. In contrast to non-HCC patients those who developed HCC did not demonstrate statistically significant improvement of bilirubin, albumin, INR and MELD values during 2yFU. Significan reduction of stiffness in elastography was noticed in both HCC and non-HCC groups. All 198 patients with available HCV RNA measurements at 2yFU were undetectable.

Conclusion: Risk of de novo HCC after OPrDR is 3 times higher in patients with liver cirrhosis compared to non-cirrhotics, but annual HCC risk rate in cirrhotics did not exceed level observed in the natural history of the disease. Since majority of de novo HCC developed within the second year of the follow-up its association with DAA is unlikely. Cirrhotics with no improvement of laboratory measures of liver function after cure of HCV infection should be closely monitored for possible HCC development. Changes in hepatic stiffness have no predictive value for HCC development after DAA treatment.

FRI-387

Antiviral therapy can prevent in HCV infected patients relapse of diffuse large B cell lymphoma

A. Pellicelli[1], V. Giannelli[1], G.M. Ettorre[2], R. Villani[1], V. Zoli[3], V. Pellicelli[1], A. Zignego[4]. *[1]Azienda Ospedaliera San Camillo Forlanini, Liver Unit Department of Liver Transplant, Rome, Italy; [2]Azienda Ospedaliera San Camillo Forlanini, Surgery Department of Liver Transplant, Rome, Italy; [3]Azienda Ospedaliera San Camillo Forlanini, hematology, Rome, Italy; [4]Univ. degli Studi di Firenze, Medicina Interna, Firenze, Italy*
Email: adriano.pellicelli@uniroma1.it

Background and Aims: Diffuse large B cell lymphoma (DLBCL) patients carring hepatitis C virus (HCV) have a higher risk of complications and liver toxicity but the role of antiviral therapy (AT) to reduce relapse of DLBCL after chemotherapy containing Rituximab (CT-R) is not analyzed in previous studies. In this context we aimed at assessing the role of AT in preventing the recurrence of DLBCL in HCV infected patients treated with CT-R.

Pts	Age	HCV gen	CT	Hematol. response	Time AT	AT	SVR	Relapse	FU (m)
1	23	1b	R-CHOP	CR	Post	Peg/RBV	Yes	No	48
2	44	2	R-CHOP	CR	Post	Peg/RBV	Yes	No	52
3	71	2	R-CHOP	CR	Post	Peg/RBV	No	Yes	18
4	40	1b	R-CHOP	CR	Post	SOF/SMV	Yes	No	18
5	54	3	R-CHOP	CR	During	SOF/DCV	Yes	No	16
6	55	1 a	R-CHOP	CR	Post	SOF/SMV	Yes	No	22
7	74	2	R-CHOP	CR	During	SOF/RBV	Yes	No	23
8	50	1b	R-CHOP	CR	Post	Peg/RBV	No	Yes	43
9	74	1b	R-CHOP	CR	Post	Peg/RBV	Yes	No	11
10	58	1 a	R-CHOP	CR	Post	Peg/RBV	Yes	No	58
11	45	1b	R-CHOP	CR	Post	Peg/RBV	No	Yes	18
12	55	1 a	R-CHOP	CR	Post	SOF/SMV	Yes	No	28
13	72	2	R-CHOP	CR	Post	Peg/RBV	No	No	53
14	64	1b	R-CHOP	CR	Post	Peg/RBV	Yes	No	50
15	59	1 a	R-CHOP	CR	Post	Peg/RBV	Yes	No	48
16	40	3	R-CHOP	CR	Post	SOF/LDV	Yes	No	18
17	67	1b	R-CHOP	CR	Post	Viekerax/Exviera	Yes	No	22
18	52	3	R-Bendamustine	CR	During	SOF/DCV	Yes	No	29

Pts patient; gen genotype; CT chemiotherapy; Hematol.response Hematological response; AT antiviral Therapy; Time AT antiviral therapy during o post chemotherapy; SVR sustained virological response; FU follow up; m months; SOF sofosbuvir; SMV simeprevir; DCV daclatasvir; LDV ledipasvir.

Method: We treated 18 consecutive HCV infected patients affected by DLBCL with pegylated interferon (PegIFN) plus Ribavirin (RBV) or II generation DAAs during or after CT-R. Eleven patients had HCV genotype 1 (62%), 8 were treated with DAAs and the remaining with the combination of PegIFN plus RBV. Three patients had compensated cirrhosis (Child Pugh A), 3 had a METAVIR score F3, 12 F0-F2 METAVIR. We have evaluated relapse of DLBCL after CT-R in patients with or without sustained virological response (SVR) to AT.

Results: Sustained virological response was achieved in 14 of 18 patients. In our series, lymphoma relapse was more frequent in patients without virological response (3 out of 4 patients without

SVR) (RR 1.75; 95% CI 0.92–3.32; p < 0.02). Three patients were treated with DAAs during chemotherapy and none presented transaminases flares or liver decompensation compared to patients treated after chemotherapy. All the characteristics of the patients are reported in Table.
Conclusion: Antiviral therapy for HCV during or after chemotherapy is an important strategy to prevent relapse of DLBCL in HCV infected patients when the patients reached a SVR. Our results also suggests that HCV treatment with DAAs reduces the risk of liver decompensation when given during chemotherapy in patients with advanced liver fibrosis.

FRI-388

Prospective follow up of 80 patients with addictive behaviors and advanced fibrosis after treatment of chronic HCV infection with DAA: a suboptimal management

C. Barrault[1], Régine Truchi[2], J.-B. Trabut[3], D. Carmona[4], F. Roudot[5], E. Gelsi[6], A. Bachelard[7], Stéphanie Dominguez[7], I. Rosa[1], C. Costentin[5], C. Hezode[5], A. Tran[2]. *[1]CH Intercommunal de Créteil, gastroenterology and hepatology unit, CRETEIL, France; [2]Chu l'archet, hepatology unit, nice, France; [3]Hopital Emile Roux, addictology unit, Limeil Brevannes, France; [4]CSAPA Epice, addictology unit, creteil, France; [5]Hopital Henri Mondor, hepatology unit, creteil; [6]Chu l'archet, hepatology unit, nice, France; [7]Hopital H. Mondor, clinical immunology, creteil, France*
Email: camille.barrault@chicreteil.fr

Background and Aims: Chronic HCV infection in drug-user (DU) and/or alcohol-dependent patients can effectively be treated with DAA. However, follow up of the liver disease and addiction behaviours remains complex due to associated psychosocial problems. The aim of the study was to assess the regularity of the liver disease follow-up in these patients and the evolution of their addictological behaviour after treatment with DAA.
Method: DU and/or alcohol-dependent patients with chronic HCV infection were prospectively followed during and after DAA treatment. Liver disease follow-up was planned according to EASL recommendations (ultrasound (US) for HCC screening, biological assessment and consultation every 6 months if fibrosis ≥ F3). Data were retrieved from 2 pooled French cohorts.
Results: Between January 2014 and December 2016, 80 patients (68% male) aged 49 (±9) years started DAA. Severe fibrosis (F3) or cirrhosis was observed in 40% and 60% of the patients, respectively. Housing was precarious in 42% of the patients, 62% lived alone, 79% were unemployed, 49% had psychiatric disorders and 49% received OST. Alcohol misuse was identified in 66 cases (82%). Viral eradication rate was 92.5%. The mean duration of follow-up was 65 ± 42 weeks. At 6 months, 13 patients (16%) were lost to follow-up, among the 66 alcohol-dependent patients, 42% had excessive alcohol intake. Addiction follow-up was regular in 47.5%, irregular in 25.5%. Factors associated with addiction follow-up were patient sent from an addiction care centre (p = 0.005), not receiving alcohol withdrawal medication (p = 0.023) and unemployment (p = 0.077). Follow-up of the liver disease was regular in 46%, irregular in 34.5%, absent in 19% of the cases. US at 6 months were available in 45 cases (58%), HCC was diagnosed in 5 cases (6%). Factors associated with liver monitoring were alcohol withdrawal before treatment (p = 0.23), stable housing (p = 0.038) and employment (p = 0.014).
Conclusion: Follow-up of liver disease after HCV treatment was suboptimal in DU and alcohol-dependant patients although advanced fibrosis at risk of HCC. Treatment seems to have a moderate impact on alcohol consumption. These results warrant close cooperation between hepatologists and addictologists after HCV eradication to improve patient's compliance to advanced fibrosis follow-up guidelines. Updated results including 12 months recontamination data will be presented in April 2018.

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Predictors of clinical improvement among HCV patients with advanced liver disease treated with DAA: a single center experience

C. Mazzarelli[1,2], I. Carey[1], K. Childs[1], A. Suddle[1], M.A. Manini[1], G. Dusheiko[1], K. Agarwal[1], M.D Cannon[1]. *[1]King's College Hospital, Institute of Liver Studies, London, United Kingdom; [2]ASST Ospedale Niguarda, Hepatology and Gastroenterology, Milan, Italy*
Email: chiaramazzarelli@hotmail.com

Background and Aims: Patients with cirrhosis have been consistently shown to have lower rates of sustained virologic response (SVR) with direct-acting antiviral (DAA) therapy than those without fibrosis. However, registration trials and real-life cohorts have demonstrated that a large number of patients with advanced liver disease may experience clinical improvements following HCV eradication. We aimed to identify factors predictive of clinical improvement in patients with advanced liver disease.
Method: Retrospective analysis of cirrhotic patients treated with SOF + NS5A inhibitors (daclatasvir or ledipasvir) from 2015–17 at King's College Hospital was performed. Data was analyzed using SPSS version 22.0.
Results: 187 cirrhotic patients, including 45 with decompensated liver disease, were treated with SOF+NS5A-inhibitors for 12 weeks. 16% of those with CP-A had a prior history of decompensation with ascites or encephalopathy which had resolved with medical management. 89 patients (48%) were treatment experienced. 13 patients (6.9%) had an active HCC at the start of therapy. 13% of patients had a pretreatment MELD score >14. All the patients received a weight-based ribavirin with a mean dose of 1000 (800–1200 mg), lower in those with impaired eGFR. The demographic and clinical characteristics of the patients are reported in table below. 175/187 (93.6%) achieved SVR12. Only 6 patients failed the treatment (3 CP-A and 3 CP-B). 6 patients died or were lost to follow up. Consistent with published reports, we observed a lower SVR rate in the decompensated cohort (SVR12: 86%) compared to those with CP-A cirrhosis (SVR12: 95%). Despite the high dose of RBV, severe anemia (Hb < 10) was recorded in only 27 patients (14%). Patients with advanced liver disease had a greater risk of ribavirin-related-anaemia during the treatment (p = 0.049). Improvement in MELD occurred in 40%, 45% and 47% at week 12, 24 and 48 weeks post-treatment completion.The improvement in MELD function was more significant only in patients with MELD >14: the improvement in MELD occurred in 68.1%, 77.7% and 83.4% at week 12/24/48 post-treatment. Male sex, bilirubin and ALBI at baseline were identified as predictors of improvement at 24 or 48 weeks of follow-up. Moreover, a change in albumin at week 4 of treatment >0.4 g/L compared to baseline, as well as changes in ALBI class were both associated with improvement in liver function during the follow-up time. Albumin <3.5 and ALBI 3 were associated to a greater risk (p > 0.001) of adverse events (death, transplant, hospital admission, sepsis, HCC).
Conclusion: Viral eradication was associated in with clinical and biochemical improvement, which was maintained during longer term follow-up. A rapid improvement in albumin after only 4 weeks of treatment was the strongest predictor (p = 0.02) of long-term improvement in our patient cohort.

FRI-390

Sustained virologic response leading to improved long-term metabolic outcomes

B. Emmanuel[1], K.A. Stafford[1], L.S. Magder[2], M.E. Charurat[3], S.S. El-Kamary[2], S. Kottilil[1]. *[1]Institute of Human Virology, University of Maryland School of Medicine, Division of Clinical Care and Research, Baltimore, United States; [2]University of Maryland School of Medicine, Division of Epidemiology and Public Health, Baltimore, United States; [3]Institute of Human Virology, University of Maryland School of Medicine, Division of Epidemiology and Public Health, Baltimore, United States*
Email: ben.emmanuel@umaryland.edu

Background and Aims: Hepatitis C virus (HCV) clearance has shown rapid changes in metabolic pathways during direct-acting antiviral (DAA) therapy suggesting a direct effect of HCV viral suppression. However, long-term changes beyond sustained virologic response (SVR) and the modifying effect of HIV-coinfection remains unknown. We investigated the distribution of change over time from pre-DAA therapy to post-SVR in metabolic and inflammatory parameters among chronic HCV patients.
Method: Chronic HCV genotype 1 patients (N = 301) received DAA therapy in four clinical trials in Washington, D.C. Low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, hemoglobin A1C (HbA1C), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured at pre-DAA therapy (baseline) and repeatedly measured during the duration of: DAA therapy, pre-SVR, at SVR, and post-SVR. Statistical analyses were conducted using linear mixed effects models, adjusting for age, sex, race, fibrosis, and HIV antiretroviral therapy in SAS 9.4.
Results: 269 chronic HCV patients (194 HCV and 75 HIV/HCV) achieved SVR (89%) and were predominately male (67%), black (79%), non-cirrhotic (93%), with a mean post-SVR follow-up of 2 years. Mean LDL significantly increased from pre-DAA to during DAA therapy (90 to 111 mg/dl, $p < 0.001$). After completing DAA therapy, mean LDL decreased between SVR and each yearly post-SVR period up to year 4 (107 mg/dl at SVR to 95 mg/dl at post-SVR year 4, $p = 0.01$). During DAA therapy, 20% of patients had LDL ≥130 mg/dl, which dropped to 9% at the last post-SVR follow-up. Mean triglycerides decreased between pre-DAA and SVR (107 to 94 mg/dl, $p = 0.005$), then continued to decrease between SVR and post-SVR year 4 (94 to 73 mg/dl, $p = 0.04$). HDL and HbA1C did not significantly change between pre-DAA and post-SVR. Both mean ALT and AST decreased significantly between pre-DAA and during DAA therapy (ALT 64 to 23U/l, $p < 0.0001$; AST 54 to 22U/l, $p < 0.0001$). ALT levels continued to decrease between SVR and post-SVR year 4 (19 to 13U/l, $p = 0.04$), while AST was constant. There was no significant difference by HIV-coinfection for all parameters.

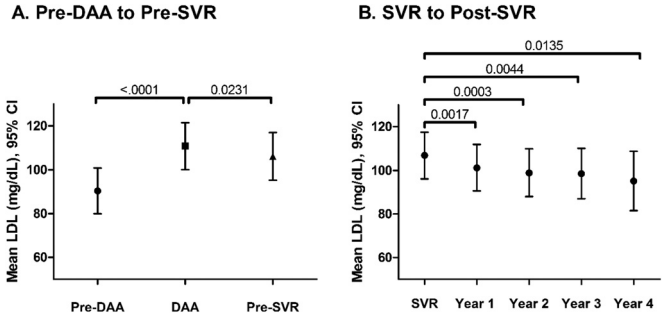


Figure: Mean LDL estimates from pre-DAA therapy to pre-SVR (A) and SVR to post-SVR (B).

Conclusion: Our longitudinal study showed chronic HCV patients treated with DAA therapy had continued improvements of metabolic (LDL and triglycerides) and inflammatory (ALT and AST) parameters after achievement of SVR.

FRI-391

High virological cure rate and low rate of reinfection in a project to eradicate HCV in people who inject drugs at risk for non-adherence to direct-acting antivirals in Vienna

A. Schütz[1], C. Schwanke[1], E. Gutic[2], T. Lang[2], R. Schubert[1], J. Luhn[1], S. Moser[2], H. Haltmayer[1], M. Gschwantler[2]. *[1]Suchthilfe Wien gGmbH, Ambulatorium Suchthilfe Wien, Vienna, Austria; [2]Wilhelminenspital, Department of Internal Medicine Iv, Vienna, Austria*
Email: michael.gschwantler@wienkav.at

Background and Aims: An important subgroup of people who inject drugs (PWID) receiving opioid agonist therapy (OAT), cannot be treated in the setting of a hepatologic center and would not regularly ingest their medication when handed to them for self-administration. Our hypothesis was that chronic hepatitis C in these patients could be ideally managed if modern, interferon-free regimens were administered together with OAT under direct observation of a pharmacist, physician or nurse at a pharmacy or a low-threshold facility.
Method: 166 PWID on stable OAT with chronic hepatitis C and high risk for non-adherence to DAA-therapy (male/female: 128/38; mean age: 38.2 ± 8.3 years; genotype (GT) 1/2/3/4: 103/2/55/6; HIV-coinfection: 13 patients; liver cirrhosis: 38 patients) started interferon-free treatment of chronic hepatitis C. Patients received antiviral therapy together with OAT under direct observation of a pharmacist, physician or nurse at a pharmacy or low-threshold facility. The DAA-regimen was selected according to GT, fibrosis stage, pretreatment and current reimbursement policy of insurances.
Results: Following this concept of directly observed therapy, adherence to antiviral therapy was excellent: Only 0.15% of scheduled dates for ingestion of the antiviral therapy in combination with OAT were missed by the 166 patients. Till now, 104 patients have completed treatment and a 12-week follow-up period. Virological cure of hepatitis C infection (sustained virologic response, SVR12) could be confirmed in all 104 patients (SVR12 rate: 100%, 95%CI: 96.5–100.0). During follow-up reinfections occurred in 6 patients. The cumulative rate of reinfection 12, 24, 48 and 72 weeks after end of therapy was 1.9%, 5.6%, 8.7% and 8.7%, respectively.
Conclusion: Directly observed therapy of chronic hepatitis C at a pharmacy or a low-threshold facility is highly effective in PWID at risk for non-adherence to DAA. By this new concept, a group of difficult-to-treat patients can be cured, who could not have been treated in settings of studies published so far. In our cohort the rate of reinfection was relatively low.

FRI-392

Circulating microparticles and thrombotic risk in patients with HCV-related cirrhosis who underwent DAA treatment

A. Zanetto[1], Elena Campello[2], E. Franceschet[1], S. Shalaby[1], A. Ferrarese[1], S. Sciarrone[1], C. Becchetti[1], M. Gambato[1], G. Germani[1], M. Senzolo[1], P. Simioni[3], P. Burra[1], F.P. Russo[1]. *[1]Multivisceral Transplant Unit, Gastroenterology, Surgery, Oncology and Gastroenterology, Padova, Italy; [2]Padua University Hospital, Department of Medicine, Italy; [3]Thrombotic and Hemorragic Diseases Unit, Medicine, Padova, Italy*
Email: francescopaolo.russo@unipd.it

Background and Aims: microparticles (MP) have been investigated for their ability to induce coagulation cascade and participate in thrombosis because of the presence of tissue factor (TF). Several studies have analysed levels of MP in patients with diseases at high risk for thrombotic complications, but there is not enough data about MP in patients with HCV related cirrhosis. Moreover, the impact of HCV clearance after DAAs in MP profile is not known. Our aim was therefore to investigate the presence and cellular origins of MP in patients with HCV cirrhosis, before and after DAAs, as well as to evaluate the possible contribution of MP in portal vein thrombosis (PVT) occurrence.
Method: HCV cirrhotic patients, treated with DAAs, were prospectively followed for 48 weeks after the end of antiviral therapy (EOT). Endothelial (E)-MP, platelet (P)-MP, TF and thrombomodulin (TM)-MP were measured by cytoflowrimetry at baseline (B), 12 weeks and 48 weeks after EOT. Pro-coagulant activity of the MP was evaluated. During follow-up, PVT onset was recorded. Fifty healthy subjects were recruited as controls.
Results: 58 patients were enrolled (Child A/B 50/8). All of them achieved SVR. Patients showed B-levels of E-, P-, TF- and TM-MP significantly higher ($p < 0.05$) and lower ($p < 0.05$) than controls, respectively. SVR was associated with a significant decrease of E, P and TF-MP, with no statistical difference when compared with controls ($p = 0.2$). On the other hand, there was a significant increase in TM-MP ($p < 0.01$). Patients showed a baseline phospholipid-dependent (PPL)

clotting time significantly shorter than controls, reflecting an increase of pro-coagulant activity due to phospholipid presence ($p < 0.05$). SVR was associated with a significant reduction of PPL ($p = 0.4$). Child B patients showed a significant reduction of TF-MP ($p < 0.05$), which, however, was not associated with a concomitant increase of TM-MP ($p = 0.1$). Two PVTs (both in Child B class) were observed, being the absolute incidence 1.1% p-yrs (95%CI, 0.18–3.58).
Conclusion: sustained virological response is associated with a significant modification in MP profile, possibly related to an improvement of liver synthesis. However, in patients with advanced liver disease, the haemostatic imbalance was not significantly modified, with a decrease of pro-thrombotic MP not associated with a concomitant increase of anti-coagulant MP. Thus, these patients seem to remain at risk of developing PVT, at least in the short term after antiviral therapy.

FRI-393
A cost-effectiveness analysis of shortened direct-acting antiviral treatment for mild chronic hepatitis C virus
C. Fawsitt[1], P. Vickerman[1], G. Cooke[2], N.J Welton[1]. [1]*University of Bristol;* [2]*Imperial College*
Email: c.fawsitt@bristol.ac.uk

Background and Aims: Hepatitis C virus (HCV) is a blood borne virus that can infect the liver, causing cirrhosis and decompensation of the liver, and hepatocellular carcinoma, requiring liver transplantation. A new class of oral medicines, called direct-acting antivirals (DAAs), have been developed to treat HCV, with cure rates observed in over 95% of patients treated for 12 weeks. DAAs are expensive; 12 weeks of therapy costs approximately £15,000 per patient. Shortened treatment durations, which have lower cure rates, have been proposed to reduce costs. We evaluate the lifetime cost-effectiveness of short-course first-line and re-treatment DAA regimens for treatment of non-cirrhotic HCV in genotype 1 patients.
Method: Assuming a UK National Health Service perspective, we use a probabilistic decision tree and Markov model to compare eight, six, and four weeks of shortened treatment regimens against a standard 12-week treatment regimen; patients for whom shortened treatment is unsuccessful are retreated with a standard 12-week treatment regimen. Evidence on efficacy of treatment and retreatment, drug and healthcare costs and utilities are taken from a review of the literature.
Results: Shortening treatment to eight or six weeks saves £6,796 and £3,317 and generates 0.06 and 0.01 more quality-adjusted life years (QALYs), respectively, per 1,000 patients compared with 12 weeks treatment. Shortening treatment to four weeks, with a 38% cure rate, costs an additional £859 and results in a QALY loss of 0.05. The probability that any shortened treatment strategy was most cost-effective was greater than the 12 weeks treatment arm, at £20,000 willingness to pay, but considerable uncertainty was observed in the four- and six-week treatment strategies due to limited evidence on efficacy.
Conclusion: Shortening treatment to eight or six weeks with retreatment in those that fail is cost-effective in genotype 1 non-cirrhotic treatment-naïve patients. Four weeks treatment is likely not cost-effective. More robust evidence on the efficacy of shortened treatment is required. Future research should also identify patients for whom shortened treatment duration is likely to be effective.

FRI-394
HCV testing and linkage to care: expanding access to HCV care through electronic health engagement and linkage to C care program in the PWID population
Z. Alam[1], D. Cook[2], H. Bui[1], I. Alam[1]. [1]*Austin Hepatitis Center, Austin, United States;* [2]*Austin Hepatitis Center, Austin, Texas, Austin, United States*
Email: ztariq@linkagetocare.com

Background and Aims: Over 75% of new hepatitis C [HCV] infections in the United States result from injection drug use. Since people who inject drugs [PWID] are at an increased risk for contracting HCV, the Center for Disease Control (CDC) recommends HCV testing in this population. Therefore, we must increase education, screening, and linkage to care by working through environments such as methadone clinics, Sober Living Homes, and drug rehabilitation centers. One challenge in testing PWID, particularly in community settings, is screening and linkage to care following a positive test. Our aim is to screen the PWID population and increase linkage of HCV RNA positive individuals to care. To achieve this goal, we plan to utilize electronic health engagement through our online patient database management system (PDMS) with our Substance Abuse Treatment Center partners.
Method: Longitudinal prospective cohort study with HCV screening at the above centers and utilization of a HIPPA compliant online patient database management system (PDMS) (www.linkagetocare.com). A centrally located Linkage to Care Specialist (LTCS) is notified immediately when an individual's information is entered in the system by the treatment center. The LTC Protocol initiates with education provided by the LTCS and ends with initial appointment with provider.
Results: January – October 2017, 609 PWID population were screened at 6 facilities; 284 (47%) were HCV Antibody positive; of the 284 RNA tests performed 201 (71%) were HCV RNA positive; 72% were uninsured; 61% of patients are between the ages of 21–40; 61% males. 159 (79%) were contacted by LTCS; 42 (21%) are still in recovery and we are still in process of gathering their contact information; 61 (38%) patients referred by the LTCS to a medical provider; 28 (18%) were awaiting further lab results; while 24 (39%) patients made it to their first appointment; 10 (16%) are in process of being seen by the doctor. PWIDs were linked to a LTCS within 2 days after referral. On average, patients were contacted twice before scheduling their first appointment.
Conclusion: The study found a high prevalence of HCV in PWID treatment centers. Approximately, 40% of patients have been referred to a medical provider. In its early phase the LTC program has increased HCV screening and compliance with linkage to care as compared to other care models in the PWID population. Our study accentuates a promising role for PWID patient engagement in electronic portals and LTCS as a tool in linking patients to the HCV care cascade.

FRI-395
Autoantibody to apolipoprotein A-1 in hepatitis C virus infection: a role in atherosclerosis?
S. Bridge[1], S. Pagano[2], M. Jones[3], G. Foster[3], D. Neely[4], N. Vuilleumier[2], M. Bassendine[5]. [1]*Northumbria University, Faculty of Health and Life Sciences, Newcastle upon Tyne, United Kingdom;* [2]*Geneva University Hospitals, Department of Genetics and Laboratory Medicine, Geneva, Switzerland;* [3]*Queen Mary University of London, The Liver Unit, Blizard Institute, London, United Kingdom;* [4]*Newcastle upon Tyne Hospitals NHS Foundation Trust, Clinical Biochemistry, Newcastle upon Tyne, United Kingdom;* [5]*Newcastle University, Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom*
Email: mbassendine@doctors.org.uk

Background and Aims: 1–3% of the world's population have hepatitis C virus (HCV) infection which is not only a major cause of liver disease and cancer but also associated with an increased risk of atherosclerosis, despite an ostensibly favourable lipid profile. Autoantibodies are frequent in HCV infection and emerging evidence shows that autoantibodies could be valuable for cardiovascular disease (CVD) risk stratification. This study investigated a novel independent biomarker of CVD, autoantibodies to apolipoprotein A-1 (anti-apoA-1 IgG) and lipids in patients with chronic HCV before, during and after direct-acting anti-viral (DAA) therapy.
Methods: 89 blinded serum samples from 27 patients with advanced chronic HCV were assayed for lipids and anti-apoA-1 IgG by ELISA.
Results: Pre-treatment HCV viral load correlated with high density lipoprotein cholesterol (HDL-C, $r = 0.417$; $p = 0.042$) and negatively

with apolipoprotein (apo)B (r = –0.497; p = 0.013) and markers of CVD risk, apoB/apoA-1 ratio (r = –0.490; p = 0.015) and triglyceride (TG):HDL ratio (r = –0.450; p = 0.031). There was no significant difference in the serum lipid concentrations at week 0 and 12 of DAA therapy, when all 27 patients had a virologic response (undetectable HCV RNA). 14/27 (52%) patients had detectable anti-apoA-1 IgG autoantibodies pre-treatment; only two became undetectable with virologic cure. Autoantibody positive sera had lower apoA-1 (p = 0.012), HDL-C (p = 0.009) and total cholesterol (p = 0.006) levels.

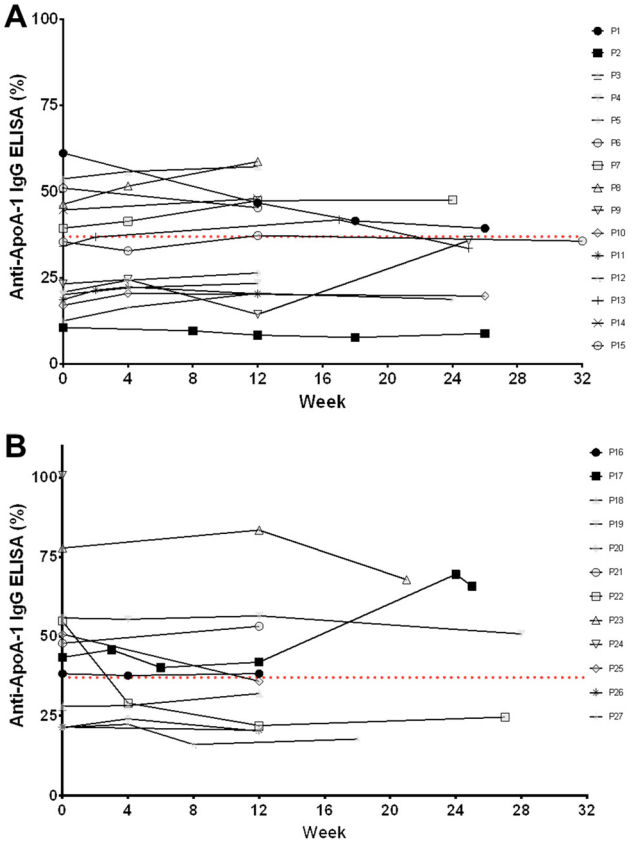


Figure: Autoantibody to apolipoprotein A-1 IgG ELISA reading [cut off 37%] in 27 patients with advanced chronic HCV before, during and after direct-acting anti-viral therapy, commenced at week 0. By week 12 all patients responded to antiviral treatment and were HCV RNA negative. **A.)** shows results in HCV genotype 1 patients, 2/15 relapsed after end of therapy; **B.)** shows results in HCV genotype 3 patients, 1/12 relapsed.

Conclusion: This is the first report of the presence of an emerging biomarker for atherosclerosis, anti-apoA-1 IgG, in some patients with HCV infection. They may be induced by apoA-1 on the surface of HCV lipoviral particles. The autoantibodies inversely correlate with apoA-1 and HDL levels and may render HDL dysfunctional. Whether these hypothesis-generating findings have clinical implications in HCV patients requires further study.

FRI-396

Treatment of HCV infection with DAAs is associated with lower HCC recurrence and improved survival after liver transplant

K. Willuweit[1], K. Piras-Straub[1], P. Andreas[2], G. Gerken[1], K. Herzer[1].
[1]*Department of Gastroenterology and Hepatology;* [2]*Department of General- Visceral- and Transplantation Surgery*
Email: kerstin.herzer@uk-essen.de

Background and Aims: High rates of sustained virological response (SVR) in patients with chronic hepatitis C (HCV) treated with direct-acting antivirals (DAAs) suggested a reduction of hepatocellular carcinoma (HCC). However, following antiviral treatment using DAAs, an unexpected high rate of HCC recurrence has been reported in certain settings. The aim of the current study was to identify the role of DAA-therapy on HCC recurrence after liver transplant (LT).
Methods: Clinical, laboratory and demographic data of 190 patients who had received LT between 2010 and 2016 at the university hospital Essen were retrospectively collected in a database. All patients received LT due to HCV cirrhosis with or without HCC or for HCC not related to HCV. Categorical data were analyzed by χ^2-tests with Pearson approximation or Fisher's exact test. The overall and HCC recurrence free survival was analyzed by Kaplan-Meier estimation and Log Rank test according to Mantel-Cox regression. The level of statistical significance was set at $p \leq 0.05$.
Results: To identify the role of DAA-therapy on HCC recurrence after LT, the cohort was divided into patients with HCV related HCC (n = 67) and patients with non-HCV related HCC (n = 74) that could be analyzed for HCC recurrence within the 2-year follow-up. HCC recurrence occurred in 21.9% (n = 31/141) of all patients. Of those patients with HCV, 50.7% (n = 34) received DAA-therapy. HCC recurrence occurred in only 9% (n = 3/34) of patients who received DAAs but in 33% (n = 11/33) of those patients who did not receive DAAs ($p \leq 0.017$). Moreover, patients who had received a DAA-therapy showed improved survival after LT compared to patients without treatment (11.6 vs 10.1 years).
Conclusion: DAA-based HCV-therapy before LT results in a significantly lower HCC recurrence risk after LT and improved patient survival. Exact mechanisms how DAAs alter the proliferative behavior of liver tumor cells and the specific immune responses in the liver influencing tumorgenesis remain to be elucidated.

FRI-397

Effect of hepatitis C sustained virological response on the endothelial dysfunction and the cardiovascular risk. HepCAR study

R.M. Hernandez[1], R. Millan[1], Y. Sánchez[2], J. Ampuero[1,2,3], H.C. Macher[4], C. Jimeno[5], Ángela Rojas[1], I. Carmona[6], A. Gil-Gomez[1], S. Rodrigo[7], M.R. Gomez[8]. [1]*Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío/CSIC/Universidad de Sevilla, SeLiver Group, Sevilla, Spain;* [2]*Hospital Universitario Virgen del Rocío, Sevilla, España, UGC Enfermedades de enfermedades Digestivas, Sevilla, Spain;* [3]*Centro Biomédico en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Spain;* [4]*Hospital Universitario Virgen del Rocío, Sevilla, España, Servicio de Bioquímica Clínica, Sevilla;* [5]*Hospital Universitario Virgen del Valme, Servicio de Digestivos, Sevilla, Spain;* [6]*hospital Universitario Virgen Macarena, Servicio de Digestivos, Sevilla, Spain;* [7]*Hospital Universitario Virgen del Rocío, Sevilla, España, Servicio de Neurología, Sevilla, Spain;* [8]*Hospital Universitario Virgen del Rocio, Sevilla. Instituto de Biomedicina de Sevilla. CiberEHD, Spain*
Email: mromerogomez@us.es

Background and Aims: To analyze the impact of the sustained virological response after therapy with direct antiviral agents (DAAs) on the cardiovascular risk in patients with hepatitis C.
Methods: We recruited prospectively 71 patients with hepatitis C who achieved sustained virological response after DAAs treatment. The cardiovascular risk was evaluated according to a) subclinical atherosclerosis by the ankle brachial index (ABI); b) lipid profile; c) endothelial dysfunction through the laser Doppler flowmetry and the measurement of adhesion and angiogenesis soluble markers; d) markers of cell and endothelial damage including endothelial apoptotic microparticles (EMPs) and cell free DNA levels (cfDNA). Patients were evaluated before and one year after treatment with DAAs.
Results: Mean age was 54 ± 10 years, 67.6% were males, BMI 27 ± 4. 52.5% were cirrhotic, 77.5% genotype 1, 28% of patients presented hypertension, 20% Diabetes Mellitus and 7% dyslipidemia. There was no difference between first evaluation and the follow-up visit in the ABI, but the laser Doppler flowmetry showed a significant improvement in the peak flow (44.8 ± 5.7 vs 67.5 ± 17.4UP; p = 0.015). The

levels of VCAM (2317.8 ± 277.8 vs 1480.9 ± 202.5 ng/µl; p < 0.001) and E-selectin (64.9 ± 4.6 vs 43.5 ± 3.9 pg/ml; p < 0.001) also improved after the treatment. We observed that the levels of total cholesterol (170 ± 6 vs 183 ± 7 mg/dl; p < 0.001), LDL (98 ± 6 vs 110 ± 6 mg/dl; p < 0.001), ApoB (88.1 ± 5.4 vs 101.3 ± 5,3 mg/dl; p < 0.001) and PCSK-9 (624.9 ± 40.1 vs 770.9 ± 44.8 ng/ml; p < 0,001) were significantly increased after the treatment, instead HDL was not modified. Regarding to cell damage markers, there was a significant decrease in the EMPs number (317.7 ± 58.5 *vs* 212.4 ± 36,7U; p = 0,04) and also in the cfDNA level (613.6 ± 82.4 *vs* 401.6 ± 46.2 ng/ml; p = 0.02).
Conclusion: The new antivirals drugs improve the endothelial dysfunction one year after treatment, being another positive factor for HCV therapy indication.

FRI-398
The impact of direct antiviral agent therapy on liver fibrosis in patient with advanced fibrosis related chronic hepatitis C
B. Kutala[1], N.B. Darrigrand[1], C. Corinne[1], B. Pierre[2], T. Asselah[1], P. Marcellin[1]. *[1]Beaujon Hospital - APHP, Department of Hepatology, Clichy, France; [2]Beaujon Hospital - APHP, Department of Pathology, Clichy*
Email: nathalie.boyer@bjn.aphp.fr

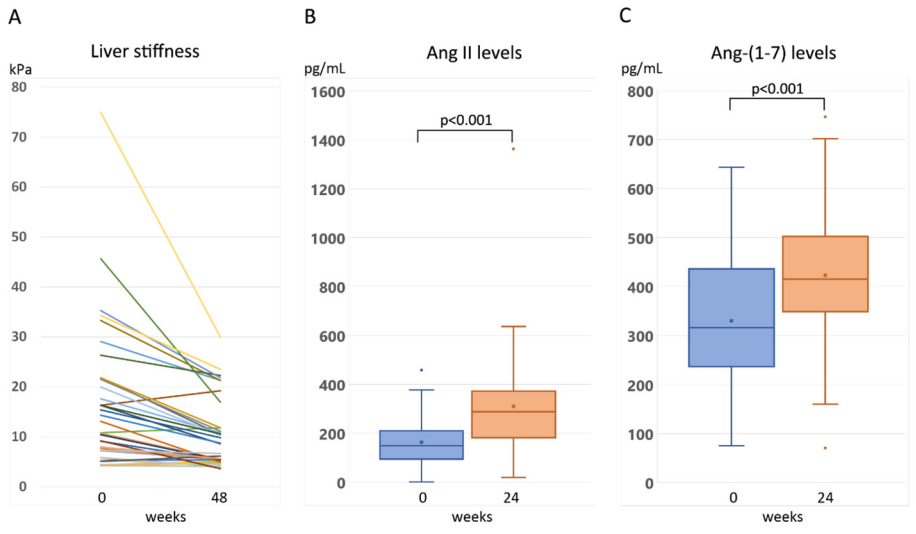
Background and Aims: The impacts of sustained virologic response (SVR) after direct antiviral agents (DAA) therapy in patients with chronic hepatitis C virus (CHC) remain unclear. The regression of cirrhosis and portal hypertension demonstrated in interferon therapy, are expected in the DAAs therapies. Transient Elastography (TE) is a noninvasive method ultrasound based, for assessment liver stiffness (LS). The aims of this study were: (1) evaluated the changes in liver stiffness and fibrosis stage (2) to examine factors influencing changes in liver stiffness measurements after DAA treatment.
Methods: We prospectively consecutive patients treated with DAAs in our department between January 2013 and September 2016. 643 patients who received a DAA based treatment for CHC were screened and 417 were included. TE values recorded before therapy initiation and within 24 months after therapy were analysed. In addition, predictors of fibrosis regression were evaluated in multivariate analysis.
Results: A total of 417 patients (375 have TE and 42 have paired biopsy) were included. Baseline characteristic: 71% were men, 54% had cirrhosis and the median age was 53 years. Median TE before DAA treatment was 12.85 kPa (IQR 9.75–19.2 kPa) and decreased to 8.55 kPa (IQR 5.87–15.23) post-treatment. This finding is statistically significant (p < 0.001) and equals a TE regression of 33.5% after DAA treatment. Median FIB-4 and APRI values significantly decreased from 2.53 (IQR 1.64–4.42) and 1.13 (IQR 0.67–2.45) to 1.78 (IQR 1.27–2.90, p < 0.001) and 0.48 (IQR 0.33–0.81, p < 0.001) respectively. Cirrhosis regressed in 15/24 patients (62%), but advanced fibrosis regressed 14/18 cases (78%) among 42 patients with liver biopsy. Multivariate analysis found a lower BMI and gender female as factors independently associated with fibrosis regression [(odds ratio (OR) 0.68, 95%CI 0.48–0.97), p = 0.037 and [(OR: 0.51, 95%CI 0.36–0.89), p = 0.0221] respectively.
Conclusions: Patients with SVR after DAA therapy showed significant regression of TE values and fibrosis regression according liver biopsy. Rapid decrease in TE was in concordance with the improvement of liver function. It remains to be examined whether this indicates a true regression of fibrosis or merely resolution of chronic liver inflammation with subsequent improvement of biopsy values in large cohort.

FRI-399
Effects of direct-acting antiviral treatment of chronic hepatitis C on macrophage activation, liver stiffness, metabolic liver function and portal hypertension in cirrhosis patients
T.L. Laursen[1], K. Kazankov[1], T.D. Sandahl[1], H.J. Møller[2], L. Hagelskjær Kristensen[3], C. Holmboe[4], C. Sølund[5], H. Arildsen[6], A. Laursen[6], H. Grønbæk[1]. *[1]Aarhus Universitetshospital. Nørrebrogade, Hepatology and Gastroenterology, Aarhus, Denmark; [2]Aarhus Universitetshospital, Skejby, Clinical Biochemistry, Aarhus, Denmark; [3]Regionshospitalet Viborg, Department of Medicine, Viborg, Denmark; [4]Aalborg Universitetshospital, Gastroenterology and Hepatology, Aalborg, Denmark; [5]Hvidovre Hospital (Kettegård Allé), Infectious Diseases, Hvidovre, Denmark; [6]Aarhus Universitetshospital, Skejby, Infectious Diseases, Aarhus, Denmark*
Email: tealaurs@rm.dk

Background and Aims: The new all-oral direct-acting antiviral (DAA) treatments of chronic hepatitis C (CHC) cure >95% of the affected patients. However, it is unclear how features of liver cirrhosis change after DAA-treatment. Soluble (s)CD163 is released from activated liver macrophages and serum levels reflects liver disease severity. We aimed to investigate changes in sCD163, liver stiffness, metabolic liver function, and portal hypertension with DAA-treatment in CHC patients with liver cirrhosis.
Method: Between 2015–2017, we assessed 14 Danish CHC patients with cirrhosis before and immediately after DAA-treatment including ombitasvir, paritaprevir, ritonavir, and dasabuvir ± ribavirin for 12 weeks. Serum sCD163 levels were quantified by an in-house ELISA. Liver stiffness was measured by transient elastography (FibroScan). Metabolic liver function was assessed by the galactose elimination capacity (GEC) test. Portal hypertension was estimated by the hepatic venous pressure gradient using lever vein catheterisation.
Results: The patients had a mean age of 56 years (SD 9); 9 males and 5 females. Eleven had genotype 1a hepatitis C virusand 3 had genotype 1b. Five were abstinent from alcohol, 8 had a previous over-intake and one drank 1 unit/week of alcohol until enrolment. All patients had Child-Pugh A cirrhosis with a mean MELD-score of 8 (1.7). All patients received 12 weeks of DAA-treatment except for one patient, who died within two months of treatment initiation. All patients, who completed treatment, achieved sustained virological response (SVR) 12 weeks after treatment cessation. The mean sCD163 level decreased from 6.8 mg/L (4.8) to 4.5 (4.9) (p = 0.005). The mean liver stiffness decreased from 22.8 kPa (11.8)–11.0 (3.5) (p = 0.008). There was a trend for improved metabolic liver function (GEC) (60.0 (11.5) vs. 55.6% (9.1), p = 0.10). There was no significant effect on the hepatic venous pressure gradient after treatment (11.6 mmHg (5.9) vs. 9.8 (3.0), p = 0.50).
Conclusion: DAA-treatment leads to SVR associated with decreased macrophage activation and reduced liver stiffness indicating reduced inflammation and beneficial effects in the liver right after DAA-treatment. Further, DAA-treatment had no significant effects on metabolic liver function or portal pressure; however, long-term follow up studies may demonstrate further improvements in these parameters.

FRI-400
Involvement of angiotensin II/angiotensin-(1–7) fibrinolytic pathway in improvement of liver fibrosis in chronic hepatitis C patients who had sustained virological response by direct-acting antiviral therapy: a prospective trial
N. Teeratorn[1], K. Thanapirom[1], S. Suksawatamnuay[1], P. Thaimai[1], S. Sittisomwong[1], K. Sonsiri[1], N. Srisoonthorn[2], S. Sriphoosanaphan[1], N. Tanpowpong[3], B. Chaopathomkul[3], S. Treeprasertsuk[1], Y. Poovorawan[4], P. Komolmit[1,2]. *[1]Division of Gastroenterology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [2]Center of Excellence in Liver Diseases, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [3]Department of Radiology, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand; [4]Center of Excellence in Clinical Virology, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*
Email: pkomolmit@yahoo.co.uk

Background and Aims: There is growing evidence that angiotensin II (Ang II)/angiotensin-(1–7) [Ang-(1–7)]/Mas receptor axis, a counter regulatory arm of renin angiotensin system (RAS), involves in fibrinolysis in *vitro*/animal models. Eradication of hepatitis C (HCV)



LSM	Median (Q1-Q3) kPa	
Week 0	14.3 (7.3-21.8)	p<0.001
Week 48	8.5 (5.3-11.8)	

Ang II	Median (Q1-Q3) pg/mL	
Week 0	149.0 (94.6-210.0)	p<0.001
Week 24	286.9 (181.3-372.4)	

Ang-(1-7)	Median (Q1-Q3) pg/mL	
Week 0	315.6 (236.1-435.9)	p<0.001
Week 24	414.3 (348.3-502.3)	

Figure: (abstract: FRI-400): Changes of liver stiffness, serum Ang II and Ang-(1–7) levels in CHC patients at baseline and after having SVR (A) Median LSM (kPa) at baseline (0 week) and 48 weeks, (B) and (C) Box plot graphs of serum Ang II and Ang-(1–7) levels (pg/ml) at baseline (0 week) and 24 weeks (SVR 12 weeks), respectively.

results in improvement of liver fibrosis by multi-mechanisms, including viral factors and stellate cells deactivation through the reduction of TGF-beta 1 stimulation and matrix enzymes changes toward the fibrinolytic stage. We hypothesize that this newly established pathway, to some extent, might involve in the improvement of liver fibrosis in chronic hepatitis C (CHC) patients who had sustained virological response (SVR) by direct acting antiviral drugs (DAA).

Methods: After exclusion of factors that might affect RAS, forty CHC patients with compensated liver disease (mean age: 57 ± 1.7 years; 52% male) were enrolled prospectively for 12-week DAA therapy and achieved SVR between July 2016 and September 2017. Baseline characteristics, HCV viral load (mean 6.2 ± 0.1 logIU/mL), HCV genotypes [1 (64.1%), 3 (23.1%) and 6 (12.8%)], liver enzymes and liver stiffness measurement (LSM) using Fibroscan® were assessed before starting the therapy. Blood samples for Ang II/Ang-(1–7) levels were collected at baseline, 12 and 24 weeks (SVR 12 weeks). LSM were repeated at 48 weeks. All patient samples (–70C storage) were evaluated simultaneously. Standard ELISA methods were used for the assays.

Results: The alanine aminotransaminase (ALT) levels were significantly decreased from 83 ± 12.6 IU/ml at baseline to 22 ± 2.2 IU/ml (p < 0.001) at 24 weeks. Mean and median LSM were significantly decreased from 17.4 and 14.3 kPa at baseline to 10.5 and 8.6 kPa at 48 weeks, respectively (Figure 1A). Baseline mean of Ang II level was 162.4 ± 17.4 pg/ml. The level at 24 weeks (SVR 12 weeks) was significantly increased to 309.0 ± 34.9 pg/ml (p < 0.001) (Figure 1B). By the same period, the mean Ang-(1–7) levels were significantly increased from 329.6 ± 22.2 pg/ml to 422.1 ± 21.4 pg/ml (p < 0.001) (Figure 1C).

Conclusion: Supporting the *in vitro and vivo* evidences, increased Ang II and Ang-(1–7) serum levels are demonstrated in CHC patients who achieved SVR from DAA therapy along with the improvement of liver fibrosis. This RAS counter regulatory axis pathway might, in part, involve in the promotion of hepatic fibrosis regression in this scenario.

FRI-401

The lack of improvement in liver stiffness after SVR in HCV compensated advanced chronic liver disease is associated with the risk of presenting liver related events

M.P. Delgado[1], J.I.E. Mur[1,2], Víctor M.V. Blasco[1,2], M.B. Ferret[1,2], R. Esteban[1,2], M.R. Barciela[1,2], B. Minguez[1,2], S. Augustin[1,2], J. Genesca[1,2]. [1]*Hospital Universitari Vall d'Hebron – Institute of Research (VHIR) – Universitat Autonoma de Barcelona, Liver Unit, Barcelona, Spain;* [2]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Instituto de Salud Carlos Iii, Madrid, Spain*
Email: monica_xina@hotmail.com

Background and Aims: Sustained virological response (SVR) after hepatitis C virus (HCV) therapy improves prognosis in cirrhotic patients. However, the risk of decompensation and hepatocellular carcinoma may persist in some patients. The aims of our study were to identify which factors were associated with liver stiffness improvement at 1 year after finishing treatment and which factors were associated to the development of liver related events in HCV compensated advanced chronic liver disease (cACLD) patients cured with oral antivirals.

Method: We included 290 cACLD patients who achieved SVR after oral antiviral therapy. All of them had a baseline liver stiffness measurement (LSM) ≥10 kPa, were Child-Pugh class A and had no prior liver decompensation. We performed LSM, laboratory work-up and an abdominal ultrasound at 1 year after finishing therapy and we registered the occurrence of liver related events during the follow-up. Improvement in LSM at follow-up was defined as a decrease ≥20% in LSM from baseline.

Results: Seven patients were lost during the follow-up and in 2 patients follow-up-LSM was not reliable. Data from 281 patients were collected during a median follow-up of 20.7 months (IQR 17.8–24.4 months). At 1 year of follow-up, mean LSM decreased significantly (baseline-LSM 19.3 kPa (SD 10.5) vs follow-up-LSM 13.7 kPa (SD 9.7); p < 0.001) with a mean decrease of 35.8% from baseline. Forty-seven

percent of patients had LSM < 10 kPa at 1 year after finishing therapy. A total of 202 patients (71.9%) presented a significant improvement in LSM (decrease ≥ 20%). Baseline predictors associated to LSM improvement were body mass index (OR 0.93; 95%CI: 0.87–0.99; p = 0.033), MELD = 6 (OR 2.3, 95%CI: 1.2–4.3, p = 0.010) and albumin (OR 2.3; 95%CI: 1.3–5.3; p = 0.008). During follow-up 6 patients (2.1%) developed de novo hepatocellular carcinoma and 1 patient presented a variceal bleeding. None of these patients had a follow-up-LSM < 10 kPa. In multivariate analysis only the lack of a significant improvement in LSM (decrease ≥20%) during follow-up (HR 12.7; 95%CI: 1.5–111.1; p = 0.020) was related to the risk of presenting liver related events.

Conclusion: In HCV cACLD patients successfully treated with oral antivirals, liver stiffness decreases significantly during the first year of follow-up. Patients without significant improvement in LSM are more likely to develop liver related events during follow-up.

Project code: PI15/00066. ISCIII-FEDER CO-FUNDING.

FRI-402

Health utilities in Spanish chronic hepatitis C patients treated with direct acting antivirals in real life conditions

R. Juanbeltz[1,2], Iván Martínez-Baz[2,3,4], Jesús C. Catalán[2,3,4], S.Goñi Esarte[5], J. Úriz[2,5], José M. Zozaya[2,5], Ramón S. Miguel[1,2].
[1]Complejo Hospitalario de Navarra, Pharmacy; [2]Instituto de Investigación Sanitaria de Navarra (IdiSNA); [3]Public Health Institute of Navarra; [4]CIBERESP; [5]Complejo Hospitalario de Navarra, Liver – Unit
Email: regina.juanbeltz.zurbano@navarra.es

Background and Aims: Health utilities are global measurements of quality of life, which are typically used to estimate quality-adjusted life years in the cost-utility analyses of therapeutic interventions. The aim of this study was to assess EQ-5D health utilities scores in Spanish patients with chronic hepatitis C treated with direct acting antivirals (DAAs), previous, during and after treatment. Predictors of health utilities after the end of treatment were identified.

Method: Prospective, observational study. Patients treated with all direct acting antiviral regimens, between May 2016 and April 2017, were included. Health utilities were assessed by using the EuroQol survey (EQ-5D-5L) at baseline, week 4 of treatment and 12 weeks after the end of therapy (post12). Analysis was limited to patients with sustained virological response.

Results: 206 patients were enrolled, 32% HIV/HCV co-infected and 28% with cirrhosis. The most prescribed combinations were ombitasvir/paritaprevir/ritonavir+/-dasabuvir (39%), sofosbuvir/ledipasvir (33%) and sofosbuvir + daclatasvir (22%). Ribavirin was used in 52% of regimens. Median baseline utility value was 0.857, with no change after 4 weeks of treatment and 6.2% of relative improvement in post-12 (0.857 baseline vs 0.910 post-12, p < 0.001). This increment in utility scores was observed in F4 patients (0.809 baseline vs 0.857 post-12, p = 0.027) and F2-F3 (0.857 baseline vs 0.910 post-12, p = 0.002), without statistical signification in mild fibrosis (0.893 vs 0.932, p = 0.061). HIV/HCV co-infected patients also had a higher score after treatment (0.871 vs 0.910, p = 0.036). In multivariate analyses, age > 64 years (β = 0.13; CI95% 0.01–0.26), comorbidity by Charlson ≥ 2 (β = –0.14; CI95% –0,22 to –0,05), problems of baseline mobility (β = –0.25; CI95%–0.32––0.17), cirrhosis (β = –0.11; CI95% –0.19 to –0.04), baseline depression (β = –0.11; CI95%, –0.19 to –0.04) and ribavirin use (β = 0.06; CI95% 0.01–0.12) were the most consistent predictors of post-12 utilities. Ribavirin had no impact on week 4 utility score (–0.01; p = 0.276).

Conclusion: The cure of chronic hepatitis C infection with DAAs has a short term positive impact on HRQoL. This study provides utility values derived directly from HCV patients treated with DAAs in real-life setting, which contributes to future cost-utility studies.

FRI-403

Hepatitis C virus infection a new reversible cardiovascular risk factor in cirrhotic patients after viral eradication?

T. Cuciureanu[1], A.-M. Singeap[1], S. Chiriac[1], C.-M. Muzîcă[1], L. Huiban[1], I. Girleanu[1], C. Stanciu[2], A. Trifan[1]. *[1]University of Medicine and Pharmacy Gr.T.Popa, Gastroenterology, and, Hepatology, Iasi, Romania; [2]Institute of Gastroenterology and Hepatology, Iasi, Romania*
Email: drcuciureanutudor@gmail.com

Background and Aims: The increase of the cardiovascular risk was recently recognized among a large spectrum of extrahepatic manifestations of chronic hepatitis C virus (HCV) infection. Recent studies evaluate its involvement in cardiovascular pathology due to its proatherogenic effects on the vascular endothelium and metabolic alterations. The aim of this study was to evaluate the role of HCV as a proatherogenic cardiovascular risk factor, and to verify if the alterations induced by the virus are reversible after therapy with interferon free direct acting antivirals.

Methods: 130 patients (female 59%, median age 56 years) with genotype 1b and chronic HCV infection, with 4 cardiovascular risk factors (dyslipidemia, hypertension, sedentariness, obesity), treated with paritaprevir/ritonavir, ombitasvir and dasabuvir (PrOD) ± ribavirin were prospectively included in the study group, from January 1st 2016 to October 31 2017. The control group included 50 patients with the same 4 cardiovascular risk factors and no history of liver or cardiovascular disease. The patients were completed evaluated according to the national protocol, the degree of fibrosis was determined by transient elastography, concomitant we assessed the intima media thickness (IMT) and the ankle arm index (AAI) as markers of subclinical atheromatosis.

Results: At the baseline the study group registered higher values of IMT compared with the control group (0.98 ± 0.4 vs 0.92 ± 0.28, p = 0.001). After the sustained viral response (SVR) the IMT decreased in 56 patients (43%). The AAI registered lower values in the study group compared with controls (0.93 ± 0.2 vs 1.0 ± 0.2, p = 0.034). After SVR the AAI was improved in only 20 patients (15.3%). The lipid profile improved in only 41 subjects (31.5%), triglycerides decreased in 48 patients (33%). An abnormal increase after SVR in LDL cholesterol was assessed in almost 30 patients (23%). The degree of fibrosis had a major role in the prediction of subclinical atherosclerosis. Thirty patients (23%) with liver stiffness greater than 30 kPa registered higher values of IMT.

Conclusion: An increase of incipient carotid atherosclerosis and peripheral arterial disease was observed in case of patients with HCV cirrhosis compared to subjects without hepatic disorders and improvement of the IMT, AAI and lipid profile confirmed the possible reversibility of the atherosclerotic lesions after antiviral treatment.

FRI-404

Controlled attenuation parameter values of Fibroscan® compatible with steatosis in patients with chronic hepatitis C and changes after sustained virological response

T. Broquetas, L. Canillas, M. Puigvehí, R. Fernández, G. Díaz, S. Coll, M.G. Retortillo, N. Cañete, X. Bessa, R.S. Lamoglia, J.A. Carrión. *Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), UAB, (Universitat Autònoma de Barcelona), Liver Section, Gastroenterology Department, Barcelona, Spain*
Email: 95565@parcdesalutmar.cat

Background and Aims: Steatosis worsen the prognosis of chronic hepatitis C (CHC) *(Everhart et al; Gastroenterology 2009).* Controlled attenuation parameter (CAP) of FibroScan® evaluates and quantifies steatosis non-invasively. In patients with CHC a CAP (db/m) value >250, correlates with significant steatosis (over 33% of hepatocytes). Aim of the study was to identify significant steatosis by CAP before and after achieving sustained viral response (SVR12) in patients with CHC and to recognize independent variables related to steatosis increase.

Method: Patients with CHC, treated with direct acting antivirals (DAA) between April 2015 and December 2016, were retrospectively included. Steatosis was defined as a CAP >250 at baseline (CAPb) or after SVR12 (CAPf).
Results: 350 patients with SVR were evaluated. 60 (17%) patients were excluded due to the lack of CAPb and/or CAPf. The median (range) age was 55 (24–86). The median (range) body mass index (BMI), waist circumference (WC) and skin-capsule distance (SCD) at baseline were 26.5 (16–41) kg/m², 98 (70–128)cm and 16 (8–30)mm, respectively. At baseline, transient elastography (TE) was 9.8 (2.8–72) kPa and CAPb was 229 (129–374) db/m. Patients with a CAPb >250 (n = 94, 32%) showed independently (OR, 95% CI, p) higher values of WC (1.5, 1.01–1.09, p = 0.011), SCD (1.3, 1.2–1.5, p < 0.001) and GGT (1.01, 1.01–1.01, p < 0.001). After SVR12, values of TE decreased to 7.1 kPa (2.8–57) (p < 0.001). However, median (range) CAPf did not change after SVR12 being 234 (100–394) (p = ns). Among patients with a CAPb <250 the CAPf increased in 21.4%. Patients with increasing CAPf showed higher values of WC (1.11, 1.06–1.16, p < 0.001) at baseline and weight increasement during antiviral treatment (1.12, 1.054–1.195, p < 0.001).
Conclusion: A third of patients with chronic hepatitis C have significant steatosis according to the Controlled Attenuation Parameter (CAP) values with FibroScan®. Moreover, around 21% of patients with low values of CAP before antiviral treatment showed steatosis after SVR12, especially in those with a high waist circumference or weight gain during treatment. Long-term follow-up of these patients would be recommended to know the clinical implication of these findings.

FRI-405
Recurrent viremia after successful hepatitis C virus therapy with direct-acting antivirals in a cohort of people who use drugs
A. Alimohammadi, J. Holeksa, A. Bassi, Y. Bhutani, A. Thiam, B. Conway. *Vancouver Infectious Disases Centre*
Email: arshia.alimohammadi@vidc.ca

Background and Aims: People who use drugs (PWUD) are disproportionately represented within the hepatitis C virus (HCV)-infected population of Canada. Ongoing risky injection practices and sharing of equipment increase the risk of recurrent viremia (RV) after successful HCV therapy. Long-term engagement of this vulnerable population within a multidisciplinary care program with enhanced long-term follow-up post-SVR may be critical to reducing the rate of HCV re-infection in a population of "core transmitters".
Methods: An observational, retrospective analysis was conducted among HCV-infected patients who achieved cure of HCV infection with all-oral regimens initiated between 06/15–05/17. The cohort of interest has continued to use recreational drugs on an ongoing basis (documented by urine drug screen) and has also continued to receive multidisciplinary care at our centre to address medical, psychiatric, addiction-related, and social needs prior to, during and after HCV therapy. The endpoint of this analysis was the occurrence of RV by serial measurement of HCV RNA every 6 months after the achievement of SVR.
Results: A total of 134 active or recent PWUD (66/40% heroin/cocaine use in the past 6 months) achieved SVR and are included in this analysis. Key demographic characteristics include: median age 69 years, 79% male, 63% GT1a, 23% cirrhotic, 10% HIV co-infected, 33% treatment-naive. Treatment regimens included SOF/LDV (n = 46), PrOD (n = 46), EBV/GZV (n = 13), SOF/VPV (n = 6), others (n = 23). Follow-up period ranges from 24–105 weeks (mean 66 weeks). To date, there were no documented cases of recurrent viremia.
Conclusion: We have previously documented high SVR rates among PWUD receiving HCV treatment at our centre. We hypothesized that maintenance in long-term multidisciplinary follow-up post-SVR may serve to consolidate SVR and reduce the RV rate despite ongoing risk behaviors. No cases of RV were documented in our most recent cohort, treated with all oral agents. This supports the hypothesis that maintenance of more intensive follow-up post-SVR may reduce the likelihood of RV in the weeks/months that follow successful HCV therapy. The long-term benefits and feasibility of this intervention requires further ongoing study.

FRI-406
Changes in liver steatosis and lipid metabolism accompanied by successful interferon-free DAAs therapy in HCV infected patients; a comprehensive analysis
N. Kawagishi, G. Suda, K. Morikawa, K. Ogawa, N. Sakamoto. *Hokkaido University, Gastroenterology and Hepatology, Sapporo, Japan*
Email: gsudgast@pop.med.hokudai.ac.jp

Background and Aims: HCV hijack hepatocyte lipid metabolism, resulting in liver steatosis and decrease in serum LDL level. After successful HCV eradication, existence of liver steatosis is associated with hepatocarcinogenesis, and elevated LDL might cause vascular event. Thus, to clarify the factors associated with those disorders after successful HCV eradication is required. We conducted comprehensive analysis to clarify the factors associated with those disorders after HCV eradication in patients treated with IFN-free DAAs.
Method: Patients who were treated with IFN-free DAAs therapy between 2014 and 2016 in Hokkaido University Hospital, and were conducted transient elastography including Controlled Attenuation Parameter (CAP) at pre- and post-treatment, and achieved SVR were enrolled. Liver steatosis was evaluated by CAP value. Changes in liver steatosis, lipid metabolism, blood test, and genetic factor, including PNPLA3:rs738409, MTP493:rs1800591, TMS6FS2:rs58542926, ALDH2:rs671 were analyzed.
Results: A total of 117 patients were included. 79 and 38 patients were infected with genotype 1 and 2 respectively and treated with DCV/ASV, SOF/RBV, SOF/LDV or OBT/PTV/r. Overall, mean CAP value and serum LDL levels were significantly elevated at post treatment point. However, in patients with baseline CAP value ≥220 dB/m, mean CAP value were significantly decreased. In patients with baseline LDL value ≥108 mg/dl, mean LDL values were significantly decreased. At baseline, LDL value and CAP value didn't have significant association, however, after HCV eradication both values were significantly associated (r = 0.317 p = 0.01). Univariate analysis revealed that patients with liver steatosis (CAP > 248 dB/m, n = 21 (18%)) after HCV eradication had significantly higher baseline BMI and lower HDL level. Patients with LDL more than 140 mg/dl at post-treatment had significantly higher baseline T-chol, LDL level, and non-LC. Patients with ALDH2 GG allele had significantly higher CAP value at baseline and post-treatment (p = 0.03, GG vs AG/AA) and MTP493 T allele was significantly associated with baseline lower LDL and higher ratio of HDL elevation at post-treatment.
Conclusion: Successful HCV eradication by IFN-free DAAs restored liver steatosis in patients with baseline higher CAP value, except for patients with baseline high BMI and/or low HDL level. Patients with non-LC and/or higher baseline T-chol level should be paid attention for hyperlipidemia after HCV eradication.

FRI-407
Impact of direct acting antiviral drugs on HCV- related decompensated liver cirrhosis
M. Essa, A. Sabry, E. Abdelsameea, E.-S. Tharwa, M. Salama. *National Liver Institute, Hepatology and gastroenterology, Shebin El Kom, Egypt*
Email: salamamohsen@yahoo.com

Background and Aims: HCV was considered as a major health problem in Egypt before evolution of direct acting antiviral drugs (DAAs). The benefit of treatment of HCV with DAAs in patients with decompensated liver cirrhosis (DLC) is still unclear. We aimed to evaluate the degree of improvement in hepatic decompensation events and quality of life in treated and untreated patients with DLC.
Methods: One hundred and fifty patients with HCV related DLC were included, 75 of them received treatment (group I) in form of sofosbuvir with either daclatasvir or ledipasvir for 24 weeks

without ribavirin or for 12 weeks with ribavirin while the other 75 patients didn't receive treatment as a comparable group (group II). Patients achieved SVR at 12 weeks were assessed regarding to decompensation events, MELD score, Child Turcotte Pugh (CTP) score, biochemical changes and quality of life (applied on Mcguill quality of life questionnaire) before starting treatment and 6 months after treatment and compared them with untreated patients.

Results: Forty two patients (56%) received sofosbuvir with daclatasvir for 24 weeks without ribavirin and 19 (25.3%) patients received sofosbuvir with ledipasvir for 24 weeks without ribavirin. MELD score improved in treated patients (mean change was −1.73) but worsened in untreated patients (mean change was + 11.8) before and after 6 months. Also, CTP score improved significantly ($p < 0.001$) [table 1]. Serum albumin, prothrombin time, bilirubin, alpha fetoprotein and ALT improved in treated patients ($p < 0.001$). Health related quality of life improved in treated patients (mean change was + 17.65) and worsened in untreated ones (mean change was −18.68) [$p < 0.001$].

Table: Comparison between the two studied groups according to Child Turcotte Pugh (CTP) score before and after 6 months

	Group I				Group II			
	Before		After		Before		After	
	No.	%	No.	%	No.	%	No.	%
CTP class	(n = 75)		(n = 75)		(n = 75)		(n = 75)	
A	0	0.0	30	40	0	0.0	0	0.0
B	58	77.3	34	45.3	57	76	42	56
C	17	22.7	11	14.6	18	24	33	44
Significance	$p_1 < 0.00^*$, $p_2 < 0.001^*$, $p_3 < 0.001^*$							
CTP score	(n = 75)		(n = 75)		(n = 75)		(n = 75)	
Min.–Max.	7.0–11.0		5.0–11.0		7.0–11.0		7.0–15.0	
Mean ± SD.	8.37 ± 1.19		7.14 ± 1.58		8.41 ± 1.22		10.16 ± 2.64	
Median	8.0		7.0		8.0		9.0	
Significance	$p_1 < 0.001^*$, $p_2 < 0.001^*$, $p_3 < 0.001^*$							

p_1: p value for Mann Whitney test for comparing between before and after 6 months in cases group.
p_2: p value for Mann Whitney test for comparing between before and after 6 months in control group.
p_3: p value for Mann Whitney test for comparing between cases and control after treatment.
*: Statistically significant at $p < 0.05$.

Conclusion: Treated patients with DLC showed improvement in their liver functions and health related quality of life. Those patients need longer durations of follow up for decompensation events.

FRI-408

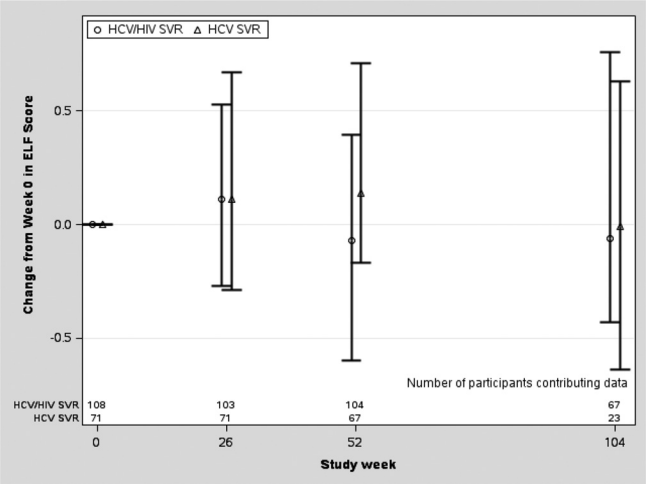
No evidence of fibrosis regression in HCV/HIV co-infected and HCV monoinfected participants up to 3 years after achieving SVR with DAA treatment: Interim results for the ACTG A5320 Viral Hepatitis C Infection Long-term Cohort Study (V-HICS)

M. Peters[1], M. Kang[2], R. Murphy[3], R. Matining[2], W. Rosenberg[4], D. Wyles[5]. [1]*University of California San Francisco, Gatroenterology, San Francisco, United States;* [2]*Harvard School of Public Health;* [3]*Northwestern University;* [4]*University College London, Medicine;* [5]*Denver Health, Infectious Diseases*
Email: Marion.peters@ucsf.edu

Background and Aims: A5320/V-HICS is an observational, prospective, long-term follow-up study in HCV/HIV and HCV participants enrolled within 1 year of completion of DAA-based HCV treatment. Enhanced Liver Fibrosis (ELF) test, validated in HCV mono-infection, utilizes direct measures of extra-cellular matrix components. ELF was shown to be superior to APRI and FIB-4 in predicting all-cause mortality in HIV/HCV co-infected women. We sought to study long-term fibrosis outcomes following sustained virologic response (SVR) in V-HICS. Changes from baseline in APRI of 0.25, FIB-4 0.5, and ELF 0.5 are considered clinically significant.

Method: Participants who achieved SVR, enrolled in V-HICS within a year of treatment completion and had at least 1 year of follow-up in V-HICS were included. ELF test used stored serum specimens at weeks 0 (entry), 26, 52 and 104 in V-HICS. APRI and FIB-4 were calculated at weeks 0, 52 and 104. Absolute score changes from week 0 were calculated and summarized by infection group.

Results: Of the 111 HCV/HIV and 71 HCV participants: 44% Black non-Hispanic, 22% female, 46% prior IV drug users, 62% genotype 1a; with a median of 30 weeks between DAA treatment completion and V-HICS entry. HCV/HIV participants had median CD4+ T-cell count 703 cells/mm^3, and 95% had undetectable HIV-1 RNA. APRI, FIB-4 and ELF scores were low and similar between the two groups at V-HICS entry: median ELF score was 8.93 and 9.01 in HCV/HIV and HCV groups. Overall, 1% had APRI > 1.5, 7% FIB-4 > 3.25 and 4% ELF ≥ 11.3 (cirrhosis cutoffs). At week 104, 1% by APRI, 6% by FIB-4 and 2% by ELF showed cirrhosis: median changes from baseline in APRI were −0.04 and −0.06 in HCV/HIV and HCV groups, respectively; similarly, −0.14 and −0.2 for FIB-4, −0.06 and −0.01 for ELF. There were no clinically significant changes from baseline in fibrosis scores. The figure shows the median (Q1, Q3) change from week 0 in ELF Score by group at study weeks



Conclusion: While "indirect" fibrosis tests have been reported to decrease during the 1st year post SVR, this may be mainly due to loss of inflammation. Fibrosis decreased over time but changes out to week 104 were small and likely not clinically important. The low number of participants with advanced fibrosis may have limited our ability to detect clinically important decreases in fibrosis. Whether fibrosis continues to decrease 3–5y after SVR is not clear and patients should be followed to determine long-term outcomes.

FRI-409

Direct acting anti-viral treatment for hepatitis C results in a rapid reduction in MRI measures of hepatic microstructure

R. Scott[1], C. Bradley[2], N. Palaniyappan[1], S. Ryder[1], G. Aithal[1], W. Irving[1], S. Francis[2], N. Guha[1]. [1]*National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre at the Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham Digestive Diseases Centre, University of Nottingham, Nottingham, United Kingdom;* [2]*Sir Peter Mansfield Imaging Centre, School of Physics and Astronomy, University of Nottingham, Nottingham, U. Kingdom*
Email: robertscott@doctors.org.uk

Background and Aims: Direct acting antivirals (DAAs) for the treatment of hepatitis C virus (HCV) infection achieve high sustained virological response (SVR) rates, even in patients with cirrhosis. However, the effect of viral clearance on the liver and clinical outcomes are inadequately described. We aimed to prospectively characterise changes in serial quantitative MRI measures of

microstructure and haemodynamics within the liver and splanchnic system in patients accessing DAA therapy.

Method: Patients eligible for DAA therapy were invited to attend research MRI scans pre- and post- DAA treatment in a single UK research centre. Multiparametric MRI scans were performed on a Philips 1.5T Achieva (16-channel SENSEXL Torso receive coil) using a previously published protocol. DAA therapy consisted of treatment with sofosbuvir, plus either ledipasvir or daclatasvir, with or without ribavirin. Data was tested for normality (Shapiro-Wilk test). Paired t-test and Wilcoxon signed rank tests were used to compare pre- and post-treatment measures.

Results: 17 HCV patients with cirrhosis (10 HCV genotype 1, 6 genotype 3 and 1 genotype 2) had a MRI scans pre- and post- DAA treatment. 8/17 had decompensated cirrhosis (4 previous variceal haemorrhage, 2 ascites, 2 jaundiced). All patients underwent DAA therapy within 1 week of their pre-treatment MRI scan. Post-treatment MRI scans were performed at a median of 22 days (3–79 days) after the last dose of DAA. 16/17 (94.1%) achieved SVR. Changes in paired study data are summarised in Table 1. No significant changes were observed in any haemodynamic MRI measure (hepatic, splenic, superior mesenteric artery or portal vein flow, or liver perfusion) following DAA therapy.

Table 1: Comparison of paired serum markers and quantitative MRI measures of 17 patients pre- and post- HCV treatment with DAAs.

Variable	Pre-treatment	Post-treatment	Significance
Serum markers			
ALT	86.3 ± 104.3	32.5 ± 25.3	p = 0.038
Fib4	4.7 ± 3.0	2.9 ± 1.5	p = 0.006
APRI – median (inter-quartile range)	2.2 (1.0–3.9)	0.8 (0.6–1.2)	p = 0.006
MELD	7.8 ± 2.2	9.3 ± 2.9	p = 0.032
Structural MRI measures:			
Liver T_1 (ms)	762 ± 22.6	728.8 ± 23.6	p < 0.0001
Liver T_2 (ms)	44.3 ± 7.6	41.9 ± 7.7	p = 0.01
Liver T_2^* (ms)	29.1 ± 8.4	26.0 ± 8.9	p < 0.001
Splenic T_1 (ms)	1251.8 ± 21.7	1254.7 ± 22.9	p = 0.75

Conclusion: We observed changes in liver relaxation times (T_1, T_2, T_2^*) reflecting hepatic microstructure in a short time window following DAA therapy. These MRI changes are a likely a result of reduced pro-inflammatory milieu, including interstitial oedema, within the liver after viral clearance. The ability of MRI to characterise changes in the angio-architecture of patients with cirrhosis after intervention in the short term will enhance our understanding of the natural history of regression of liver disease and potentially influence clinical decision algorithms.

FRI-410

Clinical consequences of occult HCV infection in a post-liver transplant population

B.R. Bang[1], B. Kim[1], T. Harper[1], S. Chopra[2], G. Kanel[2], K. Jerome[3,4], L. Cook[3,4], T. Saito[1], B. Lee[1], Y. Genyk[5], J. Emamaulee[5], J. Kahn[1]. *[1]Keck School of Medicine of USC, Medicine, Division of Gastrointestinal and Liver Diseases; [2]Keck School of Medicine of USC, Pathology; [3]Fred Hutchinson Cancer Research Center, Vaccine and Infectious Disease Division; [4]University of Washington, Laboratory Medicine, Seattle, United States; [5]Keck School of Medicine of USC, Department of Surgery, Division, Hepatobiliary/Pancreatic Surgery and Abdominal Organ Transplantation, Los Angeles, United States*
Email: jkahn@usc.edu

Background and Aims: Post-transplant recurrent HCV infection develops in most patients with viremia at the time of orthotopic liver transplant (OLT). Antiviral therapy with direct acting agents (DAA) is indicated to preserve graft longevity. We have observed that up to 11% of patients who achieve a sustained virologic response (SVR) with DAA therapy continue to exhibit clinical and histological features of viral hepatitis, while HCV RNA remains undetectable in the serum. HCV is capable of persisting in the liver and peripheral blood mononuclear cells (PBMC) after attaining SVR, defined as occult HCV infection (OCI), however, the prevalence and clinical significance of the phenomenon remain elusive, especially in immunocompromised hosts. To better understand this emerging clinical entity, this pilot study focused on the prevalence and clinical outcomes of OCI.

Methods: Patients who were post-OLT with liver test abnormalities after achieving SVR and were having liver biopsies were enrolled under an approved IRB protocol. A portion of liver biopsy and PBMC were collected, followed by total RNA extraction. The RNA was then applied for one-step RT-qPCR with TaqMan probe for the detection and quantification of HCV-RNA. In addition, DNA was extracted for IL-28B genotyping from liver tissue and PBMC.

Results: 12 patients who underwent OLT and had SVR after DAA treatment participated in the study. Of those, 6 had OCI, 4 with adverse clinical outcomes: 1 with frequently abnormal liver tests requiring intervention, 1 with graft failure requiring re-transplant, 1 with IgA nephropathy likely due to HCV infection and 1 with chronic aminotransferase, alkaline phosphatase and bilirubin elevation. Most of the 6 patients without OCI had no significant clinical event except for 1 patient who had intermittent liver test abnormalities responding to immunosuppression modulation. Of those patients with OCI, 4/6 were IL-28B genotype TT, 1 was TC and 1 unknown. Of the 6 patients without OCI, 3 were TC, 1 was CC and 2 were unknown.

Conclusions: We found an unexpectedly high prevalence of OCI in patients who attained SVR with DAA for recurrent HCV post-OLT. Our preliminary results also suggest that the presence of OCI is correlated with an increased risk of adverse clinical consequences despite attaining serologic SVR, especially in recipients who are IL-28B TT genotype. The prevalence and clinical outcomes of OCI should be investigated in larger clinical cohorts in the post OLT population.

FRI-411

Incidence of de-novo hepatocellular carcinoma after treatment with direct antiviral agents for hepatitis C: A multicenter prospective cohort study from Latin America

F. Piñero[1], E. Ridruejo[2,3], M. Mendizabal[1], C. Alonso[1], A. Varon[4], A. Soza[5], A. Palazzo[6], M. Sixto[7], N. Hernandez[8], M.I. Schinoni[9], S. Ceballos[10], C. Gadea[11], D. Perez[6], M.V. Reggiardo[12], V. Moreno[10], S.E. Mengarelli[10], A. Bruno[13], C. Mendoza[14], J. Vila[15], F. Barreyro[16], M.G.V. Zuain[17], Raymundo Parana Filho[9], M. Silva[18]. *[1]Hospital Universitario Austral, Hepatology and Liver Transplant Unit, Pilar, Argentina; [2]Hospital Universitario Austral, Hepatology and Liver Transplant Unit., Argentina; [3]Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC"., Hepatology Section, Department of Medicine; [4]Fundacion Cardio Infantil, Hepatology Section; [5]Pontificia Universidad Católica de Chile, Department of Gastroenterology; [6]Hospital Padilla, Department of Gastroenterology; [7]Hospital Cullen, Department of Gastroenterology, Santa Fe, Argentina; [8]Hospital de Clinicas, Department of Gastroenterology; [9]Hospital Universitario de Bahia, Gastro-Hepatology Unit; [10]Hospital San Roque, Department of Gastroenterology; [11]Hospital Centro de Salud Zenon Santillan, Department of Gastroenterology, Tucuman, Argentina; [12]Hospital Centenario, Department of Gastroenterology; [13]Hospital Argerich, Hepatology Section, CABA, Argentina; [14]Nuevo Hospital de Rio Cuarto, Department of Gastroenterology, Rio Cuarto, Argentina; [15]Hospital Corrientes, Department of Gastroenterology; [16]Hospital Posadas, Hepatology Section; [17]OSECAC, Hepatology Section; [18]Hospital Universitario Austral, Hepatology and Liver Transplant Unit.*
Email: fpinerof@cas.austral.edu.ar

Background and Aims: Information about the development of de-novo hepatocellular carcinoma (HCC) after achieving sustained virologic response (SVR) with all-oral direct antiviral agents (DAA) in Latin America is scarce. The aim of this study was to evaluate the incidence of HCC after therapy with DAA in patients with advanced fibrosis.

Methods: A prospective cohort from the Latin-American Liver Research, Educational and Awareness Network (LALREAN) was analyzed. Patients from Argentina, Brazil, Chile, Uruguay and Colombia who received DAAs since their approval in 2015–2016 were included. Advanced fibrosis was defined as liver fibrosis grade 3 or 4 (METAVIR F3-4/LSM > 9.5 kPa). De-novo HCC was defined as the newly development of HCC after DAA regimens. All patients underwent routine ultrasound screening every 6 months before, during and after DAAs therapy.
Results: Of the 378 patients who received DAA therapy, a total of 229 patients with F3 (n = 45) and F4 (n = 184) were included for the analysis. Baseline patient characteristics were: age 55 ± 11, male sex 48.5%, HIV co-infection 3.5%, HBV co-infection 0.4%. Proportion of genotypes was as follows: 1a 19%, 1b 57%, 2 10%, 3 4% and 4 1% (genotype 1 without subgenotype in 8%). Median elastography assessment before treatment was 33 kPa (IQR 15–55 kPa), with a pre-treatment MELD score of 9 ± 3, Child Pugh A 84%, B 15% and C 1% (32 patients were listed for liver transplantation). Overall, 88.3% of the initial cohort completed DAAs treatment, with an SVR12 of 96.9%. During post-SVR12 follow-up 3 patients developed ascites, 2 encephalopathy and 2 variceal hemorrhage. Seven (22%) patients were delisted. Cumulative incidence of HCC in the overall cohort was 3% (n = 7) during a median follow-up since end of treatment of 14.5 weeks (IQR 8.6–31.3 weeks) with an incidence rate of 0.003 per person/weeks (HCC per Child Pugh A 2.7% and Child Pugh B 7.4%; p = NS). All patients who developed de-novo HCC achieved SVR12; only one was F3. At HCC diagnosis, 2 patients presented with extrahepatic HCC with a median major tumor size of 40 mm.
Conclusions: Our study demonstrates that there still exists a high-risk of newly HCC development in patients with advanced fibrosis treated with DAA. Routine screening of HCC in this population should be strict during the first months after treatment with DAAs.

FRI-412
Impact of sustained virological response in the use of concomitant drugs in hepatitis C virus infected patients with comorbidities

E. González-Colominas[1], M. Batlle[2], Inés Monge-Escartín[1], M. Puigvehí[2], T. Broquetas[2], N. Cañete[2], M.G. Retortillo[2], S. Coll[2], R.S. Lamoglia[2], S.G. Cerrato[1], J.A. Carrión[2]. *[1]Hospital del Mar, Pharmacy Department, Barcelona, Spain; [2]Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), Hepatology Unit, Gastroenterology Department, Barcelona, Spain*
Email: 95565@parcdesalutmar.cat

Background and Aims: More than 70% of patients with chronic hepatitis C virus infection (CHC) whom start direct-acting antivirals (DAAs) take concomitant drugs (*Gonzalez-Colominas E et al; doi:10.1111/jgh.14014).* Sustained virological response (SVR) reduces both hepatic and extrahepatic morbidity and mortality. Our objective was to evaluate the impact of SVR with DDAs (SVR12) in the use of concomitant drugs.
Method: Prospective study (January 2015–September 2016) including patients treated with DAAs. Routine medication (RM) was collected at the beginning of treatment and at least after one year of achieving the SVR12. The RM was defined as those drugs prescribed for a chronic disease (>6 months). Patients were classified according to treatment changes: (A) no change (B) change (B.1: increase; B.2: decrease; B.3: same number of drugs).
Results: 343 patients with median age (range) of 58 (30–87) were included, 39.1% women, 20.1% HIV co-infection and 46.6% with cirrhosis. Out of 336 (98%) patients with SVR, 79.5% (n = 267) were receiving concomitant treatment before starting DDAs with a median of 4 (1–14) drugs per patient. After a follow-up of 98 (56–147) weeks, a change in the usual treatment was seen in 205 (61%) of the patients, with a median of 2 (1–10) changes per patient. Of them, 49.8% (n = 102) increased (B.1), 28.3% (n = 58) decreased (B.2) and 22% (n = 45) maintained the same number of drugs (B.3). Patients increasing the number of drugs presented in a higher proportion: cirrhosis (61.8% vs 39.5%; p < 0.001), advanced age >65 (42.2% vs 29.6%; p = 0.025) and high Charlson Index (4.7 vs 3.6; p < 0.001). Charlson Index (OR = 1.19; 95CI% = 1.04–1.36) and cirrhosis (OR = 1.84; 95%CI = 1.05–3.22) were associated with an increase on the number of drugs after SVR. Decrease (B.2) in the number of drugs was due to diuretics (14%), anxiolytics (12.5%), antiacids (10.7%) and antihypertensives (8.9%).
Conclusion: Half of patients with CHC increased the number of drugs received after achieving SVR, especially in patients with comorbidities. However, a quarter of patients achieving the SVR show a decrease in the number of drugs taken. Further follow-up is needed to know the impact of the SVR in comorbidities of patients with CHC.

FRI-413
Noninvasive diagnosis of fibrosis in the patients with hepatitis C virus infection treated with direct-acting antivirals

H. Numao, K. Shimaya, K. Hasui, K. Igarashi. *Aomori Prefectural Central Hospital, Gastroenterology, Aomori, Japan*
Email: qqqc2c79@celery.ocn.ne.jp

Background and Aims: Noninvasive biomarkers are widely used in assessing liver fibrosis; however, there is lack of knowledge about changes in their values during the course of disease. The aim of this study is to assess the chronological changes of fibrosis using noninvasive biomarkers in patients with HCV treated with direct-acting antivirals (DAA).
Method: One hundred fourteen patients with biopsy-proven HCV infection who attained sustained virological response (SVR) with DAA (57 men; mean age, 66.6 ± 10.5 years; mean body mass index, 23.3 ± 3.56 kg/m^2) were enrolled. The liver biopsy specimen was evaluated according to the METAVIR system. Liver fibrosis was assessed at the baseline (BL), SVR12, SVR24, SVR48, and SVR72 using real-time shear wave elastography (SWE), magnetic resonance elastography (MRE), mac-2 binding protein glycosylation isomer (M2BPGi), fibrosis-4 index (FIB-4), and platelet count (PLT). Albumin (ALB) and alanine transaminase (ALT) were also evaluated at the same time.
Results: Inflammatory activity was A0/A1/A2/A3 in 2/60/47/5 patients respectively, and fibrosis severity was F0/F1/F2/F3/F4 in 5/45/24/22/18 patients respectively. The mean SWE (m/s), MRE (kPa), M2BPGi (COI), FIB-4, PLT (×10^4/μl), ALB (g/dL), and ALT (IU/l) at BL/SVR12/SVR24/SVR48/SVR72 were 1.75/1.66/1.65/1.64/1.65, 4.85/4.44/3.54/3.65/3.71, 3.25/2.08/1.75/1.51/1.28, 4.13/3.28/3.19/2.90/2.73, 14.5/15.2/15.2/15.7/16.1, 4.01/4.26/4.26/4.31/4.24, and 57.4/22.5/21.3/22.8/21.0 respectively. Significant differences were observed between BL/SVR12 in SWE, M2BPGi, and FIB-4 and SVR12/SVR72 in M2BPGi. In a cohort of significant fibrosis (F2-F4), significant differences were observed between BL/SVR12 in M2BPGi and FIB-4, SVR12/SVR72 in M2BPGi, and BL/SVR48 in MRE. ALB and ALT showed significant difference between BL/SVR12 and no significant changes thereafter. The rates of change in SWE and M2GPGi during the period between BL and SVR12 showed no correlation with those in ALB and ALT. Only FIB-4 showed correlation with ALT (r = 0.51).
Conclusion: SWE, M2BPGi, and FIB-4 suggested improvement in fibrosis at SVR12. Although these changes were accompanied with significant changes in ALB and ALT, the rates of change in SWE and M2BPGi did not correlate with those in ALB and ALT. All the fibrosis markers except for M2BPGi showed no significant changes between SVR12 and SVR72.

FRI-414

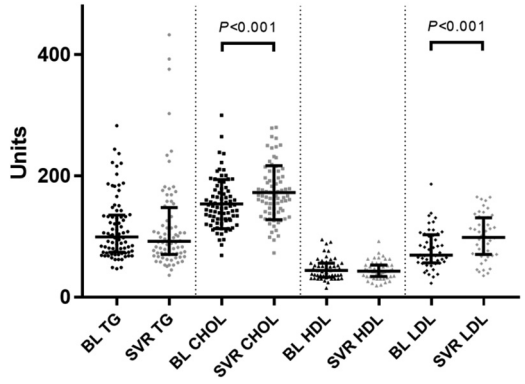
Impact of SVR to IFN-free DAA therapy on steatosis in HIV/HCV coinfected patients

D. Chromy[1], P. Schwabl[1], T. Bucsics[1], B. Scheiner[1], C. Schmidbauer[1], M. Aichelburg[2], P. Ferenci[1], M. Trauner[1], T. Reiberger[1], M. Mandorfer[1].
[1]*Medical University of Vienna, Department of Internal Medicine Iii, Division of Gastroenterology and Hepatology, Vienna, Austria;* [2]*Medical University of Vienna, Dermatology, Immunology, Allergy and Infectious Diseases, Vienna, Austria*
Email: n1142399@students.meduniwien.ac.at

Background and Aims: Hepatic steatosis (HS) and dyslipidemia contribute to the burden of liver disease among HIV/hepatitis C (HCV) coinfected patients (HIVHCV). Previous studies suggested a steatogenic effect of HCV. We evaluated the impact of sustained virologic response (SVR) to IFN-free direct-acting antivirals (DAAs) on HS and dyslipidemia in HIVHCV.

Methods: HIVHCV attending our HIV/Liver outpatient clinic and achieving SVR to IFN-free DAA treatment were assessed. Patients with paired controlled attenuation parameter (CAP®, FibroScan®, Echosense, France) measurements pre and post SVR were included in this retrospective study. CAP® values were adjusted according to Karlas et al (J Hepatol 2017).

Results: The majority of all HIVHCV (73%; 62/85) were male and (52%; 44/85) had intravenous drug abuse as suspected route of transmission. Patient characteristics: Median age at baseline (BL): 50 (15) years; mean BMI: 23.9 kg*m-2 ± 4.52; *PNPLA3* genotype (GT): C/G 41% (34/82) and G/G 4% (3/82); HCV-GT-1a 51% (43/85), HCV-GT-1b 14% (12/85), HCV-GT-3 20% (17/85) and HCV-GT-4 14% (12/85). Liver transaminases and bilirubin levels showed a significant decrease after SVR. Furthermore, total cholesterol (CHOL; 154 ± 40.6 vs. 172 ± 44.6; $p < 0.001$) and low density lipoprotein (LDL; 69.4 (46.3) vs. 98.6 (60.4); $p < 0.001$) levels significantly increased after SVR (Figure), while no changes in triglycerides (TG), high density lipoprotein (HDL) levels, or CAP® were observed. The prevalence of HS (defined by CAP® ≥ 248 dB/m) at BL and SVR was 35% (30/85) and 41% (35/85), respectively. Predictive factors for a decrease in HS after SVR were high BL CAP® values (253 dB/m ± 55.7 vs. 210 dB/m ± 47.6; $p < 0.001$) as well as protease inhibitor (PI) intake (47% (18/38) vs. 20% (9/46); $p = 0.007$) as part of antiretroviral therapy (ART) at BL. Noticeably, HIV PI were discontinued in 16% (14/85) to avoid drug-drug interactions with DAAs. In these patients, CAP® values decreased from 252 dB/m ± 51.3 at BL to 210 ± 64.3 dB/m ($p = 0.046$) at SVR.



Conclusions: In HIV/HCV, achieving SVR to IFN-free therapies had no impact on CAP® values. Thus, the proportion of HIV/HCV affected by HS remained high after SVR. Moreover, HCV eradication increased CHOL and LDL levels. Hence, further studies investigating metabolic changes in HIVHCV post SVR are warranted. Interestingly, switching from a HIV PI to an integrase inhibitor based regimen was associated with a significant decrease in CAP®, which might indicate a beneficial effect on HS.

FRI-415

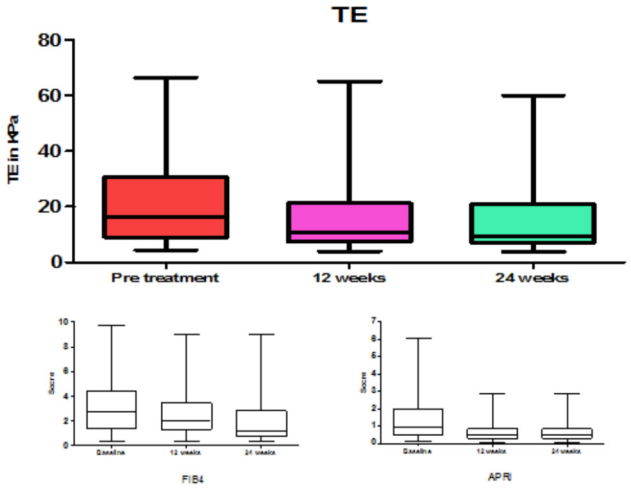
Sustained virological response predicts fibrosis regression in chronic hepatitis C patients treated with direct acting antivirals-a single tertiary care centre experience

R. Gunjal, K. Devadas, V. Tadkalkar. *Government Medical College, Medical Gastroenterology, Trivandrum, India*
Email: dr.rajendragunjal@gmail.com

Background and Aims: Treatment with Direct Acting Antivirals (DAA) results in sustained viral response (SVR) in more than 90% of treated individuals with subsequent improvement in liver function and fibrosis. The aim of our study was to assess changes in liver fibrosis by transient elastography (TE) and fibrosis-4 (FIB-4) score and AST-Platelet ratio (APRI) in patients with chronic hepatitis C (CHC) treated with DAA.

Method: Between April 2015 to April 2017, 110 consecutive CHC patients treated with DAAs at our centre were included. TE, FIB4, APRI score were performed before treatment and after 12 weeks of completion of therapy, the time of assessing sustained virological response (SVR12) and after 24 weeks of completion of therapy. Changes in scores were analysed by paired t test.

Results: The median age of the patients was 51 years, 57% had compensated cirrhosis, 79% were treatment naïve, 92.7% achieved SVR12. Most common genotype was type 3 (62%). There was significant improvement in fibrosis scores among all patients. Median TE improved from 18 KPa to 13.4 KPa ($p < 0.01$), median FIB4 score from 2.85 to 1.90 ($p < 0.01$), median APRI score from 0.95 to 0.54 ($p < 0.01$) before treatment to 12 weeks post treatment. Patients with advanced fibrosis (F3-F4, TE > 9.5 KPa) had significant improvement in fibrosis scores compared to those without advanced fibrosis (F0-F2, TE < 9.5). For F3-F4 patients median TE, FIB4, APRI scores improved from 23.8 KPa, 3.97, 1.73 before treatment to 17.8 KPa, 2.44, 0.63 at 12 weeks post treatment respectively. For F0-F2 patients median TE, FIB4, APRI scores improved from 6.7 KPa, 1.17, 0.34 before treatment to 6.5 KPa, 0.97, 0.28 at 12 weeks post treatment respectively. Patients who have not achieved SVR12 had increment in fibrosis scores. Median TE increased from 19.7 KPa to 28.8 KPa, median FIB4 from 3.6 to 4.3, median APRI from 1.35 to 2.07 before treatment to 12 weeks post treatment respectively. In the patients who had completed 24 weeks post treatment (78.4%), median TE, FIB4, APRI scores improved from 10.6 KPa, 1.95, 0.52 at 12 weeks post treatment to 9 KPa, 0.85, 0.32 at 24 weeks post treatment respectively. Trend for these patients has been shown in figure below.



Conclusion: SVR12 using DAA therapy predicts a significant regression in liver fibrosis, particularly in those with advanced fibrosis. A nonsignificant trend towards continued regression of fibrosis was maintained at 24 weeks post treatment.

FRI-416

Long-term evolution of thrombocytopenia in patients with chronic hepatitis C and advanced fibrosis after sustained virological response with direct antiviral agents

J. Gómez- Camarero[1], P. Linares[2], S. Calvo[1,3], M.I. Martín Arribas[4], C. Almohalla[5], F. Jorquera[2,6,7], H.A.R. Rosario[1], F. Jiménez Vicente[8], M. de Benito[5], Belén B. Cabredo[1], Begoña A. Cuenllas[2], E. Badia-Aranda[1], F. Sáez-Royuela[1]. *[1]Hospital Universitario de Burgos; [2]Complejo Asistencial Universitario de Leon; [3]Fundacion Burgos Investigacion por la Salud; [4]Complejo Asistencial Universitario de Salamanca; [5]Hospital Universitario Rio Hortega, Valladolid; [6]CIBERehd, Madrid; [7]IBIOMEDLeon; [8]Hospital Universitario de Salamanca*
Email: jgomcam@hotmail.com

Background and Aims: Thrombocytopenia (TP) is frequent in patients with hepatitis C virus infection (HCV) and advanced fibrosis. The platelet count (PC) evolution after the elimination of HCV infection with direct antiviral agents (DAA) is fairly unknown. The aims of the present study were to analyse the changes of PC and TP in patients with sustained virological response (SVR) after treatment of HCV infection with DAA and their relationship with fibrosis evolution.

Methods: Multicentric, prospective, observational study performed in patients with HCV infection and advanced fibrosis (F3/F4 measured by transient elastography, TE, Fibroscan, EchoSens, Paris) who were treated with DAA in a real-world setting. The study was carried out in 4 hospitals from Castilla y León, Spain. PC and TE value at baseline, 24 (W24), 48 (W48) and 72 (W72) weeks after the end of treatment were collected. As patients without SVR were retreated during the follow-up period, we considered for the analysis only patients with SVR after the first DDA treatment. We studied the evolution of PC and TP (PC < 150 x109/l) along the time and the relationship between these variables and the changes in fibrosis (cut-off values: F3 ≥ 9. kPa, F4 > 12.5 kPa).

Results: From April 2015 to November 2016, 386 consecutive patients were included; 366 (95%) achieved SVR. A) Baseline characteristics: 67% men, mean (SD) age 57 (11.7) years, BMI 26 (4.4) kg/m2, ALT 81 (60)UI/ml and HCV RNA 2725329 (3879053)IU/ml; 74% of patients had genotype 1 HCV and 65% had received a previous treatment. Median (IQR) fibrosis was 16 (9.5–75) kPa; 71% of patients had cirrhosis (91% Child-Pugh A). The most frequently used AAD combinations were: SOF+SMV (32%), 3D/2D (26%) and SOF+LDV (19%). B) PC: At baseline, W24, W48 and W72 median (IQR) PC was 147.5 (100–189)x109/l, 151 (106–199)x109/l, 158 (108–197)x109/l and 159 (117–198)x109/l, (p = 0.000); median (IQR) fibrosis was 16 (12–23) kPa, 10.8 (11–18) kPa, 12 (8–20) kPa and 10.5 (7.5–15) kPa, respectively (p = 0.007). PC at W72 was directly correlated with baseline albumin (rho = 0.29; p = 0.001) and inversely correlated with baseline INR (rho = –0.20; p = 0.021), bilirubin (rho = –0.18; p = 0.036) and with W72 fibrosis (rho = –0.37; p = 0.002). At this time of the study, in W72 64 patients have TE measurement. Median (IQR) PC at W72 was 126 (84.5–167.5)x109/l in patients who remained at F3-F4 stage vs 176 (151–213) x109/l in those who moved to F0-F2 (p = 0.000). C) TP: TP was present in 191(52%) patients at baseline; at W72 only 26.5% had TP. The proportion of patients with TP decreased from 73% in those who stayed at F3-F4–19% in those who improved to F0-F2 stage (p = 0.000).

Conclusion: In clinical practice, PC increases progressively until W72 after the end of treatment in patients with chronic hepatitis C and advanced fibrosis who achieve SVR. Both PC and TP improve significantly in patients who obtain fibrosis decrease after DDA treatment.

FRI-417

Treatment of patients with decompensated cirrhosis with DAAs improves clinical symptoms without affecting their MELD score

J. Romano[1], O. Sims[2], J. Richman[3], M. Tansia[4], M. Shoreibah[5], P. Fitzmorris[5], Y. Guo[6], V. Kommineni[1], K. Lakshmi[1], O. Massoud[5]. *[1]University of Alabama at Birmingham, Medicine; [2]University of Alabama at Birmingham, Social Work; [3]University of Alabama at Birmingham, Surgery; [4]Birmingham Va, Medicine; [5]University of Alabama at Birmingahm, Division of Gastroenterology & Hepatology; [6]University of Alabama, School of Social Work*
Email: jaromano@uabmc.edu

Background and Aims: There is currently a paucity of data on the impact of HCV treatment with DAAs on the clinical manifestations of hepatic decompensation. The primary aim of this study was to assess the changes in ascites, hepatic encephalopathy (HE), and variceal bleed (VB) after achieving sustained virologic response (SVR). The secondary aim of this study was to compare pre-treatment and post-SVR MELD and CP scores and alpha-fetoprotein (AFP) levels.

Method: A retrospective analysis was conducted between November 2014 and January 2016 of all decompensated HCV cirrhosis patients who achieved SVR with all-oral DAAs at single tertiary medical center. The McNemar-Bowker test was used to assess changes in ascites, hepatic encephalopathy (HE), and variceal bleeding (VB) by comparing pre-treatment cases to cases 3 month post-SVR. Changes in MELD and CP scores and AFP levels were compared using the Wilcoxon Signed Rank test.

Results: 249 patients were reviewed. A sample of 37 patients met inclusion criteria. 81% of patients were treated with ledipasvir/sofosbuvir. The pre- and post- treatment prevalence of ascites were 65% and 29%, respectively (p < 0.01). The pre- and post- treatment prevalence of HE were 70% and 16%, respectively (p < 0.01). The pre- and post- treatment prevalence of VB were 35% and 3%, respectively (p < 0.01).There were no differences of statistical significance between pre-treatment and post-SVR median (interquartile range [IQR]) MELD scores 15 [8–28] vs. 15 [6–36] (p = 0.20) and median CP scores 7 [5–11] vs. 7 [5–15] (p = 0.60). Post-SVR median AFP levels 4.24, [0.06–15.7] were significantly lower than pre-treatment median AFP levels 6.45, [0.81–39.7] (p < 0.01).

	Pre-Treatment n (%)	3 Months Post-SVR n (%)	% Change
Ascites	24 (65%)	9 (29%)	36%
Hepatic Encephalopathy	26 (70%)	5 (16%)	54%
Variceal Bleeding	13 (35%)	1 (3%)	32%

Conclusion: This study showed achieving SVR was associated with significant improvement of clinical hepatic decompensation without significant change in MELD score. That means improvement of patients' quality of life without affecting their chance of obtaining liver transplantation. Further studies are needed to assess long-term sustainability of these reductions in a larger sample and over a longer study period.

FRI-418

Development of hepatocellular carcinoma following HCV eradication by direct-acting antivirals: Real-life experience from Japanese multicenter cohort

E. Ogawa[1], N. Furusyo[1], N. Hideyuki[2], K. Dohmen[3], N. Higashi[4], K. Takahashi[5], A. Kawano[6], K. Azuma[7], T. Satoh[8], M. Nakamuta[9], T. Koyanagi[10], S. Shimoda[11], M. Kato[12], E. Kajiwara[13], J. Hayashi[14]. *[1]Kyushu University Hospital, Department of General Internal Medicine, Fukuoka, Japan; [2]Shin-Kokura Hospital, The Center for Liver Disease, Kitakyushu, Japan; [3]Chihaya Hospital, Department of Internal Medicine, Fukuoka, Japan; [4]Steel Memorial Yawata Hospital, Department of Hepatology, Kitakyushu, Japan; [5]Hamanomachi Hospital, Department of*

Medicine, Fukuoka, Japan; [6]Kitakyushu Municipal Medical Center, Department of Medicine, Kitakyushu, Japan; [7]Kyushu Central Hospital, Department of Medicine, Fukuoka, Japan; [8]Kokura Medical Center, The Center for Liver Disease, Kitakyushu, Japan; [9]Department of Gastroenterology, Kyushu Medical Center, Fukuoka, Japan; [10]Fukuoka City Hospital, Department of Medicine, Fukuoka, Japan; [11]Kyushu University, Department of Medicine and Bioregulatory Science, Fukuoka, Japan; [12]Kyushu University, Department of Medicine and Biosystemic Science, Fukuoka, Japan; [13]Kajiwara Clinic, Kitakyushu, Japan; [14]Haradoi Hospital, Kyushu General Internal Medicine Center, Fukuoka, Japan
Email: eogawa@gim.med.kyushu-u.ac.jp

Background and Aims: Japanese HCV patients characteristically are older than patients in Europe and the United States. Advanced age has been proven to be an independent risk factor for the development of hepatocellular carcinoma (HCC). The purpose of this study was to evaluate the risk of HCC development among Japanese patients with chronic HCV infection, including compensated cirrhosis and previous HCC, following the achievement sustained viral response (SVR) by sofosbuvir-based regimens for 12 weeks.
Method: This large-scale, multicenter cohort study included 1,675 consecutive patients who achieved SVR by treatment with interferon-free sofosbuvir-based regimens, divided into groups with (n = 152) or without previous HCC (n = 1,523). The Kaplan-Meier method and Cox proportional hazard analysis were used to calculate the cumulative HCC incidence and related factors of HCC.
Results: During the follow-up period (median: 23 months), 76 (4.5%) patients developed HCC. The one-year cumulative rates of de novo HCC were 0.5% and 5.2% for the non-cirrhosis and cirrhosis groups, respectively (log-rank test: $p < 0.001$). Among the 565 patients without severe fibrosis/cirrhosis or metabolic disease including obesity (body mass index >25 kg/m^2) and/or diabetes, none developed de novo HCC. For cirrhotic patients, serum alpha-fetoprotein level at the end of treatment (EOT-AFP) was the strongest predictor of de novo HCC. The one-year cumulative de novo HCC rates were 1.3% and 14.1% in the EOT-AFP < 9.0 ng/ml and ≥9.0 ng/ml groups (cut-off value), respectively (log-rank test: $p < 0.001$). For patients with previous HCC, the one-year cumulative HCC recurrence rates were 9.7% and 21.2% in the non-cirrhosis and cirrhosis groups, respectively (log-rank test: $p < 0.05$). In multivariable Cox analysis, cirrhosis (HR 2.45, $p = 0.007$), time from previous HCC treatment to initiation of DAA of <1 year (HR 3.94, $p < 0.001$), number of HCC nodules ≥2 (HR 1.95, $p = 0.034$), and non-curative procedure with transarterial chemoembolization (HR 1.96, $p = 0.036$) were extracted as independent factors of HCC recurrence. Age, sex, ALT level, diabetes, and prior experience with interferon did not influence de novo HCC or recurrence in the short term.
Conclusion: The serum EOT-AFP level is a useful marker for predicting de novo HCC for cirrhotic patients. Moreover, close HCC surveillance should be required for patients with a past history of HCC, especially for patients treated with non-curative procedures.

NAFLD: Diagnostics and non-invasive assessment

FRI-421
Prevalence and stratification of NAFLD/NASH in a UK and US cohort using non-invasive multiparametric MRI

S. Harrison[1], H. Wilman[2], M. Kelly[2], V. Bachtiar[2], A. Dennis[2], C. Kelly[2], A. Paredes[3], J. Whitehead[3], S. Neubauer[2], R. Banerjee[2]. *[1]University of Oxford, Oxford, United Kingdom; [2]Perspectum Diagnostics Ltd, Oxford, United Kingdom; [3]San Antonio Military Medical Center, San Antonio, United States*
Email: henry.wilman@perspectum-diagnostics.com

Background and Aims: Given the societal impact of NAFLD, there is a clear need to accurately assess population prevalence, and approaches to non-invasively stratify those at risk. The MRI-derived quantitative Liver Inflammation and Fibrosis (LIF) score has been shown to correlate with liver inflammation and fibrosis, and can effectively stratify patients with NASH and cirrhosis [1, 2]. This study investigates the effectiveness of multiparametric MRI for the assessment and stratification of NAFLD/NASH in two large UK and US cohorts.
Method: 2825 individuals in the UK Biobank cohort and 402 individuals from the US San Antonio area received multiparametric MRI (Liver*MultiScan*™ protocol, <5 min) to estimate liver fat fraction (PDFF) and LIF. High risk participants in the US-cohort (PDFF ≥ 5%, LIF ≥ 2, MRE ≥ 3 kPa or FibroScan ≥ 7kPa) were asked for a liver biopsy (n = 140). Liver biopsies were double-blind evaluated with consensus using the NASH CRN scoring system by two expert pathologists. The US-cohort were individuals with no prior history of liver disease or alcohol abuse referred for routine colon cancer screening. Recruitment of UK-cohort were part of an ongoing national study that will collect imaging data from 100,000 individuals.

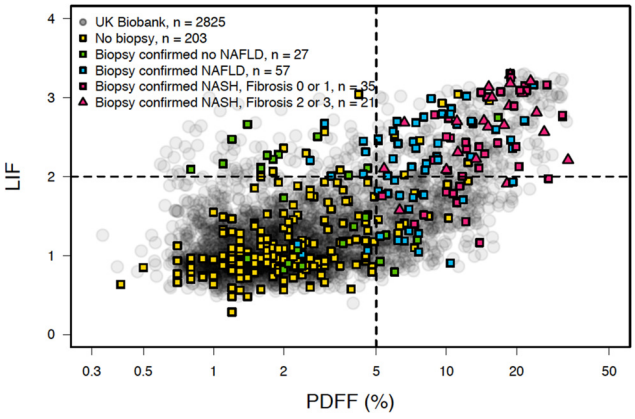


Figure 1: Distribution of cT1 and PDFF for UK-cohort (Grey) and US-cohort (Colour).

Results: Of the biopsied subjects from the US cohort, 99% with PDFF ≥ 5% & LIF ≥ 2 had NAFLD and 56% had NASH. 90% of NASH subjects with Kleiner-Brunt F2-3 had PDFF ≥ 5% & LIF ≥ 2. None of the subjects with PDFF < 5% & LIF < 2 had NASH and only 2% had NAFLD. Projecting onto the UK cohort would give an estimated NASH prevalence of 8.4%.
Conclusion: Multiparametric MRI is an effective non-invasive method to identify and stratify individuals with NAFLD and NASH at a population level. It can be used for high-throughput analysis of a general population and can identify individuals less likely to benefit from a liver biopsy.

FRI-422
Serum bile acids are markedly elevated in patients with compensated cirrhosis due to nonalcoholic steatohepatitis (NASH)

A. Sanyal[1], S. Harrison[2], M. Charlton[3], S. Caldwell[4], J. Chuang[5], L. Wang[5], G. Chen[5], C. Chung[5], S. Djedjos[5], R. Myers[5], N. Afdhal[6], J. Bosch[7,8], V. Ratziu[9], R. Loomba[10]. *[1]Virginia Commonwealth University, Richmond, VA, United States; [2]Pinnacle Clinical Research, San Antonio, TX, United States; [3]University of Chicago, Chicago, IL, United States; [4]University of Virginia, Charlottesville, VA, United States; [5]Gilead Sciences, Inc., Foster City, CA, United States; [6]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, United States; [7]Inselspital, Bern University, Bern, Switzerland; [8]IDIBAPS, University of Barcelona, Barcelona, Spain; [9]Hôpital Universitaire Pitié-Salpêtrière, Paris, France; [10]University of California, San Diego, United States*
Email: asanyal@mcvh-vcu.edu

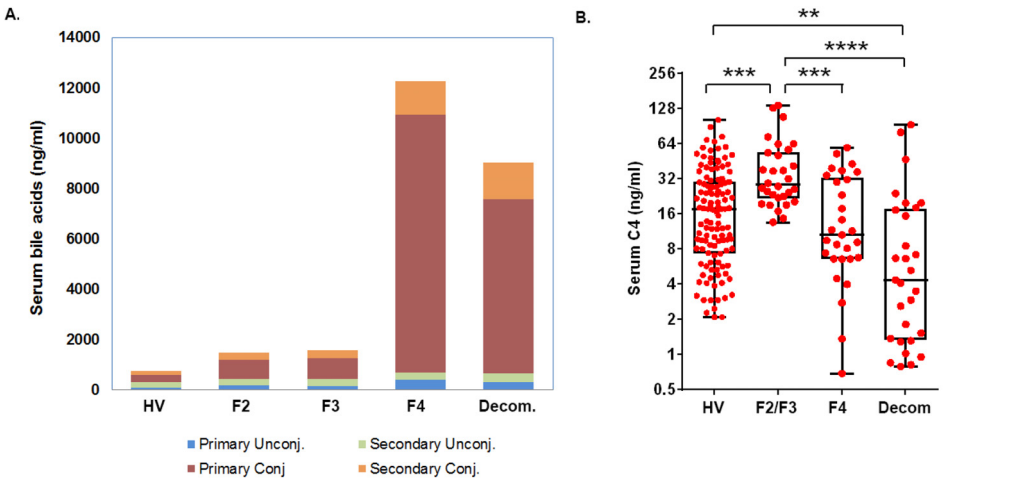


Figure1. Serum bile acid profiles are significantly altered in patients with NASH. (A) Primary conjugated bile acids are the main species that are elevated in cirrhotic subjects that subsequently developed liver decompensation. (B) Serum C4 levels are increased in patients with F2-F3 NASH, but are decreased in compensated cirrhotic subjects and at the time of decompensation.**p<0.01, ***p<0.001, ****p<0.0001. Decom, decompensated F4; HV, healthy volunteer.

Figure 1: (abstract: FRI-422)

Background and Aims: Bile acid (BA) metabolism is altered in NASH. Data describing the association between circulating BAs and NASH-related fibrosis, particularly cirrhosis, are limited. Our aim was to characterize circulating BAs and the intermediate, 7α-hydroxy-4-cholesten-3-one (C4), in patients across the spectrum of NASH severity.
Methods: Levels of 15 BAs were quantified by LC-MS/MS (Agilent 1290/Sciex, Metabolon) in fasting serum samples from healthy controls (n = 118), NASH patients with F2-F3 fibrosis (n = 68), and NASH patients with compensated cirrhosis (n = 29). In cirrhotic patients, analysis of serum BA was performed at BL and following hepatic decompensation (median 14.8 months [IQR 10.0, 22.3] from BL). Serum C4 levels were measured by LC-MS/MS to assess bile acid synthesis. Differences in BA and C4 levels between groups were determined using Kruskal-Wallis tests.
Results: Median total fasting serum BA levels in patients with NASH were greater than in healthy controls (2,533 vs. 878 ng/mL; $p < 0.0001$) and increased with fibrosis stage: F2, 1,619 (IQR 1,078–2,508); F3, 1,825 (1,226–2,848); and F4, 12,160 ng/mL (5,614–22,112) ($p < 0.0001$; Figure A). An increase in BAs in patients with compensated cirrhosis was primarily due to increased conjugated BAs (median: F4, 12,117 vs. F2-F3, 1,277 ng/mL; $p < 0.0001$). Primary conjugated bile acids (glycocholate [GCA], taurocholate [TCA], glycochenodeoxycholate [GCDCA], and taurochenodeoxycholate [TCDCA]) were the major BA species elevated in F4 vs. F2-F3 NASH. GCA and TCA were ~15 and 34-fold higher, respectively, in F4 vs. F2-F3 NASH. The ratio of secondary to primary bile acids in subjects with NASH (F2-F4) was lower than in healthy controls (15% vs. 56%; $p < 0.0001$). In patients with cirrhosis, serum BA levels were numerically lower at the time of hepatic decompensation ($p = 0.48$ vs. BL), but still at levels ~10-fold higher than in controls ($p < 0.0001$; Figure A). In contrast, BA synthesis as reflected by median serum C4 levels was lower in patients with cirrhosis vs. F2-F3 fibrosis (10.5 vs. 28.4 ng/mL; $p < 0.001$) and decreased further upon decompensation (4.3 ng/mL; $p < 0.05$ vs. BL; Figure B). C4 levels were in higher in NASH F2-F3 patients compared with healthy controls (28.4 vs. 17.4 ng/mL; $p < 0.001$).
Conclusions: BA profiles are altered in patients with NASH. In cirrhosis, decreased BA synthesis is accompanied by a relative increase in primary BA and decrease in secondary BA. These changes likely reflect decreased canalicular BA transport and/or impaired dehydroxylation in the intestine.

FRI-423

Non-invasive liver tests in electronic health records of patients with non-alcoholic fatty liver disease: combined analysis from four European countries

N. Dhalwani[1], M. Alexander[2], K. Loomis[3], N. Sattar[4], D. Waterworth[5], M. Mosseveld[6], P. Rijnbeek[6], J. van der Lei[6], T. Duarte-Salles[7], D. Prieto-Alhambra[7], D. Ansell[8], A. Pasqua[9], F. Lapi[9], P. Egger[10], S. Kendrick[2], W. Alazawi[11]. *[1]Diabetes Research Centre, Leicester, United Kingdom; [2]GlaxoSmithKline, Stevenage, United Kingdom; [3]Pfizer, United States; [4]BHF Glasgow, Glasgow, United Kingdom; [5]GlaxoSmithKline, United States; [6]Erasmus Medical Centre, Netherlands; [7]IDIAP Jorgi Gol, Spain; [8]Quintile Ims, United Kingdom; [9]Health Search, Italy; [10]GlaxoSmithKline, Uxbridge, United Kingdom; [11]The Blizard Institute, London, United Kingdom*
Email: myriam.n.alexander@gsk.com

Background and Aims: International guidelines for the management of non-alcoholic fatty liver disease (NAFLD) recommend the use of non-invasive liver tests (NILTs). NILTs utilise routinely collected clinical parameters as a primary screen for fibrosis risk and require very little or no extra investigations. We aimed to assess the proportion of patients in whom each NILT could be calculated, the concordance between the tests in terms of risk categories and the differences between European territories in the risk category of patients with a recorded diagnosis of NAFLD.
Method: We combined data on NAFLD patients from The Health Improvement Network (THIN, UK), the Integrated Primary Care Information (IPCI, The Netherlands), the Health Search Database (HSD, Italy) and the Information System for Research in Primary Care (SIDIAP, Spain). AST/ALT Ratio, FIB-4, NAFLD Fibrosis Score (NFS) and BARD Score were calculated and categorised using the recommended cut-offs. Markers were compared to NFS in patients with complete data on all four markers.
Results: Of the total 143,384 NAFLD patients included, AST/ALT ratio could be calculated for 54.4% patients, followed by FIB-4 (46.8%), BARD (36.3%) and NFS (8.1%). AST/ALT ratio was the most complete in HSD (67%), FIB-4 and BARD score were the most complete in SIDIAP (62.8% and 46.9% respectively), and NFS was the most complete in THIN (11.4%). In the 11,731 (8.1%) patients with complete data, 50.3% and 8.8% were low and high risk respectively using NFS; 59.6% and 7.6% using FIB4; 42.8% and 32.5% using AST/ALT ratio, and 33.3% and 66.7% using BARD score. There was good concordance between NFS and FIB-4 for patients in high or low risk categories (Table 1).

Table 1: Concordance between NILTs

	Low NFS N= 5897		Indeterminate NFSN = 4808		High NFSN = 1026		N = 11731	
	N	%	N	%	N	%	N	%
FIB-4								
Low	5069	86.0	1849	38.5	79	7.7	6997	59.6
Indeterminate	822	13.9	2586	53.8	428	41.7	3836	32.7
High	6	0.1	373	7.8	519	50.6	898	7.7
AST/ALT								
Low	3235	54.9	1591	33.1	189	18.4	5015	42.7
Indeterminate	1392	23.6	1299	27.0	215	21	2906	24.8
High	1270	21.5	1918	39.9	622	60.6	3810	32.5
BARD								
Low	3014	51.1	827	17.2	64	6.2	3905	33.3
High	2883	48.8	3981	82.8	962	93.8	7826	66.7

Conclusion: Less than half of NAFLD patients had sufficient data to calculate most NILTs. Good concordance at extremes of risk suggests that the choice of NILT should be pragmatic and based on availability of data. Lack of concordance in patients with indeterminate risk supports use of a second, alternative modality (e.g. biomarker or transient elastography) in this group.

FRI-424

Algorithm to identify patients with an activity grade > 2 in type 2 diabetic patients with non-alcoholic fatty liver disease (NAFLD)- development in a large prospective multicenter UK study

P. Eddowes[1], M. Allison[2], E. Tsochatzis[3], Q. Anstee[4], D. Sheridan[5], I.N. Guha[6], J. Cobbold[7], Valérie Paradis[8], P. Bedossa[8], P. Newsome[1].
[1]NIHR Birmingham Liver Biomedical Research Unit and Centre for Liver Research, University of Birmingham, Birmingham, United Kingdom; [2]Liver Unit, Cambridge Biomedical Research Centre, Addenbrookes Hospital, Cambridge, United Kingdom; [3]UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom; [4]Institute of Cellular Medicine, Newcastle-upon-Tyne, United Kingdom; [5]Institute of Translational and Stratified Medicine, Plymouth University, Plymouth, United Kingdom; [6]NIHR Nottingham Biomedical Research Centre, NHS Trust and University of Nottingham, Nottingham, United Kingdom; [7]Department of Gastroenterology, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Oxford, United Kingdom; [8]Department of Pathology, Physiology and Imaging, Beaujon Hospital Paris Diderot University, Clichy, France
Email: p.n.newsome@bham.ac.uk

Background and Aims: To address the problem of high screen failure rates NAFLD clinical trials, we aimed to develop a simple algorithm to detect the presence of NASH with an activity (A) from SAF score >2 in patients with diabetes.

Method: FibroScan examination was undertaken within 2 weeks of a clinically indicated liver biopsy (LB) for suspected NAFLD. Recruitment took place (Mar 2014-Jan 2017) at seven UK centres. LB were read in a blinded manner with consensus by two expert pathologists using the (steatosis, activity, fibrosis) SAF score. Activity was the sum of ballooning (graded 0-2) and lobular inflammation (graded 0-2) scores. NASH was diagnosed using the FLIP algorithm. Only those patients with T2DM were considered in this analysis.

An algorithm was developed to identify patients with A > 2 with the following objectives:

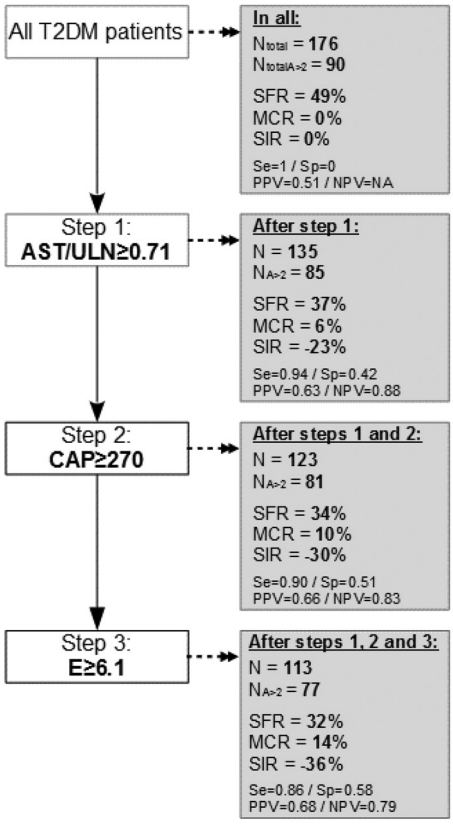
- Improve the screen failure rate (SFR = 1-PPV) of at least 30%,
- Keeping the missed cases rate (MCR = 1-sensitivity (Se)) below 15%.

The following steps were repeated 3 times:

(1) Univariable analysis between the patients with A > 2 and the bio-clinical parameters (E, CAP (controlled attenuation parameter), Fib-4, NAFLD fibrosis score, Forn score, BARD score, AST to Platelet Ratio Index (APRI), body mass index (BMI), age, liver enzymes normalized by the upper limits for normal (ULN), fasting glucose, lipid parameters, platelet, albumin, creatinine, urea, phosphatase alkaline, ferritin, hypertension, hypercholesterolemia and gender),
(2) Keep for comparison parameters significantly different in the target patients (at the given step+those initially significantly associated),
(3) Compute cutoffs based on high Se ≥ 0.95 for all parameters in the comparison list,
(4) Select the parameters that has the highest sum Se+specificity (Sp),
(5) Exclude patients with parameters value < cutoff,
(6) Compute performances: SFR and MCR.

Results: Among the 408 patients who completed the study, 188 were diabetic (46%). 176 were considered in the present analysis due to missing data. 49% were female, with a median age 58 [IQR 14] years and BMI 34.4 [8.7] kg/m². 77% had NASH. 51% had A > 2.

The algorithm was devised with the 3 optimally determined parameters: ALT /ULN ≥ 0.71, CAP ≥ 270 dB/m and E ≥ 6.1 kPa. Performance is presented in the figure below.



Legend:
SFR: screen failure rate (1-PPV)
MCR: missed cases rate (1-Se)
*SIR: screen improvement rate ((N-Ntotal)/Ntotal*100)*
Se: sensitivity / Sp: specificity
PPV-NPV: positive and negative predictive values
ULN: upper limit of normal

Conclusion: A simple algorithm based on FibroScan E, CAP and ALT was developed to improve detection patients with A > 2 in NAFLD diabetic patients. If applied as a pre-screening tool in clinical trials, it

improved the SFR by 35% and reduced the number of patients that would undergo a LB by 35% with missed cases being below 15%.

FRI-425

Noninvasive mapping of fibrosis and inflammation in nonalcoholic fatty liver disease: isolating fibrogenesis in the Space of Disse with MRI R2 multicomponent relaxometry

P. Clark[1], W. Chua-Anusorn[1], C. Oliveira[2], M. Rocha[3], F.J. Carrilho[2], F. Lima[4], V. Alves[4], B. Oliveira[3], H.L. Filho[3]. *[1]MagnePath Pty Ltd, Perth, Australia; [2]Universidade de Sao Paulo, School of Medici, Sao Paulo, Brazil; [3]Universidade de Sao Paulo, Department of Radiology, Sao Paulo, Brazil; [4]Universidade de Sao Paulo, Department of Pathology, Sao Paulo, Brazil*
Email: paul@magnepath.com

Background and Aims: Magnetic resonance relaxometry techniques sensitive to the increase in extracellular water with fibrosis and inflammation offer MRI biomarker maps of these pathologies. However, blood vessels in the maps require thresholding or exclusion by defining vessel-free regions, the placement of which is hampered by the heterogeneity of fibrosis and inflammation in the liver.
Our aim is to isolate the Space of Disse (focal to fibrogenesis) by eliminating contribution of the blood pool in extracellular water fraction maps. Moreover, relaxation parameters for the Space of Disse and blood pool may provide further biomarkers for discriminating fibrosis from inflammation.
Method: 109 NASH patients with liver biopsy were selected within 6 months for MRI exam. A spoiled multi-gradient echo sequence was used to derive fat fraction maps, and a multi-spin echo sequence was used for R2 multicomponent relaxometry (3T Philips Achieva, ~8 minutes). Images were analysed by a radiologist and physicist with ~15 years of experience each in liver imaging. Biopsies were reviewed by a pathologist with 15 years of experience using the NASH-CRN score. In total, 104 paired biopsy and MRI results were obtained. 16 volunteers with no known liver disease were used for control.
Results: MRI fat fraction (ρ_{fat}) was well correlated with biopsy fat grading (Spearman's $r_s = 0.72$), and quantified steatosis ($\rho_{fat} > 5.6\%$) with a specificity (Sp) of 93% and sensitivity (Sn) of 92% (AUROC = 0.98). The proton density of free water associated with blood in the sinusoids and vessels (ρ_{blood}) was ~16% regardless of fibrosis score ($r_s = 0.00$). The proton density of water bound to the extracellular matrix and endothelium in the Space of Disse (ρ_{Disse}) was well correlated with fibrosis, ballooning, and lobular inflammation (r_s = 0.80, 0.66 and 0.52 respectively). ρ_{Disse} was able to distinguish fibrosis from healthy liver with a Sp of 93% and Sn of 87% (AUROC = 0.95). 2-parameter predictive models incorporating ρ_{Disse} and the next most significant MR parameter for a given pathology showed improved discrimination of healthy liver from fibrosis (Sp = 94%, Sn = 87%, AUROC = 0.96), ballooning (Sp = 90%, Sn = 83%, AUROC = 0.94), and lobular inflammation (Sp = 94%, Sn = 94%, AUROC = 0.98).
Conclusion: MRI R2 multicomponent relaxometry isolating the Space of Disse from the liver blood pool provides improvements in quantifying fibrosis and inflammation, and allows entire liver slices to be assessed.

FRI-426

The EPoS staging system is a reproducible 7-tierfibrosis score for NAFLD adapted both to glass slides and digitized images (e-slides)

P. Bedossa[1], J. Arola[2], D. Susan[3], A.S. Gouw[4], G. Maria[5], K. Lackner[6], P. Schirmacher[7], L.M. Terracciano[8], Q. Anstee[9], V. Ratziu[10], T. Dina[11]. *[1]University Paris-Diderot, Pathology, Paris, France; [2]University of Helsinki, Pathology, Helsinki, Finland; [3]Cambridge University Hospitals, Pathology, Cambridge, United Kingdom; [4]University Medical Center Groningen, Dept of Pathology & Medical Biology, Groningen, Netherlands; [5]University of Padova, Dept of Pathology, Padova, Italy; [6]Medical University of Graz, Institute of Pathology, Graz, Austria; [7]Universitätsklinikum Heidelberg, Institute of Pathology, Heidelberg, Germany; [8]Institute of Pathology, Molecular Pathology Division, Basel, Switzerland; [9]Institute of Cellular Medicine, Newcastle-upon-Tyne, United Kingdom; [10]Hôpital Pitié Salpêtrière and Université Pierre et Marie Curie, Hôpital Pitié Salpêtrière and Université Pierre et Marie Curie, Paris, France; [11]Newcastle University, Institute of Cellular Medicine, Newcastle, United Kingdom*
Email: pierre.bedossa@inserm.fr

Background and Aims: Liver fibrosis is a major independent prognostic factor in NAFLD. Despite its wide use, the NASH CRN staging system is insufficiently accurate in advanced fibrosis stages (stages 3 and 4) which are the ones most strongly linked to liver-related outcomes. The aim of the study was to develop and validate a linear and expanded staging system that mirrors more accurately the different stages of liver fibrosis during NAFLD progression
Method: In a first step, 9 European liver pathologists (EPoS Histopathology consortium) and 2 hepatologists jointly reviewed a set of NAFLD liver biopsies to define consensually the various stages of the new EPOS score of fibrosis. Then, each participant reviewed independently the same set of 45 cases (glass slides) with the EPoS staging system to evaluate inter-observer variability. Three months later, the glass slides were digitized (e-slides) and re-evaluated electronically by each pathologist, blinded to their first assessment on glass slides. The inter-observer agreement was evaluated using Kappa score.
Results: The EPoS staging system includes 7 stages (from 0 to 6) that cover the whole spectrum of fibrosis in NAFLD. Compared to NASH CRN, stage 1a, b and c were grouped together while stage 3 and 4 were each expanded into 2 stages. The inter-observer agreement for EPoS staging system using glass slides was almost perfect (Kappa score = 0.84) when only pathologists were considered. It remained substantial when both pathologists and hepathologists were considered together (Kappa score = 0.72). When e-slide reading was considered, inter-observer agreement between pathologists was almost perfect (0.80). When comparing Epos scoring on glass slide and on e-slide, agreement was also almost perfect (mean Kappa coefficient = 0.85, range 0.79–0.89)
Conclusion: The EPoS fibrosis staging system provides a robust and expanded scoring system which might prove useful to assess fibrosis variation in natural history or therapeutic trials. E-slides provide material as suitable as glass slides for staging fibrosis reproducibly. The relevance of the EPoS staging system is currently being evaluated in relation to disease outcome.

FRI-427

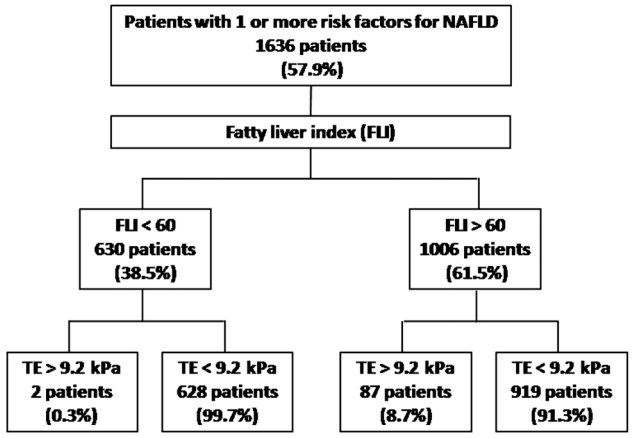
An algorythm for screening for liver fibrosis in primary care using population-based data

Llorenç Caballeria[1], I. Graupera[2], G. Pera[1], I. Arteaga[1], Lluís Rodríguez[1], Núria Fabrellas[3], C. Expósito[1], P. Torán[1], J. Caballería[2], P. Ginès[2]. *[1]Institut Català de la Salut, USR Metropolitana Nord. IDIAP Jordi Gol, Mataró, Spain; [2]Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBPAS). Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD). Barcelona, Liver Unit, Barcelona, Spain; [3]Universitat de Barcelona, Escola d'Infermeria, Barcelona, Spain*
Email: lcaballeria.bnm.ics@gencat.cat

Background and Aims: Liver cirrhosis is one of the main causes of death worldwide. Currently, most cases of cirrhosis are diagnosed when patients develop complications. Diagnosis of liver diseases in early stages of fibrosis, may help prevent development of complications and improve survival. In that regard, screening for liver fibrosis in primary care may be a useful approach. Although several algorithms have been proposed, they are not built on data from population-based studies.
Method: We used data from a population-based study including 3014 subjects aged 18–75 years, without known liver disease, identified randomly from the general population through phone calls. The assessment of liver fibrosis was performed by measuring liver stiffness (LS) with transient elastography (TE). The best cut-off of LS

for diagnosis of liver fibrosis (F2 or greater) was 9.2 kPa and was determined by analyzing LS in 92 subjects in whom liver fibrosis was assessed by liver biopsy.

Results: The overall prevalence of liver fibrosis in the whole series was 3.2%, and was due to non-alcoholic fatty liver disease (NAFLD) in most cases. The prevalence of liver fibrosis in patients with at least one risk factor for NAFLD (obesity, type-2 diabetes, hyperlipidemia, arterial hypertension or metabolic syndrome) was 5.0%, compared to only 0.4% in patients with no risk factors (1,269 subjects, 42.1%). We then analyzed the accuracy of the following variables in predicting liver fibrosis in patients with risk factors for NAFLD: AST/ALT, NAFLD fibrosis score, FIB-4, and FLI (fatty liver index, a score that estimates the amount of fat in the liver that includes body mass index, waist circumference, and serum GGT and triglycerides). Among these factors, FLI had the best negative predictive value 99.7%. Patients with a FLI value lower than 60 had very low prevalence of liver fibrosis (2 out of the 628 subjects, 0.3%). By contrast, the prevalence of liver fibrosis among subjects with FLI > 60 was of 8.6% ($p < 0.001$). With this approach, only 35.7% of the population from our series (18–75 years) would have to be screened for presence of liver fibrosis with TE. The algorithm performed equally well if subjects younger than 45yrs were excluded.



NAFLD, nonalcoholic fatty liver disease.
FLI, fatty liver index
TE, transient elastography

Conclusion: An algorithm based on assessment of liver fibrosis using TE in subjects with risk factors of NAFLD and FLI > 60 allows the identification of the majority of subjects with liver fibrosis and reduces markedly the number of subjects to be screened.

FRI-428

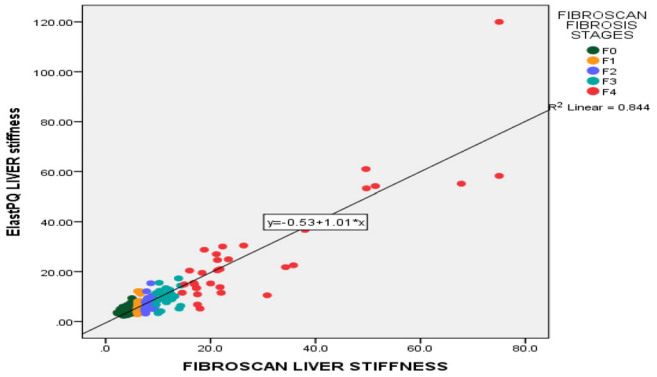
Comparison of ElastPQ Shear-wave Elastography (ElastPQ-SWE) and FibroScan Transient Elastography (F-TE) for liver fibrosis staging in patients with NAFLD

D. Roccarina, L.I. Prat, M. Guerrero, E. Buzzetti, M. Rosselli, M. Pinzani, E. Tsochatzis. *UCL Institute of Liver and Digestive Health, Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom*
Email: davideroccarina@gmail.com

Background and Aims: Shear wave Elastography with ElastPQ (ElastPQ-SWE) is a recently introduced elastography-based technique for non-invasive fibrosis assessment.
We compared liver stiffness evaluation by ElastPQ-SWE and Fibroscan (F-TE) in a cohort of consecutive patients with NAFLD. We further evaluated the performance of ElastPQ-SWE in a subgroup of patients with available histology.

Method: Anthropometric parameters (weight, height, BMI and waist circumference (WC)) were measured together with routine bloods including a lipid profile. Transient elastography (TE) was measured by FibroScan (Echosens) and ElastPQ-SWE (Affiniti 70G, Philips) in all recruited patients.

Results: We enrolled 319 consecutive patients with NAFLD, mean age 54 ± 13y, BMI 31.7 ± 5.8 kg/m^2, waist circumference (WC) 107 ± 15 cm, 56.3% male, 44% with diabetes, 55.7% hypertension, 81% hyperlipidaemia.
ElastPQ had a good correlation with F-TE (Spearman's = 0.740, $p < 0.0001$), which was better for mild and moderate stages of fibrosis (Figure 1). A ≥2 kPa difference between the two techniques was found in 89 patients. On the univariate analysis predictors of such a difference were diabetes ($p = 0.004$), BMI ($p = 0.032$), AST (0.021) and F-TE ≥ 10 kPa ($p < 0.0001$) compatible with advanced fibrosis. On the multivariate analysis the only independent predictor was F-TE ≥ 10 kPa (OR: 6.891, 95% CI 3.538–13.422, $p < 0.0001$).



In the subgroup of 112 patients with available histology, the distribution of fibrosis was as follow: F0 = 14 (12%), F1 = 40 (36%), F2 = 21 (19%), F3 = 17 (15%), F4 = 20 (18%).

	ElastPQ				FIBROSCAN			
	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUC	Cut-off (kPa)	Sensitivity (%)	Specificity (%)	AUC
F ≥ 2	6.8	81	76	0.855	7.9	82	72	0.810
F ≥ 3	8.2	89	82	0.927	10.1	76	83	0.878
F4	12.5	100	93	0.992	13.2	86	87	0.935

The optimal cut-off values of ElastPQ-SWE for individual stages of fibrosis were lower than those of F-TE. ElastPQ showed the same diagnostic performance for F ≥ 2 and a better diagnostic performance for F ≥ 3 and F4 compared to F-TE (Table 1).

Conclusion: ElastPQ and F-TE showed a good correlation in patients with NAFLD, which is better for low values of liver stiffness. The optimal cut-off values of ElastPQ are lower than those of F-TE for individual stages of fibrosis. ElastPQ seems to have a better diagnostic accuracy than F-TE in diagnosing advanced fibrosis and cirrhosis but this finding needs to be confirmed in larger cohorts.

FRI-429

Establishing reliability criteria forLiver ElastPQ Shear-wave Elastography (ElastPQ-SWE): Comparison between 3, 5 and 10 measurements

D. Roccarina, L.I. Prat, M. Guerrero, E. Buzzetti, M. Rosselli, A. Marshall, D. Thorburn, M. Pinzani, E. Tsochatzis. *UCL Institute of Liver and Digestive Health, Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom*
Email: davideroccarina@gmail.com

Background and Aims: Shear wave Elastography with ElastPQ (ElastPQ-SWE) is a recently introduced elastography-based technique for non-invasive assessment and staging of liver fibrosis. However, despite its increasing use there is a lack of validated reliability criteria for the liver stiffness measurement and thus the FibroScan criteria are currently applied.

We evaluated the reliability of 5 and 3 measurements compared to 10 measurements in a cohort of patients with different aetiologies of liver disease.
Method: All patients underwent liver stiffness measurement using ElastPQ-SWE (Affiniti 70G, Philips). The average, median, standard deviation (SD) and SD percentage (SD%) of 3, 5 and 10 measurements were collected for each patient and compared to each other.
Results: We enrolled 334 consecutive patients with different liver disease aetiologies (NAFLD, PBC, PSC and AIH). The median kPascal (kPa) value of average, median, SD and SD% for 10, 5 and 3 measurements were 5.58, 5.43, 1.27, 23–5.44, 5.47, 1.17, 19 and 4.72, 4.8, 0.55, 11, respectively. The correlation of averages and medians was better between 10 and 5 measurements (Spearman's 0.958 and 0.944, respectively) than between 10 and 3 measurements (Spearman's 0.932 and 0.922, respectively).
The difference of SD and SD% was significant comparing 10 measurements to 5 and 3. However, the difference of averages and medians was significant only in the comparison between 10 and 3 measurements. No significant difference of averages and medians was found between 10 and 5 measurements when considering NAFLD and other aetiologies separately. (Tab.1)

N. of ElastPQ measurements	ElastPQ 10	ElastPQ 5	P value	ElastPQ 10	ElastPQ 3	P value
Average	5.58	5.44	0.573	5.58	4.72	<0.0001
Median	5.43	5.47	0.575	5.43	4.8	<0.0001
SD	1.27	1.17	0.001	1.27	0.55	<0.0001
SD%	23	19	<0.0001	23	11	<0.0001

Conclusion: The median of 5 valid liver stiffness measurements using ElastPQ-SWE does not significantly differ from 10 measurements and is sufficient for the reliable estimation of liver stiffness using this technique.

FRI-430

Gender differences in body composition in lean and overweight non-alcoholic fatty liver disease: The Rotterdam Study

L. Alferink[1], K. Trajanoska[2], N. Erler[1,3], J. Schoufour[2,4], R. de Knegt[5], A. Ikram[4], H. Janssen[6], O. Franco[4], H. Metselaar[4], F. Rivadeneira[2,4], S.D. Murad[1]. *[1]Erasmus Medical Centre, Hepatology, Rotterdam, Netherlands; [2]Erasmus Medical Centre, Internal medicine, Rotterdam, Netherlands; [3]Erasmus Medical Centre, Global Public Health, Rotterdam, Netherlands; [4]Erasmus Medical Centre, Epidemiology, Rotterdam, Netherlands; [5]Erasmus MC, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [6]University Health Network, Toronto, Canada*
Email: l.alferink@erasmusmc.nl

Background and Aims: Body composition is important in identifying the risk of NAFLD. Yet, evidence on the association between muscle mass, fat mass, fat distribution, and NAFLD is scarce. We therefore aimed to study the body composition, assessed by Dual-Energy X-Ray Absorptiometry (DXA), in relation to lean and overweight NAFLD, while accounting for known risk factors.
Method: Participants in the population-based Rotterdam Study underwent an extensive work-up with DXA and ultrasonography. NAFLD was defined as hepatic steatosis in absence of alcohol abuse, steatogenic drug use and viral hepatitis. Skeletal muscle index (SMI) was defined as appendicular lean mass/height^2. Fat mass (FM) was adjusted for height and fat free mass (FFM) and vice versa, to derive FM and FFM residuals, FMr and FFMr respectively. All analyses were stratified by sex and BMI (at 25 kg/m^2) and adjusted for (1) age; (2) BMI, weight and height, or weight only; 3) socio-demographic, lifestyle, and metabolic confounders; and 4) waist-to-hip ratio (WHR) in stepwise logistic regression.
Results: We included 4455 Caucasian participants (57% women) with a mean age of 69 ± 9 years and BMI of 27 ± 4 kg/m^2. NAFLD was present in 1552 participants (35%), of which 153 were lean and 1399 overweight. SMI (in kg/m^2) was lowest in the lean NAFLD group (6.6 vs. 8.0 in overweight NAFLD, and 7.3 in no NAFLD; $p < 0.001$). An increase in SMI was consistently associated with less NAFLD in lean women (OR 0.5 CI 0.3–0.9), but not in overweight women ($p = 0.17$), nor in lean ($p = 0.88$) or overweight men ($p = 0.12$). Sensitivity analyses using alternative proxies for SMI, adjusting for weight and fat mass, yielded similar results. FMr was associated with both lean (OR 2.3 CI 1.6–3.2) and overweight NAFLD in women (OR 1.2 CI 1.0–1.4), and with overweight NAFLD in men (OR 1.3 CI 1.1–1.5) after adjustment for well-known confounders. FMr association attenuated after further adjustment for WHR, particularly in men, in which it did not remain significant. FFMr was associated consistently with less NAFLD in lean women only (OR 0.6 CI 0.4–0.8).
Conclusion: Body composition is different in lean and overweight NAFLD, particularly in women, in which both an excess of fat mass and a lack of muscle mass were associated with NAFLD. In men, fat distribution, measured by WHR, appears important. These findings could help identify NAFLD in lean individuals and add to the rationale of resistance training without the aim of weight loss in this group.

FRI-431

New diagnostic method for hepatic steatosis using attenuation measurement by B mode ultrasound: Comparison with controlled attenuation parameter

Y. Koizumi[1], H. Masashi[1], N. Yada[2], T. Nobuharu[3], O. Nakashima[4], N. Izumi[3], M. Kudo[2], Y. Hiasa[1]. *[1]Ehime University Graduate School of Medicine, Departments of Gastroenterology and Metabology, Toon City, Japan; [2]Faculty of Medicine, Kindai University, Department of Gastroenterology and Hepatology, Higashiosaka City, Japan; [3]Musashino Red Cross Hospital, Department of Gastroenterology and Hepatology, Tokyo, Japan; [4]Kurume University Hospital, Department of Clinical Laboratory Medicine, Kurume-city, Japan*
Email: masashihirooka@gmail.com

Background and Aims: Findings such as hepatic kidney contrast etc. have been used to diagnose fatty liver in B mode ultrasound, but they are based on subjective interpretation by the operator, and diagnostic accuracy is unsatisfactory. In recent years, it has become possible to measure hepatic steatosis (Controlled Attenuation Parameter: CAP) by measuring liver hardness using vibration-controlled transient elastography (VCTE) and attenuation of the ultrasonic signal. However, since VCTE cannot observe the measured section in real time, it has the disadvantage that it cannot be measured in postoperative cases or ascites. To overcome these disadvantages, we have developed a function (Attenuation: ATT) that transmits ultrasonic waves of different frequency components when measuring in B mode, and it estimates hepatic steatosis from the difference in attenuation of the received signal. The aim was to clarify the usefulness of ATT by comparing fat quantitative diagnosis by ATT and by CAP.
Method: All participants provided written, informed consent, and the study protocols were approved by the institutional ethics committee. Liver biopsies were performed from July 2015–March 2017, and 366 ATT and 105 CAP measurements were conducted. ATT measurements were performed five times with the ultrasonic diagnostic apparatus (HI VISION Ascendus; Hitachi, Ltd., Tokyo, Japan) with a convex probe (EUP-C715), avoiding the vessels in the liver from the right intercostal space, and the median was calculated. The CAP measurement was measured using M and XL probes. Steatosis grades obtained from pathological tissues were compared with the ATT and CAP values.
Results: The steatosis grades of the cases were: S0 303 cases; S1 43 cases; S2 14 cases; and S3 15 cases. In all cases, ATT measurement was possible. The area under the receiver operating characteristic curve (AUC-ROC) for ≥ S1 was 0.77, 0.80, and 0.83 for ATT, CAP M probe, and CAP XL probe, respectively. The AUC-ROC for ≥ S2 was 0.85, 0.83, and 0.84, respectively. The AUC-ROC for S3 was 0.95, 0.98,

and 0.92, respectively. Significant differences in AUC-ROC between ATT and CAP were examined by the DeLong test, and no significant differences were found for ≥ S1 (ATT vs M probe: p = 0.257, ATT vs XL probe: p = 0.061), ≥S2 (ATT vs M probe: p = 0.385, ATT vs XL probe: p = 0.717), and S3 (ATT vs M probe: p = 0.515, ATT vs XL probe: p = 0.143). From these results, the diagnostic ability for hepatic steatosis was considered to be comparable between ATT and CAP.

Conclusion: The steatosis diagnostic grade ability of ATT was similar to that of CAP. ATT does not require dedicated equipment for lipid diagnosis, it can be measured simultaneously with normal observation in B mode, and it is a useful modality considered to be measurable even in cases where measurement is impossible or difficult by CAP.

FRI-432

Evaluation of SOMAscan as a discovery platform to identify noninvasive protein biomarkers for diagnosis and monitoring of NASH

M. Lai[1], T. Libermann[1], M. Charlton[2], A.M. Diehl[3], L. Ngo[1], S. Dillon[1], E. Lawitz[4], N. Chalasani[5], B. Hameed[6], S. Caldwell[7], M. Rinella[8], T. Nguyen[9], A. Billin[9], S. Djedjos[9], M. Subramanian[9], R. Myers[9], Z. Goodman[10], R. Loomba[11], N. Afdhal[1]. *[1]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, United States; [2]University of Chicago, Chicago, United States; [3]Duke Clinical Research Institute, Durham, United States; [4]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, United States; [5]Indiana University School of Medicine, Indianapolis, United States; [6]University of California San Francisco, San Francisco, United States; [7]University of Virginia, Charlottesville, United States; [8]Northwestern Medicine, Chicago, United States; [9]Gilead Sciences, Foster City, United States; [10]Inova Fairfax Hospital, Falls Church, United States; [11]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States*
Email: stephen.djedjos@gilead.com

Background and Aims: Circulating proteins that are secreted, shed, or leak from the liver may reflect hepatic pathophysiology and are potentially useful biomarkers for NASH. Our aim was to evaluate the utility of SOMAscan, an aptamer-based proteomics platform, for identifying serum proteins associated with NASH-related liver histology and monitoring treatment response.

Methods: Using the SOMAscan assay (SomaLogic; Boulder, CO), serum proteomic signatures were analyzed in 72 subjects with NASH (NAS ≥ 5 and NASH CRN F2-3 fibrosis) enrolled in a Phase 2 trial of selonsertib (SEL). Subjects were treated with SEL alone or in combination with simtuzumab (SIM), or SIM alone for 24 weeks (W24). SOMAscan was assayed at baseline (BL) and W24, and also in 74 NASH subjects who failed screening due to ineligible fibrosis stage (F0-1, F4). Associations between the 1,310 proteins detected with SOMAscan and centrally-read liver histology (NAS and NASH CRN fibrosis stage) were assessed using both Kruskal-Wallis and Jonckheere-Terpstra trend tests. Multivariate analyses using a two-step approach were performed to combine markers for the discrimination of F0-2 vs. F3-4 fibrosis at BL, and prediction of ≥1-stage/grade improvements in fibrosis and NAS components at W24.

Results: Univariate analysis identified 28 proteins significantly associated with fibrosis stage and 32 proteins associated with the NAS at BL (all p < 0.001). Multivariate analysis identified a panel of 7 proteins at BL (C7, CL-K1, IGFBP7, spondin 1, IL-5Ra, MMP-7, and TSP2) that accurately discriminated between early and advanced fibrosis (F0-2 [n = 72] vs F3-4 [n = 74]: AUROC 0.83 [95% CI 0.77, 0.90]). Longitudinal changes in a panel of 7 proteins (PTEN, CD70, caspase 2, cathepsin H, LAG1, PDXK, and GITR) accurately predicted fibrosis improvement at W24 (AUROC 0.90 [95% CI 0.83, 0.98]; Figure). Longitudinal analysis of other circulating proteins revealed additional panels that effectively identified improvements in hepatocellular ballooning (AUROC 0.97 [95% CI 0.93, 1.00]), lobular inflammation (AUROC 0.88 [0.78, 0.98]), or hepatic steatosis (AUROC 0.89 [0.82, 0.97]).

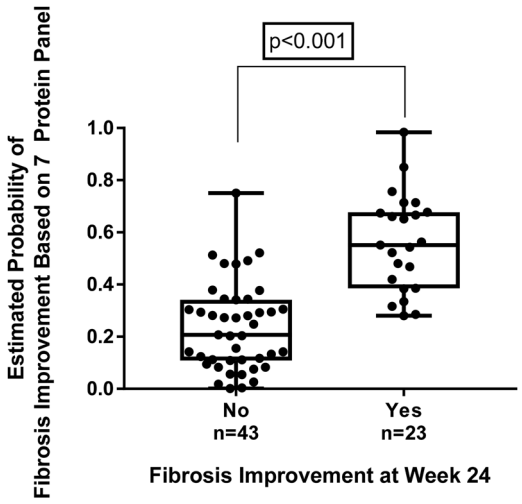


Figure 1: SOMAscan identified a panel of 7 serum proteins that accurately predicted fibrosis improvement after 24 weeks of SEL treatment in subjects with NASH.

Conclusion: The SOMAscan platform identified novel circulating protein biomarkers that correlated with disease severity and were responsive to changes in liver histology in patients with NASH. The utility of these protein biomarkers for the diagnosis and monitoring of NASH requires validation in future studies.

FRI-433

Electronic-nose breath print distinguishes non-alcoholic fatty liver disease from healthy lean control: A pilot study

R. Sinha[1], I. Gallagher[2], K.A Lockman[1], R. Chamuleau[3], A. Jaap[4], P. Hayes[1], J. Plevris[1]. *[1]Royal Infirmary and The University of Edinburgh, Hepatology Laboratory and Centre of Liver and Digestive Diseases, Edinburgh, United Kingdom; [2]University of Stirling, Health & Exercise Research Group, Stirling, United Kingdom; [3]Academic Medical Centre, University of Amsterdam, Surgical Laboratory and Tytgat Institute for liver and intestinal research, Amsterdam, Netherlands; [4]Royal Infirmary and The University of Edinburgh, Edinburgh Centre for Endocrinology & Diabetes, Edinburgh, United Kingdom*
Email: rohit.sinha@nhs.net

Background and Aims: Human breath contains numerous volatile compounds which reflect metabolic activity. Electronic nose (eNose) technology can rapidly detect these volatile metabolites to provide breath prints non-invasively. Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome. We hypothesized breath prints obtained from eNose could distinguish healthy individuals from those with NAFLD.

Method: The study was prospective single-center cohort study (ClinicalTrials.gov: NCT02950610) with training cohort and one-against all (leave-one out) cross validation verification (CVV). eNose (SpiroNose) is a custom-made device made up of five-sensor arrays each containing four sensors, previously validated in respiratory and liver disease [1, 2]. eNose on exhaled breath was performed on well characterised NAFLD patients; (a) NAFLD Child's A cirrhosis (n = 30; n = 4, liver biopsy; n = 20, endoscopic features of portal hypertension; n = 6, radiological features), (b) NAFLD non-cirrhosis [n = 30; n = 8, liver biopsy; n = 22, non-invasive markers e.g. NAFLD fibrosis score, Fib4, hyaluronic acid, transient elastography etc. and (c) self-declared healthy subjects [n = 30]. Data were analyzed using R (v 2.3.2) and Orange (v 3.4.1) software. Data reduction to 3 principal components (PCs) explained 97.8% of total variance. Data was further classified by *k*-nearest neighbor's (k-NN) algorithm, a non-parametric machine learning algorithm for classification.

Results: In patients with NAFLD cirrhosis, eNose was able to accurately classify with 100% sensitivity ($p < 0.001$, cross-validation verification [CVV] 96%) from healthy subjects, independent of age and gender. Sensor 1, Sensor 2, Sensor 3 and Sensor 4 identified NAFLD cirrhosis patients with AUC 0.96 (standard error = 0.043; $p < 0.001$), 0.89 (standard error = 0.046; $p < 0.001$), 0.98 (standard error = 0.016; $p < 0.001$) and 0.96 (standard error = 0.022; $p < 0.001$) respectively. eNose was able to differentiate between healthy from; non-cirrhotic NAFLD ($p < 0.001$, CVV 96.8%) and NAFLD cirrhotic ($p < 0.001$, CVV 95.1%). However, it could not differentiate non-cirrhotics from cirrhotic in NAFLD ($p = 0.88$). 60 participants (30 healthy and 30 NAFLD cirrhotic) were analyzed using a leave-one-out CVV for creating training sets and validation sets. This method, designed to reflect the generalization property of the k-nearest neighbor's classifier, scored a classification rate of 96%.

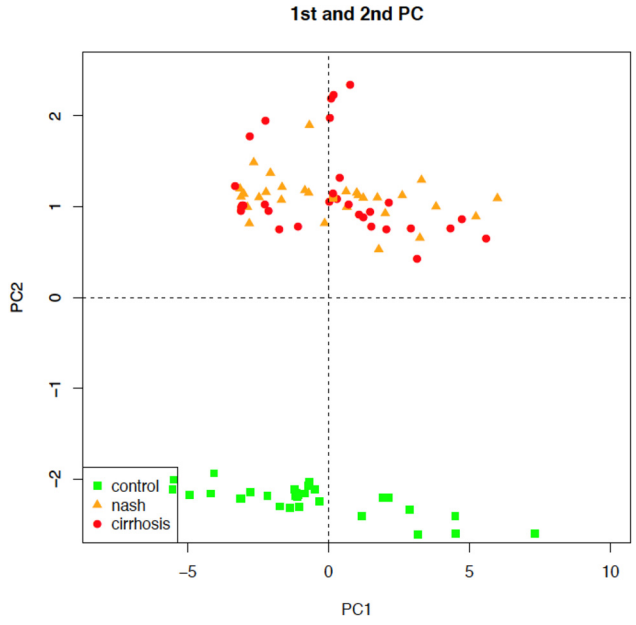


Figure 1: Principal component analysis of 3 study groups

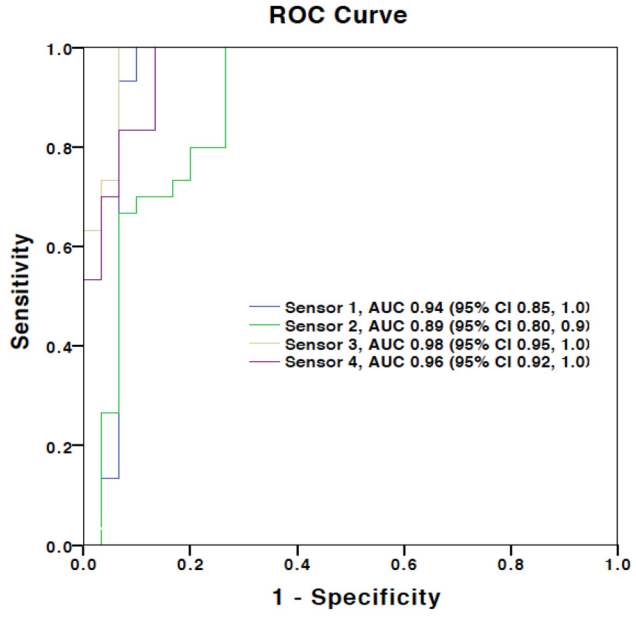


Figure 2: Individual sensor ROC curve in in discriminating NAFLD cirrhosis

Conclusion: Our study demonstrates the ability of eNose to accurately distinguish NAFLD from healthy individuals. Thus, eNose technology can provide rapid, non-invasive point-of-care screening to risk stratify patients, which can reduce the burden of liver biopsy.

FRI-434

A study of breath metabolome in Non-alcoholic fatty liver disease

R. Sinha[1], K.A Lockman[1], N. Homer[2], E. Bower[2], P. Brinkman[3], H. Knobel[4], R. Chamuleau[5], A. Jaap[6], P. Hayes[1], J. Plevris[1]. *[1]Royal Infirmary and The University of Edinburgh, Hepatology Laboratory and Centre of Liver and Digestive Diseases, Edinburgh, United Kingdom; [2]Edinburgh Clinical Research Facility and Queen's Medical Research Institute, Mass Spectrometry, Edinburgh, United Kingdom; [3]Academic Medical Centre, University of Amsterdam, Dept. Respiratory Medicine, F5-259, Amsterdam, Netherlands; [4]Philips Innovation Labs, Material Analysis, Eindhoven, Netherlands; [5]Academic Medical Centre, University of Amsterdam, Surgical Laboratory and Tytgat Institute for liver and intestinal research, Amsterdam, Netherlands; [6]Royal Infirmary and The University of Edinburgh, Edinburgh Centre for Endocrinology & Diabetes, Edinburgh, United Kingdom*
Email: rohit.sinha@nhs.net

Background and Aims: Breath-omics is gaining popularity as a method for non-invasive measure of biomarkers for various diseases. Breath metabolome is a multitude of volatile organic compounds (VOCs) reflecting pathological metabolic processes. The purpose of this study was to compare breath VOCs in patients with non-alcoholic fatty liver disease (NAFLD) and healthy controls.

Method: Breath samples were collected from well characterised NAFLD patients; a) NAFLD Child's A cirrhotics ($n = 15$; $n = 14$, endoscopic features of portal hypertension; $n = 1$, radiological feature), b) NAFLD non-cirrhosis [$n = 14$; $n = 3$, liver biopsy; $n = 11$, elevated transient elastography and fibrosis scores and c) self-declared healthy subjects [$n = 15$]. Exhaled breath collection and breath condensate analysis has been previously well described [1]. VOCs were identified using mass spectrometry analysis; comprising of abundant and trace compounds. Compounds based on the mass spectra and a peak appearing at a retention time that was consistent in all samples. The mass spectra of each compound were matched in the chromatogram and further identified using AMDIS® software. The peak areas of the compounds were collected from extracted ion chromatograms of the most dominant parent ion of the compound and the peak automatically integrated using Xcalibur®. All compound peak areas were normalised by internal standard (d8-toluene), which was added to all samples when it was analysed. Data were analysed by non-parametric ANOVA (Kruskal–Wallis) and Dunns *post-hoc*. Receiver Operating Characteristic (ROC) curves were used to determine the diagnostic accuracy of the volatiles compound.

Results: Body mass index adjusted exhaled breath levels of acetone, dimethyl sulphide, d-limonene, acetophenone and alfa-terpinene were significantly higher ($p < 0.001$, $p < 0.01$, $p = 0.005$, $p < 0.001$, $p = 0.001$, $p < 0.001$) in patients with NAFLD cirrhosis than that seen with healthy subjects. D-limonene is found to provide the most discriminatory power for NAFLD cirrhosis, AUROC = 0.91(95% CI 0.79, 1.0; standard error 0.06) (Figure 1). Additionally, breath acetone and d-limonene concentrations can differentiate NAFLD non-cirrhosis from NAFLD cirrhosis ($p < 0.001$ and $p < 0.05$). Breath acetone level can distinguish between NAFLD non-cirrhotic and NAFLD cirrhotic; AUROC = 0.88 (standard error 0.07) and achieves a sensitivity of 90% with a specificity of 70% (Figure 2).

Conclusion: Breath VOCs have a promising future as biomarkers for a non-invasive diagnostic and prognostic tool in the management of NAFLD. D-limonene and acetone can identify NAFLD non-cirrhosis from NAFLD cirrhosis with confidence. Future validation of our finding to external cohort is needed.

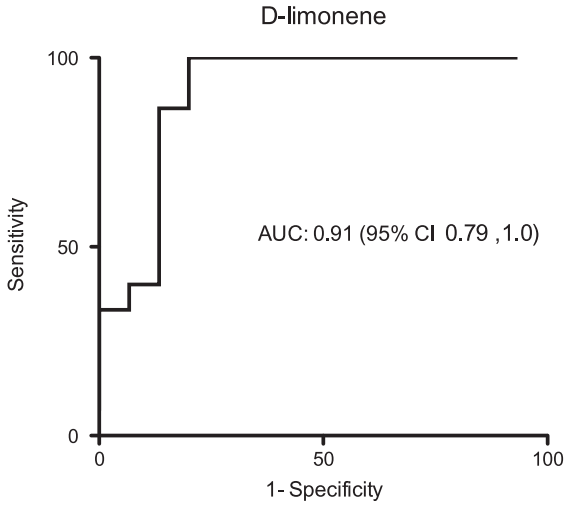


Figure 1: Receiver operating characteristic curve for D-Limonene.

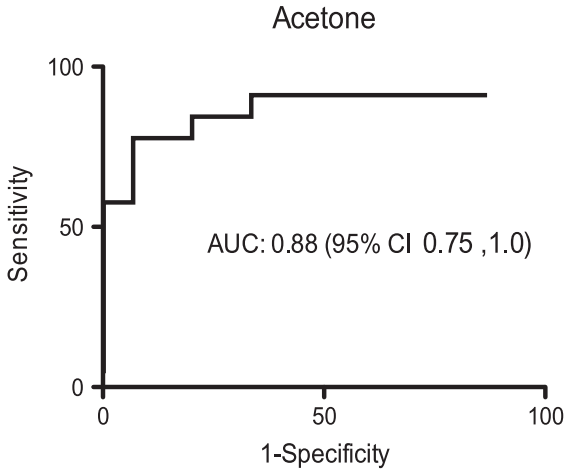


Figure 2: Receiver operating.

FRI-435

Appropriateness of inclusion criteria according to transaminases ALT in studies assessing performances of non-invasive tests in type-2 diabetes patients (T2D)

T. Poynard[1], F. Charlotte[1], V. Paradis[1], Y. Ngo[2], M. Munteanu[2], V. Peta[2], R. Pais[3], V. Ratziu[3], C. Laouenan[4], P. Stanislas[3], C. Boitard[5], D. Valla[3].
[1]APHP, Hepatology, Paris, France; [2]BioPredictive, Research, Paris, France; [3]APHP, Hepatology, France; [4]APHP, Statistics; [5]APHP, Diabetology
Email: tpoynard@teaser.fr

Background and Aims: In NASH diagnostic studies, biopsies are performed for routine clinical care in the investigation of abnormal liver function tests, often defined as "increased ALT" (iALT). This criteria, which varied according to age and gender, can impact the estimation of NASH-test performances by selecting risk factors not representative of the T2D context of use. The risk of significant fibrosis (F2F3F4), a recognized definition of significant liver disease, according to ALT value, is unknown (DiabetesCare 2017). To assess this risk, we compared T2D with and without iALT using non-invasive tests such as FibroTest (FT), routinely used in France since 2002 and validated as alternatives to biopsy for F2F3F4 diagnosis (LancetGastro 2017).

Method: We retrospectively analyzed T2D (receiving T2D treatment, or with fasting glucose > = 7, in the prospective FibroFrance cohort (NCT01927133). iALT was defined as ALT > 30 IU for men, and >20 IU for women. T2D were followed by liver tests to assess F2F3F4 with standard cut-offs (Fibrotest 0.48, Elastography TE-M, TE-XL or SWE, all 7.1 kPa). The primary endpoint was the presence of F2F3F4 ing non-iALT, and any significant difference in the main prognostic characteristics between the 2 groups: gender, age, and severity defined as the Kaplan-Meier overall survival at 10 yr. Prognostic value of iALT was also assessed after taking into account age and gender by Cox model.

Results: 230 consecutive T2D without other cause of liver diseases, were included. During a mean follow-up of 7 years 157/230 (68%) had iALT and 73/230 (32%) had non-iALT. 77 pts had at least one liver biopsy. The risk of significant liver disease in the non-iALT was not negligible, with 45% of significant activity A2A3A4 among pts with biopsy, and prevalence of F2F3F4 35%, 30% and 62%, by biopsy, FT and TE, respectively. The spectrum was significantly different, with more women, more pts younger than 65 years of age, and with a higher 10-year overall survival rate in iALT group (26 deaths) vs non-iALT group (35 deaths) (Table 1), but the significant difference disappeared when adjusted by age and female gender, risk-ratio = 0.69 (95%CI 0.40–1.16; p = 0.16).

Table 1: characteristics of T2D patients with or without increased ALT transaminases

	Increased ALT n = 133	Not increased ALT n = 97	P value
10-yr cumulative survival (95% CI)	70% (58–82)	56% (43–69)	0.02
Age younger than 65 years	95/1133 (71%)	57/97 (59%)	0.04
Female gender	65/133 (49%)	24/97 (25%)	0.0002
F2F3F4 FibroTest >0.48	58/133 (44%)	29/97 (30%)	0.04
F2F3F4 Elasticity >=7.1 kPa	62/80 (78%)	28/45 (62%)	0.10
Stage F2F3F4 FLIP-CRN biopsy	31/52 (60%)	8/23 (35%)	0.08
Grade A2A3A4 FLIP biopsy	40/52 (77%)	10/22 (45%)	0.01
No steatosis or steatosis <5% biopsy	6/54 (17%)	4/23 (11%)	0.45

Conclusion: T2D without increased ALT should be included in diagnostic studies evaluating NASH-tests to prevent a spectrum effect and a biased control population.

FRI-436

Performance and reliability of non-invasive fibrosis scores in non-alcoholic fatty liver disease with and without morbid obesity

A. Drolz, S. Wolter, M. Wehmeyer, F. Piecha, T. Horvatits, J.S.Z. Wiesch, A. Lohse, O. Mann, J. Kluwe. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
Email: a.drolz@uke.de

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is a leading etiology of chronic liver disease. Transient elastography is widely used for fibrosis-assessment, but has limitations in morbid obesity. Non-invasive scores, such as the NAFLD Fibrosis Score (NFS), are increasingly used for non-invasive fibrosis assessment.
Aim of this study was to assess the applicability and reliability of non-invasive fibrosis scores in NAFLD patients with and without morbid obesity.

Method: Patients with biopsy-proven NAFLD (143 conventional and 225 morbidly obese) were retrospectively studied. Clinical and laboratory data obtained prior to biopsy were collected, and fibrosis scores were calculated.

Results: Three hundred sixty-eight patients were analyzed. Median age was 47 years, 57% were female. Median BMI was 42.9 kg/m^2 with significant differences between our conventional and morbidly obese patients (BMI 29.0 kg/m^2 vs. 50.8 kg/m^2, p < 0.001). Overall, 42% showed mild/moderate fibrosis, and 16% advanced fibrosis (stage III/IV). All tested scores were significantly linked to fibrosis stage (p < 0.001 for all). FIB-4 (AUROC 0.904), APRI (AUROC 0.848) and NFS (AUROC 0.750) were identified as most potent predictors of advanced fibrosis, although NFS overestimated fibrosis stage in morbid obesity (Figure 1). Limiting BMI to a maximum of 40 kg/m^2 improved NFs' overall performance (AUROC 0.838). A FIB-4 value of >1.0 was

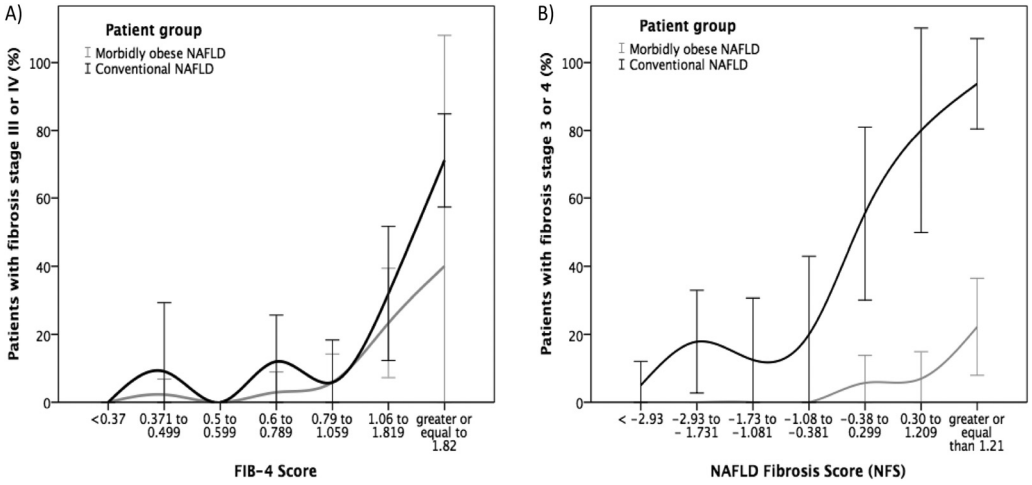


Figure: (abstract: FRI-436)

dramatically associated with presence of advanced fibrosis (OR = 29.1). FIB-4 predicted advanced fibrosis independently from age, sex, BMI and presence of morbid obesity.

Conclusion: Non-invasive scoring systems are effective tools for assessing fibrosis stage in NAFLD with and without morbid obesity. Our data suggest that FIB-4 and APRI can be applied to patients in all BMI ranges, whereas NFS may require modification in morbid obesity.

FRI-437

Controlled attenuation parameter is useful in the diagnosis of fatty liver disease and allows to identify patients with high vascular risk as well as those with advanced liver disease

M. González[1], J.A. Guerra[2], D. Escudero-García[3], María T.A. Loste[1], M. Hernández Conde[2], P. Iruzubieta[1], Ángel Estébanez[1], L. Puchades[3], E. Llop[2], J.C. Gonzalez[1], M. Serra[3], José L.C. Panero[2], J. Crespo[1].
[1]Marqués de Valdecilla University Hospital. IDIVAL. Ciberehd, Department of Gastroenterology and Hepatology; [2]Puerta de Hierro University Hospital. CIBERehd, Liver Unit; [3]University Hospital Clinic, Department of Medicine, University of Valencia, Service of Hepatology
Email: mgonzalezmtnez@gmail.com

Background and Aims: Fatty liver disease (FLD) has increased its prevalence concurrently to the rise in obesity and metabolic syndrome. Our aim is to establish FLD prevalence in Spanish general population as well as the factors associated with advanced liver disease.

Method: Population and cross-sectional study carried out between July 2015 and May 2017. Two-stage cluster sampling was performed, with stratification by gender, socioeconomic status and rural/urban area. Clinical, anthropometric and analytical data were collected. Transient elastography (TE) with controlled attenuation parameter (CAP) were performed. All subjects with abnormal liver blood test and/or TE >7 kPa underwent abdominal ultrasound and liver chronic disease etiological study.

Results: A total of 5,520 subjects were evaluated (age 49.4; male 45%). CAP was feasible in 4,761 cases, resulting in steatosis of any aetiology in 2,328 (48.9%). Diagnosis of FLD was based in CAP > 248 and/or increased liver echogenicity by ultrasound in the absence of other causes of liver disease, resulting in a prevalence of 44,8% (2420 cases). Between them, 30,8% have abnormal liver blood test and 6,3% TE >7 kPa. Most patients with high vascular risk, defined as

	Subjects without steatosis (n=2338)	P (1)	Non-advanced FLD (n=2267)	Advanced FLD (n=153)	P (1)
Male gender	865 (37)	0.00	1213 (53.5)	106 (69.3)	0.00
Age (years)	47 (20-80)	0.00	54 (18-80)	58 (23-80)	0.00
BMI	24.41 (16.42-48.55)	0.00	28.49 (16.94-47.94)	32.15 (19.31-49.13)	0.00
Normal weight	1331 (57.1)		414 (18.3)	15 (9.9)	
Overweight	790 (33.9)	0.00	1005 (44.5)	31 (20.5)	0.00
Obesity	209 (9)		838 (37.1)	105 (69.5)	
Circumference waist (cm)	83 (58-134)	0.00	97 (60-139)	119 (67-140)	0.00
sBP (mmHg)	127 (80-206)	0.00	136 (86-230)	144 (100-209)	0.00
dBP (mmHg)	78 (44-118)	0.00	82 (44-126)	85 (60-110)	0.02
Alcohol >30 g/d	132 (16)	0.018	229 (19)	38 (30.4)	0.002
S0 (CAP < 248 dB/m)	2378 (100)		65 (2.9)	9 (6)	
S1 (CAP 248-267)	0		563 (25)	19 (12.8)	0.00
S2 (CAP 268-279)	0		288 (12.8)	10 (6.7)	
S3 (CAP > 280)	0		1337 (59.3)	111 (74.5)	
Hypertension	na		210 (34.8)	67 (63.2)	0.00
DM 2	na		64 (10.6)	51 (48.6)	0.00
Hypercholesterolemia	na		244 (40.4)	58 (54.7)	0.006
Hypertryglyceridemia	na		99 (16.4)	31 (29.5)	0.001
High vascular risk	na		42 (1.9)	12 (7.8)	0.00
Abnormal liver blood test	257 (11)	0.00	649 (28.6)	97 (63.4)	0.00
ALT (U/L)	18 (3-433)	0.00	24 (4-440)	38 (8-184)	0.00
AST (U/L)	22 (8-273)	0.00	23 (9-371)	30 (13-275)	0.00
GGT (U/L)	16 (1-1204)	0.00	25 (2-1482)	47 (10-2311)	0.00
Total bilirubin (mg/dL)	0.5 (0.1-4.8)	0.00	0.4 (0.1-4.3)	0.5 (0.1-2.4)	0.00
Albumin (g/L)	4.4 (3.3-5.2)	ns	4.5 (3-6.8)	4.5 (3.1-5)	ns
Total cholesterol (mg/dL)	194 (62-311)	0.00	204 (95-366)	187 (85-361)	0.000
LDL (mg/dL)	110 (11-242)	0.00	116 (11-240)	98 (9-257)	0.00
HDL (mg/dL)	69 (28-119)	0.00	52 (22-148)	46 (20-48)	0.00
Triglycerides (mg/dL)	75 (4-964)	0.00	120 (9-1071)	591 (26-617)	0.01
HOMA-IR > 2.6	na		202 (55)	35 (68.6)	ns
HbA1c (%)	5.3 (4.2-7.9)	0.00	5.5 (4.5-10.8)	5.9 (4.8-13.7)	0.00

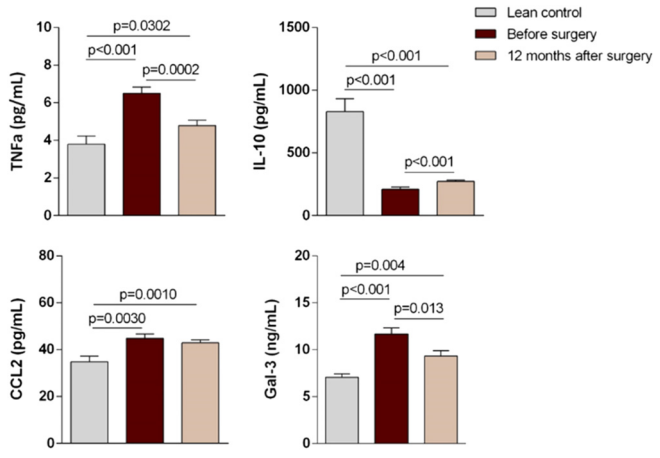
Qualitative variables: frequency (percentage). Nonparametric quantitative variables: median (range).
P (1) statistical significance between subjects with and without steatosis. P (2) statistical significance between subjects with advanced and non advanced FLD
High vascular risk: >50 years + hypertension + HOMA > 2.6 + dyslipidemia.
BMI (Body Mass Index). sPD (systolic blood pressure). sPD (diastolic blood pressure). DM2 (Diabetes Mellitus type 2). HOMA-IR (homeostasis model assessment); na (not available); ns (no statistical significance)

Figure: (abstract: FRI-437)

age >50, hypertension, dyslipidaemia and HOMA-IR >2.6, showed CAP > 280 (42/57). Age, waist circumference and the presence of diabetes mellitus were associated with advanced FLD in multivariate analysis.
Conclusion: Hepatic steatosis measurement by CAP, does not only identify patients with FLD, but can also characterise a group of patients with high vascular risk. Moreover, when it is associated to TE, allows to detect patients with advanced FLD, even in those with normal liver blood test. This high prevalence shows the need of an early diagnosis in order to plan early therapeutic strategies.

FRI-438
Effects of bariatric surgery on Non-alcoholic fatty liver disease: The role of macrophage-mediated the systemic inflammation
Noemí Cabré[1,2], F. Luciano-Mateo[1,2], P.J. Águila-Hervás[1,2], M. Català[1,2], A. Hernández-Aguilera[1,2], J. Camps[1,2], J. Joven[1,2]. *[1]Unitat de Recerca Biomèdica, Institut d'Investigació Sanitària Pere Virgili, Universitat Rovira i Virgili, Reus, Spain; [2]Instituto de Salud Carlos Iii (Grant Pi15/00285 co-founded by the European Regional Development Fund (FEDER)), Madrid, Spain*
Email: noemi.cabre@urv.cat

Background and Aims: Obesity is a pathologic condition that is characterized by a state of chronic low-grade systemic inflammation that contributes to development of comorbidities, including non-alcoholic fatty liver disease (NAFLD). The microenvironment generated by NAFLD in the liver tissue influences the proliferation and activation of a type of macrophages and the release of certain molecules that promote tissue damage. Macrophages play a major role in the immune system, especially because liver tissue homeostasis is maintained through an adequate balance of pro- and anti-inflammatory state. In order to identify potential therapeutic approaches, the aims of our study were to investigate how bariatric surgery modulates the inflammation and, in addition, whether this fact influences the pathogenesis of NAFLD.
Method: We carried out an observational, prospective, single-site and cross-sectional study with a pre-set duration of 1 year with patients who underwent bariatric surgery (n = 120) as a model of obesity-induced NAFLD and lean healthy (n = 50) as a control group. Liver biopsy and a blood collection were obtained immediately before bariatric surgery and after a 12-month period. We performed immunohistochemical, western blot and ELISA analysis to evaluate several inflammatory changes such as infiltration of macrophages (CD68) and expression/location of Chemokine (C-C motif) Ligand 2 (CCL2), Tumor Necrosis Factor alpha (TNF- alpha), Interleukin 10 (IL-10) and Galectin-3 (Gal-3).



Results: After bariatric surgery there was a significant improvement of liver tissue corresponding with a significant decrease in the presence of hepatic steatosis, acute inflammation and fibrosis after one year. These results contrasted with a significant profile change regarding the presence of macrophages in the liver, on the same line the alterations in the expression/secretion of CCL2-CCR2 axis, TNF-α, IL-10 and Gal-3. In addition, plasma levels of CCL2, TNF-α, IL-10 and Gal-3 showed significant differences after 12 months in patients who underwent bariatric surgery.
Conclusion: Bariatric surgery modulates the proliferation and activation of macrophages, especially, it modifies the secretion/release of molecules associated with the progression of NAFLD. Therefore, the expression of CCL2, TNF-α, IL-10 and Gal-3 has been proposed as possible therapeutic targets and biological markers of the stages of NAFLD.

FRI-439
Magnetic Resonance Elastography versus Transient Elastography in detection of fibrosis in nonalcoholic fatty liver disease: A systematic review and meta-analysis of individual participant date
C. Hsu[1], C. Caussy[1,2], K. Imajo[3], J. Chen[4], S. Singh[1], K. Kaulback[5], M. Le[1], J. Hooker[6], R. Bettencourt[1], M. Yin[4], C. Sirlin[6], R.L. Ehman[4], A. Nakajima[3], R. Loomba[7]. *[1]University of California at San Diego, Nonalcoholic Fatty Liver Disease Research Center, Department of Medicine, La Jolla, United States; [2]Université Lyon; [3]Yokohama City University Graduate School of Medicine, Department of Gastroenterology, Yokohama, Japan; [4]Mayo Clinic, Department of Radiology, Rochester, United States; [5]Research in Practice, Toronto, Canada; [6]University of California at San Diego, Liver Imaging Group, Department of Radiology, La Jolla, United States; [7]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States*
Email: c6hsu@ucsd.edu

Background and Aims: Magnetic resonance elastography (MRE) and transient elastography (TE) are noninvasive imaging techniques used to diagnose liver fibrosis in patients with nonalcoholic fatty liver disease (NAFLD). Previous studies comparing the efficacy of MRE versus TE have been single-center studies. Therefore, we aimed to perform a meta-analysis of individual participant data from published studies to compare the diagnostic performance of MRE versus TE for the staging of liver fibrosis in NAFLD using liver biopsy as the gold standard.
Method: A computer-aided systemic literature search of multiple databases from January 1, 2005 to September 05, 2017 identified 3 studies (Imajo et al. Gastroenterology 2016, Park et al. Gastroenterology 2017, Chen et al. Radiology 2017) with MRE and TE assessment for the detection of liver fibrosis in patients with NAFLD, using liver biopsy as a reference. Data for 318 participants, including baseline characteristics, histologic fibrosis stage, MRE, and TE measurements, were collected by contacting the study authors and of those, data from 230 participants with MRE, reliable TE measurement and liver biopsy available were included in the analysis using a pre-specified meta-analysis protocol. Through pooled analysis, the cluster-adjusted area under the curve (AUROC) of MRE and TE was calculated for the detection of each stage of fibrosis, and AUROC comparisons between MRE and VCTE were performed using the Delong test.
Results: The pooled analysis included 230 participants with biopsy proven NAFLD with mean (± sd) age and BMI of 52.2 (± 13.9) years and 31.9 (± 7.5) kg/m^2, respectively. The distribution of stage 0, 1, 2, 3 and 4 fibrosis was 31.7%, 27.8%, 15.7%, 13.9%, and 10.9%, respectively. The AUROC (95% CI) of TE versus MRE for the detection of fibrosis stages ≥1 was 0.82 (0.76–0.88) vs. 0.87 (0.82–0.91), p <0.05, fibrosis stage ≥ 2 was 0.87 (0.82–0.91) vs. 0.92 (0.88–0.96), p < 0.05, fibrosis stage ≥ 3 was 0.84 (0.78–0.90) vs. 0.93 (0.89–0.96), p < 0.001, and fibrosis stage ≥ 4 was vs.0.84 (0.73–0.94) vs. 0.94 (0.89–0.99), p < 0.01, respectively.
Conclusion: In this pooled analysis of data from individual participants with NAFLD in 3 independent studies, MRE

demonstrated a higher diagnostic accuracy than TE for the detection of individual stages of fibrosis using liver biopsy as a reference. Both MRE and TE have a role in the detection of fibrosis in NAFLD depending upon the desirability for accuracy.

FRI-440

Gut-liver interactions in celiac disease: FGF-19 and GLP-1 link disease activity to hepatic steatosis and liver injury

S. Sydor[1], P.P. Manka[2], J. Schänzer[2], I. Messerschmidt[2], S. Kinner[3], A. Link[1], H. Moshage[4], K.N. Faber[4], G. Gerken[2], A. Canbay[1], L.P. Bechmann[1]. *[1]Otto-von-Guericke-University Magdeburg, Department of Gastroenterology, Hepatology and infectious diseases, Magdeburg, Germany; [2]University Hospital Essen, Department of Gastroenterology and Hepatology, Essen, Germany; [3]Universitätsklinikum Essen, Institut für Diagnostische und Interventionelle Radiologie und Neuroradiologie, Essen, Germany; [4]University of Groningen, University Medical Center Groningen (UMCG), Faculty of Medical Sciences Gastrointestinal and liver diseases, Groningen, Netherlands*
Email: svenja.sydor@med.ovgu.de

Background and Aims: We and others have previously identified celiac disease (CD) as a risk factor for hepatic steatosis and non-alcoholic steatohepatitis (NASH). NASH in CD is associated with cellular stress and hepatocellular apoptosis. The underlying mechanisms leading to hepatic steatosis in CD have yet to be shown. Bile acid (BA) signaling has recently been identified as an important mediator in gut-liver interactions and the pathogenesis of NASH. With this study, we aim to analyze parameters of BA signaling and liver injury in patients with CD compared to healthy controls (HC).
Method: We included 20 patients with known CD and 20 healthy volunteers and analyzed transaminases, cell death markers (M30, M65) as well as markers of BA and fatty acid metabolism (FGF-19, serum BA, FGF-21, GLP-1). Hepatic steatosis was determined using controlled attenuated parameter (CAP) via Fibroscan and by MRI-HFF.
Results: In CD, ALT and hepatocellular apoptosis (M30) were increased compared to HC (ALT: 19.3 vs. 26.5 U/l; $p < 0.0001$; M30: 88.9 vs. 142.4 U/l; $p = 0.03$). Accordingly, in CD hepatic steatosis was abundant as indicated by higher CAP and MRI-HFF. In order to associate steatotic liver injury with disease activity in CD, we further analyzed CD subgroups (anti-transglutaminase antibody positive (tTg-Ab-pos; $n = 10$) vs. negative (tTg-Ab-neg; $n = 10$). In tTg-Ab-pos individuals, M30 as indicator of hepatocellular injury was significantly induced (88.9 vs. 158.7 U/l; $p = 0.043$). CD patients with a CAP $\geq$ 283 dB/m (established cutoff for diagnosis of fatty liver) were exclusively tTG-Ab-pos. While total BA were not different between groups, FGF-19 levels were significantly lower in CD compared to HC, which was not related to CD activity. In contrast, GLP-1 levels were significantly higher in tTG-Ab-pos compared to tTG-Ab-neg and controls (1144.0 vs. 616.9 pg/ml; $p = 0.02$). In this cohort increased CAP was positively correlated to an increase of MRI-HFF, M30, ALT, fecal calprotectin, and GLP-1. In contrast increased FGF-19 serum levels were negatively correlated to steatosis as assessed by MRI-HFF.
Conclusion: In this cohort, CD was associated with steatosis, hepatocellular injury, hepatic inflammation, and reduced FGF-19 serum levels. Abundance of tTG-Ab in CD was associated with steatosis, liver injury and increased GLP-1 levels as an indicator of metabolic alterations in CD. Both, FGF19 and GLP-1 (via TGR5 receptor) are associated with BA signaling. Thus, we hereby elucidate a novel role for BA signaling in CD associated fatty liver.

FRI-441

Utility and limitation of non-invasive fibrosis markers for predicting the prognosis in biopsy-proven Japanese NAFLD patients

T. Ito, M. Ishigami, Y. Ishizu, T. Kazuya, T. Honda, K. Hayashi, T. Ishikawa, Y. Hirooka, H. Goto. *Nagoya University Graduate School of Medicine, Department of Gastroenterology and Hepatology, Nagoya, Japan*
Email: tahkun56@gmail.com

Background and Aims: Fibrosis stage of nonalcoholic fatty liver disease (NAFLD) is closely associated with long-term prognosis. Non-invasive fibrosis markers used in lieu of liver biopsy have been reported to be useful for assessing the liver fibrosis and prognosis, especially liver-related mortality. However, it is not yet clear whether these markers can predict the incidence of non-liver-related complications. In the present study, we clarified the prognosis including non-liver-related diseases based on hepatic pathology and non-invasive fibrosis markers in Japanese NAFLD patients.
Method: A total of 246 patients with Japanese NAFLD diagnosed by liver biopsy were enrolled. We investigated the mortality and the prognosis based on hepatic pathology and non-invasive fibrosis markers, FIB-4 index and NAFLD fibrosis score (NFS).
Results: The cumulative incidental number of death, hepatocellular carcinoma (HCC), complications related to liver cirrhosis (LC) other than HCC, extrahepatic malignancies, and cardiovascular disease (CVD) were 8 (3.3%), 9 (3.7%), 10 (4.1%), 16 (6.5%) and 12 (4.9%) during follow-up period (median 7.0 years), respectively. When these patients were categorized based on the severity of liver fibrosis as F0-2 ($n = 196$) and F3-4 ($n = 50$), the patients with F3-4 had significantly poorer prognosis in overall survival rate and all complications ($p < 0.05$) other than CVD. Non-invasive fibrosis markers, FIB-4 index and NFS, were useful to predict overall survival, the incidence of HCC and complications related to LC, but not extrahepatic malignancies and CVD. Multiple logistic regression analysis revealed severe liver fibrosis was independently associated with overall survival and malignancies including HCC: hazard ratio (HR) 6.512 (95% confidence interval [CI], 1.433–29.592) for survival; HR 7.622 (95% CI, 1.401–41.459) for HCC; HR 3.989 (95% CI, 1.335–11.913) for extrahepatic malignancies, respectively. Although FIB-4 index was an independent risk factor of complications related to LC (HR 26.560, CI, 3.320–212.494), both FIB-4 and NFS were not selected as an independent risk factors of extrahepatic malignancies and CVD.
Conclusion: The progression of liver fibrosis was associated with not only liver-related complications but also extrahepatic malignancies in Japanese NAFLD. NFS and FIB-4 were useful for predicting liver-related complications, but they had limitation for extrahepatic malignancies and CVD.

FRI-442

FibroScan stiffness and CAP in the evaluation of cardiovascular risk assessment in patients with NAFLD

R. Lombardi[1], S. Petta[2], A. Giannetti[2], R. Boemi[2], G. Pisano[1], C. Bertelli[1], A. Craxi[2], S. Fargion[1], A.L. Fracanzani[3]. *[1]Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; [2]University of Palermo, Department of Gastroenterology and Hepatology Di.Bi.M.I.S, Palermo, Italy; [3]Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Italy*
Email: anna.fracanzani@unimi.it

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) may progress to advanced fibrosis and exposes patients to high

cardiovascular mortality, independently of other metabolic factors. FibroScan® is a widely used tool to detect both hepatic steatosis and fibrosis, but its role in defining a cardiovascular risk profile is still unexplored. To evaluate if FibroScan® is able to detect NAFLD patients at higher cardiovascular risk.

Method: Four-hundred thirty-three biopsy proven NAFLD were enrolled in two Italian hepatology centres. All patients underwent FibroScan®, carotid Doppler US and echocardiography. Controlled attenuation parameter (CAP) value ≥248 dB/m and liver stiffness measurement (LSM) ≥7.9 kPa defined the presence of steatosis and significant fibrosis, respectively.

Results: Mean age was 50 ± 14 years and 66% patients were males. Prevalence of diabetes was 29%, hypertension 38%, dyslipidemia 54%, 24% of whom on statins. Carotid plaques were present in 45% of patients, mean IMT was 0.8 ± 0.2. Mean epicardial adipose tissue was 7.5 ± 2.5 mm, diastolic dysfunction (E/A < 1) was present in 33%. Only 4% patients reported cardiovascular events. LSM ≥7.9 kPa was present in 195 patients (45%) and at univariate analysis correlated with carotid plaques ($p < 0.001$), IMT ($p = 0.007$), diastolic dysfunction ($p < 0.001$) and cardiovascular events ($p = 0.004$), at multivariate analysis adjusted for confounding factors, LSM ≥7.9 kPa remained independently associated with age (OR 1.055; 95% CI 1.001–1.111), waist circumference (WC) (OR 1.047; 95% CI 1–1.096), plasmatic insulin (OR 1.058; 95% CI 1.005–1.114) and histology stage F2 (OR 4.949; 95% CI 1.858–13.182). CAP ≥248 dB/m at multivariate analysis correlated with severe histology steatosis and inflammation (OR 7.9, 95% CI 1.6–63 and OR 6.4, 95% CI 1.01–126). Differently from fibrosis defined by LSM assessment, histological fibrosis was independently associated with IMT and history of cardiovascular events.

Conclusion: Transient elastography, a non-invasive method for the diagnosis and staging of NAFLD, confirms its association with metabolic parameters, showing a good correlation with histology. Our results indicate that FibroScan® is unable to detect NAFLD patients at higher cardiovascular risk, suggesting a complex and multifactorial underlying scenario predisposes to the cardiovascular disease.

FRI-443
Repeatability and reproducibility of multiparametric magnetic resonance imaging of the liver

H. Wilman, J. Jacobs, R. Newbould, M. Halberstadt, M. Gyngell, A. Herlihy, C. Fernandes, C. Kelly, M. Maguire, N. Jayaratne, S. Linden, K. Groves, V. Bachtiar, A. Mckay, M. Kelly, S. Neubauer, R. Banerjee.
Perspectum Diagnostics, Oxford, United Kingdom
Email: henry.wilman@perspectum-diagnostics.com

Background and Aims: MRI-based technology for quantitative analysis of hepatic fat, T2*, iron corrected T1 (cT1) and MR elastography has considerable utility in NASH clinical trials. To be clinically effective, a measurement should be consistent across sites with good reproducibility. Trout (Radiology 2016; 281:793) evaluated the cross-vendor performance of MRE, and demonstrated a CoV of 10.7%. cT1 has been shown to correlate with fibro-inflammatory disease and predict clinical outcomes. We test the robustness of Liver*MultiScan*-derived metrics across different MRI scanner manufacturers, models, software versions and field strengths.

Method: cT1, T2* and Proton Density Fat Fraction (PDFF) maps were acquired from 61 participants on combinations of three Siemens (1.5T Avanto-Fit, VE11C, MyoMaps; 3T Prisma, VE11C, MyoMaps; 3T Skyra, VE11C, MyoMaps) and two Philips (1.5T Ingenia, 5.3.0, CardiacQuant; 3T Ingenia, 5.3.0, CardiacQuant) scanners. Participants were adult volunteers with mixed liver disease aetiology and those without any history of liver disease to represent a range of physiological values of these metrics. Two acquisition repeats were conducted for each scan, with subjects leaving the scanner in between. Participants were scanned on at least two different scanner models and field strengths in pseudorandomised order with up to 1-week between scans. Standardisation of T1 maps across scanner models and software versions was based on phantom-derived mappings from 90 acquisitions on the above MRI systems. Phantoms were purpose built to span the clinically-relevant range of liver T1s.

Results: Standardised cT1 in participants demonstrated high reproducibility across different scanner models, software versions and field strengths (CoV 3.3%; bias 6.5 ms, 95% LoA of –76.3 ms–89.2 ms). Both T2* (CoV 6.6%; bias –1.7 ms, 95% LoA of –6.6 ms to 3.2 ms) and PDFF measurements (CoV 17%; bias 0.06%, 95% LoA of –0.69%–0.82%) also showed excellent reproducibility at both field strengths and across different scanners models. Bland-Altman analysis of the T1 phantom measurements showed a clear reduction in bias (from –20 ms–4.7 ms), tightening of the 95% Limits of Agreement (LoA: from –59.2 ms – 19 ms, to –25.3 ms – 15.9 ms) and reduction in mean coefficient of variation (CoV: 2.5%–1.0%) after standardisation.

Conclusion: We demonstrate standardised cT1 is a robust metric independent of vendor (Philips or Siemens) and field strength (1.5T or 3T). Combined with the excellent reproducibility of T2* and PDFF, LMS represents a robust and reliable non-invasive tool for characterising liver tissue.

FRI-444
The Community based management of NAFLD Study (COMMANDS): Improved diagnosis and referral using a novel integrated care pathway

L. Burke, B. Williams, G. Abouda, L. Corless. *Hull and East Yorkshire Hospitals*
Email: lynsey.corless@nhs.net

Background and Aims: In the United Kingdom, most non-alcoholic fatty liver disease (NAFLD) is diagnosed after identification of

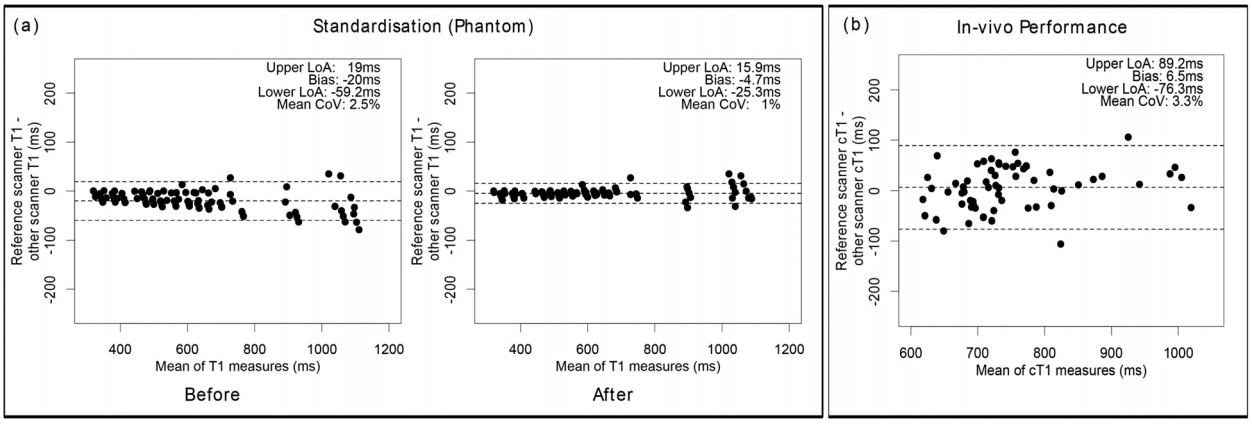


Figure: (abstract: FRI-443): Bland-Altman plots demonstrating **(a)** standardization of T1 in phantoms, and **(b)** reproducibility of *in vivo* cT1 measurements.

abnormal liver function tests (LFT) in primary care (PC), with subsequent referral to liver specialists (LS) for investigation. Despite high prevalence there is currently no standardized community management pathway for those with abnormal LFT and suspected NAFLD. Our previous study showed practice varies extensively leading to both unnecessary referrals and suboptimal identification of high-risk patients with advanced fibrosis requiring LS management. We created an electronic-Integrated Care Pathway (eICP) to support PC through a clear, concise diagnostic and staging process, including evidence-based management and referral advice.

Method: eICP effectiveness was tested against standard care (SC) in a randomised controlled trial in 3 domains: accuracy of diagnosis, adequate risk assessment, and appropriateness of referral decision (keep in PC or refer to LS). Patients with persistently deranged LFT (at least 2x ALT > 70) and suspected NAFLD were randomised by PC practice to either e-ICP or SC management. Enhanced Liver Fibrosis (ELF) testing was used to assess fibrosis severity in the cohort but was not part of standard PC management.

Results: 52 patients (29% female, median age 52 [26–76], median BMI 33 [25–49]) were included (eICP n = 22; SC n = 30). Patients were well matched for BMI, metabolic syndrome features and disease severity (median ELF 8.9 kPa eICP vs. 9.33 kPa SC).

Exclusion of alternate diagnosis was performed in significantly more eICP than SC: ultrasound 100% vs. 57.7%, hepatitis virus serology 86.3% vs. 6.7%, liver antibodies 90.9% vs. 20% and ferritin 100% vs. 23.3% respectively (all $p < 0.005$). This allowed secure PC NAFLD diagnosis in 64% (n = 14) of eICP, with median time from presentation to confirmed diagnosis of 40 days. In contrast due to incomplete investigation, no SC patients had a confirmed diagnosis ($p < 0.005$), including several who were not referred to LS and remained in PC with unexplained abnormal LFT.

Median NAFLD fibrosis score (NFS) was −2.1 [−2.5–−0.33] in the eICP arm. Notably, NFS could not be calculated in any of the SC group, as none had undergone all the required investigations, and therefore PC decision-making could not include fibrosis risk assessment. In the eICP moderate/high risk NFS triggered LS referral advice, which also captured all high risk ELF in the group (n = 4; 18.2%). Conversely, those in SC with high ELF were not identified until the trial team relayed results and advised LS referral (n = 3; 10%).

Conclusion: eICP use was associated with significant improvements in secure NAFLD diagnosis and risk stratification, and supported safe PC NAFLD management or appropriate LS referral. A 5-year prospective observational study of the cohort is underway to track clinical outcomes and factors associated with disease progression.

FRI-445

Enhanced liver fibrosis (ELF) score accurately detects advanced fibrosis in nonalcoholic fatty liver disease (NAFLD)

R.E. Stauber[1], K. Staufer[2], J. Stift[3], R. Marculescu[4], B. Obermayer-Pietsch[5], M. Trauner[6], K. Lackner[5]. *[1]Institute of Pathology, Graz, Austria; [2]Medical University of Vienna, Department of Surgery, Vienna, Austria; [3]Medical University of Vienna, Clinical Institute of Pathology, Vienna, Austria; [4]Medical University of Vienna, Department of Medical and Chemical Laboratory Diagnostics, Vienna, Austria; [5]Medical University of Graz, Department of Internal Medicine, Graz, Austria; [6]Medical University of Vienna, Division of Gastroenterology and Hepatology, Vienna, Austria*
Email: rudolf.stauber@medunigraz.at

Background and Aims: The Enhanced Liver Fibrosis (ELF) test is a noninvasive fibrosis panel composed of hyaluronic acid (HA), procollagen-3 N-terminal peptide (P3NP), and tissue inhibitor of metalloproteinase-1 (TIMP1). Nonalcoholic steatohepatitis (NASH) with advanced fibrosis (F3) or cirrhosis (F4) causes increased liver-related mortality. Noninvasive tests are needed to identify patients with these advanced stages of NASH who are eligible for enrolment in clinical trials. Aim of the present study was to determine the diagnostic accuracy of ELF score for prediction of advanced fibrosis/cirrhosis in non-alcoholic fatty liver disease (NAFLD) with or without NASH.

Method: We enrolled 122 consecutive patients with NAFLD admitted to two Austrian outpatient liver clinics who underwent liver biopsy. Histological NASH was defined as presence of steatosis >5%, hepatocellular ballooning and lobular inflammation. Fibrosis was staged according to the clinical research network (CRN) score. Serum samples obtained at the time of liver biopsy were used to perform ELF test (Siemens Health Care, Vienna, Austria). The predictive value of ELF score for diagnosis of fibrosis stage was assessed by receiver operating characteristic (ROC) analysis and compared to that of FIB-4, a simple fibrosis test based on age, AST, ALT and platelet count.

Results: Our study cohort contained 122 patients with NAFLD. On liver histology, NASH was present in 63 patients (52%) and advanced fibrosis stage (F3–4) in 34 patients (28%). ELF score was significantly higher in fibrosis stages F3-4 vs. F0-2 (10.5 ± 1.5 vs. 8.6 ± 1.3, $p < 0.001$). ROC analysis revealed superior diagnostic accuracy of ELF score (AUROC 0.88 [CI 0.81–0.95]) vs. FIB-4 (AUROC 0.78 [CI 0.68–0.89]) for prediction of fibrosis stage F3-4. At a cut-off of 9.1, ELF score accurately detected or excluded fibrosis stage F3-4 (sensitivity 94%, specificity 75%, PPV 58%, NPV 97%).

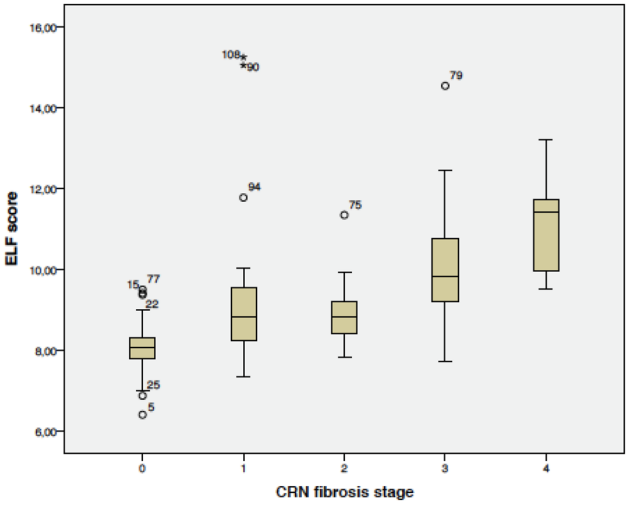


Figure: Boxplot of ELF score by CRN fibrosis stage.

Conclusion: Based on our findings, ELF score shows good diagnostic accuracy for detection or exclusion of advanced fibrosis in NAFLD and thus may be very useful to assess eligibility of NAFLD patients for clinical trials with anti-inflammatory and/or antifibrotic drugs.

FRI-446

Genetic variations of three important anti-oxidative enzymes: SOD2, CAT and CPX1 in non-alcoholic steatohepatitis

Y.-S. Huang. *Taipei Veterans General Hospital, Division of Gastroenterology and Hepatology, Taipei, Taiwan*
Email: yshuang@vghtpe.gov.tw

Background and Aims: Why only part of people under same predisposing factors progress to non-alcoholic steatohepatitis (NASH) remains to be elucidated. Steatosis may increase the reactive oxidative stress (ROS), which has been proposed as one crucial pathogenic factor of NASH. Superoxide anion radical, the main product of ROS, can be reduced by manganese superoxide dismutase (SOD2) to hydrogen peroxide, which is further reduced by catalase (CAT) and glutathione peroxidase (CPX) to water. Functional genetic polymorphisms of these 3 important anti-oxidative enzymes have been found; however, little is known regarding these genetic variants with the risk of NASH. We aimed to investigate the association of genetic variants of SOD2, CAT and CPX1 with the susceptibility to NASH.

Method: 122 adults with liver tissue-verified NASH, 54 patients with liver tissue-proved non-alcoholic fatty liver (NAFL), and 170 healthy controls were enrolled in this study. Their DNAs were retrieved for genotyping SOD2 47T > C (rs4880), CAT −262C > T (rs1001179) and GPX1 593C > T (rs1050450) variation by polymerase chain reaction.
Results: There was statistical difference in the frequency of SOD2 and CAT genotypes among NASH, NAFL and control groups, but there was no difference in CPX1 genotype. The NASH group had higher frequency of subjects with SOD2 C allele than NAFL and control groups had (36.9% vs. 25.9% and 22.9%, p = 0.03). Similarly, the NASH group had higher percentage of CAT T allele than NAFL and control groups had (20.5% vs. 11.1% and 6.5%, p = 0.001). After adjustment for confounders (age, body mass index, DM and hyperlipidemia), the CAT T allele still possessed the higher risk of NASH (OR: 2.57, 95% CI: 1.10–5.97, p = 0.029), followed by SOD2 C allele (OR: 2.10, 95% CI: 1.16–3.81, p = 0.014).
Conclusion: Functional genetic variations of anti-oxidative enzymes CAT −262C > T and SOD2 47T > C may affect the disposition of ROS, and increase the risk of NASH.

FRI-447

Comparison of conventional ultrasound signs to current state-of-the-art MRI method for detection of hepatic steatosis

M.M. Kim[1], D.W. Jun[2], B.-K. Kang[1], Y.C. Joo[3], H. Oh[2], E.C.J. Jang[4], J.H. Sohn[5], J.Y. Jeong[5], S.B. Ahn[6]. *[1]Hanyang University School of Medicine, Department of Radiology; [2]Hanyang University School of Medicine, Department of Internal Medicine; [3]Hanyang University Graduate school of Biomedical Science and Engineering, Department of Translational Medicine; [4]Soonchunhyang University College of Medicine, Department of Occupational and Enviroment Medicine; [5]Hanyang University, College of Medicine, Guri Hospital, Department of Internal Medicine; [6]Eulji university college of medicine, Department of Internal Medicine*
Email: noshin@hanyang.ac.kr

Background and Aims: To compare conventional ultrasound signs with MRI proton density fat fraction (PDFF) for detection of hepatic steatosis (HS) and to determine the diagnostic performance of ultrasound for the grading of HS using recently determined MRI PDFF cut offs.
Method: This study includes 182 patients who simultaneously underwent ultrasound and MRI PDFF between February 2014 and October 2016. Four ultrasound signs (abnormal hepatorenal echo, loss of echogenicity of the portal vein, poor diaphragm visualization, poor diaphragm visualization) were evaluated independently by two radiologists. The hepatic fat fraction is defined as the average of 24 non-overlapping regions of interest (ROIs) obtained by drawing three ROIs within each segment in MRI. The diagnostic performance in assessing the diagnosis and severity of HS was assessed using receiver operating characteristic (ROC) analyses.
Results: A sensitivity of 96.6%, a specificity of 74.8% and a negative predictive value (NPV) of 97.9% were achieved by using abnormal hepatorenal echoes to detect HS with a value of area under the ROC curve (AUROC) of 0.875. Combination of 2 signs (Abnormal hepatorenal echoes and loss of echogenicity of the portal vein) had a sensitivity of 100%, a specificity of 85.9%, and an AUROC of 0.930 in detecting moderate fatty liver. There was a strongly positive correlation between the sonographic findings and hepatic fat fraction (r = 0.754, p < 0.001).
Conclusion: The sensitivity and NPV for the detection of HS with abnormal hepatorenal echo were good and ultrasound is useful screening tool for "rule-out" of HS.

FRI-448

Responsiveness of controlled attenuation parameter (CAP) and its correlation with magnetic resonance imaging-proton density fat fraction (MRI-PDFF) in a multi-center clinical trial of subjects with nonalcoholic steatohepatitis (NASH)

M. Noureddin[1], Z. Kayali[2], S. Harrison[3], P. Ruane[4], N. Gitlin[5], E. Lawitz[6], M. Bennett[7], R. Vuppalanchi[8], B. Freilich[9], E. Harting[10], B. Mccolgan[10], R. Myers[10], M. Middleton[11], C. Sirlin[11], M. Charlton[12], M. Lai[13], P. Mantry[2], R. Loomba[14]. *[1]Cedars-Sinai Medical Center, Los Angeles, United States; [2]The Liver Institute at Methodist Dallas, Dallas, United States; [3]Pinnacle Clinical Research, San Antonio, United States; [4]Ruane Medical and Liver Health Institute, Los Angeles, United States; [5]Atlanta Gastroenterology Associates, Atlanta, United States; [6]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, United States; [7]Medical Research Associates Group, San Diego, United States; [8]Indiana University School of Medicine, Indianapolis, United States; [9]Kansas City Gastroenterology and Hepatology, Kansas City, United States; [10]Gilead Sciences, Inc., Foster City, United States; [11]University of California at San Diego, San Diego, United States; [12]University of Chicago, Chicago, United States; [13]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, United States; [14]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States*
Email: rob.myers@gilead.com

Background and Aims: CAP is a quantitative, ultrasound-based measure of hepatic steatosis. Our objectives were to assess the: (1) correlation between CAP and MRI-estimated proton density fat fraction (PDFF), and (2) responsiveness of CAP to change in a clinical trial of subjects with NASH.
Method: CAP (FibroScan; Echosens, France) and MRI-PDFF were measured at baseline (BL) and Week 12 (W12) in a Phase 2, multi-center trial of NASH subjects treated with the acetyl-CoA carboxylase (ACC) inhibitor GS-0976 20 mg, GS-0976 5 mg, or placebo orally once daily for 12 weeks. MRI-PDFF was read centrally and CAP was performed locally where available. A ≥30% relative reduction in MRI-PDFF between BL and W12 was considered clinically significant. Spearman correlations (ρ) were used to evaluate associations between CAP and MRI-PDFF, and changes in MRI-PDFF and CAP by treatment arm were evaluated using Wilcoxon rank-sum and Fisher exact tests.

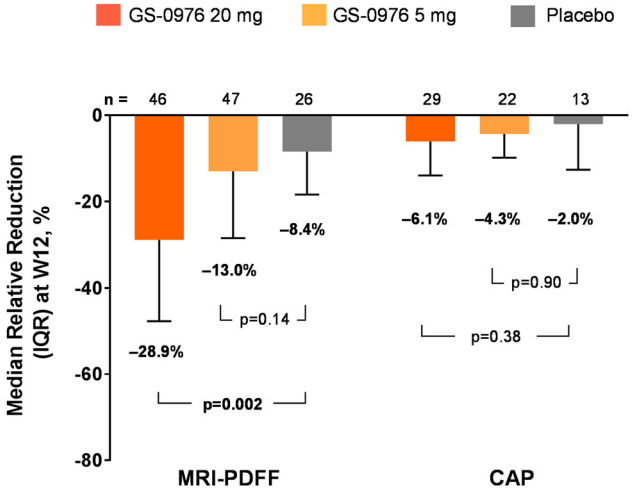


Figure: Relative Changes in MRI-PDFF and CAP between BL and W12.

Results: The majority of subjects were female (65%) and diabetic (60%); median BL MRI-PDFF (n = 126) and CAP (n = 69) were 14.37% (IQR 11.07, 18.98) and 329 dB/m (298, 359), respectively. 52% (72/138) of all CAP measurements were obtained using the FibroScan M probe. Among demographic and BL clinical parameters, CAP was correlated

with body mass index (ρ = 0.32, p = 0.008), waist circumference (ρ = 0.31, p = 0.010), and fasting serum glucose (ρ = 0.24, p = 0.046). CAP and MRI-PDFF were significantly correlated at BL (ρ = 0.29, p = 0.016) and W12 (ρ = 0.32, p = 0.009). However, absolute (ρ = 0.22, p = 0.094) and relative changes (ρ = 0.21, p = 0.096) in CAP and MRI-PDFF between BL and W12 were not significantly correlated. In subjects treated with GS-0976 20 mg daily, a 28.9% median relative reduction in MRI-PDFF was observed between BL and W12 (p = 0.002 vs. placebo); a 13.0% reduction in the 5 mg group was not statistically different from placebo (Figure). Relative reductions in CAP were smaller and did not differ between treatment groups (Figure). Relative reductions ≥30% in MRI-PDFF in the GS-0976 20 mg, GS-0976 5 mg, and placebo groups were observed in 48%, 23%, and 15% of subjects (p = 0.004 vs. GS-0976 20 mg; p = 0.43 vs. GS-0976 5 mg), respectively. Relative CAP reductions ≥30% were observed in 10%, 0%, and 7.7% of subjects, respectively (both p > 0.05 vs. placebo). The median relative change in CAP in 23 MRI-PDFF responders was −7.5% (IQR −14.8, 1.8) compared with −3.0% (−10.8, 9.9) among non-38 responders (p = 0.23).

Conclusion: Among NASH subjects in this multi-center trial of GS-0976, measures of hepatic steatosis quantified by CAP and MRI-PDFF were moderately correlated. However, changes in these parameters were not correlated and CAP was less responsive to change than MRI-PDFF. Further validation of CAP is necessary before it can be considered a valid endpoint for use in clinical trials of interventions for NASH.

FRI-449

A non-invasive biomarker of hepatic inflammation based on magnetic resonance imaging

M. House[1,2], L.L. Lai[3], W.-K. Chan[3], N.R.N. Mustapha[4], A. Vijayananthan[5], S. Mahadeva[3], L. Adams[6], J. Olynyk[7,8], S. Boulos[2], T.S. Pierre[9]. *[1]The University of Western Australia, Physics, Australia; [2]Resonance Health Ltd, Australia; [3]University of Malaya, Gastroenterology and Hepatology Unit, Malaysia; [4]Hospital Sultanah Bahiyah, Department of Pathology, Malaysia; [5]University of Malaya, Department of Biomedical Imaging, Malaysia; [6]The University of Western Australia, Medicine and Pharmacology, Australia; [7]Fiona Stanley Fremantle Hospital Group, Department of Gastroenterology, Australia; [8]Edith Cowan University, School of Medical and Health Sciences, Australia; [9]The University of Western Australia, Physics*
Email: mikeh@resonancehealth.com

Background and Aims: Inflammation and ballooning are pathological hallmarks of non-alcoholic steatohepatitis (NASH), but their detection and the diagnosis of NASH relies on an invasive liver biopsy. The non-invasive detection of inflammation and ballooning would therefore be a significant step in diagnosing, monitoring and treating NASH. In this preliminary study, we report on a magnetic resonance imaging (MRI) approach for identifying patients with mild to severe grades of inflammation and ballooning.

Method: The participants for this research were drawn from two independent studies. The participants in the first study were from Australia (n = 39) and comprised 10 healthy controls with normal body mass index (18.4–24.9) and 29 patients with biopsy-confirmed NAFLD. The participants in the second study were from Malaysia (n = 51) and comprised patients with biopsy-confirmed NAFLD. An identical gradient echo MRI protocol was acquired for both cohorts and a non-invasive imaging biomarker of inflammation (NIIBI) was developed from the images via post-processing. From the histopathologists' grading of the biopsies, an inflammation score (IS) was generated from the sum of the lobular inflammation and ballooning components of the NAFLD activity score (NAS), with the healthy controls assigned an IS of 0. The data from two cohorts were then pooled before dividing participants with no inflammation (IS 0) from those with some inflammation (IS 1–5). The mean difference between the groups was assessed using the Student's t-test. Area under the ROC curve (AUROC) analysis was used to assess the diagnostic potential of the MRI biomarker for predicting inflammation.

Results: There were 28 participants with an IS of 0 (12 female, 16 male) and 62 participants with an IS between 1 and 4 (36 female, 27 male). No participant had an IS score of 5. The mean (standard deviation) NIIBI value was 0.25 (0.23) for the IS 0 group and 0.72 (0.36) for the IS 1-4 group (Figure 1). The difference between the mean NIIBI values of the two groups was statistically significant (p < 0.0001). The AUROC for distinguishing no inflammation from some inflammation was 0.87 (95% CI 0.80–0.95) and the sensitivity and specificity was 81% (95% CI 69% to 90%) and 79% (95% CI 59% to 92%) at an NIIBI cut-off value of 0.43.

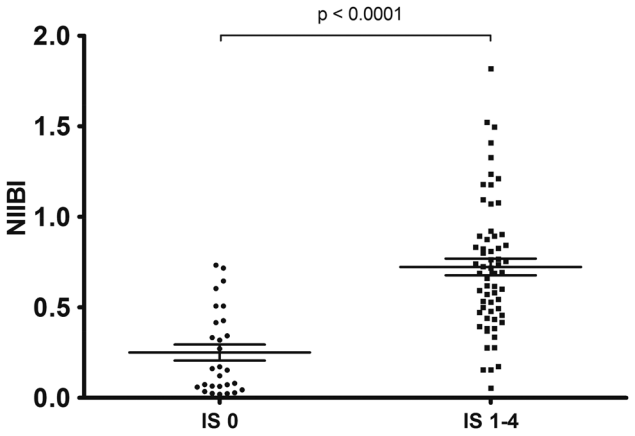


Figure 1 Scatter plot of NIIBI values for the two groups of subjects. The lines through the data are the mean and the standard error on the mean.

Conclusion: A new, rapidly acquired MRI-based parameter has been developed for detecting inflammation and ballooning in the liver. This new measurement tool has the potential to assist in the identification of patients with NASH and to help pre-screen patients for recruitment into NASH clinical trials.

FRI-450

Temporal assessment of the non-invasive fibrosis scores FIB-4 and Non-Alcoholic Fatty Liver Disease Fibrosis Score (NFS) in a retrospective cohort study among patients with Non-Alcoholic Fatty Liver Disease (NAFLD)

M. Pérez-Carreras[1], C. Muñoz Codoceo[1], M.M. Ortega[2], M.R. Castro[1], F.M. Alfonso[1], A.M. Algibez[1], Y.R. Gil[3], G.C. Tortajada[1]. *[1]University Hospital "12 de Octubre". Medicine Faculty. Complutense University of Madrid. Spain, Gastroenterology and Hepatology, Madrid, Spain; [2]University Hospital "12 de Octubre". Medicine Faculty. Complutense University of Madrid. Spain, Epidemiology, Madrid, Spain; [3]University Hospital "12 de Octubre". Medicine Faculty. Complutense University of Madrid. Spain, Pathology, Madrid, Spain*
Email: mpcarreras@salud.madrid.org

Background: FIB-4 and NFS scoring systems have been validated to identify advanced liver fibrosis in patients with NAFLD. However, there are no longitudinal studies that support their usefulness in monitoring this disease.

Aims: To assess the diagnostic performance of both scoring systems in comparison to the liver biopsy (LB) in our setting and to analyze their temporal evolution.

Method: We included those patients who had baseline and follow-up visits at our specialized medical consultation for NAFLD from 1995 through 2016. Data on patient demographics, anthropometrics and metabolic risks, blood test results and fibrosis degree on LB were registered. NFS and FIB-4, their receiver operating curve (ROC) and their area under the curve (AUC) (95% CI) were calculated. Sensitivity (S), Specificity (Sp), Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for the cut-off points (CP) suggested in the

literature were analyzed. According to those CP, the degree of fibrosis was classified as "advanced", "not advanced" or "indeterminate". Five evaluation periods were established: the moment of NAFLD diagnosis, 3–6 years later, 7–10 years later, 11–14 years later and 15 years after the diagnosis.

Results: 109 patients were included, 48% men, mean age 50 ± 12 years. Metabolic factors: 81% were obese (BMI 29.8 ± 5), 31% had diabetes. Histologic diagnosis: 70 patients had an initial LB: 36 (51%) showed fibrosis (F1: 16 patients, F2: 9, F3:7, F4: 4); NFS (62 patients): AUC 0.83 (95% CI: 0.67–0.98). Low CP (−1.455): S 87.5%; Sp 54.1%; PPV 29.2%; NPV 95.2%. High CP (0.676): S 25%; Sp 94.6%; PPV 50%; NPV 85.4%; FIB-4 (98 patients): AUC 0.58 (95% CI: 0.35–0.81). Low CP (1.3): S 80%; Sp 23%, PPV 16.7%, NPV 85.7%. High CP (2.67): S 30%; Sp 82.7%, PPV 25%, NPV 86%; NFS Temporal evolution: 29 patients (46.8%) had a basal NFS <−1.455 (F0-F2, no advanced fibrosis), and only one of them progressed to advanced fibrosis (NFS > 0.676, F3-F4) 11–14 years later. Among the 26 patients (41.9%) that had an initial indeterminate NFS value, 5 (19.2%) progressed to an advanced fibrosis according to NFS value, three of them after 11–14 years and two of them after 15 years of follow-up.

Conclusion: 1. We confirm the diagnostic value of the NFS as a non-invasive scoring system for advanced liver fibrosis, with a better diagnostic performance than FIB-4 in our sample of Spanish NAFLD patients 2. NFS values under −1.455 at diagnosis rarely progress to advanced fibrosis. However, those patients with an indeterminate NFS value at diagnosis seem to have a higher risk of developing an advanced fibrosis. In both cases, the progression was identified after 10 years of follow-up, suggesting this could be the optimal time to perform a LB 3. Our sample size and the number of patients lost during follow-up limit the extrapolation of our results. These should be confirmed in a larger cohort of patients.

FRI-451

In non obese NAFLD increased plasma saturated fatty acids and insulin resistance are metabolic signatures of severity of liver disease

F. Carli[1], M. Gaggini[1], C. Rosso[2], C. Saponaro[1], C. Barbieri[1], V.D. Latta[1], E. Buzzigoli[1], D. Ciociaro[1], M.L. Abate[2], M. Marietti[2], R. Younes[2], E. Bugianesi[2], A. Gastaldelli[1]. *[1]Institute of Clinical Physiology, CNR, Cardiometabolic Risk Unit, Pisa, Italy; [2]Division of Gastroenterology and Hepatology and Lab. of Diabetology, Dept. of Medical Sciences, University of Turin, Turin, Italy*
Email: amalia@ifc.cnr.it

Background and aims: Alterations in lipid metabolism and insulin resistance (IR) are related to the development and progression of NAFLD. Previous lipidomic analyses in morbid obese subjects with NAFLD have found that having a high prevalence of saturated fatty acids (FA) in hepatic triglycerides (TAGs) was related to HOMA-IR and worse histological profile. Given the need of biomarkers of NAFLD, we evaluated if if high plasma saturated FA were associated with Hepatic-IR and Adipose tissue IR and with severity of NAFLD in non obese and mild obese NAFLD.

Methods: In 44 subjects with biopsy proven NAFLD (29 non obese NAFLD-NO and 15 obese NAFLD-Ob, BMI= 25.6 ± 0.5 and 32.4 ± 2.2) and 9 non-obese CT without fatty liver we evaluated TAG composition by LC/MS-QTOF and FFA composition by GC/MS. We measured also several metabolic parameters: IR in adipose tissue (AT-IR = FFA × insulin), liver (Hep-IR = EGP × Insulin where EGP is the hepatic glucose production measured using stable isotope tracers) and HOMA-IR, plasma concentration of Monocyte Chemoattractant Protein-1 (MCP-1), hepatic fat in biopsy; we also calculated the index of de novo lipogenesis (DNL = palmitic/linoleic acid), the ratio of saturated to unsaturated FFAs (SFA/PUFA), SCD-1 activity (palmitoleate/palmitate). We then correlated SFA/PUFA and the percent of unsaturated FA in TAG (determined by the number double bonds, db) with the above measurements. We considered low plasma unsaturated FA if there were less than 2 db in each fatty acyl chain.

Results: Plasma TG (84 ± 8 vs 103 ± 8 mg/dl in CT vs NAFLD) were composed mainly by TAG (85% in both groups). Composition analysis showed that NAFLD-NO had more saturated TAG than NAFLD-Ob. In the whole cohort TAG with more saturated FA (1db and 2db) were associated with increased hepatic fat, DNL-index, SCD-1 activity, SFA/PUFA, MCP-1, AT-IR, HEP-IR and HOMA-IR. For the same analyses we found that TAG with higher % of unsaturated FA were inversely correlated with the above variables (p = 0.0001–0.03) indicating a more favourable profile. Severe fibrosis F3-4 was also associated with presence of more saturated TAG and FFA compared to F0-2 (all p < 0.05).

Table 1: association between % unsaturated FA in plasma TAG and FFA and metabolic profile

	SFA/PUFA	TAG 1db	TAG 2db	TAG 3db	TAG 4db	TAG 5db
Hepatic fat %	0.32	0.53	0.31	−0.49	−0.34	−0.35
DNL index	0.73	0.49	0.29	−0.48	−0.29	−0.30
SCD-1 activity	ns	0.50	0.43	−0.53	−0.48	−0.41
SFA/PUFA	–	0.58	0.30	−0.52	−0.35	−0.33
MCP-1	0.31	0.49	0.29	−0.45	−0.36	−0.36
AT-IR	0.33	0.46	0.24	−0.46	−0.36	−0.29
Hep-IR	0.43	0.51	ns	−0.53	ns	ns
HOMA-IR	0.39	0.48	ns	−0.52	ns	ns

Conclusion: In subjects with NAFLD, plasma composition of TAG and FFA revealed that the presence of saturated TAG is associated with a worse metabolic profile (higher IR) and increased fibrosis especially in non obese NAFLD.

Funded by: Horizon2020 under grant agreement no.634413 for project EPoS.

FRI-452

Excess weight has a major impact on hepatic fibrosis by users of psychoactive substance

François Habersetzer[1,2,3], M. Doffoël[1,3], C. Frederic[3], H. Carmen[4], T. Baumert[1,2,3], L.J. Philippe[3], F.D. Nino[3], E. Florence[1,3]. *[1]Pôle Hépato-digestif, Hôpitaux Universitaires de Strasbourg, Strasbourg, France; [2]Unité 1110, INSERM, Strasbourg, France; [3]SELHVA - Service Expert de Lutte contre les Hépatites Virales d'Alsace, Hôpitaux Universitaires de Strasbourg, Strasbourg; [4]SOS Hépatites Alsace Lorraine, SOS Hépatites, Strasbourg, France*
Email: francois.habersetzer@chru-strasbourg.fr

Background and Aims: Excess weight may increase the risk of liver damage in patients addicted to psychoactive substances. This study aimed to investigate the impact of being overweight on hepatic fibrosis among drug users.

Method: Overall 1248 drug users from nine addiction treatment centers were included. Their mean age was 46 years and most of them (75%) were men. In total, 65% of them were addicted to alcohol, 74% to tobacco, 23% to cannabis, 11% to heroin, and 5% to cocaine. All our users were offered to undergo a FibroScan and screening tests for hepatitis B (HBsAg, anti-HBc Ab, and anti-HBs Ab), hepatitis C (HCV Ab), and HIV (HIV−1 and −2 serological screening).
They were then divided into two groups based on their body mass index (BMI): Group A included users whose BMI was <25 Kg/m² and Group B those whose BMI was >25 Kg/m².

Results: Overall, 524 drug users (42%) were overweight (BMI >5). The rates of opioid replacement therapy and addiction to alcohol and cocaine did not differ between the two groups. Addiction to tobacco, cannabis, and heroin, however, was less common in Group B (p < 0.01). Intravenous and intranasal drug abuse along with tattoos were also less common in Group B (p = 0.01). The other risk factors were less common but did not differ significantly between the two groups. Uptake of the FibroScan was 99% in both groups. The failure rate was 2% in Group A and 4.2% in Group B. Significant (F ≥ 2) and severe (F3–F4) fibrosis rates were higher in Group B than in Group A, respectively 31.6% *versus* 16.7% and 22.2% *versus* 10.1%, (p < 0.001). The detection

rates of hepatitis B, hepatitis C, and HIV were lower in Group B; respectively, 83.7% *versus* 89.9% for HBsAg; 86.9% *versus* 93% for HCV Ab; 85.6% *versus* 92.4% for the HIV serological tests, and 54.6% *versus* 62.7% for the three viruses ($p < 0.01$).

Conclusion: Excess weight is common among users of psychoactive substances and leads to increased hepatic fibrosis, with a severe fibrosis rate of more than 20% compared with users who were not overweight.

FRI-453

Hepatic microRNA and phosphoproteomic analysis provide insights about hepatic collagen deposition and stage of fibrosis in non-alcoholic steatohepatitis

Z. Younossi[1], A. Karrar[1], K. Tokarz[2], M. Pierobon[3], A. Ulyanov[1], M. Stepanova[4], Z. Younoszai[1], T. Jeffers[1], S. Felix[1], D. Tan[5], J. Kianoush[3], A. Hodge[3], M. Ahmad[2], R. Iyer[2], V. Chandho[3], E. Petricoin[3], J. Deeken[2], Z. Goodman[5]. *[1]Inova Health Systems, Betty and Guy Beatty Center for Integrated Research, Falls Church, United States; [2]Inova Fairfax Hospital, Inova Translational Medicine Institute (ITMI), Falls Church, United States; [3]George Mason University, Center for Applied Proteomics and Molecular Medicine, School of Systems Biology, Manassas, United States; [4]Center for Outcomes Research in Liver Disease, Washington DC, United States; [5]Inova Fairfax Hospital, Center for Liver Diseases, Department of Medicine, Falls Church, United States*
Email: zobair.younossi@inova.org

Background and Aims: Hepatic fibrosis in NASH can predict liver-related mortality. Phosphoproteomic and MicroRNAs (miRs) technologies can elucidate pathways involved in the pathogenesis of NASH-related fibrosis.

Method: The study included patients with biopsy-proven NAFLD and available liver specimens (N = 66). All liver biopsies were read by the study hepatopathologist. Hepatic % collagen was quantified using Computer Assisted Morphometry (CAM) after Sirius red staining of the liver specimens. Quantitative analysis of phospho-signaling proteins in the hepatic tissue was performed by Reverse Phase Protein Microarrays (RPMA). Using the same liver specimen, HTG EdgeSeq sequencing technology was used to sequence ~2200 miR on NextSeq®500 system. Phosphoproteins and miRNAs independently associated with hepatic % collagen (upper quartile >5.36%) were identified by generalized linear model with adjustment for cofounders. Correlations between predictive miR and phosphoproteins were performed.

Results: Using miR data, hepatic miR-let7c-5p (SE = 0.430, p = <0.001), miR-199a-5p (SE = 0.571, p = <0.001) and miR-6756-3p (SE = 0.209, p = <0.012) were independently associated with increased % hepatic collagen. Using RPMA data, ASK1 S83 (SE = 0.028, p = 0.02), the receptor tyrosine kinase, Met Y1234/1235 (SE = 0.17, p = 0.009), p38-MAPK T180/Y182 (SE = 0.07, p = <0.001), LIMK1T508/LIMK2 T505 (SE = 0.13, p = 0.004) were independently associated with increased % hepatic collagen. There were significant correlations between these phosphoproteins and miRs which were associated with hepatic collagen deposition. In fact, miR-let7c-5p positively correlated with ASK-1 S38 (rho = 0.425, p = <0.001) and p38 MAPK T180/Y182 (rho = 0.379, p = 0.002). Similarly, miR-199a-5p correlated with ASK-1 S38 (rho = 0.481, p = <0.001) and p38 MAPK T180/Y182 (rho = 0.375, p = 0.002). In contrast, miR-6756-3p negatively correlated with ASK1 S83 (rho = –0.409, p < 0.001) and p38 MAPK T180/Y182 (rho = –0.363, p = 0.003); respectively. After controlling for diabetes, gender and BMI, miR-199a-5p remained independently associated with p38 MAPK T180/Y182 (SE = 0.0000, p = 0.046). In fact, miR-199a-5p regulates ASK-1 pathway and targets the tyrosine-protein kinase Met (hepatocyte growth factor receptor (HGFR), which are both key players in development of hepatic fibrosis.

Conclusion: These data suggest that ASK-1 phosphoprotein and miR-199a-5p are associated with increased % hepatic collagen and may serve as promising diagnostic biomarker or treatment targets.

FRI-454

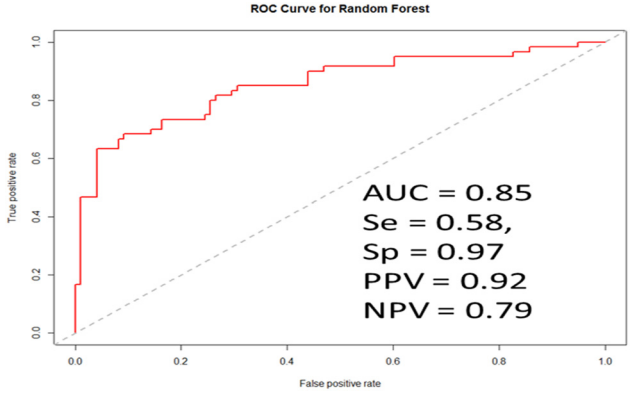
Serum metabolomics analysis to identify boilermakers for advanced fibrosis in NASH patients

Y. Luo[1], E. Charles[1], A. Oseini[2], R. Gagnon[1], P. Shipkova[1], M. Reily[1], K. Daita[2], G. Jarai[1], R. Christian[1], G. Rosen[1], A. Sanyal[2]. *[1]Bristol-Myers Squibb; [2]Viriginia Commonwealth University*
Email: yi.luo@bms.com

Background and Aims: Novel non-invasive biomarkers are needed to identify patients at high risk for NASH. Metabolomics quantifies small molecules in biofluids yielding a comprehensive view of the alterations in metabolic pathways in diseases. Previous studies have identified metabolic signatures discriminating NASH from simple steatosis or healthy control. This study aimed to explore the metabolomics biomarkers of advanced fibrosis (F3/F4) in NASH.

Method: This retrospective study comprised a cohort of 23 NAFLD patients with simple steatosis as non-NASH control and 141 NASH patients diagnosed by histologic assessment of liver biopsy according to NASH CRN criteria. The NASH cohort had fibrosis stages ranging from F0 to F4 and NAFLD Activity Score from 1 to7. Serum was collected within 6 months of liver biopsy and stored at –80°C. Metabolomics analysis was performed by Ultra-high performance liquid chromatography mass spectrometer. The Kruskal-Wallis test with FDR adjusted p-values, exploratory quantile analysis and t-test was used to test for statistically significant differences, Random Forest modeling was used to rank importance, and AUROCs to identify F3/4 were calculated.

Results: Significantly lower levels of dehydroepiandrosterone sulfate (DHEAS), taurine, uracil, and several amino acids were observed in F3/F4 patients. Lower levels of lysophosphatidylcholine and higher levels of unsaturated long chain acylcarnitines, gut microbiomes products (benzoic acid and phenylacetylglycine), as well as conjugated hydrophobic bile acids (glycodeoxycholic acid and glycochenodeoxycholic acid) were observed in F4 patients. By combining metabolomics biomarkers with previously identified collagen biomarkers Pro-C3 and Pro-C6, Random Forest analysis identified a biomarker panel with improved diagnostic performance for identification of advanced fibrosis (AUCROC 0.85, positive predictive value is 0.92, negative predictive value is 0.79) with glutamine, Pro-C3, DHEAS, Pro-C6, taurine and glycodeoxycholic acid the most important markers in the panel.



Conclusion: Metabolomics analysis suggest that advanced fibrosis in NASH patients is associated with altered metabolisms in amino acids, lipids and bile acids. The increase in gut microbiome products in these patients suggest changes in gut microbiomes and possibly intestinal barrier function. A biomarker panel which included Pro-C3, Pro-C6 and metabolites had improved diagnostic performance to identify advanced fibrosis.

FRI-455

Liver and pancreatic steatosis in children are both assosiated with metabolic syndrome but have different influence on insulin sensitivity and glucose metabolism

O. Lukianenko[1], N. Hravirovska, N.H. [2], V. Yagmur[2]. [1]*"Institute of gastroenterology of the National academy of medical sciences of Ukraine", Pediatric gastroenterology department, Dnipro, Ukraine;* [2]*"Institute of gastroenterology of the National academy of medical sciences of Ukraine", Diagnostic department, Dnipro, Ukraine*
Email: sirenkolga@gmail.com

Background and Aims: Children with obesity have high risk for ectopic fat accumulation both in liver and pancreas. It is known that liver steatosis can be independent risk factor for metabolic complications. We still don't have proved data about existence of independent association between metabolic complications and pancreatic fat. Aim of our study was to compare influence of liver and pancreatic steatosis on metabolic complications in children by estimation of the ultrasound attenuation.
Method: We examined 114 children aged 7–17 years, 67 with obesity, 48 without obesity. Anthropometry, lipid spectrum and insulin level with calculation HOMA1-IR and HOMA2-IR indices, oral glucose tolerance tests were assessed using standard techniques. Pancreatic and liver steatosis were diagnosed by ultrasound study (US). Also we estimated liver controlled attenuation parameter (CAP) with usage Fibroscan 502 Touch (France) and pancreatic ultrasound attenuation coefficient (UAC) with usage UltimaPAExpert® (Radmir, Ukraine).
Results: The prevalence of liver steatosis evaluated by ultrasound was 27.3%, pancreatic steatosis – 56.1%. CAP level positively correlated with degree of liver steatosis according to US ($r = 0.59$, $p < 0.05$), also UAC positively correlated with degree of pancreatic steatosis according to US ($r = 0.46$, $p < 0.05$). We found association between CAP and UAC in whole group and nonobese subcohorts. The CAP (233 [193.0; 263.0] dB/m^2) and UAC (2.58 [2.31; 2.75] dB/sm^2) were elevated in subjects with obesity. We found association between UAC and body mass index-standard deviation score (BMI-SDS) in whole group ($r = 0.42$, $p < 0.05$) and obesity subcohort ($r = 0.44$, $p < 0.05$), while no association between CAP and BMI-SDS was found in whole group neither in subcohorts. CAP correlated to fasting glucose level, fasting insulin level, HOMA1-IR and β-cell function (%b) (according to HOMA2-IR) in simple regression; UAC negatively correlated with glucose level 60 min after load in obese subcohort ($r = –0.40$, $p < 0.05$) and insulin sensitivity (%S) (according to HOMA2-IR) ($r = –0.38$, $p < 0.05$). Both CAP and UAC were associated with components of metabolic syndrome (MetS) such as waist circumference, systolic blood pressure. While CAP additionally correlated with level of TG ($r = 0.30$, $p < 0.05$). In nonobese subcohorts both CAP and UAC correlated with LDL and nonHDL level, also UAC negatively correlated with HDL.
Conclusion: In children with obesity, CAP is elevated and associated to MetS, fasting glucose, insulin resistance, beta-cell function, but not to glucose tolerance, or BMI-SDS. While UAC was associated with MetS, BMI-SDS, glucose 60 min after load in oral tolerance test, glucose sensitivity but not to beta-cell function. This study demonstrates that liver and pancreatic steatosis both are associated with MetS but have different influence on glucose metabolism and insulin sensitivity.

FRI-456

Prospective evaluation of serum gamma-glutamyl transferase (GGT) for the prediction of disease progression in a randomized trial of patients with primary sclerosing cholangitis (PSC)

C. Levy[1], M. Shiffman[2], H. Janssen[3], A. Montano-Loza[4], S. Caldwell[5], V. Luketic[6], D. Ding[7], B. Mccolgan[7], R. Myers[7], B. Eksteen[8], R.W.G. Chapman[9], M.P. Manns[10], Z. Goodman[11], C. Bowlus[12], A. Muir[13], G. Hirschfield[14]. [1]*University of Miami, Miami, FL, USA;* [2]*Liver Institute of Virginia, Richmond, VA, USA;* [3]*University Health Network, Toronto, Canada;* [4]*University of Alberta, Edmonton, AB, Canada;* [5]*University of Virginia, Charlottesville, VA, USA;* [6]*Virginia Commonwealth University, Richmond, VA, USA;* [7]*Gilead Sciences, Inc., Foster City, CA, USA;* [8]*University of Calgary, Calgary, AB, Canada;* [9]*University of Oxford, Oxford, UK;* [10]*Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany;* [11]*Inova Fairfax Hospital, Falls Church, VA, USA;* [12]*University of California at Davis, Sacramento, CA, USA;* [13]*Duke Clinical Research Institute, Durham, NC, USA;* [14]*Center for Liver Research, NIHR Biomedical Research Unit, University of Birmingham, Birmingham, UK*
Email: clevy@med.miami.edu

Background and Aims: The utility of serum GGT as a surrogate endpoint in clinical trials for PSC is unclear. Our objective was to prospectively validate GGT for the prediction of disease progression in a randomized trial of PSC patients.
Method: We included 234 adults with PSC enrolled in a phase 2b, controlled trial of simtuzumab (SIM). Since SIM was ineffective in this study, treatment groups were combined. GGT was measured at BL and every 12 weeks through this 96-week study. Liver fibrosis was staged according to the Ishak classification (BL, W48 and W96). Cox proportional hazards regression determined associations between BL GGT and change at W12 with PSC-related clinical events (e.g. decompensation, ascending cholangitis, cholangiocarcinoma, liver transplantation). In non-cirrhotic patients at BL, logistic regression determined the association between serum GGT and progression to cirrhosis at W96. Discrimination of GGT was determined based on the area under the receiver operating characteristic (AUROC) curve.
Results: The median age was 45 years, 64% were male, 62% were on UDCA, and the median (IQR) GGT, alkaline phosphatase (ALP), and Enhanced Liver Fibrosis (ELF) scores at BL were 236 U/L (99–524), 260 U/L (129–401), and 9.46 (8.60–10.43), respectively. 40% (n = 94) of subjects had bridging fibrosis and 11% (n = 25) had cirrhosis. At BL, GGT was significantly correlated with ALP (Spearman $\rho = 0.80$), bilirubin ($\rho = 0.34$), ELF score ($\rho = 0.42$), and fibrosis stage ($\rho = 0.36$; all $p < 0.001$). By W96, 47 patients (20%) developed a PSC-related clinical event (ascending cholangitis [n = 27], jaundice [n = 10], cholangiocarcinoma [n = 3], ascites [n = 2], encephalopathy [n = 2], variceal hemorrhage [n = 2], sepsis [n = 1]) and 30/191 biopsied subjects (16%) progressed to cirrhosis. Median BL GGT was higher in patients with than without an event (430 [IQR 212–730] vs. 188 U/L [75–482]; $p < 0.001$), whereas median change in GGT at W12 was lower in patients with an event (-28 [IQR -100, 17] vs. 1 U/L [-23, 35; $p = 0.003$). The risk of clinical events increased with higher BL GGT (HR per 10-U/L: 1.007; 95% CI 1.001–1.013; $p = 0.015$), but change in GGT at W12 was not significant (HR per 10-U/L: 0.981; 0.962–1.001; $p = 0.065$) after adjustment for BL GGT. The AUROC for BL GGT to predict clinical events was 0.67 (95% CI 0.59–0.75). After adjustment for BL serum ALP, bilirubin, ELF, and fibrosis stage, GGT was not associated with PSC-related events (HR per 10-U/L: 0.995; 95% CI 0.985–1.006; $p = 0.37$). Progression to cirrhosis was not associated with GGT at BL or its change at W12.
Conclusion: In the clinical trial setting, serum GGT levels are not associated with PSC-related disease progression after adjustment for other prognostic factors. Based on these data, GGT cannot be considered a validated surrogate endpoint for use in clinical trials of this condition.

FRI-457

Metabolomics in the progression of fatty liver disease

J. Troisi[1,2], M. Masarone[1], R. Caruso[1], M. Persico[1]. [1]*University of Salerno, Department of Medicine and Surgery - Internal Medicine and Hepatology Division, Baronissi (Salerno), Italy;* [2]*Theoreosrl – Spin-off company of the University of Salerno, Salerno, Italy*
Email: mario.masarone@gmail.com

Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD) encompasses a wide spectrum of diseases that range from simple steatosis (NAFL) to steatosis with inflammation and fibrosis (namely Non-Alcoholic Steato-Hepatits or NASH) up to cirrhosis and

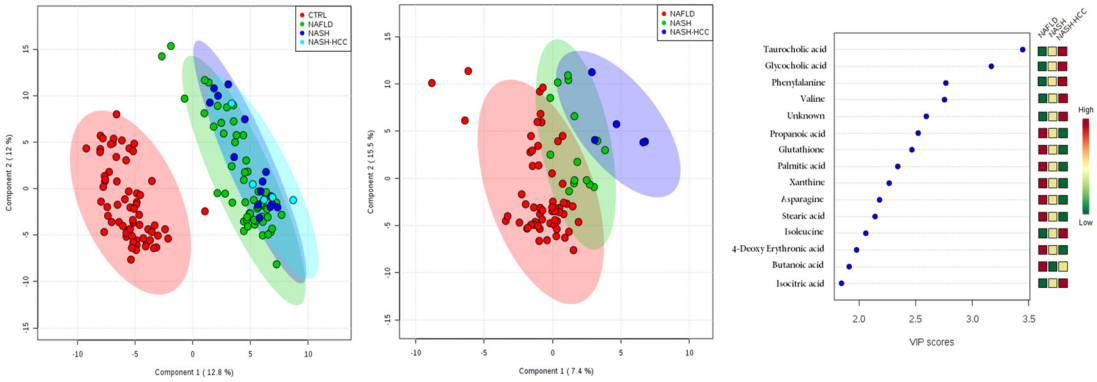


Figure 1: (abstract: 457)

hepatocellular carcinoma (HCC). The greatest challenge in this field is to recognize the patient with a more severe and/or progressive pathology. A reliable non-invasive method based on biomarkers does not exist. Metabolomics is a novel and powerful method to discover biomarkers and gives insights on diseases pathophysiology. Few studies have applied this technique to NAFLD patients.

Aims: to apply metabolomics to understand if simple steatosis, steatohepatitis and hepatocellular carcinoma occurred in NAFLD patients have a peculiar metabolites profile that can differentiate them among each other's and from healthy controls.

Method: Metabolomics signatures were obtained by means of mass spectrometry gas chromatography from 78 NAFLD patients, of whom 58 were diagnosed by liver biopsy (42 simple steatosis, 16 NASH) and 20 by clinical, instrumental and laboratory signs (15 NASH-cirrhosis, 5 NASH-HCC), and 67 age and sex matched healthy controls from a local blood bank.

Results: A statistical analysis with the "Partial Least Square Discriminant Analysis" (PLS-DA) was used to reveal class separation in metabolomics profiles between patients and controls and among each class of NAFLD, and to reveal the metabolites principally contributing to class differentiation. PLS-DA score plot showed a significant differentiation between NAFLD patients and controls (R^2 = 0.822, Q^2 = 0.743, $p < 0.001$), and also among the various clinical presentations of NAFLD (R^2 = 0.782, Q^2 = 0.698, $p < 0.05$). In particular: Glycocholic acid, Taurocholic acid, Phenylalanine, branched-chain amino acids increased at the increase of the severity of the disease from simple steatosis to NASH, NASH-cirrhosis and HCC, while glutathione decreased (ANOVA multiple comparisons with Tukey HSD correction $p < 0.001$ for each).

Conclusion: These preliminary results suggest that metabolomics profiles of NAFLD patients could be a useful tool to non-invasively diagnose NAFLD, discriminate among the various stages of the disease and give other insights into the pathophysiology of NAFLD.

FRI-458

Comparison of HepaFat-Scan and controlled attenuation parameter for the estimation of hepatic steatosis in patients with non-alcoholic fatty liver disease using histology as the reference standard

S.H. Menon[1], L.L. Lai[2], W.-K. Chan[2], N.R.N. Mustapha[3], A. Vijayananthan[1], S. Mahadeva[2]. [1]*University of Malaya, Department of Bio-Medical Imaging, Kuala Lumpur, Malaysia;* [2]*University of Malaya, Department of Medicine, Kuala Lumpur, Malaysia;* [3]*Hospital Sultanah Bahiyah, Department of Pathology, Alor Setar, Malaysia*
Email: wahkheong2003@hotmail.com

Background and Aims: We aimed to compare HepaFat-Scan, an MRI-based technology for the measurement of liver fat, with Fibroscan controlled attenuation parameter (CAP) for the estimation of hepatic steatosis in patients with non-alcoholic fatty liver disease (NAFLD).

Method: Consecutive NAFLD patients who underwent liver biopsy at the University of Malaya Medical Centre were enrolled in this study, and had MRI and Fibroscan examinations on the same day. Histopathological examination of liver biopsy specimen was performed by a single expert pathologist who was blinded to clinical data and reported according to Non-alcoholic Steatohepatitis Clinical Research Network scoring system. Area under receiver operating characteristic curve (AUROC) was used to evaluate the diagnostic accuracy of HepaFat-Scan and CAP for the estimation of hepatic steatosis using liver histology as the reference standard.

Results: Data for 72 patients were analyzed (mean age 58.3 ± 9.8 years, males 45.8%, mean body mass index 29.9 ± 4.0 kg per m^2, central obesity 95.8%). The distribution of steatosis grades was as follows: S1, 33%; S2, 57% and S3, 10%. The AUROC (95% confidence interval), sensitivity, specificity, positive predictive value and negative predictive value of HepaFat-Scan and CAP for the diagnosis of steatosis grades ≥ S2 and S3 using previously validated cut-offs are shown in Table 1.

Table 1: The AUROC (95% confidence interval), sensitivity, specificity, positive predictive value and negative predictive value of HepaFat-Scan and CAP for the diagnosis of steatosis grades ≥ S2 and S3 using previously validated cut-offs.

	≥S2	S3
HepaFat-Scan		
AUROC (95% confidence interval) (0.74–0.93)	0.90 (0.80–0.96)	0.85
Optimal cut-off, %	12.08	16.23
Sensitivity, %	84.1	27.3
Specificity, %	81.8	72.9
Positive predictive value, %	90.2	27.3
Negative predictive value, %	72.0	97.7
Controlled attenuation parameter		
AUROC (95% confidence interval) (0.47–0.71)	0.71 (0.58–0.81)	0.60
Optimal cut-off, dB/m	268	280
Sensitivity, %	95.6	100
Specificity, %	18.2	15.1
Positive predictive value, %	70.5	12.1
Negative predictive value, %	66.7	100
p for comparison of AUROC of HepaFat-Scan and controlled attenuation parameter	0.016	0.019

Conclusion: The HepaFat-Scan has higher accuracy for the estimation of hepatic steatosis in NAFLD patients compared with the CAP.

FRI-459

Measuring what matters to patients: the development of the NASH-CHECK, a new patient-reported outcome instrument for nonalcoholic steatohepatitis

L. Doward[1], M.M. Balp[2], J. Twiss[1], C. Slota[3], D. Cryer[4], A. Langford[5], R. Collen[6], N. Agashivala[7], C. Brass[7], Q. Anstee[8], A. Sanyal[6]. *[1]RTI-Health Solutions, Patient-Centered Outcomes Assessment, Manchester, United Kingdom; [2]Novartis Pharma Ag, HEOR, Basel, Switzerland; [3]RTI-Health Solutions, Patient-Centered Outcomes Assessment, Research Triangle Park, United States; [4]Global Liver Institute, Washington DC, United States; [5]British Liver Trust, Bournemouth, United Kingdom; [6]Virginia Commonwealth Univertsity, Medical College of Virginia, Richmond, United States; [7]Novartis Pharmaceuticals Corporation, East Hanover; [8]Newcastle University, Newcastle, United Kingdom*
Email: ldoward@rti.org

Background and Aims: Nonalcoholic steatohepatitis (NASH) is a progressive form of fatty liver disease characterized by excessive liver fat accumulation, inflammation, cell injury and fibrosis. Aim was to develop a NASH-specific patient-reported outcome (PRO) measure (NASH-CHECK) suitable for clinical practice and clinical trials with NASH patients.
Method: A NASH conceptual model was developed based on review of published/grey literature, social media patient narratives and medical/patient expert (US/UK) review. The model guided concept elicitation (CE) interviews with NASH patients recruited via a tertiary care centre (USA). NASH-CHECK content was generated via thematic analysis of CE data and review by clinical experts and patient representatives. Cognitive debriefing (CD) interviews evaluated NASH-CHECK content validity.
Results: Literature/social media review confirmed that NASH profoundly impacts patient functioning and health-related-quality-of-life (HRQOL). 23CE/15CD interviews were conducted. CE sample: 18 females; mean age = 55.9(31.0–73.0 yrs); biopsy-diagnosed NASH = 11(F1 = 1; F2 = 5; F3 = 10); mean yrs since diagnosis = 3.9; mean BMI = 36.4(26.1–43.3). CD sample: 7 females; mean age = 53.6 (31.0–68.0 yrs); biopsy-diagnosed NASH = 11[F1 = 3; F2 = 2; F3 = 6]; mean yrs since diagnosis = 3.2; mean BMI = 36.4(26.1–43.3). No patients had evidence of hepatic decompensation. CE interviews: key symptoms reported included pain in upper right abdomen (n = 14), fatigue (n = 18), poor sleep quality (n = 12), and cognition problems (impaired memory [n = 13; reduced focus [n = 11]); key HRQOL impacts included impaired physical functioning (reduced capacity to walk short distances), ability to conduct daily living tasks (e.g. household chores/personal care), reduced quality of relationships (e.g. pain/fatigue limited willingness/ability to engage in social activities), low mood, anxiety and self-consciousness. The 1st draft NASH-CHECK included 52 items including some duplication to allow patient-selection of preferred phrasing. CE interviews reduced NASH-CHECK to 31-items based on patient preferences for item relevance, acceptability and comprehension. The final version was considered relevant and acceptable to the CD patients.
Conclusion: The study was successful in producing a US English NASH-specific PRO measure assessing symptoms and HRQOL (NASH-CHECK) suitable for psychometric evaluation. Further work is underway to translate and validate this tool in UK and other European territories.

FRI-460

Spatial systems lipidomics reveals nonalcoholic fatty liver disease heterogeneity

K. Scupakova[1], Z. Soons[2], G. Ertaylan[3], K.A. Pierzchalski[1], G.B. Eijkel[1], S.R. Ellis[1], J.W. Greve[4], A. Driessen[5], T.M De Kok[6], S. Rensen[2], S.O. Damink[7], R.M.A. Heeren[8]. *[1]Maastricht University, M4I Institute, Maastricht, Netherlands; [2]Maastricht University, Department of Surgery, Maastricht; [3]Maastricht University, The Maastricht Centre for Systems Biology, Maastricht, Netherlands; [4]Zuyderland Medical Center, Department of Surgery, Heerlen, Netherlands; [5]Maastricht University, Department of Pathology, Maastricht, Netherlands; [6]Maastricht University, Department of Toxicogenomics, Maastricht, Netherlands; [7]Maastricht University Medical Centre, Maastricht University Medical Center, Maastricht, Netherlands; [8]M4I Institute, M4I Institute, Maastricht, Netherlands*
Email: k.scupakova@maastrichtuniversity.nl

Background and Aims: Hepatocellular lipid accumulation is the hallmark of nonalcoholic fatty liver disease. However, the types of lipids associated with disease progression are debated, as is the impact of their localization. Traditional lipidomics analysis using liver homogenates or plasma dilutes and averages lipid concentrations, and does not provide spatial information about lipid distribution. We aimed to characterize the distribution of specific lipid species in relation to fatty liver disease severity by performing label-free molecular analysis by mass spectrometry imaging (MSI).
Method: Fresh frozen liver wedge biopsies from severely obese subjects undergoing bariatric surgery (n = 23) with various degrees of nonalcoholic fatty liver disease were cryosectioned and analyzed by matrix-assisted laser desorption/ionization (MALDI)-MSI. Molecular

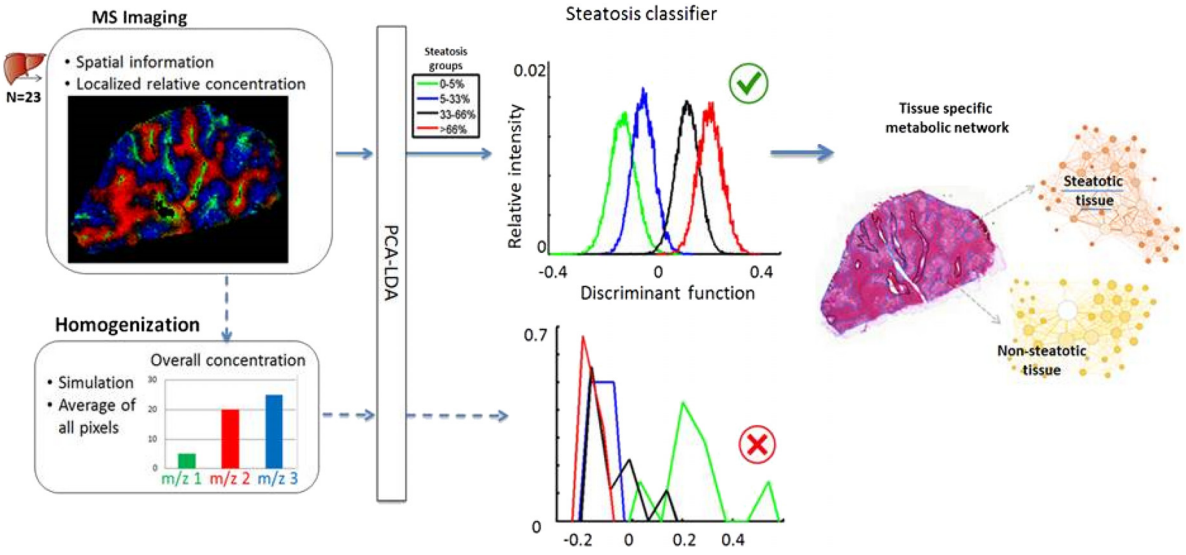


Figure 1: (abstract: 460)

identification was verified by tandem MS. Tissue sections were histopathologically stained and annotated according to the Kleiner classification before co-registration with the MSI dataset. Lipid pathway analysis was performed and linked to local proteome networks.

Results: Spatially resolved lipid profiles showed pronounced differences between non-steatotic and steatotic tissues. Lipid identification and network analyses revealed phosphatidylinositols and arachidonic acid metabolism in non-steatotic regions, whereas (very) low–density lipoprotein (LDL) and VLDL metabolism was associated with steatotic tissue regions. Supervised and unsupervised discriminant analysis using lipid based classifiers outperformed simulated analysis of liver tissue homogenates in predicting steatosis severity.

Conclusion: We conclude that lipid composition of steatotic tissue and non-steatotic tissue is highly distinct, implying that spatial context is important for understanding the mechanisms of lipid accumulation in nonalcoholic fatty liver disease. MSI combined with principal component – linear discriminant analysis linking lipid and protein pathways represents a novel tool that enables detailed and comprehensive studies of the heterogeneous nature of nonalcoholic fatty liver disease.

FRI-461

Validation of a quantitative imaging assessment biomarker metric for MRI-estimated proton density fat fraction in a large multi-center clinical trial

M. Middleton[1], W. Henderson[1], J. Cui[1], A. Mamidipalli[1], R. Myers[2], S. Djedjos[2], C. Yeaton[2], B. Mccolgan[2], R. Loomba[3], C. Sirlin[4]. *[1]Liver Imaging Group, Department of Radiology, San Diego, United States; [2]Gilead Sciences Inc., Liver Diseases Therapeutic Area, Foster City, United States; [3]UCSD School of Medicine, Department of Gastroenterology, La Jolla, United States; [4]Liver Imaging Group, Department of Radiology, La Jolla, United States*
Email: msm@ucsd.edu

Background and Aims: Drug development clinical trials increasingly rely on quantitative imaging biomarkers to support study aims. In addition to rigorous imaging intake quality control and site qualification, there is also a need to determine whether individual analyses are acceptable. For a 29-site clinical trial in adults with nonalcoholic steatohepatitis (NASH) and fibrosis stages F2-F3 (Gilead Sciences, GS-1497; NCT02466516), in a retrospective analysis we found that using a per-segment coefficient of determination (r^2; a measure of goodness of least-squares fitting to estimate proton density fat fraction [PDFF] values) cutoff value of 0.985 resulted in exclusion of 1–6 (of 9) segments per MRI in 54/204 MRIs, with no loss of reportable results (Middleton et al, AASLD poster # 2110, Washington D.C., October 20–24, 2017). We now need to validate that result in a separate, independent cohort. Thus, the aim of this analysis was to validate that there is minimal or no loss of reportable results using a PDFF-fitting r^2 cutoff value of 0.985 in an independent, multi-center study of adults with inferred NASH (PDFF ≥ 8%, MRE liver stiffness ≥ 2.5 kPa), or with biopsy-determined NASH (Gilead Sciences, GS-3989; NCT02856555).

Method: For each of the 424 study MRIs obtained across 40 study sites, ROIs were placed in each of the nine Couinaud liver segments for images acquired from a magnitude six-echo gradient-echo PDFF-estimation MRI sequence. To compare to the prior study, segmental data was deemed adequate if the r^2 value was ≥ 0.985. MRI PDFF values were calculated as the mean of PDFF values of all adequately analyzed segments. An MRI PDFF value was considered analyzable if three or more of the nine segmental PDFF values were deemed adequate.

Results: For the 414/424 (97.6%) MRIs where the correct PDFF sequence was acquired and ROIs were placed in all 9 segments, using an r^2 value of 0.985 we found that all but 2 MRIs were deemed analyzable. 129/414 (31.2%) of those MRIs showed segmental inadequacy in 1–6 segments (for those cases, there were 2.13 ± 1.52 inadequate segments/MRI, compared to 2.07 ± 1.41 inadequate segments/MRI for the prior analysis). One additional MRI in this analysis would have been marginally analyzable if the cutoff was 0.982, and one MRI was not analyzable under any circumstances. Excluding those 2 cases, the mean PDFF value of those 129 MRIs was 0.05% higher using the r^2 = 0.985 cutoff, than using no cutoff; which is not clinically meaningful.

Conclusion: This study validates in an independent study that setting a conservative, high r^2 cutoff value of 0.985 for MRI-exam PDFF analyzability to exclude segmental analyses of lesser quality can be accomplished in a large multi-center clinical trial setting without appreciable loss of reportable results. Further work is needed to determine the effect of using an r^2 cutoff on PDFF accuracy, repeatability, and reproducibility.

FRI-462

FIBROSpect®NASH serum test identifies advanced liver fibrosis in patients with nonalcoholic steatohepatitis: Results of a validation study

M. Abdelmalek[1], C. Guy[1], A.M. Diehl[1], X. LI[2], L. Mimms[2], K. Hester[2], A. Jain[2], R. Loomba[3]. *[1]Duke University, Division of Gastroenterology, Durham; [2]Prometheus Laboratories Inc., Research & Development, San Diego, United States; [3]University of California at San Diego, Division of Gastroenterology, San Diego, United States*
Email: roloomba@ucsd.edu

Background and Aims: In patients with nonalcoholic steatohepatitis (NASH), advanced (stage 3–4) hepatic fibrosis is the primary predictor for liver-related morbidity and mortality. FIBRO*Spect* NASH (Prometheus Laboratories Inc., San Diego, CA) has been developed as a potential non-invasive serum blood test to risk-stratify patients with NASH. The aim of this study was to validate the diagnostic performance of FIBRO*Spect* NASH in a second independent cohort of patients with biopsy-proven NASH.

Method: In a cohort of patients with biopsy-proven NASH (n = 396), results of FIBRO*Spect* NASH were trained against fibrosis stage (as defined by NASH CRN criteria) using serum acquired on the same day as liver biopsy. A logistic regression model was developed using concentrations of three serum biomarkers (alpha2-macroglobulin, hyaluronic acid and tissue inhibitor of metalloproteinase-1). The FIBRO*Spect* NASH test was validated in a combined independent cohort (n = 640) of patients with biopsy-proven NASH obtained from two geographically distinct locations.

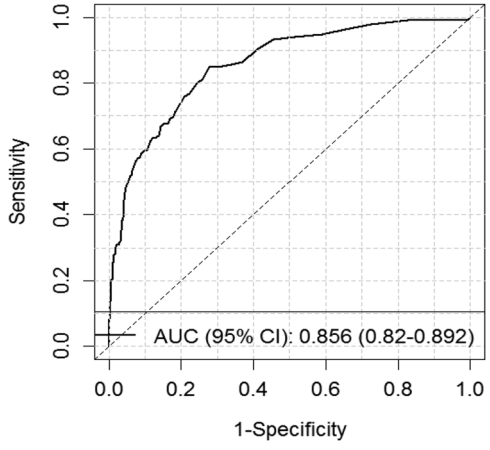


Figure 1: ROC Curve of F0-F2 vs. F3-F4 in Validation Cohort of NASH patients

Results: The mean age of the 640 patients was 49.6 ± 12.8 years and 39% were of male gender. The distribution of fibrosis stages 0, 1, 2, 3, and 4 was 209 (33%), 168 (26%), 130 (20%), 115 (18%) and 18 (3%), respectively. The prevalence of advanced hepatic fibrosis (F3/F4) of 21% in this cohort was comparable to the reported literature. The

model had an AUROC of 0.86 (95% CI: 0.82–0.89) (Figure 1). Sensitivity and specificity for identifying NASH patients with advanced hepatic fibrosis was 80% (95% CI: 72–86%) and 76% (95% CI: 72–79%), respectively.
Conclusion: FIBRO*Spect* NASH test proves to have robust performance when validated in an independent cohort of patients with biopsy-proven NASH. FIBRO*Spect* NASH can non-invasively identify those NASH patients with advanced hepatic fibrosis.

FRI-463
The association of circulating microRNAs (miRs) with liver fibrosis stage and the impact of selonsertib treatment in patients with NASH

M. Charlton[1], A.M. Diehl[2], N. Sarkar[3], B. Li[3], L. Wang[3], A. Billin[3], S. Djedjos[3], M. Subramanian[3], R. Myers[3], N. Afdhal[4], S. Caldwell[5], Z. Goodman[6], R. Loomba[7]. *[1]University of Chicago, Chicago, United States; [2]Duke Clinical Research Institute, Durham, United States; [3]Gilead Sciences, Foster City, United States; [4]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, United States; [5]University of Virginia, Charlottesville, United States; [6]Inova Fairfax Hospital, Falls Church, United States; [7]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States*
Email: stephen.djedjos@gilead.com

Background and Aims: Circulating miRs have been studied as potential biomarkers of NASH. We assessed: 1) associations between miRs and liver fibrosis and 2) the modulation of miR expression in response to selonsertib (SEL) treatment in patients with NASH enrolled in a Phase 2 trial.
Method: Plasma samples were collected from 72 subjects with biopsy-confirmed NASH (NASH CRN F2-3 fibrosis and NAFLD Activity Score [NAS] ≥5). Subjects were treated with SEL alone or in combination with simtuzumab (SIM) or SIM alone for 24 weeks. Liver biopsies were performed at baseline (BL) and week 24 (W24). Selected miRs (n = 301) were measured at BL, W12, and W24 by qPCR. Differential expression analysis using the Linear Models for Microarray Data (limma) method and Spearman correlations (r_s) were performed. The utility of miRs alone or in combination with other markers to discriminate advanced fibrosis (F3-4 vs. F1-2) or fibrosis response (≥1-stage reduction in fibrosis vs. no improvement at W24 vs. BL) was determined using areas under receiver operating characteristics (AUROC) curves.

Top 10 miRs associated with fibrosis stage F1-2 vs F3-4 at W24				Top 10 miRs with change in expression correlated with change in fibrosis stage at W24		
miRs	Fold Change (F3-4 vs F1-2)	AUROC	p-value	miRs	r_s	p-value
miR-125b-5p	1.45	0.71	0.01	miR-365a-3p	0.35	0.009
miR-29a-3p	1.27	0.71	0.01	miR-125b-5p	0.33	0.013
miR-136-5p	−2.08	0.69	0.01	miR-34a-5p	0.33	0.014
miR-30a-5p	1.37	0.67	0.02	miR-215-5p	0.30	0.025
miR-29c-3p	1.23	0.67	0.02	miR-194-5p	0.30	0.025
miR-378a-3p	1.30	0.67	0.03	miR-378a-3p	0.30	0.025
miR-34a-5p	1.60	0.66	0.03	miR-99a-5p	0.30	0.027
miR-99a-5p	1.35	0.65	0.04	miR-1260b	−0.39	0.006
miR-150-5p	1.46	0.64	0.04	let-7i-5p	−0.30	0.025
miR-375	1.46	0.63	0.05	miR-122	0.29	0.028

Results: At BL, miR-136-5p was 1.58 fold lower in patients with F2 compared to F3 fibrosis (p = 0.046). At W24, 10 miRs, including miR-136-5p, showed modest AUROCs (0.63–0.71) for distinguishing patients with advanced vs. mild fibrosis (F3-4 vs. F1-2; Table). Changes in expression of 12 miRs from BL to W24 were significantly correlated with change in fibrosis stage (all p < 0.05; Table). Expression of miR-136-5p alone or with CK18-M30 and MRE at W24 most accurately distinguished fibrosis responders from non-responders with AUROCs of 0.73 (95% CI 0.58, 0.89) and 0.89 (95% CI 0.79, 0.98), respectively. Twelve miRs were modulated by SEL treatment. Among them, miR-122-5p, miR-215-5p, miR-505-3p, miR-885-5p, and miR-34a-5p were down-regulated by SEL treatment with miR-885-5p having the largest fold change of −1.56 (p = 0.005).
Conclusion: In this Phase 2 trial, we identified a panel of miRs associated with hepatic fibrosis and changes in fibrosis following SEL treatment. The accuracy of a miR to determine fibrosis response was enhanced when combined with other biomarkers. These observations require validation in future studies.

FRI-464
ELF test in NAFLD: Poor concordance with liver stiffness values

L.I. Prat, M. Guerrero, E. Buzzetti, D. Roccarina, A. Goyale, M. Ismail, E. Tsochatzis. *UCL Institute for Liver and Digestive Health, Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom*
Email: laura.iognaprat@gmail.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the leading cause for secondary care referrals in most western countries. Despite its high prevalence, only a minority of patients develops fibrosis and subsequent liver-related outcomes. The ELF test is a validated tool for non-invasive assessment of liver fibrosis and is recommended by the National Institute for Clinical Excellence (NICE) in the UK for screening NAFLD patients for advanced fibrosis. We explored the concordance of ELF with FibroScan and its diagnostic accuracy compared to liver biopsy in consecutive patients referred because of a high ELF score.
Method: We selected all patients who had been referred from 2014 to 2017 according to local referral pathways because of a suspicion of NAFLD and an ELF test ≥9.5. Clinical and laboratory data were collected. ELF test was compared to liver biopsy and/or liver stiffness assessed with FibroScan™.
Results: 170 patients fulfilled our inclusion criteria. Characteristics of the population were: 52% male, mean age 65 ± 10 years, mean BMI 32 ± 6 Kg/m^2, 49% T2DM, 69% dyslipidaemia, 69% hypertension. Liver biopsy was available for 56 (33%) patients and FibroScan™ measurements for 117 (69%) patients. 16 (28%) liver biopsies showed advanced fibrosis and 40 (70%) showed NASH. Liver stiffness values were <10 kPa in 95 (81%) of patients, <8 kPa in 85 (73%) and <6 kPa in 58 (50%). Therefore, the concordance of FibroScan and ELF for significant fibrosis was 19% and there was also a significant discordance in 50% of the cases. Based on biopsy confirmation of advanced fibrosis, the positive predictive value of ELF > 9.5 was 32%. Thirty-four patients with a high ELF score had no or minimal fibrosis (F0-F1) on liver biopsy; only three and one of these patients had FibroScan values above 8 kPa and 10 kPa respectively. All patients with biopsy proven advanced fibrosis had FibroScan values >8 kPa. We could not find independent predictors of a false positive ELF test.
Conclusion: The ELF test has a poor concordance with liver stiffness for the diagnosis of advanced fibrosis. When ELF is used as a screening tool, the use of a second non-invasive test is warranted for positive results, in order to better stratify patients needing a liver biopsy.

FRI-465
Aetiology and severity of liver disease in HIV positive patients with suspected NAFLD: Lessons from a cohort with available liver biopsies

L.I. Prat[2], D. Roccarina[2], R. Lever[3], A. Rodger[3], A. Hall[4], S. Bhagani[5], E. Tsochatzis[2]. *[1]UCL Institute for Liver and Digestive Health, Royal Free Hospital, London, United Kingdom; [2]UCL Institute for Liver and Digestive Health, Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom; [3]Infectious Diseases/HIV Medicine, Royal Free Hospital, London, United Kingdom; [4]UCL Institute for Liver and Digestive Health, Cellular Pathology, Royal Free Hospital, London, United Kingdom;*

[5]*Infectious Diseases/HIV Medicine, Royal Free Hospital, London, United kingdom*
Email: l.prat@ucl.ac.uk

Background and Aims: The spectrum of liver injury among HIV positive people is variable; in particular non alcoholic fatty liver disease (NAFLD) seems to occur at a higher prevalence among HIV positive people compared to HIV negative. We retrospectively evaluated the aetiology and severity of liver disease in a group of HIV positive patients without viral hepatitis co-infection and with available liver biopsies. We further estimated the accuracy of two non-invasive tools (FIB4 and elastography) for the assessment of liver fibrosis.
Method: We evaluated all liver biopsies performed at Royal Free Hospital from 2000 to 2017 in HIV positive patients with abnormal transaminases. Exclusion criteria were: known viral hepatitis, opportunistic infections, liver malignancy, lack of sufficient clinical data or suboptimal histological samples. Clinical data were collected and FIB4 was calculated for every patient. Liver stiffness was assessed with FibroScan™.
Results: 97 biopsies fulfilled our criteria. Characteristics of the population were: 81% male, mean BMI 27 Kg/m^2, 11% diabetes, 47% dyslipidaemia. Median duration of HIV infection at time of biopsy was 126 months and 90% had undetectable viral load. The most common histological findings were in keeping with NAFLD (28%) and non specific changes (28%) followed by normal histological findings (13%). 19 (20%) patients had significant fibrosis and 11 (11%) had advanced fibrosis. The prevalence of FIB4 < 1.3, 1.3–2.67 and >2.67 were 38%, 46% and 16% respectively. The 1.3 FIB4 cut-off had a specificity of 82% and NPV of 95% for exclusion of advanced fibrosis. Fibroscan was available in 27 (28%) patients and 33% had a liver stiffness ≥ 7.5 kPa. Fibroscan showed a sensitivity of 80%, specificity of 77% and NPV of 94% for exclusion of significant fibrosis. Among patients with NAFLD (n = 27), 5 (18%) had advanced fibrosis while the majority (56%) did not have any fibrosis. The NPV of FIB4 and Fibroscan for advanced and significant fibrosis in these patients was 93% and 100% respectively.
Conclusion: Among HIV positive patients with elevated liver function tests and available histology, a surprisingly high number of patients had non-significant changes or even normal histological findings. The prevalence of NAFLD was lower than reported in other series. Use of non-invasive tools with a high NPV for significant fibrosis can help reduce the number of required biopsies.

FRI-466
Accurate prediction of clinical disease progression in patients with advanced fibrosis due to NASH using a Bayesian machine learning approach

J.C. Latourelle[1], J. Tu[1], R.K. Das[1], L. Furchtgott[1], B. Schoeberl[1], B. Smiechowski[1], B.W. Church[1], I.G. Khalil[1], B. Hayete[1], S. Djedjos[2], T. Nguyen[2], Y. Xiao[2], R.A. Schall[2], G. Chen[2], M. Subramanian[2], R. Myers[2], V. Ratziu[3], N. Afdhal[4], J. Bosch[5], Z. Goodman[6], S. Harrison[7], A. Sanyal[8]. [1]*GNS Healthcare, Cambrdige, United States;* [2]*Gilead Sciences, Foster City, United States;* [3]*Hôpital Pitié-Salpêtrière, Paris, France;* [4]*Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, United States;* [5]*Inselspital, Bern University, Switzerland, and IDIBAPS, University of Barcelona, Spain, Barcelona, Spain;* [6]*Inova Fairfax Hospital, Falls Church, United States;* [7]*Pinnacle Clinical Research, San Antonio, United States;* [8]*Virginia Commonwealth University, Richmond, United States*
Email: stephen.djedjos@gilead.com

Background and Aims: Fibrosis is the most important determinant of disease progression in patients with NASH. Our aim was to identify markers of disease progression using machine learning.
Methods: A Bayesian machine learning platform (REFS™; GNS Healthcare; Cambridge, MA) was applied to data from two trials of simtuzumab in adults with NASH and advanced fibrosis (NASH CRN F3-F4). The trials were stopped at Week 96 due to lack of efficacy, so treatment groups were combined for this analysis. At baseline (BL), we used clinical, histologic, serum fibrosis marker, and genetic data to construct an ensemble of models to predict risk of progression to cirrhosis in subjects with bridging fibrosis, and adjudicated clinical events in cirrhosis. The predictive performance of the models was assessed using the concordance index (C-index) in-sample and by internal 3-fold cross validation (CV) in the training set and further validated in a test sample (20% of the cohort).
Results: 477 subjects with advanced fibrosis were randomized; 248 subjects with complete genetic and histologic data were included in the training set and 77 in the test set. Predictive models that included full BL data including histology performed well (Table). Similar performance was observed in noninvasive models excluding histology and models excluding genetic data. Variables commonly identified in the predictive model ensemble for risk of progression to cirrhosis among subjects with bridging fibrosis were α-smooth muscle actin expression on biopsy (in 79% of ensembles), ELF score (64%), platelets (46%), and FIB-4 (34%) in the full model, and ELF (87%) and platelets (69%) in the noninvasive model. For the prediction of risk of clinical events in cirrhotic subjects, variables were similar in the full and noninvasive models, including direct bilirubin (94% and 92% of ensembles) and alkaline phosphatase (7.4% and 9.0%).

Table: Model Performance

		C-Index (95% CI)		
Cohort	Model*	In-sample	3-fold CV	Validation Set †
Bridging fibrosis (n = 124)	Full	0.92 (0.76–0.98)	0.79 (0.61–0.90)	0.77 (0.65–0.90)
	Noninvasive	0.90 (0.73–0.96)	0.80 (0.61–0.91)	0.79 (0.65–0.92)
Cirrhosis (n = 124)	Full	0.83 (0.64–0.93)	0.72 (0.52–0.86)	0.66 (0.55–0.78)
	Noninvasive	0.83 (0.64–0.93)	0.68 (0.48–0.83)	0.68 (0.58–0.78)

*Full models include all genetic, histologic, and clinical data at BL, including HVPG in patients with cirrhosis. Noninvasive models exclude histologic and HVPG data.
†33 subjects with bridging fibrosis and 44 with cirrhosis.

Conclusion: Models generated using machine learning utilizing only noninvasive data can accurately predict the risk of clinical disease progression in patients with advanced fibrosis due to NASH.

FRI-467
A new score to predict presence of advanced fibrosis in NAFLD and comparison with established scoring systems

H. Hagström[1], P. Nasr[2], M. Ekstedt[2], U. Hammar[1], R. Hultcrantz[1], P. Stal[1], S. Kechagias[2]. [1]*Karolinska Institutet, Sweden;* [2]*Linköping University, Sweden*
Email: hannes.hagstrom@ki.se

Background and Aims: Detection of advanced fibrosis in liver biopsy (stage 3–4) is the most robust predictor of mortality and liver-related morbidity in nonalcoholic fatty liver disease (NAFLD). Serum markers have been proposed as alternatives to biopsy but have shortcomings in diagnostic accuracy. We aimed to create a new non-invasive scoring system to identify advanced fibrosis in a well-defined cohort of biopsy-proven NAFLD patients, and to compare this to established scoring systems.
Method: We included 646 biopsy-proven NAFLD patients and investigated possible predictors of advanced fibrosis. Candidate predictors were age, sex, body mass index (BMI), type 2 diabetes, haemoglobin, platelets, glucose, creatinine, ferritin, ALT, AST, ALP, γGT, bilirubin, PK-INR, albumin, cholesterol, and triglycerides. All parameters were obtained at the time of biopsy. We used backward selection with an alpha of 0.20 to identify relevant predictors. Model performance was evaluated using 20-fold cross-validation. Missing values were imputed with predictive mean matching using 10-fold multiple imputation. AUC estimates from the different imputations were combined using Rubin's rules. The new score was compared to the FIB-4 index and the NAFLD fibrosis score (NFS).

Results: Age, AST, BMI, glucose, γGT and platelets were included in the final model. The new score was calculated as:

$$\text{Score} = -13.32 + 0.09^{*}\text{BMI} + 0.02^{*}\text{AST} + 0.31^{*}gGT - 0.008^{*}\text{TPK} + 0.04^{*}\text{age} + 1.27^{*}\text{glucose}$$

The score can be transformed into a probability for advanced fibrosis by the equation *exp(Score)/(1 + exp(Score))*.
The new score predicted advanced fibrosis with an AUC of 0.80, compared to 0.79 for the FIB-4 index and 0.76 for the NFS (figure 1). An upper cut-off for the score of –3.17 identified cases with advanced fibrosis with a sensitivity of 0.90 and a specificity of 0.39, while a lower cut-off of –0.57 had a specificity of 0.95 to exclude cases with advanced fibrosis, with a sensitivity of 0.28.

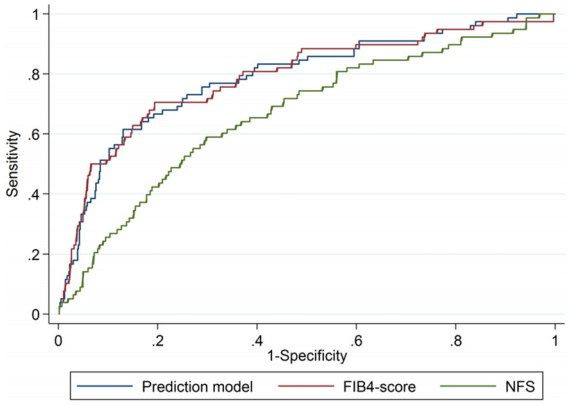


Figure 1: ROC curve for prediction of advanced fibrosis for the new score (Prediction model), the FIB-4 score and the NAFLD fibrosis score (NFS)

Conclusion: The new score performed similarly to established scoring systems for prediction of advanced fibrosis in NAFLD. Validation of the new score in other cohorts is needed in order to assess if it provides superior diagnostic accuracy compared to established algorithms.

FRI-468

Evaluation of severity of hepatic fibrosis and steatosis in biopsy-proven NAFLD patients using MR imaging, transient elastography, and serum biomarker

Y.-S. Lee[1], J.H. Kim[2], C.H. Lee[3], J.E. Yeon[4], K.S. Byun[5]. *[1]Department of Internal Medicine, Korea University College of Medicine, Seoul, Korea, Rep. of South; [2]Korea University Guro Hospital, Gastroenterology and Hepatology, Seoul, Korea, Rep. of South; [3]Korea University College of Medicine, Department of Radiology, Korea, Rep. of South; [4]Korea University Medical College, Gastroenterology, Seoul, Korea, Rep. of South; [5]Korea University College of Medicine, Department of Internal Medicine, Korea, Rep. of South*
Email: jeyyeon@hotmail.com

Background and Aims: As nonalcoholic fatty liver disease (NAFLD) is becoming a leading cause of chronic liver disease, non-invasive diagnosis of disease severity is urgently needed. For the diagnosis of liver fibrosis, transient elastography (TE) has acceptable accuracy in viral related liver disease. But in patients with severe steatosis, TE has shortage. Aim of our study was plan to analyze hepatic fibrosis, steatosis, and inflammation in patients with biopsy-proven NAFLD using MR imaging, TE, and serum biomarkers.
Method: This is a multicenter prospective study of patients with biopsy-proven NAFLD. The patients were underwent liver biopsy, MRI and TE 6 months before enrollment. MRI examination included mDIXON, MR spectroscopy (MRS), and MR elastography (MRE). TE measured liver stiffness and controlled attenuation parameter (CAP). Twenty serum biomarkers were analyzed using the Luminex Multiplex Assay.
Results: 46 patients with biopsy-proven NAFLD patients were enrolled from October 2016 to May 2017. Mean age and BMI were 51.2 ± 12.8 years and 27.6 ± 7.5 kg/m^2, respectively. Female was dominant (30, 63.4%) and other co-morbidities were diabetes (n = 18, 38.3%), hypertension (n = 16, 34.0%) and dyslipidemia (n = 15, 31.9%). For diagnosis of advanced fibrosis (stage 3–4), the AUROC of MRE tended to be superior (0.88; 95% CI, 0.74–0.97) comparing with TE (0.85; 95% CI, 0.72–0.95) (p = 0.532). For diagnosis of severe steatosis (stage 2–3), CAP (0.69; 95% CI, 0.51–0.83) showed lower AUROC compared with mDIXON (0.83; 95% CI, 0.67–0.93; p = 0.0.35) and MRS (0.83; 95% CI, 0.67–0.93; p = 0.109), respectively. In serum biomarker analysis, increased resistin had a significant association with severe steatosis (stage 2–3) compared to mild steatosis (stage 0–1) (OR = 1.44; 95% CI, 1.01–2.06; p = 0.04). Increased IFN-γ was associated with severe inflammation (stage 2–3) compared to mild inflammation (stage 0–1) (OR = 1.36; 95% CI, 1.01–1.83; p = 0.04). Total PAI-1 showed tendency of association with presence of NASH (OR = 1.063; 95% CI, 0.99–1.14; p = 0.07).
Conclusion: In our preliminary results, MRI (mDIXON, MRS and MRE) tended to identify more severe steatosis and fibrosis compared to TE in patients with biopsy-proven NAFLD. Serum IFN-γ was significantly associated with inflammation and serum resistin was also associated with steatosis. Non-invasive modalities using MRI and serum biomarker could be potential tools for diagnosis and classification of disease severity in patients with NAFLD.

FRI-469

Monocyte subpopulations for non-invasive diagnosis of NAFLD and NASH in a bariatric patient collective

K. Staufer[1,2], K. Scheuba[1], F. Winkler[1], M. Eilenberg[3], F. Langer[3], M. Trauner[4], C. Brostjan[1], G. Prager[3]. *[1]Medical University of Vienna, Surgical Research Laboratories, Vienna, Austria; [2]Medical University of Vienna, Department of Surgery, Division of Transplantation, Vienna, Austria; [3]Medical University of Vienna, Department of Surgery, Division of General Surgery, Vienna, Austria; [4]Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria*
Email: katharina.staufer@meduniwien.ac.at

Background and Aims: Up to 80% of patients with obesity suffer from non-alcoholic fatty liver disease (NAFLD) including non-alcoholic steatohepatitis (NASH). The present study investigated inflammatory-induced changes in monocyte-subpopulations for the non-invasive diagnosis of NAFLD, as well as the differentiation of NASH and non-alcoholic fatty liver (NAFL).
Method: Patients with NAFLD scheduled for bariatric surgery between 07/2015 and 05/2017, as well as healthy controls were consecutively included. The expression profile of monocyte surface markers for the differentiation of classical (CL; CD14++ CD16-), non-classical (NC; CD14+ CD16++) and intermediate monocytes (IM; CD14++ CD16+) were investigated by flow cytometry in EDTA whole blood. According to intra-operative liver biopsy patients were stratified into NAFL and NASH and disease activity was graded based on NAFLD-activity score (NAS).
Results: In total, 80 patients (m:f = 34:46, median BMI: 43,8) und 27 healthy controls (m:f = 15:12, median BMI: 25,0) were included. Seventy-nine percent of patients suffered from NASH, 21% presented with NAFL.
The median absolute concentration of monocyte subpopulations was significantly higher in patients with NAFLD than in healthy controls. In contrast, the relative number of monocyte subpopulations showed a significant rise of IM, as well as a significant decrease in CL in patients with NAFLD, whereas NC were equal in both groups.
Patients with NASH had significantly higher absolute IM/ml, as well as a significantly lower CL/IM ratio than patients with NAFL or healthy controls.
The absolute IM concentration was the most suitable diagnostic marker for NAFLD (AUC 0.861; cut-off > 18.7; sensitivity 71%;

specificity 89%). The CL/IM ratio was the most suitable marker for the presence of NASH (AUC 0.706; cut-off < 20.1; sensitivity 71%; specificity 72%).
Conclusion: Monocyte subpopulations are suited for the non-invasive diagnosis of NAFLD and NASH. The inflammatory process within NASH seems to be reflected by a strong activation of monocytes which can be non-invasively and therefore repeatedly monitored in peripheral blood.

FRI-470
Comparing of noninvasive tests in predicting diagnosis of Nonalcoholic Steatohepatitis

C.F. Braticevici, M. Alexandru, L. Tribus, P. Razvan, P. Ana, A. Necula, U. Radu. [1]*"Carol Davila" University of Medicine and Pharmacy, University Hospital Bucharest, Gastroenterology, Romania*
Email: cfierbinteanu@yahoo.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) encompasses two sub-types of conditions with different prognosis: fatty liver (steatosis) and steatohepatitis (NASH). Many studies have highlighted that the identification of the NASH sub-group is crucial due to its higher risk for liver disease progression toward cirrhosis and end-stage liver disease. The invasive liver biopsy remains the gold standard diagnostic test for NASH. **Aim**: to evaluate and compare the efficacy and clinical utility of three non-invasive methods for identifying NASH among patients diagnosed with NAFLD.
Method: 71 patients with histological proven NAFLD were included in the study. All the patients underwent stable isotope breath tests ^{13}C Methacetin (^{13}C – MBT) and ^{13}C-Octanoate (^{13}C–OBT) for microsomal and mitochondrial liver function and acoustic radiation force impulse (ARFI) elastography, a promising method for assessing liver fibrosis in patients with chronic liver disease. The main endpoint was to evaluate the diagnostic accuracy of each test using the area under receiver operating characteristic curve (AUROC) with 95%CI referring to liver histology (SAF scoring system) as gold standard. The correlation between the non-invasive measurements and liver biopsy was tested using Spearman's coefficient
Results: Patients were divided in two groups according to the histologic characteristics: 31 patients with steatosis and 40 patients with NASH. The ability of non-invasive tests in predicting NASH according to the areas under the curve for ^{13}C - OBT, ARFI and ^{13}C – MBT was: 0.930, 0.867, 0.824 respectively. The best parameter for ^{13}C-OBT was Dose at 15 min (r = 0.625, p < 0.001), for ARFI elastography was 1.20 m/s – ten measurements average (r = 0.597, p < 0.001) and for ^{13}C-MBT was Dose at 20 min (r = –0.602, p < 0.001). ROC analysis for each test: best cutoff, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) are presented in table1.

	^{13}C-MBT	^{13}C-OBT	ARFI elastography
Sensitivity	69.5%	84.6%	76.7%
Specificity	72.9%	81.8%	83.3%
PPV	74.0%	84.6%	91.6%
NPV	69.7%	81.8%	60.0%
Cut-off	27 ^{13}C%	22 ^{13}C%	1.2 m/s
AUROC	0.824	0.930	0.867
(95%CI)	0.723–0.926	0.879–1.000	0.782–0.953

Conclusion: All the noninvasive tests used in our study are promising methods with very good accuracy (for ^{13}C-OBT) and good accuracy (for ARFI elastography and for ^{13}C-MBT) in identifying patients with NASH and may become tools in clinical practice.

FRI-471
Machine learning approaches for non-invasive ultrasound. Based quantitative assessment of liver steatosis

N.D. Lascio[1], C. Avigo[1], A. Salvati[2], N. Martini[3], M. Ragucci[4], S. Monti[5], A. Prinster[4], D. Chiappino[3], M. Mancini[4], F. Bonino[2], M. Brunetto[2], F. Faita[1]. [1]*Institute of Clinical Physiology;* [2]*University of Pisa;* [3]*Tuscany Foundation G. Monasterio;* [4]*Institute of Biostructure and Bioimages;* [5]*IRCSS Sdn*
Email: f.faita@ifc.cnr.it

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is becoming a global epidemic and is considered the most common chronic liver disease in Western countries. We propose a non-invasive and easy-to-use system based on quantitative extraction of features form ultrasound (US) hepatic images and machine learning approaches for the classification of steatosis severity.
Method: The study population included 54 subjects and was divided on the percentage of fat basis assessed by magnetic resonance spectroscopy (MRS) using previously specified cut-off values correspondent to biopsy steatosis classes S0, S1, S2 and S3 as defined in guidelines (Chalasani et al., Hepatology 55: 2005–2023, 2012). In particular, 3 classifications were performed: S0 vs S1S2S3 using a MRS cut-off of 3.12%; S0S1 vs S2S3 using a MRS cut-off of 8.77%; S0S1S2 vs S3 using a MRS cut-off of 13.69%. US images were post-processed in order to assess 5 standard parameters (hepatic-renal

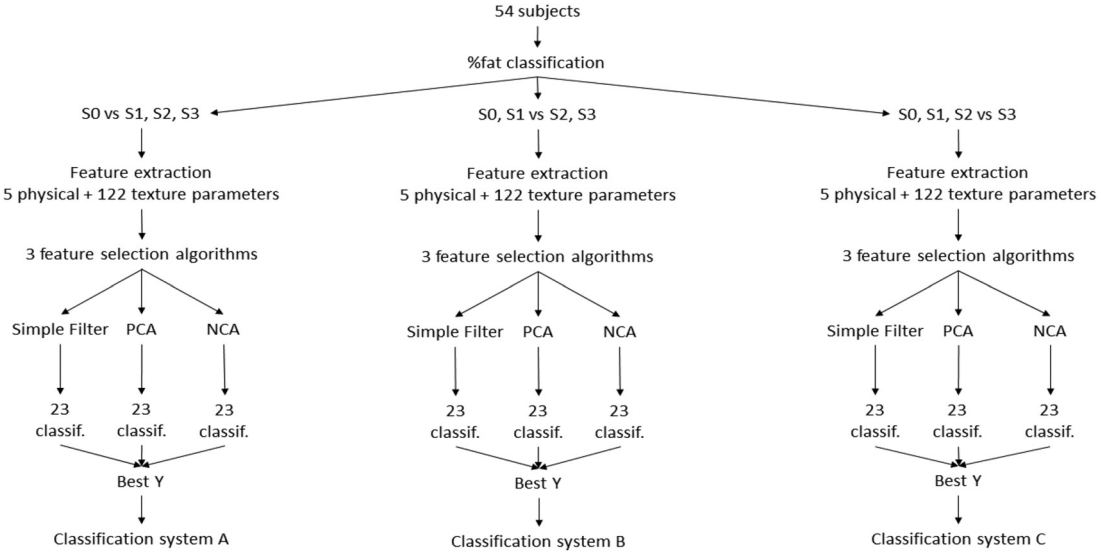


Figure 1: (abstract: FRI-471): Analysis process

ratio (HR), hepatic-portal vein ratio (HPV), attenuation rate (AR), diaphragm visualization (DV) and portal vein wall visualization (PVWvis)) and 122 indexes obtained performing texture analysis. For each MRS-based classification (S0 vs S1S2S3, S0S1 vs S2S3, S0S1S2 vs S3) 3 different algorithms of feature selection were employed (Simple Filter, Principal Component Analysis (PCA), Neighborhood component analysis (NCA)) and 23 classifiers were tested (Figure 1). The best approach for each classification was identified as that maximising the Younden Index (YI) and the area under the receiving operator characteristic (AUROC) curve was also assessed.
Results: NCA approach with Quadratic Discriminant classifier provided the best results for the classification S0 vs S1S2S3 (YI = 0.79, AUROC = 0.91), while NCA approach with Linear Discriminant classifier led to best results for the classification S0S1 vs S2S3 (YI = 0.84, AUROC = 0.99). The best results for the classification S0S1S2 vs S3 was obtained with NCA approach and the Support Vector Machine classifier (YI = 0.8, AUROC = 0.92).
Conclusion: The proposed system can represent a valid approach for quantitative steatosis assessment and could be an excellent alternative to liver biopsy.

FRI-472
Positive predictive value of a physician diagnosis of non-alcoholic steatohepatitis is low and risks high rates of unnecessary liver biopsy

A. Roskilly[1,2], J. Shearer[1,2], I. Rowe[1,2]. [1]*Leeds Institute for Data Analytics, University of Leeds, Hepatology, Leeds;* [2]*Leeds Teaching Hospitals, St James's Hospital, Leeds Liver Unit, Leeds*
Email: aroskilly@doctors.org.uk

Background and Aims Non-alcoholic fatty liver disease (NAFLD) is estimated to affect 25% of western populations and, to date, there are no licensed therapies. Non-alcoholic steatohepatitis (NASH) is its progressive subtype. Current clinical trial treatments aim to prevent progression to end-stage disease through reductions in ongoing liver injury, measured by improvements in NASH or liver fibrosis. Four agents are in phase 3 trials. Phase 2 trials which support the development of these agents provide important information about physicians' diagnosis of NASH alongside the applicability of these treatments.
The aim of this study was to understand the positive predictive value (PPV) of physician diagnosis of NASH with or without liver fibrosis in the context of clinical trial recruitment.
Method: Published phase 2 clinical trials of obeticholic acid, elafibrinor, cenicriviroc, and selonsertib were reviewed independently by two researchers. Inclusion criteria were extracted, including NASH activity (using the NAFLD activity score (NAS) and fibrosis stage. Number of individuals screened and reasons for screening failure were also noted. Where insufficient information was available, the corresponding author was contacted. The PPV was calculated for physicians' assessment of the presence of NASH and overall suitability for clinical trial entry. A subgroup analysis assessed studies that excluded individuals with stage 0 fibrosis.
Results: The four published reports contained 920 participants. The inclusion criteria for the trials showed variation. One trial required NAS ≥3, two required NAS ≥4, and one NAS ≥5. The two most recent trials required fibrosis stage ≥1. All trials excluded participants with cirrhosis. Overall, more patients were excluded than subsequently entered the studies: pooled PPV for trial eligibility 0.37 (Range 0.30–0.82). Ineligible liver histology was the most common reason for screening failure, accounting for 59% of screen failures. PPV for the identification of NASH varied from 0.46 to 0.87, with a pooled value of 0.59. Lower PPVs were observed in the two trials that excluded those with fibrosis stage 0 where the pooled PPV for the identification of NASH with fibrosis was 0.47.
Conclusion: Clinical trials for new treatments in NASH require liver biopsy for trial entry. The prediction of NASH on liver biopsy amongst physicians recruiting participants to clinical trials is poor, particularly when NASH is associated with liver fibrosis. Since these trials are done in centres with an interest in NASH it is likely that the PPV will be lower in less expert hands. In practice, in a highly prevalent disease, many individuals will be exposed to the risks of an unnecessary liver biopsy since it may not diagnose NASH and therefore impact a treatment change.

FRI-473
Screening for liver fibrosis using transient elastography by fibroscan and fibrotest in type 2 diabetic patient

J. Sandler, E. Vinnitskaya, I. Bakulin, V. Keyan, A. Polukchina, T. Chaimenova. *Moscow Clinical Scientific Center, Hepatology, moscow, Russian Federation*
Email: sandlerjulia2012@gmail.com

Background and Aims: Patients with type 2 diabetes (T2D) are at risk for non-alcoholic fatty liver disease (NAFLD) leading to advanced fibrosis, cirrhosis, and liver cancer. We examined the efficacy of a screening strategy with noninvasive fibrosis biomarkers, FibroTest and FibroMax (FT, BioPredictive, France) and transient elastography (TE, Fibroscan, Echosens, France) in patients with T2D without previous history of liver disease.
Method: We prospectively studied 104 patients without a history of liver disease seen for T2DM. The biomarker data were obtained, and patients with presumed advanced fibrosis were reinvestigated by a hepatologist using, if necessary, ultrasonography, endoscopy, or liver biopsy in order to confirm fibrosis.
Results: 104 patients were included, mean age 56.4 ± 9.5yrs. (range of 29–82), 60.6% females, mean (range) BMI 33.3 ± 5.1(22–47), 72.1% (> = 30 kg/m). According to the FibroTest biomarkers, advanced fibrosis was diagnosed in 44 out of 104 patients (42%), while the TE biomarkers confirmed the diagnosis in 45% of cases (47/104). Among of 104 patients advanced fibrosis was confirmed in 42 subjects (40%), liver cirrhosis - in 11 patients (10.6%), including 2 cases of esophageal varices, 9 cases of splenomegaly and thrombocytopenia. According to SteatoTest 66% patients had advanced steatosis (cutoff score > = 0.76) and 39.8% according to CAP (dB/m), cutoff score > = 302.0. In patients who were 50 years or older, the prevalence of confirmed advanced fibrosis was 38.5% (p-value = 0.00023 versus p-value = 0.04249). FibroTest diagnosed F4 in 10 subjects (10.4%). The comparative analysis between these results and those of the TE showed discordance in 21 cases (20.2%). The TE performed false positive diagnosis in 9 cases, while FT only in 3. At the same time, FT registered 1 case of false negative result, while TE indicated it in 4 patients. Among 44 patients with advanced fibrosis (F2-F4) according to FT normal ALT level was in 29.6% cases (p-value = 0.58267) and 45.5% (p-value = 0.00034) had normal GGT.
Conclusion: Noninvasive fibrosis biomarkers, FT and TE, might be used for the detection of advanced fibrosis in patients with T2DM. ALT and GGT are not a reliable markers to detect fibrosis.

FRI-474
Body mass index influences Controlled Attenuation Parameter (CAP) values measured with Fibroscan® M probe. When should we evaluate steatosis with the XL probe?

T. Broquetas, L. Canillas, M. Puigvehí, R. Fernández, G. Díaz, S. Coll, M.G. Retortillo, N. Cañete, X. Bessa, R.S. Lamoglia, J.A. Carrión. *Hospital del Mar, IMIM (Hospital del Mar Medical Research Institute), UAB (Universitat Autònoma de Barcelona), Liver Section, Gastroenterology Department, Barcelona, Spain*
Email: 95565@parcdesalutmar.cat

Background and Aims: The FibroScan® XL probe quantifies liver fibrosis in obese patients. Anthropometric variables should be taken into account to choose the appropriate probe. Controlled Attenuation Parameter (CAP) quantifies the degree of steatosis. Recently, CAP determination has been incorporated into the XL probe but there are no studies comparing CAP values between both probes (M and XL) in

obese patients. The aim of the study was to evaluate the correlation of CAP values with M and XL probe, in patients with BMI ≥28 kg/m².
Method: Non-randomized prospective study, evaluating all patients with chronic liver disease and BMI ≥28 kg/m^2 from April to October 2017. The measurements with the FibroScan® M and XL probe were performed the same day and by the same explorer. Clinical, anthropometric, analytical and elastographic data have been analyzed.
Results: 386 patients with BMI ≥ 28 and chronic liver disease were evaluated (37% with hepatitis C, 31% non-alcoholic fatty liver disease, 14% Hepatitis B, 18% others). Patients (n = 89) evaluated by a non-experienced explorer (<500 TE) or those without both probes (n = 116) were excluded. Thus, 181 patients assessed with both probes by an experienced explorer were included. The median (range) age was 57 (27–93), 61% were men and 52% diabetic, 37% had a BMI between 28–30, 50% between 30–35 and 13% a BMI ≥35. The skin-capsule distance (SCD) according to the BMI category was 18 (13–24) mm, 20 (11–25) mm and 22 (15–25) mm, respectively. The CAP correlation with both probes was $\rho = 0.78$ ($p < 0.001$). There were no differences between the median CAP (dB/m) values with M (275) and XL (277) probes (p = ns). However, CAP values were significantly lower with M probe (278) compare to XL probe (287) ($p = 0.014$) in patients with BMI ≥ 35 Kg/m^2, probably due to a lower distribution of fat in the cortical area of the liver.
Conclusion: Controlled Attenuation Parameter (CAP) shows a good correlation between the FibroScan® M and XL probes. However, in patients with a BMI ≥35 Kg/m^2 values with M probe underestimate the degree of steatosis, making necessary to evaluate these patients with the XL probe.

FRI-475

The easy Liver Fibrosis Test (eLIFT) avoids unnecessary specialized evaluations of liver fibrosis in NAFLD and ALD patients

B. Thomas[1], L. Adrien[1], S. Bertrais[2], P. Etienne[1], Frédéric Oberti[1,2], I.F. Hubert[1,2], P. Cales[1,2], J. Boursier[1,2]. *[1]Angers, Hepato-Gastroenterology Department, Angers University Hospital, Angers, France, Angers; [2]Angers, HIFIH Laboratory, Angers University, Angers, France, Angers, France*
Email: thomas_brou@hotmail.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) are risk factors for cirrhosis and liver-related complications. Therefore, all NAFLD and ALD patients should theoretically undergo a non-invasive evaluation of liver fibrosis. However, the best non-invasive tests of liver fibrosis are limited by their cost and/or poor accessibility. Moreover, NAFLD and ALD patients represent a very large population, with most of them having no/mild fibrosis which would induce a majority of "unnecessary" specialized evaluations of liver fibrosis. The easy LIver Fibrosis Test (eLIFT) is a very simple fibrosis test including common parameters (age, sex, GGT, AST, platelets, prothrombin time). It has been developed to identify patients at-risk of advanced liver fibrosis who require further specialized evaluation. We aimed to evaluate whether the eLIFT helps to appropriately avoid unnecessary specialized evaluations of liver fibrosis in NAFLD and ALD patients.
Method: NAFLD and/or ALD patients referred for the first time to our centre for a non-invasive evaluation of liver fibrosis between October 2014 and March 2017 were included. Patients with other causes of chronic liver disease were excluded. FibroMeter^{VCTE} (FM^{VCTE}, which includes in a single formula the Fibroscan result and the parameters of the FibroMeter^{VIRUS}) was considered as the reference for the non-invasive evaluation of liver fibrosis (best non-invasive test in a recent large series of 1946 patients, J Hepatol 2017). As previously published, eLIFT ≥8 identified patients at-risk of advanced fibrosis.
Results: 543 patients were included: 260 NAFLD, 185 ALD and 98 NAFLD + ALD. FM^{VCTE} diagnosis was no/mild fibrosis in 55.2% of patients, advanced fibrosis in 33.1%, undetermined in 11.6%. 247/543 patients (45.5%) had eLIFT <8. Among patients with eLIFT <8, 207/247 (83.8%) had no/mild fibrosis according to FM^{VCTE}. Among the 40 remaining patients, FM^{VCTE} diagnosis was advanced fibrosis in 17 and undetermined in 23. 155 NAFLD patients had eLIFT <8 and 124 of them (80.0%) had no/mild fibrosis according to FM^{VCTE}. 59 of the 66 ALD patients with eLIFT <8 (89.4%) had no/mild fibrosis according to FM^{VCTE}, and 24 of the 26 NAFLD + ALD patients (92.3%).
Conclusion: Used as first-line test in NAFLD and ALD, the eLIFT avoids unnecessary specialized non-invasive evaluations of liver fibrosis in half of the patients referred to a tertiary centre.

FRI-476

Feasibility and utility of controlled attenuation parameter and transient elastography in the assessment of nonalcoholic fatty liver disease severity in children

A. Scott[1], M. Mansouri[1], T. Okubote[1], M. Scott[1], A. Betancourt[1], G. Mesa[1], E. Lawitz[1], F. Poordad[1], N. Alkhouri[2]. *[1]Texas Liver Institute, University of Texas (UT) Health San Antonio, San Antonio, United States; [2]Texas Liver Institute, Texas Liver Institute, San Antonio, United States*
Email: ascott@txliver.com

Background and Aims: Estimating the severity of liver steatosis by controlled attenuation parameter (CAP) and liver fibrosis by transient elastography (TE) using the Fibroscan™ machine provides a noninvasive method to establish the presence of nonalcoholic fatty liver disease (NAFLD) and assess its severity. Although the use of CAP/TE is becoming routine practice in adults, limited data exist in children with suspected NAFLD. The aim of this study was to assess the feasibility and utility of measuring CAP/TE by Fibroscan™ in a cohort of children with suspected NAFLD referred to a community gastroenterology clinic.
Method: All children seen at our clinic from May to October 2017 with suspected NAFLD (elevated ALT or fatty infiltration on ultrasonography) who had CAP/TE measured were included. Fibroscan™ was performed by an experienced operator. Standard criteria for having valid measurements were applied (IQR < 30% with ≥ 70% success rate). The severity of steatosis was evaluated by CAP: <225 db/m no steatosis, 225–250 mild, 250–300 moderate, and > 300 severe. The severity of liver stiffness/fibrosis was evaluated by TE: <7 kPa no significant fibrosis, 7–10 kPa mild or moderate, >10 kPa advanced. Clinical and laboratory parameters were collected. Chi-square test was used for statistical comparison between mild-to-moderate and severe steatosis; and presence or absence of significant fibrosis. Crude and adjusted logistic regression models were used to determine associations between patients' characteristics and CAP/TE.
Results: 44 children with suspected NAFLD were referred in the specified time period. Mean age (± SD) was 14.0 years (± 3.5). Majority were males (77%), obese (95%), and Hispanic (89%). All patients (44/44) had successful Fibroscan™ measurements but the large adult probe (XL) needed to be used in 21/44 (48%) of our patients and the regular M probe was used for the rest. All patients had CAP > 225 indicating steatosis and 50% of female and 80% of male patients had severe steatosis with CAP > 300 (Figure). On multivariable analysis, the presence of elevated AST (>48 U/l) was associated with a 9.6-fold increase in the presence of severe steatosis ($p = 0.04$), whereas the presence of positive smooth muscle antibody (SMA) was significantly protective. Evidence of fibrosis based on TE was present in 43% of children and 17% of male subjects had TE > 10 kPa indicating the potential for having advanced fibrosis. Factors associated with significant fibrosis included the presence of prediabetes, hypertension, hemoglobin level, and serum bilirubin ($p < 0.05$ for all).
Conclusion: CAP/TE provides a reliable way to confirm the diagnosis of NAFLD and assess its severity in children. Larger pediatric studies that assess the correlation with liver histology and disease progression are urgently needed.

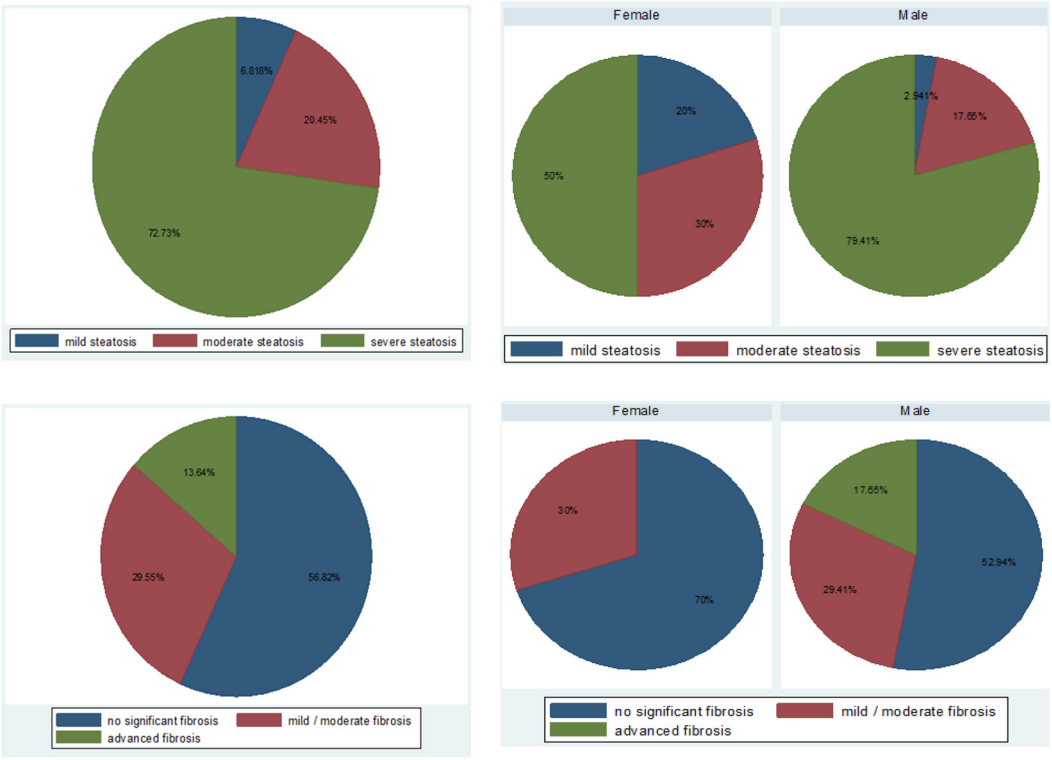


Figure 1: (abstract: FRI_476): The prevalence and severity of steatosis/fibrosis based on Fibroscan™ measurements.

FRI-477

Optimal cutoff value of assessing changes in intrahepatic fat amount by using the controlled attenuation parameter in a longitudinal setting

B.-K. Kang[1], D.W. Jun[2], M.M. Kim[1], S.B. Ahn[3], Y.C. Joo[4], H. Oh[2], E.C.J. Jang[5], J.H. Sohn[6], J.Y. Jeong[6], E. Kim[2]. *[1]Hanyang University School of Medicine, Radiology; [2]Hanyang University School of Medicine, Internal Medicine; [3]Eulji university college of medicine, Internal Medicine; [4]Hanyang University Graduate school of Biomedical Science and Engineering, Department of Translational Medicine; [5]Soonchunhyang University College of Medicine, Department of Occupational and Enviroment Medicine; [6]Hanyang University, College of Medicine, Guri Hospital, Internal Medicine*
Email: msbbogri@naver.com

Background and Aims: The controlled attenuation parameter (CAP) has shown a good correlation with the intrahepatic fat amount in cross-sectional studies. However, there is no study on whether the change of CAP scores can also show good correlation in a longitudinal setting. Therefore, we investigated the correlation between CAP and magnetic resonance imaging-estimated proton density fat fraction (MR PDFF) through serial examination in a longitudinal setting.
Method: Sixty-five patients with nonalcoholic fatty liver disease were evaluated with MR PDFF and transient elastography including CAP at baseline and 3 months later.
Results: CAP and MR PDFF at baseline showed a strong correlation in assessing hepatic steatosis ($r = 0.66$, $p < 0.001$). After treatment, the correlation between the change in CAP after treatment and the intrahepatic fat change (%) on MR PDFF was not satisfactory ($r = 0.37$, $p = 0.005$) in the longitudinal setting. The optimal cutoff value of the change in CAP for discriminating an improvement or an aggravation in intrahepatic fat percentage (>1% change in MR PDFF) was selected as 38 dB/m (area under the receiver operating characteristic curve = 0.559). For CAP changes >38 dB/m, the predictive value was 14/16 (87.5%), whereas for changes <38 dB/m, the predictive value was 12/41 (29.3%). Thereby, the accuracy of the method using the change in CAP was only 26/57 (46%). In addition, Cohen's kappa value was not significant ($\kappa = 0.11$, $p = 0.186$).
Conclusion: Careful interpretation of the steatosis change based on the CAP score is needed when the absolute change value is <38 dB/m in a longitudinal setting.

NAFLD: Therapy

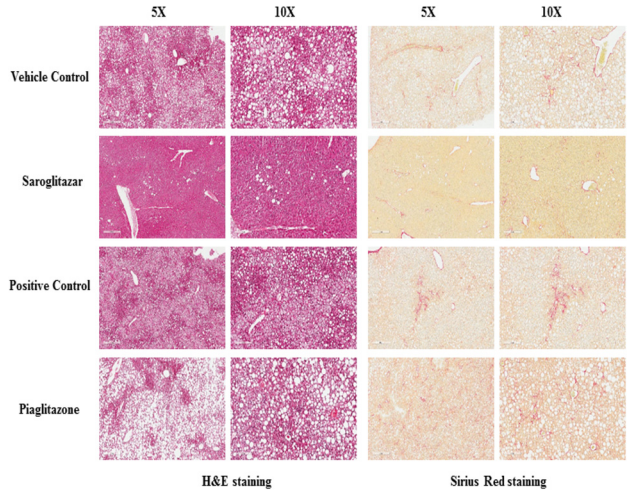
FRI-478

Saroglitazar treatment prevents NASH, eliminates hepatocyte ballooning, and significantly improves serum LFTs, lipids and insulin resistance in DIAMOND(tm) mice compared to pioglitazone benchmark

R. Caffrey[1], J. Marioneaux[1], P. Santhekadur[1], P. Bedossa[2], B. Philip[3], S. Giri[4], M. Jain[3], A. Sanyal[5]. *[1]Sanyal Biotechnology; [2]Hopital Beaujon, Anatomie Pathologique, France; [3]Zydus Cadila Healthcare, India; [4]Zydus Cadila Healthcare, Iceland; [5]Virginia Commonwealth University, Gastroenterology and Hepatology*
Email: rebecca@sanyalbio.com

Background and Aims: In this study the efficacy of the dual PPAR-α and PPAR-γ agonist Saroglitazar in preventing progression of early NASH F0 to more advanced NASH was investigated in Sanyal Biotechnology's DIAMOND™ mouse model. It has previously been demonstrated that pioglitazone attenuates measures of NASH and metabolic syndrome similarly to humans in this mouse model. We hypothesized that administration of Saroglitazar may also prevent progression of NASH. **Aims:** (1) To determine if Saroglitazar could prevent progression of NASH, (2) To compare the efficacy of Saroglitazar with benchmark pioglitazone and positive and negative natural history controls.

Method: 8 week old DIAMOND™ mice (10–12 per group) were weight randomized and placed on either normal chow/normal water (NC/NW) or Western Diet/sugar water (WD/SW) for 12 weeks. At 12 weeks on diet the WD/SW groups to progress to full metabolic syndrome with NASH F0 while NC/NW negative natural history controls remain healthy. Daily oral gavage of Saroglitazar (4 mg/kg/day), pioglitazone (30 mg/kg/day) and vehicle (water) began at 12 weeks and both dosing and diet continued for 3 months. At 24 weeks mice were necropsied and liver tissue and serum were collected. Sirius Red and H&E stained sections were made from each mouse, and scored for measures of NASH pathology. Serum LFTs, lipids, fasting insulin and glucose were measured and HOMA IR was calculated. Saroglitazar was compared to pioglitazone benchmark, vehicle control, and both Western Diet/Sugar Water (WD/SW) positive and normal chow/normal water (NC/NW) negative natural history controls.



Results: Compared to pioglitazone, Saroglitazar significantly reduced steatosis (both percent and grade), NAS score, and SAF activity score. Hepatocyte ballooning was completely eliminated in the Saroglitazar-treated group. No Saroglitazar treated mice progressed past steatosis to NASH whereas most pioglitazone and positive WD/SW controls did progress. The body weight of the Saroglitazar treatment group at end of study was significantly less than pioglitazone, vehicle control, and positive controls. Saroglitazar lowered fasting blood glucose more than pioglitazone, and lowered fasting insulin more than than all other groups. HOMA IR was improved and total serum cholesterol and triglycerides were significantly decreased in the Saroglitazar treated mice. Saroglitazar treatment successfully attenuated and even reversed some serological and pathological measures of NASH.
Conclusion: The anti-diabetic drug Saroglitazar met the primary endpoint of preventing progression of NAFLD to NASH, while simultaneously improving measures of insulin resistance and diabetes in the DIAMOND™ mouse model. This study demonstrated that Saroglitazar has significantly more beneficial effects than pioglitazone in the DIAMOND™ mice.

FRI-479
Mitochondrial uncoupler HU6 successfully treats NASH in DIAMOND mouse model

R. Caffrey[1], J. Marioneaux[1], P. Santhekadur[1], P. Bedossa[2], F. Portell[3], S. Eaton[3], J. Dennis[3], I. Onyango[3], O. Khan[3], S. Khan[3], A. Sanyal[4].
[1]Sanyal Biotechnology; [2]Hopital Beaujon, Anatomie Pathologique, Clichy, France; [3]Gencia; [4]Virginia Commonwealth University, Gastroenterology and Hepatology
Email: rebecca@sanyalbio.com

Background and Aims: The Gencia mitochondrial uncoupler compound HU6 was evaluated for utility in treating NASH in a diet-induced animal model of metabolic syndrome and NASH (DIAMOND™ mice).
Method: Mice were grouped into 5 groups: vehicle control (VC), high dose HU6 (5mg/kg), low dose HU6 (1mg/kg), WD/SW positive (PC) and NC/NW negative (NC) natural history controls. Mice were raised for 12 weeks on diet, corresponding to a baseline NASH F0 in the WD/SW groups. Treatment groups were then gavaged once daily with aqueous vehicle or drug in vehicle for 8 weeks.
Results: At necropsy, the body weight of the mice in the high dose group was significantly less than VC ($p = 0.04$), and liver weight was significantly less than the VC ($p = 0.001$) and PC ($p = 0.004$). LFTs were measured and AST, ALT, and ALP levels in the high dose group were significantly lower than in the VC ($p = 0.001$, 0.0004, and 0.0002, respectively) and PC ($p = 0.03$, 0.01, and 0.00008, respectively). Total serum cholesterol was also significantly lower in the high dose group compared to VC ($p = 0.001$). Liver tissue was embedded in FFPE blocks and slides stained with H&E and Sirius Red. Steatosis percentage and grade ($p = 0.001$ and 0.01, respectively) and ballooning ($p = 0.0000001$) were significantly lower in the high dose group compared to VC. Lobular inflammation was significantly improved in high dose group compared to PC ($p = 0.05$) and there was a strong trend to significance compared to VC and low dose group. NAS and SAF activity scores were also significantly improved in the high dose group compared to VC ($p = 0.001$, 0.0007) and PC ($p = 0.01$, 0.003). While all VC and PC mice progressed to NASH, only one mouse in the high dose group developed NASH. No significant difference in fibrosis measurements was found at this early stage of fibrosis development.
Conclusion: HU6 successfully met the primary study endpoint of treating and preventing progression of NASH. Significant improvements in body and liver weight, serum LFTs and lipids, and liver pathology were observed in the high dose group. HU6 warrants further investigation as a treatment for NASH.

FRI-480
Fibrosis stage improvement in nonalcoholic steatohepatitis: A systematic review of placebo treated participants in randomized controlled trials

A. Roskilly[1,2], E. Taylor[1,2], R.L Jones[2], I. Rowe[1,2]. *[1]Leeds Institute for Data Analytics, University of Leeds, Hepatology, Leeds, United Kingdom; [2]Leeds Teaching Hospitals, St James's Hospital, Leeds Liver Unit, Leeds, United Kingdom*
Email: aroskilly@doctors.org.uk

Background and Aims: The severity of fibrosis in patients with non-alcoholic fatty liver disease (NAFLD) is the critical determinant of liver related mortality. Consequently, improvements in liver fibrosis are being incorporated into clinical trial endpoints for new therapies for patients with non-alcoholic steatohepatitis (NASH).
The aim of this study was to estimate the proportion of patients with NASH with fibrosis improvement in timeframes relevant to ongoing trials.
Method: We undertook a systematic review of placebo controlled randomized clinical trials (RCT) with a histological endpoint including patients with NASH. Data reported were extracted and the proportion of patients with fibrosis improvement, defined as at least 1 stage improvement, were calculated per protocol. A pre-specified subgroup analysis explored fibrosis improvement in patients with fibrosis stage (F) ≥ 1 since those individuals with F0 at baseline could not improve fibrosis. The proportion and 95% confidence interval (95%CI) was calculated for each study and summarized as a pooled estimate.
Results: We identified 31 RCT of therapies for patients with NASH with a histological endpoint. Of these, 19 trials (including 898 placebo treated participants) reported the proportion of those included where fibrosis improved. In these studies, a total of 717 placebo treated participants underwent repeat liver biopsy per protocol. There was substantial variation in the proportion of participants improving fibrosis (range 0–45%, Figure). The pooled proportion

improving fibrosis in these 717 participants was 21.8% (95%CI 18.8–25.0%). 15 RCT reported fibrosis stage at baseline, and in these trials the proportion of participants with F0 was 18.8%. In a subgroup analysis excluding these participants, the pooled fibrosis improvement rate was 26.2% (95%CI 22.1–30.7%).

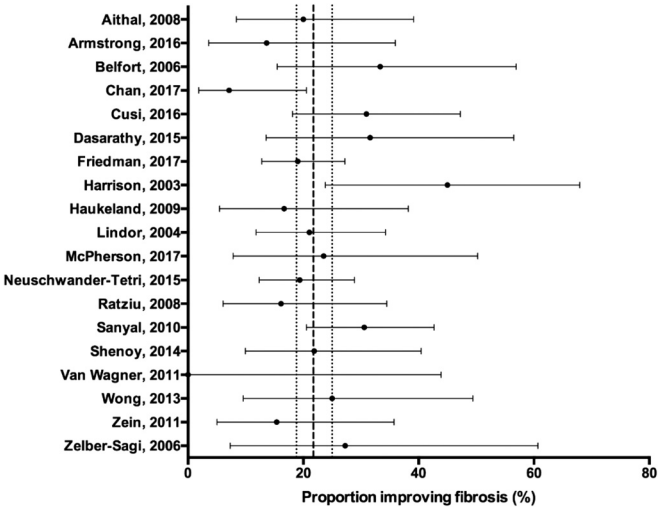


Figure 1: Proportion of placebo treated participants with NASH improving fibrosis in RCTs. Data are plotted as proportion ± 95%CI. The pooled proportion estimate and 95%CI are shown in the heavy and light dotted lines, respectively.

Conclusions: This study has important implications for current and future clinical trial design and interpretation. There is marked heterogeneity in the reported proportions of placebo treated participants with NASH improving fibrosis that requires further study. The pooled estimate for participants with F ≥ 1 at baseline improving fibrosis is 26.2%. This is consistent with previous reports of sampling variability in NASH, highlighting the deficiencies of liver biopsy to determine fibrosis endpoints in clinical trials in NASH. Validation of fibrosis stage improvement as a surrogate endpoint is an important outcome of the ongoing Phase 3 clinical trials.

FRI-481

Persistent improvement of liver function tests and health-related quality of life from an individualized exercise program in patients with histological confirmed NAFLD – the HELP study

Y. Huber[1], D. Pfirrmann[2], I. Gebhardt[1], C. Labenz[1], B. Straub[3], J. Kittner[1], M.-A. Wörns[1], P. Galle[1], P. Simon[2], Jörn Schattenberg[1].
[1]I. Department of Medicine, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany; [2]Department of Sports Medicine, Disease Prevention and Rehabilitation, Johannes Gutenberg University Mainz, Department of Sports Medicine, Disease Prevention and Rehabilitation, Mainz, Germany; [3]Institute of Pathology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany
Email: yvonne.huber@unimedizin-mainz.de

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is the fastest growing and most common cause of liver disease. The clinical spectrum of NAFLD ranges from isolated hepatic steatosis to non-alcoholic steatohepatitis (NASH), which can progress to end stage liver disease. Currently there are no approved pharmacologic therapies for NASH and lifestyle interventions are recommended. The impact of regular physical activity on the liver is poorly studied. Additionally, the capability to perform physical activity in chronic liver disease is not well explored. The aim of this prospective trial is to determine the effects of an individualized exercise program on hepatic surrogate markers and physical performance in patients with NAFLD and NASH.

Method: 44 patients with histological confirmed NAFLD were included in this prospective pilot-study (ClinicalTrials.gov Identifier: NCT 02526732). Patients underwent an independent 8-week training program consisting of combined endurance and strength exercise 3–5 times per week under qualified instruction. An online support platform with an individualized access and weekly bidirectional feedback by Email was provided. Health-related quality of life (HrQoL) as well as metabolic and liver chemistry were measured at study entry, end-of-treatment (EoT) and follow-up (FU) 12 weeks after the supervised program. An interims analysis of 35 patients is provided and the study will be completed in March 2018.
Results: At baseline the mean age was 41.2 (± 11.8) years, 68.7% of patients were male. Mean BMI was 31.0 (± 4.5)kg/m², 78% exhibited NASH determined by histology. At EoT exercise had a positive effect on body composition with a reduction in fat mass (−4.6%), while BMI changes were marginal (−0.4 kg/m²). The maximum oxygen uptakes (VO_2max) improved by 11% and physical performance increased from 136.8–152.2 Watt. AST and ALT decreased by 16.1% and 22.5% as well as ferritin levels by 20.9%. Median liver stiffness determined by Fibroscan showed a reduction from 8.4 to 6.5 kPa. During follow-up 65.4% of participants reported continued regular physical activity. Strikingly, a significant reduction of liver function test and an additional improvement of HrQoL (increase in overall score of 8.5%, $p < 0.05$) compared to the end-of-treatment were detected during FU.
Conclusion: A temporary, individualized exercise program supported by an online platform in patients with NAFLD leads to improvement in physical performance and hepatic surrogate markers even after cessation of counseling.

FRI-482

Treatment with obeticholic acid in patients with NASH does not show increased markers of liver toxicity based on evaluation of drug-induced serious hepatotoxicity

A. Sanyal[1], A. Shah[2], P. Pockros[3], R. Shringarpure[2], L. Macconell[2], D. Shapiro[2]. *[1]Virginia Commonwealth University, Richmond, United States; [2]Intercept Pharmaceuticals, Inc., San Diego, United States; [3]Scripps Clinic, La Jolla, United States*
Email: arun.sanyal@vcuhealth.org

Background and Aims: Evaluation of drug-induced serious hepatotoxicity (eDISH) is a tool used to assess and identify potential cases of drug-induced liver injury. eDISH was used to evaluate obeticholic acid (OCA) and placebo profiles in 2 double-blind, placebo-controlled studies in patients with nonalcoholic steatohepatitis (NASH). FLINT was a 72-week study, which demonstrated statistically significant improvements in hepatocellular ballooning, steatosis, lobular inflammation, and fibrosis in patients treated with OCA compared to placebo. CONTROL was a 16-week study, which showed that the addition of low-dose atorvastatin reversed OCA-associated changes in LDL-C. The objective of this analysis was to use eDISH to determine if patients with NASH treated with OCA show increased markers of liver injury or whole liver dysfunction.
Method: eDISH methodology was applied to 278 patients treated with placebo (n = 140) or 25 mg OCA (n = 138) from FLINT and 84 patients treated with placebo (n = 21), 5mg OCA (n = 20), 10 mg OCA (n = 21), or 25 mg OCA (n = 22) from CONTROL. Individual subject peak values of alanine aminotransferase (ALT) and total bilirubin throughout the double-blind treatment phase were plotted on an x–y chart as logarithm_{10} values of multiples of elevations above the upper limit of the normal reference ranges (x ULN).
Results: Overall, no OCA-treated patients were in the Hy's law quadrant (>3 × ULN for ALT and >2x ULN for total bilirubin) compared with 1 placebo-treated patient in FLINT. The proportion of patients with peak ALT and total bilirubin values in the lower left quadrant (representing normal or near normal range) was higher in OCA-treated patients compared with placebo (FLINT: 91% OCA vs 84% placebo; CONTROL: 91% OCA vs 86% placebo). 8% of OCA-treated patients from both FLINT and CONTROL presented in the Temple's

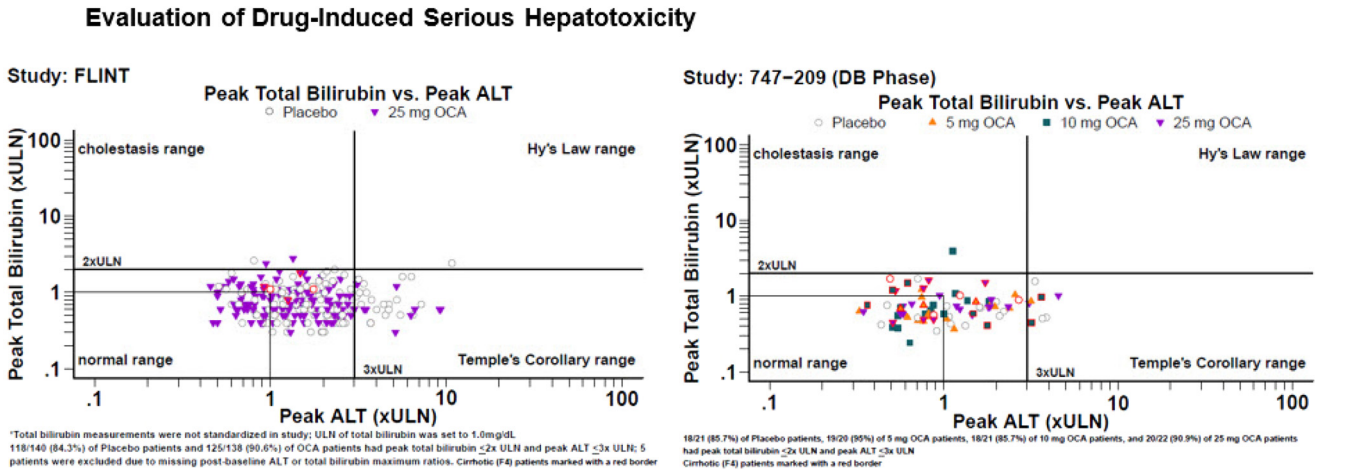


Figure 1: (abstract: FRI-482)

corollary quadrant (>3x ULN for ALT and <2x ULN for total bilirubin) vs 14% (in both studies) for the placebo-treated patients. Across both studies (n = 362), 4 patients were in the cholestasis quadrant (>2X ULN total bilirubin and <3X ULN for ALT); 1 placebo-treated patient and 3OCA-treated patients, including 1 patient with Gilbert's syndrome.

Conclusion: In these 2 placebo-controlled, double-blind NASH studies, the eDISH analysis showed no trend for liver injury with OCA at doses up to and including 25 mg.

FRI-483

The effect of semaglutide on liver enzymes in subjects with obesity and elevated alanine aminotransferase: Data from a randomised Phase 2 trial

P. Newsome[1], S. Harrison[2], Søren Rasmussen[3], T.M. Hansen[3], L.V. Gaal[4]. [1]*Queen Elizabeth Hospital, Liver Unit, Birmingham, United Kingdom;* [2]*University of Oxford, Radcliffe Dept. of Medicine, Oxford, United Kingdom;* [3]*Novo Nordisk A/S, Søborg, Denmark;* [4]*Antwerp University Hospital, Dept. of Endocrinology, Diabetology & Metabolism, Antwerp, Belgium*
Email: tmnh@novonordisk.com

Background and Aims: The glucagon-like peptide 1 analogues semaglutide and liraglutide improve glycaemic control and reduce elevated liver enzymes in subjects with type 2 diabetes (T2D), and reduce body weight in subjects with or without T2D. Histological resolution of non-alcoholic steatohepatitis has also been seen for liraglutide in subjects with or without T2D. A randomised, placebo-controlled phase 2 trial (NCT0243711) of once-daily subcutaneous semaglutide (0.05, 0.1, 0.2, 0.3, or 0.4 mg following 4-weekly escalations) in subjects with obesity without T2D, showed mean weight losses of –6.0% (0.05 mg) to –13.8% (0.4 mg) with semaglutide vs –2.3% with placebo at week 52. The effect of semaglutide on liver enzymes in subjects with elevated baseline alanine aminotransferase (ALT) was evaluated in a *post hoc* sub-analysis from this trial.

Method: Baseline fibrosis was categorised by the non-alcoholic fatty liver disease (NAFLD) fibrosis score (NFS) and Fibrosis-4 (FIB-4) score. Changes in ALT were estimated at week 52 (mixed model on log-transformed data) and semaglutide-to-placebo group ratios and 95% confidence intervals (95%CI) calculated from this model for subjects with high baseline ALT (>30U/l [male]; >19U/l [female]).

Results: Mean (range) baseline characteristics of the 957 treated subjects (35% male) were: age 47 (18–86) years, weight 111 (70–244) kg, body mass index 39 (30–80)kg/m^2, NFS–0.49 (–4.70–4.66) and FIB-4 0.72 (0.14–3.31); 52% (n = 499) had high ALT, 18% a high NFS (>0.676), and <1% a high FIB-4 (>3.25). ALT ratios (95%CI) at week 52 in those with high baseline ALT were: 0.88 (0.76–1.01; 0.05 mg); 0.94 (0.82–1.08; 0.1 mg); 0.82 (0.71–0.95; 0.2 mg); 0.79 (0.68–0.91; 0.3 mg), and 0.82 (0.70–0.95; 0.4 mg). p values were <0.01 at doses >0.1mg, unadjusted for multiple testing. ALT changes at week 52 were broadly comparable across weight loss categories from <2% to ≥10% of baseline weight. Normalization of high baseline ALT was seen at week 52 in 29% (17/58; 0.05 mg), 25% (15/59; 0.1 mg), 38% (19/50; 0.2 mg), 43% (23/54; 0.3 mg), and 46% (21/46; 0.4 mg) of subjects on semaglutide, versus 18% (14/76) of subjects on placebo.

Conclusion: In subjects with obesity and high ALT, semaglutide 0.2–0.4 mg daily reduced ALT to an extent that was broadly comparable across weight loss categories, and resulted in dose-related ALT normalization in up to 46% of subjects after 52 weeks. These data suggest a potential role for semaglutide in the treatment of NAFLD with elevated liver enzymes.

FRI-484

Effet of bariatric surgery in biopsy-proven NASH patients after 5 years

G. Lassailly[1], C. Robert[2], V. Gnemmi[3], A. Louvet[1], L. Emmanuelle[3], F. Artru[1], M. Ningarhari[1], Valérie Canva[1], S. Dharancy[1], F. Pattou[4], P. Mathurin[1]. [1]*CHRU de Lille, Service des maladies de l'appareil digestif, Lille, France;* [2]*CHRU de Lille, General & bariatric surgery, Lille, France;* [3]*CHRU de Lille, service d'anatomopathologie, Lille, France;* [4]*CHRU de Lille, General & Bariatric surgery, Lille, France*
Email: guillaume.lassailly@gmail.com

Background and Aims: Bariatric surgery induces disappearance of NASH from nearly 85% of patients and reduced the pathologic features of the disease after 1 year of follow-up. The outcome at 5 years, in NASH patients is not well established.

Method: in the Lille bariatric Cohort, 198 morbidly obese patients with biopsy-proven NASH were referred for bariatric surgery from 1994 through 2017, at the University Hospital of Lille, France (the Lille Bariatric Cohort). Clinical, biological, and histologic data were collected before, at 1 and 5 year after surgery. Primary outcome was disappearance of NASH and secondary outcomes included NAS (Nafld Activity Score) and individual score of lobular inflammation, ballooning and fibrosis. Primary and secondary outcomes and changes in parameters (continuous, ordinal, binary variables) were analyzed from baseline to 1 year and from 1 year to 5 year using the Wilcoxon signed rank tests and mantel-haenszel test.

Results: At time of analysis, about 70% of patients with NASH performed the one year liver biopsy and 31% at 5 year.
A/ At baseline, the cohort characteristics were as follow: BMI 46.8kg/m² (42.8–52.3), type 2 diabetes and dyslipidemia were present in 68% and 66% of cases respectively. Histological characteristics were: steatosis was 60% (40–75), Ballooning (1.2 ± 0.6), lobular inflammation (1.8 ± 0.7) and fibrosis (1.17 ± 1.16) (Metavir score).

B/ At 1 year after surgery, NASH disappeared in 86% of cases and all histological features improved: steatosis, (from 60 to 10%), ballooning (1.2 ± 0.6 to 0.2 ± 0.4), lobular inflammation (1.8 ± 0.7 to 0.4 ± 0.6), NAS (4.7 ± 1.3 to 1.7 ± 1.4) and fibrosis (according to Metavir) (1.6 ± 1.1 vs 0.9 ± 1.1) (For all $p < 0.001$).
C/ Comparison between 1 and 5 year: patients with disappearance of NASH at 1 year remained free of NASH at 5 years. As compared to 1 year, liver fibrosis continue to improve (0.9 ± 1 vs. 0.5 ± 0.8 $p < 0.003$). For all the other histological features of NASH, the initial improvement obtained at one year after surgery was sustained until 5 years: steatosis (10–10%), ballooning (0.17 ± 0.4 to 0.11 ± 0.3), lobular inflammation (0.36 ± 0.5 to 0.5 ± 0.5) and NAS (1.5 ± 1.1 to 1.4 ± 1.5) ($p > 0.05$ for all comparison).
The improvement of clinical features and biological parameters sustained between 1 and 5 years after surgery: BMI (37.7 ± 7 to 36.6 ± 8), AST (23 ± 8 to 26 ± 14), γ-glutamyltransferases (32 ± 23 to 41 ± 60), LDL (2.7 ± 0.9 to 2.8 ± 0.9), HDL (1.29 ± 0.29 to 1.33 ± 0.29) and mean insulin resistance index (HOMA-IR: 1.86 ± 2.6 to 1.65 ± 1.25), A1c glycated hemoglobin (6 ± 0.9 to 6 ± 0.9%) ($p > 0.05$ for each comparison).
Conclusion: Disappearance of NASH occurred in more than 80% of case after bariatric surgery. Disappearance of NASG and all histological features of NASH improvement appeared a 1 one year and sustained until 5 year. Moreover, extend of fibrosis continue to improve from 1 year to 5 year.

FRI-485
Safety, tolerability, pharmacokinetics and pharmacodynamics of a liver-targeting ACC inhibitor (PF-05221304) following single and multiple oral doses

A. Bergman[1], S.C. Gonzalez[1], S. Tarabar[2], A. Saxena[3], W. Esler[3], N. Amin[3]. *[1]Pfizer, Inc., Early Clinical Development, Cambridge, MA, United States; [2]Pfizer, Inc., Clinical Research Unit, New Haven, CT, United States; [3]Pfizer, Inc., Internal Medicine Research Unit, Cambridge, MA, United States*
Email: arthur.bergman@pfizer.com

Background and Aims: Elevated hepatic de novo lipogenesis (DNL) is a distinct characteristic of patients with nonalcoholic steatohepatitis (NASH). Pharmacologic inhibition of acetyl-CoA carboxylase (ACC), the rate limiting enzyme for DNL, has been shown to reduce hepatic steatosis in rodents and humans. PF–05221304 is a potent, selective, and reversible dual ACC 1/2 inhibitor (ACCi) designed to have asymmetric distribution to the liver. This asymmetric distribution enables potent inhibition of hepatic ACC to normalize hepatic DNL in patients with NASH, while minimizing systemic DNL inhibition.
Method: A 3-part study was conducted to evaluate (1) safety/tolerability and pharmacokinetics (PK) of single ascending doses from 1 mg to 240 mg in 2 interleaving cohorts (n = 6 active/2 placebo per dose-level), (2) safety/tolerability, PK, and pharmacodynamics (PD) of repeated, ascending doses ranging from 2 to 200 mg daily (as Q12H or QD regimens) with PK assessed on Day 7 and PD assessed on Day 14 (demonstrated by inhibition of oral fructose-stimulated hepatic DNL via ^2H_2O incorporation into triglyceride palmitate; n = 8 active/2 placebo per dose-level), and (3) effect of food on single dose PK versus fasted state in healthy adult subjects (n = 10).
Results: *Safety and tolerability*: PF-05221304 was well tolerated at all single and multiple oral doses. Upon repeated dosing, asymptomatic decline in platelet count at doses ≥60 mg/day, plus fasting and postprandial triglyceride increases at doses ≥40mg/day, were observed. *PK:* Steady state AUC (over the dosing interval) increased approximately in a dose proportional manner over the range of multiple oral doses studied. Mean terminal half-life ranged from 11 to 18 hours over the doses studied. Food had minimal effect on the plasma PK of PF-05221304. *PD:* Fructose stimulated hepatic DNL was inhibited in a dose-dependent manner with near complete DNL inhibition following 14 days of dosing at the highest doses studied.
Conclusion: In healthy subjects, well tolerated doses of PF-05221304 demonstrated robust DNL inhibition, sufficient to normalize DNL in patients with NASH, while exhibiting minimal effects on platelet count and serum triglycerides. PF-05221304 is suitable for further clinical development.

FRI-486
Regular aspirin use is not protective against advanced fibrosis in type-2 diabetics with biopsy-proven nonalcoholic fatty liver disease

A. Singh[1], F. Gosai[2], R. Lopez[1], A. Vigni[3], A. Tabbaa[4], E. Lawitz[3], F. Poordad[3], A. Scott[3], T. Okubote[3], M. Scott[3], M. Mansouri[3], N. Alkhouri[3]. *[1]Cleveland Clinic - Main Campus, Cleveland, United States; [2]Cleveland Clinic - Fairview Hospital, Cleveland, United States; [3]Texas Liver Institute, San Antonio, United States; [4]UC San Francisco, San Francisco, United States*
Email: singha4@ccf.org

Background and Aims: Patients with type 2 diabetes (T2DM) frequently use aspirin as a cardioprotective agent and are commonly affected by nonalcoholic fatty liver disease (NAFLD). Recent analysis of a nationally representative databased suggested that aspirin use was protective from advanced fibrosis based on noninvasive indices in individuals with suspected NAFLD. However, limited data exist on the association of aspirin use with histologically-proven advanced liver fibrosis (AF) in diabetics with NAFLD. The aim of this study was to assess this association in a large cohort of patients with T2DM and biopsy-proven NAFLD.
Method: All patients with T2DM who had a liver biopsy for suspected NAFLD were included. Patients with secondary causes of hepatic steatosis (excessive alcohol consumption, hepatitis C etc.) were excluded. Biopsies were assessed by an experienced pathologist and the stage of fibrosis was determined (F0-F4) with AF being F3-4. Laboratory data and use of various medications within 24 months of liver biopsies were used for the analysis. Univariable and multivariable logistic regression analyses were performed to assess any association.
Results: Our cohort consisted of 592 patients with T2DM and biopsy-proven NAFLD. The mean age at biopsy was 52.2 ± 11.7 years, 62.7% were female, 84.8% were Caucasian, 92% were overweight or obese, and the median HbA1C was 6.4% [5.7–7.5]. Sixty six percent of our

Table 1: (abstract: FRI-485).

	Placebo	1 mg Q12H	3 mg Q12H	10 mg Q12H	30 mg Q12H	100 mg Q12H	40 mg QD	100 mg QD
PK: AUC_t*	–	737.3 (27)	2216 (23)	8060 (29)	22640 (34)	89030 (21)	27010 (22)	88120 (20)
Platelets#	9 (0, 19)	0 (−13, 13)	16 (3, 29)	−5 (−17, 8)	−15 (−28, −2)	−51 (−63, −38)	19 (6, 31)	−27 (−40, −14)
Fasting TG†	−3 (−9,3)	−11 (−18, −3)	−16 (−22, −8)	0 (−8, 9)	41 (29, 53)	47 (35, 60)	46 (34, 59)	32 (21, 43)
TG $AUEC^{\dagger}_{24}$	−1 (−8,6)	8 (−1, 18)	−4 (−12, 5)	−8 (−16, 1)	36 (24, 48)	57 (44, 72)	20 (10, 31)	33 (22, 46)
DNL‡	0 (−11, 11)	47 (33, 62)	53 (38, 67)	80 (66, 94)	91 (77, 100)	94 (79, 100)	91 (76, 100)	98 (84, 100)

*geometric mean (%CV) [μg · hr/mL];
#Day 15 change from baseline [10^3/μL];
†Day 13% change from baseline (80% CI);
‡Day 14% inhibition (90% CI)

patients had no or early fibrosis (F0-2) and 34% had AF (F3-4). A total of 146 patients were on regular aspirin therapy (98% on 81 mg daily and 2% on 325 mg daily), out of which 51 patients had AF. Unadjusted odds ratio (OR) for association of aspirin use with AF was 1.04 (0.71, 1.5) (p = 0.83) and after adjusting for age, gender, race and body mass index OR was 0.77 (0.51, 1.2) (p = 0.22).
Conclusion: Aspirin use is not protective against AF in T2DM patients with NAFLD. Future studies to assess the effects of other medications commonly used in diabetics on liver fibrosis are warranted.

FRI-487
Preliminary efficacy and safety of acetyl-CoA carboxylase inhibitor GS-0976 in patients with compensated cirrhosis due to NASH

S. Harrison[1], M. Noureddin[2], R. Herring, Jr.[3], P. Ruane[4], B. Mccolgan[5], B. Kirby[5], C. Nelson[5], R.A. Schall[5], C. Jia[5], M. Subramanian[5], R. Myers[5], M. Middleton[6], C. Sirlin[6], M. Fitch[7], K. LI[7], M. Hellerstein[7], E. Lawitz[8].
[1]Pinnacle Clinical Research, San Antonio, United States; [2]Cedars-Sinai Medical Center, Los Angeles, United States; [3]Quality Medical Research, Nashville, United States; [4]Ruane Clinical Research Group, Los Angeles, United States; [5]Gilead Sciences, Inc., Foster City, United States; [6]University of California at San Diego, Liver Imaging Group, San Diego, United States; [7]University of California Berkeley, Berkeley, United States; [8]University of Texas Health San Antonio, Texas Liver Institute, San Antonio, United States
Email: rob.myers@gilead.com

Background and Aims: Elevated *de novo* lipogenesis (DNL) contributes to the pathogenesis of NASH. Acetyl-CoA carboxylase (ACC) catalyzes the first and rate-limiting step in DNL. Here, we describe the efficacy, safety, and pharmacodynamic effects of GS-0976, a liver-targeted inhibitor of ACC, in subjects with compensated cirrhosis due to NASH.
Method: In a proof-of-concept study, 10 subjects with suspected compensated cirrhosis (Child-Turcotte-Pugh [CTP]-A) due to NASH (defined by any one of biopsy, liver stiffness by magnetic resonance elastography [MRE] ≥4.67 kPa or transient elastography ≥14.0 kPa, or Fibrotest ≥0.75) received GS-0976 20 mg orally once daily for 12 weeks. Centrally-read magnetic resonance imaging-proton density fat fraction (MRI-PDFF) and MRE, and serum markers of fibrosis were measured at baseline (BL), Week 4 (W4), and Week 12 (W12). For DNL determination, heavy water (^2H_2O, 35 mL) was administered three times daily for one-week cycles prior to baseline, W4, and W12. Deuterium incorporation into palmitate was measured in fasting plasma samples by GC/MS, and mass isotopomer distribution analysis was used to calculate hepatic DNL and its inhibition by GS-0976.
Results: Compared to BL, statistically significant reductions in hepatic PDFF (median: 9.2 vs. 4.6%; p = 0.004) and serum ALT (46 vs. 32U/l; p = 0.008; Figure 1) were observed after 12 weeks of GS-0976 treatment. Reductions in PDFF were significant by W4. A ≥30% relative decline was seen in 5 subjects at W4 (50%) and 7 subjects (70%) at W12. No significant changes in MRE-stiffness or serum fibrosis markers were observed. Decreases in PDFF correlated with changes in ALT, ELF score, and PIII-NP. GS-0976 was well-tolerated; no subjects prematurely discontinued study medication. Median (IQR) fasting triglycerides increased from 147 mg/dl (105, 231) at BL to 159 mg/dl (142, 248) at W12 (p = 0.008), but other lipid parameters were unchanged. One subject had asymptomatic Grade 3 hypertriglyceridemia and responded to fibrate therapy. Data regarding the impact of GS-0976 on fasting hepatic DNL are pending.
Conclusion: In a proof-of-concept study, 12-week therapy with the liver-targeted, oral ACC inhibitor GS-0976 in subjects with compensated cirrhosis due to NASH was safe and associated with significant improvements in hepatic steatosis and serum ALT.

FRI-488
Characterization of changes in lipoprotein profiles of patients with nonalcoholic steatohepatitis treated with the acetyl-CoA carboxylase inhibitor GS-0976

P. Mantry[1], Z. Kayali[2], M. Noureddin[3], P. Ruane[4], B. Mccolgan[5], J. Tarrant[5], L. Wang[5], T. Nguyen[5], E. Harting[5], S. Djedjos[5], A. Ray[5], R. Myers[5], M. Lai[6], M. Charlton[7], E. Lawitz[8], S. Harrison[9], R. Loomba[10].
[1]The Liver Institute at Methodist Dallas, Dallas, United States; [2]Inland Empire Liver Foundation, Rialto, United States; [3]Cedars-Sinai Medical Center, Los Angeles, United States; [4]Ruane Medical and Liver Health Institute, Los Angeles, United States; [5]Gilead Sciences, Inc., Foster City, United States; [6]Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, United States; [7]University of Chicago, Chicago, United States; [8]Texas Liver Institute, University of Texas Health San Antonio, San Antonio, United States; [9]Pinnacle Clinical Research, San Antonio, United States; [10]University of California San Diego, La Jolla, United States
Email: rob.myers@gilead.com

Background and Aims: GS-0976 is an oral, liver-targeted inhibitor of acetyl-CoA carboxylase (ACC). In a Phase 2 trial, GS-0976 20 mg daily improved hepatic steatosis and markers of fibrosis in subjects with nonalcoholic steatohepatitis (NASH); however, increased serum triglycerides (TG) were observed in some subjects. Our aim was to further characterize lipid changes that occur with GS-0976 therapy.
Method: In a Phase 2 trial, 126 non-cirrhotic subjects with NASH were randomized to receive GS-0976 20 mg (n = 49), GS-0976 5 mg (n = 51), or placebo (n = 26) orally QD for 12 weeks (W12). This analysis focuses on subjects treated with GS-0976 20 mg QD (the efficacious dose) or placebo. In addition to standard lipids (TG, total cholesterol [TC], LDL-C, and HDL-C), lipoproteins were measured by NMR (NMR LipoProfile®, LabCorp) in fasting samples at BL, W1, W4 and W12. Changes from baseline (BL) in GS-0976-treated subjects were evaluated using Wilcoxon sign-rank tests and comparisons vs placebo using Wilcoxon rank-sum tests (all Bonferroni-adjusted).
Results: The median age was 56 years, 69% were female, 63% had diabetes, and 43% were on lipid lowering therapy at BL (37% statins, 4% fibrates, 12% other). TG elevations in subjects on GS-0976 peaked at W1 and declined thereafter (Table 1). At W12, a median (IQR) TG

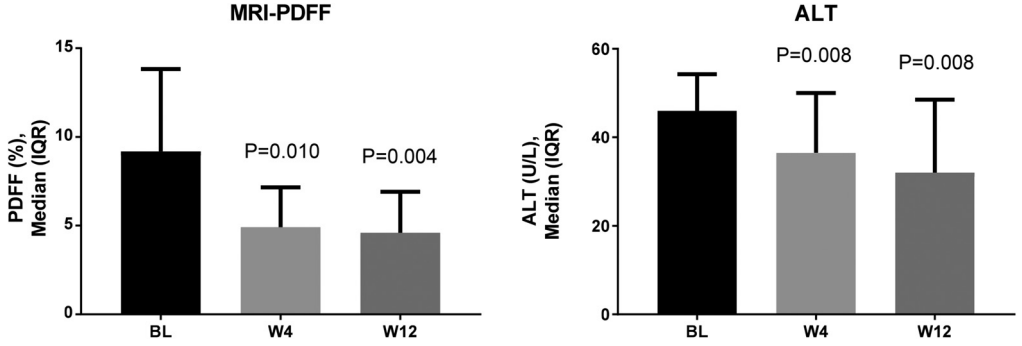


Figure 1: (abstract: FRI-487): Changes in MRI-PDFF and ALT during GS-0976 Treatment in Subjects with Compensated Cirrhosis due to NASH

increase of 14mg/dl (−6, 72) was observed among GS-0976-treated subjects compared with a reduction of 5.5 mg/dl (−24, 26) in those on placebo (p = 0.14). In subjects on GS-0976, significant increases in VLDL particles and VLDL-TG at W1 were not significant at W12. Changes at W12 in HDL-C, TC, and LDL-C were not significant in subjects on GS-0976, but TC and LDL-C declined in those on placebo. No significant changes in total HDL or LDL particles were observed in subjects on GS-0976.

Table 1: Lipid Parameters in Subjects Treated with GS-0976 20 mg Daily

Parameter	BL	W1	W4	W12
TG (mg/dl)	160 (125,201)	191 (136,290)*,†	188 (142,270)*	177 (116,277)*
VLDL-TG (nmol/l)	93 (66,133)	120 (73,236)*,†	97 (69,200)*	96 (68,175)
VLDL-P (nmol/l)	53 (36,73)	72 (39, 121)*	52 (43,90)	52 (31,93)
TC (mg/dl)	179 (152,203)	192 (162,215)†	184 (159,215)†	182 (158,220)†
LDL-C (mg/dl)	99 (82,125)	102 (72,134)	96 (72,124)	99 (71,139)†
LDL-P (umol/l)	1397 (1074,1664)	1256 (990,1558)	1365 (995,1688)	1230 (1013,1592)
HDL-C (mg/dl)	42 (35,53)	39 (33,52)*	39 (33,47)*	42 (33,50)
HDL-P (umol/l)	30 (25,37)	30 (26,36)†	30 (25,36)	30 (25,34)

Data are median (IQR).
HDL-P, total HDL particles; LDL-P, total LDL particles; VLDL-P, total VLDL particles; VLDL-TG.
*p < 0.05 for comparison with BL.
†p < 0.05 for comparison of change from BL vs. placebo.

Conclusion: TG elevations in NASH patients treated with GS-0976 are greatest during the first week of therapy and may relate to a transient increase in hepatic release of VLDL particles. Despite the increase in serum TG concentration, HDL and LDL particles did not change significantly. Longer term studies will be completed to understand the effects of GS-0976 on lipids beyond 12 weeks.

FRI-489

Pharmacokinetics, pharmacodynamics, and safety of EDP-305, in healthy and presumptive NAFLD subjects

A. Ahmad[1], K. Sanderson[1], D. Dickerson[2], N. Adda[1]. [1]*Enanta Pharmaceuticals Inc., Watertown, United States;* [2]*PRA Health Sciences, Lenexa, United States*
Email: nadda@enanta.com

Background and Aims: EDP-305 is a novel oral Farnesoid X Receptor (FXR) agonist under development for the treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis and cholestatic liver disorders.
Method: A randomized, double-blind, placebo-controlled (PBO), first-in-human study was conducted to evaluate the safety, tolerability, PK, and PD of single ascending doses (SAD) and multiple ascending doses (MAD) of EDP-305 in healthy (HV) and PN subjects (PN = presumptive NAFLD; obese with or without prediabetes or type 2 diabetes mellitus). Subjects received EDP-305/PBO as a single dose (SAD, 6 cohorts, 1–80 mg) or QD for 14 days (MAD, 12 cohorts, 0.5–20 mg), (6 active: 2 PBO/cohort) while fasting, except in the SAD food effect cohort (8 active: 2 PBO). PD measurements included plasma fibroblast growth factor 19 (FGF19) and serum 7-α-hydroxy-4-cholesten-3-one (C4).
Results: A total of 146 subjects (n = 50 in SAD; n = 96 (48 HV and 48 PN) in MAD) received at least one dose of EDP-305 or PBO. Dose proportional increases in exposure were observed, with median $t_{1/2}$ following multiple doses from 10–23 hours. Strong FXR target engagement (increased FGF-19, reduced C4) was demonstrated at EDP-305 doses as low as 2.5 mg in HV, and 0.5 mg in PN subjects. EDP-305 was generally well tolerated at all doses. No clinically significant laboratories were reported except one transient Grade 2 ALT/AST elevation in n = 1 (MAD-HV-20 mg) that led to drug discontinuation. Pruritus was 9% for EDP-305, 3% in placebo: the majority was mild or moderate and occurred at multiple doses of 20 mg, with no cases below 10 mg. No dose-related changes in lipids were observed in HV subjects at any doses; and no dose-related changes in lipids were observed in PN subjects except for reductions of total cholesterol and HDL cholesterol at the multiple 20mg dose, with no concomitant increase in LDL cholesterol.
Conclusion: EDP-305 was generally safe over a broad range of single and multiple doses with PK suitable for once daily oral dosing. Significant elevations of FGF19 and diminutions of C4 demonstrated potent activity on FXR with an opportunity to engage the pharmacological target at the lower multiple dose range of 0.5–5 mg that neither elicits adverse effects on lipids nor results in pruritus. These results support clinical evaluation of EDP-305 in patients with NASH, PBC and PSC.

FRI-490

An integrated safety analysis of phase 2 studies of BMS-986036, a PEGylated fibroblast growth factor 21 analogue for the treatment of non-alcoholic steatohepatitis

D. Halegoua-Demarzio[1], E. Charles[2], B. Tetri[3], S. Kundu[2], G. Tirucherai[2], R. Christian[2]. [1]*Thomas Jefferson University, Philadelphia, United States;* [2]*Bristol-Myers Squibb, Lawrenceville, United States;* [3]*St. Louis University, St. Louis, United States*
Email: dina.halegoua-demarzio@jefferson.edu

Background and Aims: BMS-986036 is a PEGylated analogue of human fibroblast growth factor 21 (FGF21), a key regulator of energy and lipid metabolism, and it improves steatosis, liver injury, and biomarkers of fibrosis and liver stiffness in patients (pts) with non-alcoholic steatohepatitis (NASH). This analysis evaluated the safety and tolerability of BMS-986036 in 2 randomized, placebo (PBO)-controlled phase 2 trials.
Method: Obese pts with type 2 diabetes (T2DM; MB130-002, NCT02097277; n = 120) or pts with biopsy-proven NASH (MB130-045, NCT02413372; n = 78) received treatment (tx) for 12 or 16 wks, respectively, with subcutaneous injections of once-daily (QD; 1, 5, 10, or 20 mg) or once-weekly (QW; 20 mg) BMS-986036 (n = 146) or PBO (n = 52). Safety data, including adverse events (AEs), lab parameters, drug immunogenicity, and bone mineral density (BMD) by dual-energy X-ray absorptiometry, were integrated.
Results: Baseline (BL) characteristics were comparable between the BMS-986036 and PBO groups (table). The most frequent AEs in BMS-986036–treated pts were diarrhoea and injection site bruising; most were of mild or moderate intensity. Median onset of diarrhoea was 21 d after the first dose and resolved after a median of 65 d. There were no deaths or drug-induced liver injury events. During the tx period, 2 pts receiving BMS-986036 experienced serious AEs of depression and suicide attempt, and valvular heart disease; none were tx-related. Two pts discontinued BMS-986036 due to tx-related AEs of moderate fatigue and severe injection site reaction. Anti-BMS-986036 and anti-FGF21 antibodies were detected in >50% of BMS-986036–treated pts; however, titres were generally low (<64), not associated with immune-related AEs, and stable or declining in most pts post-study. BMS-986036 tx did not result in clinically relevant changes in ECG or BMD.

BL characteristics	PBO (n = 52)	BMS-986036 (n = 146)
Men	24 (46.2)	70 (47.9)
Mean age (range), years	51.4 (23–75)	54.2 (23–75)
White	49 (94.2)	121 (82.9)
Mean BMI (range), kg/m^2	35.9 (29.4–57.4)	34.7 (25.7–47.7)
T2DM	35 (67.3)	113 (77.4)
Safety Summary		
Any AE	31 (59.6)	94 (64.4)
Tx-related AE	16 (30.8)	33 (22.6)
Serious AE	2 (3.8)	2 (1.4)
Diarrhoea	4 (7.7)	23 (15.8)
Injection site bruising	6 (11.5)	18 (12.3)

Values are n (%) unless noted

Conclusion: This integrated safety analysis of phase 2 data showed that BMS-986036 was generally safe and well tolerated, supporting further clinical trials to evaluate the safety and efficacy of BMS-986036 in the tx of NASH.

FRI-491

Improvement of liver steatosis achieved byprobiotics in patients with nonalcoholic fatty liver disease

I. Copaci, A. Franculescu, L. Micu, G. Chiriac, M. Mihaila, E.L. Iliescu. *Fundeni Clinical Institute, Department of Internal Medicine, Bucharest, Romania*
Email: laurentiumicu2000@yahoo.com

Background and Aims: Diet-induced weight loss and probiotics are associated with changes in the gut microbioma composition in humans and mice. The aim of the study was to assess the efficacy of this combination in patients with nonalcoholic fatty liver disease (NAFLD).
Method: In a prospective observational study, 92 overweight subjects (54 men, 38 women) with steatosis were recruited after excluding other etiologies. Patients were assigned a moderate caloric restriction (1200–1500 Kcal/day), with less than 30% calories from fat. Group A (40pts) received a combination of B. longum and L. rhamnosus (ZirComBi, Alfasigma), 1 sachet/day, 12 days/month for six months. Group B (52 pts) remained only on diet. Blood samples (biochemistry, HOMA-IR, cytokine levels, steatotest) were collected at entry and at months 6 and 12. All subjects underwent abdominal CT to assess visceral and subcutaneous adipose tissue area (VAT/SAT).
Results: After 12 months, baseline descriptive characteristics (weight, BMI, waist circumference) decreased significantly. Biochemical parameters that decreased significantly in group A vs group B were: GGT (32.2 ± 14 vs 43 ± 18; p = 0.01), ALT (33.8 ± 14.3 vs 59.1 ± 22.5; p = 0.05) and HOMA-IR (3 ± 0.43 vs 4.83 ± 0.65; p = 0.018). Steatotest improved significantly (0.38 ± 0.13 vs 0.68 ± 0.16; p = 0.02). Modification of cytokine levels was significant for leptin (5.9 ± 2.8 vs 13.6 ± 4.7 ng/ml; p = 0.018), adiponectin (11.6 ± 4.9 vs 7.1 ± 3.1 µg/ml; p = 0.003) and IL-6 (1.2 ± 0.3 vs 2.8 ± 2.2 pg/ml; p = 0.02). VAT/SAT did not differ significantly. Multivariate logistic regression showed the following factors related to improved steatosis: BMI < 25 kg/m^2, ALT < 42IU/l, leptin < 10.5 ng/ml, adiponectin > 8.4 µ/ml, and treatment with probiotics.
Conclusion: 1. A 6-month course of lifestyle intervention and probiotics reduces steatosis. 2. Association of probiotics significantly influences ALT, HOMA-IR, IL-6, adipocytokines and steatosis.

FRI-492

Endoscopic sleeve gastroplasty improves liver enzymes and hepatic steatosis index

R. Rosenblatt, S. Kumar, R. Schwartz, R. Sharaiha. *New York Presbyterian Hospital*
Email: RussellRosenblatt@gmail.com

Background and Aims: Increasing numbers of patients with metabolic syndrome also develop nonalcoholic fatty liver disease (NAFLD). The mainstay of treatment of NAFLD is diet and exercise for weight loss, as patients with greater than 10% of total body weight loss have improvement in hepatic steatosis and fibrosis. Some patients undergo surgical procedures for more lasting weight loss. Novel endoscopic techniques have been developed as treatment of obesity, such as endoscopic sleeve gastroplasty (ESG), which utilizes noninvasive and endoscopic suturing to reduce gastric volume. Prospective data evaluating endoscopic methods of weight loss as a safe and effective potential treatment for NASH are lacking. The aim of this study is to evaluate the impact of endoscopic sleeve gastroplasty on NAFLD using the hepatic steatosis index.
Method: Forty-eight patients undergoing endoscopic sleeve gastroplasty for obesity treatment were enrolled in this pilot study. Clinical examination, body mass index, and laboratory evaluation (e.g. liver function tests) was completed before and 6 months after ESG treatment. The hepatic steatosis index (HSI) was calculated using these indices, the patient's gender and presence of diabetes.
Results: Of the 48 patients enrolled in the pilot study, the average age was 42 and the median BMI was 38.2 and significantly decreased at 6 weeks to 32.5, p = 0.0002. The median ALT decreased from 30 to 21 (p = 0.004) while AST decreased from 24 to 21 over 6 weeks (p = 0.005). The HSI significantly decreased from 50.5 to 42.6 in 6 weeks (p = 0.02).
Conclusion: Endoscopic sleeve gastroplasty significantly reduced transaminases, body mass index, and HSI. It remains an intriguing option to improve NASH in obese patients as a less invasive option to bariatric surgery.

FRI-493

Effects of rosuvastatin and pioglitazone long therapy on NASH and coronary heart disease courses

N. Virstyuk[1], I. Vakalyuk[2], O. Virstyuk[3]. [1]*Iwano-Frankiwsk, Internal therapy, Iwano-Frankiwsk, Ukraine;* [2]*Ivano-Frankivsk National Medical University, Internal Medicine department, Ivano-Frankivsk, Ukraine;* [3]*Ivano-Frankivsk Central Clinical Hospital, neurological department, Ivano-Frankivsk, Ukraine*
Email: virstyukn@gmail.com

Background and Aims: Non-alcoholic steatohepatitis (NASH) with fibrosis have been identified as an independent cardiovascular disease (CVD) risk factor. Rosuvastatin treatment at high doses is effective in patients with CVD and nonalcoholic fatty liver disease (NAFLD). The aim of this study was to evaluate the effects of rosuvastatin at low doses and pioglitazone at low doses on NASH and Coronary Heart Disease (CHD) courses.
Method: 42 patients (pts) with stable CHD (postinfarction cardiosclerosis: myocardial infarction 1–3 years ago) and NASH were observed. General clinical examination, ECG, EchoCG, liver elastography, AST, ALT, GGT, lipids, serum C-reactive proteins (CRP), N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and type IV collagen levels were performed. 22pts have been received rosuvastatin 10mg/day for 1 year (group I), 20 NASH pts have been received rosuvastatin 10mg/day and pioglitazone 15–30 mg/day for 1 year (group II). Examination of the pts was conducted at baseline and after 1 year of treatment.
Results: After treatment, in pts of groups I and II blood circulating triglycerides (p = 0.04 vs. p = 0.006), cholesterol of low density lipoprotein (p = 0.02 vs. p = 0.007), CRP (p = 0.03 vs. p = 0.008), NT-proBNP (p = 0.04 vs. p = 0.009), type IV collagen (p = 0.06 vs. p = 0.02) levels were reduced. In group II AST, ALT, GGT levels were normalized compared with group I and were associated with a shear wave velocity decreased (p = 0.03). Liver fibrosis was decreased in 27.2% pts and remained stable in 40.9% pts, and increased in 31.9% pts of group I. In group II liver fibrosis was decreased in 60.0% pts, 35.0% pts and 5.0% pts respectively. After treatment in pts of group II improvement of the structural-functional state of the heart was observed: left ventricle mass index decreased on 6.1%; left ventricle ejection fraction increased on 8.5%; segmental left ventricular contractility increased on 10.2%. Progression of heart failure from II class NYHA to III class NYHA was in 18.6% pts (group I), vs. 5.0% pts (group II).
Conclusion: Combination of Rosuvastatin and Pioglitazone at low doses for 1 year treatment has metabolic, anti-inflammatory and antifibrotic effects in NASH patients with postinfarction cardiosclerosis and reduces progression of NASH and CHD courses.

FRI-494

Correction of intrahepatic microcirculation disorders by L-ornithine-L-aspartate at the chronic liver diseases patients

T. Ermolova[1], S. Ermolov[2]. [1]*North-Western State Medical University named after I.I.Mechnikov, Internal Medicine, St.-Petersburg, Russian Federation;* [2]*North-Western State Medical University named after I.I. Mechnikov, Therapy and Nephrology, St.-Petersburg, Russian Federation*
Email: t.v.ermolova@mail.ru

Background and Aims: The basis of initial component of increased intrahepatic vascular resistance at the chronic liver diseases are endothelial disfunction, activation of hepatic stellate cells, hyperammoniemia. In some only experimental studies in vivo and in vitro was demonstrated effect of hypoammoniemic drugs for liver microcirculation due to decrease of activity of hepatic stellate cells, portal hypertension, increase of endothelial nitric oxide synthase. Aims of our study are to estimate intrahepatic microcirculation and efficacy of hypoammoniemic L-ornithine-L-aspartate (LOLA) for correction of intrahepatic hemodinamics disorders at the chronic liver diseases patients.
Method: We investigated 78 patients with NASH and 60 chronic viral hepatitis C patients, minimal fibrosis 0–1 stage. Stage of liver fibrosis was estimated by transient elastography (FibroScan). Intrahepatic hemodinamics are determined by polyhepatography – modificated hepatic impedansometry, non-invasive method (PHG). PHG registers a blood flow in projection of zone of hepatic right, left lobes and spleen, integral body impedansography. For verification of functional disorderes induring PHG we use test with deep respiration and nitrates. Our study manifested a high degree of sensitiveness (99%) and specificity (89%) of PHG for definition of localization of hemodynamic disorders in liver (presinusoidal, sinusoidal). For correction of blood flow disorders we used hypoammoniemic drug LOLA in dosage 3 grams 3 times daily 4 weeks. Efficacy of LOLA we looked in 2 and 4 weeks via the control PHG.
Results: Analysis of PHG demonstrated, that at all patients we revealed a liver microcirculation disorders – increased blood resistance, abnormal forms and amplitude of waves in sinusoidal level (out flow zone) at the NASH patients and in presinusoidal level (in flow zone) at the viral patient. Analysis of efficacy of LOLA showed, that LOLA was effective for correction of all hepatic hemodinamic disorders. In 2 weeks of the treatment we observed normalization or improvement of the wave form, in 4 weeks – wave amplitude.
Conclusion: chronic liver diseases are characterized by disorders of intrahepatic microcirculation at different levels, depending on etiology of chronic liver diseases, even in 0–1st stage of liver fibrosis. LOLA improved liver microcirculation at the all patients.

FRI-495

The anti-fibrotic agent, tipelukast (MN-001) reduces serum triglyceride significantly in non-alcoholic steatohepatitis and non-alcoholic fatty liver disease patients with hypertriglyceridemia after 4 weeks of treatment, an interim analysis of ongoing clinical trial, MN-001-NATG-201

K. Matsuda[1,1], J. Gutierrez[2], T. Hassanein[2], Y. Iwaki[1]. [1]*MediciNova, Inc., Clinical R/D, La Jolla, United States;* [2]*Southern California Liver Centers, Coronado, United States*
Email: matsuda@medicinova.com

Background and Aims: Tipelukast (MN-001) is known as an anti-fibrotic agent (AASLD 2014). Also, it was observed that tipelukast reduced serum triglyceride levels in previous clinical studies targeting healthy volunteers and patients with chronic asthma and interstitial cystitis. In this study, we evaluated the effect of tipelukast on non-alcoholic steatohepatitis (NASH) and non-alcoholic fatty liver disease (NAFLD) patients with hypertriglyceridemia.
Method: The MN-001-NATG-201 is a multi-center, open-label study designed to evaluate the efficacy, safety, and tolerability of tipelukast (MN-001) in subjects diagnosed with NASH or NAFLD with hypertriglyceridemia. Subjects receive tipelukast 250 mg qd for the first 4 weeks and increase dosage to 250 mg bid for 8 weeks. In this study, 9 subjects who completed tipelukast (MN-001) 250 mg qd first 4 weeks treatment were analyzed. Of 9 subjects, 3 received tipelukast (MN-001) 250 bid for another 4 weeks.
Results: After 4 weeks of treatment with tipelukast (MN-001), the serum triglyceride level was significantly reduced in 8 of 9 subjects. For 8 patients who reduced their serum triglyceride after the first 4 weeks treatment, pre-treatment mean serum triglyceride was 229.1 mg/dl which was reduced to 174.7 mg/dl ($p < 0.005$). However, for a patient whose serum triglyceride level was not reduced after 4 weeks of tipelukast (MN-001) treatment, a reduction of serum triglyceride was observed after 8 weeks of treatment (24% reduction). There were no significant issues in safety and tolerability.
Conclusion: From this interim analysis, tipelukast (MN-001) significantly reduced serum triglyceride in NASH and NAFLD patients with hypertriglyceridemia, warranting continuation of this ongoing trial.

FRI-496

Lifestyle intervention is effective in treating non-alcoholic fatty liver disease in morbidly obese patients

S. Hohenester[1], C. Simon[2], D. Gerald[1], B. Gert[2], C. Rust[2]. [1]*LMU Munich, University Hospital, Department of Medicine II, Munich, Germany;* [2]*Krankenhaus Barmherzige Brüder, Department of Medicine I, Munich, Germany*
Email: simon.hohenester@med.uni-muenchen.de

Background and Aims: The prevalence of obesity-related non-alcoholic fatty liver disease (NAFLD) is rising worldwide. NAFLD may result in non-alcoholic steatohepatitis (NASH) and progress to liver cirrhosis. Weight loss is recommended to treat obesity-related NASH. Lifestyle intervention has been shown to improve NASH in a few trials, however, these focused on mild obesity, i.e. overweight patients. In contrast, real-life obesity programs typically address patients with morbid obesity. In addition, reports on the efficacy of lifestyle intervention to treat liver fibrosis are scarce. We aimed at evaluating the effect of lifestyle intervention for weight reduction on NAFLD in a real-life cohort of mostly morbidly obese patients.
Method: In this observational single center study, 152 patients underwent lifestyle intervention and were followed for 52 weeks. Measures of obesity, the metabolic syndrome and established non-invasive markers of liver steatosis, damage, and fibrosis were analyzed.
Results: In our cohort of morbidly obese patients (obesity class I, II and III in 13%, 28% and 59% of patients, respectively), treatment response in terms of weight loss was achieved in 85.1%. Dysglycemia and dyslipidemia, i.e. markers of the metabolic syndrome, greatly improved. The proportion of patients with fatty liver, as determined by the fatty liver index (FLI) dropped from 98.1% to 54.3% during follow up ($p < 0.001$). Weight loss >10% was associated with a better treatment response ($p = 0.0009$) in terms of steatosis. Prevalence of abnormal serum alanintransferase (cut-off 30U/L for females, 19U/l for males) fell from 81.0% to 50.5% ($p < 0.001$). The proportion of patients with established liver fibrosis, as determined by the NAFLD fibrosis score, dropped from 11.8% to 0% of patients ($p < 0.05$). Adiponectin correlated inversely with serum ALT ($r = -0,32$, $p < 0.05$), and adiponectin serum levels rose during follow up.
Conclusion: Lifestyle intervention was effective in improving liver steatosis, liver damage and liver fibrosis in a real-life cohort of morbidly obese patients. Improvement was most significant in patients with weight loss of >10%. While 5–7% weight loss is recommended in current guidelines to target NAFLD, >10% might be favorable in patients with morbid obesity.

Acute liver failure and drug induced liver injury

FRI-498

Tauroursodeoxycholic acid protects against valproic acid-induced sensitization to acetaminophen hepatotoxicity

S. Torres[1,2,3], A. Baulies[4], N. Insausti-Urkia[1,2,3], C. Alarcón-Vila[1,3,5], R. Fucho[1,3,5], E. Solsona[1,3,5], S. Núñez[1,3,5], M.C. Garcia-Ruiz[1,2,3,6], José Fernandez-Checa[1,2,3,6]. [1]*Institute of Biomedical Research of Barcelona, Barcelona, Spain;* [2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Liver, digestive system and metabolism, Barcelona, Spain;* [3]*CIBER of Hepatic and Digestive Diseases (CIBEREHD),*

Barcelona, Spain; [4]Francis Crick Institute, London, United Kingdom; [5]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [6]The Southern California Research Center for ALPD & Cirrhosis (USC), Los Angeles, United States
Email: sandra88tn@gmail.com

Background and Aims: Drug-induced liver injury (DILI) is a potentially fatal adverse event. Although valproic acid (VPA), an anticonvulsant drug, has been shown to interact with acetaminophen (APAP), a pain reliever, the impact of this event in DILI has not been fully explored as a potential adverse drug combination. VPA-derived metabolites target mitochondria, inducing mitochondrial permeability transition and disruption of glutathione (GSH) homeostasis as a consequence of reactive metabolites produced by VPA metabolism. Moreover, APAP can cause liver necrosis and acute liver failure in case of overdose due to the generation of NAPQ1, which depletes GSH and covalently bind to mitochondrial proteins. As both drugs have been described to generate endoplasmic reticulum (ER) stress and since StARD1, a protein involved in the intramitochondrial trafficking of cholesterol, is ER stress target gene, thus our aim was to investigate the role of ER stress response in the sensitization of VPA to APAP hepatotoxicity.
Method: Fasted or fed WT mice were treated three times every 12 h with VPA (400 mg/Kg, sc) or TUDCA (250 mg/Kg, ip) followed by a single dose of APAP (300 mg/Kg, ip). Liver damage by ALT and H&E, cholesterol trafficking, GSH homeostasis and mitochondrial function was examined in these animals. Expression of StARD1, MLN64, ER stress markers and lipogenic transcription factors were examined by qPCR and WB.
Results: During fasting, APAP-induced liver injury was independent of VPA. However, in fed mice VPA + APAP treatment significantly increased serum ALT levels and induced centrilobular necrosis compared to control, VPA and APAP groups. TUDCA fully abolished the VPA + APAP hepatotoxic response, revealed by the H&E staining and the significant decrease in serum ALT release. mRNA analysis revealed an induction of StARD1 (2,5 fold) in mice treated with VPA + APAP compared to VPA and APAP treated groups, as well as an upregulation of BiP, CHOP and MLN64 at 4 and 24h after VPA + APAP treatment. TUDCA treatment prevented VPA + APAP-mediated ER stress markers and abolished StARD1 upregulation. These events mirrored the replenishment of GSH levels in mitochondria in VPA + APAP-treated mice following TUDCA administration.
Conclusion: TUDCA protects against the hepatotoxic effects of VPA-induced sensitization to APAP hepatotoxicity, thus suggesting that ER stress is an important player in the liver injury induced by the combination of VPA plus APAP.

FRI-499

s-ademetionine effectively prevents drug-induced liver injury in overweight patients with acute leukemia

I. Skrypnyk, G. Maslova. *Ukrainian Medical Stomatological Academy, Internal Medicine, Poltava, Ukraine*
Email: inskrypnyk@gmail.com

Background and Aims: Overweight patients are in high-risk group of hepatic injury on the background of acute leukemia (AL) chemotherapy. Without preventive medications the incidence of hepatotoxic reactions of varying severity in the dynamics of chemotherapy in patients with obesity can reach 70%.
The aim – to assess the effectiveness of S-ademetionine (S-AME) in the prevention of DILI in overweight patients with AL in chemotherapy dynamic.
Method: The study involved 44 overweight patients with newly diagnosed LA (34 – acute myeloid leukemia (AML), 10 – acute lymphoblastic leukemia (ALL)), ECOG I-II, aged 20–67 years, 21(47.7%) women, 23(52.3%) – men. The body mass index (BMI): 25–29.9 – in 32 (72.7%), BMI > 30 – in 12(27.2%) patients. The liver function was assessed by the activity of alanine aminotransferase (ALT), aspartate (AST) aminotransferase, alkaline phosphatase (ALP), gamma-glutamyltranspeptidase (GGT), bilirubin, total protein in the blood serum twice: at baseline and on the 56-thth day after starting induction of remission therapy, according to the ALL (prednisolone, doxorubicin, vincristin, asparaginase, cyclophosphamide, cytarabine, mercaptopurine) and AML (cytarabine, doxorubicin) treatment protocols. To assess the severity of hepatotoxic reactions the CTCAE scale was used.
Depending on the assigned treatment, the patients were divided into 2 groups: I (n = 23) – chemotherapy + S-ademetionine (S-AME) 1000 mg/day; II (n = 21) – chemotherapy.
Results: In all patients of groups I and II with overweight in the debut of AL ALT activity was increased in 1.4, AST – in 1.2 times, ALP and GGT in 1.3 times compared to the normal values ($p < 0.05$) and reached grade I level, and not significantly different from healthy people in bilirubin and total protein levels.
On the 56-th day of treatment in 6(26%) patients of group I on the background of S-AME prophylactic appointment the functional liver state violation was revealed: the increased activity of ALT in 1.5, AST – in 1.2, ALP – in 1.5, GGT – in 1.6 times compared to normal, the bilirubin and total protein levels remained in within the normal, that consistent with grade I. Hepatotoxicity was detected in 15(71.4%) patients of group II, which was characterized by the increased activity of ALT and AST in 2.7 and in 2.3 times, GGT and ALP in 2.7 and 3.2 times respectively, the level of bilirubin increased in 3.1 times, of which in 6(28.6%) patients hepatotoxic reactions were of grade I and in 9(42.9%) – of grade II level.
Conclusion: Obesity in patients with AL significantly increases the frequency and severity of hepatotoxic reactions in the dynamics of chemotherapy. Appointment of S-AME on the background of induction therapy can reduce the grade of the functional liver state injury and prevent DILI.

FRI-500

Drug exposure and risk of Acute Liver Failure leading to registration for liver Transplantation (ALFT): Results of the SALT III study in adults in France

D. Larrey[1], L. Meunier[1], G.-P. Pageaux[1], S. Maleyran[2], S. Micon[2], S. Lorrain[2], R. Lassalle[2], C. Droz@u-Bordeaux. Fr[2], N. Moore[2,3]. *[1]CHU St Eloi Montpellier, Liver and Transplant Unit, MONTPELLIER, France; [2]Bordeaux Pharmacoepi, CIC Bordeaux Cic 1401, Bordeaux, France; [3]NSERM U1219, Bordeaux, France*
Email: dom-larrey@chu-montpellier.fr

Background and Aims: Acute liver failure leading to liver transplantation (ALFT) indication is largely related to drugs (DILI), as shown by our previous SALT-I 2005–2007 and SALT-II 2008–2013 retrospective multicentre studies and the American DILI network. SALT-III study is aimed to estimate the evolution of the risk of DILI-induced ALFT in France in 2015–2016.
Method: Multicentre, prospective and retrospective, case-population study focused on adults patients registered on transplant list for ALF over 2 years (2015–2016). Data are collected in 17 liver transplant centres. Cases are classified in 2 groups: ALFT "with identified non-DILI cause" (viral, autoimmune hepatitis) and ALFT with well-identified DILI cause, cases with drug exposed ALFT and undetermined ALFT. Drug exposure within 30 days prior to index date (initial symptoms of liver disease) is investigated for all cases, whatever the cause of ALFT. The risk of drug-exposed ALFT, expressed as rate per million treatment-years (tt-yrs), will be calculated using reimbursement data of EGB (permanent random sample of the national healthcare insurance system database). This incidence rate will be compared to that of ALFT "with identified non-DILI cause" in order to identify drugs increasing the risk of ALF.
Results: To date, 119 of 148 cases ALFT cases have been adjudicated by a hepatologist group in the 17 liver transplant participating centres. Among them: 53 cases (44.5% of ALFT) have been classified as ALFT with non-DILI cause (autoimmune hepatitis n = 17 (14.3%); vascular liver injury n = 10 (8.4%); hepatitis B n = 8 (6.7%); other viruses n = 4 (3.4%); alcoholic ALF n = 6 (5.0%); mushroom intoxication n = 4 (3.4%); other causes n = 4 (3.4%) and 50 cases (42% of ALFT) related to paracetamol including 30 cases (25%) with voluntary overdosage

and 21 cases (17.6%) of accidental paracetamol-DILI; 10 cases (8.4%) exposed to drugs 30 days prior to liver injury including 4 DILI with probable causality: amoxicillin (1 case), anti-tuberculous (1 case), antiepileptics (1 case) chemotherapy (1 case) and 6 cases with possible other DILI (several concomitant drugs) and 5 cases (4.2%) not exposed to drugs 30 days prior to liver injury.
Conclusion: In France, over the years 2015–2016, the role of paracetamol in ALFT is further increasing, with a significant proportion of accidental counterpart. Other drugs account for 8.4% of ALFT. Non identified causes is significantly reduced. The results for the whole 143 patients will be available for April 2018. This study was supported by ANSM.

FRI-501

Long-term liver safety of lomitapide in patients with homozygous familial hypercholesterolemia: Three-year data from the lomitapide observational worldwide evaluation registry (LOWER)

D. Larrey[1], J. Underberg[2], C. Cannon[3], L. Makris[4], A. Jurecka[5], D. Blom[6].
[1]Hôpital Saint Eloi, Montpellier School of Medicine, Department Hépato-gastro-entérologie, Montpellier cedex 5, France; [2]NYU Medical School & NYU Center for CV Prevention, Division of General Internal Medicine, New York, United States; [3]Baim Institute for Clinical Research, Boston, United States; [4]Stathmi Inc., New Hope, United States; [5]Aegerion Pharmaceuticals, Cambridge, United States; [6]University of Cape Town, Department of Medicine, Cape Town, South Africa
Email: agnieszka.jurecka@aegerion.com

Background and Aims: Phase 3 clinical study for a microsomal triglyceride transfer protein (MTP) inhibitor, lomitapide, in the treatment of Homozygous Familial Hypercholesterolemia (HoFH) has been associated with asymptomatic transaminase elevations and liver-fat accumulation. Lomitapide prescribing information therefore carries a warning of the risk of hepatotoxicity with use, thus, lomitapide is only available through the restricted REMS Program.
Method: The Lomitapide Observational Worldwide Evaluation Registry (LOWER), is an international, multicenter, observational registry, established to prospectively assess long-term safety and efficacy of lomitapide. This analysis examines 3 years of data among patients enrolled in the registry.
Results: As of March 1, 2017, 163 patients with mean age of 52.3 years were enrolled in LOWER in the USA, EU, Taiwan and Canada. Exposure duration was up to 47.1 months, with 72.4% of patients receiving the drug for >12 months and 38% for 2–5 years. Mean dose was 10 mg (range 5 mg QOD-40 mg QD). The median time to elevated transaminases was 7.7 months. Patients were referred for additional liver-related evaluations for 21 (67.7%) patients with ALT or AST ≥3× ULN to <5× ULN and 10 (90.9%) patients with ALT or AST >5× ULN. Further, elevated transaminases >3× ULN (n = 35, 22.3%) with data following escalation resolved spontaneously or after dose reduction or drug discontinuation. There has been no case with symptomatic hepatitis. Across the 3 years of the registry, only 7 of163 (4.3%) patients had confirmed event of special interest of hepatic transaminase elevations resulting in discontinuation of lomitapide.
Conclusion: The 3-year duration of LOWER afforded the opportunity to assess the effect of chronic MTP inhibition on liver safety. Our data confirm that lomitapide is associated with frequent asymptomatic increase of transaminases, however the percentages of ALT/AST increase are less than those reported in clinical trials. The reduction of lomitapide dose or temporary interruption was associated with resolution allowing the continuation of treatment. There was no significant liver injury and no Hy's law cases.

FRI-502

Proof-of-concept of full-length genome sequencing as diagnostic tool of acute viral hepatitis

I. Ruiz[1], G. Gricourt[2], S. Fourati[1], C. Stephane[2], A.L. Bouter[2], H. Regnault[2], V. Demontant[2], Frédéric L. Gal[3], E. Gordien[3], C. Hezode[2], C. Rodriguez[2], J.-M. Pawlotsky[2]. *[1]INSERM U955, France; [2]CHU Henri Mondor, APHP; [3]Hôpitaux Universitaires de Paris Seine Saint-Denis, Site Avicenne, Bobigny, France*
Email: isaac.ruiz@me.com

Background and Aims: Acute hepatitis is a common clinical condition with serious complications such as fulminant hepatitis. The cornerstone of acute hepatitis management remains the identification of the etiological cause. Indeed, PCR or serological tests available for viral diseases are all specific for one virus making diagnosis difficult. The aim of this study was to evaluate full-length-genome sequencing (FLGS) as a diagnostic tool.
Method: "Acute hepatitis cohort" enrolled 11 patients with a causal diagnosis of acute viral hepatitis; "Hepatitis-related-virus cohort" enrolled 71 patients without acute hepatitis but with viral infections associated with hepatitis. Full medical history was recorded and acute hepatitis was diagnosed as recommended by the EASL guidelines. Samples were tested by means of an original in-house patent-protected shotgun metagenomics method using MetaMIC® process. A universal extraction (whole microbes, DNA and RNA) followed by library preparation using Total RNA and Nextera XT kit (Illumina) and sequencing with NextSeq500 (Illumina) were performed. Then, sequences were analyzed using MetaMIC software (quality, filtering, identification, genome reconstruction and comparison) for rate mutation calculation in whole viral genome (cut off at 15%).
Results: Shotgun metagenomics provided different levels of characterization of viral infections depending on their viral load: Low viral load could be only "Detected", while high viral load is associated with a "FLGS". The results are summarized in table 1. In addition, viruses not detected by routine test panels viruses not detected by routine test panels, such as human Pegivirus 1, were also detected in 3 cases.
Conclusion: FLGS by means of shotgun metagenomics using deep sequencing technology identifies all common viruses causing acute hepatitis, as well as non-common hepatitis-virus-related infections. In addition, the technique detects viruses not detected by routine test panels in diagnostic laboratories, including co-infections. Thus, we have established a FLGS technology able to blindly detect any pathogen in the context of acute hepatitis, regardless of the disease

Table 1: (abstract: FRI-501): Peak Transaminases (Peak ALT or AST by Time Period Elevation Category at Any Time Point during Analysis Windows – Full Analysis Set), Cases of Hy's Law and Hospitalizations due to LFT elevations in Phase 3 clinical study and LOWER 3 Year data

Time Point	Normal n (%)	<3× ULN n (%)	≥3× – <5× ULN n (%)	≥5× – <10 × ULN n (%)	≥10 × – <20 × ULN n (%)	≥20 × ULN n (%)	Hy's Law*	Hospitalizations due to LFT elevations
Phase 3 Clinical Study Safety Phase 26–28 weeks (N = 23)	14 (61)	4 (17)	3 (13)	2 (9)	0 (0)	0	0	0
LOWER 3 Year Baseline value (N = 143)	128 (89.5)	14 (9.8)	0	0	0	1 (0.7)	0	0
LOWER 3 Year Any time point after start of treatment (N = 157)	54 (34.4)	68 (43.3)	25 (15.9)	8 (5.1)	0	2 (1.3)	0	0

*criteria: AST or ALT ≥ 3× ULN and bilirubin ≥ 2× ULN

Table 1: (abstract: FRI-502)

Virus	Approved biological test	#n patients	Positives by standard test	Positives by FLGS	FLGS Characteristics	
					Detected	FLGS
Acute hepatitis cohort						
HAV	anti-HAV IgM	4	4	4	0	4
HBV	HBsAg +, anti-HBs Ab	4	4	4	1	3
HCV	anti-HCV IgM + HCV PCR	1	1	1	1	1
HEV	anti-HEV IgM	2	2	2	2	2
Hepatitis-related-virus cohort						
HDV chronic	anti-HDV IgM	12	12	12	12	12
HBV chronic	anti-HBc Ab+, HBsAg –	8	8	8	3	5
HCV chronic	anti-HCV Ab	34	34	34	10	24
HCMV	CMV PCR	4	4	4	4	4
HVS1	HSV1 PCR	1	1	1	0	1
HVS2	HSV2 PCR	1	1	1	0	1
VZV	VZV PCR	1	1	1	0	1
EBV	EBV PCR	1	1	1	1	0
HHV6	HHV6 PCR	1	1	1	0	1
Dengue	Dengue PCR	1	1	1	0	1
HIV	Anti-HIV1 Ab	7	7	7	3	4

severity. This tool will prove to be essential for the diagnosis of acute hepatitis, especially the severe cases in emergency, allowing for more accurate diagnosis.

FRI-503

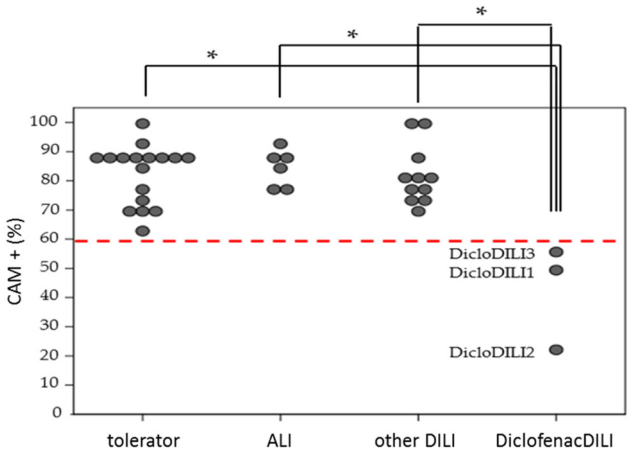
MH cells in combination with proteomics identify a potential biomarker for Drug-induced Liver Injury by Diclofenac

A. Benesic[1,2], D. Dragoi[2], G. Pichler[3,4], N. Kulak[3,4], H. Bartsch[5], A. Gerbes[6]. *[1]University Hospital Grosshadern Munich, Department of Medicine 2, Liver Centre Munich, Munich, Germany; [2]MetaHeps GmbH, Martinsried, Germany; [3]Preomics GmbH, Martinsried, Germany; [4]Max Planck Institute for Biochemistry, Department of Proteomics und signal transduction, Martinsried, Germany; [5]Institute of Pathology, Medical School Ludwig-Maximilians University Munich; [6]University Hospital Grosshadern Munich, Department of Medicine 2, Liver Centre Munich*
Email: andreas.benesic@med.uni-muenchen.de

Background and Aims: Drug-induced liver injury (DILI) is the most frequent cause of acute liver failure and the single most important reason for regulatory actions on drugs. Idiosyncratic DILI (iDILI) is not predictable by pre-clinical models and its diagnosis is very challenging. Drug causality may be impossible to determine in polymedicated patients. These difficulties in case characterization impede with efficient development of novel iDILI biomarkers. We have developed a method to diagnose or exclude iDILI using hepatocyte-like cells derived from peripheral monocytes (MH cells) which can improve causality assessment in polymedication. Aim of this study was to investigate whether proteomics analyses of patient derived MH cells allow the identification of novel specific iDILI biomarkers.

Method: MH cells were generated from 22 donors (study NCT02353455): 12 were exposed to diclofenac (3 patients who tolerated diclofenac, 4 patients who suffered iDILI by diclofenac, 2 patients with iDILI by another drug and 3 patients with acute liver injury (ALI) of non-drug cause). 10 patients without diclofenac intake were used as additional controls (3 healthy, 4 iDILI by other drugs and 3 ALI patients). MH cells were treated with diclofenac in vitro and analysis of MH cells was performed using mass spectrometry (MS)-based proteomics. From over 2700 proteins that could be quantified in MH cells derived from individual patients, we identified a cell adhesion molecule (CAM) to be specifically upregulated in Diclofenac-treated MH cells from Diclofenac-DILI patients compared to control groups.

Results: Flow cytometry of whole blood and histological staining of liver biopsies derived from additional patients diagnosed with Diclofenac-DILI and controls shoed a decrease of CAM-positive cells in blood samples of patients with Diclofenac DILI (Figure) whereas an increased CAM-signal was found in liver biopsies of these patients. These results suggest a recruitment of CAM-positive cells in the liver during iDILI by diclofenac.



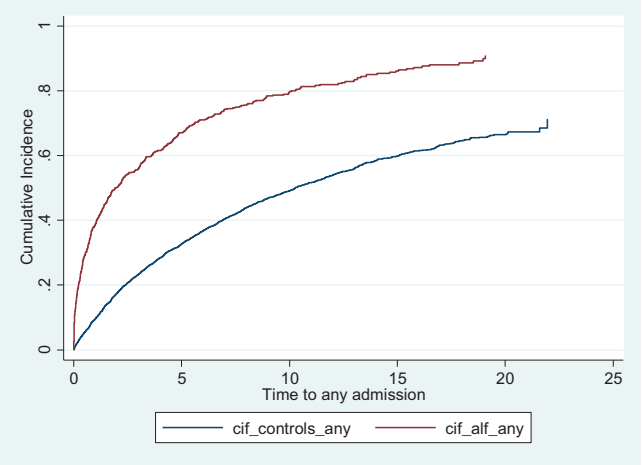
Conclusion: Proteomics analysis of these MH cells from patients with Diclofenac DILI show distinct changes in protein expression induced by diclofenac treatment. The cell adhesion molecule (CAM) as identified biomarker candidate showed distinct changes in blood samples and liver biopsies from patients with diclofenac DILI. The combination of MH cells and MS-based proteomics may present a novel tool to identify drug-specific biomarkers for iDILI.

FRI-504

Health care utilisation in spontaneous survivors of acute liver failure

M. Donnelly[1], L.J. Williams[2], B. Murray[3], C. Taylor[3], A. Springbett[3], J. Davidson[4], A. Baird[4], K. Martin[4], J. Moore[4], N. Lone[2], K.J. Simpson[4]. *[1]Royal Infirmary of Edinburgh, Hepatology, Edinburgh, United Kingdom; [2]University of Edinburgh, Centre for Population Health Sciences, Edinburgh, United Kingdom; [3]Electronic Data Research and Innovation Service, NHS Information Services Division, Edinburgh, United Kingdom; [4]Royal Infirmary of Edinburgh, Department of Hepatology and Scottish Liver Transplant Unit, Edinburgh, United Kingdom*
Email: mhairi.donnelly@nhs.net

Background and Aims: In Scotland, patients with severe acute liver injury or failure (ALF) are managed in a single centre (Scottish Liver Transplant Unit; SLTU). Patients surviving ALF without transplantation ("spontaneous survivors"; ALF-SS) are expected to return to normal health without lasting morbidity. Little research has been undertaken on the long-term morbidity and health care utilisation of ALF-SS. Our aims were to analyse health care resource use in ALF-SS compared with a matched sample of the general Scottish population.
Method: The study cohort was patients admitted to the SLTU (01/11/1992–30/12/2014) surviving to hospital discharge without transplantation. The general population control cohort was matched for year of birth, sex and postcode sector. Units of resource use were identified from the SMR01 database and costs calculated. Independent predictors of hospital readmission were identified by negative binomial multivariable regression modelling. Fine and Gray models were used in analysing time to first readmission with death as a competing risk.
Results: In ALF-SS, the cumulative incidence of first readmission was 12.6% at 30 days, 38.3% at one year, 66.9% at five years, 79.4% at 10 years and 90.9% at 20 years compared with 1.3%, 9.6%, 32.7%, 49.2% and 67.4% in the matched controls – see Figure.
The ALF-SS experienced their first readmission significantly earlier than the matched controls (mean years to any readmission: ALF-SS 5.3; matched controls 11.8: $p < 0.0001$). The adjusted relative rate (RR) of any readmission (for ALF-SS compared with matched controls) was 2.99 (RR 95% CI 2.64–3.39; $p < 0.0001$) and emergency readmissions was 4.65 (RR 95% CI 4.00–5.38; $p < 0.0001$). Total costs of readmissions in the ALF-SS were £9,316,125 with a cost of £13,536/10 person years (py) for all admissions. The cost/10py was £4366.81 in the matched controls.
Predictors of time to any readmission in the ALF-SS were: age, count of elective and emergency admissions pre SLTU admission, previous psychiatric admissions, and non-paracetamol aetiology. Predictors of time to emergency readmission were: age, count of elective and emergency admissions pre SLTU admission, Carstairs decile, non-paracetamol aetiology and bilirubin. In analysing rate of readmissions per-person year, bilirubin was a predictor of readmission, in addition to those variables reported as predictors of time to any readmission.



Cumulative incidence of any admission in ALF-SS (cif_alf_any) and matched controls (cif_controls_any) (years since hospital discharge).

Conclusion: Due to the rarity of ALF, the long-term implications of surviving ALF have not previously been recognised. We have shown that spontaneously surviving ALF is associated with increased health care utilisation. We must now begin to develop follow up protocols for ALF-SS, to reduce readmission rates and the resource use burden in this population.

FRI-505

Amatoxin poisoning in Germany – important clues for clinical practice

B. Schlevogt[1], N. Jedicke[2], H. Heinzow[1], I. Kabar[1], M. Busch[2], M.P. Manns[2], H. Schmidt[1], C. Wilms[1]. *[1]University Hospital Münster, Gastroenterology and Hepatology, Münster, Germany; [2]Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany*
Email: bernhard.schlevogt@ukmuenster.de

Background and Aims: Intoxication with amatoxins is a rare but often severe cause of acute liver injury requiring even liver transplantation in some cases. As most mushroom intoxications are not related to amatoxins and therefore do not have serious consequences there is a need for early identification of those who require treatment in a transplant center due to acute liver failure. The aim of this study was to better characterise the patients at risk and to test a temporal cutoff for safe termination of laboratory follow-up after symptomatic mushroom ingestion.
Method: In a multicenter retrospective cohort study (2 tertiary referral transplant centers) 31 patients with a history of mushroom ingestion and subsequent liver injury were included from 2002 until 2017. Clinical and laboratory data was collected from chart review.
Results: Patients with amatoxin intoxication predominantly came from countries from the former USSR. A much smaller group of patients presented during the European refugee crisis in 2015 whereas only 2 patients came from Germany (Table 1). Occurrence of amatoxin poisoning was clearly seasonal as 87% of the patients presented during August and September. All patients developed gastrointestinal symptoms after a median 10h (range 2–24h) and presented at the hospital after a median 25h (range 13–104h). At initial presentation 90% of the patients already had an elevated alanine transaminase (ALT) after a median 30h (range 16–104h). The 3 initial ALT negative patients developed an increased ALT at 30h, 37h and 51h. The latter patient was excluded from further analysis because of a peak ALT reaching just 65 U/l. When taking 48h from ingestion as a cutoff for termination of the laboratory surveillance only 8 patients had their first available ALT (range 391–8293 U/l) after a longer period of time. Due to these strongly increased ALT values it is highly likely ALT would have been tested positive at the cut-off of 48h post ingestion if they had just presented earlier.

Table 1: Origin of patients with amatoxin poisoning in 2 tertiary referral transplant centers from 2002–2017

country of origin	patients
Kazakhstan	6
Russia	5
Rumania	4
Poland	2
Syria	2
Iraq	2
Germany	2
Lithuania	1
Hungary	1
Turkey	1

Conclusion: In this study we describe for the first time that people who originated in countries from the former USSR are the main population at risk for amatoxin associated liver injury. With this knowledge more targeted awareness campaigns can be launched. Very often, it is difficult for the clinician to identify the exact mushroom species in order to predict toxicity. Based on our results, we suggest that severe mushroom poisoning can be excluded safely if ALT values are still within normal range at 48h past mushroom ingestion.

FRI-506

Opal, but not MARS improves patients albumin binding function measured by Electron Spin Resonance (ESR) in a prospective multicenter trial

A. Kortgen, J. Stange, C. Sponholz, H. Schmidt, C. Wilms, H.U. Gerth, S. Mitzner, M. Dollinger, T. Hassanein
Email: jstange@ucsd.edu

Background and Aims: In patients with decompensated cirrhosis, endogenous accumulation of toxins results into overload of patient's albumin as a toxin carrier and reduction of patient's albumin binding functions measured by Dansylsarkosine binding (ABiC), a marker for bile acid binding (Klammt et al. EJGH 2007) or Electron Spin Resonance (ESR), a marker for long chain fatty acid binding (Jalan et al. Hepatology 2009). Both markers have been shown to be associated with survival. Extracorporeal albumin dialysis (ECAD) using MARS has been reported to be ineffective to improve ESR parameters in decompensated cirrhosis, indicating the reduction seen in this condition is either irreversible or insufficient removal of albumin bound toxins, or both. Open albumin dialysis (OPAL), employing new membranes and more efficient adsorbents was tested versus MARS in a multicenter randomized cross over study to test the hypothesis if these changes can be reversed by more effective ECAD.
Method: 30 subjects in 4 sites with chronic liver disease and progressive jaundice and/or hepatic encephalopathy and/or renal failure and/or pruritus were treated first randomly with OPAL or MARS and after wards crossed over to the other. Patient's albumin binding was measured by ESR using a long chain fatty acid as a marker.
Results: Subjects initiated with MARS and initiated with OPAL were comparable with respect to age, gender, baseline MELD. Detoxification Efficacy (DE) was unchanged during MARS (0.11 ± 0.07 vs. 0.11 ± 0.09; n.s.) while it was significantly increased after OPAL (0.085 ± 0.07 vs. 0.14 ± 0.09; $p < 0.05$). Binding Efficacy (DE) was unchanged during MARS (0.23 ± 0.09 vs. 0.22 ± 0.09; n.s.) while it was significantly increased after OPAL (0.2 ± 0.06 vs. 0.26 ± 0.07; $p < 0.05$).
Conclusion: These data indicate that the reduction of patient's albumin binding for long chain fatty acids is at least in part reversible provided effective adsorbents are used to remove albumin bound toxins. A prospective randomized study is planned to re-examine the consequence of improving this prognostoic marker on survival.

FRI-507

Etiology and clinical features of patients with drug-induced liver injury diagnosed by liver biopsy

G. Chen[1,2], D. Ji[1,2], C. Wang[3,4], J. Chen[3], Q. Shao[1,2], B. Li[1,2], F. Li[1,2], Z.B. Li[1], Y. Wang[3], T. Wu[3], V. Wu[3], G. Lau[5]. *[1]302 Hospital, Second Liver Cirrhosis Diagnosis and Treatment Center, Beijing, China; [2]Beijing 302-Hong Kong Humanity and Health Hepatitis C Diagnosis and Treatment Centre, Beijing, China; [3]Humanity and Health Research Center, Hong Kong, Hong Kong; [4]State Key Laboratory of Organ Failure Research, Guangdong Provincial Key Laboratory of Viral Hepatitis Research, Department of Infectious Diseases, Nanfang Hospital, Southern Medical University, Guangzhou, China; [5]Humanity and Health Research Centre, Unit 1505, 15/F, No. 9 Queen's Road Central, Hong Kong, Hong Kong*
Email: gkklau@netvigator.com

Background and Aims: Drug-induced liver injury (DILI) is a rare adverse drug reaction and it can lead to jaundice, liver failure, or even death in some patients. Antimicrobials and herbal and dietary supplements are among the most common therapeutic classes to cause DILI in the Western world. This study aimed to investigate the etiology and clinical features of Chinese patients with DILI.
Method: A total of 194 consecutive DILI inpatients, who underwent liver biopsy in Beijing 302 hospital from January 2015 to December 2015, were enrolled in the study. The etiology, laboratory markers (alanine transaminase, aspartate aminotransferase, total bilirubin, gamma-glutamyl transferase and alkaline phosphatase), and the pathological features were analyzed retrospectively. The relationship between liver fibrosis stage and non-invasive measurements, e.g. liver stiffness measured (LSM) by FibroScan® (Echosens, Paris, France), APRI, FIB-4 and portal vein diameter were analyzed by Spearman correlation analysis.
Results: Chinese traditional medicine (TCM) was the most common cause of DILI, which accounted for 46.9% of patients, followed by acetaminophen-containing regimen (14.4%), antibiotics (9.3%), environmental toxins (4.6%), antidepressant (4.6%), dietary supplement (3.1%), lipid-lowering drugs (3.1%), chemotherapeutic agents (3.1%), and others (11.3%). Of 194 DILI patients, hepatocellular type was observed in 78 (40.2%) patients, cholestatic type in 63 (32.5%) patients, and mixed type in 53 (27.3%) patients. Histological findings showed that 70 (36.1%) patients had an acute injury, 124 (63.9%) patients had chronic damages, which composed by G0 (9.8%), G1 (19.1%), G2 (21.6%), G3 (9.8%), and G4 (3.6%) inflammation level. LSM, APRI and FIB-4 were positively correlated with liver fibrosis stage, but portal vein diameter had no relationship with liver fibrosis stage.
Conclusion: In Chinese population, almost half of DILI was induced by TCM. Liver stiffness measured by non-invasive biomarkers is correlated with grading from liver biopsy in Chinese patients with DILI.

FRI-508

Acute Liver Failure-Organ Failure (ALF-OF) score is better than King's College Hospital criteria in predicting mortality in patients with non-paracetamol-related acute liver failure (ALF)

F. Figorilli[1], A. Putignano[1], B. Agarwal[2], R. Jalan[1]. *[1]UCL Institute for Liver and Digestive Health, UCL Medical School, Royal Free Campus, Liver Failure Group, London, United Kingdom; [2]Royal Free Hospital, Royal Free Hampstead NHS Trust, University College London, Intensive Care Unit, London, United Kingdom*
Email: francesco.figorilli@gmail.com

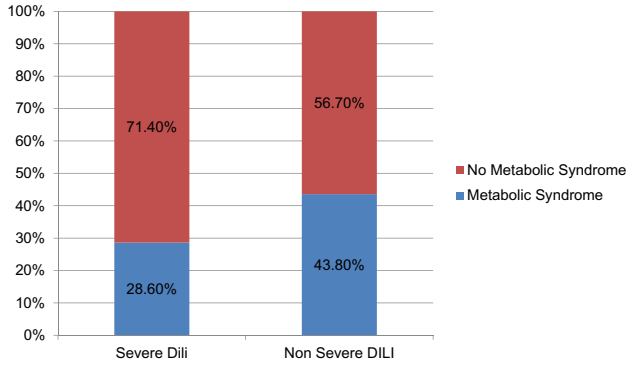
Background and Aims: ALF is a critical illness and a liver transplant (LT) is often the only life-saving treatment. King's College Hospital criteria (KCH) are currently used to identify LT potential candidates among patients with ALF of all aetiologies. Given high mortality and the organ shortage, a more sensitive score is needed. ALF-OF score is a modified version of CLIF-OF score recently created for paracetamol related-ALF. A cut-off of 4.5 has been proposed as a poor prognostic criteria. In this study we compared the new prognostic score with KCH and SOFA score to find the best predictor of free-LT survival in the context of non-paracetamol related ALF.
Method: We included all consecutive patients admitted to the intensive care unit of the Royal free Hospital between 2001–2016 with ALF not related to paracetamol overdose. Clinical and laboratory data were collected and ALF-OF, KCH and SOFA were calculated at the admission. Primary endpoint was the 3-month mortality of any cause. For each score we assessed the area under the curve (AUC), the best cut-off value, sensitivity, specificity and positive predictive value (PPV). Cox regression analysis was used to identify the best predictor of 3-month mortality.
Results: 75 patients were included: 76% fulfilled poor prognostic KCH criteria. Of them, 35 were listed for LT but 3 died while on the waiting list. The 3-month mortality among the 32 transplanted patients was 15.6%. 22 patients despite fullfiling poor prognostic criteria, did not receive LT (2 were not listed for psychiatric problems, 15 were considered too unwell for LT and 5 improved). 43/75 were not transplanted showing a 3-month mortality of 46.5%. ALF-OF had the best AUC (0.766) with 60% sensitivity and 75% PPV; it was also the best mortality predictor in the multivariate analysis ($p < 0.001$; HR 3.3; 95%CI 1.78–6.1). SOFA showed the second highest AUC (0.665) with a higher sensitivity (90%) but the lowest specificity (47.8%). KCH criteria showed the lowest AUC (0.620) with the lowest sensitivity (50%). Non-transplanted patients achieving an ALF-OF score >4.5 showed a higher 3-month mortality in Kaplan Meier analysis (56% vs

11%, p = 0.025) while no significant difference was observed according to KCH criteria (62%vs37%; p = 0.083).
Conclusion: ALF-OF score is better than KCH criteria in predicting the mortality among patients with non-paracetamol related ALF. This new score could be used to select the optimal candidates for emergency LT.

FRI-509
Drug induced liver injury – A study on the factors affecting severity and prognosis with special emphasis on metabolic syndrome

S. Narayanan, K. Devadas. *Trivandrum Medical College Thiruvananthapuram, India*
Email: sanpnr@gmail.com

Background and Aims: The factors predicting outcome in DILI has not been well understood. Of late several studies have linked DILI severity with underlying NASH as both the disorders has been linked with mitochondrial dysfunction. Objective of the study was to whether metabolic syndrome is an independent predictive factor for severity and mortality in drug induced liver injury. Secondary objective was to identify other factors influencing outcome.
Method: Severe DILI was defined as either INR > 1.5 or Ascites or hepatic encephalopathy or other organ failure.Metabolic Syndrome was defined by IDF Criteria. **Inclusion criteria:** Documented exposure to drug ingestion resulting in hepatotoxicity satisfying DILI criteria with RUCAM score 6 or more. **Exclusion Criteria:** Viral marker positivity, Decompensated cirrhosis s. USG, FBS, FLP, anthropometric measurements, BP measurement and BMI was obtained for all patients.
Results: A total of 76 patients were included in the study, out of which 28 had severe DILI. There was 7 cases of fatal DILI, out of which 3 had underlying cirrhosis. Females formed 59.2% of the cohort. Thee most common cause of DILI was ATT(27.6%), followed by CAMS (15.8%), Chemotherapeutic drugs (13.2%) and antiepileptics (13.2%). Most of the severe DILI cases were due to ATT (46.4% of all severe DILI cases). Of the 76 cases, 38.2% had metabolic syndrome. Metabolic syndrome was present in 28.6% of severe DILI cases compared to 43.8% of non severe DILI cases (P > 0.05). When ATT DILI was excluded, the proportion of Metabolic Syndrome in the severe DILI cohort rose to 44.4%. Fatty liver was seen in 39.5% of the patients. Only 14.3% of severe DILI patients had fatty liver compared to 56.3% of non severe DILI patients (p = 0.001). Of the seven cases of mortality due to DILI, two (28.5%) satisfied the criteria for metabolic Syndrome. Mean latent period was 91.9 days in the ATT group compared 27.6 days in the non ATT group. In severe DILI the mean latent period was 73.9 days compared to 28.4 days in the non severe DILI group (p < 0.05). Mean bilirubin in the DILI group was 18.8 compared to 5.7 in the non severe group. Mean ALT was 988.8 in the severe group compared to 390.8 in the non severe group.



Conclusion: Metabolic syndrome showed no correlation with the severity or mortality in DILI. Paradoxically metabolic syndrome was lower in the severe DILI group though the results were not statistically significant. The proportion of patients in the DILI cohort was higher than population prevalence.

FRI-510
Serum CXCL10, CXCL11, CXCL12 and CXCL14 chemokine patterns in patients with acute liver injury

A. Chalin[1,2], B. Lefevre[1,2], C. Devisme[1,2], V. Carrière[1,2], L. Amiot[1,2,3], M. Samson[1,2]. *[1]IRSET - U.1085 Inserm, Rennes, [2]Université de Rennes 1, Rennes, [3]Université de Rennes 1/CHU Pontchaillou de Rennes*
Email: michel.samson@univ-rennes1.fr

Background and Aims: CXCL10 (interferon ϒ-inducible protein 10 [IP-10]), CXCL11 (Human interferon inducible T cell alpha chemokine [I-TAC]), CXCL12 (stromal cell derived factor 1 [SDF-1]) and CXCL14 (breast and kidney-expressed chemokine [BRAK]) chemokines are known to be involved in recruitment, migration, activation and homing in liver diseases and have been shown to be upregulated during acute liver injury (ALI) in animal models. However, to our knowledge, no data has been reported on their expression in patients with ALI. Here, we aim to provide evidence on the presence of circulating CXCL10, CXCL11, CXCL12 and CXCL14 chemokines during human ALI to propose new biomarkers of inflammation during ALI.
Methods: The 4 chemokines were measured on sera samples from 149 patients and 36 healthy volunteers using ELISA assay. Inclusion criteria for ALI patients were ALT activity superior to 129 UI/L (or 3 × upper normal limit). Patients with acute on chronic liver injury or hepatocarcinoma were excluded or if other source of ALT activity was suspected (rhabdomyolysis, myocardial infarction …). Patients were separated into 8 groups depending on the cause of the ALI. The degree of association between two variables was assessed by Pearson's parametric test rank correlation. Comparisons of parameters between two different groups were analysed by the Student t-test.

Table: (abstract: FRI-510): Serum chemokine levels mean fold increase among the different groups of patients compared to healthy donors. (*p < 0.05, **p < 0.01, ***p < 0.001; statistical significance was determined by Student's t-test for difference in means)

	CXCL10		CXCL11		CXCL12		CXCL14	
	Mean fold increase	Significance	Mean fold increase	Significance	Mean fold increase	Significance	Mean fold increase	Significance
Ischemia reperfusion post liver graft	4.5	**	3.7	***	3.8	***	1.43	ns
Acute viral infection	11.4	***	8.1	***	3.3	***	3.8	**
Biliary	2.0	ns	1.8	*	2.1	**	−2.9	ns
Congestive hepatopathy	2.5	*	2.5	***	4.5	***	3.4	*
Toxic	3.8	*	3.1	***	5.6	***	2.4	ns
Auto-immune	9.0	***	6.6	***	3.9	***	−3.2	ns
Vascular	10.5	***	3.5	***	6.1	***	5.3	***
Obstetrical	3.4	**	6.4	***	5.0	***	−1.1	ns

Results: CXCL10 was mainly found in acute viral infection, autoimmune, vascular diseases and to a less extent in liver ischemia post graft and obstetrical aetiologies. CXCL11 and CXCL12 were strongly upregulated for all aetiologies excepted biliary diseases. CXCL14 was found only in acute viral infection and vascular aetiologies.
Conclusion: These data provide evidence on circulating CXCL10, CXCL11, CXCL12 and CXCL14 chemokines during ALI and confirm data obtained on animal models. CXCL11 and CXCL12 are the most and CXCL14 the less represented chemokines while CXCL10 shows an intermediate profile. Differential expression patterns were obtained according to ALI aetiologies suggesting a potential use of these chemokines as biomarkers of ALI.

FRI-511

The proportion of patients waitlisted for transplantation for HDS induced liver injury is increasing and differs by race

J. Odin[1], V. Kesar[2], N. Roth[1], P. Grewal[1], J. Ahmad[1]. *[1]Icahn School of Medicine at Mount Sinai, Transplantation Institute, New York, United States; [2]Lenox Hill Hospital, Department of Medicine, New York, United States*
Email: joseph.odin@mountsinai.org

Background and Aims: Cases collected by the US Drug Induced Liver Injury Network (US DILIN) have suggested that the incidence of DILI from herbal and dietary supplements (HDS) has increased in the past five to ten years and may be a growing health problem. We previously examined data on US liver transplantation recipients and found that those of Asian race were disproportionately transplanted for HDS-DILI for unknown reasons. Whether or not proportionately more Asians are waitlisted for transplant for HDS versus nonHDS induced liver injury was not determined in our original study.
Method: We searched the Organ Procurement and Transplantation Network (OPTN) database for those waitlisted for liver transplantation for "acute hepatic necrosis-drug" between January 1, 1994 and October 31, 2014. We identified patients waitlisted for transplant for HDS-DILI (n = 51) and nonHDS-DILI (n = 433), excluding DILI due to acetaminophen or "other/unknown" causes. Each group was evaluated on the basis of sex, age, race/ethnicity, and education (Table).

Table: Characteristics of Patients Waitlisted for nonHDS- versus and HDS-DILI

	NonHDS-DILI (n = 433)	HDS-DILI (n = 51)	p-value
Sex:			
Female	303 (70.0%)	37 (72.6%)	0.70
Male	130 (30.0%)	14 (27.5%)	
Age (years):			
0–29	130 (30.0%)	15 (29.4%)	0.16
30–44	118 (27.3%)	20 (39.2%)	
45–73	185 (42.7%)	16 (31.4%)	
0–39	204 (47.1%)	27 (52.9%)	0.43
40–73	229 (51.9%)	24 (47.1%)	
Median (IQR)	41 (27–54)	38 (22–52)	0.42
Race/Ethnicity:			
White	219 (50.6%)	26 (51.0%)	<0.001
Black	112 (25.9%)	3 (5.9%)	
Hispanic	65 (15.0%)	6 (11.8%)	
Asian	24 (5.5%)	13 (25.5%)	
Other	13 (3.0%)	3 (5.9%)	
Education beyond high school:[1]			
No	152 (54.5%)	15 (42.9%)	0.19
Yes	127 (45.5%)	20 (57.1%)	

Significance calculated with chi-squared tests for categorical variables and Kruskal-Wallis rank tests for continuous variables.
[1]Missing for n = 170 patients.

Results: There were no significant differences between the two groups with regard to sex, age, or educational level. Race did have a significant effect (p < 0.001). Asians were disproportionately waitlisted for transplant for HDS-DILI (25.5%) versus nonHDS-DILI (5.5%). Conversely, Blacks were disproportionately more likely to be waitlisted for nonHDS-DILI (25.9%) versus HDS-DILI (5.9%). Differences for both races were statistically significantly different on multivariate analysis. Using univariate logistic regression models, we determined that proportionately more individuals were waitlisted for transplant caused by HDS-DILI during the years 2005–2014 (14.4%) versus 1994–2004 (7.8%) (p = 0.02).

Conclusion: The proportion of patients waitlisted for liver transplantation for HDS induced liver injury is increasing and differs by race. Proportionately more Asians are being both waitlisted and transplanted for HDS-DILI compared to nonHDS-DILI. The role of cultural and genetic factors in this racial difference remains uncertain.

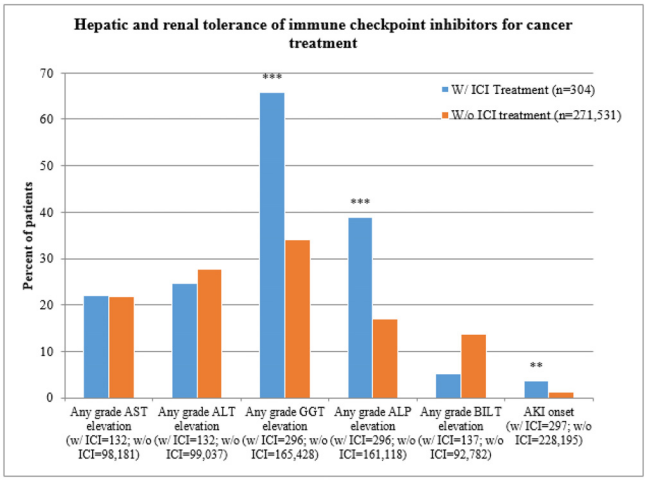
FRI-512

Hepatic and renal tolerance of immune checkpoint inhibitors for cancer treatment: A retrospective monocentric cohort study

L. Parlati[1], A.V. Pichard[1], H. Alain[2], A. Bellesoeur[3], J. Arrondeau[3], P.B. Rouquette[3], F. Goldwasser[3], N. Kramkimel[3], O. Huillard[3], J. Alexandre[3], S. Aractingi[4], J. Chapron[5], B.D. Fischer[6], M.L.B. Piat[7], R. Batista[7], R. Coriat[8], F. Helene[9], M. Cororuge[9], P. Sogni[9], P. Stanislas[9], V. Mallet[9]. *[1]Cochin University Hospital, Hepatology, Paris, France; [2]Cochin University Hospital, Biology Service; [3]Cochin University Hospital, Medical oncology; [4]Cochin University Hospital, Dermatology Service; [5]Cochin University Hospital, Pneumology Service; [6]Cochin University Hospital, Hematology Service; [7]Cochin University Hospital, Pharmacy Service; [8]Cochin University Hospital, Gastroenterology Service; [9]Cochin University Hospital, Hepatology Service*
Email: lucia.parlati85@gmail.com

Background and Aims: Immune checkpoint inhibitors (ICI), including those interfering with the CTLA-4 (ipilimumab [IPI]) and PD-1/PD-L1 axes (nivolumab [NIVO]/pembrolizumab [PEMBRO] and avelumab [AVE]/atezolizumab [ATE], respectively), will be given to a growing number of patients with cirrhosis and hepatocellular carcinoma (HCC). There is a gap of knowledge on the safety profile of these molecules.
Method: We conducted a retrospective cohort study among consecutive and non-selected adult patients (N = 271,835) with at least one blood test (median (interquartile range [IQR]) 2 [1–5] measures per patient) at Cochin University Hospital between 2010 and 2017. During the observational period, 304 (0.11%) patients received ICI treatment, including NIVO (n = 187, 61.5%), PEMBRO (n = 97, 31.9%), IPI (n = 10, 3.3%), NIVO/IPI (n = 3, 4.5%), AVE (n = 3, 1.0%), ATE (n = 3, 1.0%). Other patients served as controls.
All liver function tests and creatinine measures (N = 1,483,106) were retrieved. Severity of liver injury and acute kidney injury (AKI) were graded according to the CTCAEv4 and KDIGO guidelines, respectively. Baseline measure was first measure under ICI treatment or first measure at institution for controls. Characteristics were compared with the use of T-test, chi-square test and binary logistic regressions.
Results: ICI patients were older (median [IQR] age: 65 [55–73] versus 51 [34–67]) and preferentially of male sex (56.6% versus 41.3%). Adjusted on age and sex, ICI treatment was associated with grade 3 and 4 GGT (n = 53, 17.9%; P < 0.001) and ALP (n = 7, 2.4%; P < 0.05) elevations and not with AST, ALT, and total bilirubin elevations. AKI concerned 11 (3.7%) ICI patients (P = 0.001) (see figure). Adjusted risk (95% CI) of AKI under ICI treatment was 2.5 (1.4–4.6). Any grade of ALP elevation was associated with NIVO (P < 0.001) and PEMBRO (P < 0.001); any grade of GGT elevation was associated with IPI (P = 0.007), NIVO (P < 0.001), and PEMBRO (P < 0.001); any grade of total bilirubin elevation was associated with IPI (P = 0.020); there was a trend for ALT elevation with PEMBRO and IPI (P = 0.056); AKI was electively associated with NIVO (P < 0.001). In multivariate analysis, IPI (P < 0.001), NIVO (P < 0.001), and PEMBRO (P < 0.05) were associated with

GGT increase and IPI ($P < 0.05$) with ALP increase. The adjusted risk (95% CI) of AKI under NIVO was 3.1 (1.5–6.2).



Note: ICI: immune checkpoint inhibitor; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; BILT: total bilirubin; AKI: acute kidney injury; w/:with; w/o: without; **P<0.01 and *** P<0.001

Conclusion: ICI treatments are associated with cholestatic liver disease and renal impairment. Adjusted on age and sex, NIVO is associated with AKI. Studies are needed to explore the clinical implications of these findings, including in cirrhotic and HCC patients who are at risk for AKI.

FRI-513
Impact of early corticosteroid treatment in patients with indeterminate acute severe hepatitis

E. Mohr[1], R. Sucher[2], T. Müller[3], T. Kaiser[4], D.M.Z. Büschenfelde[5], B. Thomas[1]. *[1]University Clinic Leipzig, Gastroenterology, Division of Hepatology, Leipzig, Germany; [2]University Clinic Leipzig, Department of Visceral- Transplant, Thoracic and Vascular Surgery, Leipzig, Germany; [3]Charite Berlin, Gastroenterology, Division of Hepatology; [4]University Clinic Leipzig, Department of Laboratory Diagnostics, Leipzig, Germany; [5]Charite Berlin, Department of Laboratory Diagnostics*
Email: elisabeth.mohr@medizin.uni-leipzig.de

Background and Aims: Discrimination of acute severe autoimmune hepatitis AS-AIH and drug induced liver injury (DILI) in patients with indeterminate acute severe hepatitis (ASH) is challenging due to insufficient clinical diagnostics for both diseases. Early corticosteroid therapy, which is not widely applied in clinical routine, may prevent the progression to acute liver failure and the need for liver transplantation. We aimed to investigate the clinical outcomes of patients with AS-AIH and DILI with particular focus on the role of corticosteroids.
Method: A retrospective analysis of data (years: 2013–2016) identified 1039 patients presenting with ASH (defined by ALT > 5 × ULN) in two German liver centers.
Results: Out of the 179 patients identified with early corticosteroid treatment 67 patients were diagnosed with AS-AIH, 52 with DILI, and 56 with other diseases, e.g. steatohepatitis, alcoholic hepatitis etc. Only 34% of the patients with AIH displayed a positive AIH score, whereas 66% showed an indeterminate (34%) or negative (32%) score. Histology confirmed AIH in only 14% of cases, whereas 86% of the liver biopsies showed findings being either only compatible (46%) or atypical (40%) for AIH. Interestingly, patients with DILI had a significant higher MELD score when compared to patients with AIH (MELD 21 range 6–40 vs. MELD 15 range 6–26 $p < 0.01$). In parallel, initial ALT values in patients with DILI (mean 1846 U/L range 356–12330 U/L) were significantly higher when compared to AIH patients (mean 1208 U/L range 304–4095 U/L $p = 0.01$) and decreased significantly faster upon corticosteroid treatment ($p < 0.01$). Hence, DILI patients required a significant shorter course of steroid therapy (mean 87 days range 3–300 vs. mean 366 days range 60–1080 ($p < 0.0001$). Moreover, steroid tapering in AIH was commonly associated with an ALT flare requiring an intensified immunosuppressive regimen, which was not detected in patients with DILI (0% ALT flares, $p < 0.001$). 1-year patient survival was 97% for AIH and 95% for DILI. In the whole cohort infection rates remained low (mild infection: 7%; severe infection: 6%). Seven patients (6%) with DILI required liver transplantation. Within the DILI cohort, they displayed significant higher MELD scores and Quick levels at time-point of admission (MELD: 30, range 23–40; Quick: 29 range 12–47, $p < 0.05$) as indicators for a severe stadium of disease. One-year transplant survival was 85%.
Conclusion: Early corticosteroid therapy is warranted in patients with acute severe hepatitis suspicious for AS-AIH or DILI and results in good response and survival rates avoiding liver transplantation.

FRI-514
Evaluation of the hepatoprotective effects of polygonum multiflorum thunb in acetaminophen induced liver injury

A. Chagnaadorj. *Mongolian National University, Department of Medicine, Ulaanbaatar, Mongolia*
Email: ch.amarzaya@mnu.edu.mn

Background and Aims: Acetaminophen (APAP-Paracetamol) is a safe and effective analgesic at therapeutic dosage, however, overdose of APAP is the principle cause of acute liver failure. Formation of toxic metabolite NAPQI is considered to be the trigger of liver injury via the rapid depletion of intracellular glutathione (GSH) and the generation of excess reactive oxygen species (ROS) that damage hepatocytes. PME is an ethanol extract derived from polygonum multiforum thunb, a traditional herbal medicine, reportedly has strong anti-oxidant, anti-inflammatory and anti-tumor properties.
Nrf2 transcription factor is a key transcription factor that regulates anti-oxidant defense mechanisms and phase II anti-oxidant defense genes. In this study, the hepatoprotective effect of the PME was evaluated using APAP induced acute liver injury model.
Aim: Our study aiming to evaluate the hepatoprotective effects of Polygonum Multiflorum Thunb in Acetaminophen induced acute liver injury.
Method: *In vivo* and *in vitro* studies were intended for prevention. We established 4 weeks old male ICR mice to induce liver injury by single dose of APAP (400mg/kg) injection. Mice were treated with PME for 3 consequtive days at daily dose of 120 mg/kg by oral gavage before APAP injection. The serum transaminases were measured and histological examinations were performed. In vitro study we used HepG2 (Human hepatocellular carcinoma) cell line and primary isolated hepatocytes. Cell viability and cell toxicity were determined by MTS and LDH assay. The number of ROS (+), ROS (-) cells were measured by flow cytometry. Nrf2 transcription factor activation was identified by immune-histochemical analysis, western blotting and mRNA expression levels of antioxidant genes such as HO-1, NQO1, GCLc, GCLm were analyzed by q-PCR in both *in vivo* and *in vitro* study.

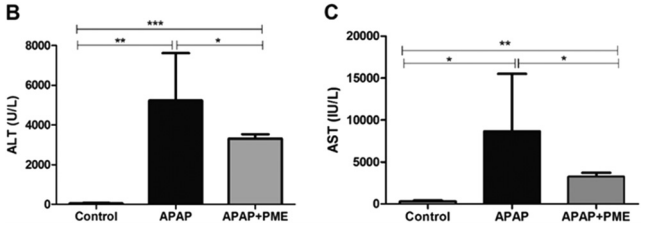


Figure 1: Pretreatment with PME protects mice from APAP induced liver injury Serum ALT (b), AST (c).

Results: PME showed no cytotoxicity and reduced APAP mediated HepG2 cell death. APAP treated cells exhibited a remarkable increase of ROS (+) cells while ROS production was diminished in PME pre-incubated cells.Treatment with PME induced Nrf2 transcription factor

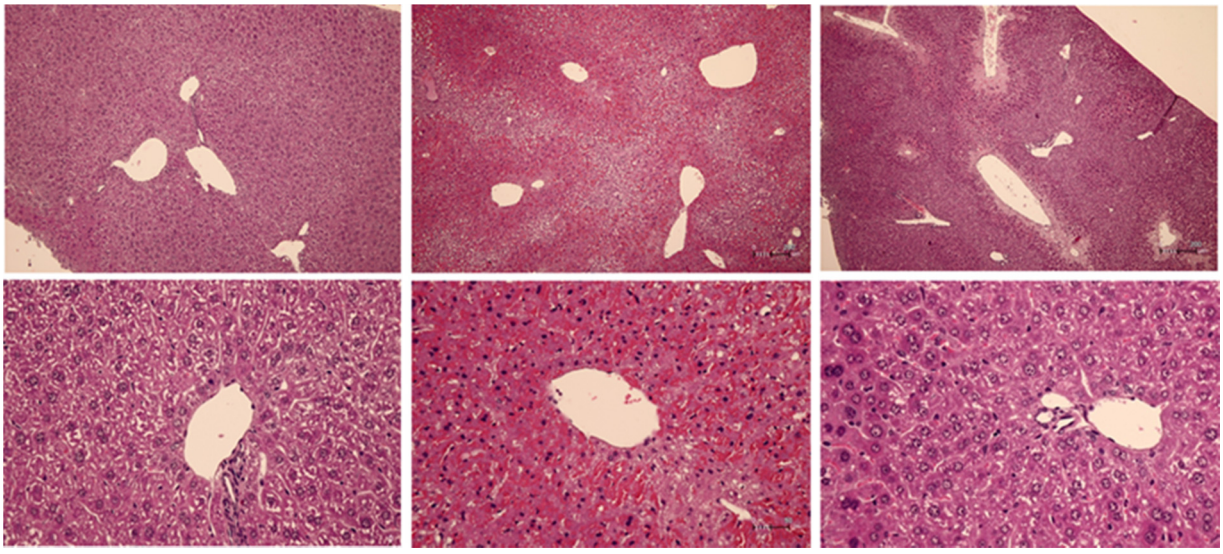


Figure 2: (abstract: FRI-514) Representative histological sections of the liver. Control (a) APAP (b) PME + APAP (c).

activation and up-regulated down-stream anti-oxidant response element genes expressions. Pre-treatment with PME induced Nrf2 nuclear translocation and protect the toxicity of overdosed-APAP induced animal death, elevation of the serum transaminases and hepatocytes damages.

Conclusion: The study had shown that the PME, ethanol extract of Polygonum Multiforum Thunb has a protective effect against APAP induced liver injury by activating Nrf2 transcription factor and it's phase II downstream antioxidant response genes. PME may be useful for prevention of oxidative stress induced acute liver injury.

FRI-515

Prophylactic use of entecavir for lymphoma patients with past HBV infection: A randomized controlled trial

W.P. Liu[1], X.B. Xiao[2], M. Xue[3], G.Q. Wang[4], X.P. Wang[5], Y.Q. Song[5], J. Zhu[5]. *[1]Peking University Cancer Hospital & Institute, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Beijing, China; [2]Affiliated Hospital, Academy of Military Medical Sciences, Affiliated Hospital, Academy of Military Medical Sciences, China; [3]Air Force General Hospital, Air Force General Hospital, China; [4]Peking University First Hospital, Peking University First Hospital, China; [5]Peking University Cancer Hospital & Institute, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), China*

Email: dreaming2217@126.com

Background and Aims: Hepatitis B virus (HBV) reactivation may occur in lymphoma patients with past HBV infection (HBsAg-negative/anti-HBc-positive/HBV DNA-negative) as a result of treatment with chemotherapy or rituximab-containing immunotherapy. However, the cost effectiveness of antiviral prophylaxis in preventing hepatitis B virus (HBV) reactivation in lymphoma patients with past HBV infection is unclear.

Method: Lymphoma patients with past HBV infection were randomly assigned to chemotherapy alone (control) or prophylactic entecavir (ETV) before chemotherapy and up to 6 months after completion of chemotherapy. All patients underwent close virologic and biochemical surveillance. HBV DNA and alanine aminotransferase (ALT) levels were tested at baseline, before each cycle of chemotherapy, and every 3 months until 18 months after the last cycle of chemotherapy. Therapeutic ETV was used to treat patients with HBV reactivation in the control group. The primary endpoint was the incidence of HBV reactivation (appearance of HBV DNA) and HBV reactivation-related hepatitis (defined as a greater than 3-fold increase in serum ALT levels exceeding 100 IU/L).

Results: A total of 190 patients were included, 141 (74.2%) of whom were positive for anti-HBs. Rituximab-containing treatment was administered in 142 (74.7%) patients. The incidence of HBV reactivation and HBV reactivation related hepatitis were 0 (0/95) and 0 (0/95) in the prophylactic ETV group, 3.2% (3/95) and 1.1% (1/95) in the control group, respectively, but the difference had not statistical significance (*P* value were 0.246 and 1.000, respectively). Among the three patients with HBV reactivation, two were negative for anti-HBs, and one was positive. HBV reactivation-related hepatitis flare occurred in one patient who exhibited elevated ALT levels (1217 IU/L) after seven cycles of chemotherapy, resulting in premature termination of chemotherapy. Two patients experienced HBV reactivation without hepatitis flare after two cycles of chemotherapy and cessation of chemotherapy, respectively. Serum HBsAg became positive in two of the three patients with HBV reactivation. All patients with HBV reactivation recovered after therapeutic ETV treatment. No HBV-related deaths were observed during the follow-up period. Cost-effectiveness analysis showed that the cost in the prophylactic ETV group was higher than that of the control group by $160 per month. No significant difference in effectiveness was observed between the treatment groups over the follow-up period.

Conclusion: Prophylactic antiviral therapy is not a cost-effective strategy for management of lymphoma patients with past HBV infection (NCT01765231).

FRI-516

Inhibition of pyruvate dehydrogenase complex and lactate dehydrogenase for therapy of acute liver failure

R. Ferriero[1], E. Nusco[1], R.D. Cegli[1], A. Carissimo[1], G. Manco[2], N. Brunetti-Pierri[1,3]. *[1]Telethon Institute of Genetics and Medicine, Pozzuoli; [2]National Research Council, Institute of Protein Biochemistry, Naples; [3]Department of Translational Medicine, Federico II University of Naples*

Email: ferriero@tigem.it

Background and Aims: Acute liver failure is a rapidly progressive deterioration of hepatic function resulting in high mortality and morbidity. Metabolic enzymes can translocate in the nucleus to regulate histone acetylation and gene expression.

Method: Levels and activities of pyruvate dehydrogenase complex (PDHC) and lactate dehydrogenase (LDH) were evaluated in nuclear fractions of livers of mice exposed to various hepatotoxins including

CD95-Ab, acetaminophen, and α-amanitin. Whole-genome gene expression profiling by RNA-seq was performed in livers of mice with acute liver failure and analyzed by Gene Ontology Enrichment Analysis (GOEA). Efficacy of the histone acetyltransferaseinhibitor garcinoland LDH inhibitor galloflavin at improving survival and reducing liver damage was evaluated in mice injected with CD95-Ab.
Results: Levels and activities of PDHCand LDH were increased in nuclear fractions of livers of mice with acute liver failure. The increase of nuclear PDHC and LDH was associated with increased concentrations of acetyl-coA and lactate in nuclear fractions, and histone H3 hyper-acetylation. Gene expression in mouse livers with acute liver failure suggested that increased histone H3 acetylation induces the expression of genes related to response to damage. Reduced histone acetylation by the histone acetyltransferase inhibitor garcinol decreased liver damage and improved survival in mice with acute liver failure. Knock-down of PDHC or LDH improved viability in cells exposed to a pro-apoptotic stimulus. Treatment with the LDH inhibitor galloflavin that was also found to inhibit PDHC reduced hepatic necrosis, apoptosis, and expression of pro-inflammatory cytokines in mice with acute liver failure. Mice treated with galloflavin showed a dose-response increase in survival.
Conclusion: PDHC and LDH translocate to the nucleus and are targets for therapy of acute liver failure.

FRI-517
Pyrrolizidine alkaloid-induced hepatic sinusoidal obstructive syndrome: clinical characteristics, imaging signs and pathological findings

Y. Song[1], F. Liu[2], X. Rong[2], H. Guo[2], D. Xu[2]. *[1]Tongji Medical College, HUST, Union Hospital, Wuhan, China; [2]Tongji Medical College, HUST, Union Hospital, China*
Email: yuhusong@163.com

Background and Aims: One major etiology of hepatic sinusoidal obstruction syndrome (HSOS) in China is the intake of pyrrolizidine alkaloids (PA)-containing products. Since PAs-induced HSOS is a rare disease that has not been clearly characterized until now. This study investigated clinical characteristics, CT features, and pathological findings of PA-induced HSOS.
Method: This retrospective cohort study included 116 patients with PAs-induced HSOS from January 2006 to June 2016. We collected medical records of the patients, and reviewed image features of CT, and analyzed pathological findings.
Results: Common clinical manifestations of PAs-induced HSOS were abdominal distention (98.26%), ascites (100%), jaundice (53.27%), abdominal pain (36.36%). Abnormal liver function was observed in most of PAs-induced HSOS. On CT scan, common findings of PAs-induced HSOS included: ascites, hepatomegaly, gallbladder wall thickening, pleural effusion, patchy liver enhancement, and heterogeneous hypoattenuation. Most of the PAs-induced HSOS patients had low ascitic AFTP (<25 g/L) and high SAAG (≥11.0 g/L). In acute stage, pathologic features were massive sinusoidal dilatation, sinusoidal congestion, the extravasation of erythrocytes, hepatocellular necrosis, the accumulation of macrophages, the deposition of hemosiderin. In chronic stage, complete loss of pericentral hepatocytes, sinusoidal dilatation, the deposition of pigment granules were observed.
Conclusion: The PAs-induced HSOS patients displayed distinct clinical characteristics, imaging features, and pathological findings, which made a further understanding and provided evidence for the diagnosis of PA-induced HSOS.

FRI-518
Low serum hepcidin and high transferrin saturation are associated with a poor short-term survival in adults with acute liver failure

I. Spivak[1], J. Arora[2], C. Ellerbe[2], V. Durkalski-Mauldin[2], W.M. Lee[3], R. Fontana[4], P. Strnad[1]. *[1]University Hospital Aachen, Medical Clinic III, Aachen, Germany; [2]Medical University of South Carolina, Department of Public Health Sciences, Charleston, SC, United States; [3]University of Texas, UT Southwestern Medical Center at Dallas, Dallas, TX, United States; [4]University of Michigan, Ann Arbor, MI, United States*
Email: ispivak@ukaachen.de

Background and Aims: The liver is a key player in iron homeostasis through synthesis of the serum transporter transferrin and the iron hormone hepcidin. In a single-center analysis high ferritin and low transferrin levels associated with worse outcome in patients with acute liver failure (ALF). We explored associations of parameters of

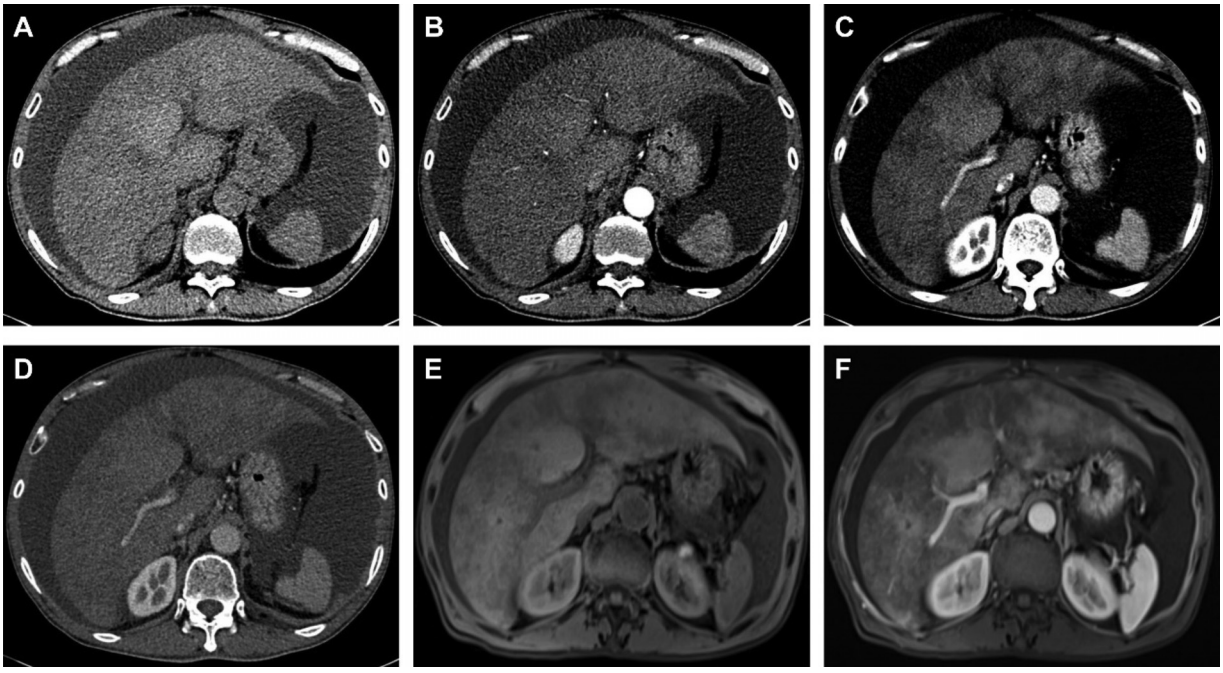


Figure 1: (abstract: FRI-517): 67-year-old man diagnosed with gynura segetum-induced HSOS received contrast-enhanced CT and MRI scan. (A–D) images of plain and contrast-enhanced CT scan; (A) plain CT scan; (B) arterial phase; (C) porta-venous phase; (D) equilibrium phases. (E–F) images of pre-contrast and portal-venous phase on dynamic contrast-enhanced MRI scan; (E) pre-contrast MRI scan; (F) portal-venous phase of MRI scan.

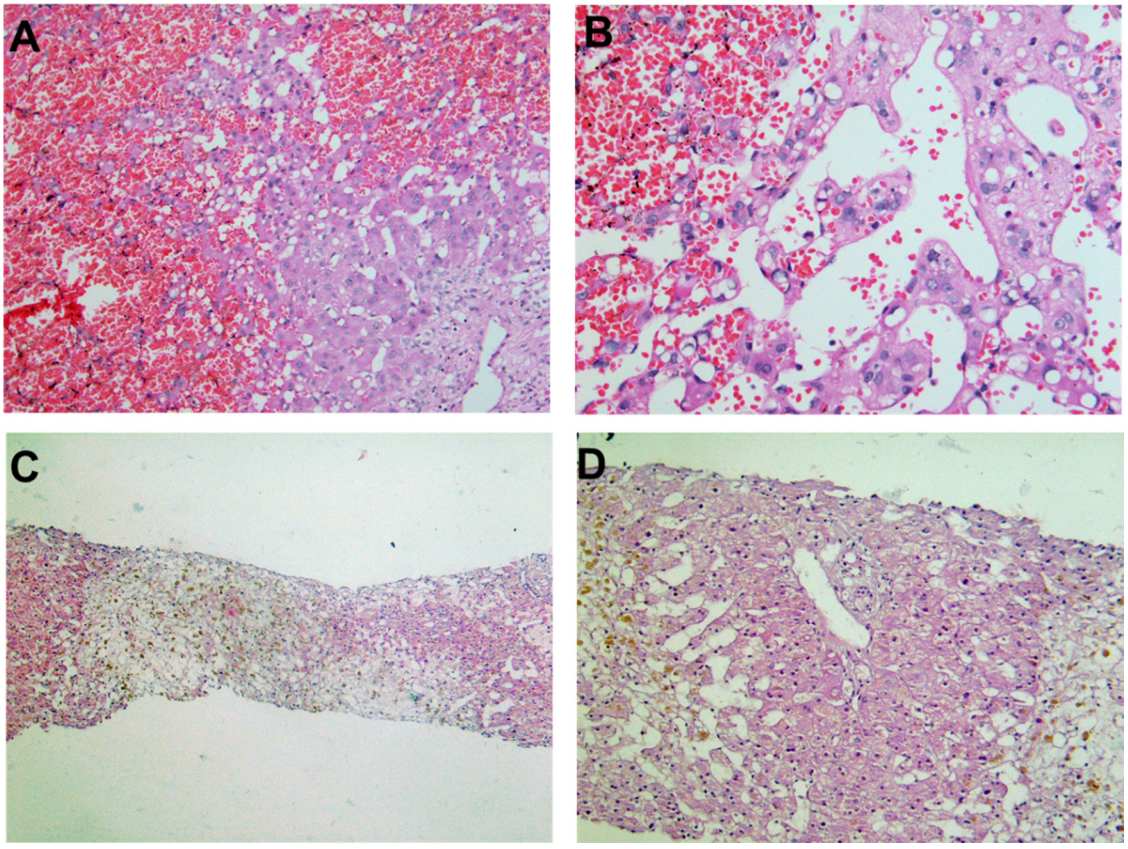


Figure 2: (abstract: FRI-517): Patients histology; (A–B): Early pathological changes of PAs-induced HSOS; (A) significant congestion around the central vein of the hepatic lobule (H&E ×200); (B) higher magnification of peri-central region which demonstrated sinusoidal congestion, sinusoidal dilatation, extravasation of erythrocytes into space of Disse and congestive necrosis of some hepatocyte (H&E ×400); (27) Histology of PAs-induced HSOS in subacute or chronic stage. (C) low power image of PAs-induced HSOS of longer duration showing complete loss of pericentral hepatocytes and sinusoidal dilatation (H&E ×100); (D) Medium power image showing the deposition of pigment granules. (H&E ×200).

iron metabolism with the etiology and outcome of adults with ALF in a multicenter retrospective study setup. We also analyzed an acetaminophen (APAP)-induced ALF mouse model.

Method: A representative subset of 121 adults with ALF enrolled in the US ALFSG had a day 1 or 2 serum sample tested for serum ferritin, transferrin, iron, and hepcidin. In mice, these parameters were measured prior to (controls) and 18 hours after injection of 500 mg/kg APAP. Outcomes at 3 weeks after enrollment were categorized as spontaneous survivor (SS) vs. death/transplantation. Univariate models of predicted survival were compared to the current ALF prognosis model.

Results: 66 patients with APAP-related and 55 patients with non-APAP-related ALF were assessed, who had a 3-week SS rate of 57.6% and 38.2%, respectively. ALF patients often displayed altered iron parameters (medians: iron 33.3 µmol/l; transferrin 186 mg/dl; transferrin saturation (TSAT) 71.8%; ferritin 2866.8 ng/ml; hepcidin 5.7 ng/ml). APAP-induced ALF presented with significantly higher ferritin, transferrin and hepcidin values than non-APAP cases ($p < 0.05$ for all). SS had lower iron levels (29.1 vs. 34.5 µmol/l; $p < 0.05$) and TSAT (60.9 vs. 79.1%; $p < 0.001$), but higher hepcidin levels (8.2 vs. 2.7 ng/ml; $p < 0.001$) and hepcidin/ferritin ratio (0.0047 vs. 0.0009; $p < 0.001$). The univariate model of log transformed hepcidin and square-root transformed hepcidin/ferritin ratio had a C-statistic of 0.727 and 0.699 respectively, whereas the current ALF prognosis model had a C-statistic of 0.852. Compared to controls, APAP-treated mice displayed lower serum hepcidin (24.3 vs. 37.8 ng/ml), a negative correlation between hepcidin and ALT ($r = –0.79$) and lower hepcidin/ferritin ratio (0.0018 vs. 0.05; $p < 0.0001$).

Conclusion: Our findings demonstrate that several serum iron parameters significantly associate with 3-week SS in ALF adults. In mice, hepcidin levels inversely correlate with the surrogate of liver injury. Preliminary results indicate that hepcidin (and hepcidin-ferritin ratio) is a promising univariate predictor of survival and may demonstrate increased prediction in the multivariate model.

FRI-519

43 candidate SNPs were not found to be associated with drug induced liver injury

L. Pang[1], W. Yang[2], K. Tan[2], F. Hou[3,4]. *[1]Peking University First Hospital, Beijing, China; [2]Department of Infectious Diseases, Beijing, China; [3]Peking University First Hospital, Department of Infectious Diseases, Beijing, China; [4]Peking University International Hospital, Department of Infectious Diseases, Beijing, China*
Email: houfqys@139.com

Background and Aims: Drug induced liver injury (DILI) is suspected to have a heritable component. With genome-wide association study and candidate gene approaches, some genetic variants were reported to have associations with DILI but few of them can be repeated or validated. The aim of this study is to investigate the asso ciation between some gene polymorphisms and DILI.

Method: 43 candidate SNPs were sequenced by Sequenom MassARRAY SNP in 144 Chinese DILI patients admitted to the Peking University First Hospital and 221 healthy controls.

Results: Three SNPs ever reported to be associated with DILI were not be validated in our study. Allele frequencies of T for rs2741045 in UGT1A9, T for rs2287622 in ABCB11 and C for rs3740065 in ABCC2 among patients and controls were 0.025 vs 0.035, 0.269 vs 0.264 and

0.367 vs 0.392 respectively (both P > 0.05). The frequencies of the T allele for rs1801133 in MTHFR and A allele for rs5747933 in PRODH were lower in patients than controls (0.538 vs 0.622, P = 0.027 and 0.120 vs 0.188, P = 0.012). The allele frequencies of other 38 SNPs in 31 genes (IL-10, CYP2C9, SLCO1B1, NEU2, NAT2, FAM65B etc.) were same in two groups.
Conclusion: We did not find any significant associations between UGT1A9, ABCB11, ABCC2 and DILI which were ever reported. The associations between MTHFR, PRODH and DILI need further studies to validate.

FRI-520
CC10 protein attenuates hepatic injury in MHV-3 induced fulminant hepatitis by inhibiting fgl2 expression on macrophages
H. Yu, H. Wang, X. Wan, J. Huang, W. Yan, D. Xi, X. Wang, Q. Ning. *Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Infectious Disease*
Email: qning@vip.sina.com

Background and Aims: Fulminant hepatitis (FH) is a serious life-threatening disease with massive necroinflammation during a short time. Macrophages are the major immune cells population for innate immune response which are considered to be central for FH initiation and progression. Fibrinogen-like protein 2 (FGL2) is a procoagulant protein that is induced substantially on macrophage upon viral infection and amplified inflammatory cascade and hepatocytes necrosis and FGL2 depletion resisted murine hepatitis virus strain 3 (MHV-3) infection. Clara cell 10KDa (CC10) protein is a secretory protein with anti-inflammatory property in the upper airway disease, however, the mechanism and pathogenic role in other disease settings are still unclear. In this study, we sought to determine the role of CC10 on FH and the regulation of CC10 on FGL2.
Method: FH was established by peritoneal injection MHV-3. The mice were received CC10 protein with tail vein injection prior to viral infection. Liver histology, fibrin deposition, necrosis and survival rate was measured. The regulatory effects of CC10 on the expression of the FGL2 gene were investigated in vitro by THP-1 cells and mouse peritoneal macrophages. DNA microarray was applied to validate the altered expression of selected genes at mRNA level.
Results: In the FH model induced by MHV-3, the survival rate increased from 0 to 12.5% in CC10 group compared with saline group. Meanwhile, the levels of ALT and AST in serum were significantly decreased and the liver damage was improved. Further more, the hepatic FGL2, TNF-α and IL-1β expression was significantly decreased combined with reduction of hepatic fibrin deposition and hepatocyte apoptosis after administration of CC10 protein. In vitro, we found that CC10 significantly inhibit the expression of FGL2 in IFN-γ treated THP-1 cells and MHV-3 infected mouse peritoneal macrophages. However, there is no direct interaction between CC10 and FGL2 as manifested by co-immunoprecipitation. Further microarray suggested that HMG-box transcription factor 1(HBP1), was significantly lower in CC10 treated THP-1 cells than that in IFN-γ primed THP-1 cells. HBP1-SiRNA treatment abrogated the inhibitory effect of CC10 on FGL2 expression in HUVEC cells.
Conclusion: CC10 protects against MHV-3 induced FH via suppression of FGL2 expression on the macrophages. Such effect may be mediated by a transcript factor HBP1.

FRI-521
Role and regulation of mitophagy by ROS in hepatic stellate cells during acute liver failure
Z. Tian, Y. He, T. Chen, Y. Zhao. *Institute of hepatology, Department of Infectious Disease, Xi'an, China*
Email: tianzen1984@163.com

Background and Aims: We previously found that acute liver failure (ALF) is accompanied by hepatic stellate cells (HSCs) activation. HSCs also integrate cytokine-mediated inflammation responses in the sinusoids and relay them to the liver parenchyma in immune-mediated hepatitis. Oxidative stress has been shown to promote

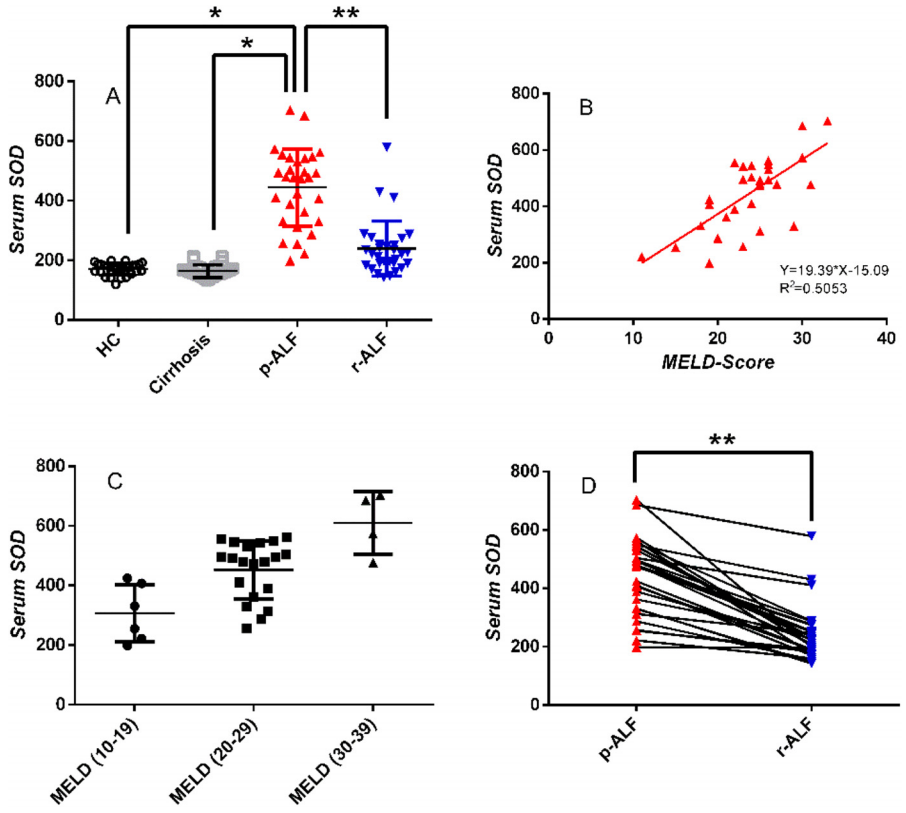


Figure 1: (abstract: FRI-521): Increased SOD level was associated with poor prognosis of ALF.

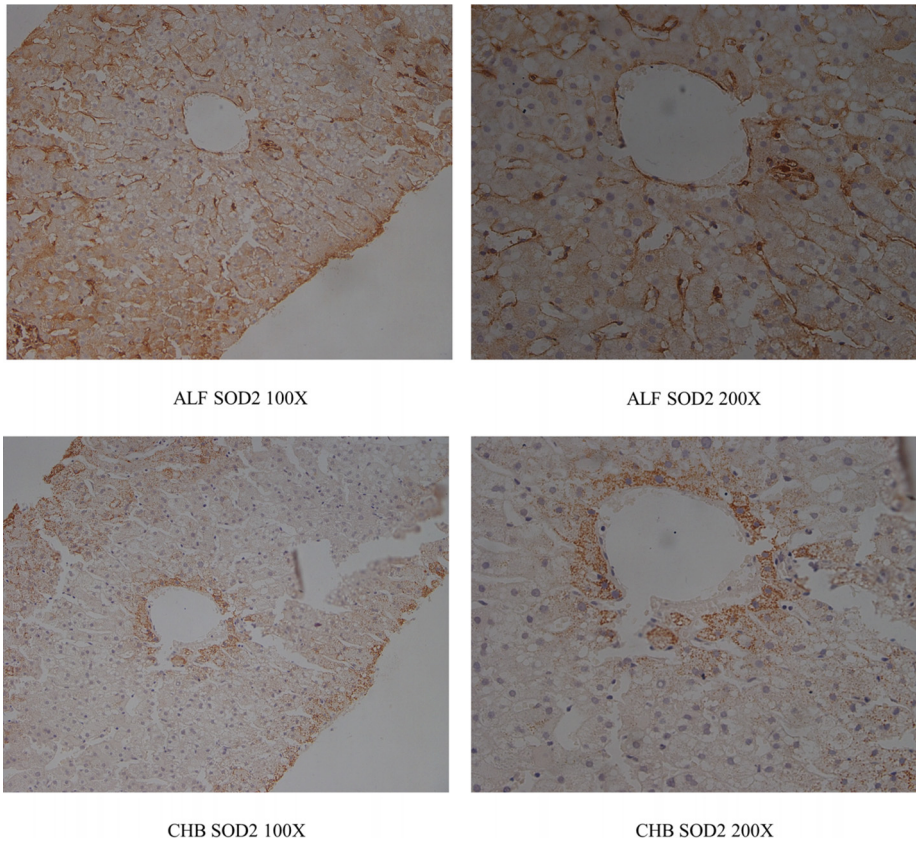


Figure 2: (abstract: FRI-521): Immunohistochemical SOD2 staining were conducted in liver tissues from patients with chronic cirrhosis (A, B) and ALF (C, D) to show SOD2 expression. Original magnification x100 or 200.

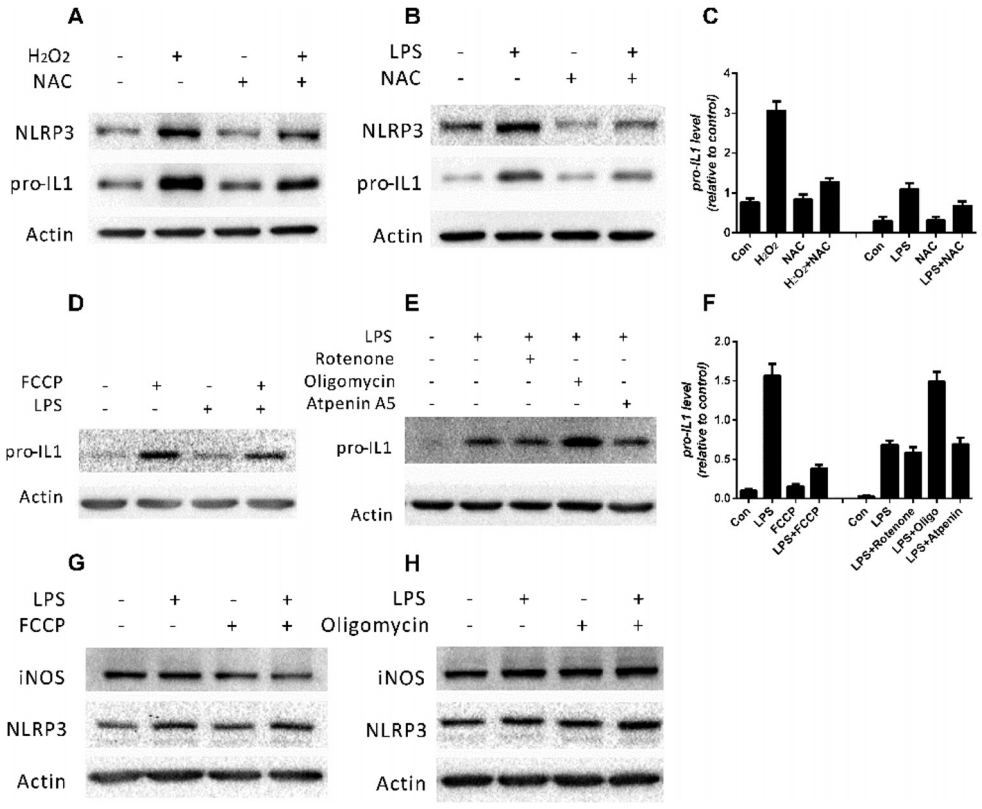


Figure 3: (abstract: FRI-521): Mitophagy rescues ROS induced inflammation in HSCs.

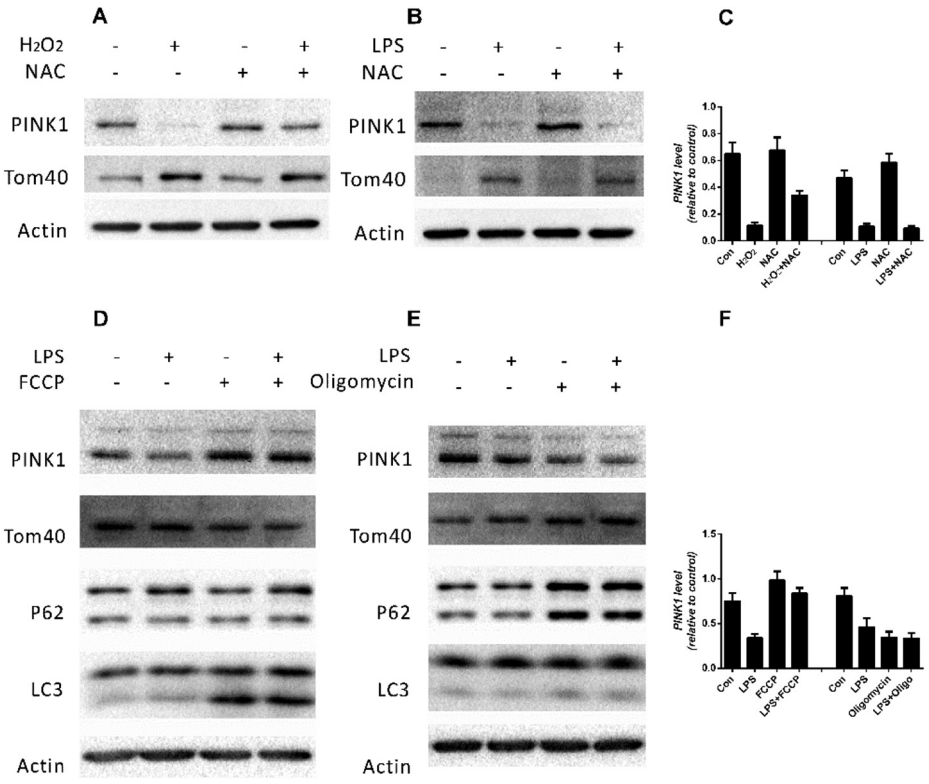


Figure 4: (abstract: FRI-521): ROS inhibits mitophagy in HSCs.

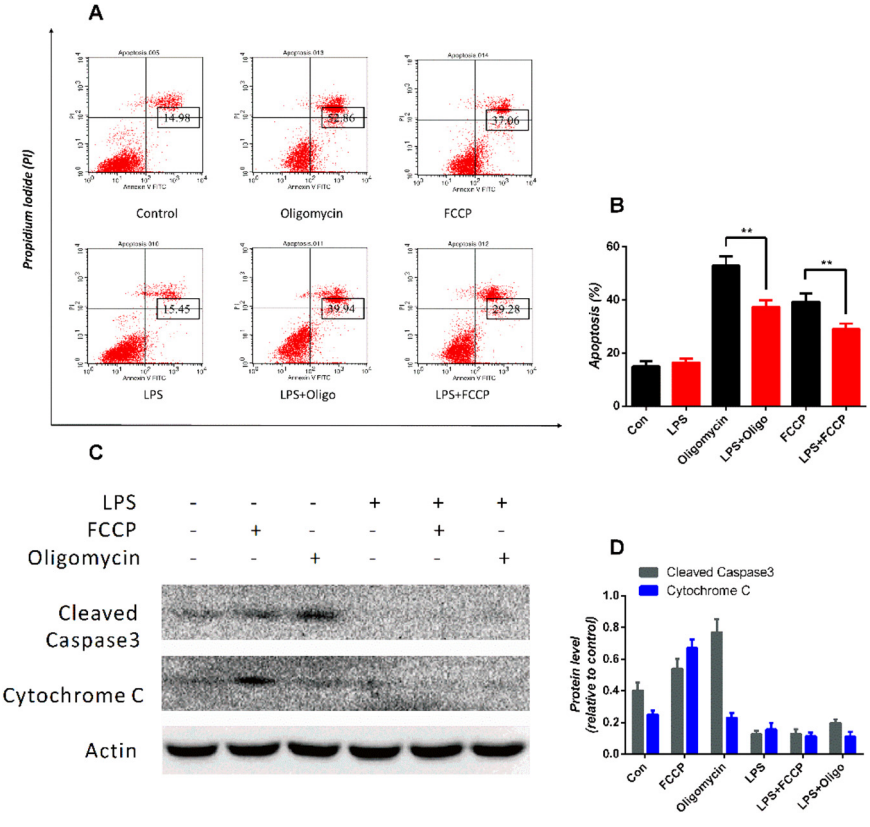
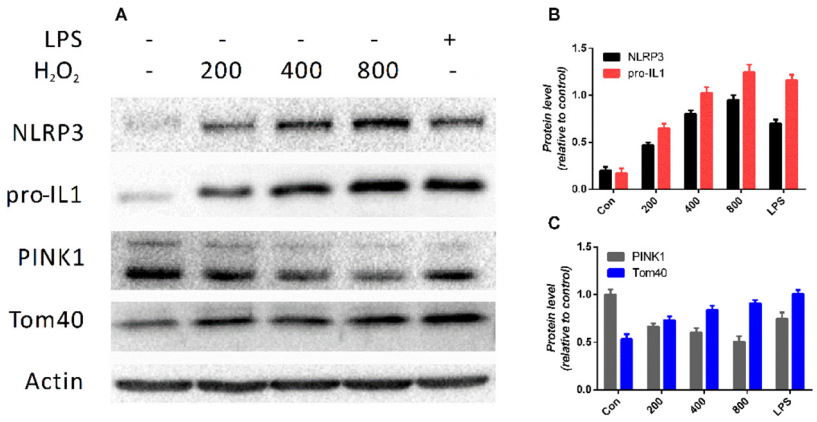


Figure 5: (abstract: FRI-521): Mitophagy but not apoptosis regulates inflammation in HSCs.



Supplementary Figure 1: (abstract: FRI-521): H_2O_2 promotes inflammation and inhibits mitophagy in a dose dependent manner.

inflammation. Whether and how oxidative stress is involved in ALF and HSCs inflammation remains unclear.

Method: ALF patients were recruited to investigate the correlation between plasma superoxide dismutase (SOD) levels and clinical features. Liver tissues were collected from chronic hepatitis patients by biopsy and from ALF patients who had undergone liver transplantation. The expression of SOD2, hepatic stellate cell activation (α-SMA) and mitophagy activity (Tom40) were investigated by immunohistochemistry. Inflammation, mitophagy and apoptosis were investigated by immunoblot analysis, confocal microscopy and flow cytometry in HSCs treated with LPS and reactive oxygen species (ROS) donors.

Results: Plasm SOD level was significantly increased in patients with ALF compared to those with cirrhosis (444.4 ± 23.58 U/mL vs 170.07 ± 3.52 U/mL, P < 0.01) and positively correlated with MELD-score (r = 0.5053, P < 0.01). In vivo observation revealed that mitophagy was inhibited in HSCs based on increased Tom40 immunostaining, and in vitro experiments demonstrated that ROS can promote inflammation via inhibition of mitophagy. Moreover, regulation of inflammation in HSCs was apoptosis independent.

Conclusion: Increased oxidative stress induced by LPS participants in promoting inflammation through mitophagy inhibition in HSCs during the process of ALF, providing a novel strategy for the treatment of patients with ALF.

FRI-522

DRESS cases included in the Spanish and Latin-American DILI registries: clinical phenotype and outcome

I. Medina-Caliz[1], M. Almarza[1], C. Stephens[1], M. Robles-Díaz[1], J. Sanabria-Cabrera[1], A. Gonzalez-Jimenez[1], Rocío Sanjuan-Jimenez[1], A. Ortega-Alonso[1], M.G. Cortes[1], B. García-Muñoz[1], M. Quiros-Cano[1], F. Martin-Reyes[1], A. Cueto[1], M. Fernández[2], P. Ginès[3], M.R. Gomez[4], G. Soriano[5], M. Prieto[6], I. Conde[6], F. Bessone[7], N. Hernandez[8], M. Arrese[9], M. Cabello[1], M.I. Lucena[1], R.J. Andrade[1]. *[1]UGC Aparato Digestivo y Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Malaga, Spain; [2]Hospital Torrecardenas, Almeria; [3]Liver Unit. Hospital Clinic de Barcelona. CIBERehd, Barcelona, Spain; [4]Hospital Universitario Virgen del Rocio, Sevilla. Instituto de Biomedicina de Sevilla. CiberEHD., Hospital Nuestra Señora de Valme, Sevilla, Spain; [5]Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, Barcelona, Spain; [6] Hospital Universitario y Politécnico La Fe. CIBERehd, Valencia, Spain; [7]Hospital Provincial del Centenario, Rosario, Argentina; [8]Hospital de Clínicas, Montevideo, Uruguay; [9]Pontificia Universidad Católica de Chile, Santiago, Chile*
Email: imcaliz@uma.es

Background and Aims: Severe cutaneous adverse reactions can manifest in a wide spectrum of heterogeneous clinical presentations, including drug reaction with eosinophilia and systemic symptoms (DRESS), a severe idiosyncratic drug reaction. DRESS is characterized by presence of rash, fever, eosinophilia and/or lymphopenia, and liver injury but there is no consensus for the definition of this condition. We aimed to evaluate clinical phenotype, outcome and causative agents associated with DRESS.

Method: Dress cases were defined according to the International Registry of Severe Cutaneous Adverse Reaction (RegiSCAR). Demographics, clinical presentation and outcome were compared between DILI cases without hypersensitivity features (non-DRESS DILI) and DRESS cases included in the Spanish (n = 35/920) and Latin-American (n = 25/269) DILI registries.

Results: Sixty patients with DRESS syndrome were identified compared to 620 non-DRESS DILI cases, with a slightly higher proportion of women in the latter group (53% vs 50%). Mean age at onset was similar in both groups, 53 vs 49 years. Duration of treatment and time to onset were shorter in the DRESS cases (40 vs 107 and 35 vs 95 days, respectively) although the differences were not statistically significant. All DRESS cases presented rash (three with severe toxicoderma), 19 (33%) lymphopenia and 46 (78%) eosinophilia. Jaundice was present in 73% of DRESS patients and 64% of non-DRESS DILI patients. Positive autoantibodies were detected in 24% of non-DRESS DILI vs 9% of DRESS patients (p = 0.021). Hospitalization was higher for DRESS cases (78% vs 51%, p = 0.001). Type of liver injury differed between the groups, with cholestatic-mixed damage predominating in DRESS (58%), and hepatocellular damage (67%) in non-DRESS DILI, (p = 0.001). Severity also differed, with 14% severe and no fatal cases in DRESS and 7% severe and 5% fatal cases in non-DRESS DILI (p = 0.046). The most frequent causative drugs in the DRESS group were amoxicillin-clavulanate (7 cases), carbamazepine (7), allopurinol (5) and lamotrigine (5).

Conclusion: Compared to non-DRESS DILI, DRESS cases presented a predominance of cholestatic-mixed pattern and greater severity without mortality. Amoxicillin-clavulanate stands out as a leading cause of DRESS syndrome in the Spanish DILI Registry, while antiepileptic predominates in Latin-America, similar to previously published studies.

Funding: AEMPS, FEDER
(PI15-01440, PI-0274/2016, PI-0285-2016).CIBERehd-ISCIII.

FRI-523

Independent cohort validation of hepatic metabolism, daily dose and comorbidities as features associated with delayed symptom onset in drug-induced liver injury

A. González-Jiménez[1], I. Medina-Caliz[1], M. Robles-Díaz[1], F. Bessone[2], N. Hernandez[3], A. Sánchez[3], M. Arrese[4], R.P. Filho[5], M. Lizarzábal[6], M. Tagle[7], M.I. Lucena[1], C. Stephens[1], R.J. Andrade[1]. [1]*UGC Aparato Digestivo y Servicio de Farmacología Clínica, Instituto de Investigación Biomédica de Málaga (IBIMA), Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain;* [2]*H Provincial del Centenario, Rosario, Argentina;* [3]*H de Clínicas, Montevideo, Uruguay;* [4]*Pontificia Universidad Católica de Chile, Santiago, Chile;* [5]*H U Prof Edgard Santos, Universidad Federal da Bahía, Salvador de Bahía, Brazil;* [6]*H U de Maracaibo, Maracaibo, Venezuela;* [7]*Clinica Anglo Americana, Lima, Peru*
Email: cstephens@uma.es

Background and Aims: Most patients with drug-induced liver injury (DILI) manifest liver injury while on drug treatments, however some patients do not manifest hepatotoxicity until after treatment completion (delayed onset). The underlying mechanism of delayed onset is unknown, but believed to be influenced by both host factors and drug properties. In a previous study of 413 Spanish DILI patients we found low hepatic metabolism, high daily dose and absence of preexisting conditions to be associated with increased risk of delayed onset in DILI (Hepatology 2015;62(S1): 504A). The aim of the current study was validate these results in an independent cohort of Latin American DILI cases.

Method: External validation of previous findings was performed using information corresponding to 188 Latin American DILI cases induced by drugs associated with at least 3 cases in the Latin American DILI Network. The cases were classified as delayed onset (DO) or no delayed onset (NDO) according to the temporal relationship between the first DILI manifestation and time of treatment cessation.

Results: Of the 188 DILI cases, 32 (17%) manifested DILI with DO and 156 (83%) NDO DILI. The drugs associated with DO were amoxicillin-clavulanate, nitrofurantoin, azithromycin and ibuprofen. Similar to the previous study, the Latin American DO cases were associated with higher daily dose treatments (mean: 1717 vs 493 mg, p = 0.001) and hepatic metabolism <50% (75% vs 13%, p = 0.0174). Drugs in BDDCS class 3 (low metabolism/high solubility) were overrepresented in DO cases (50% vs 9%, p = 0.0012). In addition, a higher proportion of NDO cases had preexisting conditions (68% vs 45%, p = 0.0484). In contrast to previous findings, eosinophilia and presence of positive autoantibody titres did not differ significantly between the two groups.

External validation of the logistic regression model previously identified with the Spanish DILI cases demonstrated that low hepatic metabolism (OR: 85.86, p = 0.0001), daily dose ≥200 mg (OR: 3.84, p = 0.0333) and absence of preexisting conditions (OR: 2.86, p = 0.0484) also had good predictive capacity of DO in the Latin American DILI cohort.

Conclusion: The current validation study confirmed results previous identified in a Spanish DILI cohort. Hence, healthier DILI patients with regards to comorbidities, taking higher daily doses of medications with low hepatic metabolism are at higher risk of manifesting DO.

Funding: FondosFEDER (PI15/01440), AEMPS, CIBERehd by ISCIII.

FRI-524

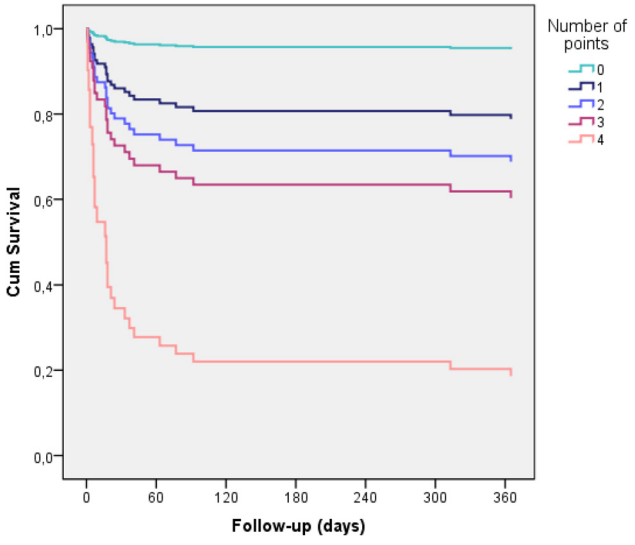
Prediction of early mortality despite liver transplantation in acute liver failure

M. Cardoso[1], R. Costa[2], E. Tsochatzis[1], D. Patch[1], J. Ryan[3], R. Westbrook[4]. [1]*Royal Free Hospital NHS Foundation Trust, Sheila Sherlock Liver Centre, London, United Kingdom;* [2]*Hospital of Braga, Gastrenterology Department, Braga, Portugal;* [3]*Royal Free London NHS Trust, UCL Institute of Liver and Digestive Health, The Royal Free Sheila Sherlock Centre, United Kingdom;* [4]*Royal Free Hospital, London, United Kingdom*
Email: marianafcardoso@gmail.com

Background and Aims: In patients with acute liver failure (ALF) who meet poor prognostic criteria correctly identifying those with a poor outcome despite LT is challenging. Previous attempts at risk stratification consider ALF and subacute liver failure (SALF) as a single entity. It is increasingly recognised that hyperacute/ALF and SALF have different phenotypes and clinical courses. We investigate predictors of mortality despite LT, in ALF and SALF as two distinct cohorts.

Method: Retrospective review of a prospectively collated database of all LT for ALF at our unit since 1990 until the present. Data on the recipient (age, gender, aetiology of ALF/SALF, clinical and laboratorial variables prior to LT), graft/ surgery (size, steatosis, cold ischemic time) and donor (age, gender, status) were collected. Patients with ALF (jaundice to encephalopathy ≤ 28 days) and SALF were studied separately. In each group, variables associated with hospital mortality (p < 0.1) in univariate analysis were included in a multivariate logistic regression.

Results: 166 patients aged ≥ 16 years were transplanted for ALF/SALF (122/44). Patients with SALF were older (44.4 vs 37.1-years, p = 0.002) and more often males (47.7% vs 31.1%, p = 0.049). Hospital survival post LT did not differ between ALF/SALF (77.0% vs 75.0%, p = .783). In ALF, predictors of hospital mortality on multivariate analysis included age ≥ 55 years (p = 0.019), serum sodium (p = 0.026), history of organ support (p = 0.051) and cold ischemic time (p = 0.006). A prognostic score was created by assigning points according to odds ratio values (age ≥ 55: 2 points; sodium < 135 mmol/L: 1 point; organ support: 1 point), which were then added. Hospital survival according to the total number of points was: 100% (0 points), 81.9% (1 point), 69.2% (2 points), 60.0% (3 points) and 20.0% (4 points). A Cox proportional hazards regression limited at 1 year showed a significant correlation between the number of points and mortality (p < 0.001) (See Figure). In SALF, only female gender (p = 0.031) and encephalopathy grade ≥ 3 (p = 0.030) were associated with decreased hospital survival on multivariate logistic regression.



Conclusion: This data highlights that in patients undergoing LT for ALF mortality despite LT can be predicted pre-operatively based on a simple scoring system. The proposed score, if validated further, could potentially avoid use of a valuable organ in patients with extremely poor predicted 1-year survival.

FRI-525

Should age be an absolute contraindication to liver transplantation in acute liver failure?

M. Cardoso[1], R. Costa[2], E. Tsochatzis[1], D. Patch[1], J. Ryan[3], R. Westbrook[4]. [1]*Royal Free Hospital NHS Foundation Trust, Sheila Sherlock Liver Centre, London, United Kingdom;* [2]*Hospital of Braga, Gastroenterology Department, Braga, Portugal;* [3]*Royal Free London NHS Trust, UCL Institute of Liver and Digestive Health, The Royal Free Sheila Sherlock Centre, United Kingdom;* [4]*Royal Free Hospital, London, United Kingdom*
Email: marianafcardoso@gmail.com

Background and Aims: Liver Transplantation (LT) for acute liver failure (ALF) has a high early mortality when compared to elective LT and utilises a significant proportion of high quality organs. Candidate selection to define those with poor outcome without LT has been extensively evaluated; however in those that meet ALF listing criteria, identifying those with a poor outcome despite LT remains challenging with little data existing to support decision making. We explore how age impacts on outcome in ALF.

Method: Retrospective review of a prospectively collated database of all LT for ALF at our unit since 1990 until the present. Data on aetiology, age, ALF (jaundice to encephalopathy ≤ 28 days) vs subacute liver failure (SALF), hospital mortality, 1-year and 5-year survival was collated.

Results: 166 patients aged ≥ 16 years were transplanted for ALF/SALF (122/44). Mean age was 39.0 ± 13.4 years and 64.5% were female. Aetiology was paracetamol in 15.7%, other drugs in 18.1%, viral in 13.3%, AIH in 13.3%, other known causes in 9.0% and indeterminate in 30.7%. In hospital, 1-year and 5-year survival in 1990–2003 and 2004–2017 were 59.0%, 57.4%, 54.1% and 86.7%, 84.0%, 79.2%, respectively (p =< 0.001, p < 0.001, p = 0.005). Mean ages at transplant for the defined time periods were 37.3 ± 13.7 vs 40.0 ± 13.1 years. Overall 104 patients were <45 years (62.7%); 41 patients were 45–55 years (24.7%); 21 patients were ≥ 55 years (12.7%). Hospital survival decreased along these age groups (81.7% vs 73.2% vs 57.1%, p = 0.045), as did 1-year (78.6% vs 74.4% vs 44.4%, p = 0.010) and 5-year survival (72.4% vs 64.3% vs 20.0%, p = 0.005), with ≥ 55 years appearing to be a more relevant cut-off. When excluding those with SALF, age ≥ 55 years was indeed associated with significantly lower hospital (41.7% in ≥55 years vs 80.9% <55 years, p = 0.006), 1-year (36.4% vs 78.6%, p = 0.005) and 5-year (0.0% vs 72.8%, p = 0.002) survival. Conversely age ≥55-years had no significant impact on hospital (77.8% vs 74.3%, p = 1.000), 1-year (57.1% vs 72.7%, p = 0.410) and 5-year survival (40.0% vs 60.9%, p = 0.624) in the 44 patients with SALF.

Conclusion: Patients greater than 55-years undergoing LT for ALF have a poor outcome with 41% surviving to hospital discharge and 0% alive at 5-years. This data suggests that in patients >55-years with ALF who meet poor prognostic criteria, LT is a poor utilization of a valuable organ resource and should not be undertaken.

EASL JOURNAL OF HEPATOLOGY

Posters Saturday, 14 April 2018

Gut microbiota and liver disease

SAT-001

miR-21 contributes to the onset and progression of liver disease through the deregulation of small intestine permeability

A.A. Santos, M.B. Afonso, P.M. Rodrigues, R.E. Castro, C.M.P. Rodrigues.
Research Institute for Medicines (iMed.ULisboa), Faculty of Pharmacy, Universidade de Lisboa, Lisbon, Portugal
Email: afasantos@ff.ulisboa.pt

Background and Aims: The gut-liver axis influences the onset and progression of a wide variety of liver diseases. High fat, choline-deficient (HFCD) diet and common bile duct ligation (BDL) are experimental models of liver disease associated with early increased intestinal permeability, disturbed bile acid homeostasis and gut microbiota (GM) dysbiosis. Previously, we have demonstrated that oncogenic miRNA-21 (miR-21) is upregulated in experimental non-alcoholic steatohepatitis and in mice liver following BDL, mediating inflammation and fibrosis. Here we aimed to investigate the impact of whole body genetic deletion or therapeutic modulation of miR-21 in small intestine permeability as well as in the GM, which may influence miR-21 effects in the liver.
Method: Three-week old C57BL/6 mice were fed a HFCD diet or a control diet for 14 weeks. Mice were injected with antagomiR Control (Anti-C; 16 mg /kg) or antagomir-21 (Anti-miR21; 16 mg/kg) in the beginning of the study, for 3 consecutive days, and repeated each 5 weeks until the end of the experiment. In addition, 3-month old C57BL/6 wild type (WT) and miR-21 whole body knockout (KO) mice were submitted to sham or BDL surgeries for 3 days. After mice sacrifice, liver tissue and small intestine were preserved and mRNA and protein expression were analysed by qRT-PCR and immunoblotting, respectively. Serum was also collected for biochemical analysis. GM composition was evaluated by sequencing the 16S rRNA gene V3 region of the bacterial DNA present in the small intestinal lumen.
Results: BDL miR-21 KO mice showed decreased circulating levels of *hepatic enzymes*, concomitant with decreased fibrogenic gene expression in the liver, in comparison with WT mice, suggesting that miR-21 contributes to BDL-induced liver injury and fibrosis. Occludin and claudin-1 mRNA levels were decreased in small intestine of WT mice after BDL, suggesting increased permeability. Moreover, zonula occludens (ZO-1) and occludin mRNA levels were also decreased in Anti-C HFCD-fed mice. Strikingly, both genetic deletion of miR-21 and Anti-miR-21 treatment reverted mRNA levels of tight junction proteins to control. TGF-β mRNA levels increased in the small intestine of BDL miR-21 KO mice or in Anti-miR-21 HFCD-fed mice, and associated with alterations in the GM. Moreover, the GM of the WT mice became dysbiotic, with decreased *Bacteroidetes* and increased *Proteobacteria* and *Firmicutes*. In miR-21 KO mice, the GM was not affected by BDL surgery.
Conclusion: Our results indicate that miR-21 deficiency and Anti-miR-21 treatment are associated with decreased small intestine permeability after BDL or following HFCD diet, concomitant with the maintenance of GM homeostasis, which suggests miR-21 involvement in the onset and progression of liver injury by impacting on liver and small intestine targets. (Supported by PTDC/BIM-MEC/089572014 and SFRH/BPD/114924/2016).

SAT-002

Depletion of Paneth cells is associated with decreased portal hypertension and angiogenesis after partial portal vein ligation in mice

M. Hassan[1], S. Moghadamrad[1], P. Kellmann[1], C. Trentesaux[2], M. Fraudeau[3], B. Romagnolo[3], A. De Gottardi[1]. *[1]University Hosptal Bern, Department of Biomedical Research, Hepatology, Bern, Switzerland; [2]Institut Cochin, INSERM, Department of Biomedical Research, Oncogenesis of digestive epithelia, Paris, France; [3]Institut Cochin, INSERM, Department of Biomedical Research, Oncogenesis of digestive epithelia, Paris, France*
Email: andrea.degottardi@gmail.com

Background and Aims: Paneth cells may contribute to the regulation of splanchnic hemodynamics in response to microbial stimuli from intestinal flora. However, the detailed mechanistic links have not been elucidated yet. We hypothesized that conditional deletion of intestinal Paneth cells might have regulatory effects on portal hypertension and angiogenesis after partial portal vein ligation (PPVL) in mice.
Method: Math-1 Lox/LoxVilcre^{ERT2} (a tamoxifen-dependent conditional model of Paneth cell depletion) or wild type mice were injected three consecutive doses of tamoxifen and subsequently underwent PPVL or sham surgery. Portal pressure (PP) and the development of portosystemic shunts (PSS) were assessed 14 days after PPVL. Intestinal and mesenteric angiogenesis was assessed by immunohistochemistry (IHC) using anti-CD-31 and anti-Lyve-1 antibodies. Expression of genes involved in the regulation of angiogenesis was evaluated by RT2 profiler PCR array in intestinal tissue.
Results: PP was significantly attenuated in Paneth cell depleted mice compared to control mice after PPVL ($n = 7$/group, 8.78 ± 1.23 cmH_2O vs 11.75 ± 1.53 cmH_2O, respectively, $p < 0.01$). This was associated with a decrease in PSS ($n = 3$/group, $42.8\% \pm 4.6$ vs $65.3\% \pm 3.0$, $p = 0.13$). Depletion of Paneth cells also resulted in a significantly decreased density of blood and lymphatic vessels as assessed by IHC ($n = 5$, pixel ratio, $2.7\% \pm 1.9$ vs $13.9\% \pm 2.3$ $p = 0.05$ and $10.5\% \pm 2.9$ vs $29.0\% \pm 7.2$ $p = 0.03$, respectively). Quantitative gene expression measurements showed a differential expression in 69 angiogenic genes, whereby 47 proangiogenic genes including Ang-1, Angpt-1, VEGFR1&2, VEGFb, VEGFc, and Nrp1 were downregulated in Paneth cell depleted mice.
Conclusion: Portal hypertension was significantly decreased in mice lacking Paneth cells. The decreased density of blood and lymphatic vessels suggest that Paneth cell-derived factors may act on portal hypertension and angiogenesis.

ELSEVIER

SAT-003

A functional metagenomics investigation of cirrhotic patients highlights distinctive microbiota features involved in bacterial translocation, systemic inflammation and hepatic encephalopathy

V.D.I. Gregorio[1], V. Iebba[2], F. Guerrieri[3], M. Levrero[3], A. Gagliardi[2], F. Santangelo[2], A.P. Sobolev[4], S. Circi[4], V. Giannelli[1], L. Mannina[4], S. Schippa[5], M. Merli[1]. [1]*Sapienza University of Rome, Department of Clinical Medicine, Rome, Italy;* [2]*Public Health and Infectious Diseases Dept., Institute Pasteur Cenci Bolognetti Foundation, Sapienza University of Rome, Rome, Italy;* [3]*Center for Life NanoScience@Sapienza, Institute Italiano di Tecnologia, Rome, Italy;* [4]*Sapienza University of Rome, Department of Chemistry and Pharmaceutical Technologies, Rome, Italy;* [5]*Sapienza University of Rome, Public Health and Infectious Diseases Dept, Rome, Italy*
Email: vincenzadg@yahoo.it

Background and Aims: Cirrhotic patients had an altered intestinal motility, an impaired gut intestinal barrier and altered immune system leading to dysbiosis and possible bacterial translocation (BT). The presence of bacteria or their byproducts within bloodstream could thus play a role in systemic inflammation and hepatic encephalopathy (HE).
Method: We employed a 'functional metagenomics' and network approach aimed at describing the interrelationships of microbiota members (biopsies, feces, peripheral and portal blood samples, n = 109), and fecal metabolites, with clinical parameters of cirrhotic patients (n = 46) and controls (n = 14).
Results: Feces and biopsies showed a marked dysbiosis in cirrhotic patients, with a higher proportion of Enterobacteriaceae; Proteobacteria were also predominant in peripheral and portal blood. Functional metagenomics evidenced an impaired fecal bacterial metabolism of short chain fatty acids (SCFAs) and carbon/methane sources in LC, along with an enhanced stress-related response. Network analysis revealed a 'functional dysbiosis' in cirrhotic feces, with Bacteroides vulgatus and threonine as keystone elements. Sixteen species, mainly belonging to Proteobacteria phylum, were shared among cirrhotic peripheral and portal blood, and were functionally linked to iron metabolism. Fecal Enterobacteriaceae and trimethylamine were positively correlated to proinflammatory cytokines, while Ruminococcaceae and SCFAs exerted a protective role. Within peripheral blood and feces, definite species (Stenotrophomonas pavanii, Methylobacterium extorquens) and metabolites (methanol, threonine) were positively related to HE.
Conclusion: Cirrhotic patients harbor a 'functional dysbiosis' in feces and peripheral/portal blood, with specific keystone species and metabolites related to clinical markers of systemic inflammation and HE.

SAT-004

Novel characterization of the gut microbiome in patients with NASH and longitudinal changes associated with histological improvement

R. Loomba[1], Y. Gindin[2], O. Podlaha[2], Z. Jiang[2], E. Lawitz[3], S. Caldwell[4], S. Djedjos[2], R. Xu[2], D. Gong[2], M. Subramanian[2], R. Myers[2], M. Charlton[5], Z. Goodman[6], A.M. Diehl[7]. [1]*University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States;* [2]*Gilead Sciences, Foster City, United States;* [3]*Texas Liver Institute, University of Texas Health San Antonio, San Antonio;* [4]*University of Virginia, Falls Church, United States;* [5]*University of Chicago, Chicago, United States;* [6]*Inova Fairfax Hospital, Falls Church, United States;* [7]*Duke Clinical Research Institute, Durham, United States*
Email: stephen.djedjos@gilead.com

Background and Aims: Data comparing the normal human gut microbiome versus patients with biopsy-proven NASH, and associations between longitudinal changes in the microbiome and histologic responses, are limited. Our aims were to: (1) characterize differences in 16S bacterial DNA in the stool microbiome between patients with NASH and healthy controls; and (2) evaluate longitudinal changes in the gut microbiome of NASH patients and their associations with changes in liver histology.
Methods: Stool samples for microbiome analysis were collected from 69 subjects with biopsy-confirmed NASH (NASH CRN F2-3 fibrosis and NAS ≥5) enrolled in a 24 week Phase 2 study of selonsertib (SEL) ± simtuzumab and compared to 32 healthy controls from the Human Microbiome Project (HMP). The 16S ribosomal RNA region was sequenced on the Illumina MiSeq platform and genus level assignments were made from operational taxonomic unit (OTU) data. OTU abundance was normalized to allow for sample comparisons with p-values from student's t-test adjusted using false discovery rate correction. Microbial changes across time were summarized using multidimensional scaling where the distance between two samples is proportional to the difference in their microbial community at the genus level. Distance between each NASH sample and an average HMP profile was calculated using Euclidean distance. Treatment-related effects were assessed based on the change in distance to average HMP profile between baseline (BL) and W24.
Results: The mean age and BMI of patients with NASH and healthy controls were 54 yrs and 34.3 kg/m^2 versus 26 yrs and 24 kg/m^2. Compared with controls, stool from patients with NASH had significantly lower Bactereoidetes, and higher Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia (Table). Following treatment with SEL, a significant trend toward normalization of the gut microbiome was observed (p = 0.033). In addition, increases in Ruminococcaceae were significantly associated with improvement in lobular inflammation (p = 0.023). In subjects who progressed to cirrhosis (n = 5), more Fusobacteria were observed at BL compared with subjects with a ≥1-stage improvement in fibrosis (n = 21; p = 0.016).

Table: Faecal microbial composition in NASH subjects vs healthy controls.

Phylum	Median abundance in healthy controls (N = 32)	Median abundance in NASH subjects (N = 69)	p-value
Bactereoidetes	4293 (3653–5499)	1206 (158–2791)	5.74×10^{-11}
Firmicutes	2252 (1553–3582)	5768 (3669–7449)	5.58×10^{-12}
Actinobacteria	7 (2–24)	117 (42–309)	6.21×10^{-8}
Proteobacteria	97 (41–219)	145 (39–590)	2.87×10^{-5}
Verrucomicrobia	0 (0–12)	2 (0–136)	2.15×10^{-3}

Conclusion: There are significant differences in the stool microbiome of patients with NASH and fibrosis compared to healthy controls. In NASH patients treated with SEL, changes in the gut microbial pattern are associated with improvements in liver histology.

SAT-005

Iron reduction by venesection alters the gut microbiome in Haemochromatosis patients

B. Parmanand[1], M. Watson[2], V. Black[2], R. Morovat[3], E. Lund[4], J.D. Collier[2], S. Fairweather-Tait[5], A. Narbad[1], J. Cobbold[2], J. Ryan[2]. [1]*Quadram Institute Bioscience, Norwich, United Kingdom;* [2]*University of Oxford, Translational Gastroenterology Unit;* [3]*Oxford University Hospitals NHS Foundation Trust, Department of Clinical Biochemistry, Oxford, United Kingdom;* [4]*University of East Anglia, Department of Biological Sciences, Norwich;* [5]*University of East Anglia, Department of Nutrition, Norwich, United Kingdom*
Email: john.ryan@ndm.ox.ac.uk

Background and Aims: Therapeutic venesection has been the standard of care for patients with Haemochromatosis for decades. Iron depletion is associated with an improvement in liver function tests, insulin resistance, liver fibrosis, and a reduction in mortality and risk of several malignancies. The mechanisms underlying these benefits are unknown. Paradoxically, venesection promotes iron

absorption from the gut, and reduced faecal iron levels have been reported during treatment. As iron is critical to the growth and proliferation of numerous gut microbes, and excess colonic iron has been implicated in colonic inflammation and carcinogenesis, changes in faecal iron during venesection could favourably alter the gut microbiome.

Method: Patients initiating venesection for iron overload were recruited between November 2014 and June 2016. Blood and stool samples were collected baseline and 3-month intervals during treatment. Faecal iron, microbiome (16S rRNA metagenomics) and metabolomic (NMR) analyses were performed.

Results: Baseline faecal free iron levels were higher in patients with iron overload than healthy controls ($p = 0.0013$). Serum ferritin, ALT, and faecal iron levels fell significantly with iron depletion (all $p < 0.05$). Of 11 patients with paired samples, 6 had a significant reduction in faecal iron ($p = 0.017$; termed 'responders') while 5 did not ($p = 0.62$; non-responders). While no significant differences in baseline serum ferritin, age, gender or LFTs were noted between groups, significant changes in bacterial genera were only seen in responders to treatment. The genus that changed most with treatment was Faecalibacterium, which increased significantly with iron depletion ($p = 0.0084$). Indeed, levels of Faecalibacterium species are known to correlate negatively with systemic inflammatory markers, and reduced levels have been associated with IBD, obesity and NAFLD, as well as following oral iron supplementation. Similarly, significant negative correlations between Faecalibacterium levels and serum ferritin ($r = -0.41$, $p = 0.006$) and CRP ($r = -0.45$, $p = 0.013$) were seen. Significant faecal metabolomic changes were also evident, only in responders, with increased levels of faecal aspartate, glycine, methionine and tyrosine seen (all $p < 0.05$).

Conclusion: Targeted depletion of faecal iron can alter the composition and function of the gut microbiome and may represent a novel therapy for metabolic and inflammatory diseases.

SAT-006

Does the bile acid receptor TGR5 play a role in Kupffer cell response during Alcoholic Liver Disease?

M. Spatz[1,2], D. Ciocan[1,2], F. Neuza[3], D. Rainteau[3], L. Humbert[3], C. Hugot[1,2], L. Wrzosek[1,2], P. Virginie[1,2], G. Ferrere[1,2], G. Perlemuter[1,2,4], T. Tordjmann[5], A.-M.C. Doulcier[1,2]. *[1]Inflammation Chemokines and Immunopathology, INSERM, Fac. de médecine-Univ Paris-Sud, Université Paris-Saclay, Clamart, France; [2]Laboratoire d'Excellence en Recherche sur le Médicament et l'Innovation Thérapeutique (LERMIT); [3]Département de Biochimie B et LCBGM, Hôpital Saint Antoine AP-HP, Paris, France; [4]AP-HP, Hôpital Antoine Béclère, Service d'hépato-grastroentérologie, Clamart, Univ Paris-Sud, CHU Bicêtre, Kremlin-Bicêtre, France; [5]INSERM U1174, Univ Paris-Sud, Université Paris-Saclay, Orsay, France*
Email: cassard.doulcier@u-psud.fr

Background and Aims: Chronic alcohol consumption is one of the major etiological factor of chronic liver diseases in western countries. Nevertheless, among heavy drinkers, only a subset of individuals will develop liver inflammation, cirrhosis and hepatocarcinoma. Alcohol intake induces a dysbiosis and patients with severe alcoholic hepatitis, a life-threatening situation, harbour a specific configuration of the gut microbiota. The intestinal microbiota (IM) was recently identified as a major player in the mechanisms involved in alcoholic liver disease (ALD) and in the individual susceptibility to alcohol. Bile acids (BA) metabolism is dependent on IM, and BA are discriminant metabolites between alcoholic patients with or without severe liver injury. As previously described, hepatic macrophages, Kupffer cells, are involved in the inflammatory process during ALD. Therefore, we assessed the role of the BA receptor TGR5, in the inflammatory phenotype of Kupffer cells in a murine model of ALD.

Method: Wild type (WT) and TGR5-deficient mice were fed with a 5% ethanol diet for 10 days (Lieber DeCarli). Liver lesions were scored by plasma transaminases, hepatic triglycerides, histology and qPCR regarding inflammatory genes. Kupffer cells phenotype was assessed by qPCR. BA were studied in faeces, plasma and liver by mass spectrometry. Disturbances in BA metabolism were determined by qPCR regarding BA enzymes and transporters. IM composition was analysed using Illumina MiSeq technology targeting the 16S ribosomal DNA V3-V4 region and correlated to the IM composition.

Results: In WT mice, alcohol induced significant liver steatosis, with elevated plasma transaminases. Quantification by qPCR of cytokines and chemokines confirmed the inflammatory profile in the liver and specifically in isolated Kupffer cells. BA concentration in plasma, liver and faeces were modified by alcohol intake. We observed a BA overload in plasma and liver, associated with an increase in hydrophobic BA, and a decrease in faecal excretion associated with a lower expression of ileal BA transporters. In TGR5-deficient mice, alcohol diet induced more important liver steatosis and inflammatory profile than in littermate-alcohol fed mice. Kupffer cells harboured a higher inflammatory profile. Microbiota analysis showed a dysbiosis in TGR5-deficient mice, both in control and alcohol diet groups, which may at least in part contribute to the observed BA metabolism dysregulation.

Conclusion: These results showed that TGR5 deficiency worsens liver lesions in a murine model of ALD and is associated with increased Kupffer cell inflammatory phenotype and altered BA homeostasis. We will further investigate the improvement of ALD by treating mice with a TGR5 agonist.

SAT-007

Does the gut play a pivotal role in the protective effect of coffee on liver damage?

G. Mazzone[1], A. Rossi[1], P. Vitaglione[2], V. Lembo[1], G. D'argenio[1], G. Maria[3], M. Savoia[4], N. Caporaso[1], F. Morisco[5]. *[1]University of Naples Federico II, Department of Clinical Medicine and Surgery, Gastroenterology Unit, Naples, Italy; [2]University of Naples Federico II, Department of Agricultural Sciences, Portici, Italy; [3]University of Padua, Department of Medicine, Padua, Italy; [4]University of Naples Federico II, Department of Biochemistry and Medical Biotechnology, Naples, Italy; [5]Federico II University, Gastroenterology, Napoli, Italy*
Email: antonellarossi46@hotmail.it

Background and Aims: Metabolic syndrome is one of the most important health issues worldwide. Its liver phenotype is called nonalcoholic fatty liver disease (NAFLD). We have previously demonstrated that high fat diet (HFD)-induced liver damage is reverted by coffee consumption thought a reduction of fat deposition in the liver and an amelioration of antioxidant and anti-inflammatory status. Nonetheless we hypothesize that the first target organ of coffee is the gut, supporting the protective effect on the liver by modulating the gut permeability and contributing to the concept of relevant role of gut-liver link.

Method: Twenty-four C57BL/6 mice were divided into 3 groups of 8 mouse each: one group received standard diet (SD: 3.3 Kcal/g, 5% from fat), one group received HFD (5.6 Kcal/g, 58% from fat), and a third group received HFD plus decaffeinated coffee solution (HFD + Coffee) for 12 weeks. Coffee daily dosage corresponded to 6 cups of espresso coffee or 2 cups of filtered coffee for a 70 kg person. At the end of treatment, hepatic histology was examined by H&E staining. Alanine-aminotrasferase (ALT), total cholesterol levels were measured in serum samples. Gene expression of PPAR-α and LXR-α was assessed in the liver. The expression of molecular mediators of fatty acids ABCA1, ABCG1, FFAR-1 and of gut permeability Zonulin and Claudin were evaluated in duodenum and colon by RT-PCR. Cecum fecal samples were collected for triglycerides and fatty acids analysis.

Results: Mouse body weight was significantly lower in HFD + Coffee group *vs* HFD ($p < 0.003$). Coffee treatment also reduced cholesterol and ALT serum levels ($p < 0.001$ and $p < 0.05$, respectively), and ameliorated liver macrovesicular steatosis ($p < 0.001$) and ballooning degeneration ($p < 0.05$). Coffee supplementation increased the expression of PPAR-α and LXR-α in the liver and upregulated the

expression of ABCA1, ABCG1, FFAR-1, Zonulin, and Claudin in the duodenum and colon. The fecal cecum content of HFD + coffee group showed higher levels of total triglycerides and fatty acids *vs* HFD group.

Conclusion: Coffee modulates the intestinal permeability and molecular expression of fatty acids mediators increasing fat oxidation and ameliorating fatty acids efflux. Coffee by *via* of gut-liver axis exerts a beneficial effect on the liver reducing hepatic steatosis.

SAT-008

Intestinal microbiota significantly alters hepatic expression of energy metabolism genes in mice with acute cholestasis

S. Moghadamrad[1], I. Keller[2], C. Simillion[2], L. Deshanais[3], R. Bernier-Latmani[3], A. De Gottardi[1]. *[1]Berne University Hospital, BioMedical Research, Bern, Switzerland; [2]Univesity hospital of Berne, Interfaculty Bioinformatic unit, Bern, Switzerland; [3]École polytechnique fédérale de Lausanne, Environmental Microbiology Laboratory, Lausanne, Switzerland*
Email: sheida.moghadamrad@dbmr.unibe.ch

Background and Aims: We were interested in assessing the effects of intestinal microbiota on hepatic gene expression profile and plasma bile acid (BA) composition in basal conditions and in an acute cholestasis.

Method: We induced acute cholestasis in germ free (GF) and altered Schaedler flora colonized (ASF) mice by performing bile duct ligation (BDL) and we performed studies after 5 days. We evaluated gene expression profile in the liver of these mice compared to non-cholestatic control groups using next generation sequencing and pathway analysis. We also measured the plasma concentration of BA by UHPLC-HRMS analysis.

Results: We found that acute cholestasis was associated with distinct genes expression patterns mainly involved in the regulation of the immune system, oxidative processes and accumulation of extracellular matrix in both ASF and GF mice (Figure A). In addition, we observed significant differences related to the hygiene status of the mice in the expression of genes controlling the generation of precursor metabolites, energy metabolism and amino acid metabolic process pathways. In non-cholestatic mice, the absence of microbiota significantly induced or suppressed the expression level of 80 genes involved in organic acid catabolic and fatty acid metabolic processes, leukocyte migration and external side of plasma membrane (Figure B). Under basal conditions, there were no significant differences in primary BA concentrations between GF and ASF mice. The concentration of the majority of BA markedly increased after BDL in both groups without remarkable differences according to the hygiene status of the mice.

Conclusion: Intestinal microbiota significantly alters hepatic gene expression before and after acute cholestasis. Alterations observed after BDL suggest that microbial-induced differences may impact the course of cholestasis and modulate liver injury.

SAT-009

Fecal microbiota profiles as a diagnostic biomarkers in cirrhosis and hepatocellular carcinoma and the impact of life style and nutrition

Y. Lapidot[1,2], R. Nosenko[3], B. Gayshis[1], M. Likhter[1], D. Ben-Ami[1], T. Engel[1], R. Margalit[1], I. Kalisky[1], P. Weiss[1], V. Ella[1], O. Cohen-Ezra[1], Y. Davidov[4], O. Koren[3], M. Safran[1], Z.B. Ari[5]. *[1]Chaim Sheba Medical center, Liver Disease Center, Tel Hashomer, Israel; [2]Tel-Aviv University, Sackler School of Medicine, Tel-Aviv, Israel; [3]Bar-Ilan University, Safed, Faculty of Medicine, Safed, Israel; [4]Chaim Sheba Medical Center, Liver Disease Center, Ramat Gan, Israel; [5]Sheba Medical Center at Tel Hashomer, Center of Liver Diseases, Tel Aviv, Israel*
Email: michal.safran@sheba.health.gov.il

Background and Aims: Liver cirrhosis is the main predisposing risk factor for the development of hepatocellular carcinoma (HCC).

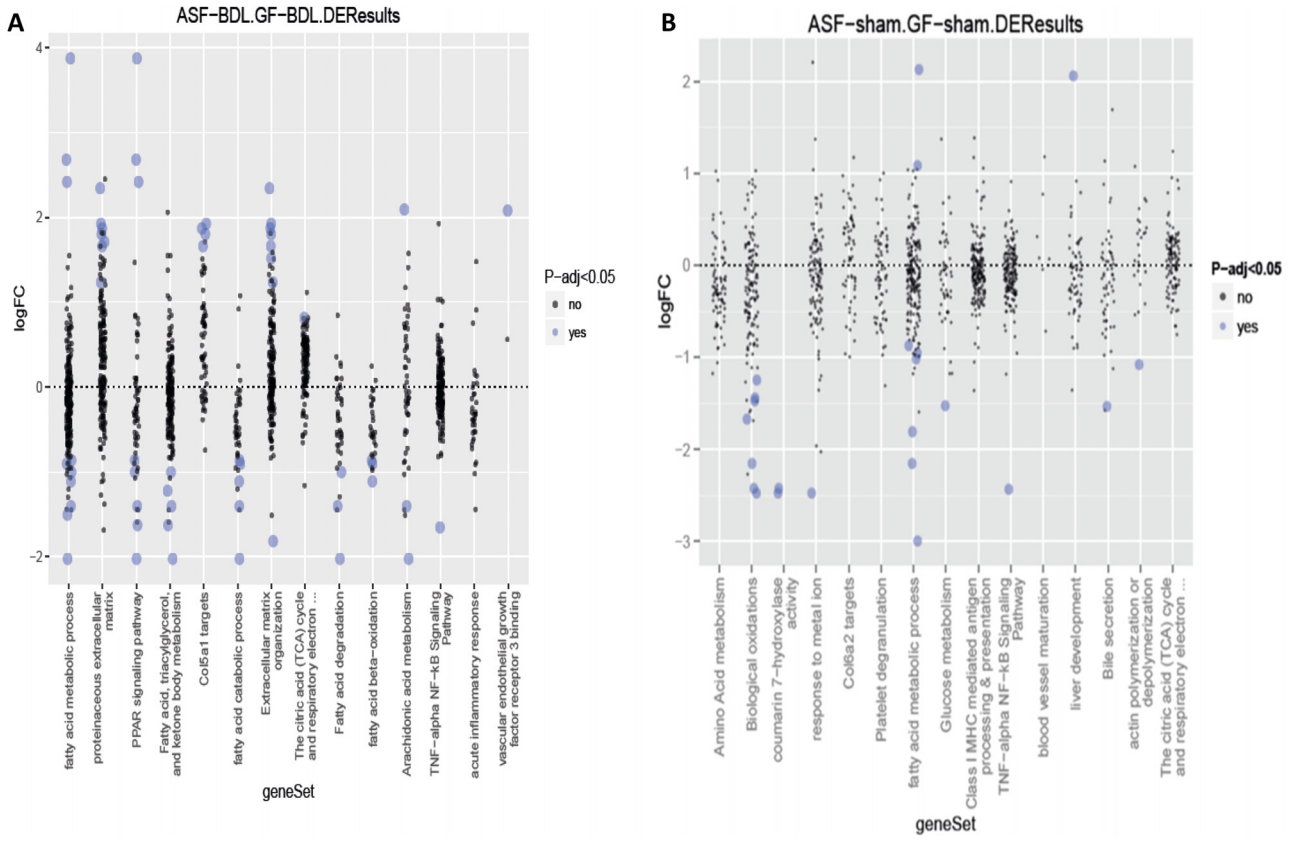


Figure: (abstract: SAT-008).

The factor(s) influencing disease progression from cirrhosis to HCC remain unknown. Gut microbiota has recently emerged as a major player in different liver diseases, however its association with HCC is still undetermined. Moreover, the association between the gut microbiota, nutrition, life style, cirrhosis and HCC was not studied previously. The aim of our study was to characterize the gut microbial signature in association with life style and nutrition of patients with cirrhosis, HCC and healthy controls.

Method: Stool samples were collected from 95 individuals (30 patients with HCC, 38 patients with cirrhosis and 27 age, gender and BMI-matched healthy volunteers,). 16S rDNA sequencing of fecal DNA was performed (MiSeq Illumina).

Results: The microbiota of patients with HCC-cirrhosis was characterized by overrepresentation of Bacteriodetes (42.3%) and lower expression of Firmecutes (46.7%) compared to healthy controls (36.1 and 52.2% respectively) and cirrhotic patients (34.2% and 50.3% respectively). However, the relative abundance of Proteobacteria in the samples of HCC-cirrhotic patients resembled the abundance of this species in patients with cirrhosis and not in healthy controls (6.1%, 6.4% and 3.8% respectively), while the relative population of the Actinocacteria in the HCC patients was closer to that of the healthy controls and not the cirrhotic patients (3.2%, 3.5% and 5.7% respectively). Nevertheless, investigating the life style and nutrition habits of HCC-cirrhosis, cirrhotic patients and the healthy controls we found that both groups of patients (HCC and cirrhosis) have very similar life style, which is different from the healthy controls. Both groups of patients reported similar dietary patterns that included high protein, low sodium and low sugar intake. On the other hand, healthy controls described consuming a low fat diet and a significantly more active lifestyle.

Conclusion: We here present the first report of the correlation between dietary habits and microbiota in liver disease patients. We have demonstrated in our study that the distribution of the fecal microbiome in HCC patients is different from both the cirrhotic patients and healthy control. This result is even more pronounced based on the results showing that both the diet and life style of HCC-cirrhosis and cirrhotic patients is very similar. Further studies are needed to confirm these findings and assess causality.

SAT-010

Gut microbes mediate liver fibrosis in chimeric mice with human hepatocytes persistently infected with hepatitis B virus

M. Sugiyama[1], T. Kanto[2], M. Masashi[1]. [1]*National Center for Global Health and Medicine, Genome Medical Sciences Project, Ichikawa;* [2]*National Center for Global Health and Medicine, Department of Liver Diseases, Ichikawa, Japan*
Email: msugiyama@hosp.ncgm.go.jp

Background and Aims: Hepatitis B virus (HBV) infection induces liver fibrosis and hepatocellular carcinomas. We previously established an in vivo model of liver fibrosis triggered by HBV infection using an uPA/SCID mouse with human hepatocytes (chimeric mouse). However, the mechanism remained unknown. Our purpose was to reveal the pathway of liver fibrosis using the chimeric mouse model.

Method: Chimeric mice were infected with HBV/C. Group A was treated with daily antibiotics cocktail (ampicillin, vancomycin, neomycin, and metronidazole), whereas Group B received normal DW for 6 months ($n = 4$ each). HBVDNA and markers in the mouse sera were determined by PCR and ELISA, respectively. The sera were determined by multiplex chemokine and cytokine assay for mouse or human. Histopathological changes in the liver were examined after the mouse dissection. The gene expression relating to liver fibrosis was determined using species-specific PCR primers in the liver specimens. The microbiome profile of mouse feces were compared between Group A and B by NGS using 16S amplicon.

Results: The serum HBVDNA level of Group A was higher than Group B ($p < 0.05$). However, Group B showed hepatic fibrosis (F1-2) 6 months post-infection, but not Group A. Alpha-SMA positive cells were stained around fibrosis in Group B. TIMP1, MMP2, and Col1a2 gene expressions were higher in Group B than Group A in the liver ($p < 0.05$ each). In particular, TLR4 expression was strongly induced in Group B ($p < 0.05$), whereas the other TLRs didn't show the significance. CD163+ monocyte cells in the liver induced the expression of the TLR4 gene in the mice with fibrosis. IL-6 gene expression was induced in mouse-derived cells. The levels of serum IL-34, IL-12, CX3CL1 and CCL25 in Group B were higher than Group A ($p < 0.05$), which were related with monocyte activity. The microbiome analysis of mouse feces determined that sixteen species of bacteria were significantly decreased in Group A, which were mainly Clostridiales.

Conclusion: These data suggested that liver fibrosis induced by HBV infection could occur by certain types of bacteria in the gut-liver axis. Especially, these pathogen could induce the activation of TLR4 pathway followed by the monocyte activation in the liver.

SAT-011

Prebiotic treatment prevents alcohol-induced liver lesions in mice with indigenous microbiota and mice with human microbiota

L. Wrzosek[1], G. Ferrere[1], D. Ciocan[1], W. Turpin[2], C. Hugot[1], P. Virginie[1], M. Spatz[1], M. Dupeux[1], F. Gaudin[1], S. Prevot[1], G. Perlemuter[1,3], A.-M. Cassard Doulcier[1]. [1]*INSERM, U 996, Clamart, France;* [2]*Mount Sinai Hospital, Division of Gastroenterology, Zane Cohen Centre for Digestive Diseases, Toronto, Canada;* [3]*Hôpital Antoine Béclère, Hepato-gastroenterology, Clamart, France*
Email: cassard.doulcier@u-psud.fr

Background and Aims: Alcoholic liver disease (ALD) is a leading cause of liver failure and mortality. In humans, severe alcoholic hepatitis is associated with key changes to intestinal microbiota (IM), which influences individual sensitivity to develop advanced ALD. In mice receiving an alcohol diet we also observed, depending on the animal facility, a difference in susceptibility to develop liver damages associated to changes in IM. Here we tested the efficiency of a prebiotic treatment in alcohol-sensitive mice to reverse dysbiosis and prevent ALD.

Method: Mice with indigenous IM (their own IM) were fed alcohol with a Lieber DeCarli (LDC) diet. First, mice were progressively adapted to the semi-liquid LDC diet, then an ethanol diet, and finally mice were fed a 5% ethanol diet for ten days. A group of mice with indigenous IM received pectin during the entire alcohol consumption period. In parallel, other groups of mice were colonized with the IM of an alcoholic patient with severe alcoholic hepatitis by fecal microbiota transplantation and then fed an alcohol diet. Once again, a group of mice with human IM received pectin during the alcohol period. Different doses of pectin were tested (from 0.4 to 6.5%). Control mice were fed a control diet containing an isocaloric amount of maltodextrin.

Results: In mice with indigenous IM and mice with human IM, ethanol induced steatosis and liver inflammation, which were associated with disruption of gut homeostasis and a modification of IM with a lower proportion of Bacteroides ($p < 0.05$) compared to control mice. We targeted IM with a prebiotic treatment (pectin) to prevent alcohol-induced liver lesions. Pectin treatment induced modifications of the IM in mice with indigenous IM and mice with human IM. Pectin treatment prevented steatosis, liver inflammation, and restored gut homeostasis in both groups of mice. Depending on the dose of pectin used, the beneficial effects of pectin were more or less pronounced.

Conclusion: Manipulation of IM with prebiotic treatment can prevent alcohol-induced liver injury. The IM should be considered as a new therapeutic target in ALD. These findings open new possibilities for treatment of human ALD through intestinal microbiota manipulation.

SAT-012

Comprehensive analysis of alcohol treatment in mouse model of acute-on-chronic liver injury

S. Furuya[1], J.A. Cichocki[2], H. Kono[1], R. Bataller[3], I. Rusyn[2]. [1]*University of Yamanashi, First Department of Surgery;* [2]*Texas A&M University, Department of Veterinary Integrative Biosciences;* [3]*University of Pittsburgh, Department of Medicine*
Email: irusyn@cvm.tamu.edu

Background and Aims: Human alcoholic hepatitis (AH) carries a high mortality rate. AH is an acute-on-chronic type of liver disease characterized by hepatic steatosis, ballooned hepatocytes, increased serum transaminases, and pericellular fibrosis, which is an important prognostic factor. Chronic alcohol consumption is accompanied by umbalance of bile acids (BAs) and intestinal dysbiosis, and the development of alcoholic liver disease requires gut-derived bacterial products. However, little is known about how alterations in the microbiome contribute to pathogenesis of alcoholic liver disease. Currently, no existing animal model of alcoholic liver disease faithfully recapitulates the pathological features of advanced forms of AH. However, little is known about how alterations in the BAs profile and the microbiome contribute to pathogenesis of alcoholic liver disease.
Method: We used adult male C57BL6/J mice were treated with 3.5-diethoxycarbonyl-1.4-dihydrocolidine (DDC) contain diet (0.05% w/w) to induce chronic liver fibrosis. Following DDC-induced fibrogenesis, ethyl alcohol (EtOH) (up to 27 g/ kg/day, up to 28 days) was administered continuously to mice via a gastric feeding tube (Tsukamoto-French surgery). Liver tissue was evaluated to characterize acute-on-chronic-alcoholic liver disease in our model. Liver total RNA was extracted for deep transcriptomic sequencing, and bacterial DNA from the feces was extracted for deep metagenomic sequencing. Targeted metabolomics assessed concentrations of BAs in the liver tissue and feces.
Results: Exposure to DDC or EtOH alone resulted in cholestasis or steatosis, respectively, as anticipated. Combined treatment with DDC and EtOH lead to an additive effect on liver injury, as evident by the development of hepatic inflammation, steatosis, and pericellular fibrosis, and by increased serum transaminase levels, compared to mice treated with either agent alone. Liver transcriptomic changes specific to combined treatment group included pathways involved in the cell cycle and DNA damage. Analyses of feces from mice revealed alcohol-associated changes to the BAs profile and microbiota, characterized by reduced conjugated BAs in liver and secondary BAs in feces.
Conclusion: Mice treated with DDC and EtOH displayed several key characteristics of human AH, including pericellular fibrosis, increased hepatic bacterial load with dysbiosis, reducing the capacity of the microbiome to synthesize secondary BAs and the proportion of Enterobacteriacae species, and especially transcriptome analysis. This model may be useful for developing therapeutics for AH.

SAT-013

The Impact of proton pump inhibitors on the intestinal microbiota in chronic hepatitis C patients

F. Wellhöner[1], N. Döscher[1], V. Marius[2], I. Plumeier[2], S. Kahl[2], A. Potthoff[1], M.P. Manns[3], P. Dietmar[2,4], H. Wedemeyer[5], M. Cornberg[1], B. Heidrich[1,2,4]. [1]*Hanover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany;* [2]*Helmholtz Center for Infection Research, Microbial Interactions and Prosseses Research Group, Braunschweig, Germany;* [3]*Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany;* [4]*German Center for Infection Research, Germany;* [5]*Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany*
Email: freya.wellhoener@stud.mh-hannover.de

Background and Aims: Proton pump inhibitors (PPI) are among the most prescribed drugs and are known to influence the intestinal microbiota. Patients with chronic liver diseases are in risk of infectious complications such as spontaneous bacterial peritonitis (SBP). Former studies on the impact of PPI use on the microbiota have been done in patients with several different liver diseases. Therefore, the aim of the present study was to elucidate the role of PPI in patients with chronic hepatitis C infection in order to exclude effects introduced by differences in the underlying liver disease.
Method: Stool samples of 141 patients with chronic hepatits C infection were analyzed. The V1-2 region of the 16S rRNA gene was amplified followed by sequencing on the Illumina MiSeq platform. Samples with less than 10,000 reads and those from patients who were taking immunosuppressives, antibiotics, oral antidiabetics, UDC, HepaMerz or Lefax were excluded. In total, 28 with and 78 without PPI intake were included. Random subsampling was performed to achieve equal numbers of reads. Alpha and beta diversity were calculated in Primer 7. Differences in relative abundances were calculated with DESeq2.
Results: Baseline characteristics of both groups were comparable. However the frequency of patients with liver cirrhosis was significantly higher in the PPI group (54% vs 32%; $p = 0.044$). In contrast to former studies no significant differences in alpha diversity were observed. Beta diversity differed significantly. However, the observed differences between both groups were only small ($R = 0.123$, $p = 0.014$). The relative abundance of 27 genera differed significantly between patients with and without PPIs. In order to exclude effects induced by the presence of liver cirrhosis we performed a second analysis for patients with (CIR) and without cirrhosis (No-CIR) separately. In CIR 28 genera differed significantly whereas in No-CIR 13 genera showed differences in relative abundance. Importantly, only the relative abundances of *Streptococcus spp.* ($p = 3.0*10^{-14}$), *Haemophilus spp.* ($p = 1.2*10^{-11}$) and *Enterobacter spp.* ($p = 3.1*10^{-8}$) were significantly increased in both groups.
Conclusion: PPIs lead to a significant change in the composition of the gut microbiota independent of the presence of liver cirrhosis. Importantly, *Streptococcus spp.* and *Enterobacter spp.* can be isolated regularly from ascitic fluid. Therefore, we recommend a careful use of PPI in patients with liver diseases in order to avoid selection of potential harmful genera.

Immunology except viral hepatitis

SAT-014

Paradoxically functioning onco-miR-155 and the tumor suppressor miR-194 consensus on PD-L1 immune checkpoint upregulation via MALAT-1 and XIST in hepatocellular carcinoma

S. Atwa[1], K. Hosny[2], H. Handoussa[3], H. El Tayebi[4]. [1]*Pharmaceutical Biology, Cairo, Egypt;* [2]*General Surgery, Kasr El Einy, Cairo, Egypt;* [3]*German University in Cairo, Pharmaceutical Biology, Cairo, Egypt;* [4]*Genetic Pharmacology Research Group, Pharmacology and Toxicology department, Cairo, Egypt*
Email: sara.mahmoud-atwa@guc.edu.eg

Background and Aims: Immunotherapy elicits nontoxic, systemic, long-lived anti-tumor activity. Anti-programmed death therapy has thrust the immunotherapy into spotlight. Nevertheless, programmed-cell-death-ligand-1 (PD-L1) targeted therapies are yet understudied in hepatocellular carcinoma (HCC). MicroRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have emerged as eminent players in human pathophysiological processes. However, interaction between miRNAs and LncRNAs in immunotherapy is inadequately studied. Our recent data described LncRNA-XIST as an upstream regulator of PD-L1. This study aims at exploring non-coding RNAs as novel intermediaries between XIST and PD-L1 in HCC.
Method: Bioinformatics softwares were used to predict PD-L1 upstream regulatory noncoding-RNAs. Twenty HCC, cirrhotic and

healthy liver tissues were surgically resected from liver transplant patients. Ectopic miR-155 and miR-194 expression manipulation was performed in Huh-7-cells followed by extraction of total RNA using Trizol, then RT-qPCR was performed. RNU6B and Beta-2-microglobulin were house-keeping genes.
Results: miR-155 and miR-194-5p were predicted to target PD-L1, MALAT-1 and XIST. MALAT-1 and XIST were predicted to target PD-L1 mRNA. PD-L1 was detected in only 30% of HCC biopsies, however, it was absent in 100% of cirrhotic tissues and minimally detected in controls. MALAT-1 was markedly upregulated in cirrhotic (p = 0.0136) and downregulated in HCC (p = 0.043) compared to controls. XIST was significantly upregulated in HCC (p = 0.048) compared to controls. Expression of MALAT-1 was inversely correlated with both miR-155 and PD-L1 in HCC and cirrhotic tissues. In contrast to miR-194 expression that was directly associated with MALAT-1 expression in cirrhotic and HCC tissues. Ectopic expression of miR-155 in Huh-7 cells resulted in significant upregulation of XIST and PD-L1 (p = 0.0477 and P = 0.0219, respectively) and downregulation of MALAT-1 (p = 0.0053) compared to miR-155 antagonised cells and untransfected controls. Intended overexpression of miR-194 led to significant upregulation of XIST and PD-L1 (p = 0.0026 and P = 0.0209, respectively) compared to miR-194 antagonised cells and untransfected controls, however, it didn't significantly affected MALAT-1.
Conclusion: Despite the contradicting functions of the overexpressed oncomiR-155 and the downregulated tumor suppressor miR-194 in HCC, unexpectedly, both microRNAs showed the same impact on XIST and PD-L1 expression via MALAT-1 downregulation. Moreover, this study showed the sensitivity of PD-L1 expression appearance to MALAT-1 expression in HCC tissues. Therefore, our data suggests a pivotal role for MALAT-1 in the intermediation between XIST and PD-L1 and recommends additional investigation of the controversial and contradicting roles of microRNAs in the context of cancer.

SAT-015

Circulating NK cells in cirrhosis are hypofunctional, with an expanded inhibitory liver-homing CD56dimCD16+/– NK cell population

N. Kumar[1], W. Khamri[1], F. Sadiq[1], E. Triantafyllou[1], F. Lebossé[1], M. Sujit[1], A. Dhar[1], M. Thursz[1], H. Antoniades[1], S. Khakoo[2]. *[1]Imperial College London; [2]University of Southampton*
Email: n.kumar@imperial.ac.uk

Background and Aims: Natural Killer (NK) cells have vital roles in anti-pathogen responses and tumour surveillance. However, cirrhosis renders patients susceptible to sepsis and cancer. Here we aim to characterise NK cells in cirrhosis.
Method: Peripheral blood mononuclear cells (PBMCs) from healthy volunteers and cirrhotic patients (n = 20 in each group) were surface stained for markers CD161, CD16, CXCR6, and maturity (KLRG1, CD57, n = 5). Transcriptomic analysis using Nanostring technology further characterised CD56/CD16 subpopulations (Healthy, Non-alcohol Fatty Liver Disease (NAFLD) related cirrhosis, Alcohol (ALD) related cirrhosis, n = 3 in each group). Function was measured against K562 targets (PBMCs:K562,5:1) using intracellular staining for cytokines (Tumour Necrosis Factor alpha (TNFα), Interferon gamma (IFNγ)), and staining for degranulation (CD107a) as a marker of cytotoxicity.
Results: Circulating CD56dimCD16+/–NK cells are increased in proportion in cirrhosis (26.4%vs7.04; p < 0.0001), and mature cytotoxic CD56dimCD16++NK cells are reduced compared to healthy controls (67.0%vs83.9%; p = 0.003). A greater proportion of CD56dimCD16+/–NK cells express inhibitory receptor CD161 (91.1% vs 82.6%, p = 0.03) and liver homing marker CXCR6 (7.57%vs1.8%, p < 0.0001) in comparison to the CD56dimCD16++NK cells. CD57 and KLRG1, mature NK cell markers, are expressed by a smaller proportion of CD56dimCD16+/–NK cells compared to CD56dimCD16++NK cells (CD57 40.1%vs57.1%, p = 0.06; KLRG1 44.6%vs52.3%, p = 0.008), and at a lower median fluorescent intensity(MFI) (CD57 6629vs8596, p = 0.03; KLRG1 926vs1303, p = 0.09). Transcriptomic comparison of CD56dimCD16+/–NK cells between NAFLD cirrhosis and ALD cirrhosis did not demonstrate significant differences, indicating the CD56dimCD16+/–NK profile may be independent of cirrhotic aetiology. Cirrhotic CD56dimNK cells demonstrate a functional deficit with regards to cytotoxicity (reduced CD107a 52.1%vs64.5%; p = 0.008) and cytokine production (39.7%vs48.1%; p = 0.04) compared to healthy NK cells. Gene expression analysis demonstrates a reduction in Granzyme A and B within CD56dimCD16+/–NK cells, and downregulation in CCL4 expression. Cirrhotic NK cells also have a significantly lower proportion of polyfunctional CD56dim NK cells (NK able to produce IFNγ, TNFα and degranulate (14.6vs21.2, p = 0.03).
Conclusion: Here we describe an increased circulating proportion of inhibitory NK cells with attenuated responses in cirrhosis. Greater knowledge of NK cell dysfunction in cirrhosis independent of cirrhotic aetiology, can aid understanding of infection and malignancy susceptibility in cirrhosis.

SAT-016

Liver sinusoidal endothelial cells are involved in the aggravation of liver injury induced by the activated NKT cells in aged mice

H. Nakashima[1], M. Nakashima[1], M. Kinoshita[1], S. Kato[2], T. Ishikiriyama[1], S. Seki[1]. *[1]National Defense Medical College, Immunology and Microbiology, Tokorozawa Saitama, Japan; [2]National Defense Medical College, Internal Medicine, Tokorozawa Saitama*
Email: hiro1618@ndmc.ac.jp

Background and Aims: The liver non-parenchymal cells such as NK cells, NKT cells and Kupffer cells maintain the innate immune functions of the liver. We previously reported that NKT cells exert two opposite effects after alpha-galactosylceramide (a-GalCer) activation. One is upregulation of anti-tumor immunity mediated by their IFN-gamma production and NK cell activation (Nakagawa R, J Immunol, 2001). The other is hepatocyte injury induced by FasL expressing NKT cells stimulated with TNF produced by recruited macrophages (Mphgs) (Inui T, J Hepatol, 2005). Furthermore, in either aged mice or mice fed high fat and high cholesterol diet, TNF production from recruited Mphgs is up-regulated and thereby NKT cells express excessive FasL to induce severe liver injury (Nakashima H, PLOS ONE, 2013). In this study, we examined the role of liver sinusoidal endothelial cells (LSECs) in aggravation of the liver injury induced by a-GalCer in aged mice.
Method: Young (8 weeks old) and aged C57BL/6 mice (50 weeks old) were i.v. injected with a-GalCer. The levels of serum ALT and MCP-1 were compared to those in young mice. Liver injury in CCR2–/– mice was also examined. Mononuclear cells (MNCs) were harvested from the liver by collagenase digestion and intracellular MCP-1 induced by a-GalCer in CD31(+) LSECs were examined by flow-cytometric analysis (FACS). Liver injury in CCR2–/– mice was also examined.
Results: In aged mice, liver injury was much more severe than that of young mice. Infiltration of TNF producing CD11b(+) Mphgs was augmented and elevated serum TNF levels in aged mice. Intracellular FACS analysis revealed that LSECs were the main producer of MCP-1 after a-GalCer administration, suggesting that LSECs recruited Mphgs via MCP-1. Serum and intracellular MCP-1 of LSECs were elevated in aged mice. In CCR2–/– mice, recruitment of Mphgs and serum TNF were downregulated, and liver injury was ameliorated.
Conclusion: Our results indicate that LSECs produce MCP-1 and play a key role in aggravation of liver injury by recruitment of Mphgs in a-GalCer hepatitis. Not only CD45(+) immune cells but also LSECs may participate in the immune system in the liver, especially in aged mice.

SAT-017

M2 macrophage specfifc gene silencing in the liver using third generations mannose coated, siRNA-loaded nanohydrogel particles

L. Kaps[1], N. Leber[2], A. Yang[3], M. Giardino[3], S. Rizelli[2], M. Aslam[3], A. Mostafa[3], R. Zentel[2], D. Schuppan[3]. [1]*Institute of Translational Immunology and Research Center for Immunotherapy, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany;* [2]*Johannes Gutenberg-University of Mainz, Institutes of Organic Chemistry;* [3]*University Medical Center of the Johannes Gutenberg-University Mainz, Institute of Translational Immunology and Research Center for Immunotherapy (FZI), Germany*
Email: detlef.schuppan@unimedizin-mainz.de

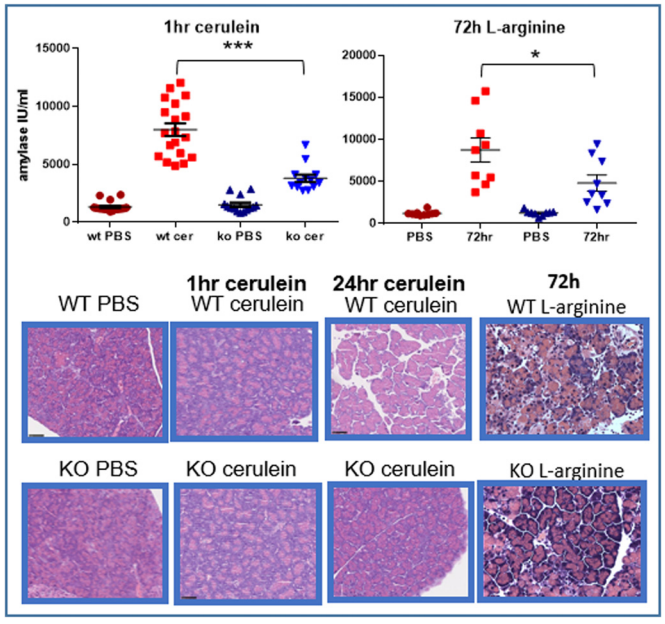
Background and Aims: Efficient *in vivo* transport of active siRNA to specific liver cells remains challenging. First and second generation cationic nanohydrogel particles (NHP) are excellent oligonucleotide carriers [Kaps L et al, Adv. Healthcare Mat. 2015; J. Contr. Rel. 2016]. We designed a third generation of NHP where mannose residues are covalently linked to the surface (Man-NHP), enabling targeting of CD206 positive M2 macrophages, which are implicated in HCC and liver fibrosis progression.
Method and Results: Man-NHP composed of block copolymers (pentafluorophenyl methacrylate and tri-(ethylene glycol) methyl ether methacrylate), with diameters around 40 nm and loaded with control siRNA (scsiRNA) up to 400 nM did not show cytotoxicity for murine 3T3 fibroblasts, Raw macrophages, SVEC endothelial cells or HepG2 human hepatoma cells. Man-NHP labelled with FITC showed a preferential binding to *in vitro* polarized CD206 high M2 compared to CD206 low non-polarized M0 or M1-polarized bone-marrow derived macrophages (BMDM), as determined by FACS analysis. Man-NHP were shielded from unspecific interactions compared to non-mannose coated NHP, which exhibited high binding to macrophages regardless of their phenotype. Man-NHP loaded with siRNA to CSFR-1, an M2 macrophage specific target, yielded a robust knock-down in M2 polarized BMDM after 48 h of incubation.
After intravenous injection in mice with CCl_4-induced liver fibrosis, near infrared (NIR, CW800-dye) labeled Man-NHP loaded with Cy5-labelled scsiRNA distributed preferentially to the liver (>80%), as determined by *in vivo* and *ex vivo* NIR imaging. *Ex vivo* colocalization studies of liver single cell suspension obtained from Man-NHP-NIR/Cy5-scsiRNA treated fibrotic mice, as well as *in vivo* knockdown (vs. the myeloid specific target CSFR-1) will be presented.
Conclusion: Third generation NHP were derivatized with surface mannose residues for effective M2 macrophage targeting via the mannose receptor CD206 *in vitro* and *in vivo*. Man-NHP are a promising tool to specifically target therapeutic siRNA to fibrosis and HCC promoting M2 macrophages.

SAT-018

The pathogenic role of Stat2 in inflammation is independent of canonical interferon signaling and is mediated by TNFa

H. Heath[1], H. Kudo[2], G. Renney[3], M. Ward[3], P. Cutillas[4], R.D. Goldin[2], R. Hutchins[4], G. Foster[1], W. Alazawi[1]. [1]*The Blizard Institute, Queen Mary University of London, London, United Kingdom;* [2]*Imperial College London, London, United Kingdom;* [3]*King's College London, London, United Kingdom;* [4]*Queen Mary University of London, London, United Kingdom*
Email: w.alazawi@qmul.ac.uk

Background and Aims: Inflammatory diseases of the liver and pancreas cause much morbidity and mortality worldwide. Even in the absence of infectious agents, tissue injury causes release of damage-associated molecular patterns (DAMPs) which activate pattern recognition receptors such as toll-like receptors (TLR). Our group has previously identified Stat2 as an important mediator of TLR4-mediated inflammation that is required for appropriate cytokine production (Alazawi et al, PNAS 2013). Here we have tested the hypothesis that Stat2 loss is protective in pancreatic inflammation, and showed the mechanism by which Stat2 mediates tissue injury.
Method: Wild type (WT) and Stat2$^{-/-}$ mice were challenged with either cerulein or L-arginine by intraperitoneal injection. Pancreata and blood were harvested 1 h and 24 h after the final dose of cerulein and up to 96 h post L-arginine.
Results: Stat2$^{-/-}$ mice are protected from cerulein-induced pancreatitis and L-arginine-induced severe pancreatitis compared to WT (Figure) shown histologically, and with significantly lower serum amylase levels and inflammatory cytokine expression (including IL-6, IL-13, TNFα, CCL2 & CXCL2). Antibody-mediated blockade of type I interferon signaling in WT mice did not recapitulate the protective effects of Stat2 loss in the cerulein model.



Global protein analysis by label-free mass spectrometry on whole inflamed pancreata identified 128 phosphoproteins that were expressed differently in cerulein-treated Stat2$^{-/-}$ compared to WT mice (66 upregulated in Stat2$^{-/-}$ and 62 downregulated in Stat2$^{-/-}$). Key differences were in activating modifications of mitogen-activated protein (MAP) kinase mediators confirmed by western blot. Nuclear translocation of MAPKp38 was impaired as was NFκB p65 in Stat2$^{-/-}$ pancreatitis and in primary pancreatic cells, assessed by confocal imaging and western blot, resulting in reduced expression of inflammatory genes such as TNFα in Stat2$^{-/-}$ mice. Indeed, antibody-mediated TNFα blockade protected WT mice but had no effect in Stat2$^{-/-}$.
Conclusion: Stat2 is a mediator of acute sterile inflammation in the liver and pancreas and is required for cytokine-mediated inflammatory injury in an interferon-independent, TNFα dependent mechanism. Stat2 or other (phospho) protein mediators identified in this study are therapeutic targets for sterile inflammation.

SAT-019

AXL-expressing monocytes indicate immuneparesis and disease severity in patients with cirrhosis

R. Brenig[1], C. Perez[1], F.H.T. Duong[2], P. Kuenzler[1], L. Besse[3], S. Wieland[2], O. Pop[4], E. Triantafyllou[4,5], T. Boldanova[2], S. Brand[1], L. Terraciano[6], J. Wendon[4], M. Heim[2], D. Semela[1], H. Antoniades[4,5], C. Bernsmeier[1,4].
[1]Cantonal Hospital St.Gallen, Liver Biology Laboratory, Division of Gastroenterology and Hepatology, St. Gallen, Switzerland; [2]University Hospital Basel, Hepatology Laboratory, Department of Biomedicine, Basel, Switzerland; [3]Cantonal Hospital St.Gallen, Oncology Laboratory, Division of Clinical Oncology, St. Gallen; [4]King's College London, Institute of Liver Studies, King's College Hospital, London, United Kingdom; [5]Imperial College London, Hepatology Department, St. Mary's Hospital, London, United Kingdom; [6]University Hospital Basel, Institute of Pathology, Basel, Switzerland
Email: robert.brenig@kssg.ch

Background and Aims: Infection related complications substantially contribute to the high morbidity and mortality in advanced cirrhosis. While susceptibility to infections has been attributed to immuneparesis, precise mechanisms of the underlying pathophysiology remain elusive. TAM-receptors (Tyro-3, AXL, MERTK), expressed on monocytes, are important regulators of innate immune responses to microbial challenge. We sought to evaluate TAM-receptor expression on monocytes in patients with cirrhosis in relation to monocyte function and disease severity.
Methods: We collected blood from patients with stable early (Child A n = 33) and advanced cirrhosis (Child B n = 22; C n = 12) at the Cantonal Hospital St. Gallen and healthy controls (HC n = 15). Ex-vivo monocyte immunophenotyping including TAM-receptor expression and cytokine production (TNF-alpha; IL-6) in response to lipopolysaccharide (LPS) were assessed using flow cytometry. GAS6 was measured by ELISA. AXL was overexpressed in THP-1 cells and TNF-alpha production upon LPS assessed by ELISA.
Results: We observed a significant upregulation of AXL on monocytes of patients with cirrhosis independent of aetiology and increasing with disease severity (HC 2.1% vs. Child A 2.9% vs. B 11.8% vs. C 17.1%, Figure A). MERTK and Tyro-3 expression were low in all groups. AXL-expressing (AXL^+) monocytes were characterised by increased expression of HLA-DR, CD16, MERTK, Tyro-3, TLR4, CCR5/7 and CX3CR1. Plasma levels of AXL ligand GAS6 were elevated in cirrhosis, also increasing with disease severity. TNF-alpha and IL-6 production upon LPS by contrast were significantly lower in cirrhosis compared to HC (22.5% vs. 51.2%, p = 0.002; 43.2% vs. 74.2%, p < 0.0001) and decreased with disease severity. Interestingly, AXL^+ monocytes produced less TNF-alpha (Figure B) and IL-6. Accordingly, AXL overexpression in THP-1 cells significantly reduced LPS induced TNF-alpha production in vitro (Figure C, D). The frequency of AXL^+ monocytes correlated with markers indicating disease severity or complications: Child Pugh (r = 0.46, p = 0.0001), MELD (r = 0.41, p = 0.001), bilirubin (r = 0.3, p = 0.03), AST (r = 0.39, p = 0.004), albumin (r = –0.35, p = 0.008), grade of ascites (r = 0.31, p = 0.01), creatinine (r = 0.37, p = 0.004) and connect the number test (r = 0.75, p = 0.03). Patients who died within 1 year or developed secondary infections within 1 month expressed higher AXL levels (MFI 581 vs. 333, p = 0.03; MFI 592 vs. 318, p = 0.008).
Conclusion: We newly observed an expansion of AXL^+ immunoregulatory monocytes in patients with advanced cirrhosis. AXL expression was crucial in dampening innate immune response to microbial challenge and may merit evaluation as an immunotherapeutic target. Moreover, AXL expression was associated with disease severity, infectious complications and death indicating its potential value as prognostic marker of cirrhosis.

SAT-020

Paired-Cell sequencing reveals global transcriptional zonation of liver non-parencymal cells

K.B. Halpern[1], S. Itzkovitz[1], R. Shenhav[2]. *[1]Weizmann institute of Science, Israel, Rehovot, Israel; [2]Weizmann Institute of Science, Israel*
Email: kerenb@weizmann.ac.il

Background and Aims: The mammalian liver consists of millions of hexagonal-shaped lobules that are polarized by morphogens and blood-borne factors. The liver lobule is comprised of hepatocytes and

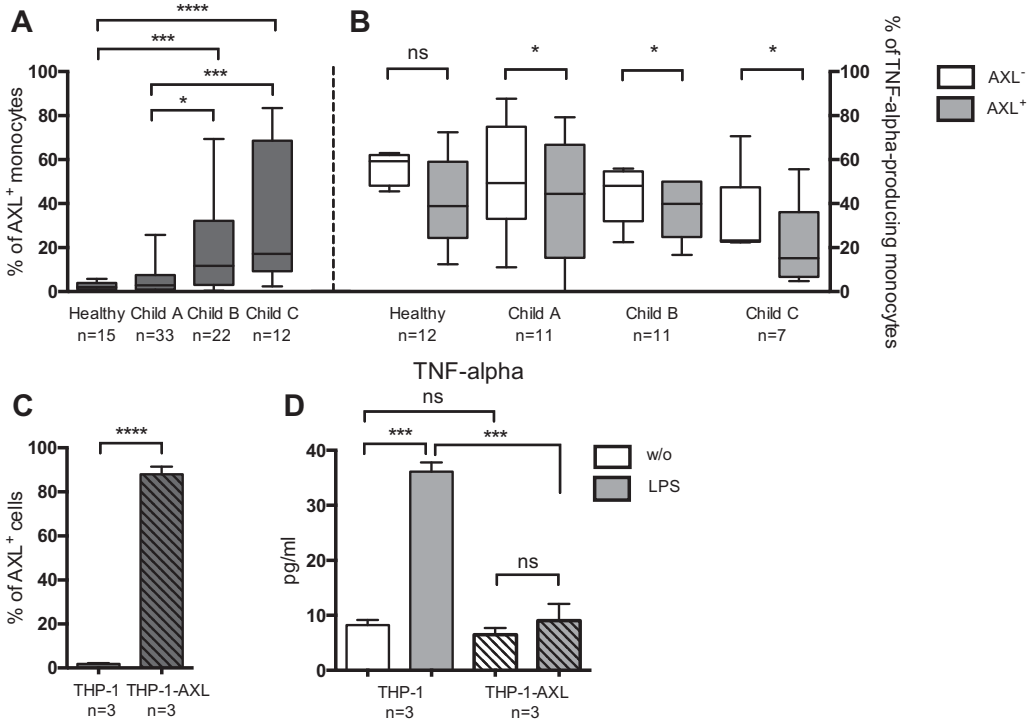


Figure: (abstract: SAT-019).

several types of non-parenchymal cells (NPCs), including endothelial cells and kupffer cells. We have recently applied spatially resolved single cell transcriptomics to reconstruct the global zonation patterns of hepatocyte genes, however it is unclear if NPCs exhibit similar spatial heterogeneity.
Method: To address this, we combined single cell RNAseq of NPCs with paired-cell sequencing of hepatocytes dissociated together with attached NPCs.
Results: We used the hepatocyte genes to infer the radial coordinate of each cell pair, yielding spatial reconstruction of NPC genes. We found a broad zonation in the expression patterns of NPCs and identified a robust expression signature for the pericentral endothelial cell niche.
Conclusion: Our approach can be used to reconstruct spatial expression maps of non-parenchymal cells in other tissues.

SAT-021
Secreted ectodomain of SIGLEC-9 and MCP-1 ameliorate acute liver failure in rats by altering bone marrow macrophage polarity
T. Ito[1], M. Ishigami[1], A. Yamamoto[2], Y. Ishizu[1], T. Kazuya[1], T. Honda[1], K. Hayashi[1], T. Ishikawa[1], Y. Hirooka[1], H. Goto[1]. *[1]Nagoya University Graduate School of Medicine, Department of Gastroenterology and Hepatology, Nagoya, Japan; [2]Tokushima University Graduate School, Department of Oral histology, Institute of Biomedical Science, Tokushima, Japan*
Email: tahkun56@gmail.com

Background and Aims: Acute liver failure (ALF) induces a poorly controlled inflammation, extensive hepatic destruction, and leads to multiple organ failure and sudden death. We previously reported that an intravenous administration of serum-free conditioned medium from stem cells derived from human exfoliated deciduous teeth (SHED-CM) improves the liver injury in the D-galactosamine (D-Gal)-induced rat ALF model. Furthermore, we recently revealed that a set of specific anti-inflammatory/tissue-regenerative macrophage (Mφ) inducers, monocyte chemoattractant protein-1 (MCP-1) and the secreted ectodomain of sialic acidbinding Ig-like lectin-9 (sSiglec-9), identified from SHED-CM ameliorates rat ALF. However, the detailed mechanism to activate intrahepatic Mφ by these two proteins is unclear. Therefore, we investigated the mechanism of MCP-1/sSiglec-9 treatment in this study.
Method: Rat ALF was induced by intraperitoneal injection of D-gal. 24-hours after D-Gal injection, MCP-1/sSiglec-9 with/without $CD206^{+}$Mφ-depletion reagent (mannosylated clodronate liposomes, m-Clodrosome), or PBS, was injected into the tail vein. We assessed serum transaminase levels, liver histopathology, and gene expression with real time RT-PCR. In addition, bone marrow Mφ or resident Kupffer cells of rat were isolated in vitro. Theses cells' morphologies and mRNA expression were examined, and proteins of these supernatants were measured by ELISA.
Results: We found that an intravenous injection of MCP-1/sSiglec-9 markedly decreased the AST and ALT levels ($p < 0.05$), and suppressed the hepatic inflammation and destruction. Conversely, treatment with m-Clodrosome abolished the MCP-1/sSiglec-9-mediated recovery from ALF. mRNA levels of anti-inflammatory markers, IL-10, Arginase-1, Ym-1 and TGF-β, were significantly elevated in MCP-1/sSiglec-9 group ($p < 0.01$), but not treatment with m-Clodrosome group. In addition, MCP-1/sSiglec-9 promoted M2-like differentiation of bone marrow-derived Mφ in vitro. However, these proteins had no effect on resident Kupffer cells. The CM from MCP-1/sSiglec-9-activated bone marrow-derived Mφ showed higher concentration of HGF compared with control.
Conclusion: The unique combination of MCP-1/ sSiglec-9 ameliorates rat ALF through the induction of anti-inflammatory/tissue-repairing macrophages, mainly induced from bone-marrow cells, not resident Kupffer cells.

SAT-022
Elevated programmed death ligand 2 (PDL2) in macrophages of BALB/c mice model of liver fibrosis associated with decreased CD80 and IL12 expressions
J. Amer[1], W. Basha[1], S. Hattab[2]. *[1]An Najah National University, Faculty of Medicine and Health Sciences, Nablus, Palestine; [2]An Najah National University, Faculty of Medicine and Health Sciences, Jerusalem, Palestine*
Email: j.amer@najah.edu

Background & Aims: BALB/c mice have been shown to easily induce Th2 type responses in several infection models. Certain macrophage phenotypes contribute to liver fibrosis. Upon injury the changing tissue microenvironment alters their phenotype and primes infiltrating monocytes toward pro-inflammatory macrophages. Here, we characterized changes in macrophages phenotype (M1/M2) during fibrogenesis in a mice model of liver fibrosis.
Methods: Carbon-tetrachloride (CCl_4) hepatic-fibrosis was induced in Balb/c-mice for 4 weeks through i.p injections/2x week. Along 1th to 4th weeks liver macrophages were isolated and were identified by the flow cytometry as CD45+/CD16+/CD68+. M1/M2 model of macrophage polarization was determined by CD80/CD273 (programmed death ligand 2 (PDL2)), respectively. Liver proteins were quantified for αSMA expressions by western blot and RT PCR, respectively. Livers were also assessed histologically and serum ALT levels were estimated.
Results: Hepatic fibrosis were gradually increased along 4 weeks injections of CCl_4 as indicated by serum ALT levels and αSMA expressions ($p < 0.02$) as well as H&E staining of liver necro-inflammatory lesions. These results were associated with increase in liver CD273 (M2 macrophage subpopulation) expressions (from 20.1% ± 3.1in naïve mice to 27.8% ± 3.2 in fibrotic mice; $p = 0.01$), however, no significant changes were observed between the mice groups of the different changes in fibrosis severity. On the other hand, gradual decrease in CD80 expressions (M2 macrophage subpopulation) were seen along fibrosis progressions (From 12% ± 6.2 in naïve mice to 1.97% ± 0.4 in fibrotic mice; $p < 0.02$). The overall data showed a decrease in M1/M2 macrophage ratio in BALB/c mice model of liver fibrosis indicating a reduced differentiation of M1 macrophages. These results were accompanied with inhibited expressions in M2 macrophages IFN-γ and IL-12 while high levels of TGF-β.
Conclusion: The known anti-inflammatory M2 macrophages were predominated prior and during liver injury. Although they were elevated by count during fibrosis, they secreted less IFN-γ and IL-12 which might indicate inability of differentiation of naïve T cells into Th1 cells. Our data could suggest pro-fibrotic role of M2 macrophages through their productions of TGF-β with reduced M1 pro-inflammatory macrophages.

SAT-023
WISP1: A novel key protein in acute liver damage
D. González, G. Campos, K. Rochlitz, J.G. Hengstler, P. Godoy. *IfADo-Leibniz Research Centre for Working Environment and Human Factors at the Technical University Dortmund, Toxicology, Dortmund, Germany*
Email: gonzalez@ifado.de

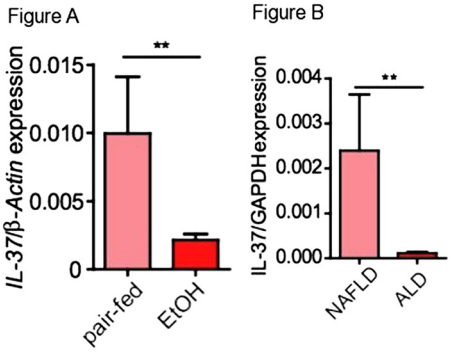
Background and Aims: Matricellular proteins from the CCN family have emerged as multitasking intermediators and have been shown to play different roles in liver pathophysiology. These highly conserved secreted proteins specifically interact with and signal through various extracellular partners, in particular integrins, which enable them to play crucial roles in various processes including development, angiogenesis, wound healing and diseases such as fibrosis and cancer. We have discovered that WISP1 (Wnt-induced secreted protein-1) also named CCN4, is induced upon intoxication and may play a protective role in liver pathophysiology. Furthermore, deletion of WISP1 leads to increased damage after acute liver injury by the hepatotoxicant CCl_4 compared with their wild type counterparts. In this context, we aim to understand how WISP1 might be

playing its hepatoprotective role studying WISP1 knock out (KO) mice.
Method: To establish the role of WISP1 in acute liver damage we used a knockout mouse model and we performed a time course after CCl_4 intoxication (460 mg/kg, i.p.) by collecting liver tissue at 30 min, 2 h, 8 h, 12 h, 18 h, and day 1. Damage was analyzed by necrotic area in hematoxylin & eosin staining and by transaminase activity. Different signal pathways were asses by western blot and the inflammatory state by real-time PCR of different cytokines and by immunostaining to detect immune cell infiltration. Re-introduction of WISP1 in KO mice was done by using a recombinant adeno-associated viral vector serotype 8. Different liver cell isolation was done using magnetic beads and macrophage depletion was performed by clodronate liposomes.
Results: Deletion of WISP1 led to a significant increase of necrotic area at d1 reaching 49% in KO vs 27% in WT mice. Importantly WT and WISP1 KO mice showed no significant differences in CYP2E1 expression, suggesting that the difference in tissue injury does not depend on alterations of CCl_4 metabolism in KO mice. Western blot analysis showed marked alterations in signal transduction pathways in liver tissue of WISP1 KO mice, with stronger activations of p-JNK at 2 h and p-STAT3 at 18 h and day 1. Furthermore, deletion of WISP1 leads to higher expression of inflammatory cytokines such us TNF and IL-6 and immune cell infiltration at 18h. Re-expression of WISP1 in WISP1 KO hepatocytes did not rescue the phenotype maybe due to the non-detectable WISP1 secretion in plasma. Liver cells isolation and WISP1 expression analysis showed a higher expression of WISP1 in liver sinusoidal endothelial cells and Kupffer cells compared to hepatocytes, supporting that hepatocytes are not the main source of WISP1 and non-parenchymal cells may play an important role in WISP1 expression-function in liver damage.
Conclusion: In conclusion, WISP1 is an interesting novel target in acute liver damage but further investigation is still need it.

SAT-024
Ethanol dampens IL-37 expression in liver tissue

F. Grabherr, G. Christoph, T. Adolph, V. Wieser, L. Mayr, M. Sangineto, S. Macheiner, A. Viveiros, H. Zoller, A. Moschen, H. Tilg. *Medical University Innsbruck, Department of Internal Medicine I, Gastroenterology, Endocrinology & Metabolism, Innsbruck, Austria*
Email: felix.grabherr@student.i-med.ac.at

Background and Aims: Hepatic inflammation is a driving force in alcoholic liver disease (ALD). Interleukin-37 (IL-37) is an anti-inflammatory member of the IL-1 family. It was described that IL-37 exerts this anti-inflammatory effects in hepatic diseases, however it is not known if IL-37 has an impact on ALD. In this study, we addressed the role of IL-37 in ALD.
Method: To address if IL-37 plays a role in the development of ALD we used IL-37 expressing transgenic mice and human recombinant IL-37 in different models of alcoholic liver disease, additionally *IL-37* expression was measured in liver samples of patients suffering from alcoholic steatohepatitis and of non-alcoholic fatty liver disease patients.



Results: IL-37 tg mice are not protected against hepatic injury and inflammation in experimental models of ALD. *IL-37* expression was suppressed in IL-37 transgenic mice (Figure A). Patients with ASH exhibited similarly reduced *IL-37* expression when compared to NAFLD patients (Fig. B). In a murine binge drinking model of ALD human recombinant IL-37 ameliorated hepatic inflammation.
Conclusion: We provide evidence for an exogenous noxae that suppresses Interleukin 37 expression which limits its anti-inflammatory effects in alcoholic liver disease.

SAT-025
Serum CXCL14 chemokine as a biomarker during murine acute and chronic hepatitis

C. Devisme, V. Carriere, V. Genet, M. Farooq, J. Le Seyec, C. Piquet-Pellorce, M. Samson. *IRSET - U.1085 Inserm, Rennes, France*
Email: michel.samson@univ-rennes1.fr

Background and Aims: Inflammation of liver is characterised by immune cells recruitment and release of chemokines. CXCL14, also called BRAK (breast and kidney cancer), is a chemokine poorly studied due to lack of knowledge of its specific receptor. In hepatic field, an up-regulation of CXCL14 mRNA has been reported in CCL4-induced liver injury in mice. However no information about the CXCL4 protein is announced. We aim to study the expression of CXCL14 protein in hepatitis developing murine models.
Method: We develop various *in vivo* models in C57Bl/6 mice: Concanavalin A-induced and murine hepatitis virus type 3 (MHV-3)-induced acute hepatitis, CCL4-induced chronic hepatitis and High Fat Diet-Induced chronic non-alcoholic steatohepatitis (NASH). Furthermore, we perform primary mouse hepatocytes (PMH) culture infected or not by MHV3 during 4 hours. ELISA, RT-qPCR, AST/ALT measurements, histology have been performed. Comparisons of parameters between two different groups were analysed by the Student t-test.
Results: Level of CXCL14 in sera of mice with acute and chronic hepatitis is increased in comparison with untreated mice. This is correlated with the increase of AST/ALT. In acute hepatitis induced by MHV3 infection, plasmatic concentration of CXCL14 is ≈10 000 pg/mL at 72 hours post-infection. Same results are observed in other acute hepatitis model as ConA administration. In chronic CCL4-induced hepatitis, serum CXCL14 concentration is ≈1000 pg/mL and remains constant during treatment. Beside, level of CXCL14 is not correlated with the progression of fibrosis, as observed by Sirius red labelling.
We found that infection of primary mouse hepatocytes by MHV3 did not induce CXCL14 mRNA expression but the lysis of MHV3 infected PMH allows a release of CXCL14 in conditioned media at 48 hours post-infection.
Conclusion: Our *in vivo* data show that CXCL14 chemokine is released in sera during acute and chronic hepatitis in mice. We show that hepatocytes could be a source of CXCL14 since virus-infected hepatocytes release CXCL14. CXCL14 is therefore a new biomarker linked to hepatitis, and could be involved in the development of the liver diseases.

SAT-026
Autophagy-related liver enzymes in chronic liver disease

G. Notas[1], D. Samonakis[2], M. Koulentaki[3], I. Voumvouraki[3], E. Kouroumalis[4]. *[1]University of Crete Medical School, Laboratory Medicine, Heraklion, Greece; [2]University Hospital of Heraklion, Dept of Gastroenterology, Heraklion, Greece; [3]University Hospital, Gastroenterology, Heraklion, Greece; [4]University of Crete Medical School, Gastroenterology, Heraklion, Greece*
Email: kouroumi@uoc.gr

Background and Aims: Autophagy, the fusion of phagosomes with lysosomes is an important mechanism in hepatic homeostasis. Abnormalities of this process are associated with liver diseases,

particularly non alcoholic steatohepatitis. Autophagy in other chronic liver diseases has not been adequately studied. Therefore the aim of the study was the quantification in liver tissue from chronic liver disease patients of the vital for normal autophagy enzyme cathepsin B1 and two lysosomal acid hydrolases, Cathepsin D and acid Lipase.

Method: We studied liver biopsy tissue from 18 patients with Primary Biliary Cholangitis (PBC) (16 females, 7 early stages I-II and 11 late stages III-IV) 34 with Alcoholic Liver Disease (14 Fatty Liver, 8 steatohepatits and 12 cirrhotics) and 13 patients with chronic viral hepatitis (CH). Controls were 5 patients with a normal liver biopsy.

Enzyme substrates were: a-N-benzoyl-DL-arginine 2-naphtylamide for cathepsin B1, 14C haemoglobin for cathepsin D and methyl umbelliferone oleate for acid lipase.

One-way Anova with Dunn post-hoc test was used for statistical analysis.

Results: Cathepsin B1 activity was significantly increased in early PBC (252 ± 65 ng/mg Protein/min^{-1}, $p < 0.01$) and reduced in late stages (70 ± 14. $p < 0.01$) compared to the normal liver (128 ± 13). It was also reduced in alcoholic steatohepatitis and cirrhosis (90 ± 12 $p < 0.05$ and 75 ± 17 $p < 0.05$ respectively) but not in CH (130 ± 45). Cathepsin D activity was increased in early PBC ($38.2 \pm 4.8.10^3$ $p < 0.001$) and less so in late stages (18.9 ± 1.4 $p < 0.05$), compared to controls (13.1 ± 2.2). It was also significantly increased in the presence of histological necroinflammation (Alcoholic hepatitis: $24.5.10^3$ dpm/mg Protein/hr^{-1}, $p < 0.01$, active alcoholic cirrhosis: 20 ± 3.6, $p < 0.05$, CH: 27.5 ± 6.8, $p < 0.01$) compared to both normal liver and inactive alcoholic cirrhosis (12.8 ± 4.5). Acid lipase activity changes paralled those of Cathepsin B1.

Conclusion: (1) A reduction of Cathepsin B1, a vital autophagic enzyme is associated with fibrosis in parallel with Acid Lipase in patients with chronic liver disease, possibly indicating a defective autophagy during the fibrotic process (2) The highly increased activity levels in early PBC might indicate an overactive autophagic process early in this autoimmune disease (3) The acid protease Cathepsin D is probably involved with the development of necroinflammation.

Rare liver diseases (including paediatric and genetic)

SAT-027

Precision medicine targeting disrupted IGF signaling in hepatoblastoma

O. Kuchuk[1,2], N. Akers[1,3], D. Sia[1,4], M. Simon-Coma[5,6], J. Carrillo[5,6], I. Martinez-Quetglas[1,4], M. Gambato[7], L. Royo[5,6], S. Yoo[3,8], M.-A. Buendia[9], S. Cairo[10], J. Zhu[3,8], V. Mazzaferro[2], B. Losic[1,3], C. Armengol[5,6], J. Llovet[1,11,12]. *[1]Mount Sinai Liver Cancer Program, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, Divisions of Liver Diseases, Department of Medicine, Department of Pathology, Recanati Miller Transplantation Institute, New York, United States; [2]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [3]Icahn Institute for Genomics and Multiscale Biology, New York, United States; [4]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, CIBERehd, Universitat de Barcelona, Liver Cancer Translational Research Laboratory, Barcelona-Clínic Liver Cancer, Barcelona, Spain; [5]Health Sciences Research Institute Germans Trias i Pujol (IGTP), Childhood Liver Oncology Group (c-LOG), Badalona, Spain; [6]CIBERehd, Barcelona, Spain; [7]Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua University Hospital, Padua, Italy; [8]Icahn School of Medicine at Mount Sinai School of Medicine, Department of Genetics and Genomic Sciences, New York, United States; [9]Centre Hepatobiliaire Paul Brousse, Villejuif, France; [10]XenTech, Evry, France; [11]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, CIBERehd, Universitat de Barcelona, Liver Cancer Translational Research Laboratory, Barcelona-Clínic Liver Cancer, Barcelona, United States; [12]Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain*
Email: olga.kuchuk@mssm.edu

Background and Aims: Hepatoblastoma (HB) is the most common primary liver cancer in pediatric patients. Surgery and chemotherapy are the mainstay therapies. No molecular targeted therapy is available for tumors at advanced stages. Thus, the identification of actionable drivers is an unmet medical need. Here, we aimed to identify the most prevalent targetable drivers in HB and evaluate therapeutic potential of precision therapies.

Method: Tumors and paired non-tumor (NT) tissues from 32 HB patients were profiled by RNA-seq and gene copy number (GCN) analysis to define the top disrupted signaling pathways. Levels of *IGF2* mRNA transcripts derived from adult (*P1*) or fetal (*P3*) promoters, *IGF1R,* and *H19* expression were assessed by RT-qPCR in human tissues and cell lines. Survival of HepG2 and HUH6 HB cells was tested *in vitro* in presence of xentuzumab, an anti-IGF1/2 monoclonal antibody.

Results: Transcriptomic analysis of HB samples revealed deregulation of multiple signaling networks, being protein ubiquitination, immune signaling and IGF pathway (FDR = 0.001) among the top ones. RT-qPCR confirmed overexpression of *P3* (>20 fold-change (FC), 78%) and *IGF1R* (5 FC, 41%), and down-regulation of *P1* (96%) and *H19* (78%) about 15 FC in HB vs NT ($p < 0.001$). GCN analysis showed allelic imbalance of a minimal region of 3.9Mb at 11p15 region, encoding for IGF2, H19, and imprint controlling regions, in 42% of HB. Epigenetic analysis of the remaining HB samples revealed hypermethylation of *P1* in 78% and hypomethylation of *P3* in 36% compared to NT. No changes in methylation were observed in 14% of HB vs NT. These results suggest a double mechanism of IGF signaling upregulation due to aberrant methylation of IGF2 promoters and allelic imbalance. HepG2 and HUH6 recapitulated the expression profile of HB tumors overexpressing *P3* and *IGF1R* (both >55 fold-change) and down-regulating *H19.* None of the cell lines expressed *P1.* Treatment with xentuzumab decreased viability of HepG2 and HUH6 to 66% ($p = 0.01$) and 77% (ns), respectively. Moreover, it reduced the amount of HepG2 colonies to 26% ($p < 0.0001$). At the protein level, xentuzumab blocked IGF1R phosphorylation preventing activation of the pathway without interfering with insulin receptor-metabolic effects.

Conclusion: IGF2 is overexpressed in 78% of HB tumors, either as a result of allelic imbalance or aberrant methylation. In experimental studies, targeted blocking of IGF1/2 with xentuzumab had potent antiproliferative effects on HB cells. Further *in vivo* studies are currently ongoing to assess the anti-cancer efficacy of xentuzumab.

SAT-028

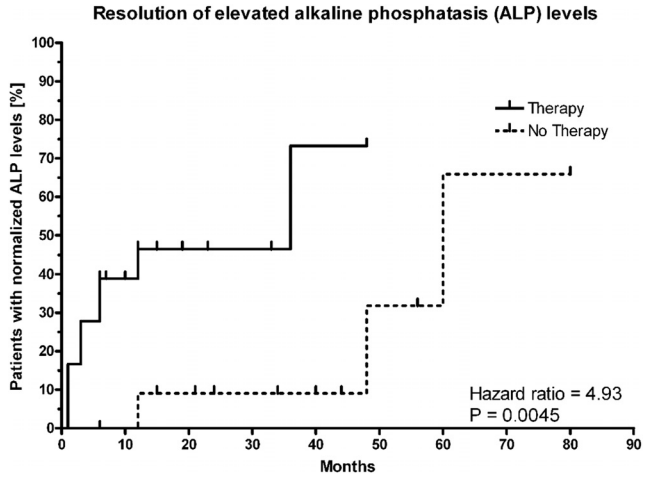
Clinical presentation, natural history and treatment of hepatic sarcoidosis: A case-series of 39 patients with histologically proven hepatic sarcoidosis

M. Wehmeyer[1], J. Lutz[1], J.S.Z. Wiesch[1], A.W. Lohse[1], C. Schramm[1,2], M. Sebode[1]. *[1]University Medical Center Hamburg-Eppendorf, I. Department of Medicine, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Martin Zeitz-Centre for Rare Diseases*
Email: m.wehmeyer@uke.de

Background and Aims: Sarcoidosis is a multisystem-disease of unknown origin with possible liver involvement. The aim of our study was to describe the natural history, effect of therapy and predictors of liver related morbidity in patients with hepatic sarcoidosis.

Method: In total, 39 patients with hepatic sarcoidosis underwent liver-biopsy between January 2009 and October 2017 at our center. Clinical and laboratory parameters at the time of biopsy were analyzed by univariate analysis to identify risk factors for hepatic fibrosis or cirrhosis. The course of the liver enzymes until October 2017 was compared between patients who received treatment for

sarcoidosis and untreated patients. The endpoint were normalized liver enzyme levels (AST, ALT, gGT, ALP) during follow-up.
Results: The mean age of patients was 44 years, 72% were male (n = 28), 46% had no fibrosis (F0; n = 18), 39% had F1 fibrosis (n = 15), 5% F2 fibrosis (n = 2) and 10% had cirrhosis (F4; n = 4). Pulmonary sarcoidosis was present in 31 patients, peritoneal and splenic sarcoidosis could be diagnosed in 7 patients, each. Patients with cirrhosis were older (mean age 62 years vs. 42 years; p < 0.001) and had a higher AST/ALT-ratio (median AST/ALT-ratio 1.24 vs. 0.67; p = 0.005) than non-cirrhotic patients. AST, ALT, gGT and ALP levels did not correlate with the degree of fibrosis. The AST/ALT-ratio (r = 0.519; n = 0.001), but not the APRI-score (r = 0.135; n = 0.413) correlated with the degree of fibrosis. Follow-up data were available of 11 patients who never received treatment, 8 patients who started treatment during follow-up and 15 patients who started treatment after biopsy. 20/23 patients received steroids ± MTX/azathioprine ± ursodeoxycholic acid (UDCA) and 3 patients where treated with UDCA alone. The median follow-up time was 22 months (no therapy; range 6-99) and 23 months (with therapy; range 6–94). 18 patients without therapy and 18 patients with therapy had an elevated ALP at baseline or before initiation of therapy (median AP 207 and 212U/l). 3 patients without therapy and 8 patients who received treatment achieved normalized ALP-levels during follow-up (p = 0.005; Figure 1).



Conclusion: Hepatic sarcoidosis can lead to fibrosis and cirrhosis in a relevant number of patients. The AST/ALT-ratio was superior to other laboratory tests to identify patients with cirrhosis. Immunosuppressive treatment may lead to a biochemical remission in a considerable proportion of patients.

SAT-029

Upregulation of miR-34c driven by JNK and FOXO3 in livers expressing mutant Z alpha1-antitrypsin

P. Piccolo[1], A. Barbato[1], F. Borel[2], P. Annunziata[1], S. Attanasio[1], R. Ferriero[1], A. Carissimo[3], S. Campione[4], L. Quagliata[5], L.M. Terracciano[5], J. Teckman[6], C. Mueller[7], N. Brunetti-Pierri[1,8].
[1]Telethon Institute of Genetics and Medicine (TIGEM), Molecular Therapy, Pozzuoli, Italy; [2]UMass Medical School, Department of Pediatrics and Horae Gene Therapy Center, Worcester, United States; [3]Telethon Institute of Genetics and Medicine (TIGEM), Bioinformatic Core, Pozzuoli; [4]Cardarelli Hospital, Pathology Unit, Naples, Italy; [5]Basel University Hospital, Institute of Pathology, Molecular Pathology Division, Basel, Switzerland; [6]Saint Louis University School of Medicine, Department of Pediatrics, St. Louis, MO, United States; [7]UMass Medical School, Department of Pediatrics and Horae Gene Therapy Center, Worcester, MA, United States; [8]Federico II University, Department of Translational Medicine, Naples, Italy
Email: piccolo@tigem.it

Background and Aims: The deficiency of α1-antitrypsin (AATD) affects ~1 in 3,000 live births and present with lung and liver disease. The common and severe Z allele of α1-antitrypsin (ATZ) causes the protein to form polymers that are retained within the endoplasmic reticulum of hepatocytes. Accumulation of the mutant protein causes liver damage, cirrhosis, and hepatocellular carcinoma (HCC) whilst the lack of circulating α1-antitrypsin predisposes to early onset emphysema. MiRNAs play key roles in a wide range of biological processes and their expression is affected in several liver diseases. Alterations of miRNA expression have not been investigated so far in AAT liver disease. We hypothesized that miRNAs play a role in the pathogenesis of the liver disease. Moreover, the identified miRNAs may inform novel therapeutic targets and disease biomarkers.
Method: Transgenic PiZ mice have been genetically engineered to express ATZ and have been a valuable experimental model for liver disease due to AAT polymerization. In these mice we studied liver miRNA expression by next generation sequencing (NGS). In vivo ATZ silencing and Laser Controlled Microdissection (LCM) were used to correlate ATZ load with miR-34c expression. PiZ/*Jnk1*$^{-/-}$ mouse was generated to investigate miR-34c regulation by JNK/FOXO3 axis. Human liver specimens from AATD patients and controls were used to assess the clinical relevance of our findings.
Results: A comprehensive analysis of liver miRNome revealed a set of miRNAs with differential expression between control and PIZ mice expressing ATZ. Among these, miR-34c was strongly upregulated and its levels correlated with the levels of intrahepatic ATZ. Expression of miR-34c is driven by Forkhead box O3 (FOXO3) and mechanistically, we found that FOXO3 activation and miR-34c upregulation were dependent upon c-Jun N-terminal kinase (JNK) phosphorylation on Ser574 residue. FOXO3 activation was lost in HCC of mice expressing ATZ. Liver specimens from AATD patients revealed the same alterations in JNK/FOXO3/miR-34c pathway found in mice.
Conclusion: Our study unravels novel insights on the pathogenesis of liver disease and HCC due to ATZ and provides a set of clinically relevant data for the development of disease biomarkers that are highly needed for AATD.

SAT-031

Refinement of diagnostic criteria and frequency estimation of LPAC syndrome: A French multicenter study

D. Catherine[1], C. Bertrand[2], P.-C. Magali[3], P. Pascal[4], C. Yves[5], N. Béatrice[6], H. Marie-Pierre[7], B. Véronique[8], M. Anware[9], G. Farid[1], C. Housset[1,5], R. Poupon[1,10], Z. David[11], O. Chazouillères[1,10], C. Corpechot[1,10]. *[1]Saint-Antoine Hospital, Assistance Publique, Hôpitaux de Paris, Reference center for inflammatory biliary diseases and autoimmune hepatitis, Paris, France; [2]French Polynesia Hospital, Hepatology and Gastroenterology, Papeete, France; [3]Aix-en-Provence Hospital, Hepatology and Gastroenterology, Aix en Provence, France; [4]Orléans Hospital, Hepatology and Gastroenterology, Orléans, France; [5]Pierre and Marie Curie University, Inserm UMR_S938, Paris, France; [6]Saint-Antoine Hospital, Assistance Publique - Hôpitaux de Paris, Radiology, Paris, France; [7]Saint-Camille Hospital, Radiology, Bry-sur-Marne, France; [8]Saint-Antoine Hospital, Assistance Publique, Hôpitaux de Paris, Molecular Biology, Paris, France; [9]Saint-Camille Hospital, Digestive surgery, Bry-sur-Marne, France; [10]Pierre and Marie Curie Paris 6 University, Inserm UMR_S938, Paris, France; [11]Saint-Camille Hospital, Hepatology and Gastroenterology, Bry-sur-Marne*
Email: christophe.corpechot@aphp.fr

Background and Aims: Diagnostic criteria of low-phospholipid associated cholelithiasis (LPAC) syndrome have been defined from very limited populations of patients and controls (Rosmorduc et al. 2003). These criteria mostly rely on the recurrence of biliary pain after cholecystectomy while surgery could be avoided if diagnosis was made earlier. Furthermore, they were originally established to predict ABCB4 alteration that is absent in more than half of patients. At last, the prevalence of the syndrome is unknown. Our primary aim was therefore to refine the diagnostic criteria of LPAC syndrome from

large populations of patients and controls, regardless of ABCB4 status. Our secondary aim was to estimate the frequency of the syndrome among patients with symptomatic cholelithiasis.
Method: This retrospective case-control study included all patients diagnosed with LPAC syndrome based on original criteria in 4 French centers (one referral center and 3 general hospitals). Patients who underwent cholecystectomy for classical gallstone disease in a general hospital served as controls. A multivariate logistic regression model adjusted on age, sex, body mass index, and metabolic syndrome was used to identify the variables independently associated with LPAC syndrome. A diagnostic score was developed and validated. Patients were compared according to ABCB4 mutation status. Frequency of LPAC syndrome was estimated based on the number of all patients cholecystectomized for gallstones during the same period.
Results: 512 adult patients (306 cases, 206 controls) were included. In addition to the 3 previously established criteria (age at first symptoms <40; recurrence of symptoms after cholecystectomy; ultrasound signs of intrahepatic microlithiasis), 2 new criteria were identified: (1) features suggestive of common bile duct lithiasis, (2) lack of cholecystitis evidence. The new score had a high diagnostic performance (c-statistic: 0.99). ABCB4 mutation was present in 43% of LPAC patients. These patients had an increased risk of intrahepatic cholestasis of pregnancy (ICP; 34% vs. 17%), chronic elevation of GGT (33% vs. 14%) and transaminases (16% vs. 8%), history suggestive of common bile duct lithiasis (80% vs. 68%), and personal or familial history of primary liver cancer (6% vs. 1%). One (1.5%) out of 68 controls who had an expert ultrasound focused on signs of intrahepatic microlithiasis showed typical features of LPAC syndrome. In line with this, the frequency of LPAC syndrome within all patients with symptomatic cholelithiasis varied from 0.5% to 1.9%.
Conclusion: Common bile duct stone in young patients with no prior history of cholecystectomy should suggest LPAC syndrome. LPAC patients with ABCB4 alteration seem more exposed to the risk of ICP, chronic cholestasis, and personal or familial primary liver cancer. LPAC syndrome represents about 1% of patients with symptomatic cholelithiasis.

SAT-032

Role of alpha-1 antitrypsin genotypes in the progression of adult liver disease

V. Pereira[1], R. Gaspar[2], C. Simões[3], L. Maia[4], D. Costa[5], J. Carvão[1], A. Oliveira[1], G. Serrão[6], V. Jesus[7], M.C. Sucena[8], C. Santos[9], J. Gomes[10], J. Lages[11], I. Abreu[12], S. Freitas[13], S. Carvalhana[14], M. Mandorfer[15], H. Cortez-Pinto[14], G. Macedo[11], M. Trauner[15], R. Liberal[16], L. Jasmins[17].
[1]Centro Hospitalar do Funchal, Gastroenterology Department, Funchal, Madeira, Portugal, [2]Gastrenterology Department, Centro Hospitalar de São João, Faculty of Medicine of Porto University, Porto, Portugal; [3]Centro Hospitalar Lisboa Norte, Gastroenterology Department, Lisboa, Portugal; [4]Gastrenterology Department, Centro Hospitalar do Porto, Porto, Portugal; [5]Gastrenterology Department, Hospital de Braga, Braga, Portugal; [6]Gastroenterology Department, Centro Hospitalar do Funchal, Funchal, Portugal; [7]Pneumology Department, Centro Hospitalar do Funchal, Funchal, Madeira, Portugal; [8]Centro Hospitalar de São João, Faculty of Medicine of Porto University, Pneumology Department, Porto, Portugal; [9]Centro Hospitalar Lisboa Norte, Pneumology Department, Lisboa, Portugal; [10]Centro Hospitalar do Porto, Pneumology Department, Porto, Portugal; [11]Pneumology Department, Hospital de Braga, Braga, Portugal; [12]Clinical Pathology Department, Funchal Central Hospital, Funchal, Madeira Island, Portugal; [13]Centro Hospitalar do Funchal, Centro de Investigação, Funchal, Madeira, Portugal; [14]Gastrenterology Department, Centro Hospitalar Lisboa Norte, Lisboa, Portugal; [15]Division of Gastroenterology and Hepatology, Department of Internal Medicine III, Medical University Vienna, Vienna, Austria; [16]Centro Hospitalar de São João, Faculty of Medicine of Porto University, Gastroenterology Department, Porto, Portugal; [17]Gastroenterology Department, Centro Hospitalar do Funchal, Funchal, Madeira, Portugal
Email: magnovitorp@gmail.com

Background and Aims: Alpha-1 antitrypsin deficiency (A1AD) is an autosomal codominant disease associated with an increased risk of liver and lung disease in adults. The association between liver disease and homozygosity for the mutant Z allele (PiZZ) is well-established, however, the contribution of other genotypes to the pathogenesis of adult liver disease is unclear. We aimed to assess the prevalence of liver fibrosis in different A1AD genotypes, including rare variants.
Method: Multicenter cross-sectional case-control study, including adult A1AD patients treated in pneumology departments of four Portuguese academic and one non-academic centers. Data pertaining pulmonary function and imaging were retrospectively collected. Clinical, biochemical, and liver stiffness (LS) measured by transient elastography (TE, Fibroscan) data were prospectively collected at time of enrollment. Significant liver fibrosis was defined by LS values ≥7.0 kPa. Patients with concomitant liver diseases were excluded. Controls were recruited within a prospective epidemiological study in the general adult population.
Results: 142 cases and 200 controls were included. Our study comprised 47 PiZZ, as well as 76 PiZ heterozygotes (38 MZ, 34 SZ, 3 MheerlenZ, 1 ZQ0s), 10 PiS (5 SS, 5 MS), and 9 PiMmalton or PiMpalermo carriers. Cases and controls did not differ in terms of age, BMI, alcohol consumption, serum lipid levels, or CAP. Cases had significantly higher serum levels of ALT, AST and GGT ($p < 0.0001$) compared to controls. CAP values were higher in A1AD patients but the difference did not attain statistical significance ($p = 0.114$).
LS was 5.2 ± 1.5 kPa in controls and 6.0 ± 4.1 kPa in A1AD ($p = 0.046$) being highest in PiZZ (7.3 ± 5.3 kPa) and PiZ heterozygotes (5.7 ± 3.6 kPa). Liver fibrosis was detected in 20% (29/142) of patients. The genotype-specific prevalence was: PiZZ 34%(16/47), PiZ- 16%(12/76), while none of the PiS carriers had significant liver fibrosis. Among patients with rare A1AD variants, one PiMmalton/PiMmalton had significant liver fibrosis. Liver fibrosis was statistically significantly associated with lower alpha-1 antitrypsin ($p < 0.0001$) and higher total cholesterol ($p = 0.024$). Importantly, only 18% (26/142) of patients with liver fibrosis had abnormal liver tests.

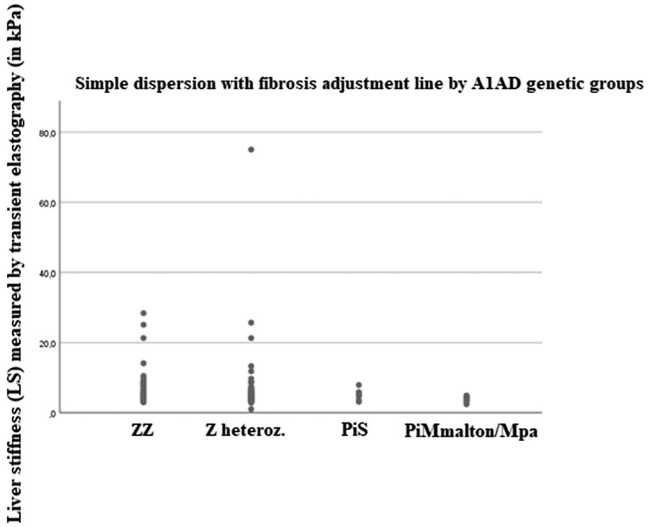


Figure 1: Liver fibrosis by alpha-1 antitrypsin deficiency genetic group.

Conclusion: Akin to PiZZ, PiZ heterozygoty is associated with liver fibrosis development. Moreover, our results suggest that rare A1AD variants may also promote liver fibrogenesis. Routine laboratory tests are not predictive of significant liver fibrosis, highlighting the need for non-invasive methods such as TE in patients with A1AD.

SAT-033

Genetic ablation of CHOP decreases hepatic accumulation of mutant Z alpha1-antitrypsin

S. Attanasio[1], R. Castello[2], N. Pastore[2], P. Piccolo[1], N. Brunetti-Pierri[1,3].
[1]*Telethon Institute of Genetics and Medicine, Pozzuoli (NA), Italy, Molecular therapy, Pozzuoli (NA);* [2]*Telethon Institute of Genetics and Medicine, Pozzuoli (NA), Italy, Scientific Office, Pozzuoli (NA), Italy;* [3]*University of Naples "Federico II", Department of Translational Medicine, Napoli, Italy*
Email: s.attanasio@tigem.it

Background and Aims: Alpha1-antitrypsin deficiency (AATD) is one of the most common genetic disorders resulting in lung and liver diseases. The vast majority of patients carry the Z mutation in the serine protease inhibitor 1A (*SERPINA1*) gene that results in a single glutamic acid to lysine substitution at amino acid position 342. The mutant Z alpha1-antitrypsin (ATZ) accumulates in the endoplasmic reticulum (ER) of hepatocytes resulting in liver disease that is a prototype of conformational disorder due to protein misfolding and protein aggregation. Although ATZ accumulation causes ER stress, the role of unfolded protein response (UPR) has been controversial in the last years. The aim of this study is to investigate the role of the transcription factor CHOP in the pathogenesis of liver disease due to ATZ accumulation.
Method: We used as mouse model the transgenic PiZ mice, genetically engineered to express the human ATZ. We generated PiZ/*Chop*$^{-/-}$ mouse and we investigated ATZ levels by ELISA, periodic acid–Schiff diastase-resistant (PAS-D) staining, immunofluorescence and qPCR.
Results: By expression array profiling of livers of PiZ mice, we previously found upregulation of genes associated with response to unfolded proteins, ER nuclear signaling pathway, and response to protein stimulus. Among the differentially expressed genes, we focused on *Chop* that was significantly upregulated in both mouse and human livers expressing ATZ. To investigate the role of CHOP in ATZ-induced liver damage, we crossed PiZ with *Chop*$^{-/-}$ mice to generate PiZ/*Chop*$^{-/-}$ mice. PiZ/*Chop*$^{-/-}$ mice exhibited marked reduction of PAS-D-positive globules compared to PiZ/*Chop*$^{+/+}$ control mice. *SERPINA1* mRNA levels in livers of PiZ/*Chop*$^{-/-}$ mice were also significantly reduced compared to PiZ controls suggesting that CHOP induces ATZ accumulation by increasing *SERPINA1* transcription.
Conclusion: The transcription factor CHOP has been involved in the pathogenesis of several liver disorders but not in hepatic disease induced by ATZ. The results of this study suggest that the CHOP is an important player in the disease pathogenesis and is a therapeutic target for correction of the liver disease due to ATZ expression.

SAT-034

Etiology of splanchnic vein thrombosis in 812 chinese patients from a single center

J. Fan[1], Q. Wang[1], H. Chen[1], J. Niu[1], B. Luo[1], J. Yuan[1], C. He[1], W. Bai[1], W. Guo[1], J. Tie[1], K. Li[1], X. Yuan[1], T. Yu[1], Z. Wang[1], Y. Zhu[1], N. Han[1], X. Li[1], Y. Lv[1], H. Liu[1], E. Wang[1], D. Xia[1], L. Liu[1], L. Zuo[1], Z. Yin[1], D. Fan[2], G. Han[1].
[1]*National Clinical Research Center for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Department of Liver Disease and Digestive Interventional Radiology, Xi'an;* [2]*National Clinical Research Center for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, State Key laboratory of Cancer Biology, Xi'an, China*
Email: hangh@fmmu.edu.cn

Background and Aims: In western countries, both inherited and acquired prothrombotic factors for splanchnic vein thrombosis (SVT), including Budd-Chiari syndrome (BCS) and portal vein system thrombosis (PVT), have been identified. These prothrombotic factors include factor V Leiden (FVL) mutation, prothrombin G20210A mutation, inherited antithrombin deficiency, inherited protein C or S deficiency, myeloproliferative neoplasms (MPNs), paroxysmal nocturnal haemoglobinuria (PNH), antiphospholipid syndrome (APS), etc, of which MPNs are the leading cause with a prevalence ranging between 20%–50%. However, the data regarding aetiological distribution in Chinese SVT patients are extremely limited. The aim of this observational study is to investigate the risk factors in chinese SVT patients systematically.
Method: Between July 1999 and July 2017, 985 patients with a diagnosis of non-malignant and non-cirrhotic PVT or primary BCS were consecutively admitted to our department. Since March 2012, all of these patients who were consecutively admitted to our department or regularly followed up were invited to participate in our study to evaluate the prothrombotic factors.
Results: A total of 812 patients with SVT were enrolled including 394 with PVT and 418 with BCS. Hepatic vein (HV)-type, combined-type and inferior vena cava (IVC)-type were involved in 114 (27%), 191 (46%) and 113 (27%) of these 418 patients with BCS. Among all of the 812 patients with SVT, FVL or prothrombin gene G20210A mutation, MPL mutation, JAK2 exon12 mutation, PNH and Systemic disorders were rarely observed and their prevalence ranged from 0 to 2%. Among patients with PVT, MPNs were diagnosed in 102 of the 361 patients tested (28.3%), in which the prevalence of JAK2V617F and CALR mutation were 22.9% and 3.5%, respectively. Among all of the patients with BCS, MPNs were diagnosed in only 24 of 384 patients tested (6.3%). However, in the subgroup of patients with HV-type of BCS, MPNs were diagnosed in 15 of the 51 patients confirmed by bone marrow biopsy and the prevalence of MPNs in HV-type was significantly higher than combined-type or IVC-type of BCS (29.4% vs 10.7% or 0%, $p < 0.001$).

Table. Prothrombotic Factors in Patients with different types of Budd-Chiari Syndrome.

Risk Factor	HV-type (n=114)	Combined-type (n=191)	IVC-type (n=113)	P-value
Local risk factor[&]	2/114(1.8%)	7/191(3.7%)	3/113(2.7%)	0.619
Inherited thrombophilia				
Protein C deficiency	10/107(9.3%)	10/183(5.5%)	8/107(7.4%)	0.451
Protein S deficiency	13/107(12.1%)	29/183(15.8%)	15/107(14.0%)	0.682
Antithrombin deficiency	0/107	4/183(2.2%)	2/107(1.9%)	0.318
Acquired thrombophilia				
MPN*	15/51(29.4%)	9/84(10.7%)	0/46	**<0.001**
JAK2V617F mutation	9/107(8.4%)	4/172(2.3%)	0/97	**0.002**
CALR mutation	1/60(1.7%)	4/101(4.0%)	0/61	0.242
APS	4/98(4.1%)	17/163(10.4%)	5/96(5.2%)	0.106
Hormonal risk factors#	3/55(5.5%)	5/97(5.2%)	4/41(9.8%)	0.570
Systemic disorder$	1/114(0.9%)	1/191(0.5%)	0/113	0.627
PNH	1/104(0.9%)	1/171(0.6%)	0/97	0.644

HV: Hepatic vein; IVC: Inferior vena cava; MPN: Myeloproliferative neoplasms; APS: Antiphospholipid antibody syndrome; PNH: Paroxysmal nocturnal hemoglobinuria.
[&] abdominal trauma, Intra-abdominal inflammation, infection, or abscess.
* All patients from the groups had a bone marrow biopsy to confirme MPN if JAK2V617F and CALR mutation were both negative.
# Oral contraceptive use or Pregnancy within 3 month before diagnosis.
$ Behcet disease, sarcoidosis, vasculitis, connective tissue disease or lymphoide hemopathy.

Conclusion: Our results confirm that, the same as in western countries, MPNs are the leading cause in HV-type of BCS or PVT but not in combined-type or IVC-type of BCS. However, unlike in western countries, other prothrombotic factors are rare in chinese SVT patients.

SAT-035

Step-wise strategy for Chinese Budd-Chiari syndrome patients: Long-term outcome of a large scaleprospective observational cohort

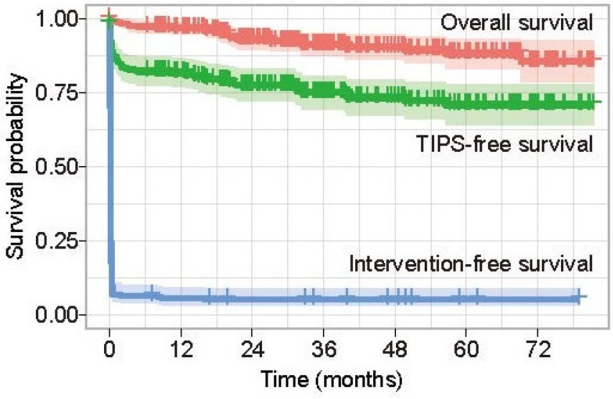
Q. Wang[1], J. Fan[1], B. Luo[1], C. He[1], W. Guo[1], X. Yuan[1], J. Tie[1], K. Li[1], W. Bai[1], T. Yu[1], J. Niu[1], Z. Wang[1], Y. Zhu[1], N. Han[1], J. Yuan[1], X. Li[1], L. Liu[1], H. Chen[1], Y. Lv[1], H. Liu[1], E. Wang[1], D. Xia[1], L. Zuo[1], J. Xia[2], Z. Yin[1], D. Fan[3], G. Han[1].
[1]*National Clinical Research Center for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Department of Liver Disease and Digestive Interventional Radiology, Xi'an, China;* [2]*Fourth Military Medical University, Department of Health Statistics, Xi'an, China;* [3]*State Key laboratory of Cancer Biology, National Clinical Research Center for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Xi'an, China*
Email: machaelia@163.com

Background and Aims: A step-wise approach has proven to provide a good long-term outcome in European Budd-Chiari syndrome (BCS)

patients. We aimed to investigate whether Chinese BCS patients, with different constitutions of aetiology and obstruction types, would achieve favourable long-term outcome under this management strategy.

Method: From September 2010 to December 2016, 252 treatment-naïve BCS patients admitted to Xijing Hospital of Digestive Disease were included and prospectively followed-up. All patients received anticoagulation as soon as diagnosed, and membranous or short-length stenosis were addressed by angioplasty with or without stent placement. Patients who did not respond to these therapeutic models underwent transjugular intrahepatic portosystemic shunt (TIPS). No patient received orthotopic liver transplantation (OLT), and OLT-free survival was not analysed. Therefore, overall survival, TIPS-free survival and intervention-free survival were calculated with Kaplan-Meier method. Cox regression analysis was used to identify prognostic factors of overall survival in the entire cohort.

Results: During a median follow-up duration of 36.6 months (interquartile range, IQR: 20.5–58.9 months), a total number of 4 patients were lost to follow-up. Since no patients received OLT in the cohort, OLT-free survival was not calculated. The 1-year, 2-year and 5-year overall survival of the cohort were 96.8%, 92.9%, and 88% respectively. Specifically, the 1-year, 2-year and 5-year TIPS-free survival 81.7%, 77.4%, and 70.7% respectively, whereas only 6%, 5% and 5% patients were amenable to mere anticoagulation therapy at these time points. In univariate analysis, platelet count, total protein, albumin, total bilirubin, and creatinine were identified as prognostic factors, whereas in multivariate analysis, only total protein and creatinine were significant prognostic factors ($p < 0.05$).



Conclusion: Compared to previous reports from other regions, the step-wise strategy was not only applicable but could achieve better long-term outcome in Chinese BCS patients even without OLT. Mere anticoagulation provided survival benefits in only a small proportion of these patients. Moreover, unlike in European countries where TIPS played a more significant role, angioplasty with or without stents appear to contribute most in improving survival in current cohort.

SAT-036

Hepatic outcomes from childhood intestinal failure: A meta-analysis of 8223 patients

A. Pierret[1], J. Wilkinson[2], J. Mann[3]. *[1]University of Cambridge, Pharmacology Department, Cambridge, United Kingdom; [2]University of Cambridge, School of Clinical Medicine, Cambridge, United Kingdom; [3]University of Cambridge, Department of Paediatrics, United Kingdom*
Email: acsp4@cam.ac.uk

Background and Aims: Paediatric intestinal failure (IF) is usually congenital or acquired neonatally and may lead to IF-associated liver disease (IFALD). Due to improved neonatal care, the prevalence of IF is increasing. Understanding its natural history is vital for decisions regarding small bowel and liver transplant however, to date, cohort studies have primarily been from single centres and of small size. Therefore, we aimed to describe natural history of hepatic outcomes in childhood-onset IF.

Method: A MEDLINE search was performed using terms including: 'intestinal failure', 'parenteral nutrition (PN)', 'liver disease', and 'IFALD'. The inclusion criteria were: IF before 18 years, reporting of clinical outcomes (e.g. liver failure, death, transplant), and >12 months follow-up. IF was defined as PN dependence for at least two months. Studies were excluded if IF patients could not be separated from non-IF patients. Studies were grouped by patient cohort: IF or IFALD. Risk of bias was assessed using the ROBINS-I tool.

Results: 1,584 abstracts were screened, from which 148 patient cohorts were included with a total of 8,223 patients.

131 cohorts (7371 patients) with intestinal failure were identified, of which 51 cohorts (3156 patients) had defined follow up. Overall mortality was 0.16 (95% CI 0.13–0.20). 46.1% patients developed IFALD and 7.5% developed hepatic failure, of the 3683 and 1644 patients respectively in which data was available. 1.0% had an isolated liver transplant and 4% had combined liver-small bowel transplant. Overall native liver survival was 89%.

17 cohorts (852 patients) with IFALD were meta-analysed. Overall mortality was 0.21 (95% CI 0.12–0.30) at 1–3 years and 0.32 (95% CI 0.15–0.50) at 3–9 years. Leading causes of death were liver-related in 50% and sepsis in 35%. Isolated liver transplant was performed in 12.5%; therefore native liver survival was 77%. Patients with IFALD were born at a younger gestational age (32.4 vs. 33.6 weeks) and with lower birth weight (1725g vs 1948g) than those with IF. Small bowel length and presence of ileocaecal valve were not associated with IFALD.

Conclusion: IFALD is associated with high morbidity and mortality, though liver failure affects a minority of all patients with IF. Non-modifiable risk factors (gestational age and birth weight) influence liver-related outcomes.

SAT-037

Characteristics and outcomes of cystic fibrosis paediatric patients admitted with cirrhosis in the United States

R. Somayaji[1], M.G. Swain[2], M. Parkins[1], K. Ramos[3], C. Goss[3], A.-A. Shaheen[2]. *[1]University of Calgary, Cumming School of Medicine, Division of Infectious Diseases, Canada; [2]University of Calgary, Cumming School of Medicine, Gastroenterology and Hepatology, Canada; [3]University of Washington, Seattle, Department of Medicine, United States*
Email: azshaheen@me.com

Background and Aims: Cystic fibrosis (CF) is the most common fatal genetic disease of Caucasians. Although lung disease is the primary cause of mortality, CF liver disease (CFLD) is increasingly important due to improvements in survival, and is the third leading cause of death in CF patients. In this study, we defined the characteristics of pediatric CF patients admitted with a cirrhosis-related diagnosis and estimated predictors of in-hospital mortality and hospitalization outcomes.

Method: We used the 2012 **K**id's **I**npatient **D**atabase (KID) to identify cirrhosis-related hospitalizations among pediatric CF patients (age 0–20 years) in the USA. An admission was considered "cirrhosis" if a diagnosis of cirrhosis or cirrhosis-related complication was identified (based on ICD-9 codes). We compared demographic, socio-economic and clinical characteristics for CF patients (e.g. demographics, insurance status, and Elixhauser comorbidities) with and without a cirrhosis-related diagnosis. Adjusted multiple linear and logistic regression models were used to identify predictors of in-hospital mortality, LOS and hospitalization charges among CF patients with cirrhosis.

Results: Of the 10,256 pediatric CF hospitalizations identified in 2012, 555 (5.4%) were cirrhosis-related admissions. Compared with CF admissions without cirrhosis, patients with cirrhosis were older

(median age: 16 vs. 14; p < 0.001), more likely male (58.2% vs. 44.2%; p < 0.001), more likely to be admitted on weekend (13.3% vs. 10.6%; p = 0.04), and had ≥2 comorbid conditions (19.3% vs. 7.7%, p < 0.001). Among pediatric CF admissions with cirrhosis, 47.4% had esophageal varices, 15.0% had ascites, and 21.8% had a previous liver transplant. CF patients with cirrhosis had higher in-hospital mortality compared to CF patients without cirrhosis (2.0% vs. 0.6%, p < 0.001). Although LOS was similar between CF patients with and without cirrhosis (median LOS 8 days, p = 0.40), CF patients with cirrhosis had higher hospitalization charges compared to those without cirrhosis (median $66,543 vs. $53,365, p < 0.001). In our age and sex adjusted models, admission with ascites was the only independent predictor of in-hospital mortality (adjusted odds ratio (OR): 5.29, 95%CI: 1.67–16.1). Predictors of increased LOS among CF patients with cirrhosis were male sex, private insurance, having multiple comorbidities and ascites. Only ascites and having multiple comorbidities were independent predictors of increased hospitalization charges in CF patients with cirrhosis.

Conclusion: Pediatric CF patients with cirrhosis had greater in-hospital mortality compared to those without cirrhosis. Having ascites was the major independent predictor of in-hospital mortality, LOS and increased hospitalization costs. Future interventions should be designed to enhance care for pediatric patients with ascites.

SAT-038

Comparison between room-temperature susceptometry and MRI with respect to the cell-specific detection of liver iron

J. Mueller[1], H. Raisi[1], V. Rausch[1], D. Simons[2], C. Ziener[2], H.-P. Schlemmer[2], H. Seitz[1], B. Straub[3,4], N. Waldburger[4], S. Mueller[1].
[1]Salem Medical Center and Center for Alcohol Research and Liver Disease, Heidelberg, Germany; [2]Deutsches Krebsforschungszentrum, Radiology Dept., Heidelberg, Germany; [3]University of Mainz, Institute of Pathology, Mainz, Germany; [4]University of Heidelberg, Institute of Pathology, Heidelberg, Germany
Email: joh-mueller@gmx.de

Background and Aims: Liver iron not only accumulates in hemochromatosis but also in various chronic liver diseases such as HCV and ALD where it has been identified as an important prognostic and cancerogenic factor. Unfortunately, the non-invasive and cost-efficient assessment of liver iron is still insufficiently resolved. We here compare the non-invasive methods Room-temperature Susceptometry (RTS) and Magnetic Resonance Imaging (MRI) with the invasive liver biopsy and lab parameters and their association to the cellular distribution of iron in the liver tissue.

Method: 106 patients with various diseases such as alcoholic and non-alcoholic liver disease or hemochromatosis were prospectively enrolled. All 106 patients underwent liver biopsy with quantitative iron determination via atomic absorption spectroscopy (AAS) and blood serum markers such as serum ferritin were determined. In 78 patients liver iron was determined histologically by semi-quantitative Prussian Blue staining (grade 0–3). In 95 patients, liver iron concentration (LIC) was also determined by RTS and in 34 patients via MRI (1.5T Magnetom Aera, Software: LiverLab, Siemens).

Results: Both MRI and RTS correlated well with AAS with Pearson correlation coefficients of 0.75 ($p < 0.001$) and 0.48 ($p < 0.001$), respectively. AAS, MRI and RTS all correlated better with hepatocellular iron scores from Prussian Blue Staining than with RES-iron. The Spearman correlation coefficients with hepatocellular iron scores for AAS, MRI and RTS are 0.60 ($p < 0.001$), 0.62 ($p < 0.001$) and 0.55 ($p < 0.001$), respectively, and in comparison with RES-iron scores are $r = 0.47$ ($p < 0.001$), 0.26 ($p > 0.05$) and 0.48 ($p < 0.001$). Serum ferritin on the other hand correlated equally well with hepatocellular and RES-iron scores with correlation coefficients of 0.52 and 0.56 ($p < 0.001$), respectively. This is also reflected in the diagnostic accuracies for the detection of the pathologic hepatocellular iron. When using a hepatocellular iron grade 2 as cutoff value, the diagnostic accuracies are as follows: AAS: 92%, cutoff 4 mg/g dry weight; RTS: 88%, cutoff 400 µg/g wet weight; MRI: 80%, cutoff $33 s^{-1}$; Ferritin: 67%, cutoff 890 ng/ml.

Conclusion: RTS, MRI and AAS are primarily detecting hepatocellular iron and not macrophage iron most likely due to the abundance of hepatocytes in the liver tissue. On the opposite side, serum ferritin is more dependent on RES-iron than on hepatocellular iron. Since RTS reaches good diagnostic accuracies in the detection of severe pathological hepatocellular iron we consider it as a promising bedside method for the screening of liver iron overload.

SAT-039

Alpha1-antitrypsin augmentation therapy is associated with an improvement in liver-related parameters in patientes with severe alpha1-antitrypsin-deficiency

C.V. Heimes[1], K. Hamesch[1,2], M. Mandorfer[3], L.S. Moeller[4], M.C. Reichert[5], V. Woditsch[1], J. Voss[1], C. Lindhauer[1], S. Janciauskiene[6], F. Lammert[5], M. Trauner[7], A. Krag[4], C. Trautwein[1,2], P. Strnad[1,2].
[1]University Hospital RWTH Aachen, Medical Clinic III, Gastroenterology, Metabolic diseases and Intensive Care, Aachen, Germany; [2]Coordinating center for alpha1-antitrypsin deficiency-related liver disease of the European Reference Network (ERN) "Rare Liver" and the European Association for the Study of the Liver (EASL) registry group "Alpha1-Liver"; [3]Division of Gastroenterology und Hepatology, Department of Internal Medicine III, Vienna, Austria; [4]Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; [5]Saarland University Medical Center, Saarland University, Department of Medicine II, Homburg, Germany; [6]Clinic for Pneumology, German Center for Lung Research (DZL), Hannover, Germany; [7]Department of Internal Medicine III, Division of Gastroenterology und Hepatology, Vienna, Austria
Email: cheimes@ukaachen.de

Background and Aims: Severe alpha1-antitrypsin deficiency ('PiZZ' genotype) constitutes one of the most common genetic disorders, and its letality is due to the associated lung and liver disease. While alpha1-antitrypsin (AAT) augmentation therapy inhibits the progression of PiZZ-related lung affection, liver transplantation constitutes the only cure for PiZZ-related chronic liver failure. Since AAT augmentation decreases the production of toxic PiZ *in vitro*, we evaluated its impact on liver-related parameters in PiZZ carriers.

Method: Overall, 364 adult PiZZ carriers without known liver disease underwent a systematic clinical and laboratory work-up to exclude hepatic comorbidities and to assess pulmonary symptoms. Liver fibrosis was non-invasively quantified by liver stiffness measurement (LSM) using transient elastography. Liver-related parameters were compared in PiZZ carriers with (221) and without (143) AAT augmentation therapy. Results were adjusted for age, sex, BMI, and diabetes mellitus.

Results: Quantitative measures are expressed as mean with standard deviation or as relative frequency (%). Abbreviations: BMI, body mass index; AAT, alpha1-antitrypsin; CAT, chronic obstructive pulmonary disease assessment test; ULN, upper limit of normal (sex-specific); APRI, AST to platelet ratio index, FIB-4, Fibrosis-4 score.

PiZZ carriers receiving AAT augmentation therapy were older and presented with more advanced lung disease, as demonstrated by higher CAT (COPD assessment test) values and a more frequent need for long-term oxygen treatment. In contrast, they displayed lower serum AST and GGT activities, lower liver stiffness, APRI and Fib4 values (surrogate markers of liver fibrosis) as well as higher platelet counts (marker of portal hypertension). Multivariate analysis confirmed the association of AAT augmentation with improved liver-related parameters.

Table 1: Features of PiZZ patients who do or do not receive alpha1-antitrypsin augmentation therapy.

	PiZZ, non-augmented $n = 143$	PiZZ, augmented $n = 221$	Multivariate p value
Characteristics			
Age (years)	49.4 ± 15.3	57.3 ± 10.4	
Women (%)	52.4	42.1	
BMI (kg/m^2)	24.3 ± 3.7	25.0 ± 4.7	
Diabetes mellitus (%)	5.6	5.8	
AATD-related features			
AAT serum level (mg/dL)	29.0 ± 17.2	104.9 ± 47.8	<0.0001
CAT score (points)	14 ± 8	18 ± 6	<0.0001
Long-term oxygen therapy (%)	7.7	34.4	<0.0001
Liver status			
LSM(kPa)	6.9 ± 6.9	6.1 ± 3.7	0.015
LSM >10 kPa (%)	15.8	10.6	0.005
AST (% of ULN)	75.9 ± 28.0	70.9 ± 25.8	<0.0001
GGT (% of ULN)	98.2 ± 128.8	89.3 ± 115.5	0.002
Platelets (G/L)	227.1 ± 68.54	233.7 ± 61.8	0.044
APRI (units)	0.43 ± 0.44	0.37 ± 0.19	0.001
Fib4	1.58 ± 1.38	1.48 ± 0.86	<0.0001

Conclusion: These data suggest that AAT augmentation might improve PiZZ-related liver phenotypes. However, further studies are needed to confirm this observation and identify the underlying mechanisms.

SAT-040

Impact of acute hepatic porphyrias on quality of life and work loss: An analysis of EXPLORE natural history study

L. Gouya[1], M. Balwani[2], D.M. Bissell[3], D. Rees[4], U. Stölzel[5], J. Phillips[6], R.K. Kauppinen[7], J.L. Langendonk[8], R. Desnick[9], J.C. Deybach[10], H. Bonkovsky[11], C. Parket[12], H. Naik[13], M. Badminton[14], P. Stein[15], E. Minder[16], J. Windyga[17], P. Martasek[18], M.D. Cappellini[19], P. Ventura[20], E. Sardh[21], P. Harper[22], S. Sandberg[23], A. Aarsand[23], F. Alegre[24], A. Ivanova[25], N. Talbi[26], A. Chan[27], K. Mccarthy[28], W. Querbes[28], C. Penz[28], S. Agarwal[28], A. Simon[28], K. Anderson[29].
[1]Centre Français des Porphyries, Paris, France; [2]Mt. Sinai Icahn, School of Medicine, New York, United States; [3]University of California, United States; [4]King's College Hospital, Molecular Haematology, London, United Kingdom; [5]Klinikum Chemnitz, Department of Internal Medicine, Chemnitz, Germany; [6]University of Utah, Internal Medicine, Salt Lake City, United States; [7]University of Hospital of Helsinki, Research Program in Molecular Medicine, Helsinki, Finland; [8]Erasmus Medical Center, Center for Lysosomal and Metabolic Diseases, Rotterdam, Netherlands; [9]Mt. Sinai, Icahn School of Medicine, New York, United States; [10]Centre Français des Porphyries, Centre de Référence Maladies Rares Porphyries, Colombes, France; [11]Wake Forest University, School of Medicine, Winston-Salem, United States; [12]University of Utah, Department of Internal Medicine, Salt Lake City, United States; [13]Icahn School of Medicine, Department of Genetics and Genomic Sciences, New York, United States; [14]University Hospital of Wales, Cardiff & Vale University, Wales, United Kingdom; [15]King's College Hospital, Haematological Medicine, London, United Kingdom; [16]Stadtspital Triemli, Zentrallabor, Zürich, Switzerland; [17]Instytut Hematologii i Transfuzjologii, Department of Disorders of Hemostasis and Internal Medicine, Warsaw, Poland; [18]Univerzity Karlovy v Praze, Department of Medicine, Prague, Czech Republic; [19]University of Milan, Department of Medicine and Medical Specialities, Milan, Italy; [20]Università degli Studi di Modena e Reggio Emilia, Department of Medical and Surgical Science for Children and Adults, Emilia-Romagna, Italy; [21]Karolinksa University Hospital, Department of Molecular Medicine and Surgery (MMK), K1, Stockholm, Sweden; [22]Karolinksa University Hospital, Department of Medical Biochemistry and Biophysics (MBB), C2, Stockholm, Sweden; [23]Norwegian Porphyria Centre (NAPOS), Bergen, Norway; [24]Clínica Universidad de Navarra, Spain; [25]St. Ivan Rilski University Hospital; [26]Centre Français des Porphyries, France; [27]Alynlam Pharmaceuticals, United States; [28]Alnylam Pharmaceuticals, United States; [29]University of Texas Medical Branch
Email: sagarwal@alnylam.com

Background and Aims: Acute hepatic porphyrias (AHPs) are rare, often misdiagnosed genetic diseases caused by a mutation in aminolevulinic acid synthase 1 enzyme responsible for heme synthesis. AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP). The enzyme defect results in accumulation of neurotoxic heme intermediates, aminolevulinic acid and porphobilinogen, that can cause life-threatening attacks; chronic, debilitating symptoms; and the need for urgent medical care and/or hospitalization. Thus, patients may experience substantial impact on their daily living activities and decreased quality of life (QoL). This analysis presents data from the largest international natural history study to describe impact on QoL and work loss among patients with AHP with recurrent attacks.
Method: EXPLORE (NCT02240784) is a prospective, international, observational study characterizing the natural history and clinical management of patients with AHP who have recurrent attacks (≥3 attacks/year) or receive prophylactic treatment to prevent attacks. EQ-5D-5L measured QoL, while work loss for patients and caregivers was self-reported by patients at baseline and 6 and 12 months. EQ-5D-5L consists of 5 domains (mobility, self-care, usual activities, pain, anxiety/depression) and a visual analog scale for health. Descriptive statistics are presented.
Results: 112 patients were enrolled (mean age, 39 years; 89% female; and 93% with AIP, 4% VP, and 3% HCP). Based on baseline EQ-5D-5L, 35% of patients had mobility issues, >50% had some difficulty performing usual activities as well as anxiety/depression, and 72% reported some pain. Similar impairment occurred at 12 months. 70% of patients were not employed full time, of whom 67% were not working full time due to porphyria. Among employed patients, 85% reported missed work days and a mean of 53 lost work days (standard deviation [SD] 77) over a year. In addition, 52% of patients reported that caregivers had lost work days (mean: 17; SD 22) per year.
Conclusion: Patients with AHP, with a mean age of 39 years in this study, reported decreased QoL most frequently in the domains of pain, anxiety/depression, and difficulty in performing usual activities and mobility. Having AHPs with recurrent attacks impacts the ability of both patients and their caregivers to work. Thus, burden of disease impacting daily living is high for these patients and their caregivers.

SAT-041

Trends in healthcare utilization in the United States and Europe associated with patient with acute hepatic porphyria with recurrent attacks in EXPLORE: A prospective, multinational natural history study of patients with acute hepatic porphyria

L. Gouya[1], M. Balwani[2], D.M. Bissell[3], D. Rees[4], U. Stölzel[5], J. Phillips[6], R.K. Kauppinen[7], J.L. Langendonk[8], R. Desnick[9], J.C. Deybach[10], H. Bonkovsky[11], C. Parket[6], H. Naik[12], M. Badminton[13], P. Stein[14], E. Minder[15], J. Windyga[16], P. Martasek[17], M.D. Cappellini[18], P. Ventura[19], E. Sardh[20], P. Harper[21], S. Sandberg[22], A. Aarsand[22], F. Alegre[23], A. Ivanova[24], N. Talbi[10], A. Chan[25], K. Mccarthy[25], W. Querbes[25], C. Penz[25], S. Agarwal[25], A. Simon[25], K. Anderson[26].
[1]Centre Français des Porphyries, Centre Français des Porphyries, France; [2]Icahn School of Medicine at Mount Sinai, Department of Genetics and Genomic Sciences, New York, United States; [3]University of California, San Francisco, United States; [4]King's College Hospital, Molecular Haematology, United States; [5]Klinikum Chemnitz, Chemnitz, Germany; [6]University of Utah, Salt Lake City, United States; [7]University Hospital of Helsinki, Research Program in Molecular Medicine, Helsinki, Finland; [8]Erasmus Medical Center, Rotterdam, Netherlands; [9]Mt. Sinai Icahn

School of Medicine, New York, United States; [10]Centre Français des Porphyries, France; [11]Wake Forest University, Winston-Salem, United States; [12]Icahn School of Medicine at Mount Sinai, New York, United States; [13]University of Wales, Cardiff, United Kingdom; [14]King's College Hospital, London, United Kingdom; [15]Stadtspital Triemli, Zentrallabor, Zürich, United Kingdom; [16]Instytut Hematologii i Transfuzjologii, Warsaw, Poland; [17]Univerzity Karlovy v Praze, Czech Republic; [18]Universita degli Studi di Milano, Milan, Italy; [19]Università degli Studi di Modena e Reggio Emilia, Modena, Italy; [20]Karolinska University Hospital, Stockholm, Sweden; [21]Karolinska University Hospital, Sweden; [22]Norwegian Porphyria Centre [NAPOS], Norway; [23]Clinica Universidad de Navarra, Spain; [24]St. Ivan Rilski University Hospital, Bulgaria; [25]Alnylam Pharmaceuticals, United States; [26]University of Texas Medical Branch, United States
Email: raili.kauppinen@hus.fi

Background and Aims: Acute hepatic porphyrias (AHPs) are rare, often misdiagnosed genetic diseases caused by an enzyme mutation responsible for heme synthesis. This results in accumulation of neurotoxic heme intermediates, aminolevulinic acid and porphobilinogen, that can cause life-threatening attacks and chronic, debilitating symptoms due to injury to the nervous system. AHPs include acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP), often requiring urgent medical care and/or hospitalization. EXPLORE (NCT02240784) is the first international, prospective study (currently ongoing) characterizing the natural history and clinical management of AHP in patients with recurrent attacks. High healthcare utilization has been previously reported in the overall EXPLORE population. Given regional differences in healthcare systems, the objective is to report differences in healthcare utilization in the United States (US) and Europe (EU).
Method: EXPLORE enrolled patients with AHP with recurrent attacks (≥3/year) or receiving hemin prophylactically. Patients' medical history and questionnaires on porphyria symptoms, quality of life, and healthcare utilization were collected at prespecified intervals and during attacks. Trends in emergency room visits, hospitalizations, and general practitioner and specialist visits in the US and EU are presented as descriptive statistics.
Results: 112 patients (US: 44%; EU: 56%) were enrolled (mean age, 39 years; 89% female; and 93% with AIP, 4% VP, and 3% HCP). Patients reported slightly higher mean emergency visits in the US vs EU (3.1; standard deviation [SD] 4.1 vs 2.6; 4.7) in the year before enrollment. Mean overnight hospitalizations in the US and EU were 5.3 (SD: 11; mean length of stay [LOS]: 5 days) and 4.0 (SD: 7; mean LOS: 7 days), respectively. 18% of patients in the US and EU visited their general practitioner monthly; 22% (US) and 15% (EU) visited a specialist monthly for porphyria-related care in the prior year. Additional data, including hemin prophylaxis and attacks that required urgent treatment in a healthcare setting (emergency, clinic, or infusion center) or hospital and/or intravenous hemin treatment, will be reported.
Conclusion: Patients with AHPs with recurrent attacks have a high degree of healthcare utilization in the US and EU. Healthcare utilization in this study was higher in the US than the EU, due perhaps to differences in healthcare systems.

SAT-042

Prevalence and predictive factors of hepatic nodules in patients with fontan surgery: the VALDIG fonliver study

E. Rodríguez-Santiago[1], L. Téllez[1], E. Garrido[1], A. Baiges[2], V.L. Mura[3], E. Garrido-Lestache[4], R. Romera[5], J. Martinez[1], D. Rincón[6], A. Clemente[6], L. Aguilera[1], A. Olavarría[5], E. Llop[7], I. Sánchez[8], F. Gea[1], M.A. Fuente[8], D.M.J. del Cerro[4], R. Bañares[6], G.P.J. Carlos[2], A. Albillos[1].
[1]Hospital Universitario Ramón y Cajal. IRYCIS. CIBERehd. Universidad de Alcalá, Gastroenterology and Hepatology, Madrid, Spain; [2]Hospital Clínic. IDIBAPS. CIBERehd. University of Barcelona., Liver Unit, Barcelona, Spain; [3]San Donato, Intenal Medicine, Milano, Italy; [4]Hospital Universitario Ramón y Cajal, Pediatric Cardiology; [5]Hospital Universitario Ramón y Cajal, Radiology; [6]Hospital Universitario Gregorio Marañón. IiSGM. CIBERehd. Universidad Complutense., Liver Unit, Madrid, Spain; [7]Hospital Universitario Puerta de Hierro. CIBERehd., Gastroenterology and Hepatology, Madrid, Spain; [8]Hospital Universitario Ramón y Cajal. Universidad de Alcalá, Pediatric Cardiology, Madrid, Spain
Email: luis.tellez@salud.madrid.org

Background and Aims: Fontan surgery (FS) allows the venous return to reach the pulmonary circulation bypassing the ventricle in patients with single ventricle. This results in sustained systemic venous hypertension and liver damage in the long-term. Frequency, characterization and risk of hepatocarcinoma in liver nodules in Fontan-associated liver disease are poorly known. The AIM was to characterize liver nodules and the predictive factors of their presence in patients with FS.
Method: Multicentre, observational, transversal and prospective study. 65 consecutive FS patients were evaluated by blood tests; Fibroscan®; abdominal Doppler-US, MRI or CT (if pacemaker); and echocardiography and other cardiological test. The main variable was the presence of nodules in CT/MRI.
Results: 65 patients were included, 39 male (60%). (mean ± SD) Age was 27 ± 8.1yr, time since FS was 19 ± 7.4yr. Tricuspid (20, 31%) atresia was the most frequent congenital cardiac defect. Nodules were detected in the liver in 58% (95%CI: 42–69%) of patients by CT/MRI and in 39% (95%CI: 27–50%) by US. US did not identify focal lesions in 8 of 27 patients with nodules detected by CT/MRI (sensitivity = 70%; 95%CI: 51–84%). Sixty-four of the 70 nodules (91%, 95%CI: 82–96%) detected by CT/MRI were hypervascular, and 7 of them (10%) in 4 patients showed late venous washout. Hepatocarcinoma (by histology, AFP >200 ng/ml) was diagnosed in 2 of the 4 patients with hypervascular and venous washout nodules. US detected 10 nodules in 6 patients that were not identified by CT/MRI, all of them were hyperechogenic with a diameter <1 cm. In univariate analysis, enteropathy, GGT > 90 IU/ml and bicavopulmonary FS variant were significantly ($p < 0.05$) associated with the presence of nodules in the CT/MRI. In the binomial logistic regression analysis, GGT > 90 (OR: 4.86, $p = 0.04$) and the bicavopulmonary variant (OR: 5.66, $p = 0.02$) remained as predictive factors.

Characteristics of nodules

US (65 patients)	**MRI/CT** (48 patients)
Patients with nodules: 25 (38.5%)	**Patients with nodules:** 27 (57.5%)
Subgroup with nodules:	**Subgroup with nodules:**
• **N° of nodules:** 65	• **N° of nodules:** 70
• **N° of nodules/patient:** 2 (1–10) (median, rank)	• **N° of nodules/patient:** 2(1–9) (median, rank)
• **Diameter:** 0.8 (0.4–4.5) cm	• **Diameter:** 1.1 (0.4–4.3) cm
• **Peripheral:** 46 (76.9%)	• **Peripheral:** 52 (74.3%)
• **Echogenicity:**	• **LiRADS:**
◦ **Hyper:** 57 (87.7%)	◦ 2: 7 (10%)
◦ **Isoe:** 5 (7.7%)	◦ 3: 34 (48.5%)
◦ **Hypo:** 3 (4.6%)	◦ 4: 8 (11.4%)
• **Hepatocarcinoma shown:** 2/2, (100%)	◦ 5: 5 (7%)
	◦ Unclassified: 16 (22.85%)
	• Hypervascular: 64 (91.4%)
	• **Washout venous/late phase:** 7 (10%), 4 nodules in 2 patients hepatocarcinoma.

Conclusion: Hepatic nodules are frequent in patients with FS, especially in those with increased GGT and the bicavopulmonary variant. Hepatic nodules in FS patients are hyperechogenic, hypervascular predominantly peripheral and can progress to hepatocarcinoma.

SAT-043

The effect of re-exposure to somatostatin analogues in patients with polycystic liver disease

R. van Aerts[1], M. Kolkman[1], F. Nevens[2], W. Kievit[3], J.P.H. Drenth[1].
[1]*Radboud university medical center, Gastroenterology & Hepatology, Nijmegen, Netherlands;* [2]*UZ Leuven, Department of Hepatology, University Hospitals Leuven, Leuven, Belgium;* [3]*Radboud university medical center, Department for Health Evidence, Nijmegen, Netherlands*
Email: rene.vanaerts@radboudumc.nl

Background and Aims: Symptomatic patients with hepatomegaly resulting from polycystic liver disease (PLD) are eligible for treatment with somatostatin analogues (SA). SA decrease liver volume and its effect is mainly achieved in the first 3–6 months of treatment while prolonged administration maintains the achieved effect and prevents further growth. In view of the apparent tolerance and extensive costs, we sought to explore alternative administration schemes. It is unknown whether re-exposure of SA results in a similar effect on liver volume. In this study we aimed to determine and compare the treatment effect of SA during two separate treatment periods separated by a drug holiday.
Method: Patients who were treated with somatostatin analogues (lanreotide or octreotide) for at least 3 months for two separate periods (On-I & On-II), spaced by a period without treatment (Off-I) for at least 3 months, were selected from our international PLD registry. Data was retrospectively retrieved from the medical chart in two tertiary centers. Effectiveness of both On-treatment periods was expressed as percentage change in height adjusted liver volume (hTLV), which was compared between the 2 periods using generalized linear mixed models with adjustment for liver volume at start of each treatment.
Results: Out of a total 741 patients, 35 patients were selected. Total length of the observation period was 44.0 months (IQR 10.0) and baseline height adjusted liver volume was 3198 ml/m (IQR 2152). Duration of On-I, Off-I and On-II were respectively 11.0 months (IQR 0), 20 months (IQR 14.0) and 11.0 months (IQR 9.0). There was no significant difference between the effect in On-I (−2.7% per 6 months) and On-II (−1.5% per 6 months) after correction for baseline hTLV, p = 0.176. 69% of patients (n = 24) had a decrease in liver volume during On-I. Out of these 24 patients, re-exposure to SA again led to a decrease in 83% (n = 20) after a period without treatment. Of all non-responders after On-1, 36% (n = 4) did show a decrease in hTLV after On-II.

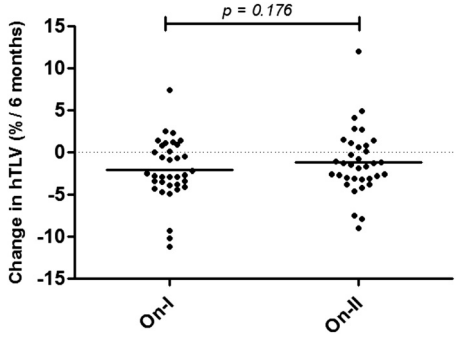


Figure 1: Percentage change in hTLV per 6 months in the first and second treatment period.

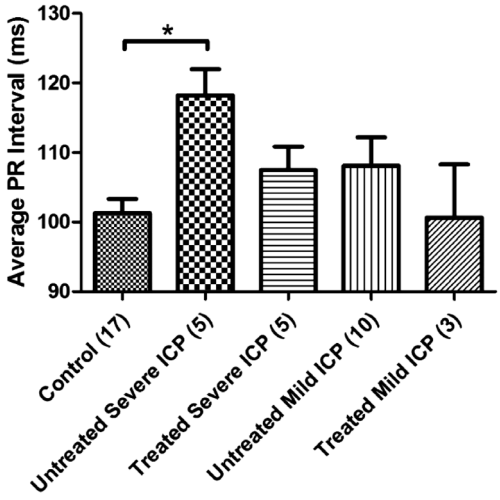
Conclusion: This study suggests that patients who have an initial response on SA are likely to show a similar response during subsequent treatment periods. Future studies should explore the effect of intermittent exposure to SA on hTLV, symptoms and quality of life in and compare this with continuous therapy.

SAT-044

The PR interval in the fetal electrocardiogram is significantly prolonged in severe intrahepatic cholestasis of pregnancy and potentially normalised by UDCA therapy

T. Vasavan[1], C. Martin[1], I.A. Jayawardane[2], S. Deepak[1], V. Geenes[1], M. Lucchini[3], J. Chambers[1], L. Kurlak[2], J. Thornton[2], F. Broughton-Pipkin[2], B. Hayes-Gill[4], W. Fifer[3], C. Williamson[1]. [1]*King's College London, Department of Women and Children's Health, London, United Kingdom;* [2]*Nottingham University, Division of Child Health, Obstetrics & Gynaecology, Nottinham, United Kingdom;* [3]*Columbia University, Sackler Institute of Developmental Psychobiology, New York, United States;* [4]*Nottingham University, Faculty of Engineering, Nottingham*
Email: tharni.vasavan@kcl.ac.uk

Background and Aims: Intrahepatic Cholestasis of Pregnancy (ICP) is typically described as mild or severe based on total serum bile acid (TSBA) concentrations; severe ICP is diagnosed when TSBA concentrations are ≥40 µmol/L and is associated with an increased risk of adverse pregnancy outcomes, including intrauterine death (IUD). ICP is often treated with ursodeoxycholic acid (UDCA). There are case reports of abnormal cardiac rhythm, e.g. supraventricular tachycardia, bradycardia and prolongation of PR intervals in ICP fetuses. Bile acids are arrhythmogenic in *in vitro* cardiomyocyte models of the fetal heart, and arrhythmia is prevented by co-administration of UDCA. We hypothesise that severe ICP causes detrimental changes in the fetal electrocardiogram (fECG) and that UDCA can protect against these changes.
Method: We used the Monica AN24, a non-invasive transabdominal ECG device, to record overnight fECGs in women who were ≥20 weeks in gestation. Controls, defined as women with uncomplicated pregnancies, were recruited in addition to patients who had been diagnosed with severe or mild ICP who were either untreated or undergoing UDCA treatment. fECG files were downloaded and analysed using Monica DK software. A 2-hour period with minimal fetal heartrate dropout and no maternal movement was identified and the PR interval was marked on an averaged fECG waveform of up to 1000 complexes in 5-minute epochs over this period.
Results: We found that the electrocardiographic fetal PR interval was significantly prolonged in patients with untreated severe ICP (118.2 ± 8.5 ms, n = 5) in comparison to controls (101.3 ± 8.4 ms, n=17, p = 0.02). This prolongation was not seen in patients with severe ICP who had been treated with UDCA. Patients with untreated mild ICP had a non-significant prolongation of PR interval (108.1 ± 12.8 ms, n = 10, p = 0.11). Statistical analysis was performed via a one-way ANOVA with post-hoc Bonferroni's test, results are presented ± standard deviation values.



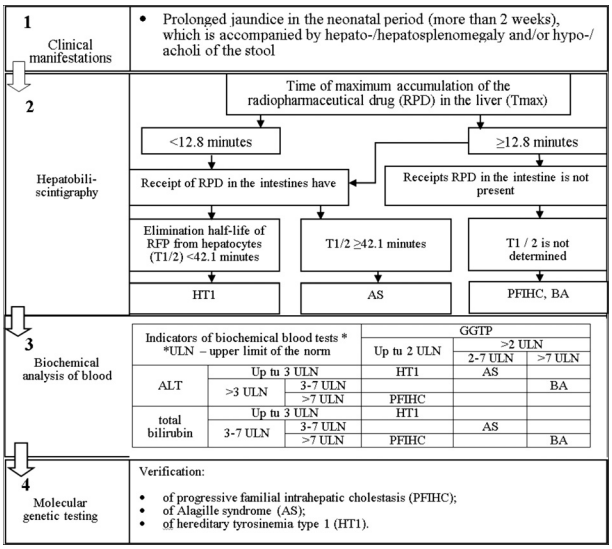
Conclusion: We have demonstrated a significant prolongation of PR interval in the fECG of patients with untreated severe ICP, a defect which is known to be a common indicator of atrioventricular block. A prolongation of PR interval is also seen in untreated mild ICP, indicating a role of increased TSBA in this defect. UDCA treatment appears to normalise the length of PR interval. More data is required to assess the clinical impact of ICP-associated prolonged PR interval on the fetal heart and the usefulness of UDCA in reversing this.

SAT-045

Differential diagnostics of congenital cholestatic diseases in children of early age

G. Volynets[1], A. Khavkin[1], A. Nikitin[2], T. Skvortsova[2], O. Komarova[1], V. Panfilova[3]. *[1]Pirogov Russian National Research Medical University (RNRMU), Separate structural subdivision Scientific Research Clinical Institute of Pediatrics named after Academician Yu.E.Veltischeva, Department of Gastroenterology, Moscow, Russian Federation; [2]Federal State Autonomous Institution "National Medical Research Center of Children's Health" of the Ministry of Health of the Russian Federation, Department of Gastroenterology, Moscow, Russian Federation; [3]Krasnoyarsk State Medical University of the Ministry of Health and Social Development of the Russian Federation, Department of Gastroenterology, Krasnoyarsk, Russian Federation*
Email: volynec_g@mail.ru

Background and Aims: Diagnosis of cholestatic diseases is very important in young children. It is necessary to develop an algorithm for differential diagnosis of congenital cholestatic diseases in children of early age.
Method: There were 81 children (49 boys and 32 girls) aged 1 month to 16 years (mean age 62 months ± 6 months): 20 children with biliary atresia (BA); 17 – with hereditary tyrosynemia type 1 (HT1), 23 – with progressive familial intrahepatic cholestasis (PFIHC) type 1 and 2; 21 – with the syndrome of Alagill (AS). Multivariate statistical analysis has made it possible to identify the criteria necessary for differential diagnosis: Hepatobiliary scintigraphy (HBSG) and biochemical blood test.
Results: Clinical manifestations of cholestatic diseases in infants are similar and characterized by prolonged jaundice in the neonatal period, which is accompanied by hepato-/hepatosplenomegaly and/or fecal hypo-/aholia of fecess. However, despite the similarity of clinical manifestations of cholestatic diseases, differential diagnostic criteria have been identified. HBSG parameters: the time of maximum accumulation (Tmax) of the radiopharmaceutical drug (RPD) in hepatocytes <12.8 minutes and the entry of RPD into the gut was recorded with HT1 and SA, which can be differentiated by elimination half-life of RPD (T1/2) from hepatocytes: at HT1 T1/2 < 42.1min, at SA T1/2 ≥ 42.1min. Tmax ≥12.8min, the RAP does not enter in the intestine (Tint), and the absence of T1/2 is characteristic of PFIHC and BA. Then analyzes the level of alanineaminotransferase (ALT), gammaglutamyltranspeptidase (GGTP) and bilirubin in serum. When BA: the GGTP level [147.0 **329.0** 577.5]U/l (>7 upper limits of the norm – ULN), ALT level [150.2 **203.0** 338.0]U/l (3–7 ULN), the level of total bilirubin [154.6 **187.2** 202.9]μmol/l (>7ULN) with predominance of the direct fraction [87.3 103.3 120.6] μmol/l. When AS: the level of GGTP was [58.0 **127.0** 178.0] U/l (2–7ULN), ALT [43.0 **50.0** 57.0]U/l (up to 3ULN), the level of total bilirubin was [158.2 **195.8** 233.4]μmol/l (3–7ULN) with predominance of the direct fraction [122.2 **124.5** 126.8]μmol/l. When PFIHC уровень ALT [148.0 **319.5** 890.7] U/l (>7ULN), of total bilirubin [75.6 **130.5** 180.6] μmol/l (>7ULN) with predominance of the direct fraction [45.0 **82.9** 113.3]μmol/l, and the level of GGTP does not interrupt 2 ULN. Cholestasis due to HT1 is characterized by GGTP level [24.0 **47.0** 99.5], which does not exceed 2ULN, ALT [14.7 **27.5** 35.0] U/L (≤3ULN), total bilirubin [15.5 **30.1** 53.0]μmol/l (≤3ULN) with predominance direct fraction [2.8 **10.7** 24.5]μmol/l.



Conclusion: The developed examination algorithm allows to differentiate congenital cholestatic diseases in infants (figure), and if suspected of a genetically determined disease, conduct molecular genetic research.
Algorithm of differential diagnosis of congenital cholestatic diseases in children of early age.

SAT-046

Quantitative and qualitative lymphocyte alterations in patients with autoimmune hepatitis: What is the clinical relevance?

A. Renand[1], S. Habes[2], J.-F. Mosnier[3], H. Aublé[4], I. Mabile-Archambeaud[2], S. Brouard[1], J. Gournay[2], S. Conchon[1]. *[1]Centre de Recherche en Transplantation et Immunologie UMR1064, INSERM, Université de Nantes, Nantes, France; [2]CHU nantes, Service Hepato-gastro-entérologie et Assistance Nutritionnelle, Nantes, France; [3]CHU nantes, Service Anatomie et Cytologie Pathologiques, Nantes, France; [4]CHU nantes, Centre d'Investigation Clinique gastro-nutrition, Nantes, France*
Email: amedee.renand@univ-nantes.fr

Background and Aims: Autoimmune hepatitis (AIH) is a rare disease characterized by an immune attack of the liver. Various lymphocyte populations have been involved in hepatocellular damage, but the relationship between immune alterations and clinical outcome during AIH is poorly understood. The aim of this study was to identify new immune markers related to the clinical status of AIH patients, which can be useful for future therapeutic research programs.
Method: A flow cytometry strategy was designed to analyze 38 relevant lymphocyte populations (including CD4 and CD8 T cell subsets, Regulatory CD4 T cell subsets, Innate lymphocyte subsets and B cell subsets) from peripheral blood of treatment-naive AIH patients at diagnosis (AIHn; n = 11), age-matched AIH patients with controlled disease (AIHc; n = 11), and healthy subjects (n = 11). Liver biopsy analyses (including immunohistochemistry and immunofluorescence) and correlations with stage of fibrosis and disease activity were performed to complete the blood phenotypic analysis.

Results: Five blood lymphocyte populations were significantly altered in AIHn patients at diagnosis compared with healthy subjects. Levels of mucosal-associated invariant T cells (MAIT; $p < 0.0001$), TH1/TH17 CD4 T cells ($p = 0.0048$), and invariant natural killer T cells (iNKT; $p = 0.001$) were decreased, while MAIT Granzyme B+ (GrB) cells ($p = 0.001$) and CD8 + CD161 + GrB+ T cells ($p = 0.0025$) increased. These immune alterations were not restored with standard immunosuppressive treatments. Disease activity was correlated with the blood decrease in TH1/TH17 CD4 T cells ($r = -0.68$; $p = 0.02$), whereas stage of hepatic fibrosis was correlated with MAIT GrB+ frequency ($r = 0.64$; $p = 0.034$). At diagnosis, AIHn patients with a hepatic fibrosis stage F3-F4 had a higher frequency of MAIT GrB+ cells ($p = 0.03$) than AIHn with a hepatic fibrosis stage F0-F2. In the livers of AIHn patients, compared with control non-inflammatory livers, CD4 and MAIT cell markers were enriched in the portal tract, and CD8, CD161, and GrB markers were enriched in the hepatic lobule. Expression of PD1 and CD161 by circulating TH1/TH17 CD4 T cells was higher in AIH patients ($p = 0.02$) compared to healthy subjects, and was correlated with disease activity ($r = 0.9$; $p = 0.006$).
Conclusion: Our work identified new immune actors of AIH pathogenesis. TH1/TH17 CD4 T cells and CD8 + CD161+ T cells are involved in disease activity. MAIT cells seem to be related to the progression of fibrosis.

SAT-047

High caloric nutrition promotes hepatocellular damage and steatohepatitis in Wilson disease rats via amplified mitochondrial damage

C. Einer[1], C. Leitzinger[1], S. Hohenester[2], K.H. Weiss[3], H. Zischka[1,4].
[1]Institute of Molecular Toxicology and Pharmacology, Helmholtz Center Munich, German Research Center for Environmental Health, Neuherberg, Germany; [2]Department of Medicine II, University Hospital, LMU Munich, Munich, Germany; [3]Internal Medicine IV, Department of Gastroenterology, University Hospital Heidelberg, Heidelberg, Germany; [4]Institute of Toxicology and Environmental Hygiene, Technical University Munich, Munich, Germany
Email: einer.claudia@gmail.com

Background and Aims: Wilson disease is a copper storage disease, caused by mutations in the copper transporter ATP7B, resulting in hepatic copper accumulation and liver damage. Steatosis is an early and frequent observed feature in Wilson disease patients, suggesting that impaired copper homeostasis associates with liver steatosis. Hepatic mitochondria are key organelles affected by copper overload in patients with Wilson disease and steatosis. Therefore, we addressed the question whether a high caloric diet promotes Wilson disease progression via amplified mitochondrial damage.
Method: Homozygous *Atp7b*$^{-/-}$ rats, a Wilson disease animal model, and their heterozygous controls were either fed a normal- (ND) or high caloric diet (HCD, approximately 2-fold amounts of calories due to elevated chow fat and fructose-containing water). The degree of liver damage, steatosis and hepatic mitochondrial impairment was assessed. As a therapeutic intervention, the copper chelating agent methanobactin was studied in HCD-fed *Atp7b*$^{-/-}$ rats.
Results: Overt hepatic injury (AST >200 U/l, bilirubin >0.5 mg/dl, hepatic injury score >10) and steatohepatitis (NAS >5) were omnipresent in HCD- but not in ND-fed *Atp7b*$^{-/-}$ rats. In contrast, HCD-fed controls only developed steatosis without signs of severe liver injury. HCD feeding strongly increased mitochondrial copper in *Atp7b*$^{-/-}$ rats that correlated with the grade of liver damage and steatohepatitis. HCD-fed *Atp7b*$^{-/-}$ mitochondria presented with copper overload, massive structural damage, elevated H_2O_2 production and severely impaired ATP production in comparison to ND-fed controls. The reduction of mitochondrial copper in HCD-fed *Atp7b*$^{-/-}$ rats by methanobactin clearly improved mitochondrial structure and function, ameliorated steatosis and cured overt liver damage.
Conclusion: A high caloric diet massively impaired hepatic mitochondria and aggravated liver damage in Wilson disease rats. Effective mitochondrial copper depletion resolved such damage and ameliorated steatosis/steatohepatitis, demonstrating the close relationship of hepatic copper and lipid metabolism.

SAT-048

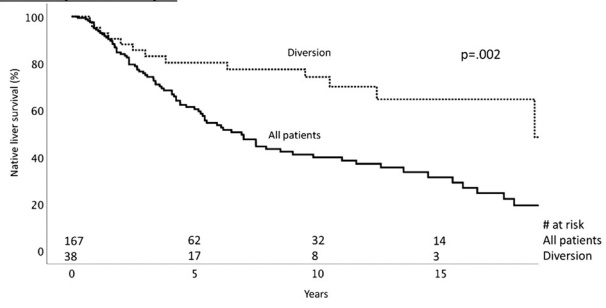
The natural course of FIC1 deficiency and BSEP deficiency: Initial results from the NAPPED-consortium (Natural course and Prognosis of PFIC and Effect of biliary Diversion)

D. van Wessel[1,2], R. Thompson[3,4], T. Grammatikopoulos[3], A. Kadaristiana[3], I. Jankowska[5], P. Lipiński[5], P. Czubkowski[5], E. Gonzales[6], E. Jacquemin[6], A. Spraul[6], E. Sokal[7], M.A. Shagrani[8], D.C. Broering[8], T. Algoufi[8], N. Mazhar[8], E. Nicastro[9], D. Kelly[10], G. Nebbia[11], H. Arnell[12], B. Fischler[12], S. Sankaranarayanan[13], J. Hulscher[2], D. Serranti[14], C. Arıkan[15], E. Polat[15], D. Debray[16], F. Lacaille[16], C. Goncalves[17], L. Hierro[18], G.M. Bartolo[18], Y. Mozer-Glassberg[19], A. Azaz[20], J. Brecelj[21], A. Dezsőfi[22], P.L. Calvo[23], A. Pizzol[23], D. Schmitt[24], E. Sturm[25], W. van der Woerd[26], B. Hansen[27], H. Verkade[1]. *[1]Beatrix Children's Hospital, Universitary Medical Center Groningen, Department of Pediatric Gastroenterology and Hepatology; [2]Beatrix Children's Hospital, Universitary Medical Center Groningen, Department of Pediatric Surgery; [3]King's College, London, United Kingdom, Paediatric Liver, GI & Nutrition Centre; [4]King's College, London, United Kingdom, Institute of Liver Studies, Division of Transplantation Immunology and Mucosal Biology; [5]The Children's Memorial Health Institute, Warsaw, Poland, Department of Gastroenterology, Hepatology, Nutritional Disorders and Pediatrics; [6]Hôpital Bicêtre, Hôpitaux Universitaire, Paris, Service d'Hépatologie et de Transplantation Hépatique Pédiatriques; [7]Clinique Universitaire St Luc, Pediatric Gastroenterology, Hepatology and Nutrition; [8]King Faisal Specialist Hospital and Research Centre, Pediatric Transplant Hepatology, Organ Transplant Centre; [9]Hospital Papa Giovanni XXIII Bergamo, Pediatric Hepatology, Gastroenterology and Transplantation; [10]Birmingham Women's and Children's NHS Foundation Trust, The Liver Unit; [11]Fondazione IRCCS Ca" Granda Ospedale Maggiore Policlinico, Service of Pediatric Hepatology and Nutrition; [12]Astrid Lindgren Children's Hospital, Karolinska University Hospital, Pediatric Gastroenterology, Hepatology and Nutrition; [13]Kanchi Kamakoti CHILDS Trust Hospital, Apollo Childrens Hospital; [14]University of Florence, Florence, Italy, Department of Health Sciences; [15]Memorial Atasehir Hospital Liver Transplantation Center, Pediatric Gastroenterology Hepatology and Nutrition; [16]Hôpital Necker, Paris, France, Pediatric Hepatology Unit; [17]University Hospital Santa Maria, Lisbon Academic Medical Centre, Lisbon, Portugal, Gastroenterology Unit, Pediatric Department; [18]University Hospital "La Paz", Madrid, Spain, Pediatric Liver Service; [19]Schneider Children's Medical Center of Israel, Pediatric Gastroenterology, Hepatology and Nutrition Institute; [20]Sheikh Khalifa Medical City, Abu Dhabi, UAE, Pediatric Department; [21]Pediatrična klinika, UKC Ljubljana, Gastroenterologijo, Hepatologijo in Nutricionistiko; [22]Semmelweis University, Budapest, Hungary, First Department of Pediatrics; [23]University of Torino, Torino, Italy, Department of Pediatrics; [24]University Medical Center Hamburg-Eppendorf, Hamburg, Germany, Department of Pediatrics; [25]University Hospital Tübingen, Tübingen, Germany, Pediatric Gastroenterology and Hepatology; [26]Wilhelmina Children's Hospital, University Medical Center, Utrecht, The Netherlands, Department of Pediatric Gastroenterology; [27]University Health Network, Toronto Centre for Liver Disease, Toronto, Canada*
Email: d.b.e.van.wessel@umcg.nl

Background and Aims: Severe deficiency of FIC1 (FIC1-def) and of BSEP (BSEP-def), due to mutations in the *ATP8B1* and *ABCB11* genes, respectively, are responsible for progressive familial intrahepatic cholestasis type 1 and 2. Because of impaired biliary bile salt secretion, patients typically present with pruritus and jaundice in early childhood. Patients may benefit from ursodeoxycholic acid or from surgical diversion (SBD) techniques. However, many patients need liver transplantation. To better understand the nature of these diseases and the efficacy of interventions, we have set up an extensive international consortium, "NAPPED".

Method: We present retrospective follow up data on individual patients from 22 European and Asian centers who were either compound heterozygous or homozygous for disease associated mutations in *ATP8B1* or *ABCB11*. We used time-dependent Cox regression for native liver survival (NLS), adjusted for gender and birthyear, in patients that had undergone SBD (SBD+) or not (SBD-). Continuous variables are expressed as median [range].
Results: We included 42 FIC1-def and 192 BSEP-def patients. Age at first visit was 6 months [0–201] in FIC1-def and 9 months [0–195] in BSEP-def. Use of ursodeoxycholic acid prior to first visit was 33% in FIC1-def and 47% in BSEP-def patients. Age at last follow up was 69 months [3–334] in FIC1-def and 63 months [1–487] in BSEP-def. SBD rates at five/ten years of age were 33/39% in FIC1-def and 27/34% in BSEP-def patients. Five/ten-year NLS was 73/51% in FIC1-def and 61/45% in BSEP-def patients. NLS was significantly higher in SBD+ than in SBD- BSEP-def patients (HR = 0.37; 95%CI (0.18–0.74), p = 0.002; Figure). NLS in FIC1-def patients did not differ significantly between the SBD+ and SBD- groups. Before the age of five/ten years 27/49% in FIC1-def and 37/53% in BSEP-def patients had been transplanted. HCC was not seen in FIC1-def and in 8% in BSEP-def patients. Pre-transplant mortality was 2% for FIC1-def and 4% for BSEP-def. The observed NLS at 18 years of age for FIC1-def and BSEP-def was 51% and 32%, respectively.

Cumulative NLS in BSEP deficiency patients that had undergone SBD or not, based on retrospective analysis



Observed native liver survival in BSEP deficiency using a clock-reset approach. The solid line represents available native liver survival data of all included patients from birth (N=167). The dotted line represents native liver survival following diversion surgery (N=38).

Conclusion: The largest cohort yet of genetically defined FIC1-def and BSEP-def patients can further improve our insights in the natural course of disease and the relationships between genotype and effects of medical and surgical treatments. A significant proportion of these patients reaches adulthood and thus becomes an important, relatively new patient entity for adult hepatology practice.

SAT-049

Mild iron overload in homozygous carriers of the alpha1-antitrypsin PiZ variant is not a major driver of liver fibrogenesis

N. Guldiken[1,2], K. Hamesch[1,3], S. Schuller[1], C.V. Heimes[1,4], S. Janciauskiene[5], C. Trautwein[1,4], P. Strnad[1,4]. *[1]RWTH University Hospital Aachen, Medical Clinic III, Gastroenterology, Metabolic diseases and Intensive Care, Aachen, Germany; [2]University Hospital RWTH Aachen, Interdisciplinary Center for Clinical Research (IZKF), Aachen, Germany; [3]RWTH University Hospital Aachen, Coordinating center for alpha1-antitrypsin deficiency-related liver disease of the European Reference Network (ERN) "Rare Liver" and the European Association for the Study of the Liver (EASL) registry group "Alpha1-Liver", Aachen, Germany; [4]RWTH University Hospital Aachen, Germany, Coordinating center for alpha1-antitrypsin deficiency-related liver disease of the European Reference Network (ERN) "Rare Liver" and the European Association for the Study of the Liver (EASL) registry group "Alpha1-Liver", Aachen, Germany; [5]Medical University Hannover, Clinic for Pneumology, Hannover, Germany*
Email: pstrnad@ukaachen.de

Background and Aims: Carriage of the common alpha1-antitrypsin (AAT) "PiZ" variant predisposes to liver fibrosis progression, but the disease-promoting factors remain largely unknown. Therefore, we studied the extent of iron overload in patients with homozygous carriage of the PiZ variant ('PiZZ') and the impact of mild iron overload on PiZ-overexpressing transgenic mice (PiZ mice).
Method: 297 PiZZ carriers and 196 subjects without an AAT mutation (non-carrier), all without known liver disease, underwent a thorough clinical and laboratory workup including measurement of serum iron, ferritin, and transferrin. FibroScan determined liver fibrosis via liver stiffness measurement (LSM) and liver steatosis via controlled attenuation parameter (CAP), respectively. Data were adjusted for age, sex, BMI, diabetes mellitus and alcohol consumption where appropriate. PiZ mice were crossbred with HFE-knockout mice (HFE-KO) and evaluated at the age of 3 and 18 months by quantitative RT-PCR, immunoblotting and histological/immunological staining.
Results: Serum parameters of iron metabolism were mostly within the normal range in PiZZ carriers. However, compared to non-carriers, PiZZ carriers had lower transferrin levels (261 vs. 280 mg/dl), but displayed higher transferrin saturation (30% vs. 26%) and ferritin levels (212 vs. 145 ng/ml; all $p < 0.001$). PiZZ subjects with LSM ≥ 7.1 kPa, indicating significant fibrosis, had higher ferritin levels than individuals with LSM < 7.1 kPa (325 vs. 177 ng/mp, $p < 0.001$). Likewise, PiZZ carriers with CAP ≥ 280 dB/m, suggesting severe steatosis, had higher ferritin levels than subjects with CAP < 280 dB/m (270 vs. 182 ng/ml, $p = 0.002$). HFE-KO and double transgenic (DTg) mice displayed similar extent of iron overload. Moreover, loss of HFE did not modify the amount of PiZ expression and accumulation in the liver. 18 months old PiZ and DTg mice showed a comparable amount of fibrosis in Sirius red staining and the hydroxyproline assay.
Conclusion: Using a large PiZZ patient cohort, we demonstrated that PiZZ accumulation does not typically lead to a clinically relevant iron overload. Studies in PiZ mice revealed that a minor iron overload is well tolerated and does not promote progression of liver fibrosis.

SAT-050

Compound library screening for the identification of a new treatment for polycystic liver disease

L. van de Laarschot, K. van der Ende, R.H.M. Te Morsche, J.P.H. Drenth. *Institute for Molecular Life Sciences, Radboud University Medical Center, Department of Gastroenterology and Hepatology, Nijmegen, Netherlands*
Email: liyanne.vandelaarschot@radboudumc.nl

Background and Aims: Polycystic liver disease is caused by genetic defects in *PRKCSH* in most patients. Pharmaceutical treatment of polycystic liver disease is aimed at curtailing cyst volume and limited to the use of somatostatin analogues. Disadvantages of somatostatin analogues are the limited efficacy, common frequency of side effects, and high costs. There is an urgent need for a safe treatment that decreases cyst proliferation, and hence cyst volume. The aim of our study is to identify pharmaceutical compounds that target cystic cell proliferation, but do not affect healthy cell proliferation.
Method: The Selleckchem FDA-approved drug screening library contains 1442 compounds with a wide spectrum of therapeutic targets. *PRKCSH* knockout H69 cholangiocytes were used as *in vitro* model for polycystic liver disease. Cells were incubated with compounds at 10 microM concentration for 24 hours in triplicate. Proliferation was measured as absorbance after addition of WST-1 proliferation reagent (Sigma-Aldrich) for 3 hours. Compounds changing proliferation >20% compared to DMSO controls were selected for incubation in wildtype H69 cholangiocytes. Compounds showing >50% of proliferation compared to control and >20% absolute difference between knockout and wildtype H69 cells were identified as most promising.
Results: 1,278 compounds showed proliferation rates of 80–120% relative to control in *PRKCSH* knockout H69 cholangiocytes. 26 compounds increased proliferation >120% of control and 138 compounds decreased proliferation below 80% of control proliferation rate. These 164 compounds were further tested in wildtype H69 cholangiocytes, while octreotide was added as reference. 18

compounds showed proliferation >50% of control proliferation rate and >20% absolute difference between knockout and wildtype H69 cholangiocytes. Of these, 7 compounds showed higher proliferation in wildtype than *PRKCSH* knockout cells. These included 3 anti cancer drugs, 1 haemostatic drug, 1 antipsychotic drug, 1 antimalarial drug, and 1 antimicrobial agent. Octreotide showed no difference in proliferation between incubated cells and controls, nor between knockout and wildtype cells.

Conclusion: We identified 7 FDA approved drugs that reduce proliferation rates in *PRKCSH* knockout cholangiocytes without large effect on proliferation rates in wildtype H69 cells. These drugs target different pathways than somatostatin analogues, and may become future pharmaceutical options for patients unresponsive to current treatment.

SAT-051

Splenic iron deficiency is characteristic for HFE-associated hemochromatosis

A. Viveiros[1], B. Schaefer[1], M. Tobiasch[1], A. Finkenstedt[1], C. Kremser[2], M. Plaikner[2], B. Henninger[2], H. Tilg[1], H. Zoller[1]. [1]*Medical University Innsbruck, Internal Medicine, Innsbruck, Austria;* [2]*Medical University Innsbruck, Radiology, Innsbruck, Austria*
Email: andre.viveiros@i-med.ac.at

Background and Aims: Non-invasive hepatic iron quantification using magnetic resonance imaging (MRI) is a staging method for patients with known iron overload and a diagnostic tool for the work-up of patients with suspected or unexplained iron overload. The aim of the present study was to assess the utility of spleen iron concentrations for the evaluation of hyperferritinemia.

Method: Of all patients who presented with high serum ferritin between July 2001 and August 2015, 443 were *HFE* genotyped and underwent non-invasive liver and spleen iron quantification by T2* weighted MRI, where the degree of iron content is expressed as R2* (=1/T2*). Liver iron overload was defined as a R2* > 60 sec^{-1} and spleen iron overload as a R2* > 50 sec^{-1}.

Results: Clinical, biochemical and radiological data are summarized in Table 1. Fifty-five patients were homozygous for the p.C282Y mutation in the HFE gene. When the latter were compared to patients with all other genotypes, median R2* was significantly higher in the liver (179.3 vs. 68.6, p < 0.001) but also significantly lower in the spleen (38.3 vs. 47.1, p = 0.003). Similar results were found when patients with compound heterozygosity for the p.C282Y and p.H63D mutations and homozygous for the p.H63D mutation were excluded from the analysis. Patient groups did not differ in terms of age, BMI and serum ferritin. Median transferrin saturation (%) was significantly higher in the p.C282Y homozygous group (77 vs. 35, p < 0.001).

Table 1: Median values are represented and the 25th and 75th percentiles are given between parentheses.

	p.C282Y homozygous (n = 55)	all other *HFE* genotypes (n = 388)	p value
Age, years	53 (36–62)	52 (42–63)	0.33
BMI, kg/m^2	25.3 (23.8–27.1)	26.3 (23.2–29.6)	0.14
Serum iron, µmol/L	34.1 (25.8–40.6)	21.5 (17.3–28.2)	<0.001
Serum ferritin, µg/L	624 (282–1344)	618 (388–961)	0.70
Transferrin, mg/dL	204 (180–220)	247 (221–271)	<0.001
Transferrin saturation, %	77 (51–83)	35 (28–46)	<0.001
Alanine aminotransferase, U/l	29 (22–50)	38 (24–66)	0.049
R2* liver, sec^{-1}	179.3 (95.9–342.1)	68.6 (53.0–91.5)	<0.001
R2* spleen, sec^{-1}	38.3 (28.8–52.3)	47.1 (34.7–63.8)	0.003

Conclusion: High ferritin is a common clinical finding that can indicate iron overload, inflammation and cell death. Our study shows that p.C282Y homozygous patients have significantly higher hepatic iron. In accordance with the low hepcidin state of hemochromatosis, reduced splenic iron concentrations in this condition indicate uncontrolled iron release and high transferrin saturation. Splenic iron can therefore be used to guide genetic testing beyond HFE genotyping, where patients with high liver but low spleen iron should preferably be tested for non-HFE mutations. In patients with high spleen iron, dietary and metabolic factors should be considered the main cause of high ferritin.

SAT-052

Transcatheter recanalization with angioplasty and/or stenting: a novel, minimally-invasive treatment option for children with chronic portal vein thrombosis with cavernous transformation

H. Justino[1], K. Kukreja[2], J.A. Hernandez[2], Y. Pham[1], S. Harpavat[1], L. Karam[1], P. Hertel[1], B. Carter[1], B. Shneider[1], T. Miloh[1]. [1]*Texas Children's Hospital, Pediatrics, Houston, United States;* [2]*Texas Children's Hospital, Radiology, Houston, United States*
Email: hjustino@bcm.edu

Background and Aims: Chronic portal vein thrombosis (CPVT) with cavernous transformation of the portal vein (PV) is a leading cause of gastrointestinal (GI) bleeding in children. We sought to evaluate the feasibility of performing transcatheter recanalization of CPVT with balloon angioplasty (BA) and/or stenting for CPVT.

Method: Retrospective study of patients (pts) taken to catheterization (cath) for recanalization of CPVT from April 2014 to November 2017.

Results: 13 pts (7 female) underwent 18 caths; median weight = 13.9 kg (range 7.5–88) and age = 4.1 years (1–15.3). Pre-procedural imaging included MRI and Doppler ultrasound in all, with CPVT and cavernous transformation diagnosed in all. 4 pts had history of prematurity and prior umbilical venous catheterization. CPVT manifestations included GI bleeding (10 pts), hyperammonemia (3), thrombocytopenia (11) and splenomegaly (11). Right heart cath & hepatic vein wedge angiography were performed, followed by percutaneous trans-splenic and/or direct puncture of intrahepatic portal veins. Additional findings at cath: mild pulmonary hypertension (1 patient) and mild hepatopulmonary syndrome (1). Median cath time was 7.2 hours (range 2–11.5). Recanalization of CPVT was successful in 4 pts (single cath in 3 pts, 4 caths in 1 patient), unsuccessful in 7, and not attempted in 2. Successful procedures entailed BA of main and right PV with rheolytic thrombectomy in left PV in one case, BA of main PV and 4 branches of right PV with rheolytic thrombectomy in another case, BA of main, right and left PV in another case, and BA of main PV and 6 intrahepatic PV branches followed by re-occlusion requiring re-angioplasty of 4 intrahepatic PV branches and placement of multiple stents during 3 subsequent caths in fourth case. Diffuse intrahepatic PV occlusion with non-confluent left and right PVs was found in 2 of 4 successful cases. There were no major complications or mortality. Minor complication of bleeding from splenic puncture requiring transfusion in 3 caths (2 among unsuccessful cases). All 4 successful cases were treated with low molecular weight heparin, with additional dual antiplatelet therapy in 1. At follow-up from final cath (range 4–20 months), the 4 pts with successful CPVT recanalization have patent PVs on ultrasound, with no recurrence of GI bleed and improved platelet count and spleen size.

Conclusion: Transcatheter recanalization of CPVT with BA/stenting is feasible in a subset of pts, including those with diffuse intrahepatic PV occlusion that would not otherwise be candidates for meso-Rex shunting. Although transcatheter recanalization is lengthy and technically challenging, it can be attempted with low risk. Further research is needed to determine the most suitable candidates, and whether this approach should be considered as a first-line option for children with CPVT.

Figure 1 (below). (a) Early phase of initial venography revealed a portal cavernoma (*), but late phase of the same angiogram (b) disclosed a hypoplastic and nearly occluded main PV (arrow) with small intrahepatic portal veins (arrowheads).

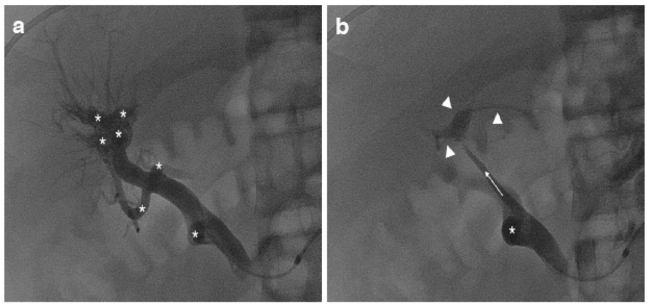


Figure 2 (right). Post-intervention venography shows increased main PV caliber (x1) with filling of the right anterior (x2) and posterior (x3) portal veins and a persistent non-occlusive thrombus in the left portal vein (arrow)

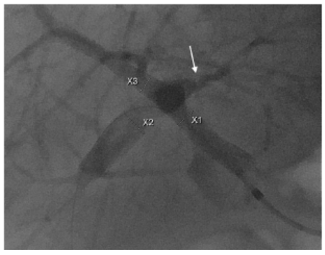


Figure 3 (below left). Initial venography revealed a portal cavernoma with no discernible main PV. Figure 4 (below right) showing early result during angioplasty with 3 guidewires in various PV branches.

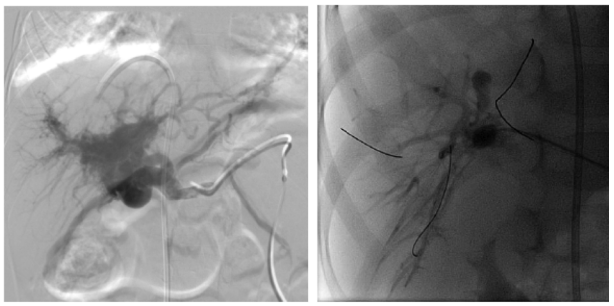


Figure 5 (right). Post-intervention venography shows patent main PV and numerous patent right PV branches.

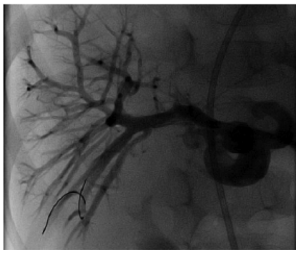


Figure: (abstract: SAT-052).

SAT-053

Clinical response after laparoscopic fenestration of large simple hepatic cysts: a systematic review

L.H.P. Bernts[1], S.G. Echternach[1], C. Rosman[2], J.P.H. Drenth[1]. [1]*Radboud University Medical Center, Gastroenterology and hepatology, Nijmegen, Netherlands;* [2]*Radboud University Medical Center, Surgery, Nijmegen, Netherlands*

Email: lucas_bernts@hotmail.com

Background and Aims: Laparoscopic fenestration (LF) is one of the treatment options for symptomatic simple hepatic cysts, either solitary or in context of polycystic liver disease (PLD), but indications and effect size are under debate. The purpose of this study was to assess the efficacy and safety of LF through a systematic review of the literature.

Method: We performed a systematic search (1950–2017) of PubMed MEDLINE, Embase, Web of Science and the Cochrane Library. We included studies that assessed symptomatic relief or symptomatic recurrence after LF in patients with simple hepatic cysts for full-text evaluation. Case reports, unpublished data and studies with a mean or median follow-up <6 months were excluded. Risk of bias was assessed by use of an adjusted Newcastle-Ottawa scale (NOS) for cohort studies. Pooled estimates and 95% confidence intervals (CI) were calculated using a random effects model for meta-analysis.

Results: We traced 5,277 citations, 248 were selected for full-text assessment and 61 studies (n = 1279) were included. Weighted average of follow-up duration was 36,2 months (range: 9,6–86,4) for reported means. In the risk of bias assessment, studies scored well on "selection" (median 3 out of 4) and "outcome" (median 3 out of 3). In view of a lack of a control arm, studies scored low (median 0 out of 2) on "comparability". The pooled estimate of full or partial symptomatic relief after LF was 90,8% (CI: 84.9–95.4). Symptomatic recurrence after LF was 9,5% (CI: 6.7–12.7) and re-intervention rate was 6,8% (CI: 4.8–9.1). Intra-operative or post-operative complications occurred in 11,9% (CI: 9.0–15.2%) of patients, typically bleeding, ascites or pleural effusion. Procedure-related mortality was 1,0% (CI: 0.5–1.6). Weighted average of hospital stay was 5,1 days (range: 1.2–17.8) for reported means. In a subgroup analysis of PLD patients (n = 135), symptomatic recurrence and re-intervention rates were significantly higher with respective rates of 30.7% (CI: 15.0–48.9) and 26,4% (CI: 12.6–43.0). Complications were more frequent in PLD patients (32.9%; CI: 20.2–46.9).

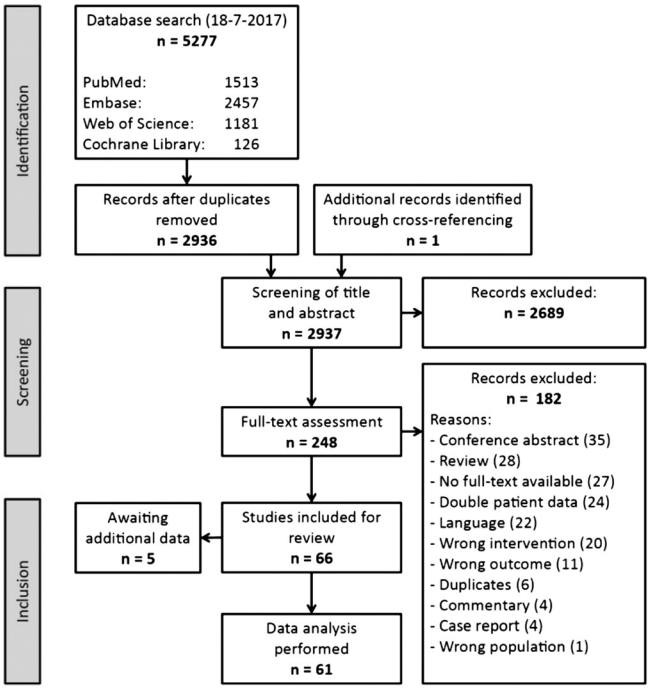


FIGURE 1. Flow chart shows elements of systematic review (identification, screening, inclusion).

Conclusion: Laparoscopic fenestration is an effective procedure for treatment of simple hepatic cysts with a low symptomatic recurrence rate. The symptomatic recurrence rate and risk of complications are significantly elevated in PLD.

SAT-054

Pertinence of liver stiffness measurement inpatients with Wilson's disease for assessment of initial fibrosis and treatment follow-up

R. Sobesky[1], M. Darce[2], H. Agostini[3], I. Fernandez[2], A. Usardi[2], R. Adam[1], D. Cherqui[1], E. Gonzales[4], E. Jacquemin[4], D. Samuel[5], A. Poujois[4], F. Woimant[4], J.-C. Duclos-Vallée[1]. *[1]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, France; [2]Plateforme d'expertise maladies rares Paris Sud, France; [3]Unité de Recherche Clinique, Hopitaux Universitaires Paris-Sud, France; [4]Centre de reference Maladie de Wilson, France, France; [5]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, F-94800, France, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France*
Email: rodolphe.sobesky@aphp.fr

Background and Aims: Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism, leading to liver cirrhosis and neurologic disorders. A liver biopsy may be useful to assist in diagnosis and to estimate the extent of fibrosis. However, non-invasive methods of fibrosis assessment seem useful considering the invasive character of the biopsy and the help of molecular biology for diagnosis. The aim is to determine the pertinence of liver stiffness measurement (LSM) in patients with WD, for assessment of initial fibrosis and for treatment follow-up.
Method: We performed a retrospective analysis of all patients with diagnosis of WD, examined in a liver reference center (Paul-Brousse Hospital, Villejuif, France). Patients were evaluated clinically, biologically, morphologically and genetically. Hepatic involvement was assessed with liver biopsy and/or LSM.
Results: We included 107 patients with hepatic symptoms of the WD, 54 (50.5%) females and 53 (49.5%) males, from 1974 to 2016. The mean age at diagnosis of WD was 20.1 (± 10.54) years. Fifty-seven (53.3%) had mixed symptoms (neurologic and hepatic) at admission. The mean follow up was 15 years [extr: 1–44 years]. 65 patients (60.7%) had liver pathological analysis and 72 (67.2%) had LSM. 73 patients (68%) had cirrhosis at diagnosis of the disease. 42 patients (75%) had cirrhosis among patients with neurologic and hepatic symptoms. Thirty-four (31%) patients were transplanted. Fourteen patients have a liver biopsy associated with LSM in a short interval of 1 month. Eleven of these 14 patients had cirrhosis at biopsy (Metavir F4). The 3 other patients were respectively F2, F1 and F0. The mean LSM for patients with cirrhosis was 32.3 (± 15.9)kPa and was 6.2 (± 2.1)kPa for patients with mild or moderate fibrosis (F0 to F2). Forty of non-transplanted patients (54.8%) had multiple measurements of liver stiffness during follow up. The mean LSM was 33.7 (± 22.5)kPa at diagnosis. Mean LSM with chelators therapy was 17.6 (± 18)kPa at 1 year, 16.5 (± 12)kPa at 2 years, 9.38kPa (± 5.4) at 5 years, 10.4 (± 4.7) kPa at 10 years, 7.7 (± 3.6)kPa at 15 years and 7.2 (± 2) after 20 years.
Conclusion: In case of a proven diagnosis of WD, LSM is pertinent for the estimation of liver fibrosis and can be useful to adapt the follow-up. During follow-up, there is a gradual decrease in the LSM under chelator treatment. The LSM can be a useful tool for monitoring the effectiveness of treatment.

SAT-055

Clinical presentation and outcome of Wilson's disease patients in a monocentric cohort of liver reference center

R. Sobesky[1], M. Darce[2], H. Agostini[3], I. Fernandez[2], A. Usardi[2], R. Adam[1], D. Cherqui[1], E. Gonzales[4], E. Jacquemin[4], D. Samuel[5], A. Poujois[4,6], F. Woimant[6], J.-C. Duclos-Vallée[1]. *[1]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, France; [2]Plateforme d'expertise maladies rares Paris Sud, France; [3]Unité de Recherche Clinique, Hopitaux Universitaires Paris-Sud, France; [4]Centre de reference Maladie de Wilson, France, France; [5]AP-HP Hôpital Paul-Brousse, Centre Hépato-Biliaire, Villejuif, F-94800, France, Inserm, Unité 1193, Université Paris-Saclay, Villejuif, F-94800, France, Villejuif, France; [6]APHP Hopital Lariboisiere, Service de Neurologie, France*
Email: rodolphe.sobesky@aphp.fr

Background and Aims: Wilson's disease (WD) is a rare autosomal recessive disorder of copper metabolism, leading to liver cirrhosis and neurologic disorders. Clinical data on larger cohorts are limited, owing to low disease frequency.
The aim is to determine clinical presentation and outcome of patients with WD in a cohort of patients from a French liver reference center.
Method: This is a retrospective analysis of patients with diagnosis of WD in a liver reference center (Paul-Brousse Hospital, Villejuif, France). Patients were evaluated clinically, biologically, morphologically and genetically. Hepatic involvement was assessed with liver biopsy and/or liver stiffness measurement.
Results: We included 107 patients with hepatic symptoms of the WD, 54 (50.5%) females and 53 (49.5%) males, from 1974 to 2016. The mean follow up was 15 years [extr: 1–44 years]. Fifty-seven (53.3%) had neurological symptoms (mixed symptoms, neurologic and hepatic) at admission. The mean age at diagnosis was 20.1 (± 10.54) years with a difference between the age concerning the patients with hepatic symptoms (17 ± 8.6 years) and mixed symptoms (23 ± 11.4 years) (p = 0.0081). 65 patients (70%) had liver pathological analysis and 72 (67%) had liver stiffness measurement. Seventy-three patients (68%) had cirrhosis at diagnosis of the disease. Forty-three patients (77%) had cirrhosis among patients with mixed symptoms and 30 (61%) in patients with isolated hepatic symptoms. Thirty-four patients (32%) were transplanted, at a mean age of 27 (± 12.2) years. Among patients who required liver transplantation 18 (52%) had decompensated cirrhosis, 8 (23%) fulminant liver failure, 8 (23.5%) severe neurological disease and 5 (14%) liver cancer. The chelating treatment was very predominantly D Penicillamine, in 104 (97%) patients. A change in treatment was necessary in 37 (35%) patients because of adverse events to Trientine or Zinc salts. Four patients died in this cohort; two after primary liver cancer (1 HCC and 1 cholangiocarcinoma), one after hemorrhagic stroke and one after liver transplantation for severe neurological symptoms.
Conclusion: At presentation of WD, two thirds of patients referred to a reference center of hepatology, had cirrhosis and one-third required liver transplantation. Cirrhosis was diagnosed in 77% patients who have neurological symptoms of the disease. Even if WD can be a severe disease, the prognosis is good for patients in charge in a specialized center.

SAT-056

Abnormalities in left ventricular geometry are associated with mortality and morbidity in children with biliary atresia and end stage liver disease

N. Gorgis, C. Kennedy, K. Thompson, J. Goss, T. Miloh, M. Desai.
Texas Children's Hospital
Email: noelle.gorgis@gmail.com

Background and Aims: Abnormalities in cardiac geometry – an essential component of cirrhotic cardiomyopathy- is associated with adverse outcomes in adults with cirrhosis. We aimed to characterize the structural abnormalities of the left ventricle (LV) in children with biliary atresia (BA) and end stage liver disease (ESLD) listed for liver transplant (LT) and evaluate their associations with perioperative morbidity and mortality. We hypothesized that markers of LV hypertrophy (LVH) correlate with serious perioperative adverse events (AE) including post-LT mortality.
Method: 73 patients with BA and a complete pre-operative 2-dimensional echocardiogram were listed for LT at our institution (2011–2016). 4 patients with congenital heart disease were excluded. In the remaining 69 patients (median age 11mo [IQR: 8–20], 65% female), LVH was defined as a LV mass indexed to BSA (LVMI) ≥ 90 g/m^2 or a relative wall thickness (RWT) ≥ 0.42 cm. Comparison of primary (post-LT death and a composite of serious AE) and secondary (ICU and hospital lengths of stay (LOS)) were made between those with and without LVH. Statistical analysis: Mann-Whitney, Fischer Exact, and Spearmen. Reported as number (%) or median (Interquartile Range).

Results: 29 (42%) of 69 patients listed for LT had LVH, including all 4 wait-list deaths. Of the 65 patients who survived to LT, those with LVH had a higher incidence of peri-LT multi-organ dysfunction, with a significantly increased need for mechanical ventilation (MV), vasopressors (VP), and dialysis (HD), as well as a higher incidence of serious AE and post-LT death (Table). Median LVMI was significantly higher in patients with a serious AE (92 [IQR: 84–112] vs. [75 [IQR:63–84], $p < 0.001$) and in those who died post-LT (96 [IQR: 84–132] vs. 77 [IQR:67–88], $p < 0.01$). ICU and hospital LOS was also longer in this cohort ($p < 0.01$).

Table 1: Comparison of characteristics between those with and without LVH

Variable	LVH (n = 25, 38%)	No LVH (n = 40, 62%)	p
Multi-organ failure	15 (60%)	6 (15%)	<0.001
MV need	20 (80%)	17 (43%)	<0.01
VP need	15 (60%)	6 (15%)	<0.001
HD need	15 (60%)	6 (15%)	<0.001
Any AE	15 (60%)	2 (5%)	<0.0001
Post-LT Death	6 (24%)	1 (3%)	0.01
ICU LOS	40 (5–117)	5 (2–20)	<0.01
Hospital LOS	97 (13–158)	16 (7–39)	<0.01

Conclusion: LVH is significantly associated with morbidity and mortality in patients with BA and ESLD requiring LT. These findings support the need to recognize and monitor for LVH while listing children with BA for LT.

SAT-057

Disease severity, obeticholic acid disposition and dose selection in patients with biliary atresia

J. Edwards[1], C. Lacerte[1], Y. Zhang[1], S. Karpen[2], J. Owens-Grillo[1], L. Macconell[1]. [1]*Intercept Pharmaceuticals, Inc.;* [2]*Emory University School of Medicine, Department of Pediatrics*
Email: jeffrey.edwards@interceptpharma.com

Background and Aims: Biliary atresia (BA) is a rare neonatal disease that presents as a progressive, obstructive cholangiopathy leading to rapid development of portal hypertension, cholestasis, and cirrhosis. A Phase 2 clinical trial evaluating the safety, tolerability, and pharmacokinetics (PK) of obeticholic acid (OCA) in pediatric patients with BA who have undergone successful hepatoportoenterostomy is currently ongoing. OCA, a selective and potent farnesoid X receptor agonist, is a modified bile acid with a metabolic disposition like endogenous bile acids. Since bile acid disposition processes appear to mature by late infancy, OCA exposure is expected to be similar for adults and children when adjusting dose by body weight. However, the PK of OCA and bile acids are expected to vary with disease severity in BA. The goal of this analysis was to explore potential relationships between biomarkers of disease status and OCA exposure in support of defining a dosing regimen for BA.
Method: OCA plasma concentrations observed after a single body weight-adjusted dose of OCA in pediatric patients with BA (N = 6; ages 3–17) were compared to exposure levels in healthy adults. Relationships were assessed between OCA exposure levels and status of portal hypertension, bilirubin levels, and markers of disease severity including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma-glutamyl transferase, platelets, and AST to platelet ratio index (APRI).
Results: The PK of OCA was altered in patients with more advanced BA. Patients with elevated bilirubin and/or portal hypertension showed higher systemic exposure of OCA with the highest levels observed in patients with both elevated bilirubin and portal hypertension (Figure 1). Relationships between the PK of OCA and liver biomarkers, ALT and APRI, were detected. These results are consistent with those previously reported, showing a relationship between disease severity and APRI in patients with BA.

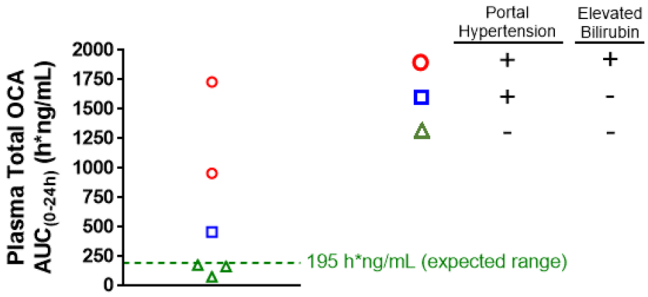


Figure 1:

Conclusion: Positive relationships were found between the systemic exposure of OCA and bilirubin, ALT, APRI, and the presence of portal hypertension or vascular shunting. Although trends were observed between drug exposure and these biomarkers, it is premature to assign OCA dosing based on these biomarkers. Instead, a conservative approach of characterizing the individual PK of OCA after a single dose in each patient with BA is used to determine an appropriate multiple-dosing regimen.

SAT-058

The Galactose Elimination Capacity test may monitor treatment response and disease progression in patients with Wilson Disease

T.D. Sandahl, J.A.E. Björklund, T.L. Laursen, P. Ott, H. Grønbæk. *Aarhus University hospital, Department of Hepatology and Gastroenterology, Aarhus*
Email: thomas.damgaard.sandahl@ki.au.dk

Background and Aims: The prognosis of Wilson disease (WD) has changed radically since the introduction of medical therapy with chelating agents and medications to block copper absorption. However, there is an unmet need for methods to evaluate the long-term treatment response in order to identify treatment failures. The galactose elimination capacity test (GEC) is a physiological measure of the total metabolic capacity of the liver, and a predictor of long- and short-term mortality in patients with liver cirrhosis. Our aim was to investigate whether repeated GEC measurements can be used to evaluate treatment response and identify treatment failures in patients with WD.
Method: We included all cases with WD in Denmark from 1992 through 2016. We retrieved data on GEC and fibroscan along with data on transplantation and survival for all patients. We analysed the development in liver function in each patient by comparing their GEC's over time.
Results: We identified 57 patients with WD. Of these 46 were alive, 10 were dead, 9 transplanted and 1 was lost to follow-up. Eighteen living non-transplanted patients had completed more than one GEC since 1993. Of these, 16 patients showed improvement in their GEC. Two patients had a decreasing GEC over time and these were clinically confirmed as treatment failures. All patients, who underwent liver transplantation or died had a prior decrease in their GEC. There was no significant difference in median values of the index GEC between patients who were later transplanted or dead and patients who were not (GEC 1.87mmol/min (IQR 1.22) vs. 1.66 mmol/min (IQR 0.64). The GEC correlated inversely with fibroscan values, rho=–0.49 p = 0.02.
Conclusion: Repeated GEC measurements may be a useful tool to monitor treatment response and identify treatment failures in patients with WD.

SAT-059

The global prevalence of lysosomal acid lipase deficiency estimated by meta-analysis of pathogenic mutations and functional variants from next-generation sequencing data

A. Carter[1], S. Brackley[2], J. Gao[2], J. Mann[3]. [1]*Manchester University Foundation Trust, Manchester, United Kingdom;* [2]*University of Cambridge, Clinical School, Cambridge, United Kingdom;* [3]*University of Cambridge, Dept of Paediatrics, Cambridge, United Kingdom*
Email: Anna.carter@nhs.net

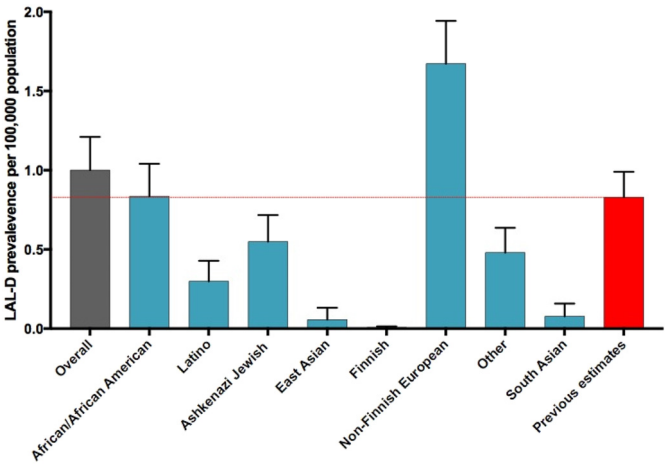
Background and Aims: Lysosomal Acid Lipase Deficiency (LAL-D) is a rare autosomal recessive disorder caused by mutations in *LIPA*. It presents with a spectrum of severity: from infantile liver failure in Wolman disease to Cholesterol Ester Storage Disease (CESD), which mimics features of non-alcoholic fatty liver disease (NAFLD). It has been suggested that CESD is under-diagnosed and may represent significant proportion of patients with NAFLD. We aimed to meta-analyse published prevalence estimates and predict the prevalence of LAL-D using population sequencing data and a validated methodology.

Method: MEDLINE and EMBASE were systematically searched for articles related to LAL-D, CESD, Wolman disease, and *LIPA*. Previous prevalence estimates were meta-analysed. All previously reported pathogenic mutations in *LIPA* were recorded from articles and ClinVar. Using Ensembl and gnomAD, a list of all predicted pathogenic variants in *LIPA* was collated and the Ensembl Variant Effect Predictor (https://ensembl.org/Tools/VEP) was used to annotate variants with allele frequencies from gnomAD and 1000G data sets. A pooled global prevalence estimate was generated using the Hardy-Weinberg equation, in addition we estimated the prevalence for 8 separate ethnicities.

Results: 341 abstracts were screened and 57 studies were included, reporting population prevalences ranging from 0.2 to 23 per 100,000. Meta-analysis of previous data gave an estimate of 0.83 per 100,000 (95%CI 0.66–0.99).

70 previously reported pathogenic variants were elucidated from publications. 28 *LIPA* variants were found from reports of *in vitro* testing. A further 47 predicted functionally significant variants were identified. From the 70 previously reported pathogenic variants, CESD had a total allele frequency of 0.0017 and prevalence 0.29 per 100,000 (95%CI 0.2–0.4).

The predicted total prevalence for LAL-D from all 141 variants was higher at 1.0 per 100,000 (95%CI 0.8–1.2). Non-Finnish Europeans had the highest estimated prevalence (1.7 per 100,000 (95%CI 1.5–1.9)) compared to only 0.007 per 100,000 ((95%CI 0.003–0.01)) in Finnish ethnicity.



Conclusion: These data provide the first global prevalence estimate of LAL-D, in addition to an unbiased description of the multi-ethnic risk. Though LAL-D may be underdiagnosed, it is a rare disorder and will account for only a minority of patients presenting with non-alcoholic fatty liver disease.

SAT-060

Correlation of autotaxin levels, serum bile acids, and pruritus in a multiple-dose, open-label, multinational study of the ileal bile acid transport inhibitor A4250

E. Gonzales[1], E. Sturm[2], U. Baumann[3], F. Lacaille[4], H. Arnell[5], B. Fischler[5], M.H. Jørgensen[6], R. Thompson[7], J. Mattsson[8], M. Ekelund[8], E. Lindstrom[8], P.-G. Gillberg[8], K. Torfgard[8], P. Soni[9]. [1]*University Hospitals of Paris-Sud, Pediatric Hepatology and Liver Transplantation, Bicetre, France;* [2]*University Children's Hospital Tübingen, Pediatric Gastroenterology and Hepatology, Tübingen, Germany;* [3]*Hannover Medical School, Klinik für Pädiatrische Nieren- Leber- und Stoffwechselerkrankungen, Hannover, Germany;* [4]*Necker- Enfants Maladies Hospital, Pediatric Gastroenterology Hepatology-Nutrition, Paris, France;* [5]*Astrid Lindgren Children's Hospital, Karolinska University Hospital, CLINTEC, Karolinska Institutet, Stockholm, Sweden;* [6]*Rigshospitalet, Pediatric and Adolescent Medicine, Copenhagen, Denmark;* [7]*Institute of Liver Studies, King's College London, London, United Kingdom;* [8]*Albireo AB, Gothenburg, Sweden;* [9]*Albireo Pharma, Inc., Boston, United States*
Email: paresh.soni@albireopharma.com

Background and Aims: The endophosphatase/phosphodiesterase autotaxin (ATX) and lysophosphatic acid have been proposed to play a role in cholestatic pruritus. Ileal bile acid transporter (IBAT) inhibition is a novel treatment approach for cholestatic pruritus and progression of cholestatic liver disease. A4250 is a potent, highly selective reversible IBAT inhibitor that decreases enteric bile acid reuptake with minimal systemic exposure. In a Phase 2, open-label study in children with cholestatic liver disease and pruritus, A4250 was well tolerated overall and reduced serum bile acid levels and pruritus in most patients. Statistically significant correlations were observed between reduction in serum bile acids and improvement on several pruritus scales. Here we report findings from this study on ATX levels and the relationship between ATX, serum bile acids, and pruritus.

Method: A4250 was administered orally once daily for 4 weeks at 5 doses (10–200 μg/kg) in 20 children. Endpoints included changes in serum bile acid levels (primary efficacy endpoint), pruritus, sleep disturbance, and ATX protein levels (measured by ELISA). Correlations between bile acids, ATX, and pruritus as measured by visual analog scale (VAS)-Itch score were also examined.

Results: At baseline, the correlation between ATX level and pruritus score was strong (VAS-Itch, Pearson $r = 0.67$; $p = 0.001$), whereas ATX was not strongly correlated with serum bile acids (Pearson $r = 0.33$; $p = 0.12$). ATX decreased in most patients following treatment with A4250, with an overall mean reduction of 21 5% (SEM). Percent decrease in ATX was strongly correlated with percent decrease in serum bile acids (Pearson $r = 0.60$; $p = 0.003$). There was a trend toward correlation of percent change in ATX and absolute change in VAS-Itch (Pearson $r = 0.39$; $p = 0.075$).

Conclusion: While improvements in pruritus have been previously reported in this study to be correlated with reductions in serum bile acids, this is the first report of a correlation between reductions in serum bile acids and reductions in ATX with an IBAT inhibitor in this patient population. Further studies to investigate the role and importance of ATX as a biomarker of cholestatic pruritus in children are warranted.

SAT-061

Liver disease in a cohort of patients with Gaucher disease from Southern Brazil: a cross-sectional study

R. Starosta[1], A.D. Dornelles[2], F.P. Vairo[1,3], M.R. Álvares-Da-Silva[4], I.V.D. Schwartz[1]. [1]*Post-Graduation Program on Genetics and Molecular Biology, Service of Medical Genetics, Porto Alegre, Brazil;* [2]*Post-Graduation Program on Child and Adolescent Health, Service of Medical*

Genetics, Porto Alegre, Brazil; [3]Mayo Clinic, Center for Individualized Medicine, Rochester, MN, United States; [4]Hospital de Clínicas de Porto Alegre, Service of Gastroenterology, Porto Alegre, Brazil
Email: rodrigo.starosta@ufrgs.br

Background and Aims: Gaucher disease (GD) is characterised by glucosylceramide build-up in macrophages, which may cause liver damage. Still little is known about the natural history of liver injury in GD, which ranges from mild steatosis to full-blown cirrhosis. We aim to describe the liver involvement found in patients followed at the Gaucher Reference Centre of Hospital de Clínicas de Porto Alegre (HCPA).
Method: A cross-sectional, retrospective study. Data were obtained from patients' electronic medical records. The most recent value for each exam was considered. When the most recent exam was older than two years, the patient was excluded from the analysis. Values were presented as median + IQR.
Results: Thirty-nine patients were included in the study (GD type I = 36, GD type III = 3; median age = 35 ± 24 yr; male = 18). Thirty-eight patients were on treatment, most with enzyme replacement therapy (ERT, n = 35). Seven patients were splenectomised (17.95%). According to the abdominal ultrasound or abdominal MRI (n = 31), 12 patients (38.7%) have had liver findings, being steatosis and cirrhosis the most frequent (n = 5 and 2, respectively). The following liver biochemical abnormalities were found: AST in 2 patients (median of all patients = 20 ± 8 UI/dl), ALT in 2 patients (median = 21 ± 11 UI/dl), γGT in 15 patients (median = 26 ± 14.5 UI/dl), alkaline phosphatase in 4 patients (median = 65 ± 22.5 UI/dl), total bilirubin in 3 patients (median = 0.6 ± 0.6 mg/dl), and albumin in 1 patient (median = 4.5 ± 0.5 g/dl). Serum ferritin in 27 patients (median = 439.7 ± 555.6 ng/ml). Hepatitis B was present in one case. Five patients had liver biopsies, which showed iron deposition in the cytoplasm of hepatocytes and in Kupffer cells in all patients, ranging from mild to severe; one of the biopsies showed a hepatic gaucheroma.
Conclusion: Liver disease may be more frequent than expected in GD. Despite treatment, many patients present at least one altered liver enzyme, which may indicate chronic liver damage activity. The high prevalence of steatosis may reflect chronic steatohepatitis due to disease activity. Hepatologists should be aware of liver involvement in GD.

SAT-062

Characteristics associated with non-response to ursodeoxycholic acid in primary biliary cholangitis

T. Dias[1], A. Santos[1], J. Carvalho[2], M. Bento-Miranda[3], M. Sant'anna[3], F. Calinas[4], R. Loureiro[4], A. Martins[5], G. Alexandrino[5], I. Cotrim[6], C. Martins[6], J. Presa[7], M. Mesquita[7], J. Nunes[8], A. Ferreira[8], A. Horta e Vale[9], A.L.C. Alves[10], I. Pedroto[11], L. Maia[11], A. Banhudo[12], I. Mocanu[13], A.M. Laranjo[13], S. Lopes[14], R. Liberal[14], C. Fonseca[15], J. Oliveira[16], M. Gomes[17], H. Cortez-Pinto[2]. *[1]Centro Hospitalar e Universitário de Coimbra, Internal Medicine, Coimbra, Portugal; [2]Centro Hospitalar Lisboa Norte/Hospital Santa Maria, Gastroenterology, Lisbon, Portugal; [3]Centro Hospitalar e Universitário de Coimbra, Gastroenterology, Coimbra, Portugal; [4]Centro Hospitalar Lisboa Central/Hospital dos Capuchos, Gastroenterology, Lisbon, Portugal; [5]Hospital Prof. Doutor Fernando Fonseca, Gastroenterology, Amadora, Portugal; [6]Centro Hospitalar Leiria/Hospital de Santo André, Gastroenterology, Leiria, Portugal; [7]Centro Hospitalar de Trás-os-Montes e Alto Douro/Hospital de Vila Real, Unit of Hepatology, Vila Real, Portugal; [8]Hospital Beatriz Ângelo, Gastroenterology, Loures, Portugal; [9]Hospital da Luz Arrábida, Gastroenterology, Vila Nova de Gaia, Portugal; [10]Centro Hospitalar Setúbal - Hospital S. Bernardo, Gastroenterology, Setúbal, Portugal; [11]Centro Hospitalar do Porto/Hospital Geral de Santo António, Gastroenterology, Porto, Portugal; [12]Hospital Amato Lusitano, Gastroenterology, Castelo Branco, Portugal; [13]Hospital do Espírito Santo de Évora, Gastroenterology, Évora, Portugal; [14]Centro Hospitalar do Porto/Hospital São João, Gastroenterology, Porto, Portugal; [15]Hospital Garcia de Orta, Gastroenterology, Almada, Portugal; [16]Exigo Consultores, Outcomes Research, Lisbon, Portugal; [17]Exigo Consultores, Outcomes Research, Lisboa, Portugal*
Email: marta.gomes@exigoconsultores.com

Background and Aims: Non-response to treatment with ursodeoxycholic acid occurs in 20–40% of patients with primary biliary cholangitis, leading to disease progression. The aim of our study is to assess the patients characteristics associated with non-response.
Method: We performed a retrospective cohort study using a nationwide registry of liver diseases, selecting exclusively patients with primary biliary cholangitis as primary diagnosis. Main endpoints included the evaluation of treatment response to ursodeoxycholic acid and the assessment of the patients' characteristics associated with non-response. Response to treatment was evaluated according to Barcelona, Paris I and Paris II criteria. Logistic regression was used to assess the patients' characteristics associated with non-response to treatment, according to Paris-II criteria. The significance level adopted was 5%. All analysis were conducted in R software.
Results: A total of 345 patients were identified with primary diagnosis of primary biliary cholangitis. At diagnosis, mean age was 55.0 years, 89.9% were women, 89.9% had positive anti-mitochondrial antibodies, 21.8% had cirrhosis and almost half (55.7%) of the population were asymptomatic. More than one fifth of patients (21.6%) developed symptoms (pruritus, fatigue and jaundice) between diagnosis and the time of assessment cut-off date, despite treatment initiation. Non-response to ursodeoxycholic acid was 33.9% (63/186), 43.7% (59/135) and 64.3% (101/157) according to the Barcelona, Paris-I and Paris-II criteria, respectively. In the multivariate analysis the presence of symptoms (OR = 7.7 [95%CI = 2.5–24.3], $p < 0.001$) and cirrhosis (OR = 4.2 [95%CI = 1.2–17.9], $p = 0.027$) at diagnosis was significantly associated with non-response to ursodeoxycholic acid according to Paris II criteria, after one year of treatment.
Conclusion: Rate of treatment response with ursodeoxycholic acid varies substantially according to different criteria. Non-response to ursodeoxycholic acid is more likely in patients with symptoms and more advanced liver disease at diagnosis. Assessment of the patient's characteristics at diagnosis can be useful to guide clinical and therapeutic decision making.

SAT-063

Evaluation of the new criteria in the diagnosis of cystic fibrosis liver disease

A. Alexopoulou[1], S. Pouriki[1], L. Vasilieva[1], T. Alexopoulos[1], F. Diamantea[2], M. Gioka[2], A. Nakou[2], D. Zampetas[1], I. Mani[1], S. Ntourakis[1]. *[1]2nd Department of Internal Medicine and Research Laboratory, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece; [2]Third Respiratory Medicine Department, Sismanogleio General Hospital, Athens, Greece*
Email: alexopou@ath.forthnet.gr

Background and Aims: In cystic fibrosis (CF), liver disease (CFLD) is the third leading cause of mortality. As liver biopsy has been considered as inconsistent in diagnosis of CFLD, a combination of modalities additional to liver histology, including physical examination, biochemical and imaging were utilized in the conventional Debray criteria (DC). More recently, noninvasive biomarkers have been applied and were included in the New criteria (NC) (Koh C et al, Hepatology 2017;66:591–601). In current study we aimed to evaluate the NC for the diagnosis of CFLD.
Method: Longitudinal data were collected from a cohort of genetically confirmed CF patients. CFLD was diagnosed by both DC and NC. According to NC, CFLD was present if there was radiologic or histologic evidence of cirrhosis or diffuse liver disease or a positive finding in at least two of the four categories including liver function tests, imaging, transient elastography (>6.8 kPa) or other noninvasive liver fibrosis biomarkers [AST/ALT ratio (AAR), ≥1, FIB-4 index ≥3.25, APRI > 0.50].

Results: 62 patents with CF, [56.5% male, median age at diagnosis 6.00 (2.25–33.00) months, age at enrollment 25 (22–31) years], were prospectively followed up for 33 (28–36) months. 16 (25.8%) patients met the classical DC for CFLD. No difference in demographics, INR, AAR and FIB4 were observed in patients with CFLD vs those without according to DC. However, AST (P = 0.012), ALT (p = 0.045), ALP (p = 0.022), g-GT (p = 0.026), liver stiffness (p = 0.03) and APRI (p = 0.032) were higher in CFLD vs no CFLD patients. According to NC, 26 (41.9%) had CFLD. No difference in age at diagnosis and enrollment, sex, genotypes and duration of follow-up were shown between CFLD and no CFLD. However, AST (p = 0.001), ALP (p = 0.002), g-GT (p = 0.002), INR (p = 0.023), liver stiffness (p < 0.001), AAR (p = 0.035), FIB4 (p < 0.001) and APRI (p = 0.001) were higher in CFLD vs no CFLD patients. 13 (50%) of patients who were classified as CFLD according to the NC had evidence of diffuse liver disease/cirrhosis in imaging and all of them had at least one additional parameter. From the 13 (50%) patients with no evidence of diffuse liver disease, 38.4%, 30.8% and 30.8% had 2, 3 and 4 of the four sets of parameters, respectively, classifying them as CFLD.
Conclusion: The New criteria are able to identify 16.1% more CFLD patients compared to historical ones. The multiple non invasive biomarkers incorporating in New criteria may enhance the ability to detect CFLD.

Non-invasive assessment of liver disease except NAFLD

SAT-065

Transient elastography as a screening method for chronic liver disease in apparently healthy population. Results from de ETHON cohort

E. Llop[1,2], P. Iruzubieta[2,3], C. Perelló[1], J. Cabezas[3], D. Escudero-García[4], M. González[3], M.H. Conde[1], L. Puchades[4], M.T.A. Loste[3], M. Serra[4], J. Crespo[3,5], J.L.C. Panero[1,5]. *[1]Servicio de Aparato Digestivo. Hospital Universitario Puerta de Hierro Majadahonda. CIBERHD. Facultad de Medicina. Universidad Autónoma de Madrid; [2]Co-author; [3]Servicio de Aparato Digestivo. Hospital Universitario Marqués de Valdecilla. IDIVAL. Santander. Facultad de Medicina. Universidad de Cantabria; [4]Servicio de Medicina Digestiva. Hospital Clínico Universitario Valencia. INCLIVA; [5]Co-Senior Author*
Email: elballop@gmail.com

Background and Aims: Transient elastography (TE) has been very useful for the diagnosis of chronic liver diseases. The aim of this study was to evaluate the use of TE in apparently healthy population and to determine the factors associated with the presence of significant fibrosis (SF) and advanced fibrosis (AF).
Method: Epidemiological, cross-sectional, population based multicenter (Santander, Madrid, Valencia) study from the ETHON cohort. The participants were selected through a random and representative sample by means of sampling by two-stage conglomerates with stratification according to socioeconomic status, rural/urban area and age, being representative of the general population. TE, an epidemiological questionnaire, laboratory test and anthropometric measurements were obtained in the same day.
Results: Between 2015 and 2017, 12519 subjects were included, in 1079 (8.6%) no reliable TE results were obtained. Data of 11440 subjects were analyzed. 53.8% of subjects aged 50–79 years, 58.1% women. 16.3% presented strict criteria for metabolic syndrome (MS) (NCEP ATP-III), 1.3% with anti-HCV+, 0.8% HBsAg+, 7.3% reported harmful alcohol consumption. 7.4% had SF (TE > 7 ≤ 12.6 KPa) and 1.6% had AF (TE > 12.6 KPa). 66.1% of patients with SF and 41.1% of patients with AF had normal liver function tests. In 48.8% of the subjects with SF Controlled Attenuation Parameter (CAP) values were suggestive of severe steatosis (S2 > 280 db/m) OR 2.2 (1.7–2.8) (p < 0.001) and in 60% of the subjects with AF CAP values were suggestive of severe steatosis (S2 > 280 db/m) OR 3.3 (1.9–5.7) (p < 0.001). In the multivariate analysis, factors independently related to the presence of SF were: age OR 1.5 (1.3–1.7) (p = 0 < 0.001), male sex OR 1.7 (1.5–2.0) (p < 0.001), the MS OR 1.8 (1.5–2.1) (p < 0.001), anti-HCV + OR 1.9 (1.1–3, 0) (p = 0.02) and HBsAg+ OR 2.5 (1.4–4.4) (p = 0.002). In AF, age OR 1.5 (1.3–1.7) (p < 0.001), male sex OR 1.7 (1.5–1.9) (p < 0.001) and the MS OR 1.8 (1.5–2.1) (p < 0.001) were independently related to its presence.
Conclusion: A high percentage of the apparently healthy population showed SF. The independent predictors of its presence were age, male sex, MS, antiHCV+ and HBsAg + . On the other hand, a non-negligible percentage of the apparently healthy population had AF. Age, male sex and MS were the independent factors of its presence. TE is a useful tool for screening chronic liver disease in healthy population, even with normal liver function tests.

SAT-066

Prognostic value of 2D-shear wave elastography for staging cirrhosis in chronic liver diseases in two severity classes according to liver-related complications

P. Pollo-Flores[1], M. Munteanu[2], A. Ngo[3], Y. Ngo[3], E. Luckina[4], T. Phim[5], H. Perazzo[6], L. Bonyhay[7], M. Rudler[7], P. Lebray[7], D. Thabut[8], V. Ratziu[8], T. Poynard[8]. *[1]CAPES, UFF Internal Medicine Department, Niteroi, Brazil; [2]Biopredictive, APHP, Paris, France; [3]Biopredictive, APHP, Paris, Brazil; [4]APHP, Inserm; [5]APHP, Biopredictive; [6]FIOCRUZ, Infectious National Institute, Rio de Janeiro, Brazil; [7]APHP, Paris, France; [8]APHP, UPMC, Paris, France*
Email: priscilapollo96@gmail.com

Background and Aims: In chronic liver disease (CLD), FibroTest (FT, BioPredictive), and transient elastography (TE M-probe, Echosens), are associated with increased overall and liver-related mortality and morbidity. Moreover, FT and TE-M were validated as markers of occurrence of cirrhosis without complications (F4.1), oesophageal varices (EV) grade 2 or more (F4.2), and severe complications (SC) (F4.3) – EV rupture, encephalopathy, ascites and hepatocellular carcinoma (HCC) (J Hepatol 2014). The aim of this study was to extend the validation of elastography by 2D-shear wave elastography (2D-SWE), as a prognostic marker of occurrence of cirrhosis without complications (F4.1) versus cirrhosis with EV and SC (F4.2-F4.3).
Method: 3,853 patients (pts) with CLD were pre-included prospectively from Jan-2012 to Dec-2013. 3627pts had 2D-SWE, and 2686pts (74.1%) had all methods. Appli-2D-SWE was defined after excluding minimal stiffness <0.2 kPa. Cirrhosis was defined by FibroTest ≥0.74 and TE-M ≥12.5 kPa respectively. The applicable 2D-SWE, TE-M, -XL and M or XL and FT were, respectively, 90.4%, 80.0%, 90.8%, 94.5% and 99.5%.
Results: 585pts with applicable-2D-SWE and cirrhosis as per FT or TE-M-XL were followed up for a median (range) 30(0–62.3) months and 13(4.2%) died. None had history of complications, after 30 months had occurred 47 varices (F4.2, incidence of 8.0%) and 50 severe complications (F4.3 8.6%), including HCC in 20 (3.4%). The survivals (95%CI) without EV/SC were: 78.8% (69.4–88.2) in the group F4.23 (2D-SWE ≥ 20 kPa); 89.9% (84.3–95.5) in F4.1 (12.5 kPa ≥ 2D-SWE < 20 kPa, p = 0.025 vs F4.23); and 94.5% (91.4–97.6) in the group without cirrhosis (noF4) (p = NS vs F4.1). (Figure 1). Among pts with concomitant appli-TE, FT and 2D-SWE, the prognostic AUROCs (95% CI) for esophageal varices and severe complications were: 0.94 (0.90–0.97), 0.92 (0.87–0.95, p = NS vs TE) and 0.79 (0.69–0.86, p < 0.01 vs TE and vs FT), respectively.

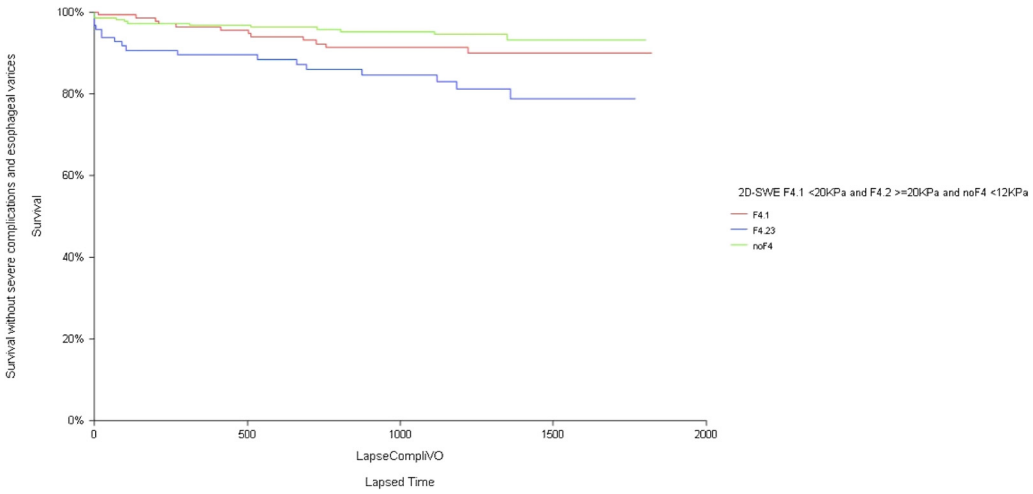


Figure 1: (abstarct: SAT-066): Survival Curves according to 2D-SWE classes of liver disease severity.

Conclusion: Liver biomarkers, such as 2D-SWE, have prognostic values in patients with CLD for predicting varices and severe complications in cirrhotic patients. Previously validated FT and TE predictions of varices and severe complications were comparable and both were superior to 2D-SWE.

SAT-067

Reliability criteria for liver stiffness measurement with ARFI

J. Boursier[1,2], C. Cassinotto[3], L. Adrien[1], S. Shili[4], J. Lebigot[5], B. Lapuyade[6], P. Cales[1,2], H. Jean-Baptiste[7], S. Michalak[2,8], B. Le Bail[9], V. Cartier[5], A. Mouries[3], F. Oberti[1,2], I.F. Hubert[1,2], F. Chermak[7], C. Aubé[2,5], V.D. Ledinghen[10]. *[1]Angers University Hospital, Hepato-Gastroenterology, Angers, France; [2]Angers University, HIFIH Laboratory, Angers, France; [3]Bordeaux University Hospital, Radiology, Bordeaux, France; [4]Bordeaux University Hospital, Hepato-Gastroenterology, Pessac, France; [5]Angers University Hospital, Radiology, Angers, France; [6]Bordeaux University Hospital, Radiology, Bordeaux, France; [7]Bordeaux University Hospital, Hepato-Gastroenterology, Bordeaux, France; [8]Angers University Hospital, Pathology Department, Angers, France; [9]Bordeaux University Hospital, Pathology Department, Bordeaux, France; [10]Bordeaux University Hospital, Hepato-Gastroenterology, Bordeaux, France*
Email: jeboursier@chu-angers.fr

Background and Aims: Acoustic Radiation Force impulse (ARFI, also named point-shear wave elastography), is an elastography modulus included in a widely used ultrasonographic device which allows for the non-invasive evaluation of liver fibrosis in chronic liver diseases through liver stiffness measurement (LSM). We aimed to determine the reliability criteria of LSM with ARFI.
Method: 1,094 patients with chronic liver diseases had liver biopsy and LSM with ARFI in two centres. ARFI examination was performed in fasting condition by experienced radiologists. Pathological examinations of liver biopsies were performed in each centre by a senior expert specialized in hepatology. Advanced fibrosis was defined as NASH CRN F ≥ 3 or Metavir F ≥ 2.
Results: LSM with ARFI failed (no measurement) in 10 patients (0.9%). Among the 1084 remaining patients included in the statistical analysis (male: 61.9%; age: 54.3 ± 13.3 years; NAFLD 48.5%, BMI: 28.9 ± 6. kg/m2), 48.5% had advanced fibrosis and 16.8% were cirrhotic. The cause of chronic liver disease was NAFLD in 48.5%, virus: 26.3%, alcohol: 12.2%, and other: 13.0%. AUROC, diagnostic cut-offs, and rate of patients correctly classified for advanced fibrosis and cirrhosis were, respectively: 0.773 ± 0.014 and 0.839 ± 0.014, 1.37 m/s and 1.87 m/s, 72.0% and 78.4%. ARFI reliability relied on the IQR/M ratio, especially for intermediate/high levels of liver stiffness. Three reliability categories were defined for LSM with ARFI: "very reliable" (IQR/M < 0.15), "reliable" (0.15 ≤ IQR/M < 0.35 or IQR/M ≥ 0.35 with ARFI median <1.37 m/s), and "poorly reliable" (IQR/M ≥0.35 with ARFI median ≥1.37 m/s). Using these new criteria, the rate of patients correctly classified for advanced fibrosis was, respectively: 80.9%, 73.7%, and 57.8% (p = 0.029 between very reliable and reliable; p < 0.001 for other paired comparisons); and for cirrhosis: 92.6%, 83.4%, and 50.0% (p < 0.001 for each paired comparison). Results were not significantly different between the two centres. 23.6% of the ARFI examinations were very reliable, 55.0% reliable, and 21.4% poorly reliable. The skin-liver capsula distance was an independent predictor of poorly reliable ARFI examination which occurred in 52.7% of patients having a distance ≥30 mm.
Conclusion: Based on IQR/M ratio and ARFI median, we defined three reliability categories for LSM with ARFI associated with significantly different diagnostic accuracies. These new reliability criteria for ARFI will help physician to accurately evaluate the severity and follow chronic liver diseases.

SAT-068

The ProC3 marker of type III collagen formation accurately reflects hepatic inflammation and fibrosis stage in asymptomatic alcoholic liver disease patients

M. Thiele[1,2,3], M.J. Nielsen[4], B.S. Madsen[1], M. Kjærgaard[1], J. Hansen[5], S. Antonsen[6], L.M. Rasmussen[7], D. Leeming[4], S. Detlefsen[8], M. Karsdal[4], A. Krag[1,2]. *[1]Odense University Hospital, Department of Gastroenterology and Hepatology, Odense C, Denmark; [2]University of Southern Denmark, Department of Clinical Research, Odense C, Denmark; [3]Odense University Hospital, OPEN, Odense Patient data Exploratory Network, Odense C, Denmark; [4]Nordic Bioscience A/S, Biomarkers & Research, Herlev, Denmark; [5]Odense University Hospital, Department of Infectious Diseases, Odense C, Denmark; [6]Odense University Hospital Svendborg, Department of Clinical Biochemistry, Svendborg, Denmark; [7]Odense University Hospital, Department of Clinical Biochemistry and Pharmacology, Odense C, Denmark; [8]Odense University Hospital, Department of Pathology, Odense C, Denmark*
Email: maja.thiele@rsyd.dk

Background and Aims: Alcoholic liver disease (ALD) is characterised by a long, compensated phase of collagen accumulation, driven by hepatic inflammation and profibrotic signalling. Most physicians therefore evaluate ALD patients using liver fibrosis markers. However,

currently available markers are static and fail to reflect the dynamics of fibrosis progression. Neoepitopes are extracellular matrix protein fragments that reflect true collagen formation and degradation. We therefore aimed to assess whether collagen formation, measured by novel neoepitope markers, reflect alcoholic liver fibrosis stage and inflammatory activity grade.

Method: Prospectively conducted study from 2013 to 2016. All investigations performed on the same day. We used liver biopsy as reference for fibrosis (Kleiner fibrosis stage F0-4) and alcoholic steatohepatitis (NAFLD Activity Score; ballooning 0–2, lobular inflammation 0–3 and steatosis 0–3). We recruited two cohorts of asymptomatic, compensated ALD patients; one from primary care (n = 132, 6% prevalence of ≥ F3) and one from secondary healthcare (n = 172, 35% prevalence) and compared them to 50 healthy controls, matched 1:6 for age and gender (no chronic illnesses, medication, alcohol or NAFLD).

Results: We screened 12 neoepitope markers. The N-terminal pro-peptide of type III collagen formation (ProC3) correlated strongest with fibrosis, steatosis and hepatic inflammation (sum of ballooning and lobular inflammation scores). ProC3 also correlated with non-invasive markers of fibrosis: Enhanced Liver Fibrosis test (r = 0.750), FibroScan (r = 0.552) and FibroTest (r = 0.534). Similarly, ProC3 correlated with inflammation markers: ActiTest (r= 0.203), cytokeratin-18 markers of apoptosis (M30, r = 0.516) and necrosis (M65, r = 0.533). ProC3 was lowest in the control population (median 8.4 ± 2.1), increased in ALD patients with fibrosis stage 0–1 and inflammation grade 0–1 (11.1 ± 5.1; p < 0.001; n = 121), and further increased (average 3.4 ± 0.3; p < 0.001) for every one fibrosis stage or activity grade elevation. We measured the highest ProC3 values in patients with both advanced fibrosis and high inflammatory activity (64.8 ± 26.6; n = 27). ProC3 diagnosed advanced fibrosis (F ≥ 3) with good accuracy, both in the primary care (AUROC 0.90) and in the secondary care cohort (AUROC 0.84). ProC3 were also good to detect patients with the highest inflammation grades in both cohorts (AUROCs 0.83 and 0.81).

Conclusion: ProC3, the N-terminal pro-peptide of type III collagen formation accurately reflects biopsy-verified fibrosis stage and hepatic inflammation grade in alcoholic liver disease patients. The marker may therefore be suited as tool to monitor disease progression.

SAT-069

Serum hyaluronic acid is an independent predictor of mortality in patients with chronic liver disease

N. Plevris[1], R. Sinha[1], A. Hay[2], J. Plevris[1], P. Hayes[1]. [1]*Royal Infirmary of Edinburgh, Hepatology, Edinburgh, United Kingdom;* [2]*Royal Infirmary of Edinburgh, Critical Care, Edinburgh, United Kingdom*
Email: n.plevris@hotmail.co.uk

Background and Aims: Hyaluronic acid (HA) is a well established non-invasive marker of liver fibrosis. Despite this its prognostic abilities still remain to be fully established. The aim of this study was to investigate the ability of a single serum HA measurement to independently predict mortality in patients with chronic liver disease (CLD) of varying aetiology.

Method: This was a retrospective single centre cohort study. All serum HA measurements in patients with CLD, irrespective of aetiology, between 1995 and 2010 were identified. Patient characteristics, blood parameters (Cr, Na, Bi, Alb, PT, INR) and MELD score at point of HA were determined from review of medical records. All cases were followed up from the date of index HA measurement until the date of death, date of transplant or censor date (1/7/2015). Patients with a known diagnosis of hepatocellular carcinoma or rheumatoid arthritis were excluded. Primary outcomes were all-cause mortality and liver-related mortality. For survival analysis patients were categorised into three groups according to their HA value (Group 1 HA < 100 µg/l, Group 2 HA 100–300 µg/l, Group 3 HA > 300 µg/l).

Results: 589/615 (95.8%) patients with HA levels fulfilled inclusion criteria. 371 (63.0%) patients were males and the median age was 58.0 (IQR 19.0–88.0). Median follow-up was 5.6 years (IQR 0.1–19.7). 207 (35.1%) patients died during the follow-up period, 29 (4.9%) were transplanted, and 353 (60.0%) were transplant free survivors. 37 (6.3%), 403 (68.4%) and 109 (18.5%) patients had HA levels < 100 µg/L, 100–300µg/l and >300 µg/l respectively. Kaplan-Meier survival analysis showed survival was significantly different between the three HA groups for liver related mortality as well as all cause mortality (p < 0.001, Figure). In multivariate Cox regression analysis, HA level (HR 1.04, 95% CI 1.02–1.06, p < 0.001) together with MELD score (HR 1.12, 95% CI 1.09–1.15, p < 0.001), age (HR 1.03, 95% CI 1.01–1.04, p < 0.001) and aetiology of liver disease (p < 0.01) were independent predictors of survival. The unadjusted area under the ROC curve for predicting all-cause and liver related mortality was: 0.75 and 0.85 for HA vs 0.80 and 0.84 for MELD at 1-year; 0.67 and 0.77 for HA vs 0.78 and 0.82 for MELD at 3-years; 0.65 and 0.77 for HA vs 0.73 and 0.78 for MELD at 5-years.

Conclusion: To our knowledge this is the largest study investigating the prognostic ability of HA in a cohort of CLD patients with varying aetiologies. In patients with CLD we have shown that a single HA measurement can independently predict liver-related and all-cause mortality with accuracy comparable to MELD.

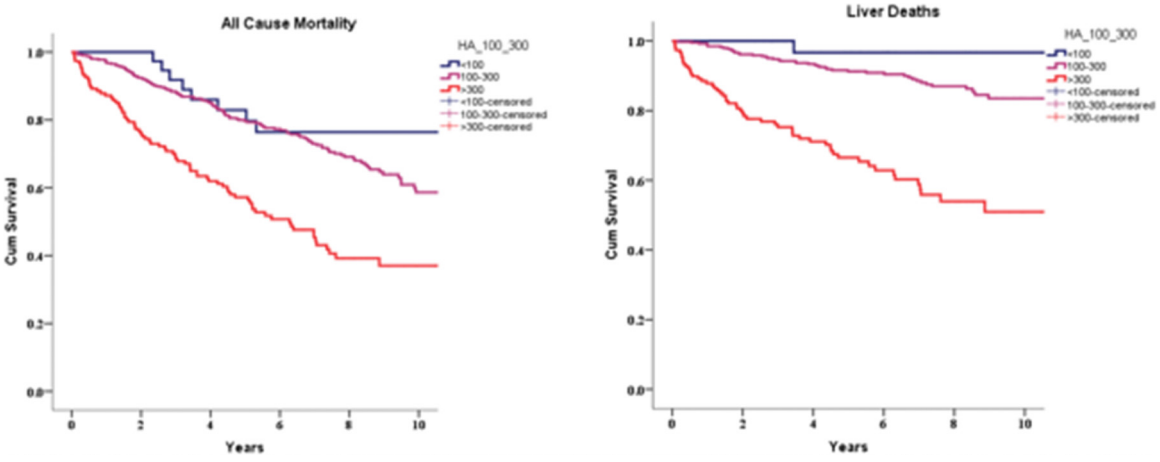


Figure: (abstract: SAT-069).

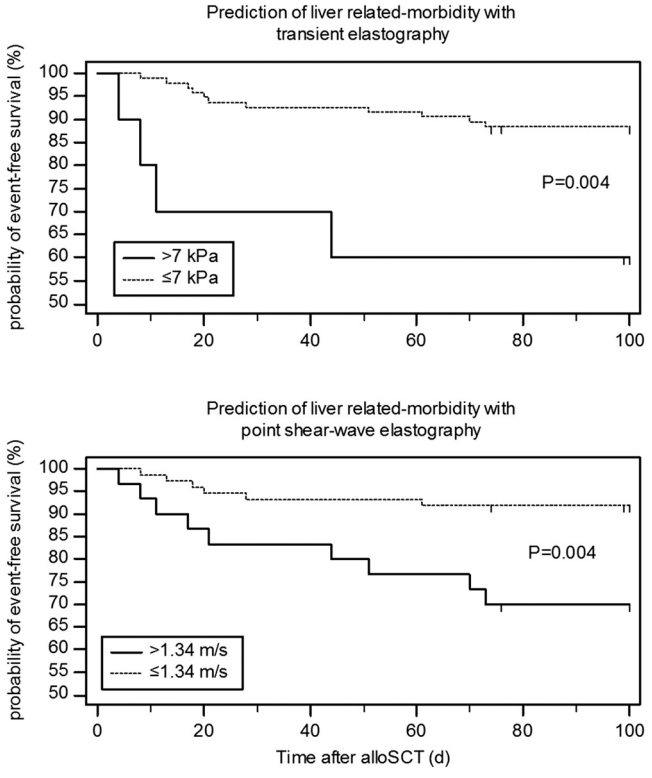
SAT-070

Liver stiffness measurement predicts short-term liver related-morbidity of allogeneic hematopoietic stem cell transplantation

T. Karlas[1], W. Tina[1], B. Sebastian[1], D. Christine[2], L. Franziska[1], D. Niederwieser[2], B. Gerhard[2], J. Mössner[1], J. Wiegand[3], V. Keim[1], G.-N. Franke[2]. *[1]University Hospital Leipzig, Division of Gastroenterology, Leipzig, Germany; [2]University Hospital Leipzig, Division of Hematology and Oncology, Leipzig, Germany; [3]University Hospital Leipzig, Division of Gastroenterology, Section of Hepatology, Leipzig, Germany*
Email: thomas.karlas@medizin.uni-leipzig.de

Background and Aims: Allogeneic hematopoietic stem cell transplantation (alloHCT) is the treatment of choice for various forms of leukemia and lymphoma. Unfortunately, the intended graft-versus-leukemia effect is frequently accompanied by potentially severe side effects of the conditioning regimen and the graft-versus-host disease (GvHD). Especially sinusoidal obstruction syndrome (SOS), drug-induced liver injury (DILI) and liver GvHD contribute to early morbidity and mortality of alloHCT. Liver stiffness measurement (LSM) may potentially help to predict these liver-related complications.

Method: For this monocentric prospective study patients (pts) scheduled for alloHCT underwent LSM with point shear-wave elastography (pSWE) and transient elastography (TE) before start of the conditioning therapy. Pts were followed up for 100 days after alloHCT and classified according to liver-related outcome. Selected symptomatic patients underwent LSM during follow-up.



Results: Of 120 screened patients, 105 fulfilled the inclusion criteria: 40% female, median age 74 (range 18–74) years, body mass index 24.6 ± 4.6 kg/m². Indications for alloHCT comprised acute leukemia/ myelodysplastic syndrome/ lymphoma and other in 50/29/21% of cases. Conditioning regimens were non-myeloablative in 56 pts, reduced intensity in 22 pts and myeloablative in 27 pts. 22 pts had a 10/10 HLA-matched related donor, 62 a matched unrelated donor (UD) and 21 a mismatched UD. 32 (30%) pts developed severe complications and 9 of these died during follow-up. 15 pts (40% female, age 59 (39–68) years) developed liver-related complications: n = 7 SOS, n= 6 liver GvHD, and n = 2 DILI. In this group, baseline TE (>7 kPa) and pSWE (>1.34 m/s) were increased in 27% and 60% of cases compared to 7% and 23% in the group without liver events ($p < 0.05$, respectively). Pts with increased LSM showed a significantly reduced event-free survival (Figure).

15 pts underwent LSM after alloHCT when a liver event was suspected. Pts with definite diagnose of liver-related complications (n = 7) had higher TE and pSWE values compared to pts without confirmed event (median/IQR): 17.3 (8.8–25.8) vs. 5.3 (4.4–7.9)kPa, and 1.77 (1.44–2.47) vs. 1.15 (1.05–1.3)m/s (p = 0.028, respectively).

Conclusion: Elevated baseline liver stiffness assessed with either TE or pSWE is associated with higher risk of liver-related morbidity in the early phase after allogeneic hematopoietic stem cell transplantation. LSM can be useful to diagnose liver complications after alloHCT.

SAT-071

Liver stiffness measurement by 2D SWE from General Electric is similar with Transient Elastography in clinical significant portal hypertension diagnosis

R. Corina[1], B. Procopet[2], M. Platon[3], A. Maniu[1], F. Petra[3], C. Grigoras[3], A. Bugariu[1], M. Tantau[3], R. Badea[3], H. Stefanescu[1]. *[1]Regional Institute of Gastroenterology and Hepatology "O Fodor"; [2]University of Medicine and Pharmacy "Iuliu Hatieganu", 3rd Medical Clinic, Gastroenterology Department; [3]University of Medicine and Pharmacy "Iuliu Hatieganu", Imaging department*
Email: bogdanprocopet@gmail.com

Background and Aims: In compensated advanced chronic liver disease the occurrence of clinical significant portal hypertension (CSPH) has great negative prognostic impact. The standard method for portal hypertension assessment is hepatic venous pressure gradient (HVPG) measurement but is not widely available. Liver stiffness measurement (LSM) by transient elastography (TE) was extensively validated as valid method for diagnosis of CSPH. However, it is not technical feasible in a significant amount of patients. Lately, many other elastographic methods had emerged but still need validation. 2D shear-wave elastography from General Electric (2D-SWE.GE) is a new method developed to assess liver fibrosis.

The aim of the study is to test if 2D-SWE.GE is able to diagnose CSPH in comparison with TE and HVPG.

Method: 81 consecutive patients with advanced liver disease referred to HVPG measurement and concomitant LSM by 2D-SWE. GE and TE were included. The diagnostic performances were assessed by calculating receiver operating characteristic (ROC) curves.

Results: CSPH was found in 57 (70%) of patients [median HVPG = 16 (3–31) mmHg] and 34 (42%) had esofageal varices. There was significant difference between the median of LSM by 2D-SWE.GE in patients with or without CSPH [16.8 (6.3–36.5)kPa vs. 6.4 (3–12.4) kPa]. There was very good correlation between LSM by 2D-SWE.GE and HVPG ($r^2 = 0.750$, $p < 0.001$).

For CSPH diagnosis the AUROC for 2D-SWE.GE was 0.95 (95%CI: 0.90–0.99) ($p < 0.001$) which was identical with TE that had 0.95 (95%CI: 0.91–1.00) ($p < 0.001$). The best cut-off for 2D-SWE.GE for CSPH diagnosis according to the Youden index was 11.4 kPa (Se = 0,83 and Sp = 0.92). However, LSM by 2D-SWE.GE <9 kPa rule-out and >13 kPa rule-in CSPH.

For EV diagnosis LSM by 2D-SWE.GE's performances were lower 0.67 (95%CI: 0.54–0.80) (p = 0.01) but similar with TE 0.68 (95%CI: 0.56–0.80) (p = 0.007).

Conclusion: LSM by 2D-SWE.GE is similar with LSM by TE in CSPH. However, the performances for EV diagnosis seem to be inadequate.

This work was supported by a national grant (PN-II-RU-TE-2014-4-0356).

SAT-072

Controlled attenuation parameter reflects intrahepatic fat content in patients with compensated advanced chronic liver disease

R. Piccinni[1], S. Rodrigues[1], M. Montani[2], G. Murgia[1], M.G. Delgado[1], S. Casu[1], J.-F. Dufour[1], A. Berzigotti[1]. *[1]Inselspital, University of Bern, Swiss Liver Center, Hepatology, University Clinic for Visceral Surgery and Medicine, Bern, Switzerland; [2]Univesity of Bern, Institute of Pathology, Bern, Switzerland*
Email: rosangela.piccinni@yahoo.it

Background and Aims: Overweight/obesity and steatosis on histology have been identified as predictors of clinical decompensation in compensated Advanced Chronic Liver Disease (cACLD). Controlled attenuation parameter (CAP) is often elevated in patients with cACLD but it is not known whether in this population it correctly mirrors hepatic fat content. This study aimed at assessing the accuracy of CAP for steatosis in patients with cACLD of any cause. Secondary aim was validation of CAP IQR <40 dB/m as good quality criterion.
Method: This is a single center retrospective study including patients with liver biopsy, CAP measurement and cACLD defined according the Baveno VI criteria (LSM ≥ 10 kPa). 461 patients consecutively undergoing liver biopsy in 06/2015–06/2017 were screened. Exclusion criteria were: LSM < 10 kPa; any hepatic decompensation; no LSM/CAP available within 6 months; LSM IQR/M > 0.30.
On histology, steatosis was graded as S0 (<5%), S1 (5–33%), S2 (33–66%), S3 (>66%). Bridging fibrosis (F3) or cirrhosis (F4) of any cause was considered to confirm ACLD. For VCTE, M or XL probe were used as appropriate. The discriminative ability of CAP for any grade of steatosis and S2-S3 steatosis was studied using the area under receiving operating characteristic curves (AUROC).
Results: 124 patients with Baveno VI-defined cACLD were finally included (63% male, median age 55 y, median BMI 27.4 Kg/m^2, etiology: 30.5% NASH, 30.5% alcohol + metabolic or viral+ metabolic, 15.2% viral, 7.2% autoimmune, 4.2% alcohol, 12.4% others; median ALT 60 U/l, PTL 168). Median LS and CAP were respectively: 16.3 kPa (range: 10–75) and 272 dB/m (range 0–400; IQR < 40 dB/m in 60%). On liver biopsy, steatosis was found in 69.4% (S1 33.9%, S2 19.4%, S3 16.1%), and S2-S3 was almost exclusively seen in patients with NAFLD/NASH or metabolic syndrome + alcohol or viral disease (43 out of 44). CAP was accurate in identifying any steatosis (AUROC 0.827; 95%CI 0.746–0.908, p < 0.0001), and S2-S3 steatosis (0.864; 95%CI 0.796–0.93, p < 0.0001). Restricting the analysis to the 73 patients with bridging fibrosis/cirrhosis on histology, 55 (75%) had steatosis (S2-S3 in 27). In this subgroup CAP performance for any degree of steatosis and S2-S3 steatosis was 0.766 (0.631–0.900), p = 0.001 and 0.828 (0.727–0.930), p < 0.001 respectively. CAP performed worse in patients with CAP IQR ≥ 40dB/m (any steatosis: AUROC 0.675 vs 0.781 in patients with CAP IQR < 40dB/m; steatosis S2-S3: AUROC 0.675 vs. 0.799).
Conclusion: Steatosis is very frequent in patients with histologically confirmed advanced fibrosis and cirrhosis and clinical features of metabolic syndrome. CAP discriminative ability in this specific population is fair for steatosis and good for steatosis S2-S3. CAP IQR ≥ 40dB/m should be considered an indicator of lower diagnostic accuracy in this setting.

SAT-074

Usefulness of liver stiffness measurement by transient elastography for predicting complications in patients with alcoholic liver disease

A. Gomez, B. Redondo, M. Fraile, A. Castano-Garcia, M. Torner, M.L.G. Dieguez, V. Cadahía-Rodrigo, M. Varela, P. Alonso, C. Álvarez-Navascués, M. Rodríguez. *Hospital Universitario Central de Asturias, Liver Unit. Gastroenterology & Hepatology department, Oviedo, Spain*
Email: anagomezoutomuro@gmail.com

Background and Aims: Measurement of liver stiffness by transient elastography (TE) has shown to be useful to predict the risk of developing cirrhosis complications (CC) in patients with viral liver cirrhosis, but there are no data in patients with alcoholic liver cirrhosis (ALC). Aim: To know the ability of TE to predict the development of CC in patients with ALC.
Method: 276 patients with Child class A/B ALC, without hepatocellular carcinoma (HCC) and without decompensation at the time of inclusion were enrolled, all of them with a valid TE measurement (Fibroscan®), and clinical-demographic variables recorded at inclusion, were analyzed. 82% male sex, mean age 56.5 ± 8.4 years, 93% Child A, 80% had esophageal varices and 63.4% had had at least one previous episode of CC. Patients were followed prospectively with clinical, analytical and ultrasound controls, and CC during the follow-up were registered. For statistical analysis, the usual methods were used.
Results: During a mean follow-up of 29.2 ± 17.3 months, 73 patients developed CC (29 ascites, 17 variceal bleeding, 14 encephalopathy and 13 HCC) with a 4-year cumulative probability of 37.2%. The diagnostic accuracy of TE to predict the development of CC showed an AUC of 0.675 (0.607–0.743). TE value of 25 kPa allowed to distinguish two groups with different risk of developing CC: ≤25 and >25 with a mean annual incidence of 4.5% and 15.5% and a 2-year cumulative probability of 11.6% and 27,8% respectively (p < 0.001). Other variables that were associated in the univariate analysis with the risk of developing CC were: male sex (p = 0.04), esophageal varices (p = 0.040), platelet count < 130 × 10^3/mm^3 (p = 0.003), Child B (p < 0.001), AST > ULN (p = 0.040) and GGT > ULN (p = 0.053). On the contrary, age (p = 0.94) previous CC (p = 0.20) or ALT > ULN (p = 0.50) were not associated with the development of CC. In multivariate analysis, variables independently associated with the development of CC were male sex (OR:2.30; 95% CI:1.04 to 5.09; p = 0.039), Child B (OR:2.91; 95% CI:1.42–5.97, p = 0.003) and FS > 25 kPa (OR:2.72, 95% CI:1.41.5.24, p = 0.003).
Conclusion: Measurement of liver stiffness using elastography is useful to predict the risk of developing complications in patients with alcoholic liver cirrhosis. A value of 25 kPa allows to distinguish two groups of patients with different risk. In patients with compensated alcoholic cirrhosis, the history of previous decompensation does not influence the development of future complications.

SAT-075

Evaluation of multiparametric MRI in comparison with MR elastography in patients evaluated for chronic liver disease

S. Bravo[1], M. Kelly[2], P. Xu[2], K. Hollar[3], M. Raymer[3], R. Banerjee[2], S. Neubauer[2]. *[1]Sand Lake Imaging, Orlando, United States; [2]Perspectum Diagnostics Ltd, Oxford, United Kingdom; [3]Perspectum Diagnostics Ltd, Raleigh-Durham, United States*
Email: mattdkelly@gmail.com

Background and Aims: Liver*MultiScan*™ (LMS) uses multiparametric MR to provide surrogate markers of hepatic fat, iron content, and liver inflammation and fibrosis (LIF), which has been shown to distinguish simple steatosis from nonalcoholic steatohepatitis (NASH). We evaluated LMS in the context of a high volume Radiology practice, and compared results with those of MR Elastography (MRE).
Method: 258 patients were scheduled for MRE and LMS scanning at the same setting on Siemens 3T magnets. Clinical histories included abnormal LFTs (78), Hep B/C (41), non-alcoholic fatty liver disease NAFLD (52), liver fibrosis/NASH (27), hepatic fibrosis (50), and other (biliary cirrhosis, autoimmune Hep, hepatic transplant) (10). Examinations were performed without gadolinium contrast. MRE scores were calculated by proprietary Siemens software. The LMS LIF score was calculated with proprietary software using Perspectum Diagnostics' centralized evaluation and reporting portal. Correlations between variables were computed using Spearman's Rho.

Results: MRE was successfully calculated 96% (248/258) of patients, and a LIF score and hepatic fat (PDFF) were successfully calculated in 98% (248/253) of patients attempted. MRE stiffness values were mapped onto a F1-F4 scale to provide a rough approximation of fibrosis stage. LIF score showed a significant correlation with MRE F-score ($r_s = 0.39$; $p = 3.0e-9$), with better concordance at higher stiffness (F3-4) vs. lower stiffness (F1-2). In the subset of patients lacking concordance (LIF ≥ 2 and F1-2), 80% (90/113) had PDFF > 5% (vs. 23% (14/60) in the LIF < 2 and F1-2 group), which may indicate early stage disease.

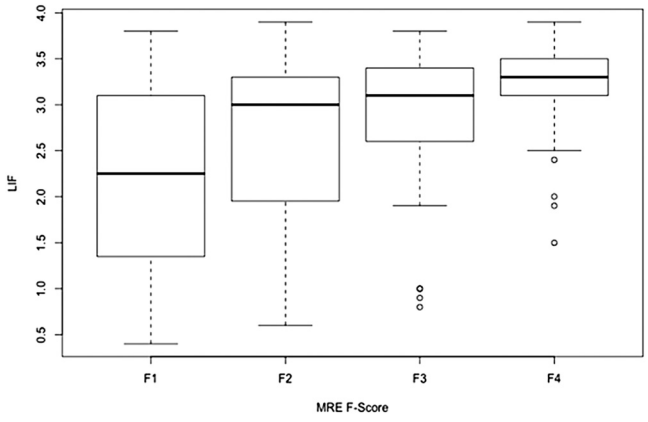


Figure 1: Relationship between LIF score and MRE-derived "F" score.

Conclusion: There is high concordance between LMS and MRE in patients predicted to have moderate to severe fibrosis. The lack of concordance in a sub-fraction of patients predicted by MRE to have mild fibrosis may be indicative of inflammation which has not yet progressed to significant fibrosis. LMS may be a more sensitive determinant of patients with elevated PDFF who are progressing to NASH.

SAT-076

Glomerular filtration rate evaluation in patients with cirrhosis, which equation shall be used in clinical daily practice?

S. Monteiro[1], M. Bibi[2], R. Lucas[3], J. Gandara[4], V. Lopes[4], D. Valadares[4], S. Ferreira[4], C.S. Macedo[4], M.T. Gomes[4], C. Rosário[2], H.P. Miranda[4], F.G.C. Nery[4]. *[1]Unidade Local de Saúde de Matosinhos - Hospital Pedro Hispano, Internal Medicine, Matosinhos, Portugal; [2]Unidade Local de Saúde de Matosinhos, Hospital Pedro Hispano, Internal Medicine, Porto, Portugal; [3]Instituto De Saúde Pública Da Universidade Do Porto, EPIUnit, Epidemiology Research Unit, Portugal; [4]Centro Hospitalar do Porto, Hospital Geral de Santo António, Porto, Portugal*
Email: amonteiro.sofia@gmail.com

Background and Aims: Kidney function evaluation is still a problem in cirrhotic patients, as the clearance of exogenous markers are expensive and may not be feasible in all centers. An incorrect evaluation of the glomerular filtration rate (GFR) has multiple implications such as, drug toxicity, omission of a kidney biopsy or simultaneous liver and kidney transplant when indicated.
This study aimed to assess, in patients with cirrhosis, which equation(s) to predict GFR is(are) the best for use in clinical practice, when compared to MDRD-6, which has been found to best correlate with GFR determined by clearance of exogenous markers.
Method: Demographic data, health status characterization, clinical evaluation and laboratorial data (serum sodium, blood urea nitrogen (BUN), creatinine, albumin and cystatin-c) were prospectively collected. GFR was determined by Cockroft-Gault formula, MDRD-4, MDRD-6, CKD-EPI Creatinine, CKD-EPI Cystatin C, CKD-EPI Creatinine-cystatin C and Larsson's. Agreement was estimated using Cohen's kappa and was stratified by variables. Mean differences between GFR calculated by MDRD-6 and all the other equations and their significance where analyzed with t-test.
Results: 123 patients with cirrhosis (91 Child A, 25 Child B, 7 Child C) were included, with mixed etiology. For all the spectrum of GFR, CKD-EPI Cystatin C correlated the best with MDRD-6 (Kappa = 1), and CKD-EPI Creatinine the worst (Kappa = 0.5505). All the other equations showed a substantial agreement of correlation with MDRD-6, with Kappa ≥ 0.7338. Liver's disease severity did not interfere with GFR measurement, but few patients were in Child-Pugh C class.
The mean differences between the equations with the poorest agreement (CKD-EPI Creatinine, MDRD-4, Cockcroft-Gault) and MDRD-6 where, in general, statistical significant ($p < 0.007$), with a pattern of overestimation of GFR.
Conclusion: Beyond demographic features, physicians shall demand for a panel of analysis gathering creatinine, cystatin c, BUN and albumin in order to calculate GFR using the abovementioned equations. As CKD-EPI Creatinine, MDRD-4 and Cockcroft-Gault may overestimate GFR, necessary interventions may be excluded, reason why caution should be taken when used. As a portion of patients included in the study had normal GFR, the power may not be enough to withdrawn other conclusions. Further studies should compare measured GFR with equations using cystatin-c.

SAT-077

Predictions from a very hard liver: The role of liver stiffness in alcoholic hepatitis

F. Petra[1], A. Horhat[1], A. Suciu[1], R. Corina[1], M. Lupsor-Platon[2], B. Procopet[1], D. Matei[1], R. Badea[2], M. Tantau[1], H. Stefanescu[3]. *[1]University of Medicine and Pharmacy "Iuliu Hatieganu", 3rd Medical Clinic, Gastroenterology Department; [2]University of Medicine and Pharmacy "Iuliu Hatieganu", Imaging department; [3]Regional Institute of Gastroenterology and Hepatology "O Fodor", Gastroenterology Department*
Email: bogdanprocopet@gmail.com

Background and Aims: Liver stiffness measurement (LSM), especially assessed by transient elastography (TE), is not considered a useful tool for the management of alcoholic hepatitis (AH) patients, because it is difficult to perform and is not reliable due to severe inflammation. However, LSM is considered a very good prognostic tool in advanced liver disease. Recently, real-time bi-dimensional shear-wave elastography (2D-SWE) became available, offering significant advantages for examination. On the other hand, in patients with severe AH (SAH) a robust predictor of mortality is still lacking.
The aim of this study was to evaluate whether LSM using TE and 2D2-SWE could predict mortality in AH patients.
Method: Consecutive patients with AH were included and liver function and severity of AH (Maddrey score (MDF)) was assessed at admission. Whenever possible and accepted by the patient, liver biopsy was performed to confirm the diagnosis. Patients with either SAH confirmed at biopsy, or with MDF ≥ 32 were treated with Prednisone, in the absence of contraindications. LSM by TE (Fibroscan, EchoSens, France) and by 2D-SWE (Aixplorer, SuperSonic Imagine, France) was also performed at baseline and after 7 days of therapy. Overall mortality was assessed during follow-up.
Results: 118 patients (80% males, mean age 52.5 years) were included. 76(64.4%) patients underwent LB and 67(56.8%) received Prednisone. 90 (76.2%) patients had MDF ≥ 32. 40 (33.9%) patients died during the mean follow up of 17.4 months.
TE could be performed in 70/90 of patients (77.8% applicability), while 2D-SWE in 59/64 patients (92.2% applicability).
LSM was significantly higher in patients with MDF ≥ 32, irrespective of the technique, but no significant difference was observed in LSM in patients who survived compared with those who died. However, baseline LSM values ≥64.5 kPa (by TE) and ≥17.3 kPa (by 2D-SWE)

predicted mortality with moderate accuracy (AUC of 0.688 [95%CI: 0.545-0.831] for TE and 0.713 [95%CI: 0.548–0869]).
A decrease in LSM after 7 days of therapy by 10% (by TE) or by 8% (by 2D-SWE) appears to be predict survival: AUC for ΔLSM of 0.712 [95% CI: 0.420–0.905] for TE and 0.745 [95%CI: 0.490–0.901].
Conclusion: LSM by 2D-SWE has a better applicability in AH compared with TE. Baseline LSM, irrespective of technique is higher in more severe patients, but there is no or limited value in predicting mortality. However, a decrease of 8–10% in LSM by 2d-SWE/TE could predict overall survival.
This work was supported by the a national grant (PN-II-RU-TE-2014-4-0356).

SAT-078

Soluble serum vascular adhesion protein (sVAP)-1: A new biomarker in primary sclerosing cholangitis?

F. Saffioti[1,2], P. Trivedi[3,4], C. Weston[3], M. Salmi[5,6], D. Roccarina[1], G. Hirschfield[3,4], W. Rosenberg[1], A. Marshall[1], D. Adams[3,4], D. Thorburn[1]. *[1]UCL Institute for Liver and Digestive Health, The Royal Free Sheila Sherlock Centre, Royal Free Hospital, London, United Kingdom; [2]University of Messina, Department of Clinical and Experimental Medicine, Division of Clinical and Molecular Hepatology, Messina, Italy; [3]University of Birmingham, National Institute of Health Research Birmingham Liver Biomedical Research Centre Institute of Immunology and Immunotherapy, Birmingham, United Kingdom; [4]University Hospitals Birmingham Queen Elizabeth, Liver Unit, Birmingham, United Kingdom; [5]MediCity Research Laboratory, University of Turku, Turku, Finland; [6]University of Turku, Department of Medical Microbiology and Immunology, Turku, Finland*
Email: fsaffioti.83@gmail.com

Background and Aims: Vascular adhesion protein (VAP)-1 is an adhesion molecule with potent amine oxidase activity recently proposed as a biomarker for primary sclerosing cholangitis (PSC). Hepatic VAP-1 expression is increased in PSC, and elevated circulating soluble levels (sVAP-1) have been shown to predict clinical outcome for these patients. Our aim was to compare sVAP-1 values in PSC patients vs. primary biliary cholangitis (PBC) and autoimmune hepatitis (AIH), correlate with clinical features and markers of disease severity, and validate predictive utility in a well characterised cohort of patients with PSC.
Method: sVAP-1 was measured by chemiluminescence ELISA in the sera of 62 PSC, 68 PBC and 51 AIH patients attending the Royal Free Hospital, London. We performed correlation between sVAP-1, laboratory values and non-invasive indices of liver fibrosis from the time of serum collection. Mann-Whitney or Kruskall-Wallis test were used due to the non normal distribution of the variables. Kaplan-Meier survival estimates were generated to stratify outcomes according to the previously reported cut-off of 923 ng/mL (Trivedi et al. Gut 2017) for the combined endpoint time to liver transplant, PSC-related death or liver cancer (EP).

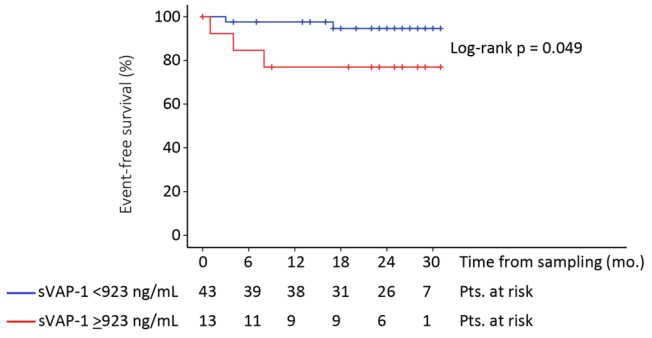


Figure 1: EP-free survival from time of serum sampling, according to sVAP-1 values.

Results: sVAP-1 values were not significantly different between the 3 aetiologies of immune-mediated liver disease. In the PSC group specifically, sVAP-1 significantly correlated with age at time of sampling ($p = 0.004$), age at diagnosis ($p < 0.001$), presence of cirrhosis ($p = 0.025$) and oesophageal varices ($p = 0.015$), absence of inflammatory bowel disease ($p = 0.005$), ELF score ($p = 0.003$), FIB-4 ($p < 0.001$), APRI ($p = 0.006$), Mayo risk score ($p = 0.002$) and Amsterdam-Oxford risk score ($p < 0.001$); but not with liver stiffness (transient elastography) and the MELD score. Spearman's Rho coefficient was ~0.4 for all the significant correlations. Remarkably, elevated sVAP-1 values predicted shorter time EP-free survival ($p = 0.047$) in PSC patients (Figure).
Conclusion: We validate across a small group of patients that heightened sVAP-1 values are predictive of EP in PSC. Moreover, sVAP-1 values are elevated in cirrhotic compared with non-cirrhotic individuals, but show varying degrees of correlation with indices of disease severity. Larger sample sizes with prospective, extended follow-up times are needed to substantiate predictive utility of sVAP as a marker of rapidly progressive vs. already advanced disease.

SAT-079

Comparison of twelve noninvasive liver reserve models in HCC patients undergoing resection

S.Y. Ho[1], T.-I. Huo[2], P.-H. Liu[2], C.Y. Hsu[2], C.-Y. Hsia[2], Y.-H. Huang[3]. *[1]Taipei Veterans General Hospital, Division of Gastroenterologist, Taipei, Taiwan; [2]Taipei Veterans General Hospital, Taipei, Taiwan, No.201, Sec. 2, Shipai Rd., Beitou District, Taipei City, Taiwan 11217, R.O.C, Taipei, Taiwan; [3]Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan*
Email: tihuo@vhgtpe.gov.tw

Background and Aims: Various noninvasive liver reserve models have been proposed, but their prognostic ability in patients with hepatocellular carcinoma (HCC) is unclear. We aimed to investigate the performance of 12 noninvasive models on HCC patients undergoing surgical resection.
Method: A total of 645 HCC patients undergoing resection were prospectively identified and analyzed. Baseline demographics, tumor status and noninvasive models were investigated. Comparison of noninvasive models by homogeneity and corrected Akaike information criteria (AICc) was performed. Tumor recurrence, overall survival, and independent prognostic factors were evaluated by the Cox proportional hazards model and Kaplan-Meier analysis.
Results: Of the 12 models, significant differences in recurrence-free survival were found in APRI, FIB-4, GUCI, King's score and PALBI ($p < 0.05$). Among these models, the King's score showed the highest homogeneity and lowest AICc value, suggesting a better predictive ability for tumor recurrence. In multivariate Cox analysis, we confirmed that King's score, tumor size and alpha-fetoprotein were independent predictors associated with recurrence. In survival prediction, ALBI, FIB-4, King's score and PALBI showed significant differences across groups ($p < 0.05$). Among these models, ALBI revealed the highest homogeneity and lowest AICc value, indicating a better prognostic performance. In the Cox model, ALBI, tumor burden, alpha-fetoprotein, vascular invasion, diabetes mellitus and performance status were independent predictors linked with overall survival.
Conclusion: The currently used liver function models have differential predictive ability for HCC patients undergoing surgical resection. The King's score is a feasible tool to predict tumor recurrence, whereas ALBI grade is a more robust model for prognostic prediction.
Grant support from Taipei Veterans General Hospital (V106C-021, V105A-011, VN106-11).

SAT-080

Enhanced liver fibrosis test predicts liver-related outcomes in postmenopausal women with risk factors in the community

P. Trembling[1], S. Apostolidou[2], A. Gentry-Maharaj[2], J. Parkes[3], A. Ryan[2], S. Tanwar[4], M. Burnell[2], S. Harris[3], U. Menon[2], W. Rosenberg[4].
[1]University College London, Institute for Liver and Digestive Health, Division of Medicine, Royal Free Hospital, London, United Kingdom; [2]University College London, Gynaecological Cancer Research Centre, Elizabeth Garrett Anderson Institute for Women's Health, London, United Kingdom; [3]University of Southampton, Primary Care and Population Sciences, Faculty of Medicine, Southampton, United Kingdom; [4]University College London, Institute for Liver and Digestive Health, Division of Medicine, Royal Free Hospital, London, United Kingdom
Email: p.trembling@ucl.ac.uk

Background and Aims: Chronic liver disease (CLD) is often clinically silent until life-threatening complications develop. Risk factors include high alcohol consumption and increased BMI. The Enhanced Liver Fibrosis (ELF) test, a liver fibrosis biomarker panel, accurately assesses fibrosis in a range of CLD aetiologies. ELF ≥ 10.51 is consistent with advanced fibrosis. We report performance of ELF in predicting CLD in postmenopausal women with risk factors in a nested case control study using the PRoBE (prospective-specimen-collection, retrospective-blinded-evaluation) design.

Method: Participants in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) provided serum samples at recruitment & 2 subsequent time points. They were prospectively followed up for first liver-related event (LRE) consistent with CLD (ICD-10: K70, K73, K74, K76, I85, Z944, C220) following recruitment using Hospital Episode Statistics, Cancer Registry and death certificate data. ELF was measured in blinded samples from 58 participants who developed LRE and self-reported alcohol use >16.5 units/week and/or BMI ≥ 25 kg/m^2 (cases), and in 115 controls matched for age, alcohol & BMI who did not develop LRE. Using conventional Cox regression unadjusted hazard ratio (HR) for LRE was calculated, then adjusted for deprivation & self-reported hypertension, heart disease, hypercholesterolaemia or diabetes, for ELF ≥ 10.51 at recruitment. To evaluate ELF as a time dependent variable, the time where ELF ≥ 10.51 was assumed to be time of the first serial sample in which ELF ≥ 10.51. Cox regression was performed with ELF ≥ 10.51 as a time dependent variable.

Results: Median recruitment age was 61 years (range 52–74). High alcohol use was reported by 19% & BMI ≥ 25 in 88%. Median time to LRE/censor was 8.5 years (range 0.5–11.4). HRs are shown in the table & cumulative hazards for the conventional Cox model in the figure. In participants who developed ELF ≥ 10.51 during follow up, risk of LRE was lower than those with ELF ≥ 10.51 at recruitment.

	Conventional Cox model		Cox model with ELF as time dependent variable	
Model	HR (95% CI)	p-value	HR (95% CI)	p-value
Unadjusted	4.88 (2.37–10.03)	<0.0001	1.94 (1.10–3.39)	0.021
Adjusted	4.62 (2.12–10.08)	<0.0001	2.05 (1.16–3.64)	0.014

Conclusion: This is the first study to evaluate performance of ELF to predict CLD in a community-based population. In postmenopausal women with risk factors, ELF ≥ 10.51 predicts LRE. In women who developed ELF ≥ 10.51 in follow up risk of LRE was increased compared to those with ELF < 10.51 but risk was lower than those with baseline ELF ≥ 10.51 highlighting the opportunity to intervene to reduce liver mortality & morbidity. Although larger studies are required, these results demonstrate the possible role for ELF as a prognostic tool in primary care.

SAT-081

Correlation between controlled attenuation parameter assessed with Fibroscan and steatosis percent objectively quantified from the entire liver biopsy specimen using a computer analysis tool: Preliminary results

M. Lupsor-Platon[1,2], G. Bianca[3], A. Maniu[1], V. Cristian[4], R. Ioana[5], H. Stefanescu[6], U. Radu[7], A.H. Nadim[3,7]. *[1]"Prof Dr Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Medical imaging, Cluj-Napoca, Romania; [2]"Iuliu-Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania; [3]"Iuliu-Hatieganu" University of Medicine and Pharmacy, Cluj Napoca, Romania; [4]Technical University, Computer Science, Cluj Napoca, Romania; [5]University of Medicine and Pharmacy "Iuliu Hatieganu", Department of Pathology, Romania; [6]"Prof Dr Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Hepatology, Cluj-Napoca, Romania; [7]"Prof Dr Octavian Fodor" Regional Institute of Gastroenterology and Hepatology, Surgery, Cluj Napoca, Romania*
Email: monica.lupsor@umfcluj.ro

Background and Aims: Usual ultrasonography is a useful method in diffuse liver disease (DLD) patients, but it cannot always differentiate steatosis from fibrosis. Liver biopsy (LB) has traditionally been considered the reference method for the steatosis and fibrosis evaluation, but its accuracy has also been questioned in relation to intra- and inter-observer variability that may lead to over- or under-staging or grading. Therefore, discovering more precise analysis of the LB specimens, rather than the subjective histological diagnosis, was desirable for the future development of noninvasive liver assessment tools, like transient elastography (TE) which measures liver stiffness

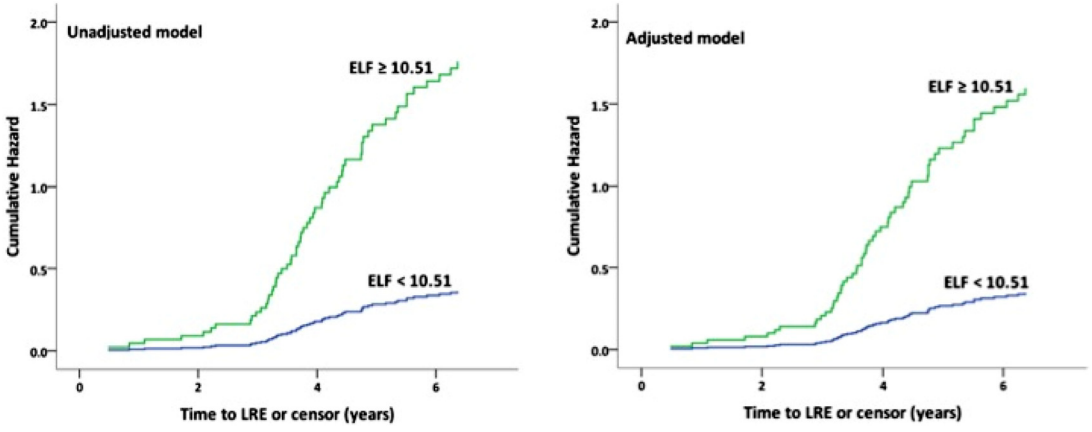


Figure: (abstract: SAT-080).

(LS) for fibrosis prediction, respectively controlled attenuation parameter (CAP) for steatosis prediction.
We aim to determine whether there is a correlation between CAP and steatosis, respectively fibrosis percent, objectively quantified from the biopsy specimen using an exact computer analysis tool.
Method: 163 DLD biopsied patients were prospectively included in the study. They underwent both LB and CAP measurements using Fibroscan with M probe. After preparation with hematoxylin and eosin, LB samples were photographed and analyzed using a special computer software for objectively determining the steatosis (SP), respectively fibrosis percent (FP), defined as the ratio between the total number of pixels labeled as steatosis, respectively as fibrosis, divided by total tissue area.
Results: CAP values varied between 160–373 dB/m. SP and FP values ranged between 0.0082–43.557 (mean 5.440), respectively 0.0642–69.0190 (mean 11.205). CAP correlated significantly with SP ($r = 0.312$, $p < 0.0001$), but not with FP ($r = 0.118$, $p = 0.211$) from the biopsy samples. The mean CAP value differed significantly in patients with SP ≤ 6 (226.29 ± 48.70 dB/m) from those with SP > 6 (254.66 ± 48.63 dB/m), $p = 0.002$. The correlation between CAP and the total area of steatosis (TSA) on the biopsy specimen is suggested in the formula Log(CAP) = 0.3624 + 0.03723 Log(TSA).
Conclusion: CAP is significantly correlated only with the steatosis percent quantified using a computer analysis tool. The mean CAP value differed significantly in patients with SP ≤ 6 from those with SP > 6. Further studies are needed to establish CAP cutoff values in relation to the steatosis area of the entire biopsy specimen.

SAT-082

Performance of shear-wave elastography to detect high-risk esophageal varices in cirrhosis is improved by spleen stiffness estimation

S.H. Kang[1], M.Y. Kim[1], Y.O. Jang[1], M. Lee[2], B.G. Jun[3], T.-S. Kim[2], K.T. Suk[4], S.K. Baik[1]. *[1]Yonsei University Wonju College of Medicine, Internal Medicine, Wonju, Korea, Rep. of South; [2]Kangwon National University Hospital, Internal medicine, Chuncheon-Si, Korea, Rep. of South; [3]University of Ulsan College of Medicine, Internal Medicine, Gangneung-si, Korea, Rep. of South, [4]Hallym University College of Medicine, Internal Medicine, Chuncheon-si, Korea, Rep. of South*
Email: drkimmy@yonsei.ac.kr

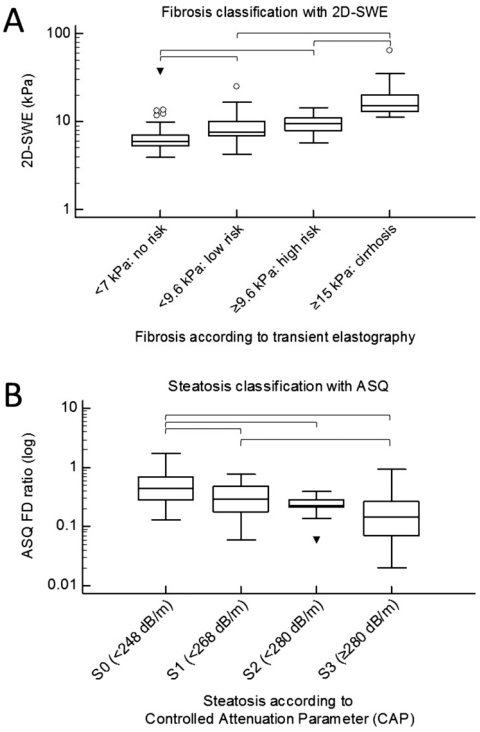
Background and Aims: There is considerable interest in developing non-invasive models to predict the presence of varices. Liver and spleen stiffness measured by 2 dimensional shear-wave elastography (2D-SWE) have become methods of interest with good reliability in detecting portal hypertension. In this regard, measurement of the spleen stiffness reflects more accurately the dynamic changes occurring in advanced stages of cirrhosis compared to liver stiffness. We investigated the feasibility of liver- and spleen-SWE for detection of esophageal varices and high-risk varices.
Method: We included 191 cirrhotic patients who underwent liver and spleen stiffness measurements and were scored for related parameters (liver stiffness spleen-diameter-to-platelet-ratio score [LSPS] and spleen stiffness spleen-diameter-to-platelet-ratio score [SSPS]), using 2D-SWE (APLIO 500, Toshiba), along with endoscopic screening. Large esophageal varices (F2 or F3) were defined as high-risk esophageal varices.
Results: Esophageal varices were present in 130 patients (68.1%). Regarding the presence of esophageal varices, diagnostic accuracy was better for stiffness in liver-SWE than in spleen-SWE (area under the receiver-operating characteristic curve [AUC], 0.830 vs. 0.740; DeLong test, $p = 0.050$). The best cut-off values in detecting esophageal varices were 14.1 kPa for liver-SWE and 16.5 kPa for spleen-SWE. Unlike stiffness in liver-SWE, that in spleen-SWE was positively correlated with the grade of esophageal varices. For the presence of high-risk esophageal varices, the AUC in spleen-SWE was higher than liver-SWE (0.764 vs. 0.742), albeit not significantly. The strongest association was found between high-risk esophageal varix and spleen-SWE ($r = 0.397$, $p < 0.001$), while the second strongest association was found between Child–Turcotte–Pugh score ($r = 0.353$, $p < 0.001$) and liver-SWE ($r = 0.314$, $p < 0.001$). The best cut-off values for predicting high-risk esophageal varices were 14.3 kPa for liver-SWE and 22.1 kPa for spleen-SWE. LSPS and SSPS, with AUC values between 0.837 and 0.799, also had good diagnostic accuracy in identifying esophageal varices.
Conclusion: In patients with cirrhosis, stiffness measurements obtained by using 2D-SWE have effective non-invasive method for detection of esophageal varices. Moreover, for high-risk esophageal varices that require prophylactic therapy, stiffness estimation in spleen-SWE carries a better diagnostic value than that in liver-SWE.

SAT-083

Non-invasive estimation of hepatic fibrosis and steatosis: comparison of 2D shear-wave elastography and acoustic structure quantification with transient elastography and controlled attenuation parameter

V. Blank[1,2], S. Wohland[1], J. Wiegand[3], V. Keim[1], T. Karlas[1]. *[1]University Hospital Leipzig, Division of Gastroenterology, Leipzig, Germany; [2]Integrated Research and Treatment Center Adiposity Diseases, MetaRot program, Leipzig, Germany; [3]University Hospital Leipzig, Division of Gastroenterology, Section of Hepatology, Leipzig, Germany*
Email: blank@medizin.uni-leipzig.de

Background and Aims: Transient elastography (TE) combined with controlled attenuation parameter (CAP) represents the reference standard for non-invasive assessment of hepatic fibrosis and steatosis. Although liver stiffness measurement (LSM) with TE is fast and easy to learn, its application is limited by the intercostal approach, patients' anthropometry, and requirement of a dedicated device. 2D shear-wave elastography (2D-SWE) techniques provide potential alternatives for LSM, but do not give information on steatosis. Recently, acoustic structure quantification (ASQ) has been proposed as an ultrasound based option for steatosis quantification. The aim of this study was the comparison of TE and CAP with 2D-SWE and ASQ.
Method: Patients with chronic liver diseases prospectively underwent LSM with TE (Fibroscan, M or XL probe) and CAP subsequently followed by 2D-SWE (Toshiba Medical Systems) and liver parenchyma speckle analysis by ASQ (focal disturbance ratio/FD ratio). Exclusion criteria comprised invalid or unreliable TE, elevated aminotransferase levels >5x upper limit of normal, ascites and focal liver lesions. Fibrosis and steatosis were classified according to established TE and CAP cut-offs. Diagnostic performance of 2D-SWE and ASQ was analyzed using receiver operating characteristics curves (ROC).
Results: 200 patients were included in the analysis (49% female, median age 54 years, body mass index/IQR 26 [24–29]kg/m², 30/25/9/36% NAFLD/viral/autoimmune/other).
LSM with 2D-SWE and TE showed a good correlation ($r = 0.775$ 95%CI [0.712; 0.825]; Figure A). 2D-SWE showed an excellent accuracy for detection of significant fibrosis (defined by TE ≥ 9.6 kPa: area under the ROC 0.927, sensitivity 88%, specificity 90%, cut-off >8.85 kPa) and cirrhosis (TE ≥ 15 kPa: AUROC 0.976, sens. 100%, spec. 94%, cut-off >11.1 kPa).
ASQ (log_FD ratio) and CAP values correlated well ($r = -0.602$ [−0.684; −0.506], Figure B). ASQ showed a good accuracy for detection of steatosis (defined by CAP ≥248 dB/m: AUROC 0.800, sens. 72%, spec. 74%, cut-off ≤0.29) and advanced steatosis (CAP ≥ 280 dB/m: AUROC 0.795; sens. 55%, spec. 90%, cut-off ≤0.15).



Conclusion: 2D-SWE shows an excellent agreement with TE and can be used for non-invasive fibrosis classification. ASQ correlates well with the reference standard CAP and provides an alternative for classification of steatosis. The combination of 2D-SWE and ASQ incorporated in a conventional ultrasound device could facilitate patient care.

SAT-084

CT-driven mfor end-stage liver disease: Comparison of survival prediction with MELD score

J.E. Lee. *Soonchunhyang University Hospital, Department of Radiology, Bucheon, Korea, Rep. of South*
Email: leeje1211@gmail.com

Background and Aims: Model for End-stage Liver Disease (MELD) score was developed as a disease severity index for patients with end-stage liver disease. Although MELD score is widely used for predicting survival, there are still some limitations. Imaging study contains important information about severity of liver cirrhosis and portal hypertension. The purpose of this study is to investigate the role of a new model with abdominal CT for prediction of survival in patients with liver cirrhosis and compare it with MELD score.
Method: 145 consecutive patients with diagnosis of liver cirrhosis and underwent abdominal CT at our institution were included retrospectively. Two radiologists reviewed the CT images and measured the imaging parameters associated with liver cirrhosis and portal hypertension, such as the maximum diameters of the main portal vein (øMPV), superior mesenteric vein (øSMV), splenic vein (øSV), and calculated the estimated spleen volumes. The grade of esophageal (EV), paraesophageal (PEV), gastric varices and amount of ascites were also evaluated with CT images semi-quantitatively. We explored the statistically significant CT features related to overall survival and established a model to calculate a risk score using multivariate Cox proportional hazard regression and validated this system using CT data (n = 86) of another hospital. To compare the prediction accuracy of two scoring systems, time-dependent ROC curve and Harrell's c-index were used.
Results: øSMV/øSV, splenic volume, grade of EV, PEV, and amount of ascites were significant imaging predictors of survival in patients with liver cirrhosis. The risk score was calculated by following formula: risk score = 0.72 × øSMV/øSV + 0.59×splenic volume + 0.88 × grade 1 EV + 0.50 × grade 2 EV + 1.00×grade 3 EV + 0.49 × grade 1 PEV + 0.61 × grade 2 PEV + 0.82 × grade 3 PEV + 1.44×moderate amount of ascites + 2.24×large amount of ascites – 1.95. All patients were divided into two groups (low- and high-risk groups) according to the cutoff value of 2.22 for risk scores. In both sets, the high risk group had significantly poor overall survival rates compared with the low risk group ($p < 0.05$). Time-dependent AUC revealed that in both sets, the MELD score was superior to the imaging model for the first 20 months. However, the imaging score showed slightly better performance than the MELD score after 50 months in the training set and after 30 months in validation set. Harrell's c-index showed that the imaging score demonstrated good properties in predicting survival in patients with liver cirrhosis, and were not significantly different from MELD score in both training and validation set ($p = 0.206$ and $p = 0.648$, respectively).
Conclusion: This prediction model with abdominal CT may predict the survival in patients with liver cirrhosis, and may even show better performance than MELD score in predicting long-term survival.

SAT-085

Non invasive assessment of liver fibrosis by three different Shear Wave Techniques: Head-to-Head Performance

S. Atzori, T. Hoogenboom, S. Taylor-Robinson, P. Manousou, H. Marcinkowski, J. Clancy, A. Dhar, M. Thursz, A. Lim. *Imperial College, Hepatology*
Email: s.taylor-robinson@imperial.ac.uk

Background and Aims: Ultrasound-based non-invasive methods for evaluation of liver disease severity are becoming increasingly used. This study aimed to compare liver stiffness assessed by 3 shear wave elastography techniques: Philips EPIQ7^{TM}; Siemens Acuson^{TM} Virtual Touch Tissue Quantification (VTQ) and Transient Elastography (TE) measured by Echosens Fibroscan^{TM}. Results were compared to histological results in patients with chronic liver disease.
Method: 109 patients underwent same-day liver biopsy, and measurement of liver fibrosis. Liver biopsy yielded insufficient tissue in 9 patients. Statistical analysis was conducted in 100 patients. Liver fibrosis and necroinflammatory activity were evaluated histologically using METAVIR score. 10 measurements in the left lobe, 10 in the right lobe were taken with EPIQ7^{TM} and VTQ and the median value obtained. The median of ten measurements was obtained with TE. Statistical analyses were performed using SPSS 24. Histological staging was correlated with median values and Spearman correlation calculated ($p < 0.05$).
Results: 100 consecutive patients with chronic liver disease were enrolled [mean age: 48.41 years, 41 female; 59 male]. 46 patients had non-alcoholic fatty liver disease, 22 patients had chronic hepatitis B and the remainder were of various aetiologies. Spearman correlation with METAVIR score was higher with EPIQ7^{TM} and Fibroscan^{TM} (EPIQ7^{TM} 0.568; TE 0.627; VTQ 0.429). Mean value for EPIQ7^{TM} in the left lobe were higher to those obtained from the right lobe of the liver (Right 8.16 kPa; Left 8.87 kPa) but this was not statistically significant ($p = 0.338$). Areas under the Curve (AUC) were: TE 0.835; EPIQ7^{TM} 0.785; VTQ 0.678 for no or mild fibrosis ($F < 2$; n = 52); TE 0.826; EPIQ7^{TM} 0.817; VTQ 0.712 for significant fibrosis (F) ($2 < F < 4$; n = 32); TE 0.865; EPIQ7^{TM} 0.820; VTQ 0.792 for cirrhosis (F4, n = 16). Bland Altman plots showed agreement between values obtained with TE and EPIQ7^{TM} with lower value measured by EPIQ7^{TM}. The mean optimal cut-off for significant fibrosis F2/3 (n = 32) was 8.45 kPa for TE (sensitivity (se) 0.76, specificity (sp) 0.78); 7.52 kPa (se 0.79, sp 0.76) for EPIQ7^{TM} and 9.3 kPa (se 0.76, sp 0.75) for VTQ. The mean optimal cut-off for cirrhosis F = 4 were 11.85 kPa for TE (se 0.79, sp 0.72); 9.01 kPa (se 0.70; sp 0.70) for EPIQ7^{TM} and 13.35 KPa (se 0.73; sp 0.79) for VTQ.
Conclusions: TE and EPIQ7^{TM} correlate well with histological scores of liver fibrosis and perform better than VTQ.

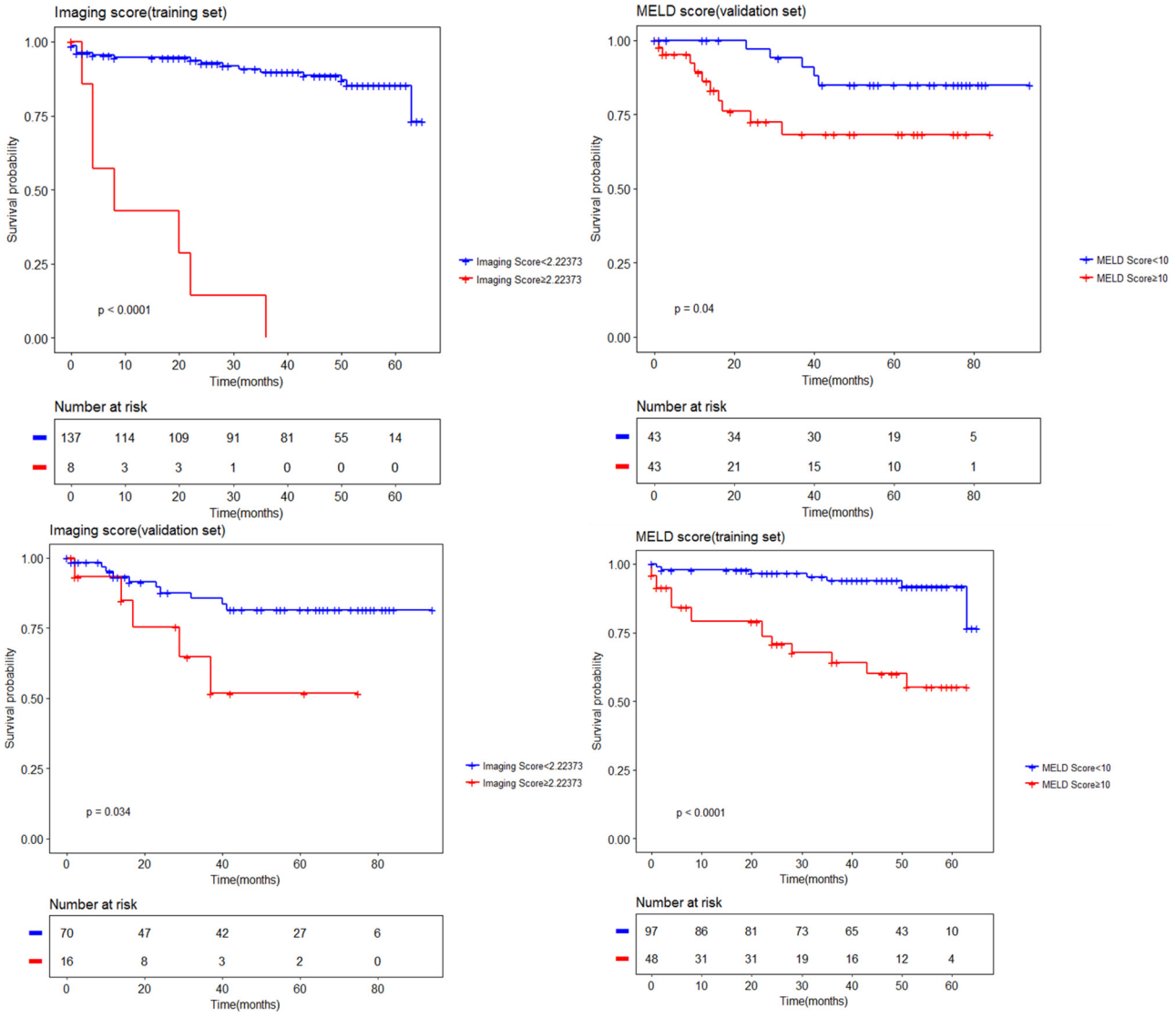


Figure: (abstract: SAT-084).

SAT-086

The gamma-glutamyl transpeptidase to platelet ratio: a novel index for predicting significant liver inflammation in chronic hepatitis B

R. Huang[1], J. Wang[1], X. Yan[1], Y. Liu[2], Y. Chen[2], Z. Zhang[1], W. Ding[3], C. Wu[1]. [1]*Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Department of Infectious Diseases, Nanjing, China;* [2]*Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Department of Experimental Medicine, Nanjing, China;* [3]*Huai'an No. 4 People's Hospital, Department of Hepatology, Huan'an, China*
Email: doctor_hr@126.com

Background and Aims: Evaluating the degree of liver inflammation is important for patients with chronic hepatitis B(CHB). However, few indexes can predict significant liver inflammation accurately in CHB patients. We aimed to develop a simple predictive index for significant liver inflammation in CHB using the routinely clinical parameters.

Method: A total of 384 treatment-naïve CHB patients who had undergone liver biopsy were enrolled in this study. The relation between hematological parameters and liver inflammation were analyzed and a novel predictive index for significant liver inflammation (≥G3) based on these parameters was developed. The diagnostic values of this novel index for liver inflammation were compared with other conventional inflammation parameters by the areas under the receiver-operating characteristic curves (AUROCs).

Results: Based on routinely clinical parameters, gamma-glutamyl transpeptidase (GGT) and platelets (PLT) were independent predictors of significant liver inflammation by multivariable analysis in entire patients ($p < 0.001$ and $p < 0.001$, respectively), hepatitis B e antigen (HBeAg) positive ($p = 0.021$ and $p = 0.019$, respectively) and HBeAg negative patients ($p = 0.009$ and $p = 0.006$, respectively). Accordingly, a novel index, the GGT to PLT ratio (GPR) was developed to amplify the opposing effects of liver inflammation on the GGT and PLT. The AUROCs of GPR in predicting significant liver inflammation were 0.793 (95%CI 0.748 to 0.839), 0.799 (95%CI 0.738 to 0.859) and 0.786 (95%CI 0.712 to 0.859) in entire patients, HBeAg positive and HBeAg negative CHB patients, respectively. Further comparisons showed the diagnostic performance of GPR for significant liver inflammation was significantly superior than that of alanine aminotransferase (ALT) (AUROC: 0.691, $p < 0.001$; AUROC: 0.679, $p = 0.002$, respectively), aspartate transaminase (AST) (AUROC: 0.716, $p = 0.006$; AUROC: 0.710, $p = 0.015$, respectively) and GGT (AUROC:0.768,

p = 0.040; AUROC: 0.764, p = 0.020, respectively) in entire patients and HBeAg positive CHB patients, but was comparable with AST (AUROC: 0.717, p = 0.123) and GGT (AUROC: 0.770, p = 0.437) in HBeAg negative CHB patients.
Conclusion: The GPR index has a better diagnostic value than conventionally predictive parameters to assess liver inflammation in CHB patients, especially for HBeAg positive CHB. The application of the novel index may reduce the need for liver biopsy in CHB patients in clinical practice.

SAT-087

Comparison of T2* and signal intensity ratio methods for MRI assessment of hepatic iron overload

C. Kagay[1], T. Frederick[2]. [1]*California Pacific Medical Center, Radiology, San Francisco, CA, United States;* [2]*California Pacific Medical Center, Transplant Hepatology, San Francisco, CA, United States*
Email: ckagay@gmail.com

Background and Aims: Excess hepatic iron (primary or secondary) can be seen in the context of chronic liver disease and may have a synergistic effect in promoting fibrosis. Patients proceeding to liver transplant with iron overload have a worse prognosis than those without. Patients with significant hepatic iron overload are at risk for cardiac iron overload. Biopsy is invasive and subject to sampling error. MRI is sensitive to hepatic iron content, as tissue iron causes paramagnetic effects on local proton spins, accelerating spin dephasing. Several methods have been described to measure hepatic iron content using MRI, including the Signal Intensity Ratio (SIR) method of Gandon et al. as well as measurement of hepatic parenchymal T2* values. To our knowledge, the performance of SIR and T2* methods with respect to histologic iron staining and quantification have not previously been compared head-to-head.
Methods: 126 iron-protocol liver MRI exams were performed between 1/1/14 and 19/4/17 including both SIR analysis (Univ. Rennes web tool) and T2* analysis (GE StarMap). 92 exams lacked pathology data, 1 exam was prospectively unreliable, 1 exam was a repeat on the same patient, and 4 exams had greater than 365 days between MRI and pathologic data. After exclusions, 28 MRI studies had data correlating to Modified Scheuer iron grade and 15 had data from pathologic iron quantification. Cutoff points were identified using the Youden method of Receiver Operator Curve (ROC) analysis. Area Under the Curve (AUC) was calculated comparing Scheuer grade to mean T2* value and estimated Liver Iron Concentration (LIC) by SIR. Pathological iron quantification was correlated to T2* and SIR-LIC by linear equation, with R^2 values calculated.
Results: Optimal cutoff points for the T2* method were ≤23.8 ms (0.987 AUC) for ≥1+ iron staining; ≤14.3 ms for ≥2+ iron staining (0.831); ≤12.5 ms for ≥3+ iron staining (0.792); and ≤6.1 ms for 4+ iron staining (0.740). Optimal cutoff points using SIR estimated LIC were >90 µmol/g for ≥1+ iron staining (0.880 AUC); >95 µmol/g for ≥2+ iron staining (0.800); >95 µmol/g for ≥3+ iron staining (0.756); and >230 µmol/g for 4+ iron staining (0.880). R^2 value correlating T2* to pathologic iron quantification was 0.48. R^2 value correlating LIC estimated by SIR to pathologic iron quantification was 0.14.
Conclusion: Performance of the T2* method with reference to Scheuer grade was superior to the SIR method as measured by AUC analysis at 3 of the 4 cutoff points, and correlation to pathologic iron quantification was also superior, but limited by small sample size. Comparison of Scheuer iron grade to T2* method closely mirrored results from Chandarana et al., suggesting that T2* is a reliable and reproducible method. As the T2* method additionally involves less scanner time and faster image analysis, this may be the preferred method for noninvasive estimation of hepatic iron overload.

SAT-088

Serum biomarker use in decentralized care sites to overcome liver assessment barriers in patientswith chronic hepatitis C and HIV co-infection

A. Loarec[1], C. Fortas[1], M. Iwamoto[1], A. Nguyen[2], A. Mesic[3], S. Balkan[4], D. Donchuk[5], D. Maman[1]. [1]*Médecins Sans Frontières, Epicentre, PARIS, France;* [2]*Médecins Sans Frontières, Medical department, Geneva, Switzerland;* [3]*Médecins Sans Frontières, Medical Department OCA, Amsterdam, Netherlands;* [4]*Médecins Sans Frontières, Medical Department OCP, Paris, France;* [5]*Médecins Sans Frontières, Medical Department OCB, Bruxelles, Belgium*
Email: anne.loarec@epicentre.msf.org

Background and Aims: A call for elimination of viral hepatitis by 2030 was endorsed in 2016. Access to Hepatitis C (VHC) diagnosis and treatment, as well as decentralization of these services to more tertiary care sites, are essential to reach this goal. Guidelines recommend a liver fibrosis assessment to identify chronic Hepatitis C (CHC) patients with advanced disease. In remote settings, only simple blood tests are usually available, without transient elastography and the use of most biomarkers is limited. In these cases, APRI (Aspartate-to-Platelet ratio Index) and FIB4 (Fibrosis-4) are two tests commonly used. Yet, questions remain about their utility in HIV-infected populations as well as their accuracy in diagnosing a patient's cirrhosis stage.
Method: Data from CHC patients in 7 clinics supported by Medecins Sans Frontieres (MSF) were collected between January 2014 and October 2017 in 4 countries (Phnom Penh, Cambodia; Dawei and Yangon, Myanmar; Manipur and Meerut, India, Maputo, Mozambique). Liver fibrosis was assessed for each patient at baseline. We used elastography using Fibroscan© as a reference method to compare the results of APRI and FIB4 biomarkers in identifying patients with an F4 liver stage, defined as ≥11 kPa by Fibroscan©. We also calculated the receiver operating characteristic (ROC) curves for all CHC patients by HIV status.
Results: A total of 3,074 CHC patients were included, among which 20% were HIV co-infected (n = 615). Elastography scores (median 13.8 kPa [IQR 10.0–23.1]) were distributed by stage as: 14.4% F0-F1, 6.57% F2, 13.11% F3, 68.88% F4. APRI tests had a median score of 1.05 (IQR 0.58–2.21), while FIB4 tests had a median score of 2.55 (IQR 1.55–4.92), with 22% of patients having a FIB4 < 1.45 and another 38.7% of patients with FIB4 > 3.25. Among APRI tests, areas under the receiver operating characteristic curve (AUROC) were 0.83 (95% CI 0.80–0.86) for HIV/HCV co-infected patients and 0.81 (0.80–0.83) for mono-infected HCV patients. Among FIB4 tests, AUROC were 0.83 (0.80–0.87) for HIV/HCV co-infected patients, and 0.82 (0.80–0.84) for mono-infected HCV patients. AUROC did not differ by HIV status in either case (p < 0.001).
Conclusion: HIV status did not influence the correlation between the two biomarkers and Fibroscan. Optimal biomarker thresholds should balance specificity and sensibility needs with screening and care strategies. Use of biomarkers will be a key tool to scale up Hepatitis C care.

SAT-089

Normal liver elasticity values in a healthy population, by age and gender, for two novel elastography systems

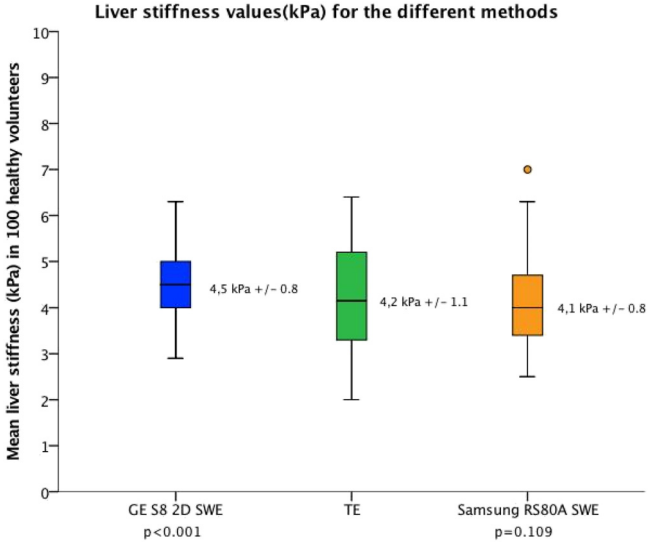
A. Mulabecirovic[1,2], M. Vesterhus[2,3], A. Mjelle[1,2], R.F. Havre[2], O.H. Gilja[2]. [1]*University of Bergen, Department of Clinical Medicine, Bergen, Norway;* [2]*National Centre for Ultrasound in Gastroenterology, Haukeland University Hospital, Bergen, Norway;* [3]*Norwegian PSC Research Center, Department of Transplantation Medicine, Division of Cancer Medicine, Surgery, Inflammatory Diseases and Transplantation, Oslo University Hospital, Oslo, Norway*
Email: anesa.mulabecirovic@gmail.com

Background and Aims: Estimates of liver stiffness may vary between elastography technologies within the same liver. The establishment of normal liver stiffness values in healthy livers for each specific

equipment model is a prerequisite for the definition of pathology and fibrotic stages. We aimed to define normal liver stiffness using two novel elastography methods for different age, weight and gender segments, and to assess inter-and intraobserver variability and reproducibility. To our knowledge, this is the first study to evaluate liver stiffness in healthy liver subjects using 2D shear wave elastography (SWE) from GE S8 and SWE from Samsung RS80A.

Method: We prospectively evaluated two novel elastography methods (Samsung RS80A SWE and GE S8 2D SWE) compared to Fibroscan (TE) by obtaining head-to-head liver stiffness measurements for each method in 100 healthy subjects. All subjects underwent B-mode ultrasound examination, elastography and biochemical laboratory analyses, including viral markers.

Results: All methods showed excellent feasibility. Mean liver stiffness (LS-mean) for GE S8 2D SWE was statistically higher than LS-mean of TE (4.5 ± 0.8 kPa vs. 4.2 ± 1.1, respectively, $p < 0.001$) and Samsung RS80A (4.1 ± 0.8 kPa, $p < 0.001$). The coefficient of variation (CV) was similar for the ultrasound based SWE methods ($p = 0.026$) whereas TE had larger CV compared to both GE S8 and Samsung RS80A ($p < 0.001$ and $p = 0.005$, respectively). The intraclass correlation coefficient (ICC) was good for both Samsung RS80A and GE S8 2D SWE ($r = 0.85$ vs. $r = 0.78$, respectively) and the methods were reproducible. LSM-mean for all SWE methods applied was significantly higher for males than for females (4.5 ± 0.9 kPa vs. 4.0 ± 0.9 kPa, respectively, $p < 0.001$) but similar across age and weight groups. There was no significant difference in LSM-mean based on 5 vs. 10 measurements for either Samsung RS80A SWE or GE S8 2D SWE.



Conclusion: LSM-mean was significantly higher for GE S8 2D SWE compared to Samsung RS80A or TE. There was no significant difference in LS between age or BMI groups, however males had higher LS. Using 5 or 10 liver stiffness measurements did not significantly affect results.

SAT-090

Detection of hereditary haemochromatosis in the clinic and community using standard haematological tests: a comparison with iron studies

N. Whalen[1], N. Adris[1], S. Hazeldine[1], P. Bentley[2], D. Trinder[3,4], A. Chua[3,4], G. Ramm[5], L. Ramm[5], J. Olynyk[1,6,7]. *[1]Fiona Stanley Hospital, Gastroenterology and Hepatology, Murdoch, Australia; [2]Austrlian Red Cross, Melbourne, Australia; [3]University of Western Australia, School of Medicine and Pharmacology, Crawley, Australia; [4]Harry Perkins Institute for Medical Research, Murdoch, Australia; [5]QIMR Berghofer Medical Research Institute, Liver Fibrosis Section, Herston, Australia; [6]Curtin University Health Innovation Research Institute and School of Biomedical Sciences, Faculty of Health Sciences, Bentley, Australia; [7]Edith Cowan University, School of Medical and Health Sciences, Joondalup, Australia*
Email: john.olynyk@health.wa.gov.au

Background and Aims: Hereditary Haemochromatosis (HH) is a common genetic disorder seen in persons of Northern European descent. Serum ferritin is the most commonly used blood test for screening and detection of HH and exhibits sensitivity and specificity values of 75% and 87%, respectively. Previous studies show that subjects with HH have significantly different haematological parameters compared to non HH control subjects. Our study determined the sensitivity and specificity of haematological parameters in the detection of HH in the general population and in subjects with chronic disease.

Method: Subjects with HH aged 20–70 years were detected in primary care and referred for diagnosis and treatment at specialist clinics between 2005 and 2015. The control group included subjects enrolled in the Busselton Population Study, Western Australia. The chronic disease cohort was identified from outpatient clinics and included male and female subjects with chronic hepatitis C (HCV), chronic hepatitis B (HBV), cirrhosis, rheumatoid arthritis (RA) and other rheumatic conditions (non-RA), diabetes mellitus (DM) and chronic pulmonary disease (Pulm). We evaluated mean cell volume (MCV), mean cell haemoglobin (MCH), and ferritin. Statistical analyses including receiver-operator-curve analyses and analysis of variance were performed using GraphPad Prism software.

Results: For HH subjects, the mean pre- and post-phlebotomy values of MCV and MCH were always significantly higher compared with all other groups whilst ferritin was only elevated in pre-treatment HH subjects (Table 1). For detection of HH in male subjects, MCV >90.8fL provided sensitivity and specificity values of 75% and 65%, respectively (AUC 0.8012) whilst MCH >31.2 pg provided sensitivity and specificity values of 81% and 75%, respectively (AUC 0.8175). In female subjects, MCV >91.9fL provided sensitivity and specificity values of 78% and 71%, respectively (AUC 0.8618) whilst MCH >31 pg provided sensitivity and specificity values of 80% and 78%, respectively (AUC 0.8295). For detection of HH in pre-treatment males and females, serum ferritin levels provided sensitivity and specificity values of 79% to 86%, respectively, compared with the general population. Serum ferritin had low sensitivity and specificity for detection of HH in chronic disease and post-treatment individuals.

Conclusion: MCV and MCH are equally as sensitive and specific for detection of HH in the population, with added advantages over ferritin including utility following successful therapy and in screening chronic disease subjects.

SAT-091

Evolving diagnostic pathways in liver disease: using quantitative magnetic resonance imaging to distinguish parenchymal and biliary disease

K. Arndtz[1,2,3], B. Irving[4], S.M. Brady[4], N. Jayaratne[4], P. Eddowes[4], M. Kelly[4], D. Green[4], R. Banerjee[4], S. Neubauer[4], G. Hirschfield[1,2,3]. *[1]Institute of Immunology & Immunotherapy, Centre for Liver Research, United Kingdom; [2]National Institute for Health Research Birmingham Biomedical Research Centre; [3]Institute of Translational Medicine, University Hospitals Birmingham NHS Foundation Trust, Centre for Rare Diseases, Queen Elizabeth Hospital Birmingham (UK); [4]Perspectum Diagnostics, 23-38 Hythe Bridge Street, Oxford (UK)*
Email: k.arndtz@nhs.net

Background and Aims: The future practice of Hepatology will include greater use of innovative technology to distinguish patterns of inflammatory liver disease in order to improve diagnosis, prognosis and treatment, and to streamline use of invasive investigations such as liver biopsy. We sought to evaluate how innovative evaluation of non-user dependent, quantitative magnetic

Table 1: (abstract: SAT-090): Mean Age, MCV, MCH and Ferritin Values for Control and Chronic Disease Cohorts

	N	Age (years)	Mean MCV (fL)	p-value pre/post	Mean MCH (pg)	p-value pre/post	Mean Ferritin (ug/L)	p-value pre/post
Male HH Pre Phlebotomy	150	43.95 +/- 13.79	93.41 +/- 3.739	N/A	32.24 +/- 1.418	N/A	1165 +/- 996.2	N/A
Male HH Post Phlebotomy	20	44.65 +/- 7.555	92.36 +/- 4.071	N/A	31.89 +/- 1.535	N/A	61.35 +/- 28.89	N/A
Female HH Pre Phlebotomy	72	45.54 +/- 14.02	95.62 +/- 5.113	N/A	32.37 +/- 1.773	N/A	486.3 +/- 290.0	N/A
Female HH Post Phlebotomy	23	49 +/- 12.78	94.56 +/- 5.325	N/A	31.87 +/- 2.002	N/A	61.78 +/- 38.07	N/A
Male Control	1970	49.34 +/- 16.44	88.82 +/- 4.097	<0.0001/ <0.0001	30.45 +/- 1.505	<0.0001/ <0.0001	163.7 +/- 119.9	<0.0001/ 0.8793
Female Control	2142	52.13 +/- 15.83	88.7 +/- 4.577	<0.0001/ <0.0001	30.18 +/- 1.711	<0.0001/ <0.0001	108.2 +/- 75.43	<0.0001/ 0.8171
Male HCV	50	53 +/- 9.195	91.86 +/- 4.84	0.0565/ 0.7941	31.15 +/- 1.8	<0.0001/ 0.0290	282.7 +/- 186.3	<0.0001/ 0.3554
Female HCV	50	51 +/- 10.23	91.12 +/- 4.754	<0.0001/ 0.0366	30.71 +/- 1.79	<0.0001/ 0.05432	164.4 +/- 211.3	<0.0001/ 0.2442
Male HBV	50	45 +/- 13.27	89.34 +/- 5.794	<0.0001/ 0.0007	30.13 +/- 2.349	<0.0001/ <0.0001	527.6 +/- 895.9	0.0005/ 0.0402
Female HBV	50	41.5 +/- 12.37	88.4 +/- 5.876	<0.0001/ 0.0002	29.27 +/- 2.544	<0.0001/ <0.0001	118.6 +/- 223.6	<0.0001/ 0.6604
Male Cirrhosis	50	52 +/- 10.22	91.72 +/- 6.509	0.0616/ 0.7344	30.75 +/- 3.41	<0.0001/ 0.0089	406.4 +/- 352.6	<0.0001/ 0.0737
Female Cirrhosis	50	58 +/- 9.394	93.04 +/- 6.788	0.0553/ 0.6132	30.8 +/- 2.938	0.0015/ 0.2172	280.8 +/- 402.1	0.0023/ 0.0184
Male RA	50	62 +/- 12.45	92.02 +/- 5.651	0.1213/ 0.9083	30.75 +/- 2.401	<0.0001/ 0.0013	236.6 +/- 188.5	<0.0001/ 0.6048
Female RA	50	58 +/- 14.17	89.86 +/- 5.768	<0.0001/ 0.0055	29.53 +/- 2.147	<0.0001/ <0.0001	166.5 +/- 173.1	<0.0001/ 0.2355
Male Non-RA	50	56.5 +/- 12.5	90.08 +/- 4.435	<0.0001/ 0.0074	30.38 +/- 1.827	<0.0001/ <0.0001	211.6 +/- 179	<0.0001/ 0.6973
Female Non-RA	50	52 +/- 12.76	90.16 +/- 4.884	<0.0001/ 0.0055	29.86 +/- 2.143	<0.0001/ 0.0008	107.1 +/- 60.34	<0.0001/ 0.7613
Male DM	50	59 +/- 12.85	87.3 +/- 4.7	<0.0001/ <0.0001	29.19 +/- 1.913	<0.0001/ <0.0001	269.1 +/- 221.3	<0.0001/ 0.5141
Female DM	50	59 +/- 12.8	87.34 +/- 5.727	<0.0001/ <0.0001	28.86 +/- 2.246	<0.0001/ <0.0001	150.8 +/- 107.6	<0.0001/ 0.6482
Male Pulm	50	67 13.58	89.52 +/- 6.277	<0.0001/ 0.0023	29.61 +/- 2.299	<0.0001/ <0.0001	299.6 +/- 361.9	<0.0001/ 0.5199
Female Pulm	50	68 +/- 14.66	88.7 +/- 4.404	<0.0001/ <0.0001	29.11 +/- 1.755	<0.0001/ <0.0001	127.5 +/- 121.9	<0.0001/ 0.5955

resonance imaging (MRI), could be used to distinguish parenchymal and biliary disease.

Method: Patients with autoimmune hepatitis (AIH), primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) were recruited from a single tertiary ambulatory practice and evaluated in a dedicated study visit, including clinical and laboratory disease phenotyping, alongside dedicated quantitative MRI. Quantitative T2* and T1, and an iron corrected T1 (cT1) quantitative map of the liver were derived from the ShMOLLI and DIXON MRI sequences, where elevation of cT1 is known to correlate with histological hallmarks of disease (inflammation, ballooning and fibrosis). Imaging features were derived to capture patterns of inflammatory liver disease, including skewness and kurtosis of the distribution of cT1 in the liver, as well as local variation of the liver parenchyma, which is a measure of texture. A machine learning classifier was used to combine the imaging features, and was trained on 60% of the cases and validated on 40% of the cases.

Results: 180 patients were recruited, 62 with AIH, 118 with either PBC or PSC. Mean age was 50 years (range 18–84), 29% were male and 85% were Caucasian. 24% had evidence of cirrhosis with portal hypertension. Serum transaminases were moderately associated with clinical diagnosis (AUROC 0.75) with improvement in this when MRI derived features with machine learning was applied (AUROC 0.84). Alkaline phosphatase (ALP) alone was a good discriminator between biliary disease and auto-immune hepatitis (AUROC 0.89) with a modest improvement in this with the addition of quantitative MRI analysis (AUROC 0.91). In patients with an ALP < 200 U/l (62 AIH and 71 biliary cases), ALP alone was moderately correlated with diagnosis (AUROC

0.76). However, addition of MRI analysis improved this considerably (AUROC 0.85, see figure).

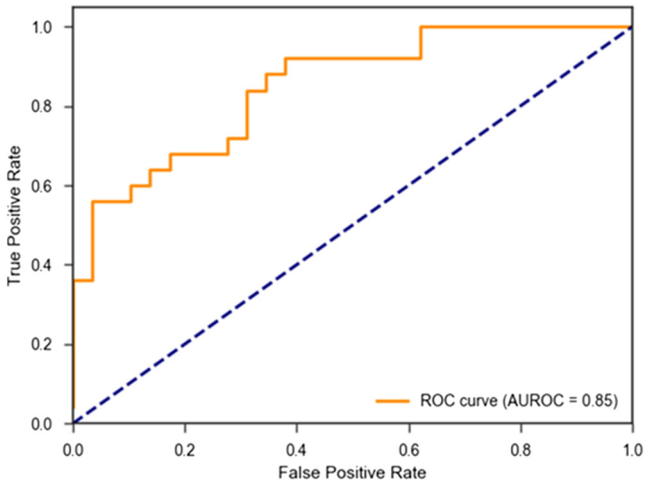


Figure 1: A receiver operating characteristic curve on the validation set showing the classification of AIH vs biliary disease with the addition of image features to cases with ALP < 200U/l.

Conclusion: Quantitative non-biased MRI imaging features have the ability to potentially be used to change how liver disease is evaluated and classified in the future.

SAT-092

Non invasive diagnostic approach for screening and grading of portal hypertension in patients with advanced liver disease

S. Kozlov[1], P. Fomin[1], A. Dolot[1], V. Sidorenko[2]. [1]*Bogomolets National medical university, General surgery #3, Kyiv, Ukraine;* [2]*B, Kyiv, Ukraine*
Email: sergiinikol@gmail.com

Background and Aims: Between 80 and 90% of totally asymptomatic patients already have an elevated PPG (measured clinically as an increase in the hepatic venous pressure gradient (HVPG) and endoscopy discloses that 40% already have esophageal varices. HPVG is an invasive test (as well as endoscopy) that demonstrates high sensitivity but low specificity for prediction first variceal bleeding. Our primary objective was to search a non-invasive screening procedure in order to substitute invasive methods (HVPG, endoscopy) for patients with chronic liver disease (CLD) and suspicion of portal hypertension (PH).
Method: Splenic artery and splenic vein volume blood flow (SAVBF/SVVBF) were evaluated in patients with clinically significant portal hypertension (CSPH) (n = 190) by means of Doppler US in comparison with that in normal controls (control 1 group– healthy volunteers, n = 36), and patients with CLD but absence of signs of PH (n = 34) – control 2 group. Volume flow was calculated as Vf = Tamx*S (vessel cross sectional area). All measurements were done by single operator according to extended sonography protocol.
Results: Means of SABF/SVBF in patients with CSPH were 1.35/1.11l/min, median 1.22/0.88l/min. There was no significant difference in patients with or without bleeding episode or ascities. In C2 and C1 groups means of SAVBF/SVVBF were 0.47/0.43l/min, median 0.46/0.41l/min and 0.30/0.26l/min, median 0.29/0.24l/min respectively. Difference in splenic arterial and venous flow means (1.35 and 1.11) could be explained by opening of retroperitioneal (for example, natural spleno-renal shunts etc) collaterals.
Elevated splenic artery and vein blood flow were significantly increased in patients with clinically significant portal hypertension compared with C1 and C2 groups (p < 0.001) and are the evidence of development a hyperdynamic circulatory state in the splanchnic circulation. According to obtained data the threshold mean of esophageal varix appearance (or any other related to portal hypertension events) could be marked at SAVBF range of 0.8–1.0l/min.
Conclusion: Splenic artery blood flow measurement is a safe non-invasive diagnostic procedure in patients with hepatic portal hypertension. It could be regarded as a predictive factor of development of portal hypertension complications. The measurement of SAVBF/SVVBF might be beneficial to make a decision to activate primary prophylaxy of first variceal hemorrhage in patients with cirrhosis but further trials are needed. Obtained data support the concept of applying partial splenic embolization for effective portal pressure control and primary prophylaxy of index variceal bleeding.

SAT-093

Circulating micro-ARNs as biomarkers of alcohol liver disease and hepatocellular carcinoma

C.-A. Papillon[1], R. Buttolo[1], M. Ingrid[1], H. Houchi[1], N. Mickaël[1], E. Nguyen-Khac[1,2]. [1]*University of Picardie Jules Verne, GRAP INSERM U1247, Amiens, France;* [2]*CHU Amiens-Picardie, Hepato-gastro enterology, Amiens, France*
Email: charles.antoine.papillon@u-picardie.fr

Background and Aims: In Europe, 60–80% of hepatocellular carcinoma (HCC) cases are an alcohol liver disease (ALD) form, which has a worse outcome than any other aetiology (HCV, non-alcoholic fatty liver disease,…).
In this study, we propose to evaluate the interest of using a combination of candidate micro-RNAs (miRNA) as potential diagnostic biomarkers of HCC related to ALD-cirrhosis. Indeed, the current non-invasive markers used for HCC diagnostic have a poor sensitivity, which could be improved by the use of miRNAs.
We have selected 4 circulating miRNAs for their implication in hepatic physiology (miR-122) and liver carcinogenesis (miR-21, miR-34a and miR-126*). The miR-155 was selected for its association to inflammatory and immune response.
Method: We have recruited 165 patients and create 3 groups: HCC due to ALD, ALD without HCC and a control group without liver disease. MicroRNAs were then extracted from blood serum and quantified using TaqMan Technology.
Results: Compared to controls, we observed in ALD patients' bloodstream an increase of the number of copies of miR-122, miR-155, miR-21, miR-34a and miR-126* (of 3-fold, 46-fold, 12-fold, 24-fold and 10-fold, respectively). In HCC patients compared to controls, we also found an increased levels of all miRNAs (of 7-fold, 1133-fold, 12-fold, 28-fold and 12-fold, respectively).
Moreover, the miR-122 and miR-155 levels were significantly higher in HCC patients than in ALD patients without HCC. We propose different thresholds corresponding to the number of copies of these miRNAs that allow us to distinguish the HCC patients from ALD cases.

Thresholds combined	PPV	NPV	p
miR-122 + 155 + 21	69.4	47.9	**0.047**
miR-122 + 155 + 34a	68.0	51.5	**0.044**
miR-155 + 21 + 34a	76.9	56.4	**<0.001**
miR-122 + 155 + 126*	68.9	44.0	0.214
miR-122 + 155 + 21 + 34a	44.8	81.3	**<0.001**

PPV: Positive Predictive Value.
NPV: Negative Predictive Value.

Conclusion: We propose the miR-122 and miR-155 as potential biomarkers for the early diagnostic of HCC. These miRNAs could be used in combination with the miR-21 and miR-34a for the follow-up of ALD patients.

SAT-094

Liver function assessment using magnetic resonance imaging with gadoxetic acid administration

C. Levick[1,2], M. Pavlides[1,2], M. Robson[2], S. Neubauer[2], E. Barnes[1,3].
[1]*University of Oxford, Translational Gastroenterology Unit, Oxford, United Kingdom;* [2]*University of Oxford, Oxford Centre for Clinical MRI Research, Oxford, United Kingdom;* [3]*University of Oxford, Peter Medawar Building, Nuffield Department of Medicine, Oxford, United Kingdom*
Email: christina.levick@gmail.com

Background and Aims: We have previously developed multiparametric magnetic resonance imaging (MRI) to assess liver fibrosis, inflammation and steatosis. However, there is no current gold standard method to assess liver function. In this study we use MRI with the contrast agent gadoxetic acid (Primovist, Gd-EOB-DTPA), which has hepatocyte-specific uptake and lowers the T_1 relaxation time. The percentage reduction in liver T_1 with gadoxetic acid (%rT_1) therefore may be a marker of liver function, with a lower value representing poorer function. Gadoxetic acid is used routinely for liver lesion evaluation. This study aims to assess the ability of MRI with gadoxetic acid to quantify liver function in comparison with standard blood parameters.
Method: In this prospective observational study, liver biochemical dysfunction was defined as either a bilirubin >21 μmol/l and/or an international normalised ratio ≥1.2. Twenty-one healthy controls, 5 patients with acute liver injury and 84 patients with cirrhosis were recruited. The acute liver injury patients had liver biochemical dysfunction with no evidence or risk factors for chronic liver disease or biliary obstruction. Participants were excluded if they had contraindications to MRI or gadoxetic acid, portal vein thrombosis, transjugular intrahepatic porto-systemic shunt or primary/secondary liver cancer. All participants were assessed following a >4 hours fast with liver MRI T_1-mapping pre and 20 minutes post 0.025 mmol/kg gadoxetic acid and blood tests. T_1 maps were analysed by region of interest and the %rT_1 calculated as 100 x (T_1baseline-T_1post contrast)/ T_1baseline.
Results: Of the cirrhotic patients, 44 (52%) had liver biochemical dysfunction. %rT_1 was lower in cirrhotic patients with liver biochemical dysfunction than without (48 vs 58%, $p < 0.001$). Patients with acute liver injury and patients with cirrhosis and liver biochemical dysfunction had lower %rT_1 than healthy controls (39% and 48% vs 64%, respectively, both $p < 0.001$). There were no significant differences between patients with compensated cirrhosis and healthy controls (58 vs 64%, $p = 0.11$) or patients with liver biochemical dysfunction with and without cirrhosis (48 vs 39%, $p = 0.15$).
The %rT_1 correlated ($p < 0.001$ for all) with bilirubin ($r = -0.58$), prothrombin time ($r = -0.33$), albumin ($r = 0.46$), Child Pugh ($r = -0.51$) and MELD ($r = -0.55$). The %rT_1 identified liver biochemical dysfunction with area under the receiver operator curve of 0.85 (0.77–0.92 95%CI). A diagnostic cut off of 55% had 0.82 sensitivity and 0.77 specificity.
Conclusion: The percentage reduction in liver T_1 with gadoxetic acid is a promising marker of liver function that is unaffected by the degree of liver fibrosis and measures liver function in an alternative way to standard blood tests. Follow up studies should assess the use of %rT_1 alone, or in combination with blood parameters as a prognostic tool.

SAT-095

Platelet and spleen volume criteria exclude more oesophageal varices needing treatment than Baveno VI criteria with 100% sensitivity

C. Levick[1,2], M. Pavlides[1,2], M. Robson[2], S. Neubauer[2], E. Barnes[3,4].
[1]*University of Oxford, Translational Gastroenterology Unit, United Kingdom;* [2]*University of Oxford, Oxford Centre for Clinical MRI Research, United Kingdom;* [3]*University of Oxford, Peter Medawar Building, Nuffield Department of Medicine, Oxford, United Kingdom;* [4]*University of Oxford, Translational Gastroenterology Unit, Oxford, United Kingdom*
Email: christina.levick@gmail.com

Background and Aims: Baveno VI consensus recommendations can reduce unnecessary screening endoscopies for varices needing treatment (VNT; grade 2 or 3, or grade 1 with red sign) in patients with compensated advanced chronic liver disease (cACLD) by only 11–33%. This study aims to develop non-invasive strategies to reduce unnecessary endoscopies further through combinations of blood tests, liver stiffness measurement (LSM) and splenic magnetic resonance imaging (MRI). This builds on our previous liver MRI work.
Method: Fourty-nine patients (71% male, mean age 61 ± 10 years) with cACLD of mixed etiologies (35% ALD; 22% NAFLD; 16% viral; 27% other) were assessed with LSM, blood tests and MRI. All had endoscopy screening for VNTs within 1 year of recruitment. MRI scans were analysed for spleen diameter, volume and iron-corrected T_1 (cT_1). Baveno VI (platelets > 150×10^9 cells/l; LSM < 20 kPa), expanded-Baveno VI (platelets > 110×10^9cells/l; LSM < 25 kPa), MELD = 6 and platelets > 150×10^9 cells/l, and platelet count to spleen size ratio criteria were evaluated. Cut off values for unestablished criteria were selected for 100% sensitivity to detect VNTs.
Results: The median time between endoscopy and study assessment was 5 days (IQR -12–43). Ten (20%) participants had VNTs. LSM was technically impossible in 8% of cases and the XL probe was used in 33%. Only the expanded-Baveno VI criteria missed VNTs (5%). The Baveno VI consensus would have saved 14% of endoscopies, saving fewer than most other criteria tested (Table 1). The criteria platelets >112×10^9cells/l and spleen volume <790 ml would have saved the most endoscopies (53%), with an 18.1 likelihood ratio ($p < 0.001$).
Conclusion: The Baveno VI consensus saves few screening endoscopies for VNTs, whilst the expanded-Baveno VI criteria misses an

Table: (abstract: SAT-095): Performance of non-invasive criteria to rule out varices needing treatment (n = 49)

Criteria	Endoscopies saved (%)	Likelihood ratio	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Baveno VI: Plts > 150×10^9 cells/l, LSM <20 kPa	7 (14)	3.48	24	24	100
Expanded-Baveno VI : Plts > 110×10^9 cells/l, LSM < 25 kPa	16 (33)	1.63	41	26	89
MELD = 6, plts > 150×10^9 cells/l	4 (8)	1.92	10	22	100
Spleen cT_1 <1244 ms	11 (23)	5.95*	32	27	100
Baveno or spleen cT1 criteria	15 (31)	9.10*	39	30	100
Spleen diameter < 138 mm	19 (39)	11.40*	49	33	100
Platelet to spleen diameter ratio < 1.267	13 (27)	7.05*	33	28	100
Spleen volume < 468 ml	23 (47)	16.92*	59	36	100
Platelet to spleen volume ratio <0.267	25 (51)	18.80*	64	39	100
Plts > 112×10^9 cells/l, spleen volume < 790 ml	26 (53)	18.10*	67	43	100

Abbreviations: Plts, platelets; LSM, liver stiffness measurement; MELD, modified end stage liver disease score.
*$p < 0.05$.

unacceptably high proportion of VNTs. More screening endoscopies could be avoided without missing VNTs if platelet count and spleen volume criteria were used. These results require validation in future studies.

SAT-096

Overestimation and underestimation of liver fibrosis stage classification assessed by transient elastography and two-dimensional shear wave ultrasound

S.G. Kim, J.-J. Yoo, Y.S. Kim. *Soon Chun Hyang University Bucheon Hospital, Gastroenterology and Hepatology, Bucheon, Korea, Rep. of South*
Email: mcnulty@schmc.ac.kr

Background and Aims: The accuracy of detailed fibrosis stage classification assessed with transient elastography (fibroscan) was only 65% and, what is more, significant discrepancy rate (≥ 2 fibrosis stage) reached up to 13%. Several causative factors such as age, elevated liver enzyme, body mass index (BMI), skin to liver distance (SLD) are considered to contribute to this discrepancy, but there are few authentic evidences of what really works. In this study, we compared the discordance of fibrosis stage classification between fibroscan and two-dimensional shear wave ultrasound (2D-SWE) and looked for which variables are related with it.
Method: Patients who had a valid measurement and an adequate liver biopsy specimen were 291. The fibrosis stage classifications derived from the cumulated cut-offs calculated for different fibrosis stage by fibroscan as well as 2D-SWE. The discrepancy score took into account the size of error between fibrosis stage (Metavir) and fibrosis stage classification (fibroscan, 2D-SWE). This score was defined as follows: 0 for correct classification, then 1, 2 or 3 as per the misclassification in fibrosis stages.
Results: Patients were male predominant (54.0%), their mean age was 48.9 ± 13.5 years old. Liver fibrosis stage consisted of F0 (13.4%), F1 (22.0%), F2 (24.1%), F3 (16.8%) and F4 (23.7%). The optimal cut-off for each fibrosis stage observed by fibroscan was 6.9 (≥F2), 7.9 (≥F3), 10.4 (F4) and 6.7 (≥F2), 7.1 (≥F3), 10.0 (F4) by 2D-SWE. Accurate assessment of fibrosis stage classification by discrepancy score showed that the proportion of underestimation and overestimation was 19.6%, 22.0% in fibroscan, and 21.0%, 17.9% in 2D-SWE. The descrepancy score of fibroscan was higher than that of 2D-SWE (p = 0.032). In multivariate analysis, viral liver disease, shorter SLD, lower prothrombin time were associated with underestimation in both fibroscan and 2D-SWE. Longer SLD and higher AST level significantly increased overestimation in fibroscan and, in 2D-SWE along with age. When a skin to liver distance is over 2.5 cm, 80.0% (12/15) of fibroscan and 46.7% (7/15) of 2D-SWE were overestimated.
Conclusion: Fairly large number of patients are misclassified by both fibroscan and 2D-SWE. Skin to liver distance rather than BMI was most important factor to affect the over and underestimation of liver fibrosis classification.

SAT-097

Using Wisteria floribunda agglutinin-positive Mac2-binding protein in combination with the FIB-4 index to predict significant liver fibrosis

T. Jun[1], Y. Tanaka[2], Y.-C. Hsu[3], M. Nguyen[1], M.-L. Yu[4]. *[1]Stanford University Medical Center, Division of Gastroenterology and Hepatology, Stanford, United States; [2]Nagoya City University Graduate School of Medical Sciences, Department of Virology and Liver Unit, Nagoya, Japan; [3]E-Da Hospital, Division of Gastroenterology and Hepatology, Kaohsiung, Taiwan; [4]Kaohsiung Medical University, Hepatobiliary Division, Kaohsiung, Taiwan*
Email: tjun@stanford.edu

Background and Aims: *Wisteria floribunda* agglutinin-positive Mac2-binding protein (M2BPGi) is a novel biomarker which has been shown to correlate with liver fibrosis. The FIB-4 index is a clinical risk score that has been validated for ruling in or out significant liver fibrosis. We conducted this study to determine whether the use of M2BPGi in conjunction with FIB-4 could improve the prediction of significant liver fibrosis.
Method: This clinical-pathological correlative study involved 116 patients with chronic hepatitis B (HBV) seen between 2001 and 2015 at a tertiary referral center in Taiwan. All patients had a serum sample drawn within 180 days of liver biopsy. Patients who had received antiviral treatment prior to serum sample collection were excluded. Significant liver fibrosis was defined as METAVIR stage 3 or 4 fibrosis. M2BPGi was measured as a cutoff index (COI). The FIB-4 index was calculated as previously described, with patients classified as low-risk (<1.45), indeterminate (1.45–3.25) and high-risk (>3.25). M2BPGi levels were also classified into low (<0.27), intermediate (0.27–1.155) and high (≥1.155) based on the 25th and 75th percentile values. We tested several combinations of FIB-4 and M2BPGi using various cutoffs of M2BPGi to reclassify FIB-4-indeterminate patients into high or low risk for significant fibrosis.

Table. Accuracy assessment of fibrosis stage classification.

Variable	By 2D-SWE				By Fibroscan				p-value
	F0-F1 (<6.7)	F2 (6.7-7.0)	F3 (7.1-9.9)	F4 (≥10.0)	F0-F1 (<6.9)	F2 (6.9-7.8)	F3 (7.9-10.3)	F4 (≥10.4)	
By liver biopsy									
F0-1	91 (31.3%)	40 (13.7%)	5 (1.7%)	0 (0%)	91 (31.3%)	47 (16.2%)	10 (3.4%)	2 (0.7%)	
F2	3 (1%)	5 (1.7%)	2 (0.7%)	1 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
F3	9 (3.1%)	19 (6.5%)	18 (6.2%)	4 (1.4%)	9 (3.1%)	11 (3.8%)	17 (5.8%)	5 (1.7%)	
F4	0 (0%)	6 (2.1%)	24 (8.2%)	64 (22%)	3 (1%)	12 (4.1%)	22 (7.6%)	62 (21.3%)	
Overall accuracy (%)	61.2%				58.4%				0.554
Under-estimated (%)	21.0%				19.6%				0.254
Over-estimated (%)	17.9%				22.0%				0.757
Discrepancy score†	0.46 ± 0.63				0.56 ± 0.75				0.030

Figure: (abstract: SAT-096)

Table: (abstract: SAT-097).

	% indeterminate	% correctly classified (excl. indeterminate)	Positive predictive value	Specificity	Negative predictive value	Sensitivity
FIB-4	25.9	88.4	0.65	0.93	0.95	0.83
M2BPGi-IQR	18.1	84.2	0.54	0.88	0.96	0.83
M2BPGi-1.8	0	87.1	0.56	0.90	0.95	0.72
M2BPGi-0.67	0	81.0	0.44	0.81	0.96	0.83

Results: Area under the receiver operating curve (AUROC) for significant fibrosis for M2BPGi and FIB-4 were 0.85 and 0.86, respectively ($p = 0.78$). Using the FIB-4 index, 25.9% of patients were indeterminate, but 88.4% of the other patients were correctly classified. A binary M2BPGi cutoff eliminated the indeterminate classification, but at the expense of sensitivity or specificity. Reclassifying the FIB-4 indeterminate patients using a three-tiered M2BPGi classification (<0.27, 0.27–1.155, ≥1.155) led to a smaller percentage of indeterminate patients (18.1%), with slightly reduced specificity (0.88 vs. 0.93) and a slightly reduced correct classification (88.4% vs. 84.2%) rate.

Conclusion: M2BPGi had a similar AUROC for predicting significant liver fibrosis as the FIB-4 index. M2BPGi could be used to stratify patients who are indeterminate by the FIB-4 index. Depending on the M2BPGi cutoff chosen, this can reduce the number of FIB-4-indeterminate patients without significantly worsening the diagnostic characteristics of the FIB-4 index.

SAT-098

Assessing liver function: Diagnostic efficacy of parenchymal enhancement and liver volume ratio during hepatobiliary phase of gadolinium-ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) enhanced-magnetic resonance imaging (MRI) studies

A. Pecorelli[1], E.B. Orsini[2], S. Famularo[3], D. Bernasconi[1], L. Gianotti[2], S. Sironi[4], D. Ippolito[2]. *[1]Ospedale San Gerardo, Statistics, Monza, Italy; [2]Ospedale San Gerardo, Surgery, Monza, Italy; [3]Ospedale San Gerardo, Radiology, Monza, Italy; [4]ASST Papa Giovanni XXIII, Surgery, Bergamo, Italy*

Email: pecorelli.anna@gmail.com

Background and Aims: To assess whether Gd-EOB-DTPA enhanced-MRI study is useful to determine liver function in comparison to Child Pugh (CP) and Model for End-stage Liver Disease (MELD) score and biochemical test.

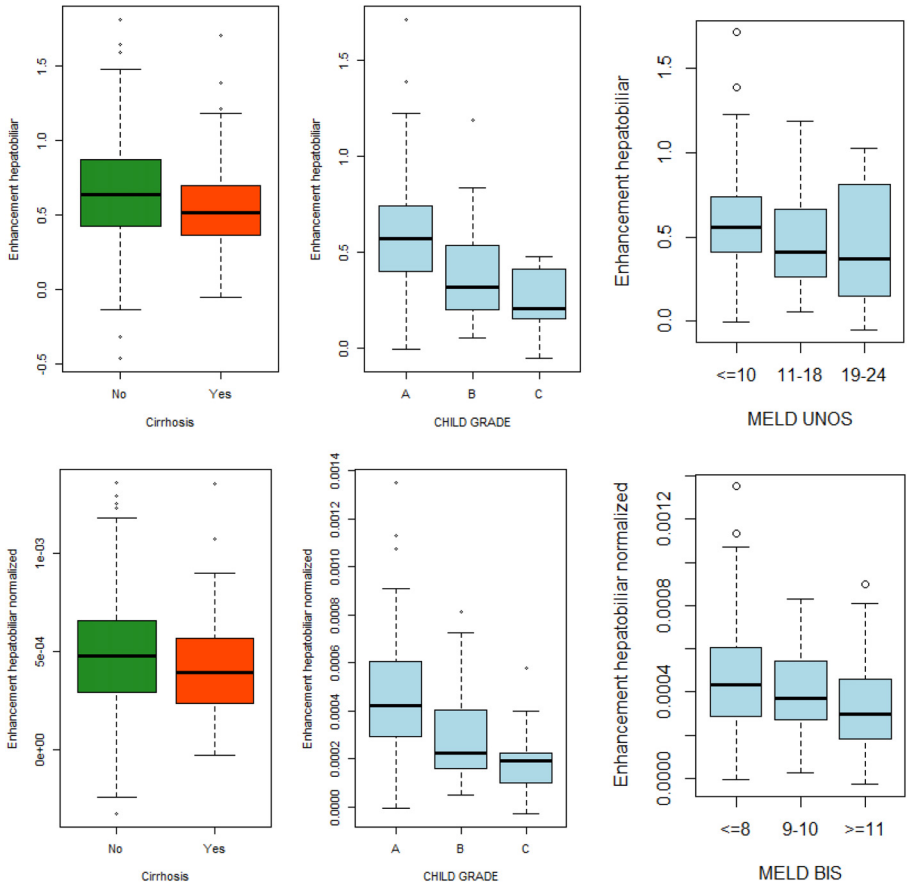


Figure: (abstarct: SAT-098): (1) Association between IrHEP and cirrhosis, Child-Pugh score and MELD score. (2) Association between IrHEP/LV and cirrhosis, Child-Pugh score and MELD score.

Method: We retrospectively reviewed all Gd-EOB-DTPA enhanced-MRI studies performed between May 2010 and September 2016 in patients with focal liver lesions. Patients were divided in study and control group according to the presence or absence of liver cirrhosis. Liver volume was calculated using the software Intellispace Portal (Philps) on hepatobiliary phase. The rate of liver-to-muscle ratio was calculated on T1 sequence in portal (irPOR) and hepatobiliary phase (irHEP) and than normalized for liver volume (irPOR/LV and irHEP/LV). Pearson correlation coefficient was computed to assess the relationship among both these indexes and CP score, MELD score and biochemical test.

Results: A total of 303 Gd-EOB-DTPA enhanced-MRI studies were included in the study. Mean age was 63.8 years (± 12.9) and the majority were male (186; 61.4%). Cirrhosis was present in 175 (57.8%) cases.

IrHEP was significantly lower in cirrhotic than in non-cirrhotic patients (0.54 ± 0.28 vs 0.66 ± 0.39, $p = 0.001$), while no difference was found in irPOR.

When considering only cirrhotic patients, irHEP significantly correlates with both CP and MELD score ($R = -0.316$, $p < 0.0001$ and $R = -0.170$, $p = 0.010$ respectively) while no correlations were found with irPOR.

The irHEP progressively decreased from CP-A to CP-C (0.59 ± 0.29 to 0.25 ± 0.19, $p < 0.0001$) and from MELD ≤ 10 to MELD 19–24 (0.58 ± 0.29 to 0.45 ± 0.41, $p = 0.030$).

Same results were observed when irHEP was normalized for liver volume.

Among biochemical parameters total bilirubin, GOT and albumin had the strongest correlation both with irHEP and irHEP/LV ($R = -0.278$ and-0.285, $R = -0.277$ and -0.291; $R = 0.282$ and 0.262 respectively).

Conclusion: Dynamic Gd-EOB-DTPA enhanced-MRI studies significantly correlates with clinical score routinely utilized to evaluate liver function. In clinical practice this imaging technique could be used both to correctly characterize focal liver lesion and to assess liver function especially in the perspective of surgical treatment.

SAT-099

Distribution and changes of FIB-4 index in normal health checkup examinees

S. Hige[1], I. Ozeki[1], J. Akaike[2], R. Tatsumi[1], M. Yamaguchi[1], M. Kimura[1], T. Arakawa[1], T. Nakajima[1], Y. Kuwata[1], T. Ohmura[1], J. Toyota[1], Y. Karino[1]. *[1]Sapporo Kosei General Hospital, Hepatology, Sapporo, Japan; [2]Sapporo Kosei General Hospital, Health Care Department, Sapporo, Japan*
Email: shuhei.hige@ja-hokkaidoukouseiren.or.jp

Background and Aims: FIB-4 index was developed as a simple noninvasive marker indicating the degree of hepatic fibrosis of various liver diseases. It has been widely used because the value can be easily obtained only by calculating with routine blood tests. The index tends to increase with age since the age is included in the formula. Therefore, the accurate estimation of liver fibrosis by FIB-4 index may be difficult especially for elderly healthy person. However, the distribution of FIB-4 index among healthy population has not been fully estimated. In this study, we investigated the distribution of FIB-4 index of health checkup examinees and determined the normal range and time course changes in healthy participants to provide the range of FIB-4 index of healthy population.

Method: A total of 22,915 people visited the Health Examination Center in our institute in 2015. Those who were undergone ultrasonography (US) and whose FIB-4 index could be calculated were selected as the subjects of this study. The presence of fatty liver was judged by US findings. As a result, 1,886 examinees who fulfilled the following criteria were judged to be "normal": within normal range in hematology and biochemistry (CBC, T. prot., Alb., T. Bil., AST, ALT, LDH, gamma-GTP, ALP, Cr., T.Chol., FBS, HbA1c), HBsAg negative, anti-HCV negative, 18.5≦BMI < 25.0, no US findings in hepatobiliary and pancreatic lesion, complications of diabetes (DM)/hypertension (HT)/dyslipidemia (DL)/malignant diseases. Changes of FIB-4 index were compared for 9,464 people (including 758 normal examinees) who underwent health checkup in both 2010 and 2015.

Results: Median value of FIB-4 index in 30's/40's/50's/60's/≥70's for "normal" examinee was 0.75/0.97/1.30/1.68/2.15. The standard deviation (SD) was 0.04/0.07/0.02/0.18/0.30. SD value was smaller than that of whole examinees (0.07/0.11/0.31/0.90/0.82). According to the regression line analysis, estimated median FIB-4 index and the 75 percentile value for each age was expressed by the following equation: [0.020×age−0.036], [0.025×age−0.006] for the group of 35–44 years old (Gr. A) and [0.038×age−0.819], [0.045×age−0.942] for the group of ≥45 years old (Gr. B). ($r = 0.99$, $p < 0.01$) Percentage of those whose FIB-4 index ≥ 3.25 in 30's/40's/50's/60's/≥70's was 0.08/0.17/0.59/1.68/9.71% for overall subjects and 0/0/0/0/4.8% for "normal" examinees. FIB-4 index was maintained low and the extent of increase by age was also low for normal examinees even in the elderly. During 5 years between 2010 and 2015, mean increase in FIB-4 index per year was 0.03 for "normal" examinees and 0.29/0.34/0.28/0.33 for the subgroup of liver diseases/DM/DL/HT.

Conclusion: FIB-4 index was maintained in a narrow range of lower value for normal examinees. Since the index tended to increase for those who had complications, high value of FIB-4 might indicate any unhealthy state.

SAT-100

Which is the chance for type 2 diabetes patients to develop severe liver disease?

I. Sporea[1], R. Lupusoru[1], R. Mare[1], R. Sirli[1], A. Popescu[1], N. Silviu[1], B. Adina[2], R. Timar[2]. *[1]University of Medicine and Pharmacy "Victor Babes" Timisoara, Department of Gastroenterology and Hepatology; [2]University of Medicine and Pharmacy "Victor Babes" Timisoara, Department of Diabetes*
Email: isporea@umft.ro

Background and Aims: The aim of the study was to assess the severity of liver fibrosis and steatosis in a cohort of type II diabetic patients, using non-invasive methods: Transient Elastography (TE) and Controlled Attenuation Parameter (CAP) and see what happen after the controlled attenuation parameter adjustment algorithm is apply.

Method: The study included 464 type II diabetic patients, who were prospectively randomized (every first 6 patients who were referred to the Metabolic Disease Outpatient Clinic on a consultation day), evaluated in the same session by means of TE and CAP (FibroScan EchoSens) to assess both liver fibrosis and steatosis. Reliable liver stiffness measurements (LSM) were defined as the median value of 10 LSM with an IQR/median <30%. A cut-off value of 10.5 kPa was used to define clinically relevant fibrosis (F ≥ 3). For differentiation between stages of steatosis we used the following cut-off values [2]: S2(moderate)-255 db/m, S3(severe)-290db/m, than we corrected the CAP values according to the presence of diabetes (we deducted 10dB/m) and according to the degree of obesity (we deducted 4.4dB/m for each BMI > 25 kg/m^2 added 4.4 dB/m for each BMI < 25 kg/m^2).

Results: Out of 464 diabetics screened we excluded those with associated viral hepatitis, those with an AUDIT-C score ≥8 and those with unreliable LSM. The final analysis included 424 subjects (55.6% women, 44.4% men, mean age 60.8 ± 9.3; BMI = 31.7 ± 6 kg/m^2) with reliable LSM. Patients with obesity grade I were 61.5%, with obesity grade II 29.1% and 9.4% with obesity grade III (IMC ≥ 40kg/m^2). Mild, moderate and severe steatosis by means of CAP was found in 20.3%, 17.1% and 66.9% cases respectively. After the correction we found moderate steatosis in 12.2% cases and severe steatosis in 59.1% cases. We found no difference in mild and moderate steatosis after the algorithm was apply, $p = 0.23$, but we found significant statistical differences regarding the severe steatosis, (66.9% vs 59.1%, $p = 0.02$). Clinically relevant fibrosis was detected by means of TE (LSM ≥ 10.5 kPa) in 12.4% (54/424) of subjects.

Conclusion: In our group, 79.3% of diabetic patients had moderate and severe steatosis by CAP, 66.9% had severe steatosis, but after applying the controlled attenuation parameter adjustment algorithm we had a signifficantly decrease (59.1%). Regarding the liver fibrosis, we found that 12.4% of them had severe fibrosis (TE ≥ 10.5 kPa), suggesting the need for their systematical assessment.

SAT-101

Intelligent liver function diagnostic pathway – Relevance of alanine transaminase normal values

E. Robinson[1], M. Miller[1], P. Brennan[1], J. Dillon[1], E. Dow[2], P. Donnan[3], B. Bartlett[2], P. Mcintyre[4], R. Neville[5], K. Boyd[6]. *[1]University of Dundee, Ninewells Hospital and Medical School, Department of Molecular and Clinical Medicine, Dundee; [2]Ninewells Hospital and Medical School, Department of Biochemical Medicine and Blood Sciences, Dundee; [3]University of Dundee, Dundee Epidemiology and Biostatistics Unit, Dundee, United Kingdom; [4]NHS Tayside, Department of Medical Microbiology and Virology, Dundee, United Kingdom; [5]NHS Tayside, Westgate Medical Practice, Dundee, United Kingdom; [6]University of Glasgow, Health Economics and Health Technology, Glasgow*
Email: e.robinson7@nhs.net

Background and Aims: Liver Function Tests (LFTs) are frequently checked in primary care although liver disease is not suspected in the majority of cases. Despite this up to 20% of LFTs are abnormal. A significant percentage are never investigated, raising the possibility of missing significant and potentially treatable liver disease at an earlier stage.

The intelligent LFT pathway (iLFT) was designed to risk stratify patients with abnormal LFTs into three categories. 1 Serious or complex liver disease that requires secondary care 2. Less significant disease that could be managed in primary care 3. Diagnostic uncertainty requiring further investigation.

Alanine transaminase in an important component of LFTs. Previous studies have suggested the accepted reference range is too high for certain diseases, leading to the possibility of missed diagnosis. It is thought that ALT < 19 in women and <30 in men is more accurate.

Method: The iLFT algorithm uses the combination of diagnostic criteria for liver disease, an investigation ordering and reporting system (ICE), and the tracked blood sciences system (Siemens). iLFT produces an automated diagnosis or description of the abnormality with staging information and suggestions for further management including referral criterion which is sent to the GP.

A step wedge design trial was conducted in 6 GP practices (covering 30,000 patients). Patients with LFTs measured in the previous 6 months with abnormalities were retrospectively used as controls. During the intervention period (6 months); GPs requested the iLFT option and those patients with abnormal LFTs were assessed.

A sub study analysis was performed within the iLFT intervention arm, an alternative normal range for ALT (male <30, Female <19) was implemented and outcomes compared to the conventional normal range (M and F < 55) including a cost effectiveness analysis.

Results: Using the lower ALT reference range: the number of subjects with abnormal LFTs increased from 64 to 140. Of those 140, 14 more patients were found to have liver disease. The majority of these additional diagnoses were NAFLD and ARLD. Detection of fibrosis is unchanged despite the lower reference range.

iLFT remained cost effective and showed an incremental care-equivalent ratio (ICER) of £137 as well as a lifetime increase in quality adjusted life years.

Conclusion: Using a reduced ALT cut off increases the rate of liver diagnosis using iLFT enabling earlier intervention. It also remains cost effective compared to standard practice.

SAT-102

The impact of inflammation grade of liver histology on the improvement of liver stiffness assessed by transient elastography

J.-J. Yoo, S.G. Kim, Y.S. Kim. *Soonchunhyang University Bucheon Hospital, Internal Medicine, Bucheon, Korea, Rep. of South*
Email: mcnulty@schmc.ac.kr

Background and Aims: Transient elastography (TE; Fibroscan) is now almost indispensable tool to estimate liver fibrosis. Although many clinical factors are known as confounding factors of liver stiffness (LS), there is no knowledge of who will achieve an improvement of liver stiffness if they have a similar liver fibrosis stage. The aim of this study is to see whether baseline hepatic inflammation may affect accurate LS measurement and which factors are associated with improvement of LS in Fibroscan.

Method: This retrospective study included consecutive 678 patients who underwent baseline liver biopsy and sequential LS assessment from 2006 to 2016 at 6 tertiary hospitals in Korea. Liver fibrosis and inflammation were graded on the basis of standard guideline proposed by the Korean Study Group for the Pathology of Digestive Diseases. LS measurement was performed at baseline and 1, 3, 5 years. Improvement of LS was defined as decreased LS value compared with baseline. Logistic regression was used to evaluate factors associated with improvement of LS in Fibroscan.

Results: Mean age of the patients was 47.12 ± 12.25 years and 48.5% were male. Six hundred 2 patients had viral hepatitis (419 HBV; 183 HCV), 76 non-viral hepatitis. Fibrosis stages 0, 1, 2, 3 and 4 were identified in 13 (1.9%), 96 (14.2%), 132 (19.5%), 186 (27.4%) and 251 (37.0%) patients, inflammation grade 0, 1, 2 and 3 were in 28 (4.1%), 278 (14.0%), 279 (41.2%), and 93 (13.7%), respectively. Baseline inflammation grade was correlated with baseline LSM value, and showed linear correlation with ΔLSM. In addition, as the grade of inflammation increased, the higher percentage of patients showed improvement of LSM. A multivariate analysis showed that higher degree of hepatic inflammation was an independent good predictor for LS improvement (adjusted hazard ratio, 3.33; 95% confidence interval, 1.20–9.26; p = 0.021) after adjustment for fibrosis stage, platelet count, total bilirubin and alanine aminotransferase level. The association of LSM and hepatic inflammation was more significant in viral hepatitis compared with non-viral etiology.

Conclusion: Baseline hepatic inflammation has significant impact on LS value and improvement of LSM, and should be considered as one of the confounding factors of measuring liver stiffness using Fibroscan.

SAT-104

Phenotypic characteristics and improvement of liver stiffness measurement during follow-up in patients with Wilson's disease

R. Iacob[1], S. Iacob[1], A. Oana[2], A.D. Cristina[1], A. Constantinescu[1], I.G. Lupescu[1], I. Popescu[1], L. Gheorghe[1]. *[1]Fundeni Clinical Institute, Bucharest, Romania; [2]University of Medicine and Pharmacy Carol Davila, Bucharest, Romania*
Email: msiacob@gmail.com

Background and Aims: Wilson's disease (WD) is an autosomal recessive genetic disorder leading to hepatic and neurologic impairement. The aim of our study was to assess phenotypic and therapeutic particularities of WD patients treated in a tertiary hospital between 2012–2016.

Method: A retrospective study has been conducted including 88 patients diagnosed with WD during the defined period.

Results: Age at diagnosis below 7 years was found in 12.9% of cases, between 7–18 years in 44.7%, 18–35years in 37.6% and >35years in 7%. At time of diagnosis, hepatic disease was encountered in 67%,

hepatic and neurologic disease in 27.3%, exclusive neurologic disease in 5.7%. In patients with hepatic WD, 30.3% had compensated and 14.2% decompensated liver cirrhosis (LC), 50% chronic hepatitis, and 5.3% acute liver failure. In patients with hepatic and neurologic impairment, 66.6% had compensated and 11% decompensated LC and 22.2% chronic hepatitis. Exclusive hepatic disease was encountered in 77.7% of children in comparison to only 50% of adults (p = 0.02). At last follow-up visit, treatment consisted in D-penicillamine 32.1%, trientine 8.3%, zinc 5.9%, D-penicillamine and zinc 41.7%, trientine and zinc 3.6%, liver transplantation being performed in 8.4% of cases. In patients with hepatic disease, clinical improvement was established in 65.8% of patients while worsening of disease in only 20.3%. In patients with hepatic and neurologic disease, clinical improvement was found in 59.1%, while worsening in 22.7%. Patients with isolated neurological impairment had a favorable clinical course in 75% of cases and the rest worsened. Liver stiffness measured in all patients with compensated liver diseases at the moment of diagnosis decreased significantly after 12 months of chelating therapy (14.6 ± 10.9 vs 8.4 ± 5.1 kPa, p < 0.0001).

Conclusion: In a romanian tertiary center, WD with hepatic phenotype is the most frequently encountered especially in children and exclusive neurological disease is rare. A favorable disease course could be confirmed in >60% of cases in all phenotypes, with significant decrease of liver stiffness. During the study period, liver transplantation was performed in <9% of cases due to timely diagnosis and effective chelating therapy.

SAT-105

Is food-intake a confusing factor for liver stiffness evaluation by 2D-SWE in normal subjects?

D. Gherhardt[1], A. Popescu[1], C. Foncea[1], T.-V. Moga[1], B. Marius[1], C. Laura[1], V. Corina[2], I. Sporea[1]. [1]*"Victor Babes" University of Medicine and Pharmacy, Gastroenterology Department, Timisoara, Romania;* [2]*Victor Babes University of Medicine and Pharmacy, Timisoara, Medical Informatics and Biostatistics, Romania*
Email: diana1310tm@yahoo.com

Background and Aims: Ultrasound based elastography has become a method frequently used by the gastroenterologist, allowing a noninvasive assessment of liver fibrosis. 2D-Shear wave elastography (2D-SWE) is a technique used for real time visualization of liver's elasticity. Our aim was to observe if the values obtained by 2D-SWE SSI were influenced by food-intake.

Method: We performed a prospective study on 42 healthy volunteers, recruited during 1 month-October 2017 from our Department of Gastroenterology. Subjects were evaluated by 2D-SWE (Aixplorer, Supersonic Imagine) 4 times: in fasting condition, at half an hour after food intake (a sandwich + water), after 1 hour as well as after 2 hours. The subjects were examined in supine position, by intercostal approach in the right liver lobe, by the same operator.
The trapezoid sample box was placed in full liver parenchymal area, avoiding large tubular structures. We placed the ROI in the most homogeneous area of the sample box, at a depth between 2.5 and 6 cm.
One examiner (with an experience of more than 50 examinations) performed 5 liver stiffness measurements (LSM) for each evaluation. Two quality technical parameters were taken into account: standard deviation/median liver stiffness <0.10 and stability index (SI) > 90%.

Results: The mean age of the 42 healthy volunteers was 27.1 ± 3.7 years. The distribution according to gender was 59.5% women (25) and 40.5% (17) men. All of them had normal weight, mean body mass index = 21.8 ± 2.5 kg/m^2.
The mean liver stiffness value at fasting was 4.8 ± 0.8 kPa (median value 4.8 kPa). Women had slightly lower LSM than men (4.7 ± 0.8 kPa vs 5 ± 0. kPa, p = 0.173).

The results of the LSM according to time spent after food-intake are illustrated in the Table 1 bellow:

Table 1: Results of LSM by 2D SWE SSI

	Fasting	30 minutes after food intake	1 hour after food intake	2 hours after food intake
Mean LSM (kPa)	4.8 ± 0.8	5.0 ± 0.8	5.1 ± 0.7	4.9 ± 0.8
P		0.25	0.07	0.56

Conclusion: Food-intake did not significantly increase liver stiffness values obtained by 2D SWE SSI method in healthy subjects.

SAT-106

Spleen stiffness decrease as mirror of portal hypertension changes after successful interferon-free therapy in chronic-HCV patients

F. Ravaioli[1], E. Dajti[1], A. Colecchia[1,2], V. Alemanni[1], G. Marasco[1], M. Tamé[1], F. Azzaroli[1], S. Brillanti[1], G. Mazzella[1], D. Festi[1]. [1]*University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy;* [2]*Azienda Ospedaliera Universitaria Integrata, UOC. Gastroenterologia, Verona, Italy*
Email: antonio.colecchia@aovr.veneto.it

Background and Aims: Interferon-free direct-acting antivirals (DAAs) have enormously increased the number of patients with advanced chronic liver disease (ACLD) achieving sustained viral response (SVR). Hepatic venous pressure gradient (HVPG) has been shown to decrease after SVR. The clinical impact of SVR in terms of changes in portal hypertension (PH) and the role of non-invasive tests (NITs) in the follow-up of SVR patients is still under discussion. We aimed to investigate the changes in spleen stiffness measurement (SSM) and other NITs at 6 months of follow-up, as well as to identify the predictors of SSM change after SVR.

Method: We retrospectively analysed prospectively collected data of compensated ACLD patients treated with DAA between January 2015 and September 2017 at our tertiary centre and with available paired SSM at baseline (BL) and 6 months after end of therapy. Changes in SSM, liver stiffness measurement (LSM), spleen diameter (SD), platelet count (PLT) and Liver Stiffness-Spleen Diameter-to-Platelet Count Ratio Score (LSPS) were investigated. According to Baveno VI Criteria, LSM ≥ 21 kPa was used as a cut-off to rule-in clinically significant portal hypertension (CSPH).

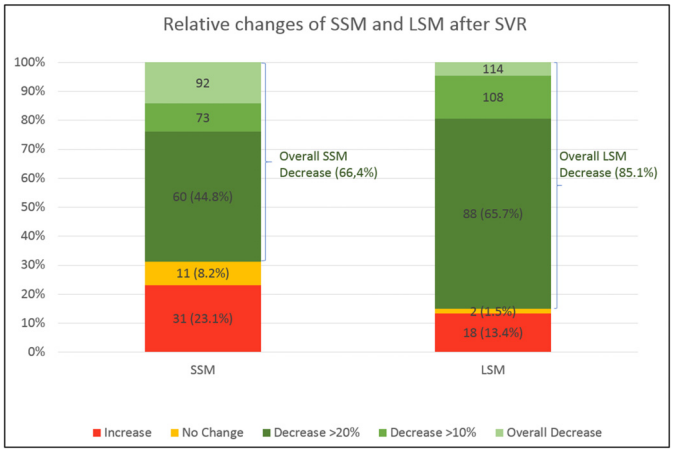


Figure: Relative changes of SSM and LSM after SVR. SSM/LSM decrease is represented as cumulative number of patients in which a decrease >20%, 10% and <10% was observed.

Results: One hundred-thirty (134) patients who achieved SVR were included in the final analysis. SSM significantly decreased from

median 58.8 kPa at BL to 38.2 kPa at SVR24; relative median change was -4.7% in patients with CSPH and -20.4% in patients without CSPH. SD and PLT differed significantly only in patients without CSPH. LSPS significantly improved after SVR. SSM decrease >20% in 60 (44.8%) patients (see Figure); independent predictor of such SSM decrease was the median relative change of LSM (OR: 0.33, 95%CI: 0–0.005, p < 0.0001). CSPH persisted in 32 (54.4%) patients after SVR; delta LSM (OR: 0.011; 95%CI: 0.0007–0154, p = 0.001) and BL SSM (OR: 1.046; 95%CI: 1.014–1.078; p = 0.004) were independent factors associated with CSPH persistence.
Conclusion: SSM faithfully reflects changes in portal hypertension. Even though LSM decrease is evident in almost all patients, a decrease >20% of SSM could more accurately identify patients with a clinically meaningful benefit in portal hypertension after viral eradication.

Liver transplantation and hepatobiliary surgery: Experimental

SAT-109
Rictor/mTORC2 signaling protects ischemic liver injury by targeting both liver parenchymal and non-parenchymal cells

H. Zhou[1,2], Z. Rao[3], J. Rao[1], Y. Xia[1], Y. Zhai[2], X. Wang[1], L. Lu[1]. *[1]The First Affiliated Hospital of Nanjing Medical University, Liver Transplantation Center, Nanjing, China; [2]David Geffen School of Medicine at University of California-Los Angeles, Department of Surgery, Los Angeles, United States; [3]The First Affiliated Hospital of Nanjing Medical University, Dept. of Anesthesiology, Nanjing, China*
Email: doc2012zhm@163.com

Background and Aims: Mammalian target of rapamycin (mTOR) signaling controls many essential cellular functions. However, the role and its underlying mechanism of Rictor/mTOR complex 2 (mTORC2) in regulating liver ischemia and reperfusion (IR) injury remains largely unknown.
Method: In a murine liver partial warm IR model, we selectively knockdown Rictor signaling in liver parenchymal and non-parenchymal cells. Hepatocellular injury and Kupffer cell (KC) pro-inflammatory activation were studied. Rictor signaling in human liver tissues post ischemia was also analyzed.
Results: Liver mTOR2 was constitutively active in mice. Ischemia triggered a transient inactivation followed by a rapid reactivation during reperfusion. Abrogation of mTORC2 signaling in hepatocytes by Rictor-shRNA-AAV8 resulted in significantly increased liver IR injury, as evidenced by higher sALT levels and worse preserved liver architectures. In vitro, knockdown of Rictor in hepatocyte inhibited hepatocellular autophagy, enhanced CHOP and pro-apoptosis signaling pathway activation, leading to increased TNF-a induced primary hepatocyte cell death. Studies have shown that KC medicated innate immune activation plays an important role in liver IR injury. Rictor siRNA with mannose-conjugated polymers was used to specifically block Rictor signaling in KC. KCs post IR were isolated and inflammatory cytokine secretion was evaluated. Specific Rictor knockdown in KC resulted in significant increase in TNF-α and IL-6 secretion but dramatically decreased anti-inflammatory IL-10 secretion. Interestingly, autophagy in KC was inhibited by Rictor knockdown as well. We further analyzed the role of Rictor in KC M1/M2 polarization. Interestingly, we found that Rictor knockdown inhibited IL-10-secreting M2-like macrophage polarization, as revealed by decreased Arg1 and Mrc1 gene induction accompanied by a decrease in STAT6 signaling pathway activation. In vivo Rictor knockdown decreased intrahepatic anti-inflammatory IL-10 gene induction, leading to aggravated liver IR injury. Finally, human liver tissues were collected in patients undergoing liver partial resection with blockade of hepatic portal. Rictor activation was analyzed by Western blot. We found that Rictor activation was inhibited by liver ischemia, which are consistent with our findings in mouse model.
Conclusion: Our findings defined a critical role of mTORC2 signaling in both liver parenchymal and non-parenchymal cells. mTORC2 protected livers against IR injury by inhibiting hepatocellular apoptosis and promoting KC M2 polarization. Targeting Rictor signaling pathway may shine light on ways to protect against liver ischemic injury in patients.

SAT-110
Hyperglycemia-triggered ATF6-CHOP pathway exacerbates liver ischemia/reperfusion injury: immnomodulation by beta-catenin signaling

J. Rao, C. Yang, F. Cheng, S. Yang, L. Lu, X. Wang. *The First Affiliated Hospital of Nanjing Medical University, Liver Surgery/Liver Transplantation Center, Nanjing, China*
Email: raojh@njmu.edu.cn

Background and Aims: Hyperglycemia is a risk factor for hepatic ischemia/reperfusion injury (IRI) during liver transplantation or hepatectomy; however, the underlying mechanism remains unclear. Our previous studies implicated endoplasmic reticulum (ER) stress in the pathophysiology of hepatic IRI. In this study, we addressed the question of whether and how hyperglycemia triggered ER stress and affected liver IRI.
Method: Diabetic patients and streptozotocin (STZ)-induced diabetic mice were involved in vivo. Bone marrow-derived macrophages (BMDMs) were used in vitro.
Results: The ER stress-ATF6-CHOP pathway was specifically activated in liver tissues and Kuppfer cells (KCs) from diabetic patients and STZ-induced diabetic mice. The ER stress inhibitor, 4-phenylbutyrate (PBA), attenuated hyperglycemia-related liver IRI based on biochemistry and histology, and decreased TLR4-related pro-inflammatory responses based on inflammatory cytokines and macrophage/neutrophil trafficking. Furthermore, CHOP-knockout (CHOP-KO) had markedly reduced hyperglycemia-related liver IRI and inflammatory responses. Importantly, expression of β-catenin, as a negative regulator of inflammatory responses, was effectively inhibited, accompanied by activation of ATF6-CHOP pathway in diabetic mice, and was almost restored in liver tissues from PBA-treated or CHOP-KO diabetic mice. In addition, β-catenin small interfering RNA (siRNA) targeting KCs abrogated the CHOP-KO-related protective effects against hyperglycemia-related liver IRI. High glucose (HG) specifically activated ATF6-CHOP signaling, inhibited β-catenin expression, and enhanced TLR4-related inflammatory responses in BMDMs in vitro; these effects were partly reversed in PBA- or CHOP siRNA-treated/CHOP-KO BMDMs. However, the anti-inflammatory functions of CHOP-KO were almost abolished by β-catenin siRNA in BMDMs under HG conditions.
Conclusion: This study revealed that hyperglycemia specifically triggers ER stress-ATF6-CHOP signaling, inhibits β-catenin activity, promotes inflammatory responses, and exacerbates liver IRI, which might provide the rationale for novel therapeutic strategies aimed at managing diabetic-related liver surgery.

SAT-111
An effective defatting cocktail to reduce liver graft steatosis before transplantation

L. Aoudjehane[1,2], W.L. Goff[1,3], E. Savier[1,2,4], P. Bonnefoy[2], P. Lesnik[1,3], Y. Calmus[1,3,5], O. Scatton[1,2,4], C. Housset[1,2], F. Conti[1,2,5]. *[1]Institute of Cardiometabolism and Nutrition (ICAN), Paris, France; [2]Sorbonne Universités, UPMC Univ Paris 06 & INSERM, UMR_S 938, Centre de Recherche Saint-Antoine (CRSA), Paris, France; [3]Sorbonne Universités, UPMC Univ Paris 06 & INSERM, UMR_S 1166, Paris, France; [4]Department of Hepatobiliary and Liver Transplantation Surgery, APHP, Pitié–Salpêtrière Hospital, Paris, France; [5]Department of Medical Liver Transplantation, APHP, Pitié–Salpêtrière Hospital, Paris, France*
Email: lynda.aoudjehane@inserm.fr

Background and Aims: Graft dysfunction after liver transplantation is correlated with the percentage of donor liver steatosis. *Ex vivo* liver perfusion could be efficient to defat steatotic liver, as demonstrated in isolated perfused rat fatty liver. In this study, we designed a new defatting cocktail and tested its effect *in vitro* on primary human steatotic hepatocytes.
Method: Primary human hepatocytes were obtained from normal liver samples. They were incubated with a free fatty acid (FFA) mixture (oleic acid and palmitic acid at a molar ratio of 2:1) for 48 h, to induce steatosis. Steatotic hepatocytes were treated with a combination of pharmacological agents referred to as a defatting cocktail (DC) for 24 h. Cell viability, oxidative stress, intracellular lipid accumulation, ketone bodies and VLDL secretion were evaluated, as well as the expression of genes involved in lipid metabolism or inflammation.
Results: Oil-Red O staining and triglyceride quantification showed abundant steatosis in hepatocytes following exposure to FFA mixture. There was no significant cytotoxicity, oxidative stress or apoptosis in steatotic hepatocytes treated with the DC. The treatment of steatotic hepatocytes with the DC induced a significant reduction of intracellular fat droplet and of intracellular triglycerides when compared to controls, by 30% and 27%, respectively. The analysis of supernatants showed that DC treatment, caused an increase in the secretion of ketone bodies and a trend towards increased ApoB-containing lipoproteins export.
The DC induced a significant upregulation in the expression of enzymes (Carnitine palmitoyltransferase I (CPT-1) and Peroxisomal proliferator activated receptor coactivator (PGC-1α) implicated in FFA oxidation, as assessed by RT-qPCR. The expression of pro-inflammatory cytokines IL1-β and TNF-α was decreased in steatotic hepatocytes treated with DC, whereas an increase in IL6 mRNA expression occurred in steatotic hepatocytes incubated with DC *vs* controls.
Conclusion: We designed an effective defatting cocktail that promotes rapid mitochondrial oxidative metabolism and reduces the amount of intracellular fat droplet and triglycerides in steatotic hepatocytes without toxicity. These results suggest that our defatting cocktail could be efficient to induce the reduction of steatosis in donor livers during normothermic reperfusion before liver transplantation.

SAT-112

A merged protocol of hypothermic oxygenated machine perfusion and normothermic machine perfusion optimizes the reconditioning of marginal donor livers

Y. Boteon[1,2], A. Schlegel[1], R. Laing[1,2], L. Wallace[2], A. Smith[1], J. Attard[1,2], D. Neil[1], T. Perera[1], D.F. Mirza[1], J. Isaac[1], P. Muiesan[1], S. Afford[2], H. Mergental[1]. [1]*Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Liver Unit, Birmingham, United Kingdom;* [2]*National Institute for Health Research, Birmingham Liver Biomedical Research Centre, Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom*
Email: yurimed43@yahoo.com.br

Background and Aims: The shortage of organ for transplantation requires the acceptance of donors with extended criteria which are more susceptible to ischaemic injury during cold storage. Extra-corporeal machine perfusion of donor livers offers safer preservation and potentially allows organ reconditioning prior to transplantation. Hypothermic oxygenated machine perfusion (HOPE) was shown to improve mitochondrial function lowering oxidative injury after reperfusion. Normothermic machine perfusion (NMP) allows viability assessment and extended organ preservation. In this study we used a combination of both techniques to determine whether we could improve the rescue rate of marginal organs.

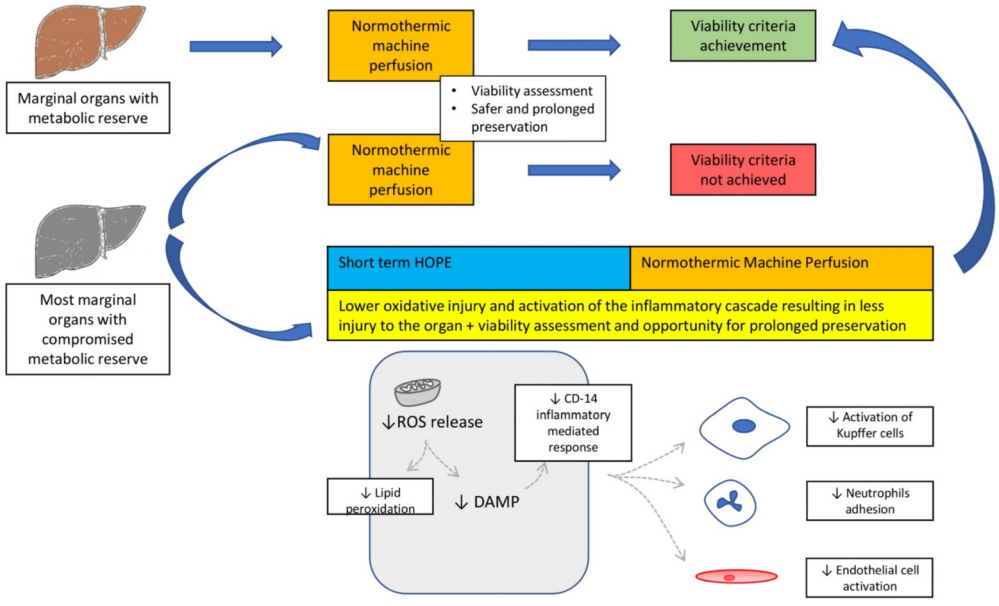


Figure 1: Pre-conditioning with short term hypothermic oxygenated perfusion lowered the oxidative stress and activation of the inflammatory cascade induced by the rewarming on the normothermic machine perfusion. This combination suggests to be fundamental for the most marginal organs to overcome the ischaemic injury and achieve viability. Therefore this technique can successfully improve the rescue rate of marginal organs.

Figure: (abstarct: SAT-112).

Method: Ten discarded human livers were randomly allocated to two experimental groups: (1) the NMP group, in which 5 organs were perfused at 37°C using an acellular oxygen carrier based perfusate for 6 hours; and, (2) the HOPE + NMP group, in which 5 organs had 2 hours of HOPE at 10°C with Belzer UW Machine Perfusion as the perfusion fluid followed by 4 hours of the previous described NMP. Viability was assessed at the end of 6 hours perfusion using the lactate clearance criteria. Perfusate and histological samples were collected for analysis throughout.
Results: Mitochondria respiratory rate decreased during HOPE (oxygen uptake: 0.009 [0.005–0.010] to 0.006 [0.001–0.007] kpa/gr/L, p = 0.043; pCO2 in the perfusate 1.27 [1.17–1.86] to 0.69 [0.57–0.82], p = 0.040) and the median ATP content increased (1.77-fold nmol/g [range: 3.89–1.33]). This resulted in slower oxygen consumption during rewarming and decreased tissue expression of markers of reactive oxygen species production (Uncoupling protein 2, p = 0.016), oxidative injury (4-hydroxynonenal, p = 0.008; TLR-4 activation, p = 0.008) and activation of the inflammatory cascade (Kupffer cells, neutrophil adhesion, p = 0.016; vascular cell adhesion protein 1, p = 0.050) for the livers that had HOPE. Liver deemed non-viable at the end of the NMP had lower ATP levels (1.10 [1.08–1.15] vs. 2.53 [2.4–10.9] nmol/gram, p = 0.050) and higher lactate levels (8.45 [5.2–11.5] vs. 1.4 [0.8–1.5] mmol/L, p = 0.020). All the livers from the HOPE + NMP group were deemed compared with three (60%) in the NMP alone group (p = 0.222).
Conclusion: The merged protocol of HOPE + NMP together combined the benefits of individual techniques increasing the rescue rate of marginal livers into the pool of transplantable organs compared with NMP alone.

SAT-113

The effectiveness of a pharmacological intervention for defatting of primary human hepatocytes and its effect on other cell types of the liver: a precursor in-vitro study to the defatting of steatotic human livers using normothermic machine perfusion

Y. Boteon[1,2], L. Wallace[2], R. Bhogal[1], A. Boteon[1], R. Laing[1,2], G. Reynolds[2], D.F. Mirza[1], H. Mergental[1], S. Afford[2]. [1]*Queen Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, Liver Unit, Birmingham, United Kingdom;* [2]*National Institute for Health Research, Birmingham Liver Biomedical Research Centre, Institute of Immunology and Immunotherapy, College of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom*
Email: yurimed43@yahoo.com.br

Background and Aims: Macrovesicular steatotic donor livers are often discarded because of the risk of graft dysfunction post-transplantation. Therapeutic interventions for defatting using extra-corporeal machine perfusion (MP) could rescue these organs into the pool of transplantable organs. We aimed to test in vitro the efficacy of a combination of drugs for defatting of primary human hepatocytes (PHH) and the effect of these drugs in the other cell types of the liver.
Method: Steatosis was induced in static cultures of isolated PHH by exposure for 48 hours to equal concentrations of 0.25 mM of palmitic, oleic and linoleic acid. This was followed by defatting using a medium supplemented with a cocktail of defatting agents for up to 48 hours. Human intra-hepatic endothelial cells (HIEC) and human biliary epithelial cells (HBEC) were isolated and incubated with the same drugs for 48 hours. The control group received the medium with only the vehicle of the drugs. MTT assay was used to estimate cell

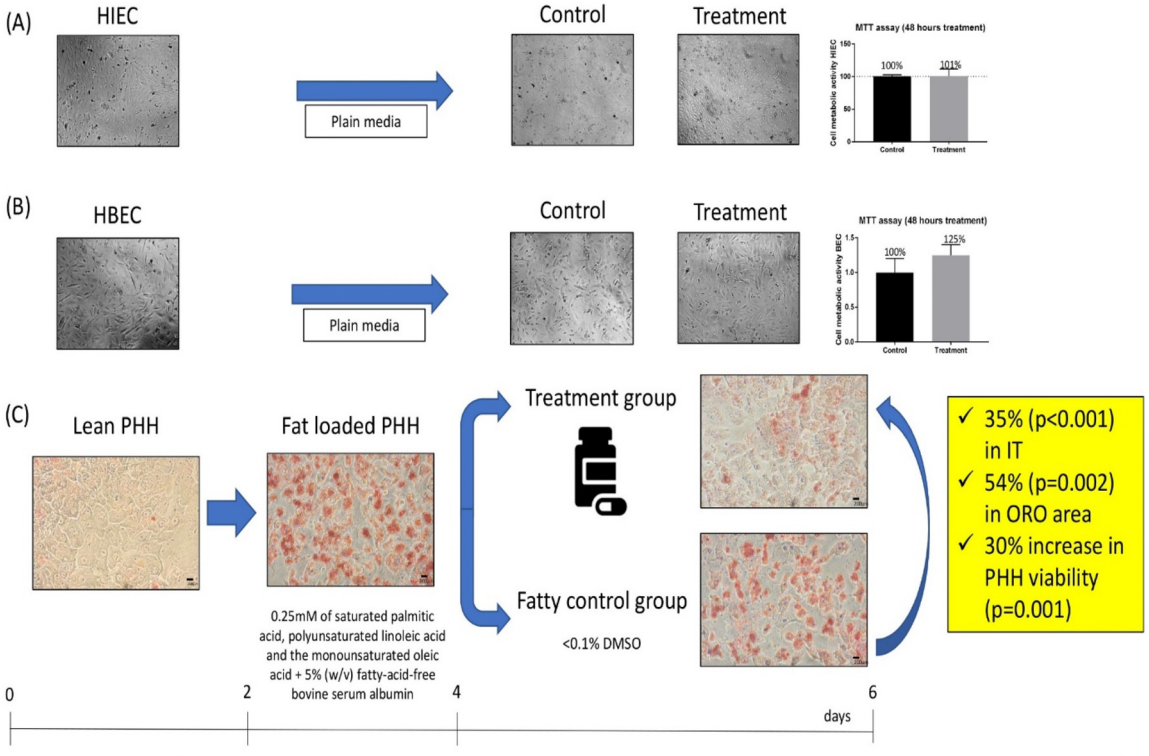


Figure 1: Schematic summary of the findings. (A) Human intrahepatic endothelial cells (HIEC) were freshly isolated from donor human livers discarded for transplantation and consented for research. These cells were left in plain media until 4 days and then randomly allocated to a control group that had the media supplemented with the vehicle of the drugs (<0.1% DMSO) and the treatment group that received the cocktail of defatting agents in the media. MTT assay for cell viability did not show any cytotoxic effect of the drugs to the cells. (B) Human biliary epithelial cells (HBEC) were also left in plain media for 4 days after harvesting and then divided into the control and treatment group as described. The viability of the HBEC increased in 25% with the treatment. (C Isolated primary human hepatocytes (PHH) were left in plain media for two to stabilise the metabolism. After that they were incubated with a media supplemented with a combination of fatty acids. Once loaded with large lipid droplets after 2 days they were allocated to two experimental groups: (1) the treatment group that received a media containing the defatting combination of drugs; and, the (2) control group which had plain media plus the vehicle of the drugs (<0.1% DMSO). After 48 hours cell viability was assessed using the MTT assay and the intracellular lipid load using the oil red O staining (ORO) and a commercial kit for measurement of the intracellular triglycerides.

Figure: (abstract: SAT-113)

viability. Intracellular triglyceride quantification (IT) and oil red O (ORO) staining were used to assess lipids content. Ketone bodies (3-hydroxybutyric acid + acetoacetic acid-mM) were measured in the supernatant up to 48 hours.
Results: Incubation of PHH with the fatty acids induced intracellular accumulation of large lipid droplets (14-fold induction in the ORO area and 8-fold in IT levels, $p < 0.050$). Treatment of fatty loaded PHH with the cocktail resulted in a median reduction of 28% (6–43%) over 24 hours and 46% (33–67%) along 48 hours in the area of lipid droplets assessed by ORO ($p < 0.050$). The IT dropped by 18% (17–19%) and 32% (28–34%) during 24 and 48 hours of treatment respectively ($p < 0.050$). Total ketone bodies measured in the supernatant increased 1.22 and 1.40-fold by 24 and 48 hours in the treated group compared with controls ($p < 0.050$). The treatment induced an increased in cell viability in more than 30% for PHH over 48 hours ($p < 0.050$), it has not affected HIEC metabolism and increased the viability of HBEC in 25% ($p < 0.050$).
Conclusion: These data showed for the first time in an in vitro primary human cell culture model that a pharmacological intervention can decrease the intracellular lipid content of PHH inducing fatty acids beta-oxidation. The treatment also increased the viability of PHH and HBEC without any harm for HIEC. These findings support future attempts to use MP as a delivery tool for extra-corporeal defatting of human livers.

SAT-114

The postoperative serumcourse of the liver regeneration-associated signaling molecules bile salts and FGF19 in cholestatic patients undergoing liver resection

K. Koelfat[1], K. van Mierlo[1], M. Schmeding[2], T. Cramer[3], I. Sauer[2], C. Dejong[1], F. Schaap[1,2], U. Neumann[2], S.O. Damink[1,2]. *[1]Maastricht University Medical Centre & NUTRIM School of nutrition and translational research in metabolism, Maastricht University, Surgery, Netherlands; [2]Uniklinikum RWTH Aachen, Aachen, Germany, Department of general-, visceral- and transplant surgery, Netherlands; [3]Uniklinikum RWTH Aachen, Aachen, Germany, Molecular Tumorbiology, Germany*
Email: k.koelfat@maastrichtuniversity.nl

Background and Aims: Systemic and hepatic bile salt (BS) levels rise shortly after partial hepatectomy (PHx) in rodents, likely providing input signals for the regenerative response. Deficiency of the nuclear bile salt receptor FXR or its target gene Fgf15/FGF19, results in delayed liver regeneration (LR) and mortality after PHx. This is due to dysregulated bile salt homeostasis and attendant bile salt-toxicity in the remnant liver, and is reminiscent of impaired LR in patients with perihilar cholangiocarcinoma (pCCA) and cholestasis. Little is known about the role of bile salt/FGF19 signaling in human LR. Here, we explored the post-resectional course of these signaling molecules in patients with different hepatobiliary malignancies.
Method: Data was collected of adult patients who underwent major hepatectomy (≥3 segments) at the Uniklinikum Aachen between 01.06.2013 and 01.02.2016 for colorectal liver metastases (CRLM, $n = 50$) and pCCA ($n = 23$). Plasma BS, FGF19 and C4 (surrogate marker of BS synthesis) levels were determined preoperatively and on postoperative days (POD) 1, 3 and 7.
Results: Preoperative bilirubin, AST, GGT and AP levels were significantly higher in pCCA-patients compared with CLRM ($P < 0.001$). At baseline, BS levels were 3-fold higher in patients with pCCA compared with CLRM ($P < 0.001$). Similar, FGF19 levels were 2.5-fold higher in patients with pCCA ($P < 0.001$). Subsequently, plasma C4 levels were significantly lower in pCCA-patients versus CLRM-patients ($P < 0.001$). Conversely, BS levels on POD7 were higher in CLRM-patients compared with pCCA ($P < 0.001$), and on the other hand FGF19 levels were significantly lower in pCCA-patients ($P = 0.03$). C4 levels on POD7 were comparable in both group. Longitudinal analysis revealed a significant postoperative rise of BS levels in CLRM patients, whereas BS levels declined on POD1 and remained low on POD3 and POD7 in pCCA-patients.
Conclusion: These data demonstrate that the postoperative rise of BS in non-cholestatic CLRM patients, potentially providing a stimulus for the regenerative machinery, is strongly attenuated in pCCA patients. Furthermore, reduced FGF19 levels in pCCA-patients after resection may negatively impact on the early course of liver regeneration in these patients.

SAT-115

Establishing a porcine model of small for size syndrome following liver resection

M. Golriz[1], A. Majlesara[1], E. Khajeh[1], O.G. Nejad[1], C. Flechtenmacher[2], A. Mehrabi[1]. *[1]Department of General, Visceral, and Transplantation Surgery, Heidelberg, Germany; [2]University of Heidelberg, Department of General Pathology, Heidelberg, Germany*
Email: Omid.Ghamarnejad@med.uni-heidelberg.de

Background and Aims: Small for size syndrome (SFSS) is responsible for a high proportion of mortalities and morbidities following extended liver resection. The aim of this study was to establish a porcine model of SFSS.
Method: Twenty-four Landrace pigs underwent liver resection with a remnant liver volume of 50% (group A, $n = 8$), 25% (group B, $n = 8$), and 15% (group C, $n = 8$). After resection, the animals were followed up for 8 days and clinical, laboratory, and histopathological outcomes were evaluated.
Results: The survival rate was significantly lower in group C compared with the other groups ($p < 0.001$). The international normalized ratio, bilirubin, aspartate transaminase, alanine transaminase, and alkaline phosphatase levels increased shortly after surgery in groups B and C, but no change was observed in group A ($p < 0.05$ for all analyses). The histopathological findings in group A were mainly mild mitoses, in group B severe mitoses and hepatocyte ballooning, moderate congestion, and hemorrhage, along with mild necrosis, and in group C extended tissue damage with severe necrosis, hemorrhage, and congestion.
Conclusion: Combination of clinical, laboratory, and histopathological evaluations is needed to confirm the diagnosis of SFSS. 75% liver resection in porcine model results in SFSS. 85% liver resection causes irreversible liver failure.

SAT-116

Induction of beta-catenin in embryonic stem cell-derived dendritic cells alleviates liver damage in mouse liver inflammatory injury

S. Yue[1], C. Li[2], L. Jiang[2], M. Ke[2], R. Busuttil[2], Q.-L. Ying[3], J. Kupiec-Weglinski[2], B. Ke[2]. *[1]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Department of Stem Cell Biology & Regenerative Medicine, Los Angeles, United States; [2]The Dumont-UCLA Transplant Center, Department of Surgery, David Geffen School of Medicine at UCLA, Los Angeles, United States; [3]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Department of Stem Cell Biology & Regenerative Medicine, Keck School of Medicine, University of Southern California, Los Angeles, United States*
Email: bke@mednet.ucla.edu

Background and Aims: Liver inflammatory injury induced by ischemia and reperfusion injury (IRI) is the major causes of hepatic dysfunction and failure following liver transplantation. Embryonic stem (ES) cell derivatives offer a potentially important renewable source of cell therapy for tissue injury. However, the host immune response leading to liver damage remains the greatest challenge during hepatic IR. This study was designed to regulate immune response through induction of β-catenin activity in ES cell-derived Dendritic cells (ES-DC) in vitro and in vivo.
Method: Mouse ES cells were cultured and maintained in MEFs/LIF conditions. ES cells were seeded onto OP9 feeder cell layers and

differentiated into DC with granulocyte macrophage colony-stimulating factor (GM-CSF). ES-DC were transfected with a CRISPR/Cas9-mediated β-catenin activation (pCRISPR-β-catenin) or knockout (pCRISPR-β-catenin KO) vector. For the in vivo study, wild type (WT) mice were subjected to 90min partial liver warm ischemia followed by 6h of reperfusion. The pCRISPR-β-catenin-modified ES-DC or control ES-DC were adoptively transferred into mice 24h prior to liver ischemia.

Results: The pCRISPR-β-catenin-modified ES-DC diminished the expression of proinflammatory cytokines (IL-12p40, TNF-α, and IL-1β) and chemokine receptors (CXCR4, CCR2, and CCR7) in response to LPS stimulation. Induction of β-catenin in ES-DC upregulated Notch1, NICD, and Hes1 with reduced IL-2 and IFN-γ, yet increased IL-10 and TGF-β production in antigen-responsive T cells after co-culture of ES-DC and OVA-stimulated CD4+ T cells. However, the pCRISPR-β-catenin KO resulted in augmented PTEN/TLR4 and reduced Akt phosphorylation in ES-DC. Unlike in control ES-DC, adoptive transfer of β-catenin-modified ES-DC improved IR-induced liver injury, as evidenced by reduced sALT levels and ameliorated liver histopathology, which was accompanied by diminished PTEN/TLR4 and increased NICD, Hes1, and Akt phosphorylation, with reduced proinflammatory mediators.

Conclusion: This study demonstrates that liver inflammatory response induced by IR can be modulated by induction of β-catenin activity in ES-DC. Our novel findings underscore the crucial role of β-catenin in stem cell-mediated immune regulation in IR-triggered liver inflammation. Using genetically modified ES-DC system, our study provides a novel approach and establishes a potential clinical feasibility for the amelioration of ischemic tissue injury in organ transplantation.

SAT-117

Sealant pathology

H. Fonouni, O.G. Nejad, E. Khajeh, E. Aydogdu, A. Mehrabi. *University of Heidelberg, Department of General, Visceral, and Transplantation Surgery, Heidelberg, Germany*
Email: hamidreza.fonouni@med.uni-heidelberg.de

Background and Aims: Despite remarkable developments in perioperative patient's care, surgical techniques, and surgical instruments, the risk of complications following liver resection such as bile leakage and hemorrhage is still high. Sealants are used frequently with the intention of reducing these complications. To our knowledge, detailed postoperative histopathological changes of sealants on liver surface after hepatectomy have not been studied so far. Accordingly, we aimed to assess and provide dependable evidence-based data to determine the impact of different sealant materials on histopathological changes after liver resection in an experimental study.

Method: Twenty-seven landrace pigs (weight: 32.6 ± 4.2 kg) underwent left hemihepatectomy and were randomized in control group (n = 9) with no sealant and treatment groups (each n = 9), in which resection surfaces were covered with collagen-based sealant and fibrinogen-based sealant. After postoperative day 5, the tissue samples were examined and graded by and indipendent pathologist using a semi-quantitive scale for degree of hepatocellular regeneration, necrosis, fibrin production, associated inflammation, demarcation, intraparenchymal bleeding, granulation tissue formation, microabscess, bacterial colonization, and parenchymal inflammation.

Results: There were no significant differences regarding preoperative cardiocirculatory parameters between three groups. Relative and absolute bleeding times were significantly lower in collagen-based sealant group (both $p < 0.01$). Hepatocellular necrosis occurred more in fibrinogen-based sealant group and less in collagen-based sealant group ($p = 0.01$). As expected, the rate of bacterial colonization and inflammation was significantly lower in control group (both $p < 0.01$). However, increased hepatocellular regeneration potential was seen in sealant groups, which was significantly higher in collagen-based sealant group.

Conclusion: The usage of sealants after hepatectomy is safe and is not associated with major morbidities. Sealants significantly decreased bleeding after hepatectomy. Furthermore, collagen-based sealant increases the rate of posthepatectomy regeneration. Future randomized clinical studies should be performed to establish indications of using sealants in clinical setting.

SAT-118

Preoperative biliary drainage reverses cholestasis-associated inflammatory and fibrotic gene signatures in patients with perihilar cholangiocarcinoma

R. van Golen[1], M. Reiniers[1], L. de Haan[1], R. Weijer[1], J. Wiggers[1], A. Jongejan[2], P. Moerland[2], L. Alles[1], A. van Kampen[2], T. van Gulik[3], M. Heger[1]. *[1]Academic Medical Center, Experimental Surgery, Netherlands; [2]AMC, Bioinformatics Laboratory, Amsterdam, Netherlands; [3]Academic Medical Center, Amsterdam, Netherlands*
Email: r.f.vangolen@amc.nl

Background and Aims: Perihilar cholangiocarcinoma (PHCC) can only be cured by major liver surgery. Preoperative biliary drainage (PBD) alleviates cholestasis in PHCC patients, but postoperative mortality rates remain high. PBD-related complications contribute substantially to perioperative morbidity. There is currently no agreement on the timing, technique, or extent of PBD for PHCC. The aims of this study were to investigate the mechanisms through which cholestasis impairs the hepatic resilience to partial liver resection and to assess the extent to which PBD reverses these changes.

Method: Eight patients with resectable PHCC underwent unilateral PBD, meaning that only the future remnant liver received biliary decompression. During surgery, paired cholestatic and post-cholestatic (after PBD) liver biopsies were collected. Control ('healty') liver biopsies were collected from 8 patients with a non-PHCC hepatic malignancy or a benign liver lesion. Patients with pre-existent parenchymal pathology, patients who received preoperative chemotherapy, or patients who underwent preoperative portal vein embolization were excluded. Gene expression profiles of the 24 collected liver biopsies were generated by microarray according to standard bioinformatics methods/protocols.

Results: The median(± IQR) duration of cholestasis in the PBD group was 87 (67–91) days. Total bilirubin levels peaked at 270 (193–304) μmol/l and dropped to 20 (12–33) μmol/l prior to surgery. The incidence of cholangitis and pancreatitis prior to surgery was 3 out of 8 and 1 out of 8, respectively. The control group comprised patients with (cyst)adenoma, giant haemangioma, hepatocellular carcinoma, intrahepatic cholangiocarcinoma, or angiosarcoma.

Cholestasis triggered the expression of extracellular matrix-related genes (e.g., collagens), pro-fibrotic (transforming growth factor beta pathway) gene sets, and pro-inflammatory (tumor necrosis factor alpha and inflammasome pathway) gene sets. In addition, gene sets reflecting hepatocyte-specific function were suppressed by cholestasis. Following unilateral PBD, the expression of hepatocyte-specific genes normalized. In addition, the aforementioned pro-fibrotic and inflammatory changes in gene expression were largely alleviated.

Conclusion: Unilateral preoperative biliary drainage reverses cholestasis-associated pro-fibrotic and inflammatory hepatic gene signatures in the future remnant liver of patients with perihilar cholangiocarcinoma.

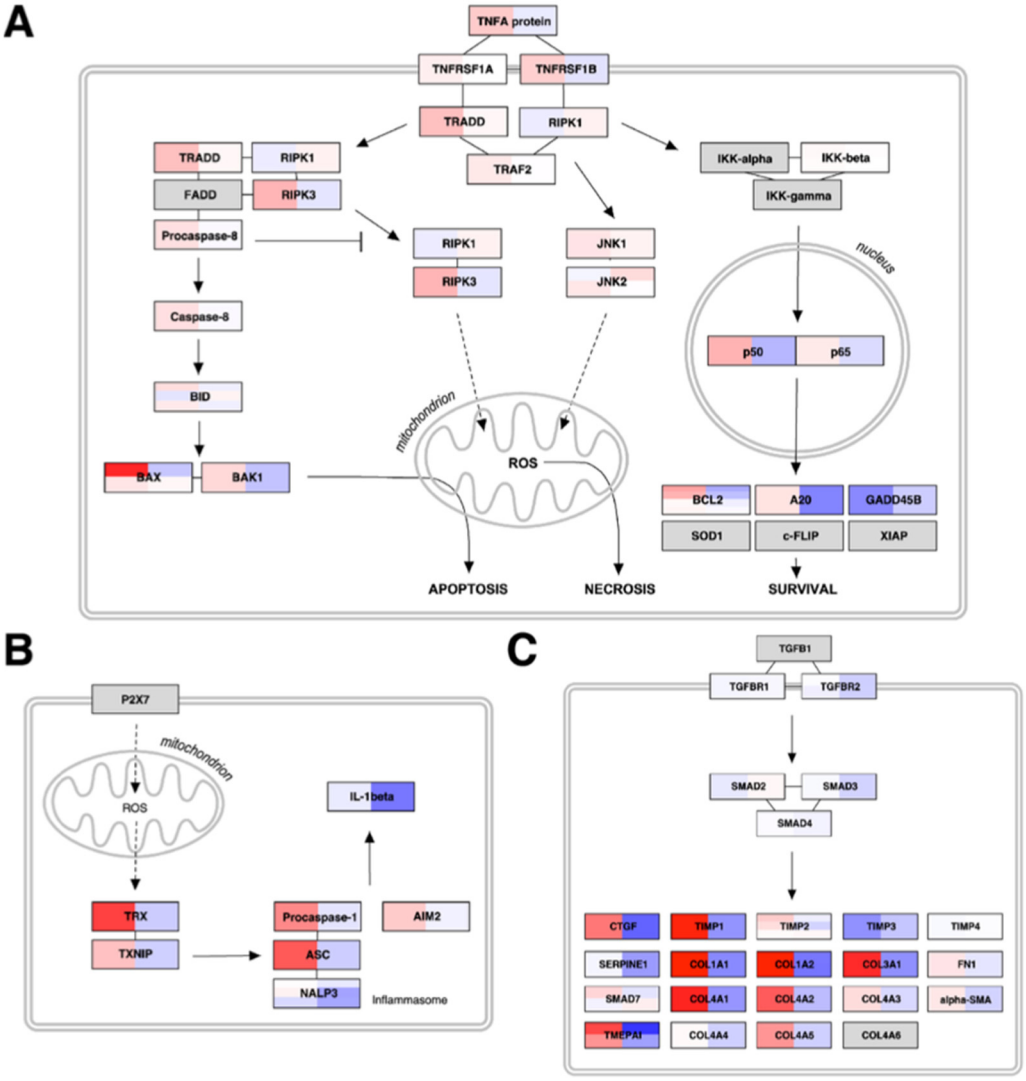


Figure: (abstract: SAT-118)

Liver tumours: Experimental and pathophysiology

SAT-122

Distinct functions of phosphorylated and un-phosphorylated STAT1 in hepatocellular carcinoma

B. Ma, W. Cao, M. Li, J. Liu, W. Wang, M. Peppelenbosch, Q. Pan.
Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands
Email: 136365449@qq.com

Background and Aims: Interferons (IFNs) with antiviral and immune-stimulatory functions have been widely used in prevention and treatment of hepatocellular carcinoma (HCC), in particular for patients with viral hepatitis. Phosphorylation of STAT1 is a hallmark for the activation of the IFN signaling. This study aims to investigate the functions of phosphorylated and un-phosphorylated STAT1 (p- and u-STAT1) in HCC and their involvement in the anti-HCC effect of IFN-alpha.

Methods: Liver tissues from 141 HCC patients has been used for detection of u-STAT1 and p-STAT1 expression by tissue microarray technique. CRISPR/Cas9 system was applied to construct STAT1 knockout.
HCC cell lines including Huh6 and Huh7. Cell cycle and apoptosis were analyzed by flow cytometry (FACS). Gene expression were measured by quantitative real-time polymerase chain in reaction (qRT-PCR).
Results: STAT1 protein level in the cytoplasma, but not in the nuclear, was significantly increased in patient HCC tumors as compared to adjacent liver tissues ($n = 141$, $p \leq 0.01$). However, p-STAT1 expression was undetectable in both tumor and adjacent tissues ($n = 37$). This is consistent with the finding in HCC cell lines, which express high level of u-STAT1, but almost no p-STAT1 expression. Knockout of u-STAT1 significantly reduced the colony formation and led to cell cycle arrest in G1 phase in HCC cell lines. We further investigated the function of p-STAT1 with IFN-alpha stimulation. As expected, knockout of u-STAT1 remarkably abolished the induction of interferon-stimulated genes (ISGs) upon IFN-α treatment in both HCC cell lines. However, IFN-α treatment with activation of p-STAT1 only exerted moderate inhibition of cell growth and induction of cell apoptosis, and this effect was not influenced by u-STAT1 knockout.

Conclusion: STAT1 is predominantly present as un-phosphorylated form and sustains the growth of HCC. Although p-STAT1 is robustly induced by IFN treatment, it is not involved in the anti-HCC effect of IFN-alpha. These findings separate the function of u-STAT1 and p-STAT1 and provide insight of the biology and therapy of IFN in HCC.

SAT-123

High fat diet induces a tumor like metabolism in the liver

J. Duarte[1,2], R. Schmieder[1,2], K. Veys[2], D. Broekaert[1,2], F. Napolitano[3], B. Holvoet[4], M. Gilis[5], K. Vriens[2,6], J.F. Garcia[2,6], T. Grünewald[7], C. Mathieu[5], C. Deroose[4], D.D. Bernardo[3,8], K. de Bock[9], S.-M. Fendt[1,2]. *[1]Vlaams Instituut voor Biotechnologie, Cencer for Cancer Cell Biology, Leuven, Belgium; [2]Katholieke Universiteit Leuven, Department of Oncology, Leuven, Belgium; [3]Telethon Institute of Genetics And Medicine, Systems and Synthetic Biology Lab, Pozzuoli, Italy; [4]Katholieke Universiteit Leuven, Department of Imaging and Pathology, Leuven, Belgium; [5]Katholieke Universiteit Leuven, Laboratory of Clinical and Experimental Endocrinology, Leuven, Belgium; [6]Vlaams Instituut voor Biotechnologie, Department of Oncology, Leuven, Belgium; [7]LMU München, Max-Eder Nachwuchsgruppe für Pädiatrische Sarkombiologie, München, Germany; [8]Federico II University, Department of Chemical, Materials and Industrial Engineering, Napoli, Italy; [9]ETH Zurich, Department of Health Sciences and Technology, Schwerzenbach, Switzerland*
Email: sarah-maria.fendt@kuleuven.vib.be

Background and Aims: Epidemiological studies have shown that there is a clear connection between high fat diet (HFD) and the development and progression of hepatocellular carcinoma (HCC). We hypothesize that HFD induces metabolic alterations in hepatocytes (HEPs), stimulating a pro-tumoral metabolism which, in turn, increases the susceptibility of HEPs to the development of HCC.
Method: We modeled hepatic metabolism using a genome scale model to predict the response of hepatocytes to lipids and investigate whether lipid induced changes overlap with HCC induced changes. Next, we verified our predictions in vivo by determining liver and HCC metabolism using ^{13}C glucose infusions in mice on HFD versus control diet. Finally, we studied the mechanistic relationship between liver metabolism and lipids using an in vitro model.
Results: Using *in silico* modelling we predicted that several metabolic pathways induced by lipids are also present in HCC. These include glycolysis, mitochondrial anaplerosis and serine biosynthesis. Indeed, we observe that all of the predicted pathways are elevated in HFD challenged livers compared to control diet livers even before the development of tumors. Moreover, we verified that these pathways are also present and exacerbated in HCC. Thus, this suggests that lipids induce a tumor–like metabolism in the liver. Next, we asked how lipids alter liver metabolism. Using an *in vitro* model, we found that lipids increase fatty acid oxidation and reactive oxygen species (ROS) production. Inhibiting these pathways resulted in decreased mitochondrial anaplerosis and glycolysis, respectively. Thus, this suggest that lipids change liver metabolism by directly impacting hepatocytes.
Conclusion: Our results show that prior to the development of HCC, HFD challenged hepatocytes exhibit a HCC-like metabolism. Therefore, HFD can be considered a "metabolic primer" for the development of HCC. In conclusion, we discovered that HFD induces a tumour-like metabolism in the liver and induces metabolic prerequisites of HCC development.

SAT-124

Nrf2 pathway plays an important role in the development of hepatocellular carcinoma: the gene expression signature of Nrf2 observed in a rat hepatocarcinogenesis model

C.D. López, J.E. Torres-Mena, P. Castro-Gil, J.I. Pérez-Carreón. *Instituto Nacional de Medicina Genómica, Liver Diseases Laboratory*
Email: davik.loto@gmail.com

Background and Aims: Schiffer's model is one of few hepatocarcinogesis models that additionally induces cirrhosis in rats. Tumors are induced by administration of weekly intraperitoneal doses of diethylnitrosamine (DEN). The liver of animals submitted to this protocol develops cirrhosis at twelve weeks and multinodular hepatocellular carcinoma (HCC) at eighteen weeks. The aim of this work was to evaluate the gene expression changes within the time-course development of HCC in Schiffer's hepatocarcinogenesis model.
Method: Four groups of rats Fisher-344 were administered with a weekly dose of DEN and sacrificed at 6, 12, 18 and 22 weeks once the treatment began. The gene expression profile of each group was compared to livers of non-treated rats using the Affymetrix Genechip Rat Gene 1.0. A set of eight genes was used to validate the differential gene expression through Western blot and real time RT-PCR.
Results: More than a thousand of differentially expressed genes were identified throughout hepatocarcinogenesis. The Nrf2-mediated gene transcription was the main dysregulated pathway with 28 differentially expressed genes. Dysregulation of this pathway was observed from week 6 with 11 overexpressed genes and this number reaches a peak of 27 at week 18. A group of seven genes, including Nqo1, Akr1B10 and Gstp1 were upregulated since week 6 until week 22, suggesting that these genes are important in HCC development. Several genes among those belonging to Nrf2 pathway were upregulated in this animal model and their human orthologs can also be found overexpressed on human liver tumors and other cancers types according with Oncomine's database.
Conclusion: Dysregulation of Nrf2 pathway occurs from early stages in Schiffer's model and seems to be a conductor of hepatocarcinogenesis. These results suggest that this animal model could be used in the investigation of different types of cancer in which Nrf2 has a significative role as well as a model in which targeted genes of this pathway may be studied.

SAT-125

ADAR-mediated A-to-I RNA editing in human hepatocellular carcinoma

G. Song[1,2], Y. Zhao[3,4,5], J. Zhu[1,2], X. Shen[1,2]. *[1]Fudan University, Zhongshan Hospital, Department of Gastroenterology, Shanghai, China; [2]Shanghai Institute of Liver Diseases, Shanghai, China; [3]University of Texas Health Science Center at Houston, Texas Therapeutics Institute, Brown Foundation Institute of Molecular Medicine, Houston, United States; [4]University of Texas Health Science Center at Houston, Graduate School of Biomedical Sciences, Houston, United States; [5]University of Texas Health Science Center at Houston, Division of Oncology, Department of Internal Medicine, and Memorial Herman Cancer Center, Houston, United States*
Email: song_guangqi@fudan.edu.cn

Background and Aims: Adenosine deaminase acting on the RNA (ADAR) proteins mediated adenosine-to-inosine (A-to-I) editing is one of the most frequent modifications during post- and co-transcription in human cells. Due to inosine (I) residues preferentially base pair with cytidine (C), edited sites in the coding and noncoding RNA sequences are recognized as guanosine (G), which may interfere in mRNA translation, alternative splicing and miRNA-3′UTR binding. Recently, several studies report that aberrant expression of ADAR proteins in different human cancers, including hepatocellular carcinoma. However, the affection and regulating mechanism of A-to-I editing in hepatocellular carcinoma are still unclear.
Method: We generated a large-scale prediction platform (***RNA Editing Plus***) for one-step identifying of the A-to-I RNA editing events and their downstream effects from RNA high-seq data. To reveal the affection of A-to-I RNA Editing in hepatocellular carcinoma, we performed the editing sites calling using ***RNA Editing Plus***. We compared the data from 20 human hepatocellular carcinoma tissues, 20 para-carcinoma tissues and 5 hepatocellular carcinoma cell line transduced with siRNA for ADAR prroteins.
Results: 714 A-to-I RNA Editing events were identified only occur in hepatocellular carcinoma tissues, including 99 events in exon region

and 5 events on intron region leading to amino acid sequences mutation, as well as 610 events on 3′UTR region. Several genes edited in exon and intron region were reported inhibiting the replication of hepatitis B virus and the proliferation of hepatocellular carcinoma, while most of 3′UTR edited RNAs involve with the DNA replication and cell proliferation.
Conclusion: These results indicat that modification of genes by A-to-I RNA editing possibly be associated with the evolution and progression of hepatocellular carcinoma. Hence, more research is needed to identify the critical editing events, which may reveal the mechanism of A-to-I RNA editing in hepatocellular carcinoma and provide novel clinical therapeutic targets. The ***RNA Editing Plus*** platform is available for free at **https://www.rnaeditplus.org/**.

SAT-126
Sulfatase 2 antagonizes starvation-induced autophagy in hepatocellular carcinoma
Y. Fang[1], P. Romecin[2], S. Wang[1], E.J. Tolosa[2], L. Flores[2], C.D. Moser[1], S. Han[1], C. Hu[1], D. Yang[1], G. Chen[1], R. Chaiteerakij[1], Y. Chen[1], A. Miamen[1], P. Kumar[1], Y. Ha[1], M.E. Fernandez-Zapico[2], L. Roberts[1].
[1]Mayo Clinic, Division of Gastroenterology and Hepatology; [2]Mayo Clinic, Schulze Center for Novel Therapeutics, Division of Oncology Research
Email: paodunromec@gmail.com

Introduction: Enzymatic removal of 6-O-sulfate from heparan sulfate proteoglycans by sulfatase 2 (SULF2) modulates the activity of heparin-binding growth factors including WNT, FGF and TGFbeta known oncogenic pathways promoting hepatocellular carcinoma (HCC). Recent studies have shown that autophagy, an essential cellular process involved HCC cancer initiation and progression, can be modulated by the aforementioned growth factors. However, to our knowledge, the role of SULF2 in the regulation of autophagy has not been reported yet. Here we demonstrate a new of SULF2 in starvation-induced autophagy through the modulation of phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) growth signaling pathway.
Methods: Autophagy was induced using serum-free starvation medium. SULF2-negative cells, Hep3B, were transfected with SULF2 expression constructs and SULF2-positive cells; Huh7, were transfected with short hairpin RNA targeting SULF2. The levels of p62, microtubule-associated protein light chain 3B (LC3B) and AKT/mTOR pathway activation were assessed by immunoblotting and immunofluorescence. The cellular effect of SULF2-regulated autophagy under starvation was examined by soft agar colony formation assay.
Results: Autophagy was inhibited by SULF2 overexpression Hep3B cells and enhances in SULF2-knockdown Huh7 cells. SULF2 inhibited the accumulation of LC3B-II, rescues p62 levels and promoted colony formation in cells cultured under starvation conditions. Transfection of SULF2 in Hep3B cells increased the phospho-AKT, phospho-mTOR and downstream factors of mTOR phospho-ULK1 (kinase 1 of type UNC-51), phospho-p70S6 kinase and phospho-4E binding protein 1. Knockdown of SULF2 in Huh7 cells decreased levels of these factors. The PI3K inhibitor LY294002 and the mTOR rapamycin inhibitor block the inhibitory effect of SULF2 on autophagy.
Conclusions: Together, these findings support a role for SULF2 in the regulation HCC cell autophagy through activation of the PI3K/AKT/mTOR pathway and suggest SULF2 as new therapeutic target for this disease.

SAT-127
In vivo knockdown of Plk1 using a novel breakable mesoporous silica particle siRNA carrier reduces tumor growth in an orthotopic xenograft mouse model of hepatocellular carcinoma
François H.T. Duong[1], A. Saviano[1], E. Robinet[1], M. Dentinger[2], G.B. About[3], C. Thumann[1], T. Sorg-Guss[3], T. Baumert[1], L.D. Cola[2].
[1]Institut de Recherche sur les Maladies Virales et Hépatiques, INSERM U1110, Strasbourg, France; [2]Institut de Science et d'Ingénierie Supramoléculaires, Université de Strasbourg; [3]PHENOMIN-ICS (Institut Clinique de la Souris), Illkirch
Email: f.duong@unistra.fr

Background and Aims: Hepatocellular carcinoma (HCC) is a major cause of cancer death worldwide. Treatment options for advanced HCC are still unsatisfactory. RNAi-based gene silencing is emerging as therapeutic clinical approach allowing personalized medicine. One challenge is the development of robust and safe vectors for delivery of active siRNA *in vivo*. We aimed to generate a trackable clinical GMP-grade nanoparticle that features a high siRNA loading capacity, is biodegradable, and efficient and safe for treatment of HCC.
Method: We used a modified Stöber process to generate controllable and uniform size breakable mesoporous silica particles. To enhance the biomaterial loading capacity of the particles, we enlarged the pore size to 10–15 nm by treating them with a swelling agent. The breaking of the particles is induced by glutathione, a natural reducing agent present in rather large amount in cancer cells. siRNA was loaded on the particles by electrostatic interactions and then wrapped with jetPEI® to protect siRNA from degradation. Transmission and scanning electron microscopy, DLS and zeta potential measurements were used to characterize the particles, and UV spectroscopy and TGA to quantify the amount of siRNA loaded. *In vitro* siRNA delivery efficacy and particles-induced cell cytotoxicity were analyzed in Huh7 cells by using luciferase reporter gene siRNA and by measuring cell viability respectively. For *in vivo* evaluation, intrahepatic injections of 1mg/kg of Plk1 siRNA-containing mesoporous silica particles or of Plk1 siRNA-carrying jetPEI® were done 3 times per week in an orthotopic model of Huh7-derived tumors. Tumor growth was monitored by echography.
Results: Mesoporous silica particles show a loading capacity of 66µg siRNA per mg of nanoparticles. Particles efficiently deliver siRNA into liver cancer cells with potent and significant gene silencing. The breaking of the particles can be followed by TEM directly after their internalization in the cells. The breaking occurs after 24 hours and it is complete after 96 hours. No nanoparticle-mediated cell cytotoxicity was observed. Intra-tumoral injection of Plk1 siRNA-loaded particles significantly delayed the onset of tumor growth in an orthotopic model of Huh7-derived tumors without detectable off-target toxicity.
Conclusion: High siRNA loading capacity breakable mesoporous and biodegradable silica particles efficiently and safely deliver Plk1 siRNA *in vivo* resulting in a reduction of tumor growth. The successful *in vivo* proof-of-concept suggests that this nanoparticle is suitable for RNA-targeted therapy of HCC. The amount of siRNA can be further increased and the breaking on demand feature, ensure a perfect timing and full release of the cargo. Furthermore, the possibility to entrap chemotherapeutics and labels allows multiple delivery and spatiotemporal visualization of the nanosystems.

SAT-128
CeO2NPs are similarly effective as sorafenib in increasing survival in rats with HCC
G.F. Varo[1,2], D. Oró[1], S.C. Restoy[1], L. Boix[3], E. Casals[4], M.P. Corominas[1], L. Oller[1], G. Casals[1], M. Morales-Ruiz[1,2], J. Bruix[3], V. Puntes[4,5], W. Jiménez[1,2]. *[1]Service of Biochemistery and Molecular Genetics, Hospital Clinic de Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS)., Barcelona, Spain; [2]Departament of Biomedicine, University of Barcelona.,*

Barcelona, Spain; [3]BCLC Group. Hospital Clinic de Barcelona, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain; [4]Vall d'Hebron Institute of Research (VHIR), Barcelona, Spain; [5]Institut Català de Nanociència i Nanotecnologia (ICN2), Bellaterra, Spain, Institut Català de Recerca i Estudis Avançats (ICREA), Barcelona, Spain
Email: guillermo.fernandez@ciberehd.org

Background and Aims: Sorafenib is the only compound that has shown efficacy increasing survival of patients with advanced hepatocellular carcinoma (HCC) in the first line. However, the emergence of resistance and tumor progression highlight the need to develop new more effective therapies. We recently reported that the administration of antioxidant CeO_2 nanoparticles (CeO_2NPs) in rats with HCC reduce cell proliferation and improve survival. The current study was addressed to investigate the therapeutic efficacy of CeO_2NPs in an experimental model of HCC.
Method: The study included 48 Wistar rats induced to HCC by a weekly intraperitoneal administration of diethyl-nitrosamine (DEN, 50 mg/kg) for 16 weeks. In the first protocol, the tissue distribution of the CeO_2NPs was analyzed by mass spectrophotometry. The animals received two weekly doses of CeO_2NPs (0.1 mg/kg, n = 10) at the 16^{th} and 17^{th} weeks by tail vein and were distributed and sacrificed sequentially after 3 days, 2 weeks and 3 weeks. In the second protocol, liver cell apoptosis and changes in the expression of proteins involved in tumor progression was evaluated. The rats were randomized into two groups receiving two weekly intravenous doses of CeO_2NPs (0.1 mg/kg, n = 10) or vehicle (0.8 mM TMAOH, n = 10) at the 16^{th} and 17^{th} weeks. The animals were sacrificed at the 18^{th} week and liver biopsies were obtained. In the third protocol, 18 rats with HCC randomly received CeO_2NPs or vehicle intravenously or an intragastric administration of sorafenib (10 mg/kg) administered daily for 14 days and the effect on survival was compared.
Results: The tissue analysis showed that the liver and the spleen are the main targets of the CeO_2NPs in DEN-treated rats. CeO_2NPs induced an increase in cellular apoptosis, as demonstrated by the TUNEL assay and the increased expression of activated caspase-3. Decreases in the phosphorylation levels of GSK-3α and ERK1/2 were observed in CeO_2NPs-treated rats compared to the animals that received vehicle. This was associated with a similar increase in overall survival of the animals treated with CeO_2NPs and those receiving sorafenib.
Conclusion: The activity of CeO_2NPs promotes changes in cellular mechanisms involved in tumor progression. CeO_2NPs and sorafenib have similar effectiveness in increasing survival in rats with HCC, thereby suggesting that CeO_2NPs may have therapeutic usefulness in patients with HCC.
Acknowledgments: Supported by grant from MINECO (SAF15-64126-R).

SAT-129

Hepatocyte c-Jun N-terminal kinases determine cell fate and carcinogenesis in NEMO-deficient mice

M.R. Mohamed[1,2], F.J. Cubero[1,3], M. Woitok[1], C. Liedtke[1], C. Trautwein[1]. *[1]University Hospital, RWTH Aachen, Department of Internal Medicine III, Germany; [2]National Research Centre (NRC), Therapeutic Chemistry Department, Cairo, Egypt; [3]Complutense University School of Medicine, Department of Immunology, Madrid, Spain*
Email: ctrautwein@ukaachen.de

Background and Aims: JNK1 and JNK2 are the two major JNK genes ubiquitously expressed in all the mammalian cells, including hepatocytes. While JNK activation mediates hepatocyte death, nuclear factor (NF)-κB promotes cell survival and protects from JNK-induced hepatocyte death. Thus, the cellular interaction between JNK and NF-κB is a major determinant in the fate of hepatocytes. Here, we sought to determine the contribution of JNK1 and JNK2 signaling to spontaneous carcinogenesis in the NEMO model of chronic liver disease.
Method: To generate mice with complete deletion of the JNK genes in NEMO mice, hepatocyte-specific NEMO and JNK1 deleted mice ($NEMO^{\Delta hepa}/JNK1^{\Delta hepa}$) were crossed with constitutive $JNK2^{-/-}$ mice ($Nemo^{\Delta hepa}/JNK^{\Delta hepa}$). We investigated activation of essential pathways in liver sections in response to deletion of JNK1 and JNK2 in hepatocytes of NEMO mice. The phenotype was characterized during disease progression. The regulation of essential genes was performed by RT-PCR and at the protein level by western blot analysis. The investigations included immunostainings for cell death and compensatory proliferation.
Results: Combined JNK1 and JNK2 inactivation in hepatocytes exacerbated liver damage caused by NEMO deletion. Interestingly, liver parenchyma of these mice was characterized by liver cysts accompanied by a significant increase of markers of liver damage (e.g.; ALT, AST, AP and GLDH). Furthermore, macroscopic examination of 1 year $Nemo^{\Delta hepa}/JNK^{\Delta hepa}$ livers showed significant decrease in number and size of HCC nodules formation compared to $NEMO^{\Delta hepa}$ and $NEMO^{\Delta hepa}/JNK1^{\Delta hepa}$ mice. Microscopic analyses of $NEMO^{\Delta hepa}/JNK^{\Delta hepa}$ livers revealed strong ductular proliferation which was further confirmed by overexpression of CK19. These mice also showed increased markers of fibrogenesis indicated by up-regulation of collagen IA1, alpha-SMA, MMP7, MMP9 and TIMP1. Overexpression of cell death markers was a main feature of $NEMO^{\Delta hepa}/JNK^{\Delta hepa}$ as assessed by TUNEL assay and cleaved caspase-3 immunoblot and staining. Additionally, overexpression of Ki67 /and PCNA, as markers for compensatory proliferation was observed in $NEMO^{\Delta hepa}/JNK^{\Delta hepa}$ livers. Next, we sought to investigate the impact of molecular pathways in response to compound JNK deficiency in NEMO mice. We found $Nemo^{\Delta hepa}/JNK^{\Delta hepa}$ livers exhibited overexpression of the EGFR-Raf-MEK-ERK cascade.
Conclusion: JNK1 and JNK2 play an essential role during carcinogenesis of NEMO deleted hepatocytes. Additionally, they are a switch to determine differentiation between hepatocytes and cholangiocytes.

SAT-130

Chemokine receptor CXCR3 modulates polarization of tumor associated macrophages limiting tumor growth and angiogenesis in murine hepatocellular carcinoma

E.F. Brandt, P. Fischer, T. Wirtz, H. Sahin, M.-L. Berres. *University Clinic RWTH Aachen, Department of Gastroenterology, Metabolic disorders and Internal Medicine Intensive Care, Aachen*
Email: elisa.brandt@rwth-aachen.de

Background and Aims: HCC progression is linked to the dynamic process of neovascularization, chronic liver inflammation and the crosstalk between tumor cells, peritumoral parenchymal cells as well as non-parenchymal cells e.g. infiltrating immune cells. The chemokine receptor CXCR3 is implicated in these processes and plays a key role during acute and chronic liver injury in mice and human. Here we aimed to investigate the role of CXCR3 in HCC progression.
Method: In *Cxcr3*$^{-/-}$ and wild-type (WT) mice, we applied a fibrosis-triggered cancer mouse model encompassing a single i.p. injection of N-Diethylnitrosamin (DEN, 14 d after birth) and weekly i.p. injections of low dose carbon tetrachloride (CCl_4, week 4–26). Tumor burden was assessed after 26 weeks. Tumor and surrounding tissue was characterized by histological staining of proliferation, apoptosis and vascularization markers (Ki67, cleaved caspase 3 and CD31). Leukocyte subpopulations were measured by flow cytometry and immunofluorescence staining (e.g. CD68, F4/80) with specific focus on tumor associated macrophage (TAM)-related immune responses. *In vitro*, *Cxcr3*$^{-/-}$ and WT bone marrow culture-derived macrophages (BMM) and TAMs were analyzed utilizing qRT-PCR, flow cytometry and immunofluorescence staining.
Results: The deletion of *Cxcr3* in a murine liver cancer model led to an increased tumor burden ($p < 0.01$) compared to WT mice which was linked to a higher number of Ki67+ tumor cells ($p < 0.05$) and

enhanced CD31+ neovascularization ($p < 0.01$). Moreover, immunofluorescence staining showed an accumulation of CD68+ macrophages ($p < 0.01$) associated with reduced number of apoptotic macrophages (cleaved caspase 3, $p < 0.01$) in tumor and surrounding tissue of *Cxcr3*$^{-/-}$ mice. These cells could be further subcategorized to an anti-inflammatory Ly6Clow/MHCIIlow phenotype by flow cytometry analysis and qRT-PCR. *In vitro* analysis of WT and *Cxcr3*$^{-/-}$ BMM and TAMs showed that *Cxcr3* deficiency fosters survival, expression of anti-inflammatory and pro-angiogenic cytokines as well as hepatic growth factor (qPCR) in macrophages, which was also reflected by expression analysis in the mouse model.

Conclusion: Our results revealed a functional link between CXCR3 and angiogenesis as well as tumor cell proliferation mediated by TAM polarization and survival in a murine liver cancer model. These data implicate CXCR3 and its ligands as new targets for HCC treatment modulating macrophage polarization and neovascularization.

SAT-131

Hepatocyte-derived Osteopontin drives the development of hepatocellular carcinoma

X. Ge[1], R. Desert[1], I. Abraham-Enachescu[2], C. Blajszczak[1], Y. Chen[1], X. Sun[2], A.P. Koh[2], G. Guzman[1], Y. Hoshida[2], N. Nieto[1,2,3]. [1]*University of Illinois at Chicago, Pathology, Chicago, United States;* [2]*Icahn School of Medicine at Mount Sinai, Medicine, New York, United States;* [3]*University of Illinois at Chicago, Medicine, Chicago, United States*
Email: rdesert@uic.edu

Background and Aims: Osteopontin (OPN) expression correlates with tumor progression and metastasis in a wide variety of cancers including hepatocellular carcinoma (HCC); yet, the mechanisms by which hepatocyte-derived OPN contribute to HCC remain unclear.

Method: To investigate the role of OPN in HCC, we analyzed *OPN* mRNA and protein expression in liver tumor and non-tumor tissue from patients with HCC of different etiologies and used a mouse model of HCC with genetic manipulation of the *Opn* gene.

Results: In human normal liver, OPN expression was modest; however, it increased in cirrhosis and dysplasia and was much higher in HCC. There was no remarkable difference in OPN expression in HCC between hepatitis B (HBV) and hepatitis C (HCV) patients. Elevated *OPN* mRNA in HBV-induced HCCs was associated with overall and disease-free survival, increased tumor stage, vascular invasion, tumor size, alpha fetoprotein and metastasis signature and negatively associated with the periportal signature typical of well differentiated HCC. Otherwise, OPN expression in non-tumor liver was associated with late recurrence, generally interpreted as novo carcinogenesis, with increased metastasis signature, tumor stage, AFP and with decreased periportal signature. In HCV patients with early cirrhosis, *OPN* mRNA was significantly associated with the progression to advanced cirrhosis, hepatic decompensation and death. In addition, a subtype of patients expressing a network of genes including *OPN* had a significant increase in HCC incidence. This group of patients also expressed signatures of extracellular matrix (ECM) remodeling, integrin signaling, liver metastasis, tumor field effect and activation of MYC or AKT as well as a decrease in signatures of normal liver, sensitivity to chemotherapy and activation of P53. Next, we injected diethylnitrosamine (DEN) in WT, Opn global knockout (*Opn*$^{-/-}$) and transgenic mice overexpressing *Opn* in hepatocytes in either WT (*Opn*^{Hep} Tg) or global *Opn* null background (*Opn*$^{-/-Hep}$ Tg) and followed them for the development of liver tumors for one year. *Opn*^{Hep} Tg mice showed significant increase in the number of preneoplastic lesions (dysplastic foci or adenoma) along with the number and size of HCCs compared to *Opn*$^{-/-}$ or WT mice. In *Opn*^{Hep} Tg mice, RNASeq analysis of non-tumor tissue revealed association with signatures of integrin activation, cell proliferation and inflammation and with a decrease in liver metabolic processes and DNA repair while in HCC tissues, it was associated with signatures of epithelial-to-mesenchymal transition, ECM remodeling, inflammation and poor outcome.

Conclusion: Hepatocyte-derived OPN drives HCC onset and progression by activating ECM-cell signaling, cell cycle and inflammation. Hence, targeting hepatocyte OPN could be a useful strategy to prevent the onset and/or the progression of HCC.

SAT-132

AAV2 viral infection in liver and tumor development

T.L. Bella[1,2,3,4], S. Imbeaud[1,2,3,4], I. Mami[1,2,3,4], S. Datta[1,2,3,4], C. Peneau[1,2,3,4], J. Calderaro[1,2,3,4,5], J.-F. Blanc[6,7,8], P. Bioulac-Sage[6,8,9], J.-C. Nault[1,2,3,4,10], J. Zucman-Rossi[1,2,3,4,11]. [1]*INSERM, UMR 1162, Génomique Fonctionnelle des Tumeurs Solides, Equipe Labellisée Ligue contre le Cancer, Paris, France;* [2]*Université Paris 13, Sorbonne Paris Cité, UFR SMBH, Bobigny, France;* [3]*Université Paris Descartes, Labex Immuno-Oncology, Sorbonne Paris Cité, Paris, France;* [4]*Université Paris Diderot, Institut Universitaire d'Hématologie, Paris, France;* [5]*AP-HP, CHU Henri Mondor, Department of Pathology, Créteil, France;* [6]*Université de Bordeaux, Bordeaux, France;* [7]*CHU de Bordeaux, Hôpital Saint-André, Department of Hepatology, Bordeaux, France;* [8]*INSERM, UMR 1053, Bordeaux;* [9]*CHU de Bordeaux, Pellegrin Hospital, Department of Pathology, Bordeaux, France;* [10]*AP-HP, Hôpitaux Universitaires Paris-Seine Saint-Denis, Site Jean Verdier, Pôle d'Activité Cancérologique Spécialisée, Service d'Hépatologie, Bondy, France;* [11]*AP-HP, Hôpital Européen Georges Pompidou, Paris, France*
Email: jessica.zucman-rossi@inserm.fr

Background and Aims: We reported the first study showing the involvement of the adeno-associated virus type 2 (AAV2) in the pathogenesis of human hepatocellular carcinoma (HCC) developed on normal liver (Nault et al, 2015). Recurrent somatic viral clonal insertions were described in 11 HCC (5%) targeting cancer driver genes, *TERT*, *TNFSF10*, *CCNA2*, *CCNE1* and *MLL4*, leading to their overexpression. The inserted sequences displayed a minimal common region that includes the 3′ inverse tandem repeat (ITR) of the virus, which is important for virus integration in host DNA and exhibit a promoter/enhancer activity. These results prompted us to investigate the natural history of AAV2 infection in the liver and the functional consequence in tumor development.

Method: Screening and quantification of AAV2 DNA were performed in a large series of benign and malignant liver tumors and their corresponding counterparts (n = 1346 patients) by quantitative PCR. The distribution of viral copy number per cell was used to test association with clinical and molecular features. The presence of both episomal and viral active forms were explored using a DNAse/TaqMan based assay and quantitative RT-PCR. *In silico* analyses using viral capture and next generation sequencing data explored new clonal insertions.

Results: We observed the presence of AAV2 DNA in 18% of the patients in the non-tumor liver tissues, with significant enrichment in non-cirrhotic ($p = 1e\text{-}6$) and female ($p = 7e\text{-}3$) patients. On the presence of AAV2 DNA, we observed a distinct pattern of viral infection in malignant and benign tumors. HCC tumors exhibited a significant higher viral copy number/cell compared to the non-tumor counterpart ($p = 2e\text{-}3$). New clonal integrations were identified in 5 cases, which displayed the highest AAV2 copy number. The new viral insertions targeted *CCNE1* (n = 2), *CCNA2* (n = 1), *TERT* (n = 1) and a new oncogene, *GLI1* in one case. In contrast, in benign tumors we observed a selection of the virus in the non-tumor tissues with frequent episomal forms (11%) versus 2% only in HCC patients. Interestingly, the presence of episomal form was found associated with the expression of viral RNA suggesting an ongoing active infection in patients with adenoma or focal nodular hyperplasia. Further analysis on viral sequences allowed us to define two distinct genotypes: one relative to the reference AAV2 genome sequence and a new genotype displaying 11% nucleotide mistmatches in the capsid.

Conclusion: We demonstrated a positive selection of clonal AAV2 viral insertion during HCC development in young patients without cirrhosis. The presence of active AAV2 infection in patients with

benign tumors suggests it may promote the development of adenoma and FNH at early stage.

SAT-133

Sorafenib increases the percentage and cytotoxicity of circulating NK cells in hepatocellular carcinoma patients

J. Hu[1], D. Xia[1], M. Zhang[1], E. Wang[1], L. Liu[1], Q. Wang[1], W. Bai[1], J. Tie[1], X. Li[1], J. Yuan[1], J. Niu[1], K. Li[1], C. He[1], W. Guo[1], H. Chen[1], X. Yuan[1], T. Yu[1], Z. Wang[1], B. Luo[1], N. Han[1], Y. Zhu[1], Z. Zhang[2], Z. Yin[1], D. Fan[3], K. Yang[4], G. Han[1]. *[1]National Clinical Research Center for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Department of Liver Disease and Digestive Interventional Radiology, Xi'an, China; [2]Northwestern University, Department of Radiology, Chicago, United States; [3]National Clinical Research Center for Digestive Disease and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, State Key laboratory of Cancer Biology, Xi'an, China; [4]Fourth Military Medical University, Department of immunology, Xi'an, China*

Email: hangh@fmmu.edu.cn

Background and Aims: Sorafenib is the first-line treatment agent for patients with advanced hepatocelluler carcinoma (HCC) that inhibits tumor-cell proliferation and angiogenesis. Furthermore, recent studies revealed that sorafenib also played a key role in antitumor response of natural killer(NK) cells. Therefore, characterizing the effects of sorafenib on NK cell immunity in HCC will be important if the clinical response with single sorafenib or combined with other immunotherapies is to be improved. However, the interaction between sorafenib and NK cells remained controversial. The present study evaluated the effect of sorafenib on the activity of peripheral NK cells in HCC patients.

Method: From June 2015 to August 2017, 59 BCLC stage B or C HCC patients were enrolled, and whole blood samples were collected at baseline and at two months with sorafenib treatment (400 mg bid). Meanwhile, blood samples from 42 healthy donors were also collected as normal controls. We evaluated the accumulation of NK cells (defined as $CD56^{+}CD3^{-}$ cells) and their subsets distribution (defined as $CD56^{bright}CD16^{neg}$ and $CD56^{dim}CD16^{pos}$ NK cells) in perpheral blood from HCC patients (n = 40) and healthy donors (n = 25) by flow cytometry analysis. The expression levels of CD107a, granzyme B and perforin in NK cells from 20 HCC patients after stimulated with ionomycin/phorbol myristate acetate were also detected (normal controls, n = 20).

Results: Compare to baseline status, the percentage of peripheral NK cells remarkably increased after sorafenib administration (mean, 13.04% vs 15.29%, p = 0.033). An increase of $CD56^{dim}CD16^{pos}$ NK cells has been also observed (mean, 91.18% vs 93.81%, p = 0.009), while the percentage of $CD56^{bright}CD16^{neg}$ NK cells reduced (mean, 2.94% vs 1.94%, p = 0.004). Sorafenib also led to a dramatically reduced ratio of $CD56^{bright}$ and $CD56^{dim}$ NK cells (p = 0.004). NK cells and their subsets from patients showed impaired expression levels in CD107a, granzyme B and perforin compared with healthy subjects. However, the expression levels of granzyme B and perforin in NK cells were higher than baseline (mean, 93.89 ± 6.48% vs 82.95 ± 19.69%, p = 0.008; 86.73 ± 12.25% vs 72.78 ± 27.67%, p = 0.025, respectively).

Conclusion: Sorafenib stimulated an increase of circulating NK cells which is mainly composed of the increase in $CD56^{dim}CD16^{pos}$ NK cells, and could revert the weakened activity of NK cells in HCC by enhancing expression levels of granzyme B and perforin.

SAT-134

Rapamycin and Zoledronic Acid strongly inhibit growth of advanced murine hepatocellular carcinoma via activation of innate and adaptive immunity

M. Ashfaq-Khan[1], M. Aslam[1,2], A. Qureshi[3], S.Y. Weng[4], D. Schuppan[4,5]. *[1]Institute of Translational Immunology, University Medical Center, Mainz, Germany; [2]Shaheed Benazir Bhutto Women University, PESHAWAR, Germany; [3]Dow university of medical sciences; [4]Institute of Translational Immunology, University Medical Centre, Mainz, Germany; [5]Division of Gastroenterology, Beth Israel Deaconess Medical Centre, Harvard Medical School, Boston, United States*

Email: m.ashfaq_biotech@yahoo.com

Background and Aims: Treatment options for hepatocellular carcinoma (HCC) remain limited. Activation of the cancer immune microenvironment opens novel therapeutic opportunities to control tumor progression and block metastatic spread. We assessed single and combined treatment of experimental HCC with Zoledronic Acid (ZA) and Rapamycin (RA), two drugs that display myeloid cell regulating potential.

Method: Mdr2(Abcb4)−/− mice were injected intraperitoneally with diethyl-nitrosamine DEN (10 μg/g of bw) at the age of 5 days, followed

A Subgroups	Normal controls (C) (n=25)	Baseline (B) (n=40)	Sorafenib treatment (S) (n=40)	P Value		
				C vs B	C vs S	B vs S
NK cells(%)	13.87±5.31	13.04 ±6.54	15.29±8.50	0.594	0.458	0.033
$CD56^{bright}CD16^{neg}$/total NK cells(%)	2.34±0.95	2.94±2.92	1.94±1.99	0.331	0.351	0.004
$CD56^{dim}CD16^{pos}$/total NK cells(%)	94.0±1.87	91.18±7.00	93.81±5.36	0.057	0.866	0.009
$CD56^{bright}CD16^{neg}$/$CD56^{dim}CD16^{pos}$(%)	2.50±1.06	3.49±3.89	2.20±2.50	0.492	0.023	0.004

B Subgroups		Normal controls (C) (n=20)	Baseline (B) (n=20)	Sorafenib treatment (S) (n=20)	P Value		
					C vs B	C vs S	B vs S
GranzymeB	NK cells(%)	94.32±3.52	82.95±19.69	93.89±6.48	0.021	0.797	0.008
	$CD56^{bright}$ NK cells(%)	66.60±18.79	57.38±25.22	75.96±18.18	0.198	0.117	0.004
	$CD56^{dim}$ NK cells(%)	94.95±2.63	83.92±18.71	94.15±4.73	0.017	0.516	0.014
Perforin	NK cells(%)	93.96±5.35	72.78±27.67	86.73±12.25	0.002	0.042	0.025
	$CD56^{bright}$ NK cells(%)	69.33±24.51	39.28±23.21	65.57±26.23	<0.000	0.642	0.001
	$CD56^{dim}$ NK cells(%)	95.71±4.05	75.52±28.50	88.42±12.08	0.001	0.032	0.049
CD107a	NK cells(%)	84.98±10.68	62.80±24.12	74.90±19.43	0.001	0.199	0.061
	$CD56^{dim}$ NK cells(%)	84.01±11.45	63.39±26.19	74.07±20.29	0.006	0.064	0.154

Figure: (abstract: SAT-133)

by 0.05% phenobarbital in drinking water starting at the age of 3 weeks. This syngenic mouse model replicates key features of human HCC, with a genetic defect found in man and an external carcinogen. Mice were treated with vehicle, (ZA thrice a week as IP injection 100 µg/kg), RA (trice a week as oral gavage 5 mg/body weight), or a combination of ZA and RA from age 5–6 months. After 6 months tumor volume and number of nodules were counted. 50% of livers were digested and CD45+ immune cells subjected to multicolour fluorescence assisted cell sorting using antibodies to CD11b, CD11c, Ly6C, Ly6G, CD86, CD4, CD8, CD25, CD3, CD90.2, CD206, F4/80, MHC-II, NK1.1, Foxp3 and CD19. qPCR and IHC were performed for target molecules of interest.

Results: Treatment with RA > ZA significantly reduced tumor growth. The combination of ZA and RA synergistically reduced the volume and number of HCC foci by 90 and 85% respectively ($p < 0.0001$). The combination significantly reduced the population of M0-($CD45^+CD11b^+LY6G^-F4/80^+$) and M2 macrophages ($CD45^+CD11b^+LY6G^-F4/80^+CD206^+$), and of myeloid derived suppresser cells ($CD45^+CD11c^+LY6C^{high}$), representing central tumor promoting myeloid cell populations, while Myeloid derived dendric cells ($CD45^+CD11c^{high}$ $CD11b^+$ $CD86^+$) that promote anti-cancer immunity were significantly upregulated. In parallel, total CD4+ T cells and especially CD4 + CD25 regulatory T cells were significantly suppressed, while CD8 + T cells were significantly increased in the combination treatment vs the untreated group. Changes in immune cell populations were confirmed by transcript patterns and IHC. Ki-67-positive cancer cells were nearly undetectable, and IHC for CD68 and YM-1 confirmed a dramatic shift from tumour associated M2 to M1 macrophages. The combination of ZA and RAPA significantly downregulated TAMs and MDSC markers like CSF-1, VEGF, TGFβ1, Cox2, HIF1α, CCL2, CCL3, CCL5 and CCL17 that attract circulating monocytes into the tumour stroma.

Conclusion: (1) Combination therapy of RAPA and ZA polarize myeloid (and T cells) towards a robust anti-HCC response; (2) Their combination is synergistic in an optimized syngenic model of murine HCC; (3) Both drugs have proven safety for other indications, and clinical studies in patients with HCC are warranted.

SAT-135

Inflammation driven hepatocarcinogenesis is associated with a progenitor-like phenotype and Trp53 dependent differentiation

M. Svinarenko[1], K. Sarah-Fee[1], H. Maier[1], Y. Sunami[2], A. Tannapfel[3], T. Seufferlein[1], A. Lechel[1]. *[1]University Hospital Ulm, Internal Medicine I, Ulm, Germany; [2]University Hospital Halle (Saale), Visceral, vascular and endocrine surgery, Halle (Saale), Germany; [3]Ruhr-Universität Bochum, Institut für Pathologie, Bochum, Germany*
Email: andre.lechel@uni-ulm.de

Background and Aims: Chronic liver damage activates the wound healing program, which in long-term promote the formation of liver cancer. In that process, the inflammatory microenvironment is of central importance for malignancy. In addition, defects in the p53-signaling pathway occur frequently in liver cancer, thereby worsen prognosis of the disease. In this study, we analyzed the influence of Trp53 deletion within an inflammatory environment on hepatocarcinogenesis.

Method: To investigate the interaction of inflammation and Trp53 deletion, we crossed two transgenic mouse models. For the modulation of an inflammatory response, we used an inducible mouse model (Tet-Off system) with a permanent expression of a constitutively active IKK2 isoform ($IKK2^{ca}$). The expression of $IKK2^{ca}$ leads to a continuous activation of the NF-kB pathway promoting a chronic inflammatory response. To modulate disruption of p53 signaling, the inducible Cre-recombinase expressing transgenic mouse line AlfpCre-ERT2 was crossed with a conditional Trp53 knockout mouse. Liver-specific Trp53 deletion was induced by the treatment with tamoxifen at the age of 4 weeks.

Results: $IKK2^{ca}$ expression in mice results in persistent liver fibrosis, increased proliferation and increased levels of inflammatory cells independent of p53 status. Accumulation of ectopic lymphoid structures, which form a microniche for liver progenitor cells, were detected in $IKK2^{ca}$ mice and were increased in absence of Trp53. Both $IKK2^{ca}$ expressing cohorts show formation of hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) as well as mixed differentiated tumors. However, mice with deleted Trp53 have a higher tumor burden and show a shift in the tumor spectrum towards ICC formation compared to Trp53 wildtype mice. Liver tumors from both $IKK2^{ca}$ expressing cohorts indicate a progenitor-like phenotype with activated YAP signaling.

Conclusion: The study shows that liver-specific Trp53 deletion in combination with an inflammatory background results in elevated tumor burden and leads to a different liver tumor entity due to a shift in the tumor spectrum towards ICC. Moreover, the expression of constitutively active IKK2 promotes tumor formation with a progenitor-like phenotype.

SAT-136

Insulin receptor isoform A is a new player in the progression of hepatocellular carcinoma

E. Benabou[1], Z. Salame[1], D. Wendum[2], M. Lequoy[3], S. Tahraoui[1], F. Merabtene[4], C. Yves[1], O. Scatton[5], O. Rosmorduc[6], L. Fouassier[1], L. Fartoux[6], F. Praz[1], C. Desbois-Mouthon[1]. *[1]INSERM, Saint-Antoine Reearch Center, Paris, France; [2]AP-HP, Saint-Antoine Hospital, department of Pathology, Paris, France; [3]AP-HP, Saint-Antoine Hospital, department of hepatology; [4]UPMC, Histomorphology platform, UMS 30 Lumic, Paris, France; [5]AP-HP, Pitié-Salpétrière Hospital, department of hepatobiliary surgery and liver transplantation, Paris, France; [6]AP-HP, Pitié-Salpétrière Hospital, department of hepatology, Paris, France*
Email: christele.desbois-mouthon@inserm.fr

Background and Aims: Hepatocellular carcinoma (HCC) is one of the most common and deadly neoplasms. Insulin receptor (IR) exists in two isoforms, IR-A and IR-B, resulting from the exclusion and inclusion of exon 11, respectively. IR-B is predominantly expressed in normal adult hepatocytes and binds insulin while IR-A is expressed in the developing liver and binds both insulin and insulin-like growth factor-II (IGF-II). Mounting evidence suggests a role for the ligand IGF-II and its receptor IR-A in cancer cells. Unfortunately, the role of IGF-II/IR-A is not known in HCC. The present study aims to evaluate the biological functions associated to IR-A overexpression in HCC in relation to IGF-II overexpression.

Method: We used a collection of 85 paired HCC /nontumour liver obtained from patients who undergone curative hepatectomy. Two human HCC cell lines expressing IGF-II (Huh7) or not (PLC/PRF5) were used. Subcutaneous xenografts of HCC cell lines were performed in 5 week-old female *nude* mice. The migration and invasion tests were conducted *in vitro* using Boyden's chambers. Hepatospheres were obtained after 14 days in culture under non-adherence conditions.

Results: The IR-A:IR-B ratio was upregulated in 70% of HCC compared to adjacent nontumour tissue and associated with clinicopathological markers of aggressive tumours (*i.e*, high serum alpha-fetoprotein (AFP), low differentiation, microvascular invasion, cytokeratin 19 expression (CK19)) and reduced patient survival after surgery. No association was observed when total IR mRNA content was considered. *IGF2* mRNA upregulation was observed in only 9.4% of HCC and was not associated with higher IR-A:IR-B ratio. The stable overexpression of IR-A in Huh7 and PLC/PRF5 cells increased their tumorigenicity *in vivo* in comparison with control cells while IR-B overexpression had no effect. IR-A-mediated tumorigenicity was associated with the induction of a pro-inflammatory gene program (evidenced by Gene Set Enrichment Analysis) involving the stimulation of *CXCL10* and *VCAM1* mRNA expression. While IR-A overexpression did not promote HCC cell proliferation *in vitro*, it stimulated migration and invasion and increased stemness/

progenitor features (such as CK19, CD133 and CD44 expression in Huh7 cells; AFP and CD133 in PLC/PRF5 cells). IR-B overexpression had no effect on migratory and invasive potential and decreased the expression of some stemness/progenitor markers.
Conclusion: These results demonstrate that the expression of total IR is not as important as the ratio of IR isoforms in HCC cells. IR-A, but not IR-B, is a new player in HCC progression by modulating cell plasticity, regardless of the presence of an autocrine IGF-II secretion loop.

SAT-137

Defective DNAM-1 mediated cytotoxicity in NK cells infiltrating hepatocellular carcinoma

B. Oliviero[1], S. Mantovani[1], D. Mele[1], M. Donadon[2], C. Soldani[3], G. Torzilli[4], R. Santambrogio[5], E. Opocher[5], S. Chiellino[6], C. Porta[6], M.U. Mondelli[7]. *[1]Fondazione IRCCS Policlinico San Matteo, Division of Infectious Diseases and Immunology Department of Medical Sciences and Infectious Diseases, Pavia, Italy; [2]Humanitas University, Department of Hepatobiliary and General Surgery, Milano, Italy; [3]Humanitas Clinical and Research Center, Department of Hepatobiliary and General Surgery, Milano, Italy; [4]Humanitas Clinical and Research Center, Department of Hepatobiliary and General Surgery, Rozzano (MI), Italy; [5]San Paolo Hospital Univiersity of Milan School of Medicine, Chirurgia 2, Epatobilio-pancreatica e Digestiva, Milano, Italy; [6]Fondazione IRCCS Policlinico San Matteo, Medical Oncology, Pavia, Italy; [7]Fondazione IRCCS Policlinico San Matteo, University of Pavia, Division of Infectious Diseases and Immunology, Department of Medical Sciences and Infectious Diseases, and Department of Internal Medicine and Therapeutics, Pavia, Italy*
Email: mario.mondelli@unipv.it

Background and Aims: Natural Killer (NK) cells play a key role in the immune response to tumors, their function being regulated by NK receptors and their ligands. It has been shown that binding of the DNAM-1 receptor, a DNAX accessory molecule, to its ligands (CD155 and CD112) expressed on target cells enhance NK cytotoxic activity and cytokine secretion. Low expression of CD155 has been associated with poor prognosis in patients with hepatocellular carcinoma (HCC). We studied DNAM-1 expression and cytotoxic-mediated activity in circulating and intrahepatic NK cells from HCC patients.
Method: DNAM-1 expression was evaluated by flow cytometry on circulating NK cells of 46 HCC patients (HCC) and 16 healthy controls (HC) as well as on liver infiltrating NK cells (n = 30). Liver-infiltrating lymphocytes were obtained from tumorous (TIL) and surrounding non-tumorous (LIL) tissue by mechanical and enzymatic treatment. DNAM-1-mediated cytotoxic NK function was studied by triggering DNAM-1 receptor in redirecting experiments using P815 as target cells and the percentage of CD107a+ NK cells was evaluated by flow cytometry in unstimulated or IL15-stimulated PBMC, LIL and TIL. Moreover, soluble CD155 (sCD155) levels were measured by ELISA in 23 HC and 57 HCC sera.
Results: There was a significantly decreased proportion of DNAM-1+ circulating NK cells in HCC patients compared with controls ($p < 0.0018$). Surprisingly, the cytotoxic activity of HCC NK was significantly higher than in HC in unstimulated conditions ($p < 0.0102$). No significant differences in DNAM-1 expression were found on NK cells isolated from LIL and TIL samples. However, TIL NK cytotoxic activity was significantly lower than that of LIL NK under both unstimulated and IL15-stimulated conditions ($p < 0.0059$ and $p < 0.0195$, respectively). Interestingly, HCC patients showed increased levels of sCD155 that directly correlated with AST, bilirubin and with the liver fibrosis indices FIB4 and APRI. Of note, soluble CD155 was also significantly higher in patients with high MELD and Child-Pugh scores and inversely correlated with serum albumin and platelet count.
Conclusion: Circulating NK cells from HCC patients showed conserved DNAM-1-mediated cytotoxic ability despite reduced receptor expression. DNAM-1-mediated cytotoxicity was instead defective in TIL compared to LIL NK cells, suggesting a possible mechanism of tumor resistance to innate immune surveillance.

SAT-138

Difference of gene mutational profile among viral- and non-viral HCC with or without prior HBV infection: Results of comprehensive deep sequencing analyses of cancer genes and HBV/AAV integration

F. Kawai-Kitahata[1], Y. Asahina[1], S. Kakinuma[1], M. Murakawa[1], S. Nitta[1], H. Nagata[1], S. Kaneko[1], E. Inoue[1], M. Miyoshi[1], T. Tsunoda[1], A. Sato[1], M. Nakagawa[1], Y. Itsui[1], S. Azuma[1], S. Tanaka[1], M. Tanabe[1], S. Maekawa[2], N. Enomoto[2], M. Watanabe[1]. *[1]Tokyo Medical and Dental University; [2]University of Yamanashi*
Email: fkawai.gast@tmd.ac.jp

Background and Aims: The incidence of hepatocellular carcinoma (HCC) without viral infection has been increasing. However, the underlying mechanism that links these non-B non-C HCC (NBNC-HCC) remains unclear. The aim is to elucidate difference of cancer gene profile among viral- and NBNC-HCC including those with or without prior HBV infection.
Method: 194 HCC patients consisting of 75 NBNC-, 78 HCV Ab positive- and 41 HBsAg positive- HCC were investigated. Of patients with NBNC-HCC, 21 had evidence for prior HBV infection (patients with HBsAg-negative and anti-HBc and/or anti-HBs positive). Genomic DNA obtained from HCC and corresponding background liver were deep-sequenced targeting 54 cancer-related genes. *TERT* promoter mutation at 2 hot spots, HBV- and AAV-human genomic junction breakpoints were also deep-sequenced on a MiSeq instrument.
Results: In 67 NBNC-HCC, recurrent mutations were frequently found in *TP53* (34.6%), *TERT* (73.7%) and *CTNNB1* (34.6%), and these gene mutational profile were similar to those in HCV Ab positive HCC (*TP53* 28%, *TERT* 84%, *CTNNB1* 61%). However, 21 NBNC-HCC with prior HBV infection had substantially different gene mutational profile compared to those in HCV Ab positive- and HBsAg positive HCC (prior HBV infection; *TP53* 71.4%, *TERT* 71.4%, *CTNNB1* 38.0%: HBsAg positive; *TP53* 67.9%, *TERT* 30.0%, *CTNNB1* 10.7%: $p < 0.05$). Although a total of 88 HBV integration breakpoints were detectable in 92.6% (26/28) of HBsAg positive HCC, 2 patients without HBV integration had no recurrence after locally curative therapy for initial HCC. In contrast to persistent HBV infection, HBV integration breakpoints were only detected in 4 (9.3%) NBNC patients with prior HBV infection, and these HCC were developed from normal liver and significantly associated with younger age (67 years old versus 75 years old, $p < 0.01$). AAV integration breakpoints were not detected in patients with prior HBV infection.
Conclusion: Mutational profile of cancer gene in most of NBNC-HCC was similar to those of HCV Ab positive HCC, but not HBsAg positive HCC. However, about 10% of NBNC HCC with prior HBV infection had HBV integration and these were developed from normal liver at a younger age. The underlying mechanism of hepatocarcinogenesis in NBNC-HCC with HBV integration among patients with prior HBV infection may be similar to those of HBsAg positive patients.

SAT-139

Therapeutics of cell-specific MAPK modulation in chronic liver disease using (siJNK2) nanodelivery

M. Woitok[1], D. Doleschel[2], M. Zoubek[1], W. Lederle[2], F. Kießling[2], C. Trautwein[1], F.J. Cubero[3]. *[1]Department of Internal Medicine III, Aachen, Germany; [2]Institute for Experimental and Molecular Imaging, Aachen, Germany; [3]Department of Immunology, Madrid, Spain*
Email: fcubero@ukaachen.de

Background and Aims: The prevalence of non-alcoholic fatty liver disease (NAFLD), including the more aggressive non-alcoholic steatohepatitis (NASH), and its complications cirrhosis and hepatocellular carcinoma (HCC), is continuously increasing in developed countries. The c-Jun N-terminal kinases (JNKs) play a crucial role in

liver physiology and disease pathogenesis. In the present study, we aimed to investigate the outcome of hepatocyte-specific *Jnk* inhibition, in an experimental model of chronic liver disease (CLD).
Method: Inhibition of *Jnk2* specifically in hepatocytes using siRNA (*siJnk2*) was first performed *in vitro* in Hepa 1–6 cells and validated *in vivo* in NEMO mice, a well-known animal model to study CLD. The effects of *siJnk2* administration were investigated at different stages of CLD. Biochemistry and molecular biology techniques, microcomputed tomography (FMT, μCT) and FACS were performed.
Results: *siJnk2* treatment in the acute phase of CLD in Nemo mice caused increased liver damage seen by elevated serum parameters, hepatocellular apoptosis and compensatory proliferation. In addition, elevated hepatic stellate cell activation/matrix deposition markers evoked deteriorated hepatic fibrogenesis progression. In contrast, chronic *siJnk2* administration in aged NEMO mice resulted in improved serum values and a significant reduction of immune cell infiltration in the liver parenchyma. Compensatory hepatocyte proliferation (PCNA) was significantly decreased in livers of NEMO + *siJnk2* alongside with the absence of MAPK signaling. Sirius red collagen staining revealed significantly improved hepatic fibrogenesis also displayed by a reduction of hepatic stellate cell activation/matrix deposition markers. In addition, FMT/μCT analysis revealed reduced hepatocellular apoptosis in these mice. Moreover, chronic si*Jnk2* treatment dramatically reduced end-stage HCC formation typically seen in NEMO mice within 52 weeks by a reduced presence of premalignant and malignant liver tumors corresponding to dysplastic nodules and differentiated adenomas, respectively.
Conclusion: *siJnk2* therapy successfully depleted *Jnk2* levels both *in vivo* and *in vitro*. Interestingly, siJnk2 treatment differentially changed stage dependent liver disease progression. In particular, siRNA formulated delivery to hepatocytes in the chronic phase leads to the amelioration of NASH and HCC progression and hence might be a novel suitable therapeutic option.

SAT-140
Deletion of MyD88 in non-parenchymal cells, but not in parenchymal cells attenuates the progression of hepatocellular carcinoma

A. Mohs[1], N. Hermanns[1], T. Otto[1], S.A.Y. Hassan[2], A. de Bruin[2,3], C. Trautwein[1]. [1]*Department of Internal Medicine III, University Hospital, Aachen, Germany;* [2]*Dutch Molecular Pathology Centre, Faculty of Veterinary Medicine, Utrecht University, Utrecht;* [3]*University Medical Centre Groningen, Department of Paediatrics, University of Groningen, NL- 9713 Groningen, Groningen*
Email: amohs@ukaachen.de

Background and Aims: Increased translocation of intestinal bacteria is a pathological hallmark in patients with chronic liver disease (CLD). Thereby, Toll-like Receptor (TLR) signaling, stimulated by bacterial components, derived from the intestinal microbiota, has been shown to trigger inflammation driven promotion of hepatocellular carcinoma (HCC). In the current study, the role of MyD88 in parenchymal and non-parenchymal cells in the development of fibrosis and tumour initiation and progression was studied in a murine model of inflammation triggered HCC development.
Method: To explore the impact of Myd88 for hepatitis, fibrogenesis and HCC formation, B6-MyD88$^{-/-}$ mice or alternatively hepatocyte-specific B6-MyD88$^{-/-}$(MyD88$^{\Delta hepa}$) were crossed with hepatocyte-specific NEMO knockout mice (NEMO$^{\Delta hepa}$) to generate NEMO$^{\Delta hepa}$/MyD88$^{-/-}$ or NEMO$^{\Delta hepa}$/MyD88$^{\Delta hepa}$ mice respectively.
Results: Surprisingly, the hepatocyte specific genetic deletion of MyD88 in NEMO$^{\Delta hepa}$ mice neither resulted in an altered onset of chronic liver disease nor in changes of tumour initiation and progression. Contrary to this, constitutional deletion of MyD88 aggravated the access of chronic liver disease (CLD) in NEMO$^{\Delta hepa}$ mice, characterized by elevated serum alanine (ALT), aspartate serum transaminases (AST) as well as glutamate dehydrogenase (GLDH) values. Histopathological examination of H&E stained liver tissue confirmed an aggravation of liver injury in NEMO$^{\Delta hepa}$/MyD88$^{-/-}$ compared with NEMO$^{\Delta hepa}$ mice which was associated with a mild increase of apoptosis. In this context, especially monocyte derived macrophages and CD4^{+} T cells were changed in NEMO$^{\Delta hepa}$/MyD88$^{-/-}$ livers. Furthermore a reduction of TNFα and MCP1 could be detected in NEMO$^{\Delta hepa}$/MyD88$^{-/-}$ livers compared to NEMO$^{\Delta hepa}$ livers.
As a consequence late stage NEMO$^{\Delta hepa}$/MyD88$^{-/-}$ mice displayed a lower cumulative tumour burden as well as reduced tumour size in comparison with NEMO$^{\Delta hepa}$ tumours. These findings were accompanied by a decrease in serum level transaminases likewise a reduction in liver body weight ratio. In line with this data, histological examination by two blinded pathologists revealed that the non-neoplastic and neoplastic phenotypes of the NEMO$^{\Delta hepa}$ livers were rescued by the concomitant constitutional deletion of MyD88 as indicated by a lower total lesions burden score and tumor incidence.
Conclusion: Deletion of MyD88 in non-parenchymal, but not in parenchymal cells in NEMO$^{\Delta hepa}$ mice leads to an accelerated onset of chronic liver disease and, but reduces HCC progression. These results indicate that MyD88 in non-parenchymal cells might be an attractive target for the treatment of chronic liver disease.

SAT-141
Interventional gene targeting of cell cycle regulators identifies Cyclin E1 as a suitable target for attenuating hepatocellular carcinoma progression

R. Sonntag, A. Mohs, M. Kohlhepp, U. Haas, D. Lambertz, C. Trautwein, C. Liedtke. *University Hospital RWTH Aachen, Department of Medicine III, Aachen*
Email: rsonntag@ukaachen.de

Background and Aims: Hepatocellular carcinoma (HCC) is one of the most severe tumor diseases with limited treatment options. Early and advanced stages of carcinogenesis are associated with sustained proliferation of hepatocytes and non-parenchymal cells (*e.g.* hepatic stellate cells, immune cells) regulated by Cyclins and Cyclin-dependent kinases (Cdks). E-Type Cyclins (E1, E2) and Cdk2 are involved in cell cycle re-entry of quiescent cells. Our previous unpublished work demonstrated that constitutive ablation of Cyclin E1 or Cdk2 in mice prevented HCC initiation. Therefore, in the present study we tested the hypothesis that Cyclin E1 or Cdk2 could be suitable targets for interventional HCC therapy.
Method: We used conditional Cyclin E1 (CcnE1$^{f/f}$) or Cdk2 floxed (Cdk2$^{f/f}$) mice in a C57B6/J background with inducible Cre expression controlled by the Mx-gene promoter. This approach allows efficient gene deletion in liver cells and in the hematopoietic cell compartment. For HCC induction, 14 days old male mice were intraperitoneally (*i.p.*) injected with a single dose of diethylnitrosamine (DEN). Cre-negative littermates were used as controls. After 22 weeks (reflecting a stage of early HCC development), interventional inactivation of Cyclin E1 or Cdk2 was performed by three *i.p.* injections of poly-I: poly-C. At the age of 40 weeks, mice were analyzed for number and size of HCC nodules. Additionally, liver microenvironment was investigated by flow cytometry at the age of 26 and 40 weeks.
Results: Sequence analysis of 337 human HCC samples provided by the publicly available data of The Cancer Genome Atlas (TCGA) revealed that 30% of the patients had inherited genetic alterations or aberrant expression of E-type Cyclins or Cdk2, supporting the rational for this study. All DEN-treated mice developed liver tumors at the age of 40 weeks. However, interventional inactivation of Cyclin E1 resulted in a significant reduction of tumor numbers, tumor size and liver weight indices compared to DEN-treated control mice. This finding was associated with a reduced overall proliferation and down-regulation of positive cell cycle regulators. Interestingly, Cyclin E1 inactivation also changed the composition of the HCC microenvironment (*e.g.* T-cells), pointing to a potential new role of Cyclin E1 for immune cell regulation during early and late liver cancer development. In sharp contrast, interventional inactivation of Cdk2 did not reveal any significant effect on tumor growth.

Conclusion: Cdk2 is fully dispensable for advanced HCC progression. However, interventional inactivation of Cyclin E1 in an early stage of HCC development has beneficial effects and attenuates the progression of HCC. Thus, Cyclin E1 could be a promising therapeutic target for treatment of HCC patients.

SAT-142

Quantitative comparison of PD-L1 immuno-histochemical assays in hepatocellular carcinoma: The Blueprint-HCC study

D.J. Pinato[1], F. Mauri[1], P. Spina[1], O. Cain[2], A. Siddique[1], R.D. Goldin[1], S. Victor[1], C. Pizio[3], A. Akarca[4], R. Boldorini[3], L. Mazzucchelli[1], J.R.M. Black[1], S. Shetty[2], T. Marafioti[4], R. Sharma[1]. *[1]Imperial College London, Surgery & Cancer, London, United Kingdom; [2]University of Birmingham, Institute of Immunology and Immunotherapy, Birmingham, United Kingdom; [3]Universita' del Piemonte Orientale "A. Avogadro", Department of Translational Medicine, Novara, Italy; [4]University College London, Histopathology, London, United Kingdom*
Email: david.pinato09@imperial.ac.uk

Background and Aims: Programmed cell death ligand 1 (PD-L1) expression by immunohistochemistry (IHC) enriches for responses to PD-1/PD-L1 inhibitors across malignancies, however its role as a predictive biomarker in hepatocellular carcinoma (HCC) is elusive and no gold standard assay exists. We evaluated the performance of 4 different PD-L1 detection assays used in landmark clinical studies.
Method: PD-L1 IHC was performed on 4 serial sections from tissue microarray (TMA) blocks containing 100 archival cases of HCC that included tumour and surrounding non-tumorous tissue. Antibody clones E1LN3, 28-8, 22c3, SP263 were compared on the basis of percentage and intensity of staining in malignant cells (M) to generate an H-score (range 0–300). Immune cells infiltrating (ICI) and at the periphery, in non-tumorous tissue (ICP) were scored on a 4-tier system (0–3).
Results: Patients were 76% males, 20% HCV-positive, 64% cirrhotic with a median age of 67 years. Median tumour size was 4 cm, 70% of patients had T1-T2 tumours and 48% were of grade 2. The proportion of PD-L1 positive cases according to M-ICI-ICP pattern was 2-6-2% for E1LN3, 10-18-19% for 28-8, 9-22-18% for 22c3 and 5-14-13% for SP263. Pairwise comparison of M H-scores revealed heterogeneity across antibodies, with highest concordance between E1L3N/SP263 ($R2 = 0.95$), E1L3N/22c3 ($R2 = 0.65$), 22c3/SP263 ($R2 = 0.66$) and increasing discordance for 28-8/22c3 ($R2 = 0.44$), E1L3N/28-8 ($R2 = 0.29$), and 28-8/SP263 ($R2 = 0.26$). Detection of PD-L1-positive immune infiltrates using a semi-quantitative scoring system revealed significantly different scores in pairwise non-parametric comparisons of ICI ($p < 0.05$) but not ICP ($p > 0.05$ for chi-square test).
Conclusion: In Blueprint-HCC we demonstrated that quantification of PD-L1 protein levels in HCC in tumour cells, intra-tumoural and peri-tumoural infiltrate is characterised by significant inter-assay discordance. This has profound implications in the clinical development of predictive correlates of efficacy to immunotherapy in HCC and sources of such discordance should be explored.

SAT-143

Mixed HCC-ICC liver cancer derives from hepatic progenitor cells-A lineage tracing investigation in mouse liver inflammation models

N. Rosenberg[1], N. Barashi[1], H. Giladi[1], D. Goldenberg[1], M. Shoshkes-Carmel[2], K. Kaestner[3], M. Van Haele[4], T. Roskams[4], E. Galun[1]. *[1]Gene Therapy Institute, Hadassah University Hospital, Jerusalem, Israel; [2]Department of Genetics and Center for Molecular Studies in Digestive and Liver Diseases, University of Pennsylvania, Philadelphia, United States; [3]Department of Genetics and Center for Molecular Studies in Digestive and Liver Diseases, Philadelphia, United States; [4]Department of Translational Cell and Tissue Research, University of Leuven, Leuven, Belgium*
Email: nofar.ros@gmail.com

Background and Aims: Primary liver cancer is the second leading cause of cancer-related death worldwide. Primary liver cancer includes: Hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC) and a mixed HCC-ICC tumor. Preceding the development of primary liver cancer, there is usually a prolonged period of chronic inflammation that leads to cirrhosis. It has been proposed that hepatic progenitor cells (HPCs) could contribute to hepatocarcinogenesis. However, this was not proven. These cells proliferate in response to injury and chronic inflammation in the liver. Although stem cells residing in highly proliferative tissues, such as skin, are essential for sustaining normal tissue homeostasis, their contribution in quiescent tissues, such as liver, is still a matter of debate. In this study, we aimed to determine whether HPCs contribute to liver cancer development in the MDR2 KO mouse model of inflammation-induced HCC.
Method: In order to enable tracing of progenitor cells, we generated a transgenic mouse based on the MDR2 KO that harbors a YFP reporter gene driven by the Foxl1 promoter, the promoter of a liver progenitor specific marker. These mice (MDR2 KO$^{Foxl1CRE;\ RosaYFP}$) develop chronic inflammation by the age of 1 months and HCC by the age of 16 months and mixed HCC-ICC by the age of 18 months.
Results: Using immunofluorescence we show that HPCs are present in the chronically inflamed livers and within dysplastic nodules at the age of a year and later. At the age of 3 months, upon severe inflammation, YFP positive progenitor cells proliferate and also differentiate, giving rise to both cholangiocytes and hepatocytes. Analysis of livers of 16-month MDR2 KO$^{Foxl1CRE;RosaYFP}$ revealed that only a minority of dysplastic nodules were positive for YFP expression. Furthermore, HCC tumors were YFP negative, containing only scattered YFP-positive HPCs, which did not exhibit hepatocyte-like morphology that expressed cancer stem-like cells (CSCs) markers. At late stages of the MDR2 KO model (18-month) these mice developed ICC and HCC-ICC mixed tumors. Surprisingly, the cholangiocytes in tumour cells were YFP positive, implying that they were derived from HPCs. The HCC-ICC YFP positive tumors accounted for 30% of the total tumors observed. Additionally, the YFP cells in the tumors expressed stem cell-like markers including: Epcam, Cd24a and Krt19. These findings recapitulate the characteristics of human ICC-HCC tumors which also have stem cell like features.
Conclusion: Taken together, our results suggest that HPCs may not be the origin for HCC but may be the origin for the mixed type HCC-ICC tumors in a chronic inflamed liver model.

SAT-144

Circulating exosomal non-coding RNAs as prognostic biomarkers in human hepatocellular carcinoma

Y.R. Lee[1], S.Y. Park[1], K. Hur[2], G. Kim[2], S.Y. Jang[3], W.Y. Tak[1], Y.O. Kweon[1], B. Jeong[1], G.-E. Kang[1], S. Seo[1], J.G. Park[4], H.W. Lee[5]. *[1]Kyungpook National University Hospital, Department of Internal Medicine, Daegu, Korea, Rep. of South; [2]School of Medicine, Kyungpook National University, Department of Biochemistry and Cell Biology, Daegu, Korea, Rep. of South; [3]Kyungpook National University School of Medicine, Internal Medicine, Daegu, Korea, Rep. of South; [4]Yeungnam University Medical Center, Department of Internal Medicine; [5]Dongsan Medical Center, School of Medicine, Keimyung University, Department of Pathology*
Email: deblue00@naver.com

Background and Aims: Exosomal non-coding RNAs (ncRNAs) have unique expression profiles reflecting the characteristics of a tumor, and their role in tumor progression and metastasis is emerging. However, the significance of circulating exosomal ncRNAs in the prognosis of hepatocellular carcinoma (HCC) remains to be elucidated. We therefore determined the prognostic significance of circulating exosomal ncRNAs (miRNA-21 and lncRNA-ATB) for human HCC.
Method: This prospective study enrolled 79 HCC patients who attended Kyungpook National University Hospital, Republic of Korea between October 2014 and September 2015. Exosomes were extracted from serum samples using the ExoQuick Exosome

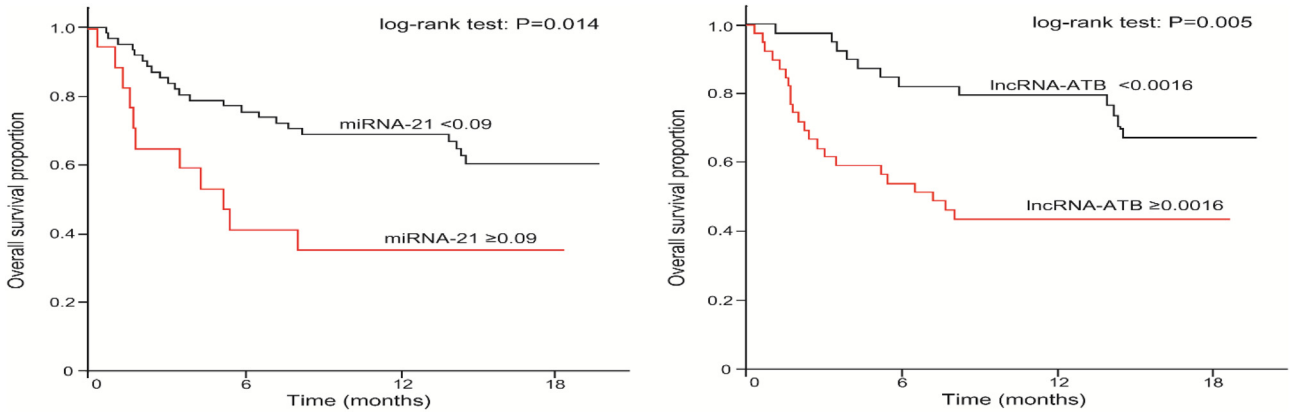


Figure: (abstract SAT-144) Kaplan-Meier plots of overall survival according to the miRNA-21 (*A*) and lncRNA-ATB (*B*) expression levels. (*A, B*) The survival rate was significantly lower in patients with higher circulating levels of exosomal miRNA-21 and lncRNA-ATB (log-rank test: both $p < 0.05$).

Precipitation Solution (System Biosciences). NcRNAs were isolated from exosomes using the miRNeasy serum/plasma micro kit (Qiagen).

Results: During the study period (median 14.0 months), disease progression and mortality were found in 44 and 34 patients, respectively. Exosomal miRNA-21 and lncRNA-ATB were successfully detected in the HCC serum samples. Both circulating exosomal miRNA-21 and lncRNA-ATB were related to TNM stage and other prognostic factors, including the T stage and portal vein thrombosis, but they were not associated with age, sex, presence of cirrhosis, or etiology. Multivariate analysis using the Cox regression test identified that both higher miRNA-21 and higher lncRNA-ATB were independent predictors of mortality and disease progression, along with larger tumor size and higher C-reactive protein (all $p < 0.05$). The overall survival was significantly lower in patients with higher circulating levels of exosomal miRNA-21 and lncRNA-ATB (log-rank test: both $p < 0.05$).

Conclusion: This study has provided strong evidence that circulating exosomal ncRNAs (miRNA-21 and lncRNA-ATB) are novel prognostic markers and therapeutic targets for HCC.

SAT-145

Fgl2 contributes to hepatocellular carcinoma via suppressing the inflammatory phenotypes and functions of dentritic cells and cytotoxic lymphocytes in tumor microenvironment

M. Yang, Z. Zhang, J. Chen, X. Luo, Q. Ning. *Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, China*
Email: qning@vip.sina.com

Background and Aims: Immunosuppressive molecules are crucial for the survival and progress of tumor cells in hepatocellular carcinoma (HCC). Our previous studies have shown that fibrinogen-like protein 2(FGL2) can promote the growth of tumor cells and angiogenesis in liver cancer. However immunological regulatory effect of FGL2 in HCC is largely unknown. The purpose was to elucidate if FGL2 contributes to HCC development via influencing tumor microenviroment.

Method: BNL cells were subcutaneously implanted into Balb/c (WT) and $fgl2^{-/-}$ mice, respectively. Different doses of fgl2 antibody (α-FGL2) were injected intratumorally twice a week when the tumor volume was over 100 mm^3. 11 days after α-FGL2 treatment, the mice were sacrificed and single cell suspension of tumor and draining lymph node (dLN) was prepared. The proportions, numbers and phenotypes of T cells and DCs were analysed by flow cytometry. Isolated by MACS, $CD8^+$T cells from α-fgl2 treated tumor were mixed with BNL cells, and the death rate of BNL cells were examined. DCs from mice injected with α-FGL2 were separated by MACS and mixed with tumor T cells, and theproliferation index of T cells was measured.

Results: The results showed that α-FGL2 inhibited HCC tumor growth in a dose-dependent manner. Similarly, the size of HCC tumor in $fgl2^{-/-}$ mice was significantly smaller than that of WT mice. Tumor and dLN of α-FGL2 treatment group contained more $CD8^+$ T cells ($p < 0.05$ in tumor and $p < 0.01$ in dLN) which expressed high level of perforin ($p < 0.05$ in tumor and $p < 0.05$ in dLN) and granzyme B ($p < 0.01$ in tumor) compared with control. The death rate of BNL cells was higher when mixed with $CD8^+$ T cells from α-FGL2 treatment mice ($p < 0.05$). Besides, DCs from α-FGL2 treatment mice presented mature state, expressing more CD80 ($p < 0.05$ in dLN), CD83 ($p < 0.05$ in dLN) and less CD31 ($p < 0.05$ in tumor and $p < 0.05$ in dLN), B7-H4 ($p < 0.01$ in tumor). These DCs promoted the proliferation of tumor $CD4^+$and $CD8^+$ T cells in *ex vivo* mixture test. Similarly, the proportion of $CD8^+$ T cells were higher in tumor and dLN of $fgl2^{-/-}$ mice compared with WT mice ($p < 0.05$ in tumor). And there was higher level of granzyme B ($p < 0.05$ in dLN) in $CD8^+$ T cells and decreased CD31 expression ($p < 0.05$ in tumor) on DCs in $fgl2^{-/-}$ mice.

Conclusion: Our data suggested that fgl2 inhibited the maturation of DCs which dampened the anti-tumor effect of T cells in HCC microenvironment and FGL2 might be a novel therapeutic target in HCC.

SAT-146

Molecular characterization of autophagic and apoptotic signaling induced by Sorafenib in liver cancer cells: In vitro and in vivo studies

M.Á. Rodríguez-Hernández[1], R. González[2], Á.J.De la Rosa[2], P. Gallego[3], L. Contreras[4,5], R. Ordóñez[6,7], E. Navarro-Villarán[1], M. Rodríguez-Arribas[8,9], J. González-Gállego[6,7], J.M. Álamo-Martínez[7,10], L.M.M. Gómez[10], J.A.D.C. Castillo[3,7], J.L. Quiles[11], J.M. Fuentes[8,9], J. De la Cruz[4,5], J.L. Mauriz[6,7], F.J. Padillo[1,7,10], J. Muntané[2,7,10]. *[1]Institute of Biomedicine of Seville (IBiS), Laboratory 209, Seville, Spain; [2]Institute of Biomedicine of Seville (IBiS), Seville, Spain; [3]University Hospital "Nuestra Señora de Valme", Unit for the Clinical Management of Digestive Diseases, Seville, Spain; [4]Institute of Biomedicine of Seville (IBiS), Laboratory 201, Seville, Spain; [5]Faculty of Biology, Department of Genetics, Seville, Spain; [6]Institute of Biomedicine (IBIOMED), León, Spain; [7]Centro de Investigación Biomédica en red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain; [8]Faculty of Nursery and Occupational Therapy, Department of Biochemistry, Molecular Biology and Genetics, Cáceres, Spain; [9]Centro de Investigación Biomédica en Red de Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain; [10]University Hospital "Virgen del Rocío"/IBiS/CSIC/University of Seville, Department of General Surgery, Seville, Spain; [11]Institute of Nutrition and Food Technology "José Mataix Verdú", Biomedical Research Center, Granada, Spain*
Email: jmuntane-ibis@us.es

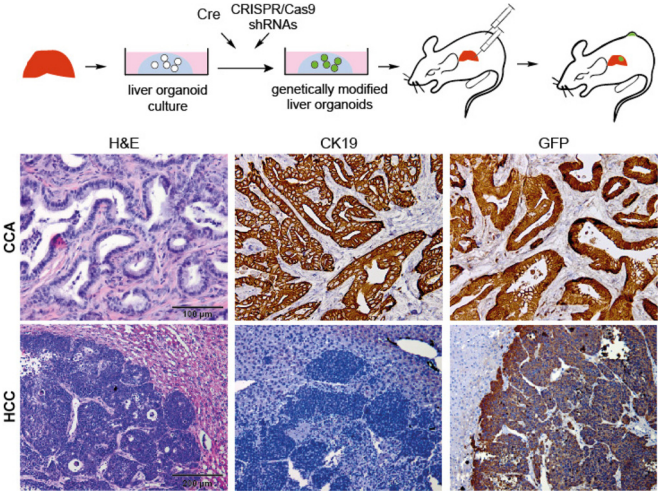
Background and Aims: Sorafenib is the unique accepted molecular targeted drug for the treatment of patients in advanced stage of hepatocellular carcinoma (HCC). The present study evaluated cell signaling regulation of endoplasmic reticulum (ER) stress, JNK, Akt, and AMPK leading to autophagy and apoptosis induced by Sorafenib.
Method: We carried out a kinetic study of autophagy and apoptosis induction by Sorafenib in HCC cells. Different parameters related to the induction of ER stress and cell signaling involved in cell survival and death were assessed. The involvement of autophagy and apoptosis in the antitumoral properties of Sorafenib were also evaluated in a xenograft mouse model.
Results: Sorafenib (10–100 μM) induced early (3–12 h) ER stress characterized by an increase of ^{Ser51}P-eIF2α/eIF2α, CHOP, IRE1α and sXBP1, but a decrease of ATF6 expression, overall temporally associated with the increase of ^{Thr183}P-JNK/JNK, ^{Thr172}P-AMPα, ^{Thr308}P-Akt/Akt and ^{Thr32}P-Foxo3a/Foxo3a ratios, and reduction of ^{Ser2481}P-mTOR/mTOR and protein translation. This pattern was related to an increase of autophagy markers (Beclin-1, LC3II/LC3I and p62), and reduction of Mcl-1 and Bcl-2 protein expression. The progressive increase of CHOP expression, and reduction of ^{Thr308}P-Akt/Akt and ^{Ser473}P-Akt/Akt ratios were associated with the reduction of autophagic flux and increase of Bim expression and caspase-3 activity (24 h). The different experimental interventions showed that ER-induced autophagy played a survival role in Sorafenib-treated HepG2 cells. Interestingly, siRNA assays and immunoprecipitation studies of Beclin-1 showed that its sequestration by Bim shifted autophagy to caspase-3-dependent apoptosis in Sorafenib-treated HepG2 cells. The *in vivo* study showed that Sorafenib increased autophagic and apoptotic markers, and reduced the size, proliferative, angiogenic and fibrotic markers in tumors derived from subcutaneous implantation of HCC cells in nude mice.
Conclusion: The induction of ER stress by Sorafenib was the driving mechanism involved in the sequential induction of autophagy and apoptosis in HepG2 cells. The early Sorafenib-induced ER stress and regulation of JNK and AMPK-dependent signaling were related to the induction of survival autophagic process (3–12 h). The sustained activity of the drug induced a progressive increase of ER stress and PERK-CHOP-dependent rise of Bim, which induced the shift from autophagy to apoptosis. However, the kinetic of Bim expression profile and apoptosis might also be related to the tight balance between Akt- and AMPK-related signaling that also modulated the Foxo3a-dependent Bim upregulation.

SAT-147

In-vivo validation of cancer genes using liver organoids

A. Saborowski[1], K. Wolff[1], S. Spielberg[1], B. Beer[1], B. Hartleben[2], Z. Erlangga[1], N. Woller[1], M.P. Manns[1], A. Vogel[1], M. Saborowski[1].
[1]Hanover Medical School, Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [2]Hanover Medical School, Dept. of Pathology, Hannover, Germany
Email: saborowski.anna@mh-hannover.de

Background and Aims: A rising incidence of intrahepatic cholangiocarcinoma (CCA) cases and a 5-year-survival rate that remains below 10% illustrates the urgent need for therapeutic advances. Recently, sequencing studies have shed light on the genetic landscape of this aggressive malignancy. To improve our understanding of the pathophysiology of CCA, as well as to address the immediate clinical relevancy of the genomic data, versatile model systems that facilitate the rapid functional annotation of putative CCA driver- and maintenance genes are needed. Here, we aimed to develop an easily tractable murine CCA model that is based on the genetic manipulation and transplantation of liver organoid cultures.
Method: Murine liver organoid lines harboring latent cancer-defining alleles are derived following established protocols. Latent alleles are activated by introduction of a Cre-recombinase, and further genetic manipulation is achieved using RNAinterference- and CRISPR/Cas9-technology. The cells are then transplanted either subcutaneously or orthotopically into syngeneic, immunocompetent mice.



Results: Liver organoids harboring the endogenous KrasG12D allele in conjunction with loss of p53 give rise to moderately differentiated CCA in recipient mice with 100% penetrance. Histologically, tumors closely resemble the human disease, displaying CK19 positive ductal structures surrounded by a dense desmoplastic stroma. Tumor formation is readily accelerated by tumor suppressor gene loss or oncogene expression, and co-transduction of a fluorescent marker gene conveniently allows for the easy identification of the epithelial tumor cells in the primary tumor, as well as at metastatic sites. Tumors are serially transplantable both as 2- and 3-dimensional cell lines, thus allowing to rapidly generate genetically defined tumor cell lines for downstream studies, such as drug screening. In addition, we show that, depending on the genetic context, liver organoids can also give rise to hepatocellular carcinoma, illustrating the plasticity of the organoid system.
Conclusion: Genetically modified liver organoids give rise to CCA and HCC and can be used for the functional annotation of candidate liver cancer genes. The organoid system combines the advantage of utilizing non-transformed, pre-malignant cells to recapitulate tumorigenesis as a multi-step process, with the convenience of a cell culture system that abrogates the need for recurrent isolation of primary cells.

SAT-148

Activated platelets contribute to the progression of hepatocellular carcinoma by altering the immune cell environment

N. Pavlovic[1], F. Heindryckx[1], L. Edlund[1], P. Gerwins[1,2]. *[1]Uppsala University, Department of Medical Cell Biology, Uppsala, Sweden; [2]Akademiska sjukhuset, Department of Surgical Sciences, Radiology, Uppsala, Sweden*
Email: natasa.pavlovic@mcb.uu.se

Background and Aims: The inflammatory process plays a critical role in the complex molecular pathogenesis of hepatocellular carcinoma (HCC). Macrophages are a key part of the inflammatory environment, and their role in tumour progression is determined by their state of activation, which can be classified as anti-tumoural (M1) and pro-tumoural (M2). Platelets have been reported to interact with different cell types in the tumour microenvironment, including macrophages and Kupffer cells. This study aimed to identify the effect of platelets on the inflammatory cell population and HCC development, as well as to determine whether anti-platelet therapy can decrease the progression of HCC.
Method: Mice were injected weekly with diethylnitrosamine to induce HCC. From week 10, mice were treated with anti-platelet drug

Clopidogrel or control, samples were taken for RNA-analysis and histology after 25 weeks. Tumour burden and collagen deposition was quantified on H&E and Sirius red staining, respectively. Platelets and macrophages were quantified by immunohistochemical stainings with CD41 and F4/80 antibodies, respectively. For *in vitro* experiments, fluorescently labelled HCC-cells (HepG2) and differentiated macrophages (PMA-treated THP1-cells) were co-cultured with platelets isolated from healthy donors.

Results: Blocking platelet activation with Clopidogrel significantly decreased tumor burden *in vivo*, compared to untreated controls. mRNA analysis confirmed a decreased expression of PCNA in Clopidogrel-treated mice with HCC, suggesting a decrease in proliferation. CD41 immunohistochemistry revealed that treatment with Clopidogrel significantly decreased the number of infiltrated platelets in the liver of mice with HCC. Anti-platelet therapy also significantly decreased collagen deposition in mice. Clopidogrel treatment led to a significant decrease in the total number of F4/80-positive macrophages, while it increased mRNA expression of several anti-tumoral M1 macrophage activation markers (TNFa, IL-1, CD40, Fpr2) and decreased M2-marker Arginase-1 expression. *In vitro* experiments showed THP1-differentiated macrophages phagocytose HepG2-cells and that adding platelets to a co-culture of macrophages and tumor cells significantly decreased the macrophage's capacity to phagocytose tumor cells.

Conclusion: These findings suggest that platelets play an important role in creating a pro-tumoural inflammatory environment and thereby facilitate HCC progression. The use of anti-platelet drugs may therefore be therapeutically relevant for patients with HCC.

SAT-149

Polyploidy and chromosomal instability correlates with proliferative traits and lack of immune-related gene signatures in hepatocellular carcinoma

L. Bassaganyas[1], S. Torrecilla[1,2], A. Moeini[1,2], F. Nadeu[3,4], D. Sia[2], I. Salaverria[3,4], L. Cabellos[1], R. Pinyol[1], J. Camps[5], V. Mazzaferro[6], J.M. Llovet[1,2,7]. [1]*Liver Cancer Translational Research Laboratory, Barcelona-Clínic Liver Cancer, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, CIBERehd, Universitat de Barcelona, Barcelona, Spain;* [2]*Mount Sinai Liver Cancer Program, Divisions of Liver Diseases, Department of Hematology/Oncology, Department of Medicine, Department of Pathology, Recanati Miller Transplantation Institute, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, United States;* [3]*Lymphoids Neoplasms Program, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain;* [4]*Tumores Hematologicos, Centro de Investigación Biomédica en Red de Cáncer (CIBERONC), Madrid, Spain;* [5]*Gastrointestinal and Pancreatic Oncology Group, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, CIBERehd, Universitat de Barcelona, Barcelona, Spain;* [6]*Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy;* [7]*Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain*
Email: laia.bassaganyas@gmail.com

Background and Aims: Chromosomal instability (CIN) is a hallmark of cancer and has been related to aggressiveness in several tumors, including hepatocellular carcinoma (HCC). CIN is characterized by the presence of somatic copy-number alterations (SCNAs) and is associated with polyploidy. However, the role of CIN, the incidence of polyploidy, and their molecular/ clinical implications on HCC remain ill-defined.

Method: 150 paired (tumor/adjacent) fresh-frozen surgically resected tissues from HCC patients were analyzed for SCNA detection (Illumina SNParray) and gene expression profiling (Affymetrix). ASCAT and saasCNV were used to define tumor ploidy and SCNA profiles, respectively. Three CIN scores were generated measuring the number of focal (low structural CIN, LS_{CIN}), arm (high structural CIN, HS_{CIN}), and chromosome (numerical CIN, N_{CIN}) SCNAs weighted by its copy number and length. Samples were clustered according to ploidy and CIN-scores. Each cluster was further characterized based on gene expression profiling and correlation with clinic-pathological data. Analysis of clonal cell fraction to define the occurrence of SCNAs is ongoing.

Results: Analysis of SCNA profiles showed that 40% of HCC of tumors displayed a pattern consistent with polyploidization (mean ploidy 3.89). Assessment of the CIN-scores revealed that N_{CIN} and HS_{CIN} were significantly higher in polyploid tumors ($p < 0.001$). In contrast, LS_{CIN} score remained homogeneous throughout the cohort. Compared to diploid tumors, polyploids showed a higher incidence of *TP53* deletions ($p < 0.01$) and were associated with gene sets related to loss of TP53/RB1 signaling, DNA replication, DNA damage response, and G2/M checkpoint evasion and lack of immune –related signatures ($p < 0.01$). Instead, diploid tumors were enriched in immune-related signatures and presented a higher degree of cell differentiation ($p < 0.05$), feature related to the less aggressive *non-proliferation* HCC class. Polyploid/high N_{CIN}/HS_{CIN} tumors showed proliferation-like traits such as enrichment of EpCAM and vascular invasion signatures ($p < 0.05$), which are associated with worse outcome.

Conclusion: Numerical and high-structural CIN both correlate with polyploidy. Polyploid tumors are associated with cell cycle deregulation signatures and proliferation-like traits. Diploid tumors are related to immune signatures and non-proliferation-like features. The study highlights the importance of CIN in exploring molecular and immune-oncology therapies in HCC.

SAT-150

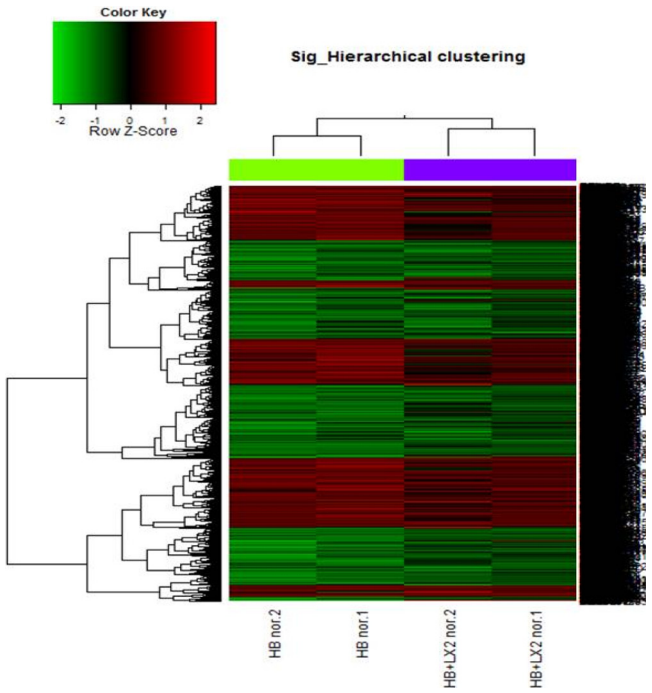
Tumor-stroma crosstalk enhances Reg3A expressions that drives the progression of hepatocellular carcinoma

Y. Cho[1], M.J. Park1[1], J.-Y. Park[2]. [1]*CHA University, Internal Medicine, Seoul, Korea, Rep. of South;* [2]*Seoul National University College of Medicine, Orthopaedic Surgery*
Email: yuricho@chamc.co.kr

Background and Aims: Crosstalk between tumor cells and their microenvironment plays a crucial role in the progression of hepatocellular carcinoma (HCC). In this study, we investigated the key signal that modulates crosstalk between HCC cells and their microenvironment.

Method: Human HCC cell lines (Huh-7, HepG2, and SNU-761) were cocultured with an activated human hepatic stellate cell line (HSCs; LX-2) under normoxic (20% O_2 and 5% CO_2, at 37 °C) conditions. Complementary DNA (cDNA) microarray analysis was performed to find the molecule which is significantly enhanced by crosstalk between HCC cells and stroma. In vivo study using a subcutaneous xenograft model by injecting MH134 cells (C3H mice) was performed to confirm the effect of coculturing HCC cells and HSC cells and the inhibitory effect by small interfering RNA (siRNA) transfection. Immunoblot analyses were used to investigate the signaling pathway.

Results: Using cDNA microarray analysis, we found the molecule, REG3A, which was significantly enhanced by coculturing Huh-7 cells and HSC cells (+ 8.2 log) as compared to mono-culturing Huh-7 cells. Coculturing HCC cells (Huh-7, HepG2, and SNU-761) with HSC cells enhanced the mRNA and protein expressions of REG3A as compared to mono-culturing HCC cells. Downregulation of REG3A by siRNA significantly decreased the proliferation of tumor cells in vitro and in vivo, when HCC cells were cocultured with HSCs (both $p < 0.05$). In immunoblot assay, downregulation of REG3A by siRNA decreased the expressions of phosphorylated p42/44 and β-catenin, especially when HCC cells were cocultured with HSCs. Immunofluorescence study also revealed that deoxycholic acid-induced HCC cell apoptosis was inhibited when REG3A was down-regulated in HSCs-cocultured HCC cells. Interestingly, crosstalk-induced REG3A up-regulation was modulated by PDGF-β in p42/44-dependent manner.



Conclusion: In conclusion, crosstalk between HCC cells and HSCs cells was modulated by up-regulation of REG3A in p42/44-dependent manner. Moreover, the up-regulation of REG3A by crosstalk between HCCs and HSCs was mediated by PDGF-β. Targeting REG3A might be a novel therapeutic target in the management of human HCCs by inhibiting crosstalk between HCCs and HSCs.

SAT-151

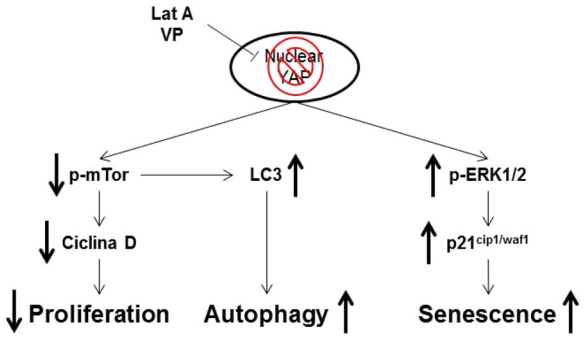
Inhibition of YAP activation induces cell senescence and autophagy while blocking cell proliferation in cholangiocarcinoma (CCA)

M. Cadamuro[1,2,3], G. Casati[1], T. Stecca[4], S. Brivio[1], C. Milani[1], V. Mariotti[3], E. Kaffe[5], C. Spirli[2,5], M. Amenduni[5], R. Fiorotto[2,5], U. Cillo[6], G. Maria[7], L. Fabris[2,3,5], M. Strazzabosco[1,2,5]. *[1]University of Milan-Bicocca, School of Medicine and Surgery, Monza, Italy; [2]University of Milan-Bicocca, International Center for Digestive Health, Monza, Italy; [3]University of Padua, Department of Molecular Medicine, Padova, Italy; [4]University of Padua, Department of Surgery, Oncology and Gastroenterology, Padova, Italy; [5]Yale University, Section of Digestive Diseases, New Haven, United States; [6]Liver Transplant and HBP Surgery Unit, Padua Universit, Padua, Italy; [7]University of Padua, Department of Medicine, Padova, Italy*
Email: massimiliano.cadamuro@unimib.it

Background and Aims: Cholangiocarcinoma (CCA) is an aggressive cancer of the biliary epithelium, with dismal prognosis due to the lack of effective treatments. Yes-associated protein (YAP) is a pleiotropic morphogen that, when expressed in the nucleus, regulates several pro-tumorigenic functions, such as proliferation, motility, survival, and chemotherapy resistance. However, its effects in CCA are not well known. YAP is regulated by several stimuli, including cell density, matrix stiffness, and cytoskeletal dynamics. We then aimed to evaluate the role of YAP in modulating proliferation, senescence and autophagy in CCA cells, and the underlying molecular mechanisms.

Methods: Nuclear expression of YAP (nYAP) was studied in 3 human CCA cell lines (EGI-1, TFK-1, and HuCCT-1) by immunofluorescence at different culture density, and upon exposure to the YAP inhibitors dobutamine (Dob), latrunculin A (Lat), Y27632 (Y), or verteporfin (VP). Expression of CTGF, ANKRD1 and Cyr61 (RT-PCR) were used as readouts of YAP activation. *In vitro,* effects of YAP inhibition on CCA cell proliferation, senescence and autophagy were analysed by BRDU assay (proliferation) and by Western blotting (WB) for ERK1/2 (MAPK pathway), p70S6K, Cyclin D1 (PI3K/AKT/mTOR pathway), p21(senescence), and LC3 (autophagy). Interactions between mTOR and ERK pathways to regulate p21 were analysed using specific inhibitors, rapamycin (rapa, for mTOR), LY294002 (LY, for PI3K). Expression of nYAP together with p-mTOR and p21 was also studied by immunohistochemistry in human archival CCA samples (n = 10).

Results: All CCA cell lines constitutively expressed nuclear YAP (nYAP) that was negatively regulated by high confluence culture conditions. Among the YAP inhibitors, Lat and VP were the most effective in reducing expression of the YAP-induced target genes (CTGF, ANKRD1, Cyr61); following YAP inhibition, mTOR and Cyclin D1 were down-regulated and CCA cells proliferation was significantly reduced. At the same time, after YAP inhibition, cell senescence (p21) and autophagy (LC3) markers increased. In fact YAP inhibition stimulated ERK1/2 phosphorylation, and hyperexpression of p21. ERK1/2 activation is selectively repressed by LY, indicating its dependence on the PI3K pathway. Consistent with the role of ERK1/2, overexpression of p21 induced by inhibition of YAP is reduced by the MEK inhibitor U0126. In human CCA specimens nYAP was expressed by CCA cells at the tumor-host interface, while p21 expression was preponderant in the bulk of tumor.



Conclusion: CCA is characterized by a strong nuclear expression of YAP both *in vitro* and *in vivo*. Targeting YAP activation blocks cell proliferation by decreasing mTOR phosphorylation and Cyclin D1 expression, and in turn, stimulates autophagy and the cell senescence program via ERK/p21. Targeting the YAP signaling could therefore be an innovative therapeutic strategy for CCA.

SAT-152

Dietary cholesterol and StARD1 overexpression aggravate chemically induced hepatocarcinogenesis in vivo

L.C. de la Rosa[1,2], V. Ribas[1,2], M.C. Garcia-Ruiz[1,2,3,4], J. Fernandez-Checa[1,2,3,4]. *[1]Instituto Investigaciones Biomédicas Barcelona (IIBB-CSIC), Cell Death and Proliferation, Barcelona, Spain; [2]Centro Investigaciones Biomédicas en Red (CIBEREHD), Enfermedades Digestivas y Hepáticas, Barcelona, Spain; [3]University of Southern California, Kerk School of Medicine, Los Angeles, United States; [4]IDIBAPS, Liver Unit Hospital Clinic Barcelona, Barcelona, Spain*
Email: lcondedelarosa@gmail.com

Background and Aims: Hepatocellular carcinoma (HCC) is a leading cause of cancer-related death worldwide and the end-stage of chronic liver disease. Hypercholesterolemia is also a growing health concern emerging as a critical factor in the progression of fatty liver disease. StARD1, responsible for cholesterol trafficking to mitochondria, has a role in the transition from steatosis to steatohepatitis which can progress to HCC. Obesity and hepatic steatosis promotes tumorigenesis, but the role of cholesterol and StARD1 overexpression in HCC progression has not been elucidated yet. **Aim**: To study the role of cholesterol and StARD1 in chemically-induced HCC and the therapeutic effect of ezetimibe *in vivo*.

Method: 14 days-old wild type mice were injected i.p. with a single dose of the carcinogen diethylnitrosamine (DEN). Mice were fed a choline-deficient diet (CD) or a cholesterol-enriched diet (HC) for 5 months. In parallel, mice were fed high fat diet (60%) containing cholesterol (0.5%) (HFHC) supplemented or not with ezetimibe (Ez) for 32 weeks. In some cases, DEN-treated mice fed HFHC were injected with adenovirus to overexpress StARD1. Liver samples were analyzed for inflammation, fibrosis and tumor markers by WB, IHC and qRT-PCR. StARD1 expression was examined in samples from patients with HCC.
Results: (**1**) CD diet increases triglyceride levels in the liver in contrast to the HC diet that specifically increases cholesterol. Liver cholesterol was higher in the HFHC fed group compared to HFHC + Ez group. (**2**) Inflammation (IL-6, Ly6D, Ly6c), proliferation (PCNA, Ki-67) and fibrosis markers (collagen 1A1, αsma, TGFβ) were increased in CD + DEN group and exacerbated in HC + DEN group. Moreover, the expression of these markers was elevated in the HFHC group compared to HFHC + Ez group. (**3**) Tumour markers (AFP, CK-19, GP-73, Birc5) induced by DEN were increased in the presence of CD and further elevated with the HC diet. The expression of these markers was elevated in mice fed the HFHC, and ezetimibe reversed this increase. (**4**) StARD1 overexpression doubled the multiplicity of tumors in DEN-treated mice fed HFHC and increased the expression of tumor, fibrosis and inflammation markers. (**5**) Liver biopsies from patients with HCC exhibit increased StARD1 levels compared to samples from control subjects.
Conclusion: Cholesterol aggravates HCC and ezetimibe reverse this effect. StARD1 overexpression increases HCC, likely by stimulating the trafficking of mitochondrial cholesterol.

SAT-153

Peribiliary glands and biliary tree stem cells are involved in the pathogenesis of cholangiocarcinoma arising in patients affected by primary sclerosing cholangitis

D. Overi[1], V. Cardinale[2], T. Folseraas[3], G. Carpino[4], K. Grzyb[5], D. Costantini[6], P.B. Berloco[7], D. Alvaro[8], E. Gaudio[1]. *[1]Sapienza University of Rome, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Division of Human Anatomy, Rome, Italy; [2]Sapienza University of Rome, Department of Medico-Surgical Sciences and Biotechnologies, Rome, Italy; [3]Oslo University Hospital, Rikshospitalet, Oslo, Norway, Norwegian PSC Research Center, Department of Transplantation Medicine, Division of Surgery, Inflammatory Medicine and Transplantation, Research Institute of Internal Medicine, Division of Surgery, Inflammatory Medicine and Transplantation, Oslo, Norway; [4]University of Rome "Foro Italico", Department of Movement, Human and Health Sciences, Division of Health Sciences, Rome, Italy; [5]Oslo University Hospital, Department of Pathology, Oslo, Norway; [6]Sapienza University of Rome, Department of Medicine and Medical Specialties, Rome, Italy; [7]Sapienza University of Rome, Department of General Surgery and Organ Transplantation, Rome, Italy; [8]Sapienza University of Rome, Department of Internal Medicine and Medical Specialties, Rome, Italy*
Email: diletta.overi@uniroma1.it

Background and Aims: Primary sclerosing cholangitis (PSC) is a chronic cholangiopathy characterized by inflammation and bile duct fibrosis. Massive proliferation of biliary tree stem/progenitor cell (BTSC), expansion of peribiliary glands (PBG) and dysplasia were observed in PSC. Cholangiocarcinoma (CCA) frequently complicates the course of PSC. The aims of the present study were to evaluate the involvement of PBGs and BTSCs in CCA emerging in PSC patients.
Method: Specimens from normal liver (n = 5), PSC (n = 20), and CCA arising in PSC patients (n = 20) were included. Samples were processed for histology, immunohistochemistry and immunofluorescence. *In vitro* experiments were performed on human (h) BTSCs isolated from extrahepatic biliary tree from organ donors, on human primary CCA cell cultures obtained from mucin producing CCA specimens and on H69, a normal human cholangiocyte cell line. Cultures were analyzed by immunofluorescence and reverse-transcription polymerase chain reaction.
Results: All CCAs emerging in PSC patients were mucin-producing tumors characterized by the involvement of PBGs and high expression of stem/progenitor cell markers. In surrounding tissue, pre-neoplastic and neoplastic lesions affected several bile ducts and the associated PBGs. Ducts with neoplastic lesions showed higher inflammation, wall thickness and PBG activation compared to PSC-affected ducts. CCA showed higher expression of nuclear factor-kappa B, interleukin-6 and vascular endothelial growth factor 1, and displayed higher microvascular density compared to non-cancerous ducts. In tissue samples, CCA cells were characterized by higher expression of epithelial-to-mesenchymal transition (EMT) traits and by the absence of primary cilia compared to controls and PSC. *In vitro* study demonstrated that CCA cells and hBTSCs, when stimulated with lipopolysaccharide and oxysterols, increased the expression of EMT traits, nuclear factor-kappa B, and interleukin-6, and showed the loss primary cilia compared to control conditions.
Conclusion: CCA arising in PSC patients is characterized by extensive PBG involvement and the activation of BTSC niche. In these patients, the presence of duct lesions at different stages (from inflammation to fibrosis and to neoplastic transformation) suggests a progressive tumorigenesis. Lipopolysaccharide and oxysterols induced, in vitro, in hBTSCs and CCA cell cultures, pathologic features similar to those detected in situ in PSC specimens.

SAT-154

Transforming growth factor-βeta and AXL collaborate to induce CXCL5 and neutrophil infiltration in hepatocellular carcinoma

C. Haider[1], H. Julia[1], W. Roland[1], H. Heidemarie[1], L. Zell[1], G. Timelthaler[1], M. Grubinger[1], C. Coulouarn[2], K. Schlangen[3], W. Sieghart[4], M. Peck-Radosavljevic[4], W. Mikulits[5]. *[1]Medical University of Vienna, Department of Medicine I, Division: Institute of Cancer Research, Vienna, Austria; [2]Inserm, UMR991, Liver Metabolisms and Cancer, Rennes, France; [3]Medical University of Vienna, Section of Biosimulation and Bioinformatics, Center for Medical Statistics, Informatics and Intelligent Systems, Vienna, Austria; [4]Medical University of Vienna, Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Vienna, Austria; [5]Medical University of Vienna, Department of Medicine I, Division: Institute of Cancer Research, Vienna*
Email: wolfgang.mikulits@meduniwien.ac.at

Background and Aims: Transforming growth factor (TGF)-beta suppresses hepatocellular carcinoma (HCC) development at early stages but triggers pro-oncogenic abilities at later stages. Recent data suggest that the receptor tyrosine kinase Axl causes a TGF-beta switch towards epithelial to mesenchymal transition (EMT) and cell invasion.
Method: Establishment of human HCC models with opposing migratory phenotypes in response to long-term TGF-beta. Analysis of TGF-beta-dependent regulatory networks and target genes underlying cell invasion by transcriptome profiling and TCGA database mining. Inhibition of Axl and TGF-beta signalling in HCC cells by CRISPR/Cas9 and RNA interference. Analysis of HCC patients (n = 130) using tissue microarrays.
Results: We exploited two human HCC models with a pro- and an anti-migratory phenotype in response to TGF-beta and analysed the TGF-beta-dependent target genes underlying the invasion of HCC cells. Both HCC models displayed dedifferentiation by EMT, autocrine TGF-beta signalling and TGF-beta-dependent cell migration. Interestingly, these HCC cell models showed reduced proliferation and clonogenicity upon TGF-beta stimulation suggesting that cells evade specific traits of TGF-beta-induced tumor suppression. Transcriptome profiling revealed a set of invasion-addicted genes, among them the chemokine CXCL5, which showed a correlation with TGF-beta expression and low survival of HCC patients by analysing TCGA datasets. Notably, the expression and secretion of CXCL5 was

dependent on the expression of Axl, suggesting that CXCL5 is a TGF-beta target gene collaborating with Axl signalling. Loss of either Axl or TGF-beta signalling abrogated CXCL5-dependent migration and attraction of neutrophils. In HCC patient samples, high levels of Axl, TGF-beta and CXCL5 correlated with neutrophil infiltration and reduced survival of patients.
Conclusion: The synergy of TGF-beta and Axl targets CXCL5 which facilitates a pro-metastatic TGF-beta switch by HCC migration and neutrophil recruitment.

SAT-155
Mitochondrial VDAC1 based peptide as a new therapeutic agent for hepatocellular carcinoma
S. Pittala, Y. Krelin, V. Shoshan-Barmatz. *ben Gurion University of the Negev, Life Sciences, Beersheba, Israel*
Email: sirinivas9@gmail.com

Background and Aims: Hepatocellular carcinoma (HCC) is the third-most cancer worldwide. Despite progress in identifying risk factors, the incidence of HCC is increasing. Moreover, therapeutic options are limited and survival is poor. Therefore, alternative and innovative therapeutic strategies are urgently required.
Method: R-Tf-D-LP4, a cell-penetrating peptide derived from the mitochondrial multi-functional protein the voltage-dependent anion channel (VDAC1) is identified here as a highly effective liver cancer treatment. Recently, we demonstrated that R-Tf-D-LP4 induced apoptosis and inhibited tumor growth in mouse models. We now demonstrate that R-Tf-D-LP4 induced apoptosis in cancer liver-derived cell lines and inhibited tumor growth in three different liver cancer mouse models. These included diethylnitrosamine (DEN)-induced HCC, metabolically high-fat diet-induced HCC, and using a sub-cutaneous HepG2 cell xenograft mice model.
Results: Intravenous injection of the peptide into tumor-carrying DEN-treated mice resulted in dose-dependent inhibition of tumor growth up to complete tumor elimination. TUNEL staining of liver sections demonstrated peptide-induced apoptosis. Haematoxylin/eosin and Sirius red staining of liver sections showed decreased stromal formation. Immunohistochemical staining demonstrated reduced numbers of α-SMA-expressing stellate cells in R-Tf-D-LP4-treated mouse livers. Additionally, macrophage infiltration in liver tissue was reduced in R-Tf-D-LP4-treated mice. Liver sections from DEN-treated mice showed non-alcoholic steatohepatitis pathology, reflected as fatty liver, inflammation, ballooning degeneration and fibrosis; all were eliminated upon peptide treatment. Peptide treatment also inhibited tumor development in a non-alcoholic steatohepatitis-hepatocellular carcinoma (NASH-HCC) mouse model induced by high fat diet. In HepG2 sub-cutaneous tumor xenografts, R-Tf-D-LP4 inhibited tumor growth.
Conclusion: The results show that the VDAC1-based peptide R-Tf-D-LP4 has multiple effects on liver cancer cells, leading to impairment of cell energy and metabolism homeostasis, induction of apoptosis, and elimination of liver cancer-associated processes and thus represents a promising therapeutic approach for liver cancer.

SAT-156
The role of Lysyl oxidase in tumor microenvironment of primary liver cancer
M. Lewinska[1], M.J. Perugorria[2], J. Banales[2], J. Andersen[1]. [1]*University of Copenhagen, Biotech Research & Innovation Centre (BRIC), Copenhagen, Denmark;* [2]*Biodonostia Research Institute, Department of Liver Diseases, San Sebastian, Spain*
Email: monika.lewinska@bric.ku.dk

Background and Aims: Lysyl oxidases (LOX) are a family of extracellular proteins involved in collagen and elastin crosslinking causing stiffening and modulation of extracellular matrix (ECM). Although LOX has been reported to play tumor-suppressive roles, members of this family often show elevated tumor expression and play an essential role in hypoxia-induced metastasis. We investigated the role of LOX in modulation of the tumor microenvironment (TME) in primary liver cancer (PLC).
Method: We have analyzed our transcriptome profiles generated from patient cohorts including 219 cholangiocarcinoma (CCA), 143 matched adjacent tissues and 9 normal dissected common bile ducts, as well as 53 hepatocellular carcinoma (HCC) with matched adjacent liver tissues to investigate expression levels of LOX family members and correlate expression with clinical outcomes (survival analysis). Next, we performed gene set enrichment analysis (GSEA) to define deregulated pathways associated with aberrant LOX expression. Importantly, we have investigated LOX expression in a subset of 23 CCAs following laser-microdissection of the intra-tumor stroma and epithelial compartments. We utilized CIBERSORT to investigate the association of LOX expression with modulation of immune cell component in TME. Using hypoxic camber conditions, we modified expression of LOX in primary normal human cholangiocytes (NHC), hepatocytes (THLE5b), and PLC cancer lines. Lastly, conditioned media transfer models were used to alter LOX expression in hepatic stellate cells (HSC).
Results: Members of the LOX family are significantly overexpressed in PLC compared to adjacent normal liver, with LOX itself showing the highest fold change. High expression of LOX is associated with decreased survival in both HCC ($p = 0.035$) and CCA ($p = 0.017$). Expected, GSEA shows hypoxia gene sets associated with increased LOX expression in PLC. We confirmed that LOX expression correlates significantly with HIF1α in PLC tissues and increase in cultured cells at hypoxic conditions (1% O_2). Analysis of dissected intra-tumor stroma and epithelium showed that LOX is expressed both by the epithelial and stromal components, with significant association linked to the desmoplastic compartment. Culture systems utilizing hypoxia and conditioned media transfer generated from PLCs significantly stimulate LOX expression in HSC. Interestingly, LOX^{high} expression in PLC patients is associates with enrichment of macrophages M0 and depletion of CD4+ resting T cells in the tumors, but not correlating with tumor size.
Conclusion: Taken together our results suggest that LOX is expressed by multiple cell types in PLCs, with high expression associated with CCA desmoplasia. Elevated LOX is predictive of poor survival, but not tumor size. LOX is a putative candidate in promoting the progression of PLCs.

SAT-157
The anti-inflammatory receptor TREM2 halts the generation of HCC in mice through the inhibition of liver inflammation and hepatocyte proliferative responses
A. Esparza-Baquer[1], I. Labiano[1], O. Sharif[2,3], F. Oakley[4], E. Hijona[1,5], R. Jimenez-Aguero[1], C.O. Rourke[6], J. Andersen[6], S. Knapp[2,3], D.A. Mann[4], L. Bujanda[1,5], J. Banales[1,5,7], M.J. Perugorria[1,5,7].
[1]*Biodonostia Health and Research Institute, Donostia University Hospital, University of the Basque Country (UPV-EHU), Department of Liver and Gastrointestinal Diseases, Donostia-San Sebastián, Spain;* [2]*Austrian Academy of Sciences, Research Center for Molecular Medicine, Vienna, Austria;* [3]*Medical University of Vienna, Department of Medicine I, Laboratory of Infection Biology, Vienna, Austria;* [4]*Faculty of Medical Sciences, Newcastle University, Institute of Cellular Medicine, Newcastle Upon Tyne, United Kingdom;* [5]*CIBERehd, Centro de Investigación Biomédica en Red, Donostia-San Sebastián, Spain;* [6]*University of Copenhagen, Biotech Research and Innovation Centre (BRIC), Department of Health and Medical Science, Copenhagen, Denmark;* [7]*IKERBASQUE, Basque Foundation for Science, Bilbo-Bilbao, Spain*
Email: matxus.perugorria@biodonostia.org

Background and Aims: Hepatocellular carcinoma (HCC) is the most prevalent primary liver tumor and the third most common cause of cancer related death. Even though a number of interventional treatment methods are currently in use, this tumor remains highly chemo-resistant and shows a poor prognosis. HCC slowly unfolds on a background of chronic liver injury, where inflammation and liver

regeneration processes are involved. Toll-like receptor (TLR) derived signaling in non-parenchymal liver cells accelerates carcinogenesis by modulating inflammatory responses. Therefore, regulation of pro-inflammatory signals arises as a promising therapeutic strategy for HCC. The triggering receptor expressed on myeloid cells 2 (TREM2) acts as an anti-inflammatory receptor, as it inhibits TLR-derived signaling in various tissues, yet its role in the liver and in HCC is still unknown. This study aims to unravel the role of TREM2 in HCC development and progression.

Method: TREM2 mRNA expression was analyzed in liver tissue samples from patients with HCC compared to control individuals and murine models of HCC and liver regeneration. To study the role of TREM2 in HCC development and progression, *wild type* (WT) and *Trem2*$^{-/-}$ mice were treated with the hepatocarcinogen diethylnitrosamine (DEN) and analyzed at different time-points during disease development. The early molecular mechanisms triggered in response to DEN were analyzed in WT and *Trem2*$^{-/-}$ mice in acute phases (6, 24, 72 h). To evaluate the role of TREM-2 in liver regeneration a ~70% partial hepatectomy (PHx) model was performed in WT and *Trem2*$^{-/-}$ mice, and animals were sacrificed at 1, 6, 36, 72 hours and 5 days post-surgery.

Results: *TREM2* mRNA expression is significantly upregulated in human HCC samples compared to control livers. Similarly, *Trem2* mRNA expression is also elevated in murine HCC and in a liver regeneration model compared to control livers. *Trem2*$^{-/-}$ mice show augmented tumor number and bigger tumors after DEN. This was accompanied by an increase in the expression of liver damage and hepatocyte proliferation markers, together with a downregulation of the anti-tumoral gene farnesoid X receptor (*Fxr*). *Trem2*$^{-/-}$ mice exhibited exacerbated liver damage in acute phases in response to DEN. Regarding liver regeneration following PHx, PCNA expression and BrDU incorporation indicated an increased hepatocyte proliferation in the *Trem2*$^{-/-}$ mice. The expression of pro-inflammatory genes was also elevated in these mice. Interestingly, the results observed in the HCC model could be rescued with an anti-inflammatory diet (BHA).

Conclusion: TREM2 is upregulated in human and murine HCC and in murine liver regeneration. This anti-inflammatory receptor inhibits proliferation and HCC tumor generation in mice through the inhibition of liver inflammation. TREM2 arises as a novel therapeutic strategy for HCC.

SAT-158

Functional genomics identified actin cytoskeleton remodeling required for the hypoxia-mediated EMT: A mechanistic link of tumor size to metastasis

S.-Y. Hsieh. *Chang Gung Memorial Hospital, Linkou, Chang Gung University College of Medicine, Taoyuan, Taiwan*
Email: siming.shia@msa.hinet.net

Background and Aims: High invasiveness is a hallmark of human hepatocellular carcinoma (HCC). Large tumors predict invasion and metastasis. Epithelial-mesenchymal transition (EMT) is crucial for cancer invasion and metastasis. However, the mechanisms whereby large tumors tend to undergo EMT remain unclear.

Method: We conducted a subgenome-wide screen for invasion suppressor genes and identified *KLHL2*. We used patient-derived HCC xenograft model to validate our hypothesis.

Results: *KLHL23* was an HCC invasion suppressor via inhibiting EMT. Downregulation of *KLHL23* was associated with invasion, metastasis, and poor prognosis of HCC and pancreatic cancer. KLHL23 binds to actin and suppresses actin polymerization. *KLHL23* silencing induced

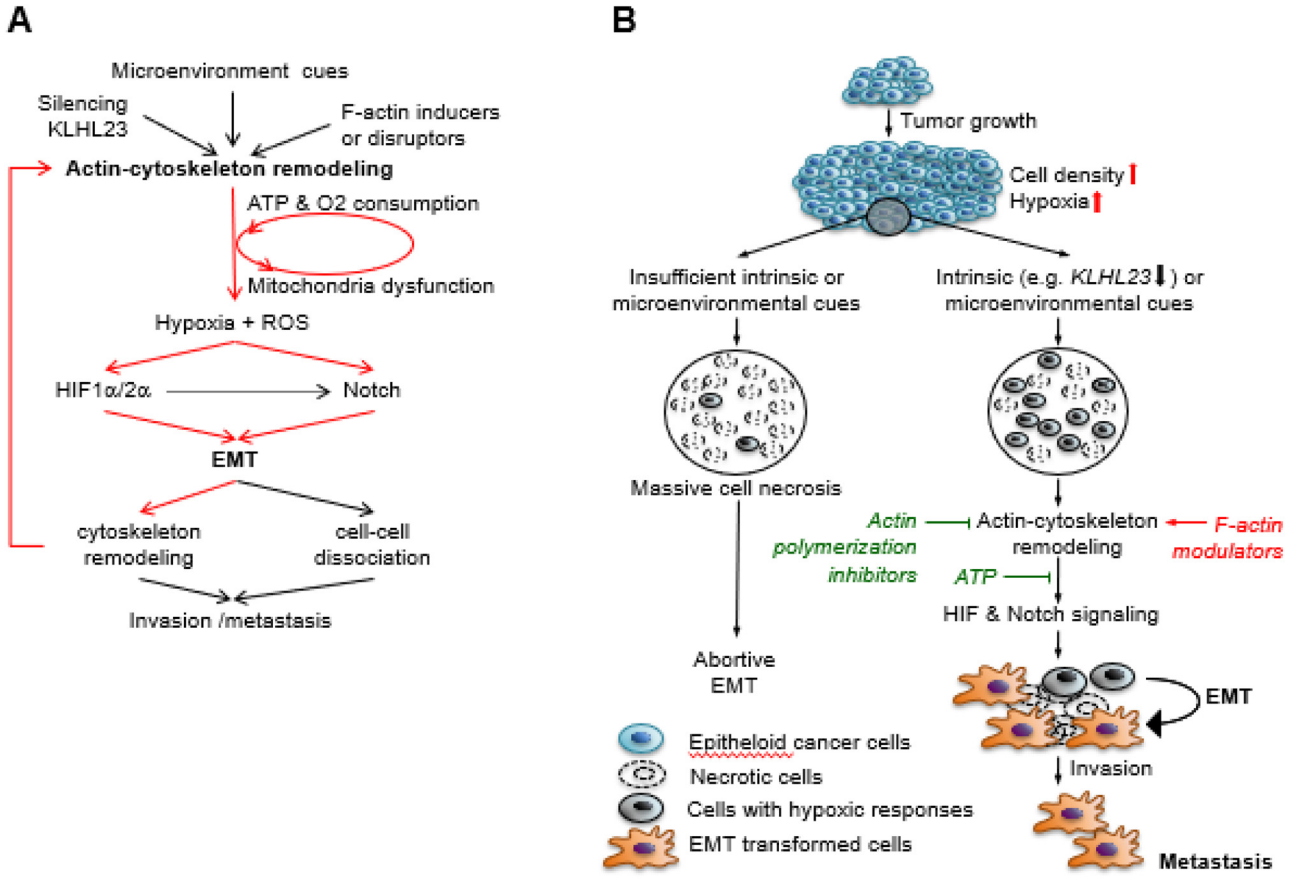


Figure: (abstract: SAT-158): **(A)** Induction of actin cytoskeleton remodeling by microenvironmental or intrinsic (such as *KLHL23* downregulation) cues drive HIF and Notch signal, thereby inducing EMT, invasion, and metastasis. (**B**) The crucial roles of actin cytoskeleton remodeling in orchestrating tumor cells

filopodium and lamellipodium formation. Traditionally, actin cytoskeleton remodeling is downstream of EMT reprogramming. It is, therefore, intriguing to ask why and how KLHL23, an actin modulator, inversely regulates EMT. Activation of actin cytoskeleton remodeling by either *KLHL23* silencing or treatment with actin cytoskeleton modulators augmented cellular hypoxic responses in a cell density-dependent manner resulting in HIF and Notch signals and subsequent EMT. Environmental hypoxia did not induce EMT unless actin cytoskeleton remodeling was simultaneously activated only were cells at high density. The EMT thus induced was reversed by either adenosine 5′-triphosphate supplementation or actin polymerization inhibitors. Correlations of tumor size with EMT and inverse association of the expression of KLHL23 with HIF-/Notch-signals were further validated in patient-derived xenograft HCCs in mice.
Conclusion: Simultaneously activation of actin cytoskeleton remodeling by intrinsic (such as *KLHL23* downregulation) or microenvironment cues is crucial for cell density-dependent, hypoxia-mediated EMT, providing a mechanistic link between large tumor size and invasion/metastasis. Our findings open a new door to development of prevention and treatment strategies for tumor invasion and metastasis.

SAT-159

The HDAC inhibitor belinostat enhances the anti-tumor efficacy of immune checkpoint inhibitors in a murine hepatocellular carcinoma model

D. Llopiz[1], M. Ruiz[1], L. Villanueva[1], T. Iglesias[1], J.J. Lasarte[1], P. Pivette[2], V. Trocon-Joseph[2], B. Vasseur[2], G. Dixon[2], B. Sangro[3], P. Sarobe[1].
[1]Centro de Investigación Médica Aplicada (CIMA), Universidad de Navarra, Pamplona, Spain; [2]Onxeo, Paris, France; [3]Clinica Universidad de Navarra-IDISNA and CIBEREHD, Liver Unit, Pamplona, Spain
Email: psarobe@unav.es

Background and Aims: Immune checkpoint inhibitors are currently being tested in different combinations in patients with advanced hepatocellular carcinoma (HCC). Nivolumab, an anti-PD-1 agent, has been approved in the US in the second line setting after Sorafenib. Epigenetic drugs have immune-mediated antitumor effects that may improve the activity of immunotherapy agents. Our aim was to study the therapeutic efficacy of checkpoint inhibitors (anti-CTLA-4 and anti-PD-1 antibodies) in combination with the histone deacetylase inhibitor Belinostat.
Method: Therapeutic efficacy and studies on antitumor immunity were performed in a subcutaneous Hepa129 murine hepatocellular carcinoma model that similar to human tumors have an infiltrate rich in CTLA-4+ regulatory T lymphocytes and effector PD-1+ T lymphocytes. Animals treated with Belinostat, an anti-PD-1 monoclonal antibody and an anti-CTLA-4 monoclonal antibody as monotherapy or in combinations as well as control animals receiving a non-immunostimulatory antibody were followed to monitor tumor growth and survival, or sacrificed at different days after treatment for obtaining tumor, spleen and blood samples for analysis.
Results: Belinostat improved the anti-tumor activity of anti-CTLA-4 but not the activity of anti-PD-1 therapy. This effect correlated with enhanced IFN-gamma production by antitumor T-cells and a decrease in regulatory T-cells. Moreover, the combination induced early upregulation of PD-L1 on tumor myeloid cells and late expression of PD-1 on tumor-infiltrating effector T-cells, suggesting the convenience of PD-1 blockade. Indeed, Belinostat combined with the simultaneous blockade of CTLA-4 and PD-1 led to complete tumor rejection in treated animals.
Conclusion: These results provide a rationale for testing Belinostat in combination with checkpoint inhibitors in order to enhance their therapeutic activity in patients with HCC.

SAT-160

Blocking the CDK1/PDK1/B-Catenin signaling by CDK1 inhibitor RO3306 increased the efficacy of sorafenib treatment with targeting cancer stem cell in preclinical model of hepatocellular carcinoma

C. Wu, X. Wang. *The University of Hong Kong, Center for Cancer Research and Department of Surgery, Hong Kong*
Email: u3003812@hku.hk

Background and Aims: Cyclin-dependent kinase 1 (CDK1) is the key regulator in promoting cell division whose role can't be substituted by any other CDKs. Sorafenib the only approved target therapy for advanced HCC treatment provides limited survival benefits till today. Here we aim to determine the efficacy of CDK1 inhibitor RO3306 alone or combination with sorafenib in the preclinical tumor models of hepatocellular carcinoma.
Method: The clinicopathological parameters CDK1 expression with HCC overall survival and CDK1 related PDK1 with disease-free survival were analyzed. Three HCC patients-derived xenograft tumor models were treated with RO3306 (4 mg/kg), sorafenib (30 mg/kg) alone or combination for one month. The relevant signaling CDK1/PDK1/β-Catenin was measured by western blot. The colony formation, single cell sphere formation and tumorigenicity assay were used for liver cancer stem cells (CSCs). Silencing CDK1 with shRNA and corresponding inhibitors for mechanism and related functional studies.
Results: We reported that CDK1 was frequently augment accounted up to 50% (21/42) of hepatocellular carcinoma (HCC) tissues, which was significantly associated with poor overall survival ($p = 0.008$). Moreover, the CDK1 and PDK1 association shows worse disease-free survival ($p = 0.03$). CDK1 inhibitor RO3306 in combination with sorafenib treatment significantly decreased tumor growth in patients-derived xenograft (PDX) tumor models. Western blot results demonstrated that combined administration resulted in synergistic decreased the pluripotency protein levels of Oct4, Sox2 and Nanog as well as concurrently down-regulating CDK1, PDK1 and β-Catenin. Furthermore, downregulation CDK1/PDK1/ β-Catenin associated with suppressing the process of epithelial mesenchymal transition (EMT) revealed with the downregulation of Snail1 and Snail2 while upregulation of E-Cadherin, which may show synergistic antimetastasis potential in combination treatment. Based on the evidences, we further verified that pharmaceutical combinatorial inhibition dramatically decreased CSCs single cell sphere formation and colony formation. Synergistic down-regulated AKT and pStat3 activation with enhancing suppression on tumorigenicity in vivo. In addition, low dose of RO3306 (2 uM) and sorafenib (2.5 uM) combination could inhibit CSCs growth via decreasing the S phase and promoting cell to enter into a pseudo-G1 phase with 4N DNA. Mechanism with functional study of silencing CDK1 with shRNA and RO3306 combined sorafenib both abolished its oncogenic function via the down-regulation of CDK1, with the downstream PDK1 and β-Catenin inactivation.
Conclusion: Anti-CDK1 treatment can boost sorafenib antitumor responses in PDX tumor models, providing the rational combined treatment to increase sorafenib efficacy in clinical.

SAT-161

Obeticholic acid, a FXR agonist, inhibits the cancerogenic potential of primary human cholangiocarcinoma (CCA) cells cultures

S.D. Matteo[1], L. Nevi[1], D. Constantini[1], M. Colantonio[1], F. Giulitti[2], C. Napoletano[3], S. Safarikia[1], E. Manzi[4], A.M.D. Rose[5], F. Melandro[6], M. Bragazzi[7], P.B. Berloco[6], F. Giuliante[5], G. Carpino[8], V. Cardinale[7], E. Gaudio[9], D. Alvaro[1]. *[1]Sapienza University of Rome, Department of Internal Medicine and Medical Specialties, Italy; [2]Sapienza University of Rome, DAHFMO Department, Italy; [3]Sapienza University of Rome, Department of Experimental Medicine, Italy; [4]Regina Elena National Cancer Institute, Gastroenterology Unit, Italy; [5]Catholic University of the*

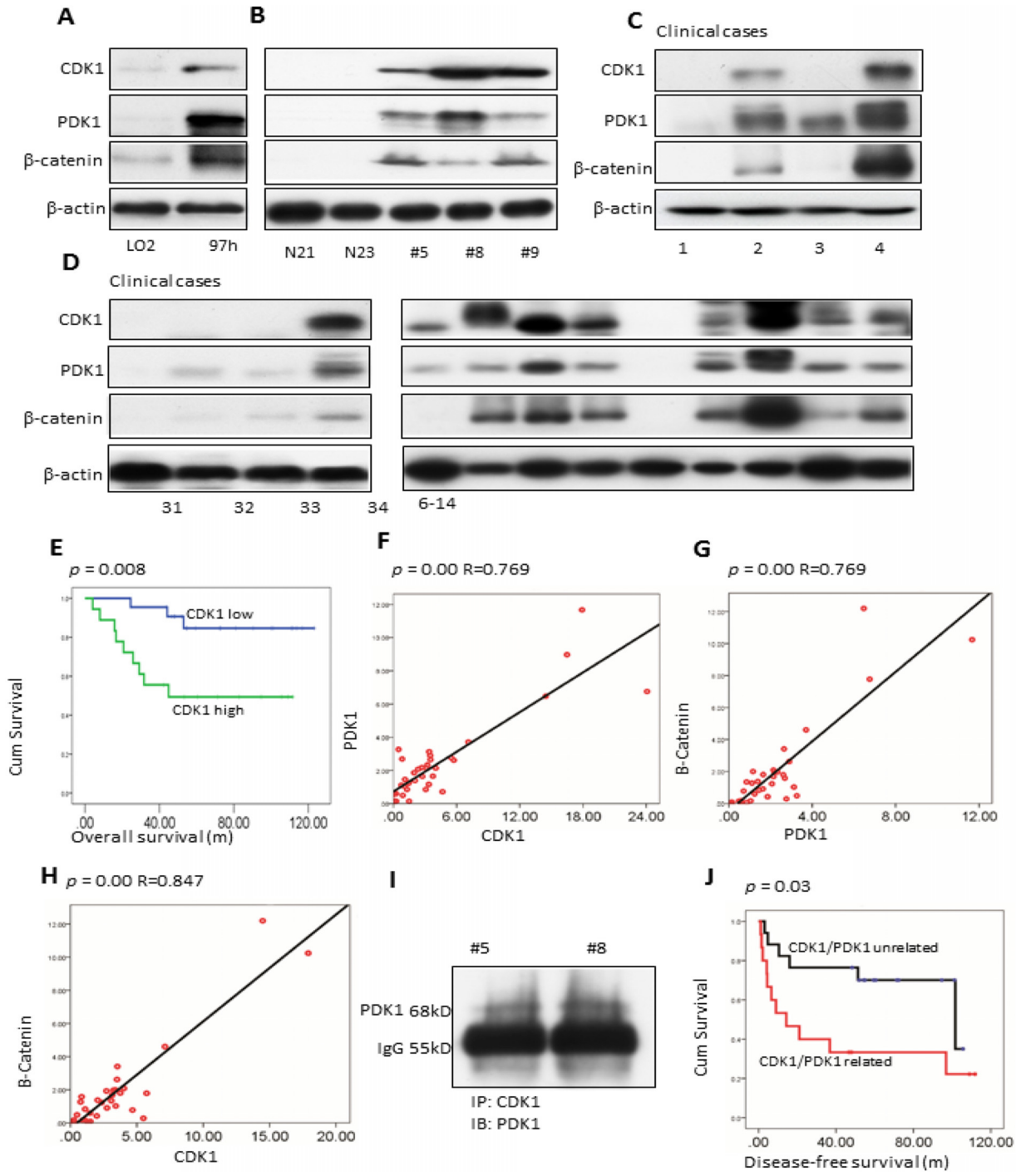


Figure: (abstract SAT-160)

Sacred Heart School of Medicine, Hepatobiliary Unit, Italy; [6]Sapienza University of Rome, Department of General Surgery and Organ Transplantation, Italy; [7]Sapienza University of Rome, Medico-surgical sciences and Biotechnologies, Italy; [8]University of Rome "Foro Italico", Department of Movement, Human and Health Sciences, Division of Health Sciences, Italy; [9]Sapienza University of Rome, Division of Human Anatomy, Department of Anatomical, Histological, Forensic Medicine and Orthopedics Sciences, Italy
Email: sabina.dimatteo@uniroma1.it

Background and Aims: Cholangiocarcinoma is an aggressive cancer, resistant to chemotherapeutics. We demonstrated that CCA is enriched of cancer stem cells associated with aggressiveness and drug resistance. FXR, involved in neoplastic transformation of stem cells and/or cholangiocytes, is down-regulated in human CCA. Our AIM was to evaluate, in primary cultures of human intrahepatic CCA (iCCA) the effects of the FXR agonist, obeticholic acid (OCA), on the cancerogenic potential of human CCA cells.

Method: Primary human cell cultures were prepared from specimens of iCCA obtained from patients submitted to surgical resection and classified into mucin- or mixed-iCCA subtypes by morphologic and immunohistochemical criteria. Increasing concentrations (0–5 μM) of OCA were added to culture media and, after 3–10 days, the effect on

proliferation (MTS assay, cell population doubling time), apoptosis (annexin V-FITC / propidium iodide), cell migration and invasion (wound healing and matrigel invasion assay) and cancerogenic potential (spheroid formation, clonogenic assay, colony formation capacity) were evaluated.
Results: FXR was downregulated (RT-qPCR) in iCCA cells vs normal human biliary tree stem cells ($p < 0.001$) and in mucin-iCCA vs mixed-iCCA ($p < 0.05$). OCA significantly ($p < 0.05$) inhibited proliferation of both mucin-iCCA and mixed-iCCA cells starting at a concentration as low as 0.05 μM (IC_{50} = 0.38 μM in mixed- and 2.1 μM in mucin-iCCA). Also CDCA (but not UDCA) inhibited cell proliferation, although to a much lower extent than OCA, consistent with the different potency in FXR activation (i.e. OCA > CDCA, no agonistic effect for UDCA). OCA significantly induced apoptosis of both iCCA subtypes and decreased the *in vitro* cancerogenic potential of iCCA cells as evaluated by impairment of colony and spheroid formation capacity and delayed wound healing and matrigel invasion. In general, these effects were more evident against mixed- than mucin-iCCA cell. When tested together with gemcitabine and cisplatin, OCA potentiated the anti-proliferative and pro-apoptotic effects of these chemotherapeutics but mainly on mixed-iCCA. OCA abolished the capacity of both mucin- and mixed-iCCA cells to form colonies when administered together with gemcitabine and cisplatin.

SAT-162

Sensitization of cholangiocarcinoma to chemotherapy by SOX17-induced down-regulation of drug export pumps ABCC3 and AGCG2

E. Lozano[1], O. Briz[1], M. Asensio[1], L. Perez-Silva[1], M. Monte[1], M. Perez[2], E. Herraez[1], M. Romero[2], M. Serrano[2], R. Macias[1], L. Bujanda[3], J. Banales[3], J. Marin[1]. *[1]University of Salamanca, IBSAL, CIBERehd, Physiology and Pharmacology, Salamanca, Spain; [2]University of Salamanca, IBSAL, CIBERehd, Biochemistry and Molecular Biology, Salamanca, Spain; [3]Biodonostia Biomedical Research Institute, Department of Hepatology and Gastroenterology, San Sebastian, Spain*
Email: jjgmarin@usal.es

Background and Aims: An important limitation for favorable cholangiocarcinoma (CCA) outcome is its poor response to chemotherapy. Among mechanisms of chemoresistance (MOC) involved, a reduced intracellular concentration of anticancer drugs due to active drug export through ATP-binding cassette (ABC) proteins, such as ABCG2 and ABCC3, plays an important role. SOX17, a transcription factor that inhibits Wnt/β-catenin pathway, has been reported to be downregulated in CCA. Restoration of SOX17 expression in CCA cells results in tumor suppression. Here we have investigated whether viral vector-mediated SOX17 over-expression may be also beneficial by sensitizing CCA to chemotherapy.
Method: Viral vectors containing SOX17 ORF were generated to transduce CCA cells (EGI-1 and TFK-1). Cell viability in response to incubation with commonly used anti-CCA drugs was determined by MTT test. Taqman Low Density Arrays were designed to measure mRNA abundance of ≈100 genes involved in several MOCs. Single RT-qPCR, WB and IF were used to evaluate gene/protein expression. ABC pumps activity of was determined by flow cytometry using specific inhibitors and fluorescent substrates. Firefly luciferase (Luc2) was fused to ABC promoters to carry out promoter-reporter assays. Mouse xenograft model was used for *in vivo* evaluation of chemotherapy efficacy.
Results: SOX17 overexpression selectively enhanced the cytostatic response of CCA cells to SN-38, 5-FU and mitoxantrone, but not to gemcitabine or cisplatin. The magnitude of chemosensitization was dependent on SOX17 expression levels. The analysis of changes in MOC gene expression profile revealed that SOX17 overexpression affected several of these genes, mainly those encoding ABC proteins. Thus, a significant reduction in *ABCC3/ABCG2* expression was found. Interference with ABC gene promoter activity seems to be involved in the mechanism of SOX17-induced *ABCC3/ABCG2* downregulation. Functional studies supported a reduced ability of SOX17-overexpressing CCA cells to export specific substrates of these pumps. Moreover, combined ABCG2/ABCC3 substrate specificity matched the observed selective chemosensitization. SOX17-induced better response to ABCG2/ABCC3 substrates was confirmed by *in vivo* experiments.
Conclusion: In addition to the tumor suppression effect of SOX17, its over-expression induces selective chemosensitization due to down-regulation of some ABC proteins, which reduces the ability of CCA cells to export anticancer drugs.

SAT-163

Defective NKp30-mediated function in hepatocellular carcinoma-infiltrating NK cells

S. Mantovani[1], B. Oliviero[2], D. Mele[2], A. Sangiovanni[3], M. Donadon[4], G. Torzilli[4], C. Soldani[4], C. Porta[5], S. Chiellino[5], R. Santambrogio[6], E. Opocher[6], M.U. Mondelli[7]. *[1]Fondazione IRCCS Policlinico San Matteo, Division of Infectious Diseases and Immunology, Department of Medical Sciences and Infectious Diseases, PAVIA, Italy; [2]Fondazione IRCCS Policlinico San Matteo, Division of Infectious Diseases and Immunology Department of Medical Sciences and Infectious Diseases, Pavia, Italy; [3]Fondazione IRCCS Ca' Granda Policlinico Hospital, University of Milan, A.M. & A. Migliavacca Center for Liver Disease, Division of Gastroenterology and Hepatology, Milano, Italy; [4]Humanitas University, Humanitas Research Hospital IRCCS, Department of Hepatobiliary and General Surgery, Rozzano, Italy; [5]Fondazione IRCCS Policlinico San Matteo, Medical Oncology, Pavia, Italy; [6]San Paolo Hospital, University of Milan School of Medicine, Chirurgia 2, Epato-bilio-pancreatica e Digestiva, Milano, Italy; [7]Fondazione IRCCS Policlinico San Matteo, University of Pavia, Division of Infectious Diseases and Immunology, Department of Medical Sciences and Infectious Diseases and Department of Internal Medicine and Therapeutics, Pavia, Italy*
Email: mario.mondelli@unipv.it

Background and Aims: Natural killer (NK) cells play a significant role in innate immune responses to cancer cells, their action being regulated by several activating and inhibitory receptors. The natural cytotoxicity receptor NKp30/NCR is critical for NK cell function. The NCR3 gene is transcribed into three major isoforms that have different biological functions. The expression levels of NKp30 isoforms can negatively impact on the prognosis and evolution of different malignancies and might be associated with advanced liver disease in HCV-infected patients. Current evidence indicates that malignant cells bypass the NK surveillance by releasing the NKp30 ligand B7H6 as soluble proteins that block NKp30 activity, suggesting that this may be an immune escape mechanism of tumor cells from NK cell-mediated killing.
We investigated the NKp30-B7H6 axis in patients with hepatocellular carcinoma (HCC).
Method: *Ex-vivo* isolated PBMC, non-tumor liver-infiltrating lymphocytes (LIL) and tumor-infiltrating lymphocytes (TIL) were examined by flow cytometry. Serum concentration of soluble B7-H6 was measured by ELISA. Expression of the three major NKp30 isoforms was analyzed by quantitative real-time PCR in PBMC, LIL and matched TIL of HCC patients and healthy controls (HC).
Results: The frequency of NKp30-expressing peripheral NK cells and the intensity of its expression were significantly lower in patients with HCC compared to HC. In contrast, NKp30-expressing NK cells were enriched in the neoplastic tissue of HCC patients compared to the non-tumorous surrounding liver. Peripheral and tumor-infiltrating NKp30-expressing NK cells showed defective degranulation capacity and cytokine release after NKp30 triggering, and had altered expression of NKp30 splice variants. Serum levels of the soluble form of B7H6 ligand were increased in HCC patients, particularly those with intermediate and advanced tumors, classified according to Barcelona Clinic for Liver Cancer (BCLC) staging classification, as compared to early stage tumors. Moreover, statistically significant positive correlations were found between sB7H6 levels and HCC nodule size and serum alpha fetoprotein values.

Conclusion: These findings provide evidence in support of a role of NKp30 and its major ligand in HCC development and evolution.

SAT-164

Cost-effective target sequencing panel for hepatocellular carcinoma mutational screening

V. Paradiso[1], A. Garofoli[1], N. Tosti[1], V. Perrina[1], M. Lanzafame[1], L. Quagliata[1], M. Matter[1], S. Wieland[2], M. Heim[2,3], S. Piscuoglio[1], C. Ng[1], L.M. Terracciano[4]. *[1]University Hospital Basel, Institute of Pathology, Basel, Switzerland; [2]University of Basel, Department of Biomedicine, Basel, Switzerland; [3]University Hospital Basel, Division of Gastroenterology and Hepatology, University Hospital Basel, University of Basel, Basel, Switzerland; [4]Institute of Pathology, Molecular Pathology Division, Basel, Switzerland*
Email: luigi.terracciano@usb.ch

Background and Aims: Commercially available targeted or exome panels miss some genes and regions frequently mutated in hepatocellular carcinoma (HCC). We aim to design and benchmark a targeted sequencing panel specific for mutational profiling for HCC.
Method: We designed a custom Ion AmpliSeq panel targeting all exons of 33 protein-coding and 2 long non-coding RNA genes frequently mutated in HCC, *TERT* promoter. We profiled DNA from fresh frozen tumor (FFT, n = 10, median depth 1495x) and/or formalin-fixed paraffin-embedded (FFPE) tumor with low input DNA (n = 36, median depth 530x), and their non-tumoral counterparts from 39 HCCs using the custom panel. We benchmarked the somatic mutations identified against those from Illumina whole-exome sequencing (WES) of the equivalent FFT samples (median depth 112x).
Results: At least one somatic mutation was identified in 35/39 cases using the custom panel. Median of 2.5 (0–74) and 3 (0–76) mutations were identified in FFT and FFPE samples, respectively. 98% (61/62) of the mutations identified from WES of the 10 FFT samples were successfully recovered using the custom panel, with the identification of an additional 6 and 32 mutations in coding and non-coding regions, respectively. Similarly, all 104 mutations identified from WES were also found based on the analysis of our custom panel of the 36 FFPE biopsies. We identified an additional 18 and 70 somatic mutations in coding and non-coding genes, respectively, using our custom panel, including 2 CTNNB1 activating mutations.
Conclusion: We have established a sequencing assay for the sensitive detection of somatic mutations in HCC-associated driver genes.

SAT-165

Lack of Osteopontin promotes non-alcoholic steatohepatitis (NASH) and fibrosis, but protects against hepatocellular carcinoma (HCC) progression and mortality in a NASH-HCC mouse model

A.D. Nardo[1], N.G. Grün[1], M. Zeyda[1], G. Oberhuber[2], M. Dumanic[3], T. Helbich[3,4], T.M. Stulnig[1]. *[1]Medical University of Vienna, Christian Doppler Laboratory for Cardio-Metabolic Immunotherapy and Clinical Division of Endocrinology and Metabolism, Department of Medicine III, Wien, Austria; [2]General Hospital of Innsbruck, Department of Pathology, Innsbruck, Austria; [3]Medical University of Vienna, Department of Biomedical Imaging and Image-guided Therapy, Division of Nuclear Medicine, Wien, Austria; [4]Medical University of Vienna, Division of Molecular and Gender Imaging, Wien, Austria*
Email: alexander.nardo@meduniwien.ac.at

Background and Aims: Osteopontin (OPN, gene *Spp1*), a multifunctional protein and inflammatory cytokine, has been proposed to play a pivotal role in many pathophysiological events related to metabolic syndrome and carcinogenesis. OPN is overexpressed in adipose tissue and liver during obesity and concurs in the induction of adipose tissue inflammation and non-alcoholic fatty liver (NAFL). Studies performed in both mice and humans demonstrated a putative role for OPN in malignant transformation and tumor growth, including hepatocellular carcinoma (HCC). Metabolic syndrome is nowadays recognized as an important risk factor for HCC. In order to fully understand the role of OPN on the development of HCC in NAFL, we reproduced in our laboratories a recently published NASH-HCC mouse model called STAM on a both wild type (WT) and OPN deficient (*Spp1*–/–) background, and evaluated its properties in non-alcoholic steatohepatitis (NASH), fibrosis and HCC.
Method: Two-days-old WT and *Spp1*–/– mice received a low-dose streptozotocin (STZ) injection in order to induce diabetes and were fed a high-fat diet (HFD) starting from week 4. Different cohorts of

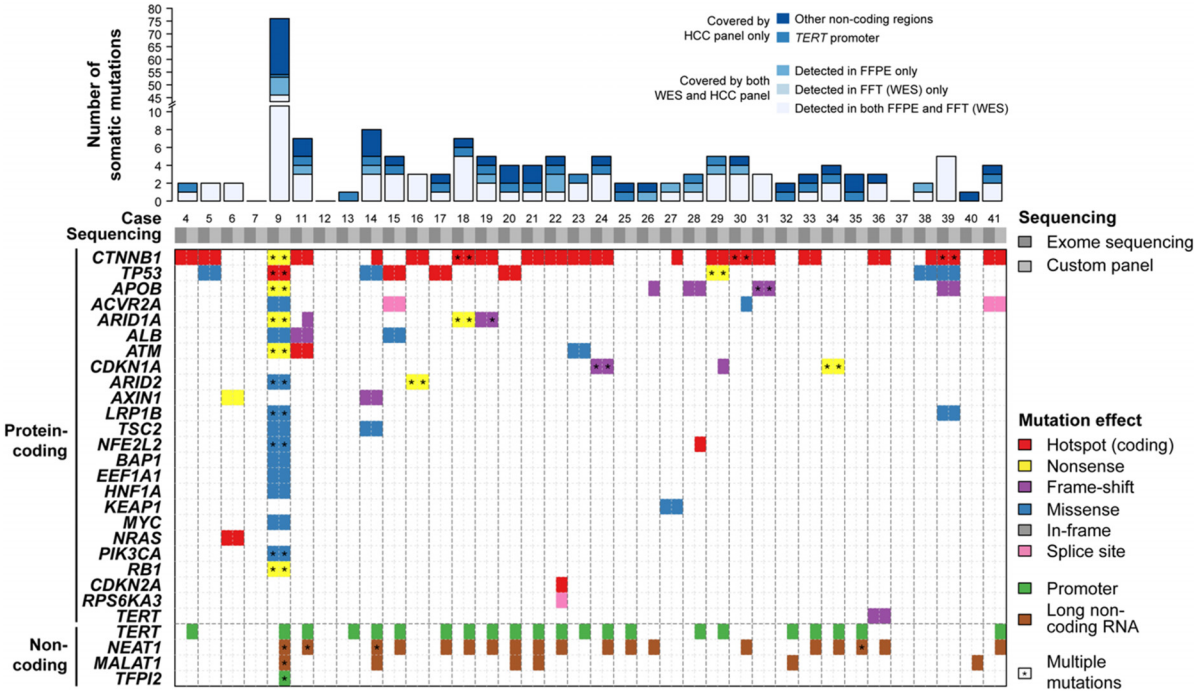


Figure: (abstract SAT-164)

mice of both genotypes were sacrificed at 8, 12 and 19 weeks of age in order to evaluate the NASH, fibrosis and HCC phenotypes, respectively.
Results: Lack of osteopontin prevented HCC progression to less differentiated tumors and improved overall survival rate while enhancing the development of well-differentiated liver tumors. On the other hand, *Spp1*–/– mice developed a stronger fibrosis due to increased hepatocellular apoptosis. OPN-deficient mice also showed an aggravated NASH due to increased *CD36*-mediated lipid uptake. The worse steatotic and fibrotic phenotypes observed in *Spp1*–/– mice were probably a consequence of overall improved metabolic condition.
Conclusion: In a model of metabolic syndrome, the lack of OPN improved overall outcomes but worsened hepatic inflammation and fibrosis. OPN appears necessary for dedifferentiation of HCCs.

SAT-166

Canonical inhibition of Transforming Growth Factor β Receptor 1 triggers proliferation of hepatocellular carcinoma andis associated with Toll like Receptor 7 upregulation

F. Mohamed[1], S. Hammad[2], S. Dooley[3]. [1]*Faculty of medicine, Department of Pathology, El Minia, Egypt;* [2]*Faculty of Veterinary Medicine, Department of Forensic Medicine and Veterinary Toxicology, Qena, Egypt;* [3]*Molecular Hepatology Section, Department of Medicine II, Mannheim, Germany*
Email: fatma.mohamed@medma.uni-heidelberg.de

Background and Aims: Our previous work showed that hepatocellular carcinoma (HCC) proliferation can be modulated by Toll Like Receptor (TLR) 7 and 9. A crosstalk between TLR and TGF-β signaling was reported previously in liver fibrosis, suggesting a possible link between them in HCC.
Our aim is to address (i) expression of TGF-βR1 (ALK5) and TLR7 in human HCC, (ii) investigate the impact of their pathways modulation on HCC proliferation in mouse model and HuH7 cell line, (iii) determine whether inhibition of the TGF-βR1 pathway can modulate TLR activity and in turn HCC proliferation.
Method: Human HCC sections were stained for TLR7 and TGF-βR1 (ALK5) using immunohistochemistry. In addition to TLR7 and TGF-βR1, pSmad2 and Ki-67 immunostaining was performed on tissue obtained from a steatohepatitis-based HCC mouse model. HuH7 cells were treated for 48 hours with imiquimod (5 µg/ml, TLR7 agonist), chloroquine (20 µM/ml, inhibitor for TLR7), siRNA targeting TLR7, 25 pmols, TGF-β1 cytokine (5 ng/ml) and LY2157299 (10 ng/ml, ALK5 inhibitor), in order to detect the effect of TLR7 and TGF-βR1 modulation on cellular proliferation using MTS assays. The expression level of TLR7 upon ALK5 stimulation and inhibition was examined on protein and mRNA levels and correlated to PCNA expression, as measured by immunoblot.
Results: TLR7 is overexpressed in the majority of HCC sections with perinuclear localization in malignant hepatocyte. ALK5 is absent in HCC, but expressed in the cytoplasm of hepatocytes in the cirrhotic surroundings of the corresponding tumor. In mice HCC, TLR7 and ALK5 expression are inversely correlated in the HCC nodules as compared to non-tumoral areas. TLR7 expression is positively correlated with the proliferative index (Ki-67). High levels of ALK5 and pSmad2 are present in fibrotic livers and dysplastic nodules and negative in HCC. Localization of pSmad2 positive signals in HCC is perinuclear instead of nuclear. Proliferation of HuH7 cells is significantly associated with TLR7 stimulation (imiquimod) and ALK5 inhibition (Ly2157299), whereas silencing or inhibiting TLR7 is cytostatic. This result is confirmed at the protein level of PCNA. Importantly, TLR7 expression is increased upon LY2157299 treatment, both at mRNA and protein level.
Conclusion: Targeting ALK5 and TLR7 signaling can be used to modulate HCC proliferation. Although LY2157299 is now in clinical trial for HCC, TLR7 expression must be taken into consideration and careful therapy tailoring is required.

SAT-167

S100a11 is part of a whole network of tumor suppressors and oncogenes deregulatedearly with hepatic steatosis and contributing to hepatocellular carcinoma development

C. Sobolewski[1], A. Daniel[2], F. Berthou[1], N. Calo[1], C. Sempoux[3], A.-S. Ay[1], P. Clavien[4], H. Bostjan[4], J.-F. Dufour[5], A. Alexander[2], M. Foti[1]. [1]*University of Geneva, Faculty of Medicine, Dept of Cell Physiology and Metabolism, Geneva, Switzerland;* [2]*University of Geneva, Faculty of Sciences, Dept of Organic Chemistry, Geneva, Switzerland;* [3]*Lausanne University Hospital, Pathology, Lausanne, Switzerland;* [4]*University Hospital Zurich, Dept of Surgery, Zurich, Switzerland;* [5]*University of Berne, Hepatology, Dept of Clinical Research, Berne, Switzerland*
Email: daniel.abegg@unige.ch

Background and Aims: Hepatocellular carcinoma (HCC) develops frequently in the context of fatty liver disease (FLD) with distinct etiologies. Genetic mutations of tumor suppressor (TS) and oncogenes (ONC) have been widely characterized in HCC. However, increasing evidence indicate that deregulations of the activity/expression of TS/ONCs may also occur with FLD independently of specific mutations. This study aimed at uncovering and characterizing major TS and ONC deregulated at early stages of FLD and potentially fostering hepatocarcinogenesis.
Method: Hepatic tissues from a mouse model of FLD spontaneously progressing towards the development of HCC (hepatocyte-specific PTEN knockout, LPTENKO mice) were used to identify through unbiased LC-MS/MS spectrometry, deregulations of TS and ONC occurring with steatosis. Expression of TS/ONC identified by mass spectrometry were then investigated in hepatic tissues of various mouse models of FLD, in mouse/human cancer cells and in HCC Human Tissue Microarrays. S100A11 functions in carcinogenesis were examined *in vitro* using human HepG2 cells.
Results: Proteomic analyses of steatotic hepatic tissues from LPTENKO mice identified a network of more than 30 TS/ONC respectively down- or up- regulated in early stages of FLD. Alterations of these TS/ONC expression were further confirmed in various diet-induced and genetic mouse models of hepatic steatosis and were found to be present also in genetically- and carcinogen-induced HCC in mice. Among these TS/ONC, S100A11 was upregulated with hepatic steatosis and further increased in mouse HCC. The relevance of S100A11 overexpression was further confirmed in human hepatic cancer cells, as well as in human HCC tissues, where it correlates in particular with HCC grade III. Finally, *in vitro* analyses showed that inhibition of S100A11 expression in hepatic cancer cells leads to decreased cell proliferation, upregulation of cell cycle inhibitors, induction of cell death, as well as inhibition of cell migration and invasion.
Conclusion: Our findings indicate that deregulation of a whole network of TS/ONCs, which may foster hepatocarcinogenesis, occurs early with steatosis. Among this deregulated network of cancer-related factors, S100a11 has relevant oncogenic functions in HCC and might represent both a target and a risk factor biomarker for high grade HCC development.

SAT-168

Low density neutrophils, as immunosuppressant, increased in HCC patients, highly correlated with advanced stage, predicted stage I HCC recurrence and all patients' survival

C.-H. Huang[1,2], C.-Y. Lin[1,3], T.-H. Wu[1], R.W.-J. Jeng[1,3], S.-K. Shih[1], Y.-C. Hsieh[1], W. Teng[1], Y.-C. Chen[1,4], C.-C. Lin[1], S.-M. Lin[1], I.-S. Sheen[1,4], Y.-C. Lin[5]. [1]*Chang-Gung Memorial Hospital, Linkou Medical Center, Taiwan, Division of Hepatology, Department of Gastroenterology and Hepatology, Taiwan;* [2]*College of Medicine, Chang-Gung University, Graduate Institute of Clinical Medical Sciences, Taiwan;* [3]*Chang-Gung University, College of Medicine, Taiwan, Taiwan;* [4]*Chang-Gung University, College of Medicine, Taiwan, Taiwan;* [5]*Division of Oncology, Chang-Gung Memorial Hospital, Linkou Medical Center, Taiwan*
Email: chunyenlin@gmail.com

Background and Aims: Hepatocellular carcinoma (HCC) is the second most common cause of cancer related deaths in the world. Current curative HCC treatments including surgical resection and liver transplantation are feasible only for less than 30% of patients due to poor liver function or advanced stage at diagnosis. Thus, new HCC therapeutic strategies are warranted. Recently, a subset of low-density neutrophils (LDNs) had been proposed that appear transiently in self-resolving inflammation but accumulate continuously with cancer progression. Their neutrophil extracellular trap (NET) was found to help metastasis in several cancers. Therefore, to investigate the role of LDN in HCC is intriguing.
Method: Peripheral blood was collected from normal controls (NC) and HCC patients (TNM stage I to IV) with Child-pugh class A status. HCC tissues were acquired during liver tumor resection. LDNs were collected from the peripheral blood mononuclear cells (PBMCs) layer after Ficoll–Hypaque density gradient centrifugation then isolated by flow cytometric methods as $CD15^{+}CD45^{+}$ neutrophils.
Results: 14 NC and 170 HCC patients were enrolled in this study. LDN percentage in PBMC increased in HCC patients when compared with normal controls (Figure 1A). The percentage of LDNs in HCC tumor tissue was also higher than that in the corresponding peripheral blood (Figure 1B). HCC patients had increased percentage of Arg-1 + LDN in their PBMC compared to that in NC (Figure 2A). They also showed decreased expressions of pro-inflammatory (anti-apoptotic) receptor TNFR2 ((Figure 2B) and higher PD-1 expressions only after PMA stimulation (Figure 2C) when comparing to NC. The phagocytosis abilities for LDN were decreased as compared to HDN in HCC patients (Figure 3). LDN also showed dose-dependent CD8 + Tcell suppression when adding to PBMC as compared to LDN-depleted PBMC control (Figure 4). They also showed decreased killing to K562 leukemia cells (Figure 5) as compared to HDN counterpart.

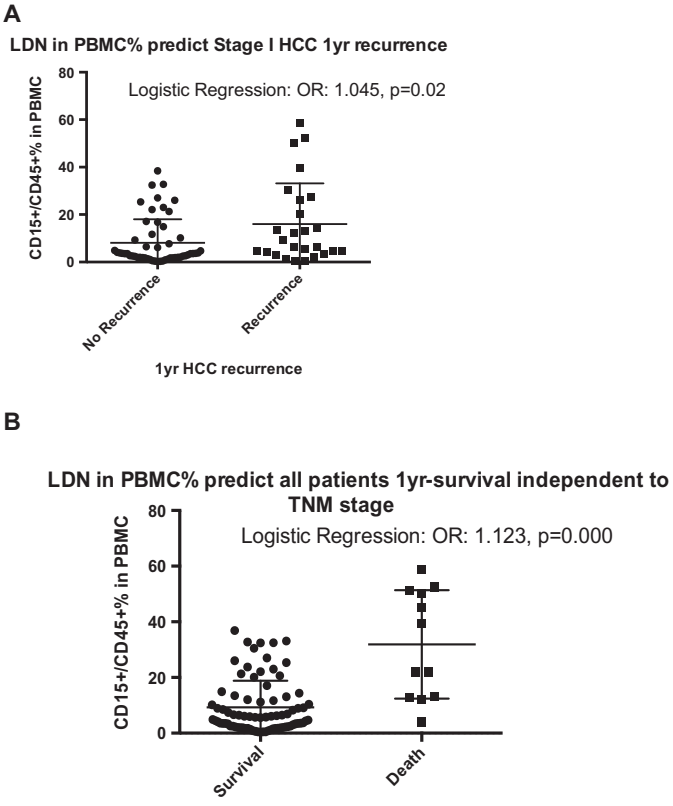


Figure 1: Predictions of 1-year recurrence in stage I HCC patients and survival in all HCC patients

As for clinical significance, LDN% in PBMC correlated with TNM staging (Figure 6). LDN% in PBMC could also predict one-year tumor recurrence in stage I HCC patients (Figure 7A) and 1-year survival in all HCC patients (Figure 7B).
Conclusion: Low-density neutrophils increased in PBMC of HCC patients, accumulated in tumor tissue and were highly correlated with tumor stage. These LDN exhibit the immunosuppressant phenotype with inhibition of CD8 + T cell proliferation, decease phagocytosis and tumor-killing ability. In addition, the percentage of LDNs could predict 1-year recurrence in stage I HCC patients and survival in all HCC patients.

SAT-169

Chemosensitizing effects of beta-caryophyllene oxide in liver cancer

S.D. Giacomo[1], L. Sanchez-Vicente[2], A.D. Sotto[1], M. Monte[2], L. Abete[1], G. Mazzanti[1], J. Marin[2], O. Briz[2]. [1]*Sapienza University of Rome, Dept. Physiology and Pharmacology "Vittorio Erspamer", Rome, Italy;* [2]*University of Salamanca, IBSAL, CIBERehd Dept. Physiology and Pharmacology, Salamanca, Spain*
Email: silvia.digiacomo@uniroma1.it

Background and Aims: Hepatocellular carcinoma (HCC) is the fifth most frequent malignant tumor, and the third leading cause of cancer-related mortality in the world. Sorafenib is the only drug available for this condition, even if its efficacy is modest due in part to the overexpression of ATP-binding cassette (ABC) proteins. The potential use of ABC-transporter inhibitors (chemosensitizers) in association with cytotoxic drugs represents a new approach to overcome multidrug resistance (MDR). In this context, the present study was aimed at evaluating the ability of the sesquiterpene ß-caryophyllene oxide (CRYO) to act as a chemosensitizer in HCC.
Method: Human HCC PLC/PRF/5 cells, both wild-type (WT) and chemoresistant (R), overexpressing MDR1, MRP1, MRP2, MRP4 and MRP5, mouse hepatoma Hepa 1–6 R cells, overexpressing MRP1 and MRP2, and human lung carcinoma COR-L23 cells, overexpressing MDR1 and MRP1, have been used as *in vitro* models. As a first step, the cytotoxicity of sorafenib and CRYO alone or in combination was evaluated by MTT assay in all cell lines. Then, the inhibition by CRYO of ABC transport function was measured by efflux assay using fluorescent substrates. The actual change in sorafenib cell content, as a result of the combined treatment with CRYO, was measured by HPLC-MS/MS. Finally, the potential chemosensitizing effect of CRYO in combination with sorafenib was investigated using the mouse xenograft model.
Results: Cytotoxicity evaluation *in vitro* revealed a lack of CRYO cytotoxicity up to the concentration of 100 μM together with different sensitivity of PLC/PRF/5 cells to sorafenib. Thus, PLC/PRF/5 WT showed a 3-fold higher sensitivity to sorafenib than R cells. In combination experiments, CRYO (50 μM) significantly increased sorafenib (10 μM) cytotoxicity by + 19% and + 35% in the PLC/PRF/5 WT and R cells, respectively. Hepa 1–6 R and COR-L23 R cells were also affected by chemosensitizing combination: sorafenib cytotoxicity was increased by + 40% and + 29%, respectively. In efflux experiments, CRYO inhibited MDR1 and MRP1/2 function by −75% and −81%, respectively, while no significant effect on MRP3, MRP4, and MRP5 function was found. CRYO was also able to increase sorafenib content by + 62% in PLC/PRF/5 R cells. Regarding *in vivo* experiments, the implant of Hepa 1–6 R cells resulted in the formation of tumors with a final volume (FTV) of 6.6 ± 0.3 cm^3. Interestingly, while the treatment with sorafenib was not able to inhibit tumor growth, its combination with CRYO determined an inhibition of tumor growth by −58% (FTV = 2.8 ± 0.6 cm^3).
Conclusion: Present results support the potential pharmacological interest of CRYO as a new chemosensitizing agent to be used in combination with sorafenib to overcome MDR phenotype in HCC. The combined treatment of CRYO with sorafenib is expected to increase the effectivity of this drug at lower doses and hence reduce the adverse effects of chemotherapy.

SAT-170

Application of patient-derived liver cancer cells for personalized treatment approach: from phenotypic characterization to therapeutic target identification

D. Castven[1], D. Becker[1], C. Czauderna[1], D. Wilhelm[1], J. Andersen[2], S. Strand[1], S. Heilmann-Heimbach[3], W. Roth[4], N. Hartmann[4], B. Straub[4], F. Mahn[1], S. Franck[1], S. Pereira[1], M. Hartmann[1], A. Haupts[4], A. Vogel[5], M.-A. Wörns[1], A. Weinmann[1], S. Heinrich[6], H. Lang[6], S. Thorgeirsson[7], P. Galle[1], J. Marquardt[1]. *[1]Johannes Gutenberg University, Department of Medicine I, Lichtenberg Research Group, Mainz, Germany; [2]University of Copenhagen, Biotech Research and Innovation Centre (BRIC), Department of Health and Medical Science, Kopenhagen, Denmark; [3]University of Bonn, Department of Genomics, Life & Brain Center, Bonn, Germany; [4]Johannes Gutenberg University, Institute of Pathology, Mainz, Germany; [5]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [6]Johannes Gutenberg University, Department of Surgery, Mainz, Germany; [7]National Cancer Institute, NIH, Laboratory of Human Carcinogenesis (LHC), Center for Cancer Research, Bethesda, United States*
Email: castvendarko@gmail.com

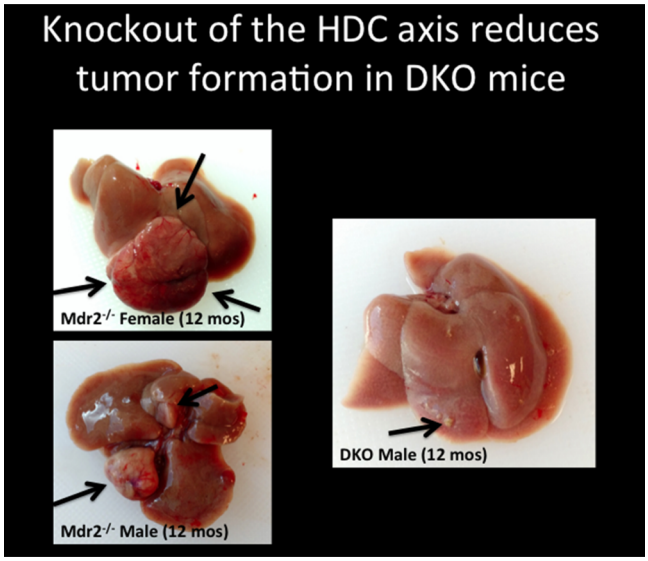
Background and Aims: Primary liver cancers (PLCs) rank among the most lethal solid cancers worldwide due to lack of effective biomarkers for early detection and limited treatment options in advanced stages. While cell lines have been of significant impact for cancer research over the last decades, development of *in vitro* models that closely recapitulate phenotypic and molecular diversity of the primary cancers is urgently needed to improve the outcome of patients.
Method: Long-term culture of 10 liver cancer cell lines of hepatocellular, cholangiocellular and metastatic origin were established using defined culture conditions. Morphological and histological characteristics of obtained cell lines and xenograft tumors were analyzed and compared to original tumors. Further, time course analyses of transcriptomic and genomic changes were performed using next-generation sequencing (NGS). Key oncogenic alterations were further identified by targeted NGS and cell lines carrying potentially actionable mutations were treated with corresponding specific inhibitors. Response to the treatments was further evaluated.
Results: The newly patient-derived cell lines (PDCL) fully resembled morphological features of the primary cancers *in vitro* and *in vivo*. Genomic alterations as well as transcriptome profiles of the PDCL showed high concordance with the primaries and remained stable for at least 30 passages. Next-generation sequencing approaches confirmed that key oncogenic mutations such as TP53, KRAS, CTNNB1 as well as potentially actionable mutations (e.g. MET, cKIT, KDR) were highly conserved in the PDCL. Integrative genomic and transcriptomic approaches demonstrate the utility of PDCL as representative model for distinct prognostic subpopulations of liver cancer patients. Moreover, the PDCL could be effectively used for therapeutic testing. Specific targeting of detected actionable mutations, such as MET and cKIT, confirmed a superior response and sustained sensitivity to specific inhibition in comparison to non-mutated control cells.
Conclusion: Together, our integrative analysis demonstrates that the use of newly established cell lines represents a sophisticated model to discover relevant molecular subgroups and to test drug sensitivity by exploring precision medicine approaches.

SAT-171

Depletion of the HDC/histamine axis ablates tumor formation, angiogenesis, EMT and inflammation in Mdr2 knockout mice

L. Kennedy[1], J. Demieville[2], L. Hargrove[1], V. Meadows[2], G. Alpini[1,2], H. Francis[1,2]. *[1]Texas A&M University HSC COM, Medical Physiology; [2]Central Texas Veteran's Health Care System*
Email: hfrancis@medicine.tamhsc.edu

Background and Aims: Primary sclerosing cholangitis (PSC) is characterized by biliary damage and fibrosis. Multidrug resistance-2 gene knockout ($Mdr2^{-/-}$) mice (i) develop cholestatic liver disease; (ii) mimic some characteristics of human PSC; and (iii) develop hepatocellular cancer (HCC) within one year. We have demonstrated that depletion of the l-histidine decarboxylase/histamine (HDC/HA) axis using 12 week old HDC/Mdr2 double knockout (DKO) mice results in decreased (i) hepatic damage; (ii) MC activation; (iii) biliary mass/proliferation and (iv) hepatic fibrosis/inflammation compared to controls. The **aim** of this study was to determine the effects of loss of the HDC/HA axis on tumor formation and progression in older $Mdr2^{-/-}$ and DKO mice.
Method: 52 week old homozygous DKO mice and aged matched $Mdr2^{-/-}$ mice were utilized. Livers were evaluated for tumor formation and lobular damage by H&E staining. In total liver we evaluated: (i) HDC/histamine receptor (HR) expression by qPCR, (ii) MC activation by qPCR for chymase, tryptase and c-Kit expression and (iii) ductular reaction by CK-19 and Ki67 immunohistochemistry. Changes in liver fibrosis were evaluated by Sirius red staining in liver sections, and qPCR for α-SMA and collagen-type 1a. Hepatic stellate cell (HSC) activation was determined by immunofluorescence and qPCR for SYP-9. Inflammation was evaluated by expression of IL-6 and TNF-α and by immunohistochemistry for F4/80. HA serum levels were measured by EIA. In livers and tumors (when present), we evaluated angiogenesis by VEGF and vWF gene expression and epithelial-mesenchmyal transition (EMT) by immunohistochemistry for vimentin and E-cadherin.
Results: Depletion of the HDC/HA axis in 52 week old DKO mice resulted in little to no tumor formation compared to -matched $Mdr2^{-/-}$ mice, which displayed large HCC tumors. The HDC/HA/HR axis and MC activation were reduced in DKO mice compared to controls. Ductular reaction and hepatic fibrosis were increased in $Mdr2^{-/-}$ mice, but were reduced in DKO mice. Further, angiogenesis, EMT, and inflammation were all reduced in DKO compared to age-matched $Mdr2^{-/-}$ mice.



Conclusion: Our data demonstrates that depletion of the HDC/HA axis blunts tumor growth and progression in $Mdr2^{-/-}$ mice. Therefore, the HDC/HA axis plays a critical role in promoting hepatic damage and tumor formation, and drugs targeting this axis may result in amelioration of disease.

SAT-172

High miR-224 expression in cholangiocarcinoma may predict survival

T. Szekerczés[1], I. Coati[2], M. Fassan[3], K. Schlachter[4], G. Lendvai[1], E. Szabó[1], M. Csengeri[1], Á. Rácz[1], K. Borka[1], Z. Schaff[1], A. Kiss[1].
[1]Semmelweis University, 2nd Department of Pathology, Budapest, Hungary; [2]University of Padua, Department of Medicine, Surgical Pathology Unit, Budapest, Hungary; [3]University of Padua, Department of Medicine, Surgical Pathology Unit, Padua, Italy; [4]National Institute of Oncology, Budapest, Hungary
Email: szekerczes.timea@med.semmelweis-univ.hu

Background and Aims: Primary liver tumours display profound dysregulation in their microRNA (miR) profiles as compared to normal liver. miR-224 is one of the most frequently analyzed miRs implicated in carcinogenesis which has demonstrated elevated expression in malignancies, such as in hepatocellular carcinoma (HCC). Information on miR-224 is limited in cholangiocarcinoma (CC), therefore our objective was to determine the expression of miR-224 in CC and make comparisons with the levels of miR-224 detected in HCC and non-malignant liver lesions.
Method: Altogether 275 samples were analysed, including 43 cases of HCC and the matched surrounding liver tissues, 63 CCs and 51 matching surrounding tissues, 13 hepatocellular adenomas (HCA), 15 focal nodular hyperplasias (FNH) and 47 normal tissues. From these samples a total of 12 tissue multi-arrays were created. The miR-224 expression was determined by *in situ* hybridization using a 5′ digoxigenin-tagged LNA probe (Exiqon) on the established tissue microarrays. The intensity of cytoplasmic miR-224 expression was semi-quantitatively categorized as negative, low, moderate (expression in <50% of the cells) and high (from moderate to strong expression in most of the cells). For statistical analyses, nonparametric Mann-Whitney test and Wilcoxon rank test were applied along with Kaplan-Meier method for generating survival curves.
Results: In comparison to normal liver, increased miR-224 level was found in HCC, HCA and FNH ($p < 0.01$). Elevated miR-224 expression was detected in CC when compared with normal and surrounding tissues ($p < 0.01$). CC showed the highest miR-224 expression when compared with the other investigated liver lesions ($p < 0.01$). Regarding etiology, miR-224 expression was significantly different in hepatitis C virus-associated HCC and HCC of unknown origin as compared to their corresponding surrounding liver. Furthermore, high miR-224 expression level was found to be associated with shorter overall survival in CC patients as compared with patients with low miR-224 levels.
Conclusion: The highest miR-224 expression was detected in CC when compared with HCC, HCA and FNH. The association between high level of miR-224 and shorter survival indicates that it might play an important role as a regulator determining the prognosis of CC.
Financial support: This study was funded by grants from OTKA K108548 from the National Scientific Research Fund.

SAT-174

Do extracellular vesicles secreted from senescent hepatic stellate cells promote or suppress cancer development?

Y. Miyazoe, S. Miuma, Y. Kanda, H. Shibata, H. Miyaaki, N. Taura, K. Nakao. *Nagasaki University Hospital, Department of Gastroenterology and Hepatology, Nagasaki*
Email: yurieast10@hotmail.com

Background and Aims: A recent study indicated that senescent hepatic stellate cells (HSCs) promoted hepatocellular carcinoma (HCC) development by the senescence-associated secretory phenotype (SASP). The effect of senescent HSCs on HCC development has been significant and is currently undergoing intense research. Similar to cytokines induced by SASP, extracellular vesicles (EVs) are important mediators of intracellular communication. However, the role of EVs secreted from senescent HSCs in HCC development is poorly understood. This study aimed to elucidate the characteristics of EVs secreted from senescent HSCs.
Method: Cellular senescence was induced by treating human HSCs (HHSteCs) with etoposide. To confirm cellular senescence, cell cycles were analyzed using 5-ethynyldeoxyuridine (EdU) staining, and 53BP1 and p21 expressions were observed by immunostaining. EVs secreted from HHSteCs were isolated using ultracentrifugation. Qualitative and quantitative changes in EVs secreted from senescent HHSteCs were examined using nanoparticle tracking and microRNA array analyses. Furthermore, we examined the incorporation of EVs secreted from HHSteCs into hepatoma cell lines (Huh7 and HepG2 cells), and these effects on hepatoma cell line proliferation by the co-cultivation of hepatoma cell lines with EVs.
Results: After examining various treatment periods and concentrations of etoposide, we found that the treatment with 25 mM etoposide for 3 days induced senescence in most HHSteCs, showing irreversible cell-cycle arrest and elevated 53BP1 and p21 expressions. The mRNA expression levels of SASP-related cytokines, including IL-8, IL-6, and ICAM-1, were elevated in senescent HHSteCs.
Nanoparticle tracking analysis revealed that EV secretion was higher in senescent HHSteCs than in normal HHSteCs. There was a difference between the microRNA profile of EVs secreted from senescent HHSteCs and those from normal HHSteCs. Co-cultivation of hepatoma cell lines with EVs demonstrated the incorporation of PKH67-labeled EVs into hepatoma cell lines. Furthermore, EVs secreted from senescent HHSteCs decreased hepatoma cells proliferation compared with those from normal HHSteCs.
Conclusion: EVs secreted from senescent HSCs exhibited different characteristics compared with those secreted from normal HSCs and may suppress cancer cell proliferation. Furthermore, we evaluated the impact of EVs secreted from senescent HHSteCs on the mRNA expression in hepatoma cell lines.

SAT-175

The role of IL-6 signaling pathway in cholangiocarcinoma

T.M.L. Nguyen[1], K.C. Bui[2], T. Scholta[2], M. Riebold[2], J. Xing[3], V. Bhuria[2], L.T. Nguyen[4], H.S. Le[5], T.P. Velavan[6], S. Beckert[7], N. Malek[2], P. Bozko[2], R. Plentz[2,8]. *[1]Medical University Hospital, Department of Internal Medicine I, Tübingen, Germany; [2]Medical University Hospital, Department of Internal Medicine I, Tuebingen, Germany; [3]Medical University Hospital, Department of Internal Medicine I, Tuebingen, Germany; [4]Vietnam Military Medical University, Department of Pathophysiology, Hanoi, Viet Nam; [5]108 Military Central Hospital, Faculty of Infectious and Tropical Diseases, Hanoi; [6]Medical University Hospital, Institut für Tropenmedizin Tübingen, Tuebingen, Germany; [7]Medical University Hospital, Klinik für Allgemeine- Viszeral, und Transplantationschirurgie, Tübingen, Germany; [8]Klinikum Bremen Nord, Innere Medizin II (Gastroenterologie, Onkologie und Diabetologie), Bremen, Germany*
Email: ruben.plentz@klinikum-bremen-nord.de

Background and Aims: Cholangiocarcinoma (CC) is the second common hepatic malignancy. Combination of Gemcitabine and Cisplastin is currently the first line treatment for inoperable patients. However, new molecular therapies are needed. Interleukin 6 (IL-6) is an anti-inflammation cytokine that operates survival in various non-solid cancers: lymphoma, myeloma, leukemia… but the anti-cancer effect of IL-6 inhibitor on CC is not totally known yet. The aims of this project are to analyze the role of IL-6 during cholangiocarcinogenesis and the effect of Siltuximab, an IL-6 antibody *in vitro, in vivo.*
Method: Extra- (TFK1) and intra-hepatic CC (SZ1) cell lines were treated with different concentrations of Siltuximab, followed by observation on invasion (2D and 3D culture models), senescence and signalling transformation. Western Blot targeting p.STAT3, EMT markers, p.Akt, Wnt/β-Catenin was performed. RT-qPCR was applied to compare IL-6 mRNA expression in CC tumours and normal livers of CC engineered mice (Alb-Cre/LSL- $KRAS^{G12D}$/$p53^{L/L}$,

n = 7). Xenograft mice were used to investigate anti-cancer effect of Siltuximab *in vivo*.
Results: Siltuximab treatment resulted in deceleration of 2D and 3D cell invasion, IL-6 mRNA and acceleration senescence. Siltuximab led to down-regulation of p.STAT3, Wnt/β-Catenin, EMT markers and up-regulation of p.Akt. On engineered mice, the expression of IL-6 mRNA in tumour tissues was significantly higher than that in adjacent normal livers. The level of mRNA IL-6 in tumours was correlated with tumour volume. On the xenograft model, Siltuximab-treated mice showed smaller tumours than control animals.
Conclusion: IL-6 plays important role in cholangiocarcinogenesis and Siltuximab might become a promising therapy for CC.

SAT-176

Exosome derived from miR-199*-modified adipose tissue-derived MSCs increase chemosensitivity of hepatocellular carcinoma

G. Lou, Y. Liu, T. Zhang, S. Li, Z. Chen, M. Zheng. *State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital of School of Medicine, Zhejiang University, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Zhejiang University, Hangzhou, China*
Email: minzheng@zju.edu.cn

Background and Aims: Hepatocellular carcinoma (HCC) displays high resistance to conventional chemotherapy. Considering the chemotherapeutic sensitization effect of miR-199*, an effective vehicle-mediated miR-199a* delivery system may supply a new strategy for improving HCC chemotherapy. Recently, exosomes as biological vehicles have been developed to deliver oligonucleotides including miRNA. Mesenchymal stem cells (MSCs) can produce large amounts of exosomes and are easy to be genetically modified, Therefore, it is an excellent genetic modify carrier production tools. This study was aimed to determine whether adipose tissue-derived MSC (AMSC) exosomes can be used for miR-199* delivery and improving the HCC chemotherapy.

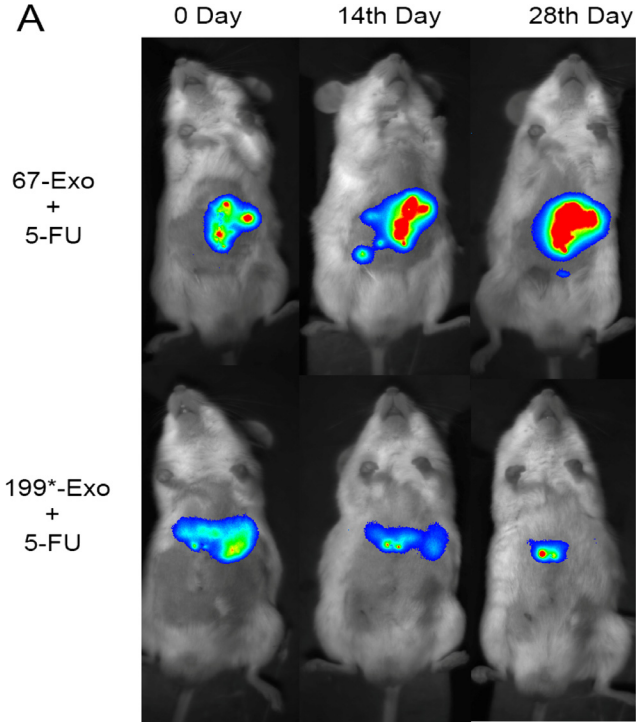


Figure 1: Tail vein injection of 199*-Exo significantly increased the antitumor efficacy of 5-FU on HCC in situ implant model in vivo. A: Imaging of mice at the 0 day, 14th day and 28th day.

Method: miR-199* plasmid was transfected into AMSCs, after 48h incubating, exosomes (199*-Exo) were harvested and added to recipient HCC cells. Expression levels of miR-199* in AMSCs, exosomes, and HCC cells were quantified by real-time PCR. The protein levels of miR-199*-target genes in recipient HCC cells were quantified by Western blot. The effects of 199*-Exo on cell viability, apoptosis of HCC cells were evaluated by MTT and flow cytometry analysis. Xenograft models were used to determine whether 199*-Exo can sensitize HCC cells to 5-FU in vivo.
Results: Data showed that the AMSC transfected with miR-199* can effectively package miR-199* into secreted exosomes, which can mediate miR-199* communication between AMSCs and HCC cells, and it render HCC cells sensitive to chemotherapeutic agents through alteration of miR-199*-target gene expression. Moreover, Tail vein injection of 199*-Exo significantly increased the anti-tumor efficacy of 5-FU on HCC in situ implant model in vivo.
Conclusion: The findings suggest that the export of miR-199* via AMSC exosomes represents a novel strategy to sensitive HCC chemotherapy.

SAT-177

A new insight on the stem cell growth factor beta as astrong predictor of therapy response in hepatocellular carcinoma

C. Sukowati[1], R. Patti[2,3], D. Pascut[1], R.B. Ladju[1,4], P. Tarchi[5], N. Zanotta[6], M. Comar[6], C. Tiribelli[1], L. Crocè[1,2,7]. *[1]Fondazione Italiana Fegato, Trieste, Italy; [2]University of Trieste, Medical Science Department, Trieste, Italy; [3]ASUITS Cattinara Hospital, Liver Disease Unit, Trieste, Italy; [4]University of Hasanuddin, Faculty of Medicine, Makassar, Indonesia; [5]ASUITS Cattinara Hospital, Department of General Surgery, Trieste, Italy; [6]IRCCS "Burlo Garofolo", Institute for Maternal and Child Health, Trieste, Italy; [7]ASUITS Cattinara Hospital, Liver DIsease Unit, Trieste, Italy*
Email: rpatti@units.it

Background and Aims: Inflammatory molecules such as cytokines and growth factors are important factors in the development of hepatocellular carcinoma (HCC). The stem cell growth factor beta (SCGFβ), a newly found protein, is a secreted glycoprotein functions as a growth factor for primitive hematopoietic progenitor cells. The level SCGFβ was elevated in several cancer types, but there is no information on this protein in the clinical study of HCC. The aim of this study is to investigate inflammatory biomarkers in predicting the responsiveness of therapy in HCC patients receiving radiofrequency ablation (RF) or trans-arterial chemoembolization (TACE) with focus on the SCGFβ.
Method: A multiplex immunoassay panel of 48 cytokines and growth factors were used to screen 64 sera from 29 patients (age mean 72 ± 7 y.o, M22/F7, 9 HCV and 20 alcohol/metabolic) at pre-treatment (T0) and 1 month (T1) after RF (n = 15) or TACE (n = 14) treatment. A quantitative real time PCR was performed to analyze gene expression of CLEC11A (SCGF) from 37 PBMC isolates. Diagnosis of HCC was established based on radiologic findings according to EASL criteria and treatment response was evaluated according to mRECIST criteria. Statistical analysis was performed by using SPSS program for non-parametric test (Whitney-Mann) and T-test.
Results: At T0, different factors including cytokines IL-8 ($p < 0.01$), IL-15, IL-12p40, IL-17 ($p < 0.05$), and growth factor SCGFβ ($p < 0.01$) could distinguish responders to non-responders. At T0 and T1, SCGFβ could predict good response (complete response, partial response *vs* stable disease, and progression of disease). Its concentration was highest in non-responders, followed by early recurrence, and the lowest in complete responders, independently from HCV, BCLC stage, and type of treatment. Low SCGF level seemed to be correlated with longer disease-free survival. Analysis of PBMC isolates showed the up-regulation of CLEC11A (SCGF) mRNA expression at the T1 only in non-responders. This pattern was confirmed by using 8 paired samples. CLEC11A T1/T0 ratio was low (0.4 ± 0.2 fold) in responders, while it was almost three times higher (1.4 ± 0.8 fold) in non-responders patients ($p < 0.05$).

Conclusion: In this study, for the first time, we demonstrate that the high level of serum SCGFβ and mRNA expression of PBMC SCGF at pre- and post-treatment is associated with HCC non-responsiveness. SCGFβ can be a potential molecule as HCC prognostic factor and a target of future therapy.

SAT-178

Disrupted cholesterol synthesis leads to female prevalent hepatocellular carcinoma in transgenic mice

K.B. Cokan[1], M. Perše[2], J. Jeruc[2], G. Lorbek[1], Ž. Urlep[1], P. Juvan[3], N. Nadižar[1], U.P. Zmrzljak[1], D. Rozman[1]. [1]*Centre for Functional Genomics and Bio-Chips, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, Ljubljana, Slovenia;* [2]*Medical Experimental Centre, Institute of Pathology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, Ljubljana, Slovenia;* [3]*Centre for Functional Genomics and Bio-Chips, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, Slovenia*
Email: kaja.blagotinsek@mf.uni-lj.si

Background and Aims: Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. Although the principal causes of its development are infection with hepatitis virus B or C and alcoholism, the non-alcoholic fatty liver disease (NAFLD) is becoming increasingly important for tumor development. About 20% of HCC evolves from NAFLD due to chronic inflammation and by oxidative stress induced fibrosis that could be activated with metabolic dysfunction. We have shown previously that disrupted cholesterol synthesis leads to severe liver injury with oval cell response and fibrosis that becomes visible in young adults and is progressing in adulthood [Urlep Ž., et al, 2017; Lorbek G., et al, 2015]. The aim of this study is to investigate the consequences of this metabolic insult during the aging.
Method: We applied the knockout (KO) mouse model of lanosterol 14α-demethylase (Cyp51) from the late part of cholesterol synthesis. Histopathology was performed on liver sections. Hepatic gene expression was assessed by expression profiling and qPCR. We measured biochemical parameters in plasma. Data were analysed by R, Bioconductor and linear regression modelling.
Results: First HCC cases were observed in livers of 1 year KO mice that also showed advanced fibrosis and oval cell response which was not significantly different from the 19-week mice. At 2 years the prevalence for tumors was 3-times higher for females. Histologically, hepatocyte *Cyp51* ablation was characterized by the sustained strong inflammation, ductular proliferation and fibrosis. The hepatocellular damage could be confirmed with elevated ALT/AST ratio.
The transcriptome data in KO mice clearly indicate up-regulated pathways in cancer and extracellular matrix interaction while multiple metabolic pathways were severely dampened, including the RORC signalling due to the lack of sterol ligands. Diminished was also the activity of transcription factors involved in the cell cycle control, circadian gene regulation and liver regeneration. Some of enriched genes and transcription factors in females suggest higher susceptibility to carcinogenesis.
Conclusion: Disturbed cholesterol synthesis leads to hepatocellular carcinoma during the aging of mice. The injury caused by blocked cholesterol synthesis activates Sox-9, which plays an important role in regulation of cell growth and differentiation. Its possible association with Wnt signalling could lead to higher susceptibility for tumor development in older females.

SAT-179

Impact of Trp53 on tumor heterogeneity in the background of liver fibrosis

U.T. Mathada, M. Svinarenko, N. Bushart, K. Steding, L. in der Stroth, T. Seufferlein, R. Schirmbeck, A. Lechel. *University Hospital Ulm, Department of Internal Medicine I, Ulm, Germany*
Email: andre.lechel@uni-ulm.de

Background and Aims: Cellular complexity along with molecular heterogeneity makes liver cancer as one of the most aggressive malignancies globally. With the global incidence rate of 782,451 new cases and 745,533 related deaths brings liver cancer to 6th most common cancer and 2nd most cancer-related deaths. Association of various risk factors from viral infections to metabolic diseases have an impact on the liver cancer initiation. In combination with *Tp53* mutation, they drive tumor progression and affects tumor differentiation. Liver fibrosis formation is an indication of ongoing liver damage and repair mechanism. Chronic liver fibrosis leads to cirrhosis and possesses itself a risk for liver cancer. Combination of disrupted p53 pathway and persistent fibrosis on liver cancer incidence and tumor differentiation is not yet well understood.
Method: We analysed tumor heterogeneity in the background of liver fibrosis and p53 deletion. For this purpose, we chose a conditional *Trp53* KO mouse, crossed with a liver-specific Cre-driver strain (*AlfpCre*). To modulate liver fibrosis formation we injected mice from 6 weeks of age for a time period of 4 months with CCl_4. We monitored the mice at 6, 9, 12 and14 months for liver fibrosis and liver tumor formation. In addition, we also analysed the inflammatory microenvironment.
Results: Liver-specific deletion of *Trp53* alone resulted in the formation of liver cancer at 12–14 month. Majority of the tumors showed tumor differentiation towards combined hepatocellular-intrahepatic cholangiocarcinoma (HCC/iCC, 80%). Interestingly, liver tumors arise in the background of *Trp53* deletion were without formation of liver fibrosis. *Trp53*−/− mice with CCl_4 treatment resulted in a dramatic increase in tumor formation and impaired survival due to an early tumor onset with 6 month of age compared to *Trp53*+/+ mice and *Trp53*−/− mice without treatment. Tumor differentiation is shifted to HCC formation upon induction of fibrosis.
Conclusion: Liver fibrosis is an important risk factor for early tumor development. Tumor heterogeneity is influenced by liver fibrosis formation in the background of *Trp53* deletion.

SAT-180

Sorafenib/Regorafenib resistance and BH3-mimetics efficacy in hepatocellular carcinoma treatment is determined by mitochondrial changes in the BCL-2 profile

A. Tutusaus[1,2], M. Stefanovic[2,3], B. Cucarull[1,2], M. Mari[1,2], L. Boix[2,4], M. Reig[2,4], J. Bruix[2,4], A. Morales[1,2,4]. [1]*Institut d'Investigacions Biomèdiques de Barcelona, Barcelona, Spain;* [2]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain;* [3]*Institut Català d'Oncologia (ICO), L'Hospitalet de Llobregat, Spain;* [4]*Barcelona clínic liver cancer, Barcelona, Spain*
Email: amorales@clinic.ub.es

Background and Aims: The multi-kinase inhibitor sorafenib has limited efficacy in the treatment of advanced hepatocellular carcinoma (HCC) and sorafenib resistance favours its clinical failure. The mitochondrial damage induced by sorafenib is known. Changes in BCL-2 proteins alter the effectiveness of BH3-mimetics, inhibitors of specific Bcl-2 proteins, in killing cancer cells. Regorafenib usage as second-line treatment after sorafenib failure has been recently approved. The influence of sorafenib and regorafenib on BCL-2 family expression may suggest potential treatment options that have not been thoroughly explored.
Method: Hepatoma cell lines sensitive or resistant to sorafenib (HepG2 and Hep3B) were treated with sorafenib and BH3-mimetics (ABT-263: BCL-2 and BCL-XL, ABT-199: BCL-2, A-1331852: BCL-xL). Western blots and qPCR were performed. Mitochondrial functionality, caspase activation and induction of apoptosis were analyzed in hepatoma cells treated with sorafenib/regorafenib. Tumor growth was determined in mouse xenografts after subcutaneous injection of HepG2 and BCLC9 cells, treated with sorafenib and/or ABT-263. In mRNA samples from control individuals (n = 10) and HCC patients (HCV/EtOH, n = 14) BCL-2 and MCL-1 expression was analyzed in tumoral and non-tumoral tissue.

Results: Sorafenib-resistant Hep3B and HepG2cells showed upregulated BCL-2/MCL-1 ratio facilitating mitochondria-dependent cell death by BH3-mimetics. ABT-263 recovered sorafenib toxicity in vitro and in sorafenib-resistant xenografts, while ABT-199, a specific BCL-2 inhibitor, or A-1331852, a specific BCL-xL inhibitor was less effective, underlining the importance of simultaneous inhibition of BCL-2/BCL-xL. Moreover, in mice xenografts from patient-derived BCLC9 cells, ABT-263 improved sorafenib effectiveness without enhanced inflammatory reaction, being tumor response dependent on the BCL-2/MCL-1 ratio. Of note, HCC patients displayed increased BCL-2/MCL-1 mRNA levels respect to adjacent non-tumoral biopsies. Finally, similar modification of BCL-2/MCL-1 ratio was detected after regorafenib administration to hepatoma cells. Consistently, navitoclax also sensitized hepatoma cells to regorafenib by a mitochondrial caspase-dependent mechanism.
Conclusion: Sorafenib, and regorafenib treatment, by increasing the BCL-2/MCL-1 ratio in HCC, sensitizes drug resistant-tumors against ABT-263 co-administration. Moreover, the anti-apoptotic BCL-2 profile, which is altered in HCC patients, modifies sorafenib/regorafenib efficacy. Tumor anomalies in the BCL-2 profile of particular patients suggest the use of specific BH3-mimetics for combined therapy in HCC treatment.

SAT-181
Maldi imaging of hepatocholangiocarcinomas: A clue to tackle tumor heterogeneity preliminary results

E. Gigante[1], R. Casadonte[2], J. Le Faouder[1], N. Poté[3], M. Albuquerque[1], O. Soubrane[4], V. Paradis[1,3]. *[1]Centre de Recherche sur l'inflammation, UMR 1149, INSERM-Paris Diderot University, Paris, France; [2]Proteopath GmbH, Trier, Germany; [3]Department of Pathology, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, Clichy, France; [4]Department of Liver Transplantation and Hepatobiliary Surgery, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris, Clichy, France*
Email: elia.gigante@hotmail.it

Background and Aims: Hepatocholangiocarcinomas (H-ChCs), are mixed primary tumors of the liver, defined by the presence of hepatocellular carcinoma (HCC) and cholangiocarcinoma (CC) components that may display stem cell features. Accordingly, H-ChC represents the most illustrative heterogeneous liver malignancies. Its tumoral heterogeneity hampers molecular analysis that may provide various signatures according to the area analyzed. The aim of this study was to assess the peptidic profiles of the different morphological patterns constitutive of H-ChC by MALDI imaging, an in situ approach able to connect molecular profiles with specific histological features, without preliminary step of molecular extraction or labeling.
Method: MALDI imaging (RapifleX and Autoflex III MALDI, Bruker Daltonik GmbH) was applied on paraffin tumor sections of tissues microarrays (TMAs) built from 60 surgical cases of H-ChC. Entire tissue sections of selected cases were also analyzed (10 cases). Peptidic spectra were obtained from the different tumor patterns constitutive of H-ChC as well as from CC (n = 29) and HCC (n = 23) and the most discriminant peaks were identified.
Results: Rich peptides spectra were obtained from all tumor cases tested, with more than 90 peptides peaks identified. The comparison of the relative intensities of each m/z value (peptidic peak) between the three tumor types (H-ChC, HCC, CC) revealed 19 discriminant peaks exhibiting a statistical significance. They showed a receiver operating curve (ROC) curve superior to 0.7 in the identification of H-ChCs when applied on cases and controls (Example, peak 1466 in Figure 1). Comparative analysis of H-ChC cases showed great heterogeneity (1) from case to case (Figure 1 lanes 1 and 2 compared to lanes 3 to 5), (2) within case from different areas of the tumor (Figure 1 lanes 2 and 3), and (3) within case from a single tumor area (Figure 1 lane 1).

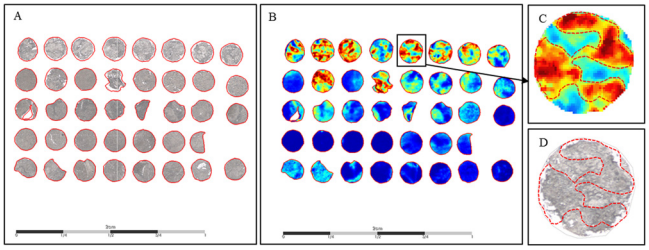


Figure 1: Expression of m/z 1466 peak on a TMA. Each lane corresponds to a H-ChC case. (A) Optical image, (B) ion density map of peak 1466, (C) magnification of core 5, showing an enhanced intensity of m/z 1466 in specific tumoral zones (D) optical image, core 5, tumoral zones are highlighted in red discontinuous line.

Conclusion: This preliminary study demonstrates that MALDI imaging is a powerful tool for providing peptidic signatures from formalin fixed paraffin-embedded tumor samples. In addition, it confirms that H-ChCs are highly heterogeneous at the molecular level both at the inter and intratumoral scale. The identification of the proteins specifically associated with the different tumor components is currently ongoing.

SAT-182
HBx/DLEU2/EZH2 co-regulation of host genes expression in HCC

F. Guerrieri[1], D. Salerno[1], L. Chiodo[2], G. Cottone[3,4], M. Pallocca[5], O. Floriot[6], M. Levrero[6,7]. *[1]Istituto Italiano di Tecnologia, Center for Life NanoScience@Sapienza, Rome, Italy; [2]Università Campus Bio-Medico, Department of Engineering, Unit of Nonlinear Physics and Mathematical Modeling, Rome, Italy; [3]University College Dublin School of Physics, School of Physics, Dublin, Ireland; [4]University of Palermo, Department of Physics and Chemistry, Palermo, Italy; [5]Regina Elena National Cancer Institute, UOSD SAFU, Roma, Italy; [6]INSERM, Cancer Research Center of Lyon (CRCL), INSERM U1052, Lyon, France; [7]Service d'Hepatologie et Gastroenterologie, Hospices Civils de Lyon, Lyon, France*
Email: massimo.levrero@gmail.com

Background and Aims: HBx regulatory protein is required for HBV cccDNA transcription/viral replication and contributes to HBV oncogenicity. HBx affects the epigenetic control of HBV viral chromatin as well as of cellular chromatin. We previously showed by RNA Immune Precipitation (RIP) that HBx binds the DLEU2 lncRNA and that DLEU2 affects viral chromatin transcription. The association of Ezh2 with lncRNAs has been shown to guide Ezh2 interaction with target genes to modulate transcription in cis and in trans. Aim of this study is to verify the formation of HBx-DLEU2-EZH2 complexes and to clarify their role in the regulation of cellular target genes in human primary hepatocytes (PHH) and HepG2-NTCP infected by HBV-infection.
Method: Chromatin Immune Precipitaion (ChIP), Chromatin Isolation by RNA Precipitation (ChIRP) and RIP were analyzed by TaqMan real-time PCR. The nCounter Nanostring technology and real-time RT-PCR were used to evaluate gene and lncRNAs expression. Specific LNA™ longRNA GapmeRs (Exiqon) were used for highly efficient inhibition of DLEU2 lncRNA functions.
Results: In silico analysis of a new model of HBx protein tertiary structure, EZH2 protein and DLEU2 tertiary structure suggested a direct interaction of all three players. RIP experiments confirmed HBx-DLEU2 and EZH2-DLEU2 interactions *in vivo*. HBx activates the promoter of the DLEU2 host gene TRIM13 and, in the absence of HBx, both EZH2 binding and H3me3K27 increase at the TRIM13 promoter. ChIP and a ChIRP experiments showed that HBx and DLEU2 RNA bind to the TRIM13 promoter. Selective degradation of DLEU2 RNA indeed resulted in reduced H4 acetylation on the TRIM13 promoter and a ~50% reduction of TRIM13 expression in HBV replicating PHH. EZH2

inhibitors increase TRIM13 expression. Thus, HBx/DLEU2/EZH2 complexes co-regulate TRIM13 expression. In addition to TRIM13, 260 additional genes were co-regulated with DLEU2 RNA in HBV-related HCC patients and 70 out of them were previously identified as direct HBx targets in ChIP-Seq experiments. We validated CCNB2 as a second direct target of the HBx-DLEU2-EZH2 complex by anti-HBx ChIP and anti-DLEU2 ChIRP.
Conclusion: Ezh2/PRC2 interaction with DLEU2 inhibits Ezh2 activity without altering Ezh2 promoter occupancy. The concomitant increase in DLEU2 and HBx recruitment in HBV replicating cells and in HBV-related HCCs, further increase transcription and freeze the promoters of a subset of Ezh2/PRC2 target genes in an active state.

SAT-183

Aspecific ECM composition regulates Smad dependent – TGFbeta1–induced EMT response in HepG2 cells engineered in cirrhotic and healthyliver 3D scaffolds

M. Marrali[1,2], A. Telese[2], K. Bottcher[2], L. Frenguelli[2], W. Al-Akkad[2], G. Mazza[2], M. Pinzani[2], K. Rombouts[2]. *[1]Engitix Ltd, London, United Kingdom; [2]University College London, Institute for Liver and Digestive Health, London, United Kingdom*
Email: k.rombouts@ucl.ac.uk

Background and Aims: Hepatocellular carcinoma (HCC) is the second cause of cancer deaths motivating the investigation of new therapeutic targets to provide alternative treatments. Recent studies highlight the role of the ECM microenvironment in modulating cancer development. A new 3D model was developed by using decellularized human liver which maintains the original tissue-specific 3D architecture and properties. TGFbeta1 prompts the progression of HCC through activation of the SMAD2/3 signalling pathway. This study investigates the effect of cirrhotic and healthy ECM on TGFbeta1-SMAD2/3 signalling in EMT-related HCC cell behaviour and on the assessment of drug sensitivity.
Method: Human liver 3D scaffolds were obtained decellularizing healthy and cirrhotic human livers. Scaffolds were repopulated with HepG2 cells (2 × 10*6) for 7 days followed by TGFbeta1 (5–10 ng/ml) treatment. Protein expression was assessed for P-SMAD2/3, SMAD2/3 and albumin. Changes in TGFbeta1 response were investigated by pre-treatment/treatment with TGFbetaR1 kinase inhibitor Galunisertib (10 μM) for 48hrs. To investigate the non-canonical TGFbeta1 pathway in HCC, Erk/P-Erk and Akt/P-Akt expression was assessed in HepG2 cells cultured on cirrhotic and healthy scaffolds.
Results: P-SMAD3 had a low expression in HepG2 cells cultured on healthy scaffolds while being highly expressed on cirrhotic scaffolds. In contrast, P-SMAD2 had a low expression in HepG2 cells cultured on cirrhotic scaffolds, while being upregulated in healthy scaffolds. SMAD2/3 proteins were expressed in HepG2 cells cultured on both cirrhotic and healthy scaffolds. Each protein was differently affected by exogenous TGFbeta1 treatment. Pre/simultaneous treatment of TGFbeta1 with Galunisertib affected protein expression depending on the ECM-scaffold used. TGFbeta1-Galunisertib treatment reduced albumin protein expression in HepG2 cultured on cirrhotic scaffolds. Erk protein expression was similar on both types of scaffolds, while Akt showed a higher expression on healthy scaffolds. Uptake/release of TGFbeta1 showed marked differences between healthy and cirrhotic scaffolds.
Conclusion: This study suggests that the ECM composition of the 3D liver scaffold itself can affect protein expression which can be further modified by TGFbeta1 treatment. Although inhibiting the TGFbeta1 signaling pathway alone may not be sufficient, as the tumor ECM microenvironment seems to play a major role, this study suggests that TGFbeta1 and its canonical signaling pathway represent potential targets for the treatment of HCC.

SAT-184

Analysis of HBV DNA integration in tumor and non-tumor liver tissues by a high-throughput viral integration detection method

D. D'aliberti[1], D. Giosa[1], G. Raffa[1], C. Musolino[1], G. Tripodi[1], D. Lombardo[1], F.C.D. Tocco[1], C. Saitta[1], O. Romeo[2], G. Navarra[3], G. Raimondo[1], T. Pollicino[3]. *[1]University Hospital of Messina, Clinical and Experimental Medicine, Messina, Italy; [2]University of Messina, ChiBioFarAm, Messina, Italy; [3]University Hospital of Messina, Human Pathology, Messina, Italy*
Email: tpollicino@unime.it

Background and Aims: HBV DNA integration is found in about 85% of HCC. Most of the data on HBV integration have been generated by specific restriction enzymes and cloning methods that may favor preferential amplification and bias identification of unique integration sites. The more recent next-generation sequencing (NGSs) approaches show a low coverage of HBV reads. Aims of this study were to conduct a high-throughput viral integration detection analysis on tumor (T) and non-tumor (NT) liver tissues, and on PLC/PRF/5 cells, using NGS of enriched HBV integrants, and to identify HBV junctures at the whole-transcriptome level.
Method: A total of 108 integration libraries were constructed from liver genomes of 4 HCC patients and PLC/PRF/5 cells. Each experiment was performed on fragmented genomic DNA by sonication. DNA was blunted and adenosine-tailed. A-tailed DNA fragments were ligated to Linkers. Virus integration sites were recovered by semi-nested PCR using 24 different HBV primers specific to the Core, X, Pol, and Pre-S/S regions. PCR products were paired-end sequenced on Illumina MiSeq. RNA-Seq was performed on an Illumina HiSeq 2500 platform. High-quality reads were mapped with BWA software against hybrid reference including the human genome reference GRCh38.p10 and HBV genome (NC_003977).
Results: A total of 7,536 HBV integration breakpoints were detected (5,186 in T, 2,071 in NT, and 279 in cells). Among them, 3,912 could be mapped to unique sites on human chromosomal DNA (3,157 in T, 484 in NT, and 271 in cells). In particular, 632 integrations occurred at level of exons (601 in T, 31 in NT, and 1 in cells). The remaining 3,624 of 7,536 integrations were located in repeated DNA sequences. The majority in LINE (21.4%), SINE (16.4), and LTR (24%). An enrichment of microhomology sequences between host DNA and integrated HBV DNA was found at the site of integration in a high percentage of chimeras (27%–97%) from each sample. PreS-S genomic sequences and the ENHI/X promoter region were the most frequent HBV integrants detected. RNA-Seq specifically confirmed the production of viral/human fusion transcripts (HBs-CCDC57 fusion in PLC/PRF/5 cells, HBx-LINE/L1 and HBs-PTPRD fusions in 2 different T samples.)
Conclusion: We developed a high-throughput viral integration detection method that allow characterizing the landscape of HBV integration events in host genome, and to identify viral-human chimeric fusion genes that my be involved in HCC development.

SAT-185

New targets for hepatocellular carcinoma therapy: the Myc/PRMT5/RNAP II circuit

C. Porcu[1], B. Illi[2], S. Nasi[2], S. Tavolaro[1], C. Balsano[1]. *[1]University of L'Aquila, Italy, Department of Life, Health & Environmental Sciences MESVA, L'Aquila, Italy; [2]CNR, IBPM, Rome, Italy*
Email: clara.balsano@cc.univaq.it

Background and Aims: HCC is highly heterogeneous from both a genomic and etiologic point of view. Myc deregulation and overexpression represent major mechanisms of tumorigenesis in a variety of cancers, including HCC. Protein arginine methyltransferase 5 (PRMT5) plays a role in chromatin remodelling and control of gene expression by methylating multiple substrates including histones, p53 and RNA Polymerase II (RNAP II). Intriguingly, Myc and PRMT5 rule distinct RNAP II activities like pause release (Myc), transcript termination (PRMT5) and mRNA splicing (both Myc and PRMT5).

Method: Hepatoma cell lines, HepG2 and HuH7, and HEK293T were used to perform in vitro experiments. We evaluated gene expression by RT-PCR, protein levels by western blot. We looked at the binding of myc and PRMT5 by immunoprecipitation (IP) and immunofluorescence analyses.
Results: We demonstrated that HEK293T cells transfected with Myc, showed a prominent increase in histone H4R3me2s. Then, we performed co-immunoprecipitation experiments, both in FlagMyc overexpressing HEK293T and in hepatocarcinoma cells, to assess the formation of a PRMT5/Myc complex. We observed that Myc and PRMT5 are physically and functionally associated.
We asked whether PRMT5 inhibition might affect Myc activation of two specific target genes: carbamoyl-phosphate synthase aspartate-carbamoyltransferase-dihydroorotase 1 (cad1) and cyclin D1 (cycD1). HEK293T cells were cotransfected with a shRNA against COPR5, the nuclear cooperator of PRMT5, to selectively target PRMT5 nuclear activity. Co-transfection of shCOPR5 impaired full transactivation of cad1 and cycD1.
Given the Myc/PRMT5 interaction and the role of Myc in ruling other RNAP II properties, we hypothesized that Myc might play a role in PRMT5-dependent RNAP II methylation. FlagMyc overexpressing HEK293T cells, FlagMyc overexpressing HEK293T cells co-transfected with a shRNA against Myc, and scrambled control cells, were analyzed for RNAP II symmetric dimethylation by immunoprecipitation with an anti-RNAP II antibody and after with a specifically recognizing RNAP II R18010me2s. Myc induces RNAP II symmetric dimethylation, allowing proper termination of transcripts. Moreover, as expected, PRMT5 is associated to RNAP II, but in the presence of low Myc levels, PRMT5 was no longer present in the immunocomplex.
Conclusion: We defined a novel Myc and PRMT5-dependent molecular circuitry, ruling transcription as a whole chromatin domain, elongation, termination, splicing possibly dysregulated in HCC cells.
Our results indicate the Myc/PRMT5/RNAP II axis as a novel druggable target for HCC therapy.

SAT-186

Novel microRNA-based drug CD5–2 reduces liver cancer development in multi-drug-resistance gene-2 knockout mice

K. Liu[1,2,3], Y. Zhao[4], J. Chen[2], J. Gamble[3,4], G. Mccaughan[1,2,3]. *[1]Royal Prince Alfred Hospital, AW Morrow Gastroenterology and Liver Center, Sydney, Australia; [2]Centenary Institute, Liver Injury and Cancer Program, Sydney, Australia; [3]University of Sydney, Sydney Medical School, Sydney, Australia; [4]Centenary Institute, Centre for the Endothelium, Sydney, Australia*
Email: kenliu51@hotmail.com

Background and Aims: Liver cancer is the second commonest cause of cancer death worldwide. Tumours are characterised by abnormal (leaky) vasculature, hypoxia and an immunosuppressive microenvironment. Current treatments for advanced disease are ineffective. Blockmir CD5-2 is an oligonucleotide-based inhibitor of the microRNA27 interaction with VE-Cadherin, the endothelial specific cadherin. Previously we have shown that CD5-2 normalises tumour vasculature by increasing VE-Cadherin expression. We aimed to study the effect of CD5-2 on liver cancer growth, vasculature and immune infiltrate in MDR2-knockout (MDR2KO) mice. MDR2 is essential for biliary phosphatidylcholine excretion and MDR2KO mice spontaneously develop sclerosing cholangitis, liver fibrosis, and liver cancer.
Method: CD5-2 or its control (scrambled Blockmir) was given (30 mg/kg body weight i.v. fortnightly) to MDR2KO mice from age 5-months until sacrifice at age 7-months. Livers from treated (CD5-2 or control), untreated and MDR2 wildtype mice were analysed using immunohistochemistry. Student t-test was used to determine statistical significance.
Results: MicroRNA27 was significantly increased in MDR2 tumours compared to adjacent normal tissue. CD5-2-treated mice had significantly fewer (38% reduction) and smaller liver tumours (26% reduction) compared to control-treated tumours. CD5-2 treatment altered the immune infiltrate. CD5-2-treated tumours had significantly higher CD3+, CD8+ and PD1+ cell numbers compared to control-treated tumours. CD5-2-treated tumours tended to have less CD34 and higher alpha-SMA expression suggesting a trend towards the normal mature vasculature phenotype.
Conclusion: CD5-2 reduces liver tumour number and size in MDR2KO mice possibly by enhancing effector CD8+ T-cell infiltration. This result suggests normalising tumour vasculature using CD5-2 is a promising novel approach to treat liver cancer.

SAT-187

KRAS-dependent AKT signaling drives hepatocyte proliferation to promote tumor development in a genetic model of liver cancer

T. Rösner[1], C. Lechler[1], K.-E. Birgit[1], K. Steiger[2], C. Mogler[2], D. Saur[3], J. Sage[4], R.M. Schmid[1], U. Ehmer[1]. *[1]Klinikum rechts der Isar, Technische Universität München, 81675 Munich, Germany, Department of Medicine II, Munich, Germany; [2]Klinikum rechts der Isar, Technische Universität München, Institute of Pathology and Unit of Comparative Experimental Pathology, Munich, Germany; [3]Klinikum rechts der Isar, Technische Universität München, Department of Medicine II, Munich, Germany; [4]Stanford University, Department of Pediatrics, Stanford, United States*
Email: roesnerthomas@gmx.de

Background and Aims: The identification of key pathways in liver carcinogenesis is a requirement for the development of novel therapies. In a genetic mouse model of liver cancer, we combine liver-specific expression of oncogenic Kras with genetic inactivation of the tumor suppressors *Rb* and p53 to mimic major molecular events in human liver cancer. Gene mutation in adult mice results in the formation of liver tumors resembling human hepatocellular carcinomas (HCC), intrahepatic cholangiocarcinomas (ICC), as well as tumors of mixed differentiation and highly undifferentiated tumor lesions. In this model, RAS-dependent MEK/ERK and AKT signaling are highly activated and likely play a key role in tumor development. Here, we aim to dissect the functional role of these pathways in liver tumor development to identify promising targets for cancer therapy in the context of activated RAS signaling.
Method: To examine the relevance of AKT signaling *in vivo* we activated Cre in hepatocytes of adult $Rb^{lox/lox}$;$p53^{lox/lox}$;$Kras^{LSL-G12D/+}$ (*RPK*) and *RPK*;$Pdk1^{lox/lox}$ mice via CreER-transposon constructs or an albumin-driven CreER. Liver samples, microdissected tumor lesions, and metastases were analyzed for mRNA and protein expression.
Results: Immunohistochemistry of *RPK* tumors shows an overall activation of both $pAKT^{Thr308}$ and pERK at early timepoints and in advanced tumors, indicating increased activity of PDK1 and MEK during Ras-driven tumor development. Genetic knock-out of *Pdk1* in *RPK*;$Pdk1^{lox/lox}$ mice results in decreased hepatocyte proliferation at early timepoints *in vivo*. Investigation of survival proportions shows longer survival as well as reduced tumor formation and metastasis development of *RPK*;$Pdk1^{lox/lox}$ mice in comparison to *RPK*-mice.
Conclusion: Altered RAS signaling is found in the majority of human HCC and ICC with poor prognosis. In our model, Kras-dependent AKT-signaling appears to act as one of the key drivers in hepatic carcinogenesis with impact on early proliferation of transformed cells, tumor and metastasis development. Inhibition of activated PDK1/PI3K/AKT signaling might therefore be a promising approach in the treatment of primary liver cancer with activated Kras signaling. The role of other Ras-dependent pathways for the development of liver tumors and their metastatic potential is under further investigation.

SAT-188

The impact of the epigenetic writer LSD1in the cell cycle control in liver fibrosis and hepatocellular carcinoma

L. Wang, X. Yu, M. Schmiel, L. Steinheuer, H. Eischeid, B. Ulmer, R. Büttner, M. Odenthal. *University Hospital of Cologne, Pathology, Koeln, Germany*
Email: lwang7@smail.uni-koeln.de

Background and Aims: Chronic liver disease is one the leading health problems, worldwide. Chronic liver disease is characterized by fibrosis with a high risk to end up in hepatocellular carcinoma (HCC). The lysine specific histone 3 demethylase LSD1 is epigenetic writer, known to be upregulated in many cancer types and to trigger tumour growth. Its function in liver disease has not yet been addressed. Therefore, in the present study we investigated its function by global transcriptomic and proteomic analysis in liver disease representative cell types such as liver cancer cells and hepatic stellate cells (HSC).
Method: LSD1 function was inhibited in different hepatocellular carcinoma cell lines (Huh7, Hep3B, and HepG2) and in myofibroblastically activated human hepatic stellate cells (HSC, LX-2) by means of RNA interference or application of a specific LSD1 inhibitor. Cells were functionally characterized by cell growth, cell differentiation, and cell cycle assays using immunostaining and FACS analysis. The microRNA (miRNA) pattern in response to LSD1 inhibition was measured by qPCR arrays followed by signalling pathway analysis for target genes of significant miRNAs. Global transcriptomics was carried out by RNA ultra-deep sequencing and protein expression profiles were analysed by protein mass spectrometry.
Results: LSD1 inhibition initiates cell growth arrest in both, hepatocellular carcinoma cells and myofibroblastically activated HSC. Notably, comprehensive bioinformatic analyses of global changes in transcriptomic and proteomic expression profiles demonstrated pronounced alterations of central mediators involved in cell cycle progression and DNA synthesis. Thus PLK1, TP53, various cycline kinases as well as a set of DNA polymerases expression levels are significantly changed in response to LSD1 inhibition. These results were even more pronounced on protein than on transcript level suggesting that posttranscriptional alterations are involved. miRNA are non-coding RNAs, controlling gene expression posttranscriptionally. Indeed, miRNA profiling reveals a change in miRNA pattern. Interestingly, in HSC LSD1 inhibition did not only alter miRNAs involved in cell cycle control such as miR-34 but additionally lead to an increase of antifibrotically acting miRNAs e.g. miR-29.
Conclusion: Our research demonstrates that LSD1 functions as a central mediator of cell cycle control in both HSC and HCC cells, by induction of global changes in expression profiles.

SAT-189

Sofosbuvir directly promotes the clonogenic capability of human hepatocellular cancer cells

J. Liu, W. Cao, B. Ma, M. Li, M. Peppelenbosch, Q. Pan. *Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology*
Email: j.liu.2@erasmusmc.nl

Background and Aims: Concern has arisen about development of hepatocellular carcinoma (HCC) in patients with hepatitis C virus (HCV) infection treated with direct-acting antivirals (DAAs). However, the mechanism remains largely unknown. This study aims to investigate whether sofosbuvir has direct effect on HCC cells.
Method: Four HCC cell lines including Huh7, Huh6, HepG2 and SNU449, and a Huh7-base HCV replicon were treated with series concentrations of sofosbuvir (0, 0.01, 0.1, 1 umol). Cell viability was investigated by Alamar blue assay and metabolic activity was determined by MTT assay. In addition, colony formation assay was performed to determine clonogenic capability of single cell. The numbers and sizes of colonies were measured and analyzed.
Results: As expected, sofosbuvir potently inhibited HCV replication in the Huh7-based HCV replicon. No major effect was observed on the growth of bulk of HCC cells by sofosbuvir treatment with clinically relevant concentrations in MTT and Alamar blue assays for 48 or 72 hours. Importantly, sofosbuvir significantly increased the colony formation capability of single HCC cells of the four cell lines. Similar effects were also observed in Huh7-based HCV replicon. Sofosbuvir treatment increased the number of formed colonies. For example, in Huh7 cells, treatment with 0.01, 0.1 and 1 umol sofosbuvir resulted in 1.65 ± 0.26, 1.71 ± 0.26 and 1.54 ± 0.20 fold (Mean ± SD, $n = 9$, $p < 0.01$) increase of the numbers of formed colonies, compared with control.
Conclusion: The present study has demonstrated that clinical relevant concentrations of sofosbuvir promote the clonogenic effect of HCC cells. Thus, these results may explain the mechanism how sofosbuvir facilitate HCC development in treating HCV patients.

SAT-190

Gene signature of HDV-associated hepatocellular carcinoma (HCC): differences with HCC associated with other hepatitis viruses

G. Diaz[1], R.E. Engle[2], A. Nice[2], M. Melis[2], S. Montenegro[2], J. Rodriguez-Canale[3], J. Hanson[3], M.R. Emmert-Buck[3], F. Zamboni[4], S. Govindarajan[5], D.E. Kleiner[3], P. Farci[2]. *[1]University of Cagliari, Department of Medical Sciences, Cagliari, Italy; [2]NIAID, National Institutes of Health, Laboratory of Infectious Diseases, Bethesda, United States; [3]NCI, National Institutes of Health, Laboratory of Pathology, Bethesda United States; [4]Hospital Brotzu, Liver Transplantation Center, Cagliari, Italy; [5]University of Southern California, Department of Pathology, Downey, United States*
Email: pfarci@niaid.nih.gov

Background and Aims: Although hepatocellular carcinoma (HCC) develops in patients with chronic hepatitis D, there are no data on the molecular mechanisms whereby HDV promotes liver cancer. Owing to the vital dependence of HDV on HBV, the specific role of HDV in promoting HCC remains to be fully elucidated. The aims were to study the gene expression profiles of patients with HDV-HCC, and to compare them with HCC-HBV alone and HCC-HCV to identify genes that are shared by the three tumors or uniquely associated with one tumor.
Method: Serum and liver specimens obtained at the time of liver transplantation from 5 well-characterized patients with HDV-HCC were analyzed. Gene expression profiling was performed on laser capture-microdissected hepatocytes (LCM, malignant and non-malignant hepatocytes) and whole liver tissue (WLT, tumor and non-tumor tissue) from patients with HDV-HCC, and compared with paired WLT and LCM microarray data from 11 patients with HBV-and 11 with HCV-HCC.
Results: Malignant hepatocytes from HDV HCC were characterized by an enrichment of up-regulated genes associated with pathways involved in cell cycle/DNA replication, damage and repair (sonic hedgehog, GADD45, DNA-damage-induced 14-3-3σ, cyclins and cell-cycle regulation, cell cycle: G2/M DNA-damage checkpoint regulation, and hereditary breast cancer). Moreover, we identified a large network of genes functionally related to DNA repair, cell cycle, mitotic apparatus and cell division, including four cancer testis antigen genes, attesting to the critical role of genetic instability in this tumor. Most genes differentially expressed in malignant hepatocytes from HDV-HCC were co-regulated and over-expressed when compared to non-malignant hepatocytes, as well as to malignant hepatocytes from HCC associated with HBV alone or HCV-HCC. Activation and co-regulation of genes critically associated with DNA replication, damage and repair point to genetic instability as an important mechanism of HDV hepatocarcinogenesis. Interestingly, we found only one pathway shared by HDV- and HBV-HCC and two pathways with HCV-HCC, whereas five pathways were found between HBV- and HCV-HCC.
Conclusion: Gene expression profiling of liver specimens both within and outside the tumor has led to the identification of distinct molecular signatures for each hepatitis virus-associated HCC. Despite

the dependence of HDV on HBV, these two hepatitis viruses appear to promote carcinogenesis by distinct molecular mechanisms.

Cirrhosis: Portal hypertension, and complication

SAT-191

Protective effect of statins in cirrhosis might be dependent on common genetic risk variants

M. Reichert[1], M. Casper[1], R. Liebe[1], R. Greinert[2], E. Vandieken[1], C. Schneider[1], F. Grünhage[1], B. Appenrodt[1], A. Zipprich[2], C. Ripoll[2], F. Lammert[1]. [1]*Saarland University Medical Center, Department of Medicine II, Homburg, Germany;* [2]*Martin-Luther University Halle-Wittenberg, Department of Medicine I, Halle (Saale), Germany*
Email: matthias.reichert@uks.eu

Background and Aims: Complications of liver cirrhosis and hepatic encephalopathy (HE) might be reduced by statins. Common variants in the *PNPLA3* and *MBOAT7* genes contribute to progressive chronic liver disease and cirrhosis, which can cause overt HE (OHE) in risk groups. The aim of this study was to assess the impact of statin therapy in a large cohort of patients with cirrhosis and to investigate its association with complications of cirrhosis including minimal HE (MHE) and OHE in patients stratified for the common genetic risk variants.
Method: During screening for the randomized controlled INCA trial, 750 patients with liver cirrhosis in two German academic medical centers in Homburg and Halle were identified between 02/2014 and 2/2017. Complications of liver cirrhosis were retrospectively assessed applying current EASL criteria. MHE was assessed with critical flicker frequency (CFF), and OHE was defined as West-Haven grade ≥ 2. The patients were genotyped for the common variants *PNPLA3* rs738409 (p.I148M) and *MBOAT7* (rs641738).
Results: In total, 112 statin-users were included in our cohort. CFF measurements were available in 175 patients, and OHE was diagnosed in 144 patients. Concerning cirrhosis complications, OHE (OR 0.46, 95%CI 0.25–0.86; p = 0.013), jaundice (OR 0.54, 95% CI 0.33–0.88; p = 0.011) and variceal bleeding (OR 0.36, 95%CI 0.16–0.80; p = 0.008) were markedly reduced in statin-users, whereas bacterial infections (OR 0.94, 95%CI 0.61–1.42; p = 0.83) or the development of ascites (OR 0.71, 95%CI 0.48–1.07; p = 0.11) where not. In logistic regressions models adjusting for confounders (albumin, bilirubin and age), OHE remained reduced in statin-users (OR 0.46, 95%CI 0.24–0.88; p = 0.018). CFF values show a trend to lower values (40.0 ± 5.9 Hz in statin-users vs. in non-users 42.2 ± 6.4 Hz; p = 0.12). Applying a cutoff of 39.0 Hz, MHE was not associated with statin-use. In total, 435 *PNPLA3* (minor allele frequency [MAF] 29.3%) and 530 *MBOAT7* (MAF 35.6%) risk alleles were detected. In carriers of the risk alleles, no significant effect of statin use on the development of OHE could be detected for the variants in *PNPLA3* (OR 0.55, 95%CI 0.27–1.12; p = 0.12) and *MBOAT7* (OR 0.64, 95%CI 0.32–1.26, p = 0.21), respectively.
Conclusion: In this large cohort, OHE and other complications were markedly reduced in patients with liver cirrhosis who were treated with statins. This effect on OHE was present only in carriers of wild-type alleles of cirrhosis risk genes. Further prospective studies in larger cohorts are warranted to confirm our results.

SAT-192

Determinants of clinical efficacy of empirical antibiotic treatment in patients with cirrhosis and bacterial infections: Results from the ICA global study

R. Maiwall[1], S. Piano[2], V. Singh[3], P. Caraceni[4], C. Alessandria[5], J. Fernandez[6], E. Soares[7], D.J. Kim[8], S.E. Kim[9], M. Marino[10], J. Vorobioff[11], R. de Cassia Ribeiro Barea[12], M. Merli[13], L. Elkrief[14], V.M.V. Blasco[15], A. Krag[16], S. Singh[17], L.A. Lesmana[18], C. Toledo[19], S. Marciano[20], V. Xavier[21], F. Wong[22], N. Intagliata[23], L. Rabinowich[24], L.A. Colombato[25], S.G. Kim[26], A. Gerbes[27], F. Durand[28], J.P. Roblero[29], J.H. Kim[30], R.D. Man[31], D.S. Song[32], C.E. Brodersen[33], A. Gadano[20], S.K. Sarin[34], P. Angeli[35]. [1]*Institute of Liver and Biliary Sciences (ILBS), New Delhi, India;* [2]*University of Padova, University and General Hospital of Padova, Padova, Italy;* [3]*Postgraduate Institute of Medical Education and Research, Chandigarh, India;* [4]*University of Bologna, Bologna, Italy;* [5]*University Hospital of Turin, Turin, Italy;* [6]*Hospital Clinic of Barcelona, Liver Unit, Barcelona, Spain;* [7]*Gastrocenter-Unicamp, Campinas, Brazil;* [8]*Hallym University College of Medicine, Chuncheon, Korea, Rep. of South;* [9]*Hallym University Sacred Heart Hospital, Korea, Rep. of South;* [10]*Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina;* [11]*Universidad Nacional de Rosario, Rosario, Argentina;* [12]*Faculty of Medicine of Bahia, Campo Grande;* [13]*Sapienza University of Rome, Rome, Italy;* [14]*University Hospital of Geneva, Geneva, Switzerland;* [15]*Hospital Vall d'Hebron, Liver Unit, Barcelona, Spain;* [16]*Odense University Hospital, Odense, Denmark;* [17]*Shri Ramachandra Bhanj Medical College, Orissa, India;* [18]*Digestive Disease and Oncology Centre (DDOC)-Medistra Hospital, Jakarta, Indonesia;* [19]*Hospital Valdivia, Universidad Australe de Chile, Valdivia, Chile;* [20]*Hospital Italiano de Buenos Aires, Buenos Aires, Argentina;* [21]*Ghent University Hospital, Ghent, Belgium;* [22]*University of Toronto, Toronto, Canada;* [23]*University of Virginia, Charlottesville, United States;* [24]*Tel-Aviv Medical Center, Tel-Aviv, Israel;* [25]*Hospital Británico de Buenos Aires, Buenos Aires, Argentina;* [26]*Soonchunhyang University, Bucheon Hospital, Bucheon, Korea, Rep. of South;* [27]*University of Munich, Munich, Germany;* [28]*Hospital Beaujon, Liver Unit, Clichy, France;* [29]*Universidad de Chile, Santiago, Chile;* [30]*Konkuk University Medical Center, Seoul, Korea, Rep. of South;* [31]*Erasmus Medical Center, Rotterdam, Netherlands;* [32]*The Catholic University Of Korea, St.Vincent's Hospital, Suwon, Korea, Rep. of South;* [33]*Hospital Carlos Durand, Buenos Aires, Argentina;* [34]*Institute of Liver and Biliary Sciences, Department of Hepatology, Vasant kunj, India;* [35]*University of Padova, Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine, DIMED, Padova, Italy*
Email: pangeli@unipd.it

Background and Aims: The early administration of an effective empirical antibiotic treatment is considered the most important measure in treating patients with cirrhosis and bacterial infections. However, the clinical response may involve several other factors that have never been investigated so far. Thus, in this study we looked for predictors of clinical efficacy to empirical antibiotic treatment in patients with cirrhosis and bacterial infections included in the International Club of Ascites (ICA) "Global Study"
Method: Hospitalized patients with cirrhosis and bacterial/fungal infection were prospectively included at 46 centers. Demographic, clinical, microbiological and treatment data were collected at the diagnosis of infection and during the hospitalization. The patients were followed until death, liver transplantation or discharge. Clinical efficacy of empirical antibiotic treatment was defined by the attending physician according to changes in markers of infection/inflammation, vital signs, improvement of organ failure and results of cultures.
Results: From October 2015 to September 2016, 1,302 patients were included. The most common infections were SBP (27%), UTI (22%) and pneumonia (19%). 26% were nosocomial infections. The most common used empirical antibiotics were third generation cephalosporins (40%), beta-lactams/beta-lactamases inhibitors (32%) and carbapenems (16%); 34% of patients received 2 or more antibiotics. The first line treatment was effective in 61% of cases. Independent predictors of lack of response to empirical treatment were C-reactive

protein (OR = 1.16; P = 0.019), leukocyte count (OR = 1.39, p = 0.008), serum albumin (OR = 0.70; p = 0.003), nosocomial infections (OR = 1.96; p = 0.003), pneumonia (OR = 1.75; p = 0.003), inadequate treatment according to antibiotic susceptibility test (OR = 5.32; p < 0.001) and the severity of ACLF grade (grade 2: OR = 1.58, p = 0.033; grade 3: OR = 4.08; p < 0.001). Patients with lack of response to first line antibiotic treatment had a lower rate of resolution of infection (55 *vs.* 96%; p < 0.001), a higher incidence of second infections (29 *vs.* 15%; p < 0.001), shock (35 *vs.* 7%; p < 0.001) and new organ failures (52 *vs.* 19%; p < 0.001) and a higher in-hospital mortality rate (44 *vs.* 9%; p < 0.001) than responders.
Conclusion: The administration of an adequate empirical antibiotic treatment is just one among factors involved in determining the outcome of infections in cirrhosis. The degree of inflammation, low serum albumin levels and ACLF grade affect clinical response to antibiotics.

SAT-193
The mechanism of irreversibility of late stage cirrhosis
I. Wanless, A. Stueck. *Dalhousie University, Halifax, Canada*
Email: iwanless@eastlink.ca

Background and Aims: Some cirrhotic livers regress with clinical improvement; others do not. Regression is largely the result of a successful bud maturation sequence, allowing repopulation with new hepatocytes by the progenitor reaction located in terminal ductules. This study describes a novel anatomic sequence that explains why some late stage cirrhotic livers fail to regress.
Method: 25 explants with non-biliary cirrhosis (Laennec 4A, 12 and 4B/4C, 13) were examined for clusters of ductules in septal regions along with associated features including progenitor activity (budding, as canals of Hering), ductal degeneration, and fibrosis, using sections stained with trichrome, PASD, and CK19.
Results: Most livers with advanced cirrhosis, but not early cirrhosis, had clusters of ductules lacking evidence of budding, located within septa (69% *vs.* 8%). Most of these clusters had degenerative features (cholangiocyte loss, thickened ductal basement membranes, or annular periductal collagen deposits). Similarly, in 4B/4C livers, the periphery of cirrhotic nodules had focal loss of ductules in 38% and ductule-associated fibrosis in 61%. Loss of ductules was often associated with loss of medium-sized ducts in adjacent septa in 4B/4C livers.
Conclusion: In normal bud maturation, distal ductules are present in small numbers as they are consumed in the maturation process. Thus, clusters of ductules lacking a budding reaction appear to represent proliferated ductules that are redundant because of arrest of the normal bud maturation sequence. These redundant ductules involute in a process that is accompanied by thickening of basement membranes, necrosis of cholangiocytes, and collagen deposition that encases ductules and basement membranes. The mechanism of this "involution sequence" is likely related to the high tissue pressure and congestion seen in late cirrhosis. Similar involution is seen in ischemic settings in liver and other organs, probably through leak of plasma components across vessel walls and basement membranes followed by local fibrosis. Involution of the ductular reaction impedes the regenerative capacity of late stage cirrhosis by the destruction of the progenitor cell niche, as well as the deposition of new fibrosis. Finding this involution signature in tissue indicates failure of the bud maturation sequence and may be a useful prognostic feature.

SAT-194
Acellular growth retardation ability (AGRA), a novel biomarker for humoral immune function, predicts the occurrence of severe bacterial infections in cirrhosis
A. Horvath[1], F. Rainer[2], B. Leber[3,4], B. Schmerboeck[3,4], P. Stiegler[3], V. Stadlbauer[5]. *[1]Department of Gastroenterology and Hepatology, Medical University of Graz, Graz, Austria; [2]Medical University of Graz, Graz, Austria; [3]Medical Universtiy of Graz, Division of Transplantation Surgery, Graz, Austria; [4]Center for Biomarker Research in Medicine, Graz, Austria; [5]Medical Universtiy of Graz, Department for Gastroenterology and Hepatology, Graz, Austria*
Email: angela.horvath@medunigraz.at

Background and Aims: Patients with liver cirrhosis often suffer from severe infections which are commonly accompanied by life-threatening complications. A method to predict the occurrence of severe infection in these patients and therefore improve the chance to prevent them is currently missing. Serum, as many other body fluids and tissues, is rich in antimicrobial peptides and proteins that can kill or inhibit the growth of pathogens, including a wide range of bacteria. Here we introduce a novel biomarker, acellular growth retardation ability (AGRA), that is based on these humoral immune responses to determine the infection risk of patients with liver cirrhosis, and describe its possible applications in liver disease.
Method: AGRA was used to quantify the growth of bacteria challenged by serum of patients with liver cirrhosis (n = 146) or pre-cirrhotic chronic hepatitis C patients (n = 81) or healthy controls (n = 42). Patients with cirrhosis of various aetiologies (n = 101) were followed-up for a median time of 36 months to determine the time to occurrence of the first severe infection after inclusion; 88 patients finished the minimum follow up of 1 year. Patients with chronic hepatitis C infection with and without cirrhosis underwent antiviral therapy and AGRA was monitored throughout its course.
Results: AGRA successfully predicted the occurrence of severe infections in patients with liver cirrhosis (AUROC [95%CI]: 0.8[0.7; 0.9]; p < 0.001) and highlighted a severe impairment of humoral immune responses in chronic hepatitis C patients with cirrhosis. Patients with hepatitis C related cirrhosis showed significantly impaired (=higher) AGRA (0.014 ± 0.012ΔOD/h) compared to patients with alcoholic (0.0016 ± 0.009ΔOD/h; p < 0.001) or other types of aetiologies (−0.0022 ± 0.0068ΔOD/h; p < 0.001) which was in accordance with higher incidence of severe infections in this group. Chronic hepatitis C patients also showed impaired AGRA in absence of cirrhosis compared to healthy controls (0.010 ± 0.013 and −0.0015 ± 0.0069ΔOD/h, respectively; p < 0.001). After antiviral therapy AGRA significantly improved in patients with (p < 0.001) and without cirrhosis (p = 0.001).
Conclusion: AGRA can be used to predict severe infection in cirrhosis and therefore identify patients at risk with increased need for preventive measures. It can also be used to show that impaired humoral immune responses are an extrahepatic manifestation of hepatitis C which can be improved by antiviral therapy.

SAT-195
Assessing Baveno VI criteria with a new point-shear wave elastography technique: The BAVElastPQ study
M. Garcovich, G. Gibiino, B.E. Annicchiarico, M.E. Ainora, L. Riccardi, M. Siciliano, M. Pompili, M.A. Zocco, A. Gasbarrini. *Policlinico A. Gemelli, Internal Medicine, Gastroenterology and Liver Unit, Italy*
Email: giulia.gibiino@gmail.com

Background and Aims: To date no study has explored the potential role of ElastPQ, a novel point-SWE technique, in the assessment of clinically significant portal hypertension. The aim of our study was to determine a liver stiffness (LS) cut-off value measured by ElastPQ and/or laboratory parameters that could help identify those patients who can safely avoid screening endoscopy, similarly to the recently proposed Baveno VI criteria which recommends a LS value <20 kPa measured by transient elastography in combination to a platelet count >150,000/μl.
Method: Data was collected on 1432 patients who underwent ElastPQ measurement from January 2013 to January 2016 in our Department. Inclusion criteria were a LS value of ≥7 kPa (to reasonably rule-in all patients with advanced fibrosis and cirrhosis) and an upper gastrointestinal endoscopy within 12 months, with a diagnosis of compensated chronic liver disease. Exclusion criteria

were history of decompensated liver disease, evidence of porto-spleno-mesenteric vein thrombosis and non-cirrhotic portal hypertension. Varices were graded as low risk (grade <2) or high risk (grade ≥2).

Results: The study included 195 patients (120[61%] HCV, and 171 [88%] Child-Pugh A). Varices were present in 35% cases, with 10% prevalence of high risk varices. According to ROC curve analysis LS measurement and platelet count were evaluated as predictors of high risk varices. Overall 75/195 (38%) met the "BAVElastPQ" criteria (that is, LS <12 kPa and platelet count >150,000/μl). Within this group 11/64 (17%) had any grade of varices and only 1/74 (1%) had high risk varices. The BAVElastPQ criteria gave sensitivity of 0.95, specificity of 0.42, positive predictive value of 0.15 and negative predictive value of 0.99. The AUROC for LS and platelet count was 0.80 and 0.76, respectively.

Conclusion: The BAVElastPQ criteria correctly identified 99% of patients without high risk varices. By applying such criteria we could have potentially avoided 38% surveillance endoscopies in our cohort.

SAT-196

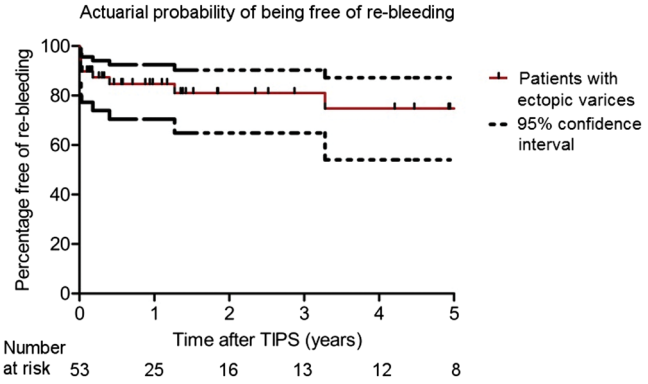
The efficacy and clinical outcome of transjugular intrahepatic portosystemic shunts in the management of ectopic variceal bleeding: a multicenter retrospective study

R. Oey[1], K. de Wit[2], A. Moelker[3], T. Atalik[1], O. van Delden[4], G. Maleux[5], N. Erler[6,7], B. Takkenberg[2], R. De Man[8], F. Nevens[9], H. Van Buuren[8].
[1]Erasmus MC University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [2]Academic Medical Center, Department of Gastroenterology and Hepatology, Amsterdam; [3]Erasmus MC University Medical Center, Department of Radiology, Rotterdam, Netherlands; [4]Academic Medical Center, Department of Radiology, Amsterdam, Netherlands; [5]University Hospitals Leuven, Department of Radiology, Leuven, Netherlands; [6]Erasmus MC University Medical Center, Deapartment of Biostatistics, Rotterdam, Netherlands; [7]Erasmus MC University Medical Center, Department of Epidemiology, Rotterdam; [8]Erasmus MC University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [9]University Hospitals Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium
Email: r.oey@erasmusmc.nl

Background and Aims: Ectopic varices – portosystemic venous collaterals located outside the gastro-esophageal region – cause up to 5% of all variceal bleeding. Current evidence suggests that transjugular intrahepatic portosystemic shunts (TIPS) is usually effective for bleeding ectopic varices, but research has been largely restricted to small series. We aimed to study the efficacy and clinical outcome of TIPS for ectopic variceal bleeding and to assess the benefit of concomitant vascular embolization.

Method: Retrospective analysis of chronic liver disease patients with ectopic variceal bleeding, who received TIPS in 3 tertiary centers between 1995–2015.

Results: The study included 53 patients with TIPS placement for ectopic variceal bleeding (70% male, mean age 58 years (±18), median MELD 11 (IQR 9–17)). The ectopic varices were most often located around the insertion of stomas (40%), followed by the duodenum (23%), rectum (17%), and other sites (20%). Before TIPS was created, 76% of the patients had been unsuccessfully treated with endoscopy, medication, surgery, and/or vascular embolization. TIPS decreased the portosystemic gradient from 14 mmHg (IQR 10–20) to 6 mmHg (IQR 4–7). The median follow-up time was 14.0 months (IQR 3.8–45.9). After TIPS placement, the estimated cumulative re-bleeding rate was 23% at 1 year, 26% at 3 years and 32% at 5 years. The hazard ratio for re-bleeding was higher in patients with TIPS dysfunction (HR 9.46; 95%CI 2.46–36.33), and a high MELD score (HR 1.11 per point; 95%CI 1.02–1.20). Post-TIPS hepatic encephalopathy (HE) manifested or worsened in 16 patients (30%). HE could be managed with medication in 12 patients; however, in 4 patients a stent diameter reduction was necessary. In this cohort, 41 patients died, 5 underwent liver transplantation, 6 were alive at the end of follow-up and 1 was lost to follow up. The estimated 30-day, 1-year, and 5-year mortality rates were 11% (SE 0.04), 41% (SE 0.07) and 75% (SE 0.07), respectively. Multivariate analysis identified the presence of gastro-esophageal varices (HR 3.89; 95%CI 1.23–12.29) and MELD score (HR 1.08 per point; 95%CI 1.01–1.15) as independent risk factors for poor survival. Concomitant embolization during the TIPS procedure was performed in 13 patients. The hazard ratios of concomitant embolization compared to TIPS alone, were 0.83 (95% CI 0.30–4.43) for re-bleeding and 1.13 (95%CI 0.52–2.43) for mortality.



Conclusion: TIPS is an effective treatment in patients with ectopic variceal bleeding, preventing re-bleeding in approximately 70% of cases after 5 years. However, overall survival was poor and mainly associated with the severity of the underlying liver disease. Concomitant embolization seemed not associated with a lower risk for re-bleeding or improved survival, but considering the study design and the limited number of patients treated, we were unable to reliably assess the value of embolization as an adjunctive measure.

SAT-197

Outcomes of pregnancy in women with cirrhosis – a national, population-based cohort study

H. Hagström[1,2], J. Höijer[3], H.-U. Marschall[4], C. Williamson[5,6], M. Heneghan[7], R. Westbrook[8], J.F. Ludvigsson[9], O. Stephansson[2,10].
[1]Karolinska University Hospital, Center for Digestive Diseases, Unit of Hepatology, Stockholm, Sweden; [2]Karolinska Institutet, Department of Medicine Solna, Clinical Epidemiology Unit, Sweden; [3]Karolinska Institutet, Unit of Biostatistics, Department of Environmental Medicine, Stockholm, Sweden; [4]University of Gothenburg, Sahlgrenska Academy, Institute of Medicine, Department of Molecular and Clinical Medicine and Wallenberg Laboratory, Gothenburg, Sweden; [5]Imperial College London, Institute of Reproductive and Developmental Biology, United Kingdom; [6]King's College London, Women's Health Academic Centre, United Kingdom; [7]King's College Hospital, Institute of Liver Studies, United Kingdom; [8]Royal Free Hospital, London, United Kingdom; [9]Karolinska Institutet, Department of Medical Epidemiology and Biostatistics, Stockholm, Sweden; [10]Karolinska Institutet, Division of Obstetrics and Gynecology, Department of Women's and Children's Health, Stockholm, Sweden
Email: hannes.hagstrom@ki.se

Background and Aims: Pregnancy in women with cirrhosis is considered a rare event, with little published data on possible complications. We examined pregnancy-related and liver-related outcomes in women with cirrhosis.

Method: We used Swedish population-based registers to define exposure and outcomes. All Swedish women admitted for antenatal care with singleton births were included. Exposure status was defined as an ICD 10-code for cirrhosis obtained prior to or during pregnancy. Pregnancy- and liver-related outcomes during pregnancy were investigated. Poisson regression with cluster robust standard

errors was used to estimate relative risks (RR), adjusted for age, smoking and body mass index.
Results: Between 1997–2011, we identified 68 pregnant women with cirrhosis. These were compared to 1 361 427 women without ICD-coding for cirrhosis. The most common causes of cirrhosis were viral hepatitis and autoimmune hepatitis (14 cases each). During the study period, pregnancy in cirrhotic women increased from 5 cases in 1997–2001 to 16 cases in 2002–2006 and 47 cases in 2007–2011.
Compared to women without cirrhosis, women with cirrhosis were at increased risk of Caesarean section (23 cases, RR 1.88, 95%CI 1.29–2.75), low birth weight (10 cases, RR 3.51, 95%CI 1.60–7.70), preterm delivery (14 cases, RR 3.85, 95%CI 2.20–6.73), neonatal death (1 case, RR 12.42, 95%CI 1.75–88.39), but not from maternal mortality during pregnancy (0 cases), gestational diabetes (0 cases), pre-eclampsia (2 cases, RR 0.74, 95%CI 0.11–5.02), small for gestational age (5 cases, RR 0.69, 95%CI 0.10–4.86), stillbirth (1 case, RR 5.34, 95%CI 0.78–36.33) or malformations (1 case, RR 0.53, 95%CI 0.08–3.58).
During pregnancy, twelve cases were hospitalized due to liver-related events (RR 2369, 95%CI 1052–5336) including five cases with therapy of esophageal varices (RR 2369, 95%CI 1052–5336). There were no cases of liver-related deaths.
Conclusion: In this population-based cohort, cirrhosis was a rare but increasingly common diagnosis in pregnant Swedish women. Women with cirrhosis were at increased risk for hospitalization for liver-related events, and an increased risk for some pregnancy-related outcomes was found. However, severe maternal and fetal adverse events were rare, and a successful pregnancy in cirrhotic women is likely a realistic outcome.

SAT-198

Prevalence and resistance rates of infections with enterococci in patients with cirrhosis

T. Bucsics[1,2], M. Emich[1,2], M.-C. Nackenhorst[1,2], E. Berger[1,2], P. Schwabl[1,2], M. Mandorfer[1,2], B. Scheiner[1,2], A. Ferlitsch[1,2], T. Reiberger[1,2], M. Trauner[1]. *[1]Medizinische Universität Wien, Internal Medicine III, Wien, Austria; [2]Medical University of Vienna, Hepatic Hemodynamic Laboratory, Vienna, Austria*
Email: theresa.bucsics@meduniwien.ac.at

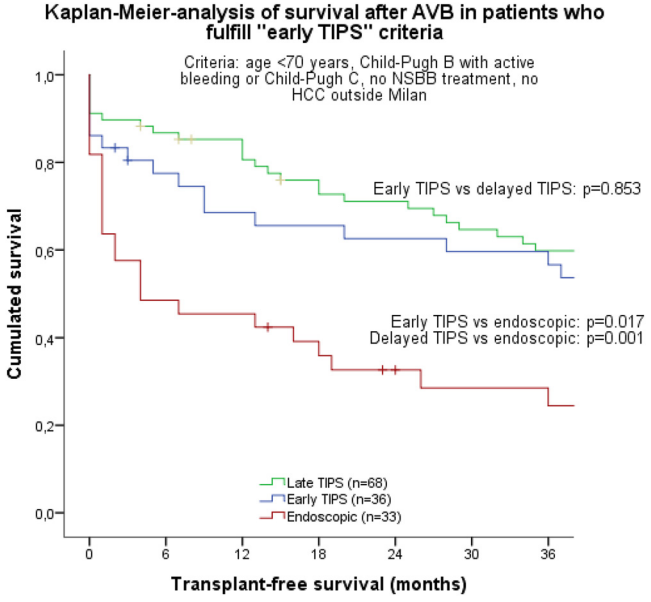
Background and Aims: We and others have recently observed an increase in infections with enterococci in patients with liver cirrhosis. Enterococcal infections comprise a considerable threat to cirrhotic patients, since cephalosphorins (lacking activity against enterococci) are often recommended by guidelines as empirical antibiotic therapy in cirrhosis, and multi-drug resistant enterococci strands might emerge. Thus, we assessed microbial epidemiology and antibiotic resistance (AR) of enterococcal infections in patients with cirrhosis.
Methods: Microbiologic reports of samples collected from consecutive patients treated at a tertiary liver center were systematically screened for bacterial infections. Only patients with a confirmed diagnosis of cirrhosis were considered. Blood stream infections (BSI), urinary tract infections (UTI), respiratory tract infections (RTI), and ascites cultures/spontaneous bacterial peritonitis (SBP) including the respective antibiograms were retrospectively evaluated.
Results: We evaluated 1963 positive cultures (UTI: n = 422, BSI: n = 673, SBP: n = 467; RTI: n = 401) from 7,077 samples of patients with cirrhosis. Enterococci were found in 17.2% of positive cultures (UTI: 25.4%, BSI: 13.4%, SBP: 21.2%, RTI: 6.2%) and AR was tested in 85.3%. Resistances to ≥1 antibiotic classes (AC) were found in 37.9%; 10.9% of cultivated enterococci were resistant to at least 2 AC. While no resistance to aminopenicillins was found in outpatient enterococcal infections, aminopenicillin-resistant strands from nosocomial infections were tested in 36.7% (n = 91/248; UTI: n = 29/76, 38.2%; BSI: n = 19/53, 26.8%; SBP: n = 29/81, 35.8%; RTI: n = 14/20, 70.0%). Vancomycin-resistant enterococci (VRE) were found in 12.1% (UTI: 7.9%; BSI: 15.5%; SBP: 16.0%; RTI: 0.0%). We did not observe any resistance of isolated enterococci species to linezolid.
Conclusions: Enterococci are common pathogens in SBP, respiratory and urinary tract infections in patients with cirrhosis. Thus, we cannot recommend the use of cephalosporins or quinolones for empiric treatment of suspected infections in patients with cirrhosis. Multiclass-resistance and VRE were found in about 10% of cases, respectively. For cirrhotic outpatients or uncomplicated infections, we recommend aminopenicillins as empiric antibiotic treatment, while for nosocomial infections a combination of penems and Gram-positive agents should be used. Our data underline the importance of assessing the local microbial epidemiology and resistance profiles in patients with cirrhosis.

SAT-199

Effectiveness of "early" TIPS implantation versus "late" TIPS versus standard endoscopic treatment for acute variceal bleeding in patients with liver cirrhosis

T. Bucsics[1], M. Schoder[2], M. Mandorfer[1], P. Schwabl[1], F. Riedl[1], D. Bauer[1], M. Trauner[1], M. Peck-Radosavljevic[1,3], J. Karner[4], F. Karnel[5], T. Reiberger[6]. *[1]Medical University of Vienna, Internal Medicine III, Vienna, Austria; [2]Medical University of Vienna, Biomedical Imaging and Image-guided Therapy, Vienna, Austria; [3]Klinikum Klagenfurt am Woerthersee, Internal Medicine, Klagenfurt am Woerthersee, Austria; [4]Sozialmedizinisches Zentrum Sued, Kaiser-Franz-Josef-Spital, Surgery, Vienna; [5]Sozialmedizinisches Zentrum Sued, Kaiser-Franz-Josef-Spital, Radiology, Vienna; [6]Medical University of Vienna, Internal Medicine III, Vienna*
Email: theresa.bucsics@meduniwien.ac.at

Introduction: Early implantation of a transjugular intrahepatic portosystemic shunt (TIPS) within 72 h is recommended for the treatment of acute variceal bleeding (AVB) in selected patients. However, early TIPS may not always be readily available.
Methods: In this retrospective analysis, we evaluated outcomes of patients who were treated for AVB and fulfilled criteria for early TIPS implantation. We compared patients who received "*early TIPS*" (<72 hours, n = 36), to eligible patients who underwent TIPS implantation at a delayed time point (72h-28 days after AVB, "*delayed TIPS*", n = 68) and to eligible patients who underwent rebleeding prophylaxis by combined endoscopic/nonselective betablocker treatment ("*EBL/NSBB*", n = 33).



Results: With a mean age of 60.5 ± 10.9 years, patients in the "EBL/NSBB" control group were older than TIPS patients (early TIPS: 54.3 ± 9.3 years, p = 0.013; delayed TIPS: 52.2 ± 10.0 years; p = 0.001).

Baseline MELD scores were comparable between groups ("early TIPS" patients: 12.8, 11.7–15.7 *vs.* "delayed TIPS" patients: median 12.4, IQR: 10.4–15.0; p = 0.242 *vs.* "EBL/NSBB" controls: 13.6, 10.5–16.7, p = 0.687). TIPS implantation was generally associated with low early re-bleeding (early TIPS: 8.3% *vs.* delayed TIPS 2.9%, p = 0.338) and low overall re-bleeding rates (early TIPS: 30.6% *vs.* delayed TIPS: 33.8%, p = 0.735) when compared to "EBL/NSBB" controls (36.4% and 51.5%, respectively, p = 0.005 and p = 0.077 *vs.* "early TIPS").
Similarly, bleeding-related mortality within 6 weeks (early TIPS: 16.7%; delayed TIPS: 8.8%) and mortality at one-year (early TIPS: 30.6%, delayed TIPS: 13.2%) appeared lower with TIPS as compared to "EBL/NSBB" controls, who showed a bleeding-related mortality of 35.7% (p = 0.081 *vs.* early TIPS; p = 0.003 vs. delayed TIPS) and 1-year mortality of 53.6%. (p = 0.063 *vs.* early TIPS, p < 0.001 *vs.* delayed TIPS). After adjusting for age and MELD as established risk factors for mortality in Cox regression analysis, both "early TIPS" (OR: 0.524, p = 0.041) and "delayed" TIPS (OR 0.548, p = 0.021) were effective in reducing mortality after AVB.
Conclusions: TIPS implantation effectively prevents variceal re-bleeding and reduces mortality in selected patients after AVB as compared to EBL/NSBB combination therapy – even if not placed not within <72 h but within <28 days. Thus, we recommend TIPS implantation for AVB in all patients who fulfill "early TIPS" criteria, even when "early TIPS" implantation within 72 h is not possible.

SAT-200

Cholemic nephropathy is frequently observed in jaundiced patients and associated with increased mortality

M. Young-Seon[1], J. Schmitz[2], R. Schmitt[3], M.P. Manns[1], J.H. Bräsen[2], I. Mederacke[1]. *[1]Hannover Medical School, Gastroenterology, Hepatololgy, and Endocrinology, Hannover, Germany; [2]Hannover Medical School, Pathology, Hannover, Germany; [3]Hannover Medical School, Nephrology and Hypertension, Hannover*
Email: mederacke.ingmar@mh-hannover.de

Background and Aims: Impairment of renal function often occurs in patients with liver disease and is associated with an increased mortality. Hepatorenal syndrome is a significant cause of acute kidney injury (AKI) in cirrhotic patients (HRS-AKI, type 1), however, a kidney biopsy to exclude structural causes of kidney disease is rarely performed owing to increased risk of bleeding in this cohort. Causes of non-HRS AKI include cholemic nephropathy (CN), a disease that has regained attention recently and that is characterized by intratubular cast and tubular injury. As data on patients with CN is mostly obtained from case reports or autopsy studies, we aimed to investigate the prevalence and clinical course of CN in a tertiary care hospital over a 16-year period.
Method: We identified 149 patients who underwent kidney biopsy from 2000 to 2016 at the Department of Gastroenterology, Hepatology and Endocrinology. Of these 79 had a history of liver disease and deterioration of renal function and were included into this study. Laboratory values and clinical course of the patients were obtained by retrospective chart analysis. Biopsies were reevaluated to confirm the diagnosis of CN.
Results: The mean age of the patients was 52.2 ± 10.8 years and 71% were male patients (56/79). One quarter of the patients had a history of organ transplantation (liver or kidney), cirrhosis detected by liver biopsy or ultrasound was observed in 43 of 79 patients (54.4%). The average creatinine at the time of biopsy was 256 ± 181 µmol/l. Consistent with the increased risk of bleeding in patients with advanced liver disease 25 patients had an INR >2 or platelet count <100.000/µl. Biopsy related complications occurred in six of 79 patients, one of them required surgical therapy. Renal biopsy revealed the diagnosis of CN in 10.1% of the patients (8/79). Patients with CN presented with significantly higher bilirubin (779 ± 306 *vs.* 66 ± 110 µmol/l, p < 0.001), whereas creatinine, ALT, AST, INR, liver function and blood count were similar in both groups. Of note, patients with CN secreted bilirubin (100%) and urobilirubinogen (50%) in the urine, compared to 15% and 13 of the non-CN patients, respectively (p < 0.05). Most importantly, diagnosis of CN was linked with increased mortality (p < 0.05).
Conclusion: Cholemic nephropathy is associated with increased mortality and should be considered as a cause of impaired renal function in patients with liver disease and elevated bilirubin levels.

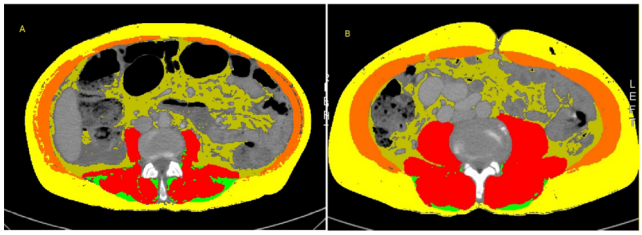
SAT-201

The area of the paarspinal muscle mass in patients with cirrhosis although not different from controls predicts cirrhosis-associated complications and death in a large mono-centric study

C. Engelmann[1,2], I. Nonnenmacher[3], L. Werlich[4], M. Moche[4], S. Ulrich[4], T. Kaiser[5], K. Sandra[3], K. Zeller[3], M. Bartels[6], T. Kahn[4], A. Surov[4], D. Seehofer[6], S. Schob[7], T. Berg[3]. *[1]University College London, ILDH, London, United Kingdom; [2]University Hospital Leipzig, Section Hepatology, Department of Gastroenterology and Rheumatology, Leipzig, Germany; [3]University Hospital Leipzig, Section Hepatologie, Department of Gastroenterology and Rheumatology, Leipzig, Germany; [4]University Hospital Leipzig, Clinic and Policlinic of Diagnostic and Interventional Radiology, Leipzig, Germany; [5]University Hospital Leipzig, Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics, Leipzig, Germany; [6]University Hospital Leipzig, Department of Visceral, Vascular, Thoracic and Transplant Surgery, Leipzig, Germany; [7]University Hospital Leipzig, Department for Neuroradiology, Leipzig, Germany*
Email: cornelius.engelmann@medizin.uni-leipzig.de

Background and Aims: Loss of skeletal muscle mass (sarcopenia) has been increasingly recognized as a complication of cirrhosis potentially predicting patients' outcome. At present, it is not clear whether sarcopenia contributes to the occurrence of cirrhosis complications or survival after transplantation. We therefore conducted a large retrospective trial exploring the impact of the skeletal muscle mass on complications and survival in cirrhosis.
Method: Of the 1328 patients with liver cirrhosis listed for liver transplantation between March 2001 and September 2014 at the University Hospital Leipzig, 795 met the in- and exclusion criteria including an abdominal CT-scan (± 200 days). 109 patients without liver diseases who received a CT scan as part of the initial work-up for polytrauma served as controls. The area of the paraspinal muscle, the abdominal wall muscles and the combination of both were assessed at L3 and normalized to the height (displayed in cm^2/m^2) (Figure 1). Data were retrospectively analysed and correlation with clinical data obtained from medical records. As the normalized paraspinal muscle mass (nSM1) was the most reliable parameter, data is primarily described for nSM1.

Figure 1: CT-scan at L3 level in a patients with reduced muscle mass (A) and control patients (B)



SM1 (red) – paravertebral muscles; SM2 (orange) – abdominal wall muscles; SMtotal – SM1 + SM2

Results: Of 795 patients with liver cirrhosis 493(62%) had an alcoholic liver disease and 561(70.6%) were male. The majority had a MELD score between 12–24(57.3%) and were allocated to Child-Pugh (CP) class B (45.7%). Median nSM1 of 24.9(12.1–46.2) in cirrhosis was not significantly different to 25.7(12.6–40) in controls. In subgroups of patients with history of cirrhosis-related complications median nSM1 was significantly smaller then in controls (hepatorenal syndrome (HRS) 21(12.1–33.9); hepatic encephalopathy

(HE) 23,6(12.1–40); SBP 22.5(14,5–36.5); ascites 23((12.1–40); p < 0.0001). Patients with high CP class and high MELD score had also a reduced median nSM1. In a multivariate regression model adjusting for gender, age, BMI, MELD a reduced skeletal muscle mass in cirrhosis was associated with an increasing risk for the occurrence of new complications such as SBP (HR 0.93, p = 0.006), HE (HR 0.934, p = 0.046), HRS (HR 0.946, p = 0.013) and variceal bleeding (HR 0.935, p = 0.039). The discrimination of nSM1 (1-year survival on the waiting list) was 0.625 (0.573–0.678). Combining the nSM1 with MELD in a score increased the AUC to 0.697 (0.647–0.746), which was superior to MELD (0.678 (0.628–0.727). The post transplant survival was not associated with any of the muscle parameter.
Conclusion: This is until now the largest study evaluating the impact of skeletal muscle mass on patients' outcome in cirrhosis. The paraspinal muscle mass is a reliable predictor for the occurrence of cirrhosis related complications. This shows, that a reduced skeletal muscle mass is a sign for end-stage liver cirrhosis, necessitating preventive surveillance strategies and curative treatment approaches.

SAT-202

TLR9-mediated immune sensing of bacterial DNA in decompensated cirrhosis is stage-dependent

E. Al-Herwi, S. Stengel, C. Golembiewski, A. Steube, A. Stallmach, T. Bruns. *Jena University Hospital, Dpt. of Internal Medicine IV, Jena, Germany*
Email: eihab.alherwi@med.uni-jena.de

Background and Aims: Altered local and systemic levels of type-I interferons (IFN) have been linked to impaired antibacterial capacity in animal models of cirrhosis and to a higher risk of death in patients with alcoholic cirrhosis. DNA sensing by immune competent cells is known to elicit strong type-I IFN responses, which may play a role in the context of bacterial translocation in cirrhosis. Aim of this study was to characterize immune responses towards CpG-rich single stranded DNA oligonucleotides from E. coli (ssE.coli CpG) in monocytes from patients with decompensated cirrhosis and from healthy controls.
Method: CD14+ monocytes were isolated by density gradient separation and immunomagnetic sorting. Cells were transfected with ssE.coli CpG and bioactive type-I IFN in supernatants or serum was measured using an IFN reporter cell assay. IL-6, TNF, and IL-10 were quantified using ELISA and qRT-PCR.
Results: Serum type-I IFN bioactivity was elevated above 30 pg/ml IFN-β equivalent in 32% of patients with decompensated cirrhosis and ascites. As compared to healthy individuals, purified monocytes from patients with decompensated cirrhosis secreted higher levels of IL-6 (p= 0.007) and type-I IFN (p = 0.001) after isolation indicating recent pro-inflammatory activation. In contrast to LPS, ssE.coli CpG was a potent inducer of type-I IFN release and IFNA, IFNB, and IFN-response gene expression. Overall, the treatment of monocytes from patients with cirrhosis with ssE.coli CpG in vitro resulted in a significantly increased release of IL-6 (p = 0.0001) and bioactive IFN (p = 0.0002) compared to healthy individuals, although some patients had diminished type-I IFN secretion. In patients with decompensated cirrhosis (n = 43), advanced disease states were associated with reduced ssE.coli CpG-induced type-I IFN release from monocytes, which correlated with serum bilirubin (r = –0.41; p = 0.008), international normalized ratio (r = –0.33; p = 0.04), and serum albumin (r = 0.41; p = 0.01). Prevention of endosomal acidification with chloroquine abrogated type-I IFN release, indicating a primary role of endosomal but not cytoplasmatic DNA sensing in this process.
Conclusion: Monocytes from patients with decompensated cirrhosis are potent producers of type-I IFN in response to bacterial DNA. Consistent with a concept of cirrhosis-associated immune dysfunction in cirrhosis, both, TLR9-mediated hyperinflammatory as well as blunted immune responses are observed in different disease states.

SAT-203

Longitudinal outcomes of the application of non-selective beta-blockers in portal hypertension: Are low-dose non-selective beta-blockers effective?

S.H. Kang[1], M.Y. Kim[1], Y.O. Jang[1], M. Lee[2], B.G. Jun[3], T.-S. Kim[2], K.T. Suk[4], S.K. Baik[5]. *[1]Yonsei University Wonju College of Medicine, Internal Medicine, Wonju-si, Korea, Rep. of South; [2]Kangwon National University Hospital, Internal medicine, Chuncheon-si, Korea, Rep. of South; [3]University of Ulsan College of Medicine, Internal Medicine, Gangneung-si, Korea, Rep. of South; [4]Hallym University College of Medicine, Internal Medicine, Chuncheon-si, Korea, Rep. of South; [5]Yonsei University Wonju College of Medicine, Department of Internal Medicine, Wonju, Korea, Rep. of South*
Email: drkimmy@yonsei.ac.kr

Background and Aims: The effect of non-selective β-blockers (NSBBs) on survival in decompensated liver cirrhosis is still disputed. Moreover, the majority of physicians use a low-dose NSBB for cirrhotic patients due to occurrence of side effects, including orthostatic hypotension, dizziness and poor intolerance instead of using the maximally-tolerated dose of NSBB, as recommended by the guidelines. We investigated whether a low-dose NSBB has beneficial effects compared to maximally tolerated doses in real life data.
Method: We conducted a retrospective study involving 260 consecutive patients with controlled esophageal variceal bleeding who had hepatic venous pressure gradient (HVPG) measurements; 195 patients were given a NSBB (NSBB group) and 65 patients were not given a NSBB (non-NSBB group). The NSBB group was divided into 2 sub-groups, as follows: low-dose group, (≤ 80 mg; n = 67); and high-dose group (>80 mg; n = 128). The primary outcome was all-cause mortality in patients receiving or not receiving NSBB as prophylaxis against variceal bleeding.
Results: The baseline characteristics between the NSBB and non-NSBB groups were similar, including the Child-Turcotte-Pugh (CTP) score. The median duration and dose of NSBB therapy were 37.5 months (Interquartile range [IQR], 15.0–58.8) and 120 mg/day (IQR, 80–160). During the median follow-up of 38.5 months, survival was better in the NSBB group than the non-NSBB group (56.4% *vs.* 27.7%; p < 0.001). Based on multivariate analysis, NSBB significantly prolonged survival after adjusting for CTP and MELD score (adjusted hazard ratio [aHR], 0.472; p < 0.001). An analysis according to the dose of NSBB showed that survival was not different between the low- and high-dose groups (59.7% *vs.* 54.7%; p = 0.503). When stratified by the baseline HVPG level, the aHR for NSBB therapy was 0.514 (p = 0.002) in patients with a low HVPG (≤20 mmHg). Among patients with a high HVPG (>20 mmHg), NSBB use was associated with increased survival (aHR, 0.350; p = 0.005). Survival did not differ significantly between the low- and high-dose groups by stratifying the HVPG level (low HVPG [66.0% *vs.* 56.4%; p = 0.113] and high HVPG [35.7% *vs.* 48.4%; p = 0.695]).
Conclusion: In patients with cirrhosis, NSBB therapy was associated with a reduced risk of mortality that was independent of the severity of portal hypertension. Moreover, our study showed that there was a similar effect on survival when a low-dose NSBB was used. This result implies that there is an additional non-hemodynamic benefit to low-dose NSBB use.

SAT-204

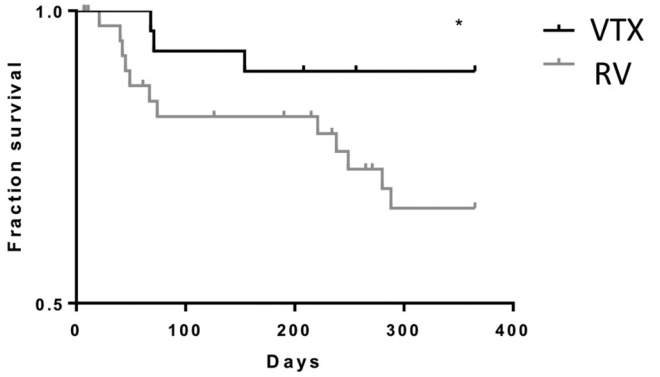
Sub maximally dilated Viatorr CX improves one-year survival compared to conventional covered TIPS: a case-control study

M. Praktiknjo[1], S. Fischer[2], C. Pieper[2], C. Jansen[1], A. Pohlmann[1], J. Lehmann[1], C.P Strassburg[1], D. Thomas[2], C. Meyer[2], J. Trebicka[1,3]. *[1]University Hospital Bonn, Department of Internal Medicine I, Bonn, Germany; [2]University Hospital Bonn, Radiology, Bonn, Germany; [3]EFCLIF, Barcelona, Spain*
Email: jonel.trebicka@ukbonn.de

Background and Aims: Transjugular intrahepatic portosystemic shunt (TIPS) is an effective treatment for complications of portal

hypertension but might also cause complications. Development of hepatic encephalopathy and/or cardiac dysfunction after TIPS might be among others due to the effective shunt diameter. Recently, we showed that all underdilated TIPS passively expand to nominal diameter, and that the use of the novel 10 mm Viatorr® Controlled Expansion (VTX) leads to less readmissions in patients after months compared to regular Viatorr® (RV) and bare-metall-stents in the case of submaximal dilated to 8 mm (EASL 2017). This abstract reports the one-year outcome of Viatorr® Controlled Expansion compared to regular Viatorr®, when both groups received 10 mm stents and are submaximal dilated to 8 mm.

Method: 35 patients receiving VTX were matched with 34 patients receiving RV. All patients reveived 10 mm stents (either VTX or RV), which were submaximal dilated to 8 mm. Indication was ascites in 25 VTX and 27 RV patients. In a subset of 10 patients receiving VTX, portal-systemic pressure gradient (PSPG) was assessed 3 to 10 days after TIPS and compared to the values at TIPS. 3D-ultrasound evaluated the passive expansion of these underdilated stents. Clinical, neuropsychiatric, lab work and duplex sonography data were assessed during follow up visits 3 months and one year after TIPS implantation.



Results: The baseline characteristics were similar in both groups (RV *vs.* VTX: MELD 12 *vs.* 13, MELD-Na 14 *vs.* 15, Child 8 *vs.* 8). After TIPS the PSPG increased significantly in the patients receiving VTX from 9.8 mmHg to 10.5 mmHg ($p < 0.01$). While RV passively dilated to nearly full diameter, VTX did not dilated significantly. 3 months after TIPS MELD did not change significantly, but MELD-Na score improved in significantly only in VTX group (15 to 13). Patients receiving the novel expansion control VTX showed significantly less readmissions for hepatic encephalopathy (16% VTX *vs.* 46% RV; $p < 0.001$) and all-cause readmission (0.46 episodes per patient in VTX group and 1.09 per patient in RV group). While in the short-term follow-up of 3 months, overall survival was not significantly different between the groups, one year follow up revealed a significant improvement in survival in VTX group (see Figure).

Conclusion: The novel Viatorr® Controlled Expansion stents reduces episodes of readmission for hepatic encephalopathy and for any cause. Importantly, this beneficial effect was only observed after 3 months of implantation and improves one-year survival. These data suggest that full passive expansion in patients with submaximal dilation of the TIPS, might be at least partly responsible for post-TIPS complications and mortality.

SAT-205

Prognosis after abdominal surgery in patients with idiopathic non-cirrhotic portal hypertension: A multicenter retrospective study

L. Elkrief[1], J. Ferrusquia[2], P. Audrey[3], L. Moga[4], T. Luis[5], M. Praktiknjo[6], B. Procopet[7], R. Yuldashev[8], H. Geovanni[2], V. Hernandez-Gea[2], A. Albillos[5], J. Trebicka[6], L. Spahr[1], A. Plessier[3], D. Valla[3], L. Rubbia-Brandt[1], C. Toso[1], C. Bureau[4], G.P.J. Carlos[2], P.-E. Rautou[3].
[1]Hôpitaux Universitaires de Genève, Geneva, Switzerland; [2]Hospital Clinic de Barcelona, Barcelona, Spain; [3]Hôpital Beaujon, Clichy, France; [4]CHU Toulouse, Toulouse, France; [5]Hospital Universitario Ramon y Cajal, Madrid, Spain; [6]University of Bonn, Bonn, Germany; [7]University of Cluj-Napoca, Cluj, Romania; [8]Pediatric surgery, Tashkent, Uzbekistan
Email: laure_elkrief@yahoo.fr

Background and Aims: Idiopathic noncirrhotic portal hypertension (INCPH) is a heterogeneous group of diseases characterized by portal hypertension in the absence of cirrhosis or other specific causes of portal hypertension. Data on morbi-mortality of abdominal surgery in patients with INCPH is very limited. Our aims were (i) to assess the outcome of patients with INCPH undergoing abdominal surgery; and (ii) to identify predictors of poor outcome.

Method: We retrospectively analyzed the charts of patients with known INCPH undergoing abdominal surgery in 8 centers of the VALDIG consortium between 2002 and 2017. We analyzed features associated with: (i) liver-related complications within 3 months after surgery; (ii) liver transplantation or death, within 6 months after surgery. Data are median (IQR).

Results: Thirty-nine patients (24 men, median age 51 years) with biopsy-proven INCPH were included. One or more extrahepatic condition known to be associated with INCPH (*i.e.* immunological or genetic disorders, infections, drugs or toxins, or prothrombotic conditions) were found in 23 (59%) patients. Surgical procedures included hernia repair (n = 10), cholecystectomy (n = 6), splenectomy (n = 5), colorectal (n = 6), urologic (n = 4), gastric/pancreatic surgery (n = 2) and other procedures (n = 6). Twelve patients had a TIPSS (n = 9) or a portocaval surgical shunt (n = 3) 0.8 (0.1–33.7) months prior to surgery to treat refractory complications of portal hypertension (n = 9) or to prepare surgery (n = 3). Liver-related complications occurred in 15 (39%) patients within 3 months after surgery. Five patients required a TIPSS for refractory complications of portal hypertension after surgery. At multivariate analysis, associated extrahepatic conditions ($p = 0.01$) and open surgery ($p = 0.02$) independently predicted liver-related complications. At 6 months after surgery, 3 patients died. No patient underwent liver transplantation. Serum creatinine >133 µmol/L before surgery predicted death at 6 months (100% *vs.* 12%, $p = 0.006$). Portal hypertension features were not associated with liver-related complications. The outcome did not differ between patients who had TIPSS or surgical shunt prior to surgery (n = 12) and those who did not.

Conclusion: Liver-related complications were observed in 39% of the patients and were more common in those with at least one extrahepatic condition associated with INCPH. Survival of patients with INCPH undergoing abdominal surgery was good when serum creatinine was normal.

SAT-206

Addition of simvastatin to standard treatment is safe, effective and improves quality of life in patients with decompensated cirrhosis

A. Muñoz[1], F. Pollarsky[1], M. Marino[1], M. Cartier[1], C. Miguez[1], D. Alvarez[2], P. Salgado[3], G. Romero[1]. *[1]Hospital Dr. Carlos B. Udaondo, Hepatology Section, Buenos Aires, Argentina; [2]Fundación Favaloro, Ultrasound Service, Buenos Aires, Argentina; [3]Universidad de Buenos Aires, Preventive and Community Dentistry, Buenos Aires, Argentina*
Email: aemunoz@intramed.net

Background and Aims: Simvastatin (SVT) has shown to increase survival in cirrhotic patients with variceal bleeding. However, decompensated cirrhosis actually is a contraindication for statin therapy because risks are largely unknown. We aimed to assess the safety of SVT added to standard therapy in patients with decompensated cirrhosis.

Method: In this open, uncontrolled, ambispective trial we analyzed patients with decompensated cirrhosis associated with different complications, a year before and during 12 months of standard treatment plus SVT 20 mg once a day for 2 weeks, and later 40 mg. The primary endpoint was SVT safety. The secondary endpoints were SVT efficacy and quality of life as measured by the Short-Form 36 (SF-36) questionnaire.

Results: Baseline parameters: 30 patients were included, aged 57 ± 10 years, male 67%. Etiology: alcohol 60%. MELD 12.3 ± 3.3. D'Amico's stages 3: 3%, 4: 47% and 5: 50%. Decompensated cirrhosis due to ascites 90%, variceal bleeding 27%, jaundice 27% and hepatic encephalopathy 17%. SVT safety: Related adverse events were myalgia 23%; myalgia plus creatine kinase increase 13%; new onset diabetes 3%; digestive symptoms 63% and headache 13%; liver injury none. SVT dose reduction by muscle symptoms 27%. No patient developed serious adverse events related to SVT or discontinued it for any reason. SVT efficacy: Survival rate: 90%. Patients with cirrhosis complications in the previous year 97% and during the trial 33%, $p < 0.001$. Hospitalizations for decompensated cirrhosis in the previous year 77% and during the trial 27%, $p < 0.001$. Child-Pugh score improved from baseline 7.3 ± 1.3 to the end of the trial 6.7 ± 1.7, $p = 0.04$. Child-Pugh class also improved from baseline/to the end of the trial: A 20%/53%, B 73%/40%, $p = 0.01$, and C 7%/7%. Liver fibrosis evaluated by transient elastography did not change from baseline (31 ± 16 kPa) to the end of the trial (30 ± 13 kPa). Quality of life: All dimensions and component summaries improved at month 12 compared to baseline. The differences in physical function, role-physical, body pain and general health dimensions, and in the physical component summary were statistically significant, $p < 0.05$.
Conclusion: Addition of SVT to standard treatment of patients with decompensated cirrhosis was safe. It was proved effective through clinical assessments although it did not improve liver fibrosis. A better quality of life was observed.

SAT-207

Characterization of systemic inflammatory response in hepatorenal syndrome in cirrhosis. A major role for il-6, TNF-alpha, and VCAM

C. Sole[1,2,3], E. Solà[1,2,3], M. Morales-Ruiz[2,3,4], P. Huelin[1,2,3], M. Carol[1,5], R. Moreira[6], I. Graupera[1,3,6], E. Pose[1,2,3], L. Napoleone[1,3,6], G. De Prada[1,2], X. Ariza[1,2,3], A. Juanola[1], N. Fabrellas[5], W. Jiménez[3,5,6], P. Ginès[1,3,6]. *[1]Liver Unit, Hepatology, Hospital Clinic of Barcelona, Barcelona, Spain; [2]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [4]Hospital Clinic Barcelona, Biochemistry and Molecular Genetics Department, Barcelona, Spain; [5]Faculty of Medicine and Health Sciences, University of Barcelona, Barcelona, Spain; [6]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain*
Email: csolem@clinic.ub.es

Background: Several lines of evidence indicate that progression of cirrhosis from compensated to decompensated state is characterized by marked inflammatory response probably related to systemic spread of bacterial products. HRS represents the end of the spectrum of pathophysiological abnormalities of cirrhosis. However, confirmation of the existence of such inflammatory response in HRS and its possible role on disease outcome is lacking.
Aim: To characterize the systemic inflammatory response in patients with cirrhosis and acute kidney injury-HRS (AKI-HRS) and its relationship with outcome. Patients with cirrhosis without AKI and with prerenal-AKI due to volume depletion were also studied for comparison.
Method: One-hundred and seventy-eight patients admitted for acute decompensation of cirrhosis were studied: 57 without AKI, 63 with prerenal-AKI, and 58 with AKI-HRS. Systemic inflammatory response was estimated by measuring plasma levels of 18 cytokines using a multiplex kit.
Results: Overall, levels of fraktalkine, IL-8, IL-6, MIP-1α, TNF-α, and VCAM were significantly different among the 3 groups of patients. Patients with AKI-HRS had high levels of IL-8, IL-6, and TNF-α and low levels of fraktalkine and MIP-1α; levels of G-CSF were also higher in AKI-HRS compared to prerenal-AKI. Levels of IL-6 and TNF-α were particularly increased in AKI-HRS compared to prerenal-AKI (IL-6: 45 (19–104) *vs.* 14(3–46) pg/mL; TNF-α: 47(35–61) *vs.* 30(18–73) pg/mL ($p < 0.003$ for both). Cytokine levels were unrelated to the severity of AKI-HRS because patients meeting the diagnostic criteria of type-1 HRS had levels similar to those not meeting these criteria. In AKI-HRS, cytokine levels were unrelated to bacterial infections except for IL-6 and IL-1RA, which were higher in infected patients. Of the 58 patients with AKI-HRS, 31 (53%) had resolution of AKI-HRS and 21 survived 3 months without liver transplantation. VCAM was the only cytokine independently associated with lack of resolution of AKI-HRS and transplant-free mortality.
Conclusion: AKI-HRS is characterized by marked systemic inflammatory response with increased serum levels of proinflammatory cytokines, particularly IL-6 and TNF-α. The inflammatory status appears to be particularly intense in AKI-HRS compared to pre-renal AKI. The association between increased VCAM levels and lack of resolution of AKI-HRS and mortality suggests that endothelial dysfunction has a major role in the outcome of AKI-HRS.

SAT-208

Skeletal muscle index indicates mortality risk more accurately than psoas muscle index in patients with cirrhosis. From the FLEXIT consortium.

A.J. Montano-Loza[1], E. Carey[2], M. Ebadi[1], C. Wang[3], S. Dasarathy[4], M.R. Kappus[5], M.A. Dunn[6], J. Lai[7]. *[1]University of Alberta, Gastroenterology, Edmonton, Canada; [2]Mayo Clinic College of Medicine, Division of Gastroenterology and Hepatology, Phoenix, United States; [3]University of California, Gastroenterology, San Francisco, United States; [4]Cleveland Clinic, Division of Gastroenterology and Hepatology, Cleveland, United States; [5]Duke University Hospital, Durham, United States; [6]University of Pittsburgh School of Medicine, Medicine and Biomedical Informatics, Pittsburgh, United States; [7]University of California, San Francisco, United States*
Email: montanol@ualberta.ca

Background and Aims: Sarcopenia is independently associated with mortality in cirrhosis. Total skeletal muscle cross-sectional area in a single CT image at the level of the third lumbar vertebrate (L3) is a valid representative of whole body muscle mass. Skeletal muscle index (SMI) and individual psoas muscle assessments have been used as indicators of sarcopenia-related mortality. Controversy remains regarding applicability of psoas muscle to identify patients at greater risk. We aimed to determine psoas muscle index (PMI) association with SMI, and evaluated the capacity of PMI to predict liver transplant (LT) waiting-list mortality.
Method: We evaluated listed adult patients with cirrhosis from 2012 to 2013 at four North American LT centers. From L3-CT images within 3 months of listing, we determined SMI and PMI (cm^2/m^2). Low SMI was defined as SMI <39 cm^2/m^2 in women and <50 cm^2/m^2 in men as published by us earlier. Cut-offs for PMI to predict mortality were established using a receiver-operating characteristic analysis. Mortality predictors were determined using competing-risk analysis, with LT as a competitive event and results were reported as sub-distribution hazard ratios (sHRs).
Results: Of 353 waitlist candidates, 68% were male, mean age 56 ± 9 years, and MELD of 16 ± 8 points. Low SMI was present in 51% of men and 36% of women ($P = 0.02$). Moderate correlation between SMI and PMI was observed ($r = 0.73$, $P < 0.001$). Low PMI (men: <5.1 cm^2/m^2; women: <4.3 cm^2/m^2) yielded poor and moderate concordance with low SMI in men and women, respectively (Kappa coefficient 0.31 and 0.63). In women, both SMI (sHR 0.94, $p = 0.05$) and PMI (sHR 0.58, $p = 0.002$) were predictors of mortality while in men, SMI was significantly (sHR 0.95, $P = 0.001$) and PMI showed a trend to be (sHR 0.85, $P = 0.09$) associated with mortality. Both Low SMI and low PMI were independently associated with higher mortality in multivariable models (Table 1). Using PMI cutoffs, 66% and 28% of low SMI men and women, who have a higher risk of mortality, were classified as high PMI group.
Conclusion: Low PMI predicts mortality in patients with cirrhosis but identify only small proportions of those at risk for low SMI-associated

Table 1: (abstract: SAT-208).

	Univariate Analysis		Multivariate Analysis			
Men	sHR (95% CI)	P-value	sHR (95% CI)	P-value	sHR (95% CI)	P-value
MELD score	1.01 (0.98–1.04)	0.45	1.02 (0.99–1.06)	0.22	1.02 (0.99–1.05)	0.26
HCC	1.76 (1.07–2.90)	0.03	2.18 (1.22–3.89)	0.008	1.98 (1.12–3.49)	0.02
Low SMI	2.17 (1.29–3.66)	0.003	2.46 (1.38–4.39)	0.002		
Low PMI	1.85 (1.05–3.24)	0.03			2.04 (1.13–3.68)	0.02
Women						
MELD score	1.02 (0.99–1.05)	0.25	1.00 (0.97–1.04)	0.82	1.01 (0.98–1.05)	0.47
Albumin (g/L)	1.02 (1.00–1.05)	0.07	0.79 (0.44–1.41)	0.42	0.77 (0.43–1.36)	0.36
Low SMI	2.12 (1.14–3.93)	0.02	2.05 (1.00–4.21)	0.05		
Low PMI	2.45 (1.32–4.58)	0.005			2.47 (1.24–4.95)	0.01

mortality. SMI should not be replaced by PMI especially in men with cirrhosis.

SAT-209

Loss of subcutaneous adipose tissue associates with higher mortality risk in patients with cirrhosis

A.J. Montano-Loza[1], M. Ebadi[1], P. Tandon[1], V.C. Mazurak[2]. *[1]University of Alberta, Gastroenterology, Edmonton, Canada; [2]University of Alberta, Agricultural, Food and Nutritional Science, Edmonton, Canada*
Email: montanol@ualberta.ca

Background and Aims: Cross-sectional anthropometric assessments of muscle and adipose tissue in patients with cirrhosis at the time of liver transplant (LT) evaluation correlate with adverse prognosis. We have a limited understanding of the prognostic value of longitudinal changes in these body composition parameters. In a retrospective cohort of 136 patients with cirrhosis, our aim was to explore the rate of change in muscle and adipose tissue depots [visceral adipose and subcutaneous adipose tissue (SAT)] in the year after LT evaluation.
Method: CT images taken at the 3rd. lumbar vertebra were used to determine cross sectional areas of muscle, visceral and subcutaneous adipose tissue expressed by cm^2/m^2. The baseline CT was part of the LT evaluation and the second one was conducted at approximately one year. Differences between two consecutive CT images were reported as percentage (%) change per 100 days to enable comparison between patients. A change between –2% and 2% was considered as tissue maintenance, given the precision error of 1.5% for muscle and adipose tissue longitudinal change estimation. Cox proportional hazards models were conducted to assess associations between body composition changes and mortality.
Results: The majority of patients were male (70%) with a mean age of 57 ± 7 years, MELD score of 12 ± 6 point and mean BMI of 27 ± 6 kg/m^2. Skeletal muscle loss occurred in 50% of patients with a mean change of –3 ± 16% per 100 days (150 ± 35 *vs.* 143 ± 33 cm^2/m^2, $p < 0.001$), whereas the rate of change for SAT was 32 ± 91% per 100 days (168 ± 126 *vs.* 195 ± 129 cm^2/m^2, $p < 0.001$) with 33% of patients experiencing SAT loss. There was no difference in visceral adipose tissue areas between the baseline and second CT (114 ± 77 *vs.* 109 ± 71 cm^2/m^2, $p = 0.30$). No significant difference in median survival was observed between patients who lost and those who maintained/gained muscle (24 ± 2 *vs.* 55 ± 14 months, $p = 0.11$). However, median survival was significantly shorter in patients who lost SAT compared to patients who maintained or gained SAT (17 ± 2 *vs.* 41 ± 12 months, $p = 0.002$). SAT loss increased mortality risk by 2-fold compared to patients who gained/maintained SAT (HR 2.21; 95% CI 1.27–3.82; $p = 0.005$) after adjusting for MELD score and serum albumin.
Conclusion: SAT loss increases mortality risk in patients with cirrhosis. Given the important role of SAT in storing energy, higher mortality in patients who experienced SAT loss might be related to the depletion of body energy reservoirs.

SAT-210

Assessment of biventricular function in patients with decompensated cirrhosis and hepatopulmonary syndrome

S. Soulaidopoulos[1], M. Vlachou[2], T. Oikonomou[1], T. Tzoumari[1], P. Doumtsis[1], A. Karasmani[1], G. Giannakoulas[2], H. Karvounis[2], E. Cholongitas[1,3], I. Goulis[1]. *[1]Medical School of Aristotle University of Thessaloniki, Fourth Department of Internal Medicine, Hippokratio General Hospital, Thessaloniki, Greece; [2]Medical School of Aristotle University of Thessaloniki, First Cardiology Department, AHEPA University Hospital, Thessaloniki, Greece; [3]Medical School of National & Kapodistrian University of Athens, First Department of Internal Medicine, Laiko General Hospital, Athens, Greece*
Email: soulaidopoulos@hotmail.com

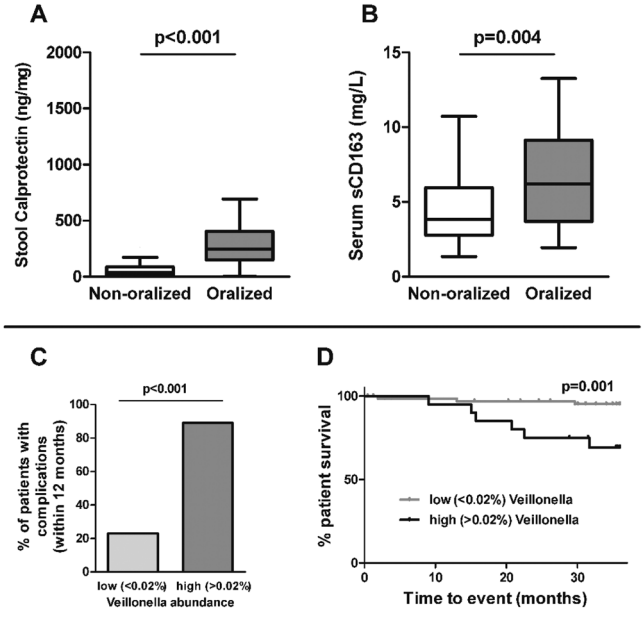
Background and Aims: The impairment of cardiac function in the setting of hepatopulmonary syndrome (HPS) in patients with end stage liver disease constitutes an issue of debate. The aim of this study was to evaluate possible correlations between the presence of HPS and biventricular cardiac systolic function in patients with decompensated cirrhosis
Method: We prospectively evaluated consecutive liver transplantation candidates with stable decompensated cirrhosis. HPS was defined as the presence of an elevated alveolar-arterial oxygen gradient and intrapulmonary vasodilatation, detected by contrast enhanced echocardiography (left atrial bubble opacification between third and sixth cardiac cycle after right atrial opacification). HPS severity was determined as mild ($PaO2 \geq 80$ mmHg), moderate ($60 \leq PaO2 < 80$ mmHg), severe ($50 \leq PaO2 < 60$ mmHg) and very severe ($PaO2 < 50$ mmHg). A semi-quantitative assessment of shunt size was performed according to the number of bubbles calculated in one still frame in left heart chambers (grade 1:<29, grade 2:30–100 and grade 3:>100). M–mode echocardiography and tissue Doppler imaging (TDI) measurements were performed. Global longitudinal strain (GLS) was calculated for left ventricular (LV) and right ventricular (RV) myocardium.
Results: 140 patients (pts) (age 52 ± 12 years, M/F: 96/44, MELD score 14.7 ± 5) were enrolled. HPS was diagnosed in 45 (32.1%) pts (mild: 57.4%, moderate: 36.2%, severe 2.1% and very severe 4.3%). Intrapulmonary vascular dilatations were present in 59 (42.1%) pts (grade 1: 84.7%, grade 2: 8.5%, grade 3: 6.8%). There was no significant difference in LVGLS (–22.2 ± 2.6 *vs.* –21.9 ± 2.4%, $p = 0.71$) or in RVGLS (–23.2 ± 4.5 *vs.* –23.3 ± 4%, $p = 0.89$) between HPS and non-HPS group. However, lower LV ejection fraction values were recorded in the HPS group (59 *vs.* 61%, $p = 0.007$). No other echocardiographic parameter was correlated to HPS. Intrapulmonary shunt grading was significant correlated to HPS classification ($\chi^2 = 18.9$, $p = 0.029$), with lower arterial oxygen values being recorded in higher stages of intrapulmonary shunt. Interestingly, patients receiving diuretics had higher LVGLS values (–22.6 ± 2.5 *vs.* –21.1 ± 2.3%, $p = 0.01$).
Conclusion: Although lower LV ejection fraction values were recorded in HPS patients, TDI and biventricular GLS was unable to predict the presence of HPS. HPS severity was significantly correlated to the echocardiographical staging of intrapulmonary shunt.

SAT-211

Loss of colonization resistance in cirrhosis facilitates proton pump inhibitor-associated oralization of the colonic microbiome

F. Rainer[1], A. Horvath[1], M. Bashir[1], B. Leber[1], B. Schmerboeck[1], A. Blesl[1], T. Madl[1], I. Klymiuk[1], A. Groselj-Strele[1], M. Durdevic[1], H. Grønbæk[2], H.J. Møller[2], D.E. Freedber[3], J.A. Abrams[3], R.E. Stauber[4], P. Fickert[1], P. Stiegler[1], V. Stadlbauer[1]. [1]*Medical University of Graz, Graz, Austria;* [2]*Aarhus University Hospital, Aarhus, Denmark;* [3]*Columbia University Medical Center, New York, United States;* [4]*Institute of Pathology, Graz, Austria*
Email: florian.rainer@medunigraz.at

Background and Aims: In patients with liver cirrhosis, gut microbial diversity, an indicator of colonization resistance, is significantly reduced. In this setting, proton pump inhibitor (PPI) use is suspected to promote stool colonization with bacteria that are highly abundant in the oral cavity. Our aim was to assess whether cirrhosis-typical alterations of the microbiome predispose for PPI-associated oralization and whether this is associated with intestinal and systemic inflammation, complications, and mortality.
Methods: We compared stool microbiome composition (16S sequencing of stool samples) and markers of intestinal and systemic inflammation (i.e. fecal calprotectin and serum sCD163) of cirrhotic patients (56 ± 9 years, 29% female) with (n = 48) and without (n = 41) PPI use. Stool microbiome composition and overgrowth of individual OTUs (i.e. the disproportional increase of an OTU compared to other members of their families) were compared to a control cohort of 12 healthy volunteers prior and after a 4-week regime of PPI intake. Patients were observed for a median time of 37 months and cirrhosis complications and mortality rates were assessed.



Results: Microbiome composition of cirrhotic patients showed alterations typical for cirrhosis, including a significant reduction in microbial diversity. Furthermore, cirrhotic patients with PPI use showed significant overgrowth of Veillonella parvula (p = 0.001) and Streptococcus salivarius (p < 0.001) compared to non-users. PPI use in healthy volunteers did not result in substantial overgrowth of these OTUs (p = 0.18 and 0.08). In cirrhotic patients with PPI use, microbial diversity was inversely correlated with abundance of V. parvula, indicating that a loss in colonization resistance facilitates the overgrowth these OTUs. Oralization (combined overgrowth of Veillonella parvula and Streptococcus salivarius) was strongly associated with an increase in intestinal and systemic inflammation (see Figure 1A, B). Especially Veillonella parvula was associated with the occurrence of complications and predictive for mortality (see Figure 1C, D).
Conclusion: Loss of colonization resistance is prominent in cirrhosis. PPI therapy in these patients is associated with an increase of oral bacteria in the stool microbiome. PPI-associated oralization is linked to increased intestinal and systemic inflammation, occurrence of complications and mortality.

SAT-212

The amelioration of muscle wasting leads to the improvement of cognitive impairment after transjugular intrahepatic portosystemic shunt: A proof of concept that sarcopenia and hepatic encephalopathy are causally related

S. Gioia, S. Nardelli, F. Pitocchi, R. Pileggi, B. Lattanzi, M. Merli, O. Riggio. *La Sapienza, University of Rome, Department of clinical medicine, Rome, Italy*
Email: stensgioia@hotmail.com

Background and Aims: in cirrhotic patients a statistical correlation between sarcopenia and hepatic encephalopathy (HE) has been shown. The transjugular intrahepatic portosystemic shunt (TIPS) induces an amelioration of the nutritional status and muscle wasting, without inducing a parallel amelioration of liver function. The aim of the study is to evaluate the evolution of the skeletal muscle index (SMI), as a measure of sarcopenia, and HE in patients submitted to TIPS.
Method: 22 cirrhotic patients submitted to TIPS were included in the study. The modification of SMI by means of CT scan and of HE (both overt and minimal, by means of the Psychometric Hepatic Encephalopathy Score, PHES) as well as of venous ammonia were evaluated before and after a mean follow up of 15 ± 10 months after TIPS.
Results: In the whole group, SMI significantly increased after TIPS, from 38.8 ± 10.7 to 44.9 ± 12.2 cm/m^2 (p = 0.0008), with a mean increase of 15%. PHES and ammonia were also significantly improved at the end of follow up compared to the values observed one week after the procedure. Comparing the patients without (n = 10) or with (n = 12) an improvement in SMI >10%, PHES (−4.4 ± 1.7 *vs.* −1.3 ± 2.2 respectively; p = 0.002) and ammonia (91 ± 31 *vs.* 48 ± 32 µmol/L, respectively; p = 0.004) significantly improved in the second group. Moreover, the prevalence of minimal HE (70% *vs.* 16.7% respectively, p = 0.001) as well as the number of episodes of overt HE were significantly reduced in the group of patients who improved SMI. MELD remained stable or worsened after TIPS and was not significantly different between the groups with or without SMI improvement.

Table 1: Prevalence of cognitive impairment (minimal and overt) in the patients with or without improvement of SMI >10% at the end of follow up compared to the basal values

	SMI improvement < 10% (n= 10)	SMI improvement >10% (n= 12)	P value
Minimal HE (PHES≤−4) (yes/no)	7/3 (70%)	2/10 (17%)	0.01
PHES score	−4.4 ± 1.7	−1.3 ± 2.2	0.002
Overt HE (yes/no)	8/2	7/5	NS
OHE in the first 3 months (N of episodes/pt)	0.8 ± 1.03	0.58 ± 0.51	NS
OHE in the following months (N of episodes/pt)	1.2 ± 1.3	0.08 ± 0.3	0.009
Venous plasma Ammonia (µg/dl)	91.3 ± 30.56	48.16 ± 32.05	0.004
Follow up (months)	17 ± 10	14 ± 10.4	NS

Conclusion: TIPS represents a model to study the relationship between sarcopenia and HE independently of liver function. The data support the causal relationship between sarcopenia and HE being the prevalence of minimal HE, the number of episodes of overt HE as well as the plasma venous ammonia levels significantly reduced in the

group of patients in whom sarcopenia ameliorated compared to the patients in whom the nutritional status remained stable.

SAT-213

Non cirrhotic portal hypertension secondary to oxaliplatin therapy: Incidence and presentation

S. Gioia[1], S. Nardelli[1], R. Pileggi[1], F. Pitocchi[1], C. Pasquale[1], M.D. Martino[2], O. Riggio[1]. *[1]La Sapienza, University of Rome, Department of clinical medicine, Rome, Italy; [2]La Sapienza, University of Rome, Department of Radiological, Oncological and Pathological Sciences, Rome, Italy*
Email: stensgioia@hotmail.com

Background and Aims: Recently, several studies have identified a possible relationship between the therapy with oxaliplatin and the development of non-cirrhotic portal hypertension. However, the incidence and the way of presentation of the disease in series of patients treated with oxaliplatin have not been yet described.
The aim of the study is to search for the development of radiological signs of portal hypertension (PH) in a series of patients submitted to therapy with oxaliplatin.
Method: From a total of 570 neoplastic patients consecutively observed, based on stringent selection criteria aimed at the elimination of all patients with active or potential portal hypertension, 94 patients undergoing oxaliplatin therapy and with a computed tomography (CT) performed prior to treatment were finally included in the study.
Changes in portal vein and spleen diameters, the appearance of esophagogastric varices and of other collaterals at the CT performed after at least 4 months from the therapy have been evaluated by an experienced radiologist. Portal hypertension was defined by the contemporaneous presence of portal vein diameter > 15 mm and longitudinal spleen diameter > 12 cm or by the presence of esophagogastric varices and/or portosistemical shunts.
Results: 85 patients were affected by colorectal cancer, 9 were affected by other gastrointestinal neoplasia for which they underwent to neoadiuvant (9) or adiuvant (85) chemotherapy. The most used therapeutic regimens were XELOX and FOLFOX. Before the chemotherapy no one of the 94 patients had portal hypertension.
After 5 ± 1.6 months from the therapy, 9 patients (9.6%) developed radiological signs of portal hypertension. In particular, 7 patients showed portal vein diameter >15 mm and splenomegaly (Table 1), one patient developed esophageal varices (1.1%) and one gastric varices (1.1%).

Table 1: Comparison between the CT scans before and after therapy with oxaliplatin

	Before Oxaliplatin	After Oxaliplatin	P value
Portal vein diameter (mm)	12.3 ± 1.8	12.9 ± 1.7	0.0009
Longitudinal diameter of the spleen (cm)	10.1 ± 2.5	11.1 ± 2.1	<0.0001
Spleen volume (cm^3)	298 ± 156	373 ± 201	<0.0001
n of pts with portal vein dilatation*	6 (6.4%)	10 (10.6%)	NS
n of pts with splenomegaly**	18 (19.3%)	26 (28%)	NS
n of pts with oesophageal varices	0	1 (1.1%)	
n of pts with gastric varices	0	1 (1.1%)	
n of pts with paraumbelical vein recanalization	0	0	
n of pts with portal dilatation* and splenomegaly**	0	7 (7.5%)	0.006

Data are expressed as mean ± SD
*portal vein diameter >15 mm
**longitudinal diameter of the spleen > 12 cm

Conclusion: Liver vascular damage causing the development of PH is common in the patients undergoing oxaliplatin-based chemotherapy regimens. Thus, this side effect should be always considered by submitting this kind of patients to specific controls to early recognize its onset.

SAT-214

The Cost-effectiveness of albumin in the treatment of decompensated cirrhosis in Italy, Spain and Germany

M.C. Runken[1], P. Caraceni[2], J. Fernandez[3], A. Zipprich[4], R. Carlton[5], M. Bunke[1]. *[1]Grifols SSNA, Research Triangle Park, United States; [2]University of Bologna, Department of Medical and Surgical Sciences, Bologna, Italy; [3]University of Barcelona, Liver ICU, Liver Unit, Barcelona, Spain; [4]Martin-Luther-University-Halle-Wittenberg, Department of Internal Medicine, Halle (Saale), Germany; [5]Xcenda, Global Health Economics and Outcomes Research, Palm Harbor, United States*
Email: rashad.carlton@xcenda.com

Background and Aims: Ascites is the most common and frequently the first complication of cirrhosis to appear signaling the presence of decompensated cirrhosis. The European Association for the Study of the Liver (EASL) guidelines support the use of albumin to treat cirrhotic patients with ascites undergoing large volume paracentesis (LVP), spontaneous bacterial peritonitis (SBP) and hepatorenal syndrome (HRS). This study's objective was to evaluate the cost-effectiveness of albumin in the treatment of complications of decompensated cirrhosis across Italy, Spain and Germany.
Method: A decision tree cost-effectiveness model from a hospital perspective, was developed to evaluate the cost-effectiveness of albumin in the treatment of patients requiring LVP, having SBP or HRS. In the LVP model, albumin was compared to saline, gelatins or no fluid. Albumin plus antibiotics were compared to antibiotics alone in SBP, and albumin plus terlipressin was compared to terlipressin alone in HRS. The models included pharmacy costs and medical complication costs in decompensated cirrhosis. The medical complications included in the LVP model were hyponatremia, renal dysfunction, and hepatic encephalopathy; renal impairment and hospital length of stay for SBP; and renal impairment for HRS. Effectiveness inputs were literature-based and included mortality and the rates of medical complications. Quality-adjusted life years (QALYs) were calculated based on existing health state utilities for decompensated cirrhosis, encephalopathy, and SBP. The primary model results were the incremental cost-effectiveness ratios (ICERs) for cost per life saved and cost per QALY.
Results: In the ICER calculation for LVP, albumin was less costly and more effective (i.e. a dominant treatment) than saline, gelatins or no fluid in both survival and QALYs in Italy, Spain and Germany. In the ICER calculation for SBP, antibiotics plus albumin were a dominant treatment in Spain in both survival and QALYs. Antibiotics plus albumin were cost-effective in Italy and Germany with ICERs less than €8,000 per life saved and below €18,000 per QALY. In the ICER calculation for HRS, albumin plus terlipressin was a dominant treatment in both survival and QALYs across all 3 countries.
Conclusion: This analysis suggests that the use of albumin in the treatment of decompensated cirrhosis associated with large volume paracentesis, spontaneous bacterial peritonitis, or hepatorenal syndrome is cost-effective in both survival and QALYs across Italy, Spain, and Germany.

SAT-215

The role of HbA1c as a risk factor for the development of spontaneous bacterial peritonitis in patients with decompensated liver cirrhosis

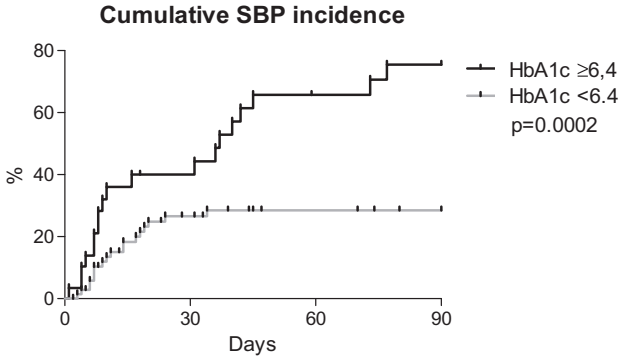
T. Tergast[1], H. Laser[2], S. Gerbel[2], M.P. Manns[1,3,4], M. Cornberg[1,3,4], B. Maasoumy[1,3]. *[1]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology; [2]Hannover Medical School, Centre for Information Management (ZIMt); [3]German Centre for Infection Research (Deutsches Zentrum für Infektionsforschung DZIF); [4]Centre for Individualised Infection Medicine (CIIM)*
Email: tergast.tammo@mh-hannover.de

Background and Aims: Type 2 diabetes mellitus (DM) is a well-known risk factor for infections. DM is frequent in patients with

cirrhosis. However, data regarding the impact of DM on the development of spontaneous bacterial peritonitis (SBP) are quite rare. Glycated hemoglobin A1c (HbA1c) is the most important marker for the 90-day surveillance of mean blood glucose levels. In patients with cirrhosis HbA1c levels are usually lower due to the increased hemolysis. In this study we investigated the role of HbA1c as a risk factor for SBP incidence and mortality in patients with liver cirrhosis and ascites.

Method: A number of 626 consecutive patients with liver cirrhosis and ascites who underwent paracentesis at Hannover Medical School between January 2012 and June 2016 were included and further followed up (mean 200days). DM diagnosis was based on patients' medical records. HbA1c was assessed at the time of the first paracentesis. To identify optimal HbA1c cut-offs ROC analyses were performed. Log-rank test was used for survival analysis and uni- and multivariate Cox-regression analysis for the identification of risk factors for mortality and SBP.

Results: DM was present in 152 patients (24%). Patients with DM were more likely to develop a SBP during follow-up (DM: 42% vs. no-DM: 33%; HR = 1.5, p = 0.03). Risk for SBP development was particularly high in patients with higher HbA1c levels. We identified 6.4% as the optimal HbA1c cut-off to predict SBP. Individuals with HbA1c values ≥6.4% were at a significantly higher risks for SBP than patients with HbA1c values <6.4% and those without DM within 90 days (HbA1c ≥6.4%: 66% vs. HbA1c <6.4%: 25%; HR = 4.16; p = 0.0002 and HbA1c ≥6.4%: 66% *vs.* no-DM: 26%; HR = 6.3; p < 0.0001, respectively) (Figure 1). Interestingly, the risk for SBP development in DM patients with HbA1c values <6.4% was not different from patients without DM (HbA1c <6.4%: 25% and no-DM: 26%; p = 0.78). High HbA1c values remained a statistical significant risk factor for SBP development in the multivariate analysis (HR: 3.5; p = 0.005). Of note, presence of DM as well as the HbA1c level had no impact on 90-day mortality in patients with SBP (DM: 32% *vs.* no-DM: 25%; p = 0.56 and HbA1c ≥6.4%: 32% *vs.* HbA1c <6.4%: 29%; p = 0.79, respectively).



Conclusion: HbA1c values may identify patients with a higher risk for SBP and be useful to select patients for antibiotic prophylaxis. Due to the increased hemolysis in individuals with liver cirrhosis modified HbA1c target values might be necessary.

SAT-216

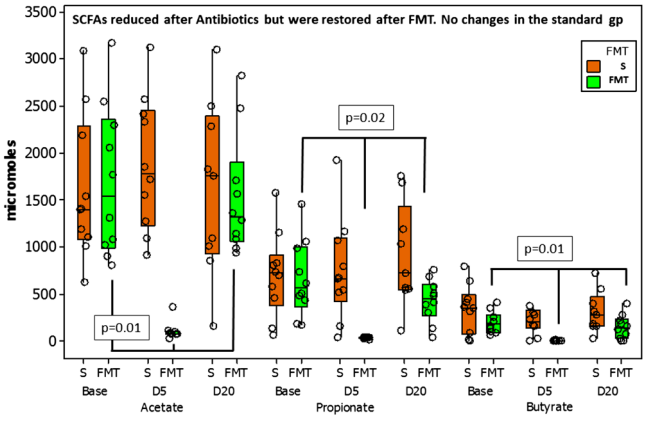
Antibiotic-associated disruption of microbial composition and functionality is restored after fecal transplant in cirrhosis

J.S. Bajaj[1], A. Fagan[1], G. Kakiyama[1], T. Savidge[2], E. Gavis[1], M. Sikaroodi[3], D. Heuman[1], H. Nittono[4], H. Takei[4], Z. Kassam[5], M. Fuchs[6], P. Boonma[2], A. Haag[2], P. Gillevet[3]. *[1]Virginia Commonwealth University and McGuire VA Medical Center, Richmond, United States; [2]Baylor College of Medicine, Houston, United States; [3]George Mason University, Manassas, United States; [4]Junshin Clinic Bile Acid Institute, Tokyo, Japan; [5]Openbiome and Finch Therapeutics, Boston, United States; [6]Virginia Commonwealth University and McGuire VAMC, Richmond, United States*
Email: jasmohan.bajaj@vcuhealth.org

Background and Aims: Cirrhotic pts are often prescribed antibiotics (Abx) which impact microbial diversity and functionality. These can result in antibiotic resistance and fungal infections but there are few options to restore these disruptions. Short-chain fatty acids (SCFA) and secondary bile acids (BAs) are bacterially produced molecules that help intestinal barrier function and may prevent superinfections. We aimed to determine the impact of fecal microbial transplant (FMT) on restoring microbiota functionality after antibiotics in cirrhotic patients.

Method: Decompensated cirrhotic patients on rifaximin were randomized 1:1 to receive standard of care(SOC) or FMT after 5 days of broad-spectrum Abx (ciprofloxacin, amoxicillin and metronidazole) as part of a trial to treat hepatic encephalopathy (HE). FMT was administered by enema (90ml) from a single well-characterized donor after pre-treatment Abx. MELD score, microbial diversity, fecal BA and SCFA profiles were studied at baseline, day 5 and day 20 in both groups. Bacterial metabolism of BAs (deconjugated/secondary BA) was evaluated.

Results: Among 20 HE participants, 10 patients were randomized to SOC and 10 to Abx followed by FMT, in addition to SOC. Sample analysis was performed at days 0, 5 and 20 in both groups. Groups were matched on MELD score (13 *vs.* 12) at baseline. Overall, there was a decrease in microbial diversity after Abx that recovered post-FMT (Table 1). MELD score increased significantly after Abx, which reduced post-FMT. Deconjugation and secondary BA conversion capacity and SCFA levels (Figure) reduced post-Abx but were restored after FMT to baseline levels. No changes were seen in the SOC group.



Conclusion: Antibiotic-associated disruptions in microbial diversity and production of SCFAs and secondary BAs were restored to baseline with one FMT enema. FMT could be promising to restore microbiota composition and functionality disruptions in decompensated cirrhotic patients on rifaximin.

SAT-217

Beta-blocker use in cirrhosis is independently associated with minimal hepatic encephalopathy

C. Acharya, A. Fagan, L. Thacker, M. White, J.S. Bajaj. *Virginia Commonwealth University and McGuire VA Medical Center, Richmond, United States*
Email: jasmohan.bajaj@vcuhealth.org

Background and Aims: Minimal hepatic encephalopathy (MHE) is epidemic in cirrhosis. MHE can predict overt HE (OHE) and mortality. Beta-blockers (BB) are used in cirrhosis for variceal bleeding prevention & have underlying CNS effects that could worsen cognition. We aimed to determine the effect of BB use on MHE diagnosis in cirrhotic outpts.

Method: We enrolled cirrhotic pts at 2 tertiary-care centers. All pts underwent testing per guidelines using two strategies (Psychometric

Table 1: (abstract: SAT-216).

Median values for BAs; mean ± SD for rest	Fecal Microbial Transplant			Standard of Care (no intervention)		
	Baseline	Day 5 (post-Abx)	Day 20 (post-FMT)	Baseline	Day 5	Day 20
MELD score	12.0 ± 2.9	13.5 ± 3.2‡	11.6 ± 3.0†	13.2 ± 3.7	12.5 ± 3.4	13.4 ± 3.8
Shannon diversity	6.46 ± 1.07	4.59 ± 1.67‡,*	6.42 ± 1.42†	7.23 ± 0.77	7.21 ± 0.95	7.34 ± 0.86
Total BAs	3.81	4.18	3.69	2.1	2.0*	2.86
Total Primary BAs	1.1	3.76‡,*	1.32†,*	0.20	0.31	0.69
Total Secondary BAs	0.88	0.13‡,*	0.75†	0.93	0.96	1.11
Total Conjugated BAs	0.12	1.75‡,*	0.21†	0.07	0.02	0.08

*p < 0.05 between groups,
†p < 0.05 within gp compared to day 5,
‡p < 0.05 within group compared to baseline, BAs in μg/gm stool

hepatic encephalopathy score PHES and EncephalApp Stroop). Impaired performance on both was considered MHE. Demographics, cirrhosis and prior OHE details, and BB use and reasons were recorded. Two sets of analyses were performed (1) Logistic regression: 2 models with MHE as dependent variable using age, gender, education, MELD, alcoholic etiology, prior OHE were created. Model 1 had BB use (yes/no) in the entire population while model 2 used an ordinal variable for BB use (0 = no BB, 1 = BB for primary prophylaxis/ selective BB, 2 = BB for secondary prophylaxis) (2) Propensity matching using OHE and MELD score and then comparing the impact of BB on MHE diagnosis.

Results: 218 cirrhotic outpts (45% MHE, 93 OHE, MELD 11 ± 8, 60 ± 9 yrs age, Education 13 ± 4 yrs, 19% women) were included. 84 patients were on BB (37% Selective, 50% primary & 18% secondary prophylaxis). Logistic regression (Table 1): model 1 with BB (yes/no) showed independent association of BB use on MHE. Model 2 showed that selective/primary BB use was associated with MHE but not secondary prophylaxis. (2) Propensity matching: Matching by OHE & MELD resulted in 152 pts (76/gp) of BB+/BB-. Despite matching by these variables, MHE prevalence was significantly higher in BB users (n = 45, 59%) compared to those without (n = 29, 38%, p = 0.01). This trend was seen when MHE by PHES alone (BB + 59% *vs.* BB- 41%, p = 0.02) or Stroop alone (BB + 86% *vs.* BB- 71%, p = 0.04) were used.

Conclusion: BB use, regardless of selective or non-selective, is associated with a higher diagnosis of MHE using both PHES and Stroop using propensity matching and logistic regression approaches. Controlling for BB use may be needed for MHE data interpretation. Alternative s to BB may be needed if patients continue to have impaired cognition despite HE therapy.

SAT-218

Validation of the baveno criteria for endoscopic surveillance of varices in cholestasic diseases

S. Tasayco[1], M.P. Delgado[1], V.M.V. Blasco[1,2], S. Augustin[1,2], J. Genesca[1,2]. [1]*Servicio de Medicina Interna-Hepatología, Hospital Universitari Vall d'Hebron, Institut de Recerca (VHIR), Universitat Autònoma de Barcelona, Barcelona, BARCELONA, Spain;* [2]*Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain*
Email: stephanietasayco0105@gmail.com

Background and Aims: The Baveno VI and AASLD 2016 guidelines recommend the use of non-invasive diagnostic tools (mainly transient elastography-TE) in the identification of patients with compensated advanced chronic liver disease (cACLD) in whom upper endoscopy (UE) screening for varices can be safely avoided, especially in those who require treatment (VNT: large varices or small varices with high-risk stigmata). These recommendations are a liver stiffness mesurement (LSM) by TE <20 kPa and a platelet count >150,000/mm^3. Later, the expanded Baveno VI criteria (a LSM <25 kPa and a platelet count >110000/mm^3) have suggested a significant increase in UE saved, without increasing the risk of undetected VNT. This tool has not been investigated in patients with cholestasic liver diseases. The aim of this study was to evaluate the performance of Baveno VI criteria in a group of patients with primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) with cACLD.

Method: This was a retrospective-prospective cross-sectional study including patients with PBC or PSC assessed with UE between 2009 and 2017 and with paired LSM within one year of the UE. During the study period, criteria to perform an UE were the presence of cACLD as assessed by a LSM ≥10 kPa. Patients with previous complication (ascites, variceal bleeding, hepatic encephalopathy), being on primary prophylaxis for variceal bleeding, HCC diagnosis and liver transplant were excluded from the analysis.

Results: Of 194 patients diagnosed with PBC, 29 were excluded. In 17 of the 165 patients included TE was not performed and 39 of the remaining 148 had a TE ≥10 kPa. UE was performed in 34 of the 39 patients with cACLD; 11 (32%) had varices and 2 (6%) were VNT. 20 of these 34 patients were within the Baveno VI criteria and 5 varices were detected, none with VNT. In addition, 24 of the 34 patients were within the expanded Baveno VI and again no VNT were missed. Regarding PSC, 23 patients were included and in 4 of them it was not possible to perform TE. 13 of the remaining 19 patients had a TE

Table 1: (abstract: SAT-217): Logistic regression models with MHE on Stroop and PHES as the dependent variable

Model 1: using BB yes/no			Model 2: using BB divided according to indications		
Variables	p-value	OR (95% CI)	Variables	p-value	OR (95% CI)
Age	<0.0001	1.11 (1.06, 1.16)	Age	<0.0001	1.12 (1.06, 1.17)
Female Gender	0.002	0.21 (0.08, 0.56)	Female Gender	0.0021	0.20 (0.07, 0.56)
Education	0.04	0.86 (0.75, 0.99)	Education	0.0263	0.85 (0.73, 0.98)
MELD	0.01	1.08 (1.02, 1.15)	MELD	0.0049	1.10 (1.03, 1.17)
OHE	0.0001	3.98 (1.97, 8.03)	OHE	<0.0001	4.59 (2.19, 9.61)
BB Use	0.04	1.97 (1.01, 3.86)	BB Group	0.02	
			0 (no BB)		–
			1 (prim/selective)		1 vs 0–2.57 (1.24, 5.33)
			2 (secondary)		2 vs 0–0.57 (0.15, 2.24)

≥10 kPa. UE was not performed in 1 patient. In this group, 4/12 (33%) had varices and 2/12 (17%) were VNT. None of de 4 and 7 patients within the Baveno VI and expanded criteria, respectively, presented VNT.
Conclusion: The original and expanded Baveno VI criteria are valid for avoiding endoscopy screening in cACLD due to cholestasic diseases. Project code: PI15/00066. ISCIII-FEDER CO-FUNDING.

SAT-219

High-dose but not low-dose enoxaparin substantially improves survival in cirrhotic patients with portal vein thrombosis

L. Turco[1], N. Gualandi[1], R. Vukotic[2], M. Bianchini[1], F. Schepis[1], P. Andreone[2], E. Villa[1]. [1]*Azienda Ospedaliero-Universitaria Policlinico di Modena, University of Modena and Reggio Emilia, Division of Gastroenterology, Modena, Italy;* [2]*Centro di Ricerca per lo Studio delle Epatiti, Università degli Studi di Bologna, Dipartimento di Scienze Mediche e Chirurgiche, Bologna, Italy*
Email: erica.villa@unimore.it

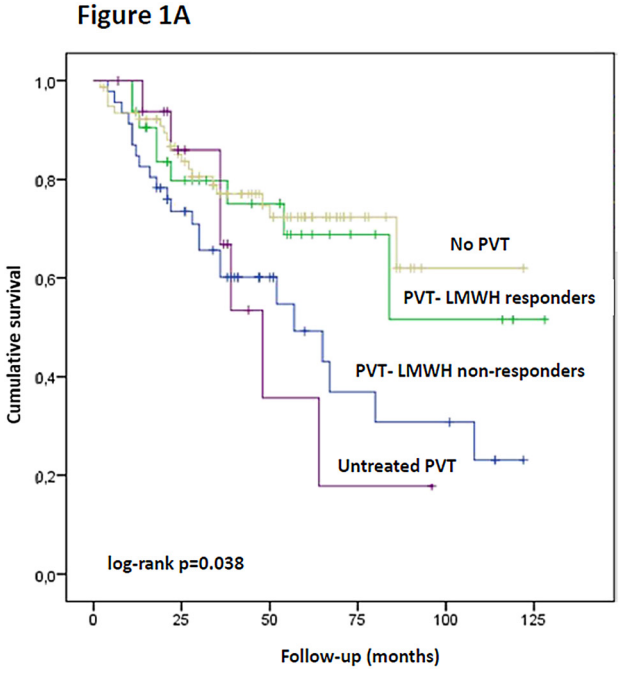
Background and Aims: Discordant data are present in the literature on the influence of portal vein thrombosis (PVT) on mortality of cirrhotic patients. Similarly no sound data are available on the effect of low molecular weight heparin (LMWH) on survival. We evaluated the impact of PVT and LMWH dose on survival of cirrhotic patients in a retrospective case-control study.
Method: 78 consecutive cirrhotic patients with LMWH-treated non-neoplastic PVT (cases) were matched 1:1 by age, sex, Child-Pugh score and presence of gastro-esophageal varices with untreated cirrhotic patients with PVT and with cirrhotic patients without PVT (controls). PVT characteristics, clinical features, dose of LMWH, bleeding events and survival were collected and analyzed by Kaplan-Meier (K-M) and Cox regression analysis. Patients with neoplastic PVT (diagnosed by imaging and/or biopsy) were excluded.
Results: Cases had lower platelets count ($p = 0.0001$), higher C-reactive protein levels ($p = 0.018$) and higher HCC prevalence ($p = 0.005$) than controls. Cases had lower, although non-significantly different, survival than controls (LMWH-PVT 74.5 ± 52.8 *vs.* untreated PVT 51.7 ± 36.0 *vs.* controls 91.2 ± 55.4 months respectively, log rank $p = 0.095$) (K-M). However, stratifying the cases by achievement of complete portal vein recanalization, cases achieving complete recanalization (PVT-LMWH-responders) had similar survival to controls while PVT-LMWH-non-responders clustered with untreated PVT (log rank $p = 0.038$, K-M, Figure 1A). Additionally, only cases treated with high-dose LMWH (≥12.000 IU daily) had a substantial survival advantage (log rank $p = 0.043$, K-M, Figure 1B). At Cox regression analysis, high-dose LMWH (OR 0.330, 95%CI 0.132–0.883, $p = 0.017$), HCC at baseline (OR 2.984, 95%CI 1.142–7.798, $p = 0.026$), and bilirubin levels at baseline (OR 1.408, 95%CI 1.126–1.760, $p = 0.003$), were independently related with survival. No differences in term of bleeding events were found between cases and controls ($p = 0.490$).
Conclusion: In cirrhotic patients, untreated PVT or PVT unresponsive to LMWH–mediated recanalization has significantly lower survival than PVT-LMWH-responders or no-PVT controls. High-dose LMWH (≥12.000 IU daily) is required to improve survival while low-dose LMWH is unsuccessful. The final outcome of the patients in term of survival independently depends on the clinical condition (e.g. stage of disease and HCC at enrollment) and on high-dose LMWH.

SAT-220

Higher in-hospital and post-discharge mortality and hospital charges in cirrhotic patients with acute respiratory illness in the United States

B. Zou[1], Y.H. Yeo[1], D. Jeong[1], E. Sheen[1], H. Park[2], P. Nguyen[1], Y.-C. Hsu[3], G. Garcia[1], M. Nguyen[1]. [1]*Stanford University Medical Centre, Division of Gastroenterology and Hepatology, Palo Alto, United States;* [2]*University of Florida College of Pharmacy, Pharmaceutical Outcomes & Policy, United States;* [3]*Fu-Jen Catholic University Hospital, Division of Gastroenterology, New Taipei, Taiwan*
Email: mindiehn@stanford.edu

Background and Aims: Both cirrhosis and acute respiratory illness (ARI) carry substantial disease and financial burden. Cirrhotic patients are more vulnerable to develop an ARI requiring hospitalization. This study aimed to explore the ARI burden among hospitalized cirrhotic patients.
Method: A retrospective cohort study was performed using the California Office of Statewide Health Planning and Development database for three recent influenza seasons (2010–2013). The prevalence of ARI, and hospital charges, and mortality risk among



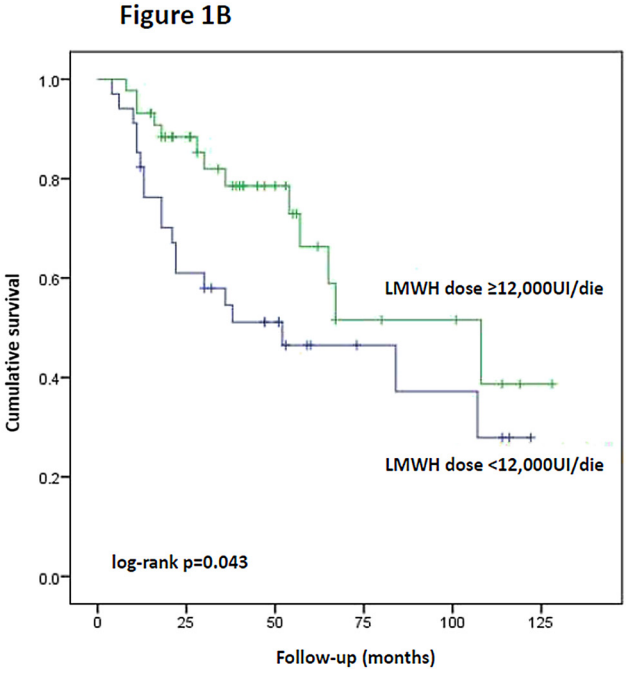


Figure: (abstract: SAT-219)

hospitalized cirrhotic patients was compared to cirrhotic patients without ARI. Propensity score matching (PSM) was used to control for imbalances in the groups. Survival analysis was used to determine variables associated with higher mortality.

Results: A total of 46,192 cirrhotic patients were identified during the three influenza seasons (14,049, 15,699, and 16,444 patients, respectively) which yielded 4244, 4551, 4791 patients in 2010–11, 2011–12 and 2012–13 after PSM. In the 2011–12 influenza season, the prevalence of ARI was 8.4% in all cirrhotic patients consistent across the three seasons. Older, Asian, non-Hispanic, Medicare, and Medicaid subgroups experienced significantly higher prevalence rates ($p \leq 0.002$). Compared to the matching controls, cirrhotic patients with ARI had 53.8% higher adjusted hospital charge ($122,555 vs.$79,685 per patient per admission, $p < 0.0001$), longer stay in hospital (16.92 *vs.* 14.23 days, $p < 0.0001$) but fewer hospital admissions (1.82 *vs.*1.96, $p = 0.001$) (Figure). Cirrhotic patients with ARI suffered 35.0% higher adjusted in-hospital mortality ($p < 0.0001$),13.0% higher adjusted 30-day post discharge mortality ($p = 0.023$), 19% higher adjusted 1-year post discharge mortality ($p = 0.001$) and twice the rate of respiratory deaths (5.0% *vs.* 2.3%, $p < 0.0001$) than cirrhotics without ARI. Older patients, patients with alcoholic liver disease or hepatocellular carcinoma were at particularly higher risk (adjusted hazard ratio = 2.94, 1.22, and 2.17 respectively, $p = 0.028$ to <0.001).

Conclusion: Hospital charges and mortality risk in hospitalized cirrhotic patients with ARI are higher than in cirrhotic patients without ARI. Research is needed to determine what preventive measures to include. Influenza and pneumococcal vaccinations could be recommended to decrease the significant burden of ARI in cirrhotic patients especially in the older patients and those with hepatocellular carcinoma, or alcoholic liver disease.

SAT-221

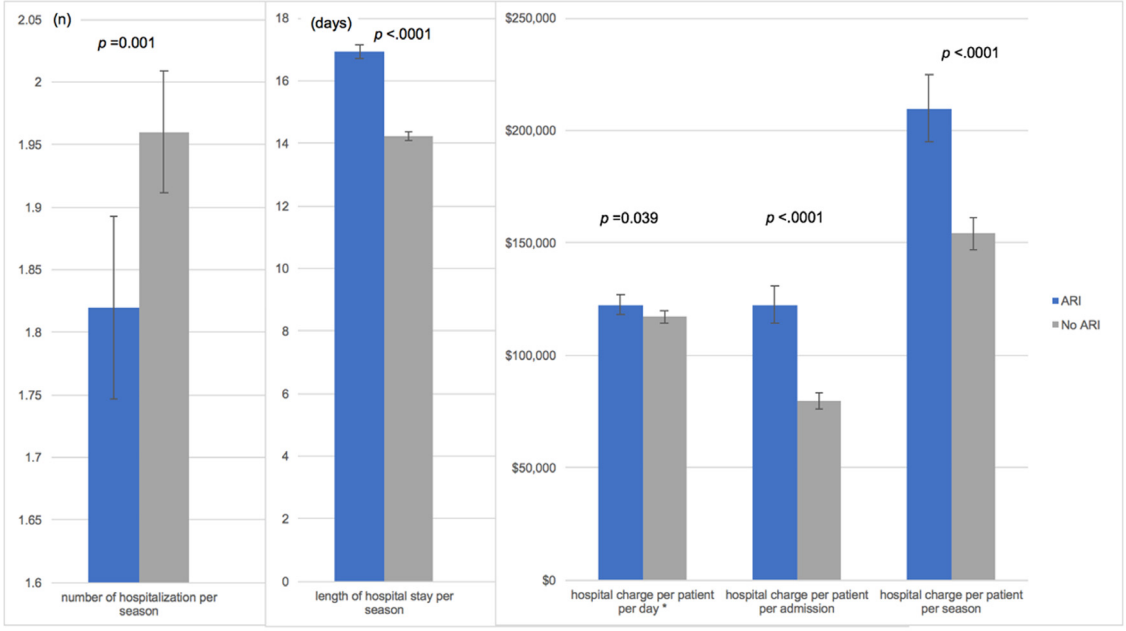
Sepsis in HBV associated decompensated cirrhosis: A comparison between SIRS (Sepsis-1) and qSOFA (Sepsis-3) based criteria

Z. Cao[1], Y. Liu[2], X. Lu[2], L. Chen[3], S. Yin[3], Z. Li[1], R. Mo[2], P. Ren[2], L. Chen[2], J. Lu[1], X. Wang[2], G. Zhao[2], W. Tang[2], X. Xiang[2], H. Wang[2], W. Cai[2], H. Li[4], Q. Xie[1]. [1]*Shanghai Jiaotong University School of medicine, Ruijin Hospital, Department of Infectious disease, Shanghai, China;* [2]*Shanghai jiaotong university of medicine, Ruijin Hospital, department of infectious disease, Shanghai, China;* [3]*Shanghai jiaotong university of medicine, Renji Hospital, department of Gastroenterology, Shanghai, China;* [4]*Shanghai Jiaotong University School of medicine, Renji Hospital, Department of Gastroenterology, Shanghai, China*
Email: xieqingrjh@163.com

Background and Aims: The proposed Sepsis-3 criteria based on sequential assessment of quick SOFA (qSOFA) and delta SOFA score has been shown to predict poor outcomes in general population with suspected bacterial infection and was validated in cirrhosis recently (Piano.S, et al. Gut 2017). The current study aimed to compare the Sepsis-1 criteria (based on the combination of SIRS and infection) and Sepsis-3 for the ability of risk stratification and prognostic value.

Method: This is a retrospective observational cohort study. Patients with HBV associated cirrhosis were identified from medical records data between 2005 and 2010 at two tertiary teaching hospitals in China. The qSOFA, delta SOFA and SIRS was calculated for each patient at admission and during hospitalization. Pre-admission SOFA was set to 4 based on previous publications (Piano.S, et al. Gut 2017). The primary outcome was 90-day survival. Outcomes were measured using a time-to-event format and were analyzed using competing risk approach with the Fine and Gray method. Liver transplantation was considered as a competing event for death.

Adjusted number of hospitalizations, length of hospital stay, hospital charge per patient per day, hospital charge per patient per admission, and hospital charge per patient per season for cirrhotic patients with and without acute respiratory illness (ARI) in the 2011-2012 season



Adjusted for age, sex, race, ethnicity, insurance, severity of cirrhosis, cause of cirrhosis, cause of cirrhosis, comorbidities and history of severe comorbidities *: The value of charge on the y axis equals to the *hospital charge per patient per day* times 10

Figure: (abstract: SAT-220)

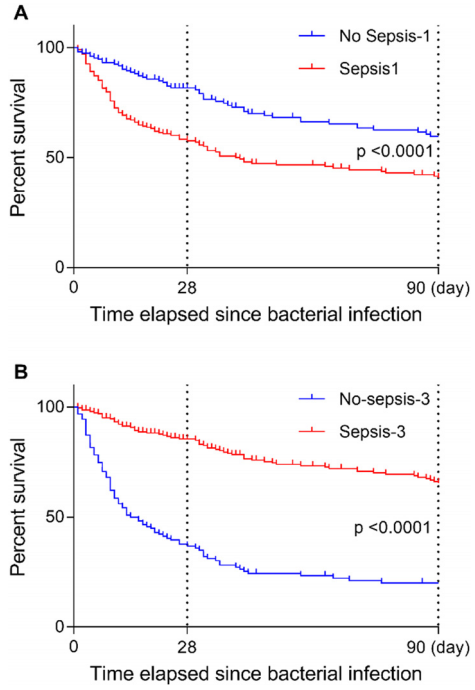


Figure 1. 90-day survival according to Sepsis-1 or Sepsis-3 in HBV-DC patients with bacterial infection.

Result: A total of 359 decompensated cirrhotic patients with bacterial infection met all study criteria were included from 5102 unique patients with HBV associated cirrhosis. Two hundred and ten (59%) were confirmed within 48h of admission and 149 (41%) were diagnosed afterwards, *i.e.*, nosocomial infection. The prevalence of positive SIRS (≥2 points in four parameters), qSOFA (≥2 points in three parameters) and positive delta SOFA (increase of 2 SOFA score) at admission was 29%, 15% and 55%, respectively. Accordingly, Sepsis-1 was diagnosed in 80 (22.3%) patients with 53% of resolution from BI and 65% transplant-free mortality; Sepsis-3 was diagnosed in 41 (11.4%) patients with 29% of resolution from BI and 79% transplant-free mortality. However, patients with Sepsis-1 had a similar 90-day survival with those without Sepsis-1 (40% *vs.* 59%, p < 0.001), though the difference reach significance. In contrast, patients with Sepsis-3 had strikingly lower 90-day survival in comparisons with those without Sepsis-3 (35% *vs.* 80%, p < 0.001) (Figure 1). In the multivariate analysis, Sepsis-3 (sHR, 2.90 [95%CI, 1.74–4.83]) rather than Sepsis-1 was an independent predictor for 90-day mortality. In addition, appropriate empirical antibiotics reduce the risk of 90-day mortality by 56% (sHR, 0.44 [95%CI, 0.28–0.69]) independent of the presence of Sepsis-1 or -3.

Conclusion: In patients with bacterial infection, Sepsis-3 is better than Sepsis-1 in prognosticating cirrhotic patients with bacterial infection. The results may be extended to patients with fungal infection but remains to be confirmed.

SAT-222

Assessment of portal hypertension evolution in hepatitis C virus cirrhosis patients with baseline large oesophageal varices after sustained virological response

M. Abadia, M. Montes, D. Ponce, Rubén Fernandez, J. Poza, E. Marín, M. Romero, T. Hernández, C. Froilán, A. García-Sánchez, J. Novo, P. Castillo, F.J. Garcia-Samaniego Rey, A.O. Martin. *Madrid, Spain*
Email: mabadiab@gmail.com

Background and Aims: There's scarce information on evolution of portal hypertension after sustained virological response (SVR). Furthermore, current guidelines do not address how to manage large oesophageal varices in HCV-cirrhosis after SVR. Therefore, data are needed on their evolution as well as their non-hemodynamic evaluation.

Method: Single-centre, prospective study. Patients were included if: 1) HCV cirrhosis with baseline large oesophageal varices; 2) SVR after direct-acting antivirals (DAA). Hepatic venous pressure gradient (HVPG) was performed. On the same day, upper gastrointestinal endoscopy (UGE), and liver stiffness measuring with transient elastography (TE; Fibroscan, Echosens, France) and bidimensional shear-wave elastography (2D-SWE; Aplio 500, Toshiba, Japan) were also performed. Betablockers were stopped 5 days before.

Results: 30 patients were included (male 56%, median age 66 years, Child-Pugh A/B 73%/27%, median MELD 10 [7–14], overweight 76%, median TE before DAA 27.3 kPa, median time from end of DAA treatment to GPVH 67 weeks [30–171]). GPVH was <12 mmHg (bleeding threshold; BT) in 12/30 (40%) and <10 mmHg (clinical significant portal hypertension; CSPH) in 6/30 (20%). UGE showed regression of varices in 21/26 (81%; 4 patients refused). Feasibility rates for TE and 2D-SWE were 93% (28/30) and 100% (30/30), respectively. Correlation of UGE, TE, and 2D-SWE with HVPG is shown in Table 1 (per protocol).

Table 1: (abstract: SAT-222).

	HVPG ≥12 mmHg (n = 14)	HVPG 10–12 mmHg (n = 6)	HVPG <10 mmHg (n = 6)
Varices (%)			
Large	3 (21)	1 (16)	1 (16)
Small	10 (72)	4 (68)	5 (84)
Absent	1 (7)	1 (16)	0

	HVPG <12 mmHg	HVPG <10 mmHg
Transient elastography		
AUROC (CI95%; *p*)	0.72 (0.67–0.76; 0.04)	0.84 (0.82–0.86; 0.0001)
Best cut-off (kPa)	20.3	20.6
Se/Sp/NPV/PPV/Acc (%)	82/55/67/73/71	69/84/42/84/72
Rule in/out ≥90% (kPa)	26.4/15.8	23.1/14.1
Bidimensional shear-wave		
AUROC (CI95%; *p*)	0.68 (0.63–0.73; 0.13)	0.88 (0.86–0.89; 0.0001)
Best cut-off (kPa)	21.2	20.3
Se/Sp/NPV/PPV/Acc (%)	78/50/60/70/67	80/67/45/91/77
Rule in/out ≥90% (kPa)	27.1/18.6	21.9–14.1

Conclusion: After >1 year of SVR in patients with baseline large oesophageal varices, portal hypertension evolved below the BT in 40% and below the CSPH in 20%. In this situation, there's a weak correlation between endoscopic variceal size and HVPG. TE and 2D-SWE perform well and similarly to detect CSPH; results are poorer for BT.

SAT-223

The impact of hepatic steatosis on portal hypertension

B. Scheiner, G. Semmler, P. Schwabl, T. Bucsics, M. Mandorfer, M. Trauner, A. Ferlitsch, T. Reiberger. *Medical University of Vienna, Dep. of Internal Med. III, Div. of Gastroenterology & Hepatology, Vienna, Austria*
Email: bernhard.scheiner@meduniwien.ac.at

Background and Aims: Studies in animal models suggested an effect of hepatic steatosis on portal pressure, since diet-induced hepatic steatosis has been shown to promote liver sinusoidal endothelial dysfunction and increase intrahepatic resistance. Thus, we aimed to evaluate the effect of hepatic steatosis on portal pressure in patients with chronic liver disease.
Method: Patients who underwent paired hepatic venous pressure gradient (HVPG) and controlled attenuation parameter (CAP®, FibroScan®, Echosense, France) measurements between 01/2014 and 12/2016 were included in this retrospective study.
Results: In total, 243 patients with valid HVPG and transient elastography (TE)-based CAP®-measurements were identified. The majority of patients (n = 194, 79.8%) had cirrhosis, as according to published disease-specific cut-offs, and 72.8% had clinically significant portal hypertension (CSPH; HVPG ≥10 mmHg). The most common etiologies of liver disease were virus hepatitis (n = 116, 47.7%) and alcohol abuse (n = 72, 29.6%). Any hepatic steatosis (S1/2/3; CAP®-value ≥248 dB/m) was present in n = 101 (41.6%). Overall, HVPG was comparable between patients with and without hepatic steatosis (14 (2–34) vs. 17 (3–41) mmHg; p = 0.612). Apart from BMI (Pearson's ρ: 0.136; p = 0.034), no baseline characteristics showed a correlation with CAP®.
To control for severity of liver disease, the correlation between CAP® and HVPG was analyzed within HVPG-strata. Neither in patients with subclinical portal hypertension or normal portal pressure (HVPG < 10mmHg; p = 0.383) nor in patients with CSPH (HVPG ≥ 10; p = 0.495) any correlation between CAP® and HVPG could be found. The subgroup analysis in different etiologies of liver disease also showed no positive correlation between CAP® and HVPG. Interestingly, in patients with F2/3 liver fibrosis as assessed by TE, there was a significant negative correlation between CAP® and HVPG (Pearson's ρ: –0.470; p = 0.004). This may be explained by the fact that TE could overestimate liver fibrosis stage in patients with pronounced hepatic steatosis. This negative correlation vanished in patients with cirrhosis (F4; Pearson's ρ: –0.096; p = 0.183).
Conclusion: Hepatic steatosis does not increase portal pressure. Liver stiffness assessment by TE tends to overestimate liver fibrosis stage in patients with hepatic steatosis.

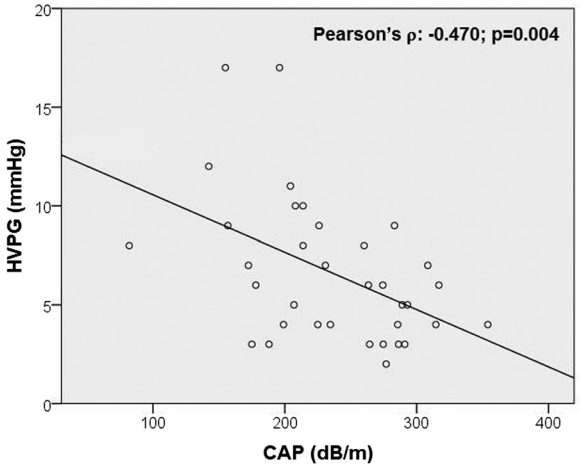


Figure: Correlation of CAP® and HVPG in patients with F2/F3 fibrosis

SAT-224

Controlled attenuation parameter does not predict hepatic decompensation in patients with advanced chronic liver disease

B. Scheiner, L. Steininger, G. Semmler, P. Schwabl, T. Bucsics, R. Paternostro, A. Ferlitsch, M. Trauner, T. Reiberger, M. Mandorfer. *Medical University of Vienna, Dep. of Internal Med. III, Div. of Gastroenterology and Hepatology, Austria*
Email: bernhard.scheiner@meduniwien.ac.at

Background and Aims: Transient elastography (TE)-based controlled attenuation parameter (CAP®) is a non-invasive marker of hepatic steatosis. Recently, CAP® has been proposed as a predictor of decompensation in patients with compensated advanced chronic liver disease (cACLD), although there was no association with liver-related events in another study. Therefore, our aim was to evaluate the prognostic value of CAP® in patients with cACLD and decompensated cirrhosis (DC).
Method: 189 patients who underwent simultaneous TE (stiffness ≥10 kPa) and hepatic-venous pressure gradient (HVPG) measurements between 01/2014 and 12/2016 were included in this retrospective analysis based on prospectively collected data. In cACLD-patients, hepatic decompensation was defined by new onset of ascites, hepatic encephalopathy, or variceal bleeding. In patients with DC, the following events were considered as (further) hepatic decompensation: requirement of paracentesis, admission for grade III/IV hepatic encephalopathy, variceal (re-)bleeding or liver-related death.
Results: For analysis, the study population was stratified into patients with cACLD (without prior hepatic decompensation, n = 86) and patients with DC (n = 103).
Hepatic decompensation occurred in 13 (15.1%) cACLD patients and in 33 (32.0%) patients with DC during a mean follow-up of 23.2 and 16.1 months, respectively. CAP® was not predictive of (further) hepatic decompensation in cACLD patients (per 10 dB/m; OR: 0.991, 95%CI: 0.906–1.084, p = 0.884) or in patients with DC (OR: 0.983, 95%CI: 0.925–1.045, p = 0.587). Adjusting for baseline characteristics including the presence of clinically significant portal hypertension/HVPG did not affect these results. Using the well-established CAP®-cutoff of ≥248 dB/m for any steatosis, the incidence of (further) hepatic decompensation was comparable between CAP® groups (cACLD: p = 0.657; DC: p = 0.743). Serum albumin level (per mg/dL; OR: 0.773, 95%CI: 0.684–0.874, p < 0.001) and HVPG (per mmHg; OR: 1.087, 95% CI: 1.005–1.175, p = 0.036) were the only parameters independently associated with (further) hepatic decompensation in patients with cACLD and DC, respectively.
Conclusion: CAP® does not predict the development of (further) hepatic decompensation in patients with cACLD or decompensated cirrhosis, while serum albumin levels and HVPG are of prognostic value.

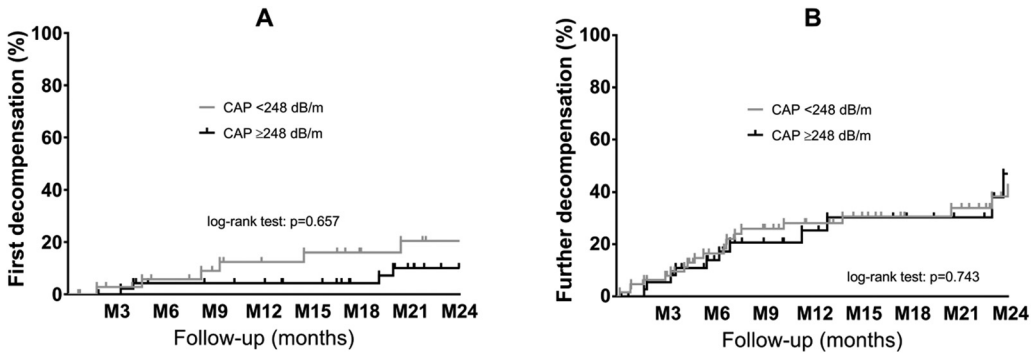


Figure: (abstract: SAT-224) Incidence of (further) hepatic decompensation in **A.** patients with cACLD and **B.** patients with decompensated cirrhosis.

SAT-225

Thromboelastography guided blood product transfusion in cirrhosis patients with acute variceal bleeding: A randomized controlled trial

G. Rout, D. Gunjan, S. Kedia, B. Nayak, S.J. Mahapatra, A. Iqbal, Shalimar. *All India Institute of Medical Sciences, New Delhi, India, Department of Gastroenterology, New Delhi, India*
Email: drshalimar@yahoo.com

Background and Aims: Coagulopathy (low platelet count and prolonged prothrombin time) is common in cirrhosis with acute variceal bleeding. Consensus guidelines recommend correction of prolonged international normalized ratio >1.8 and platelet count <50,000/mm^3 prior to invasive procedures. We aimed to assess use of thromboelastography (TEG) directed blood product transfusion in patients with acute variceal bleeding.
Method: In this randomized control trial, patients were randomly allocated to TEG-guided transfusion or standard of care (SOC) from Jan 2017 till September 2017. Patients with acute on chronic failure and hepatocellular carcinoma were excluded.
Results: Of the 43 recruited patients, 21 were randomized to the TEG group and 22 to the SOC. There were no statistical differences in patient characteristics between the two groups. Among the SOC group- 11 (50.0%) received fresh frozen plasma (FFP), 14 (63.6%) received platelet transfusion and 3 (13.6%) received both FFP and platelets. Among the TEG group- 2 (9.5%) received FFP (p = 0.004) and 2 (9.5%) received platelets (p < 0.001). The median (IQR) red blood cell transfusions in the TEG and SOC groups were 1 (0–3) and 1 (0–3), respectively (p = 0.729). The control of bleeding was achieved in 21 (95.5%) and 21 (100%) of patients in SOC and TEG groups (p = 0.323), respectively. Re-bleeding rates in SOC and TEG groups at 5 days and 6 weeks were (13.6% *vs.* 0%, p = 0.079) and (27.3% *vs.* 9.5%, p = 0.135), respectively. Survival rates in SOC and TEG groups at 5 days and 6 weeks were (95.5% and 100.0%, p = 0.323) and (77.3% and 90.5%, p = 0.241), respectively.
Conclusion: TEG-guided blood product transfusion strategy, when compared to standard of care, is associated with similar control of bleeding and survival in patients with acute variceal bleeding. The use of TEG can prevent unnecessary prophylactic transfusions of FFP and platelets.

SAT-226

Chronic kidney disease in patients with cirrhosis surviving an episode of acute kidney injury. Frequency and impact on patient's outcome

O. Bassegoda[1,2,3,4], P. Huelin[1,2,4,5], E. Pose[1,2,4,5], L. Napoleone[1,2,4,5], A. Juanola[1,2,4,5], R. Moreira[6], M. Carol[2,3,4,6], G. De Prada[1,3,4,6], N. Fabrellas[1,2,3,4], C. Solé[1,4,7], I. Graupera[1,4,5,7], E. Solà[1,4,5,6], P. Ginès[1,2,4,5]. *[1]Hospital Clinic de Barcelona, Liver Unit, Barcelona, Spain; [2]University of Barcelona, Faculty of Medicine and Health Sciences, Barcelona, Spain; [3]IDIBAPS, Barcelona, Spain; [4]CIBEReHD, Barcelona, Spain; [5]IDIBAPS, Barcelona, Spain; [6]Hospital Clinic de Barcelona, Barcelona; [7]University of Barcelona, Barcelona, Spain*
Email: pgines@clinic.ub.es

Background and Aims: AKI is common in cirrhosis and is associated with poor prognosis. However, there is little information on outcome of patients who survive an episode of AKI. Specifically, it is not known how often the acute injury leads to chronic impairment of kidney function, known as chronic kidney disease (CKD), and whether this has a negative influence on patient's outcome. The primary endpoint was to investigate the frequency of CKD in patients surviving an episode of AKI. Secondary endpoints were to evaluate whether CKD had a negative impact on natural history, as assessed by new episodes of AKI, liver transplantation rate and survival.
Method: We analyzed a prospective database including all patients admitted for management of complications of cirrhosis during a 6-year period. All patients were evaluated using the same protocol which included assessment of kidney function at regular intervals during and after hospitalization. CKD was defined as an estimated GFR(eGFR) < 60 mL/min at 3 months of AKI. Patients with previous CKD (n = 231), those who where dead, lost to follow-up or transplanted at 3 months of AKI (n = 127) and those in whom baseline creatinine value before AKI was not available (n = 36) were excluded. Of the remaining 375 patients, 122 developed AKI (32,5%) and constitute the study population.
Results: Twenty-nine of the 122 (23.8%) patients had developed CKD at 3 months (mean eGFR 45 ± 15 mL/min). This rate of CKD was much higher than that observed in the contemporary group of patients admitted for complications of cirrhosis who did not develop AKI (6/253; 2.4%, p < 0.001). Factors independently associated with development of CKD were diabetes and baseline serum creatinine before AKI. During follow-up, the frequency of new episodes of AKI was higher among patients with CKD compared to patients without (62% vs 39%; p = 0.027). Need for renal replacement therapy was also significantly higher (7% *vs.* 0%, p = 0.001). Patients with CKD were more frequently transplanted during follow-up (28% *vs.* 12%, p = 0.04). However, transplant-free survival was not significantly different among groups.
Conclusion: Approximately one fourth of patients with cirrhosis surviving an episode of AKI have developed CKD after 3 months of follow-up. This is associated with higher frequency of new episodes of AKI and higher need for renal replacement therapy and liver transplantation.

SAT-227

Non-selective beta-blockers increase liver mortality when MELD is ≥12 in a prospective 5-year follow-up cohort of alcoholic cirrhosis

P. Cales, S. Bertrais, J. Boursier, I.F. Hubert, L. Adrien, F. Oberti. *University of Angers, Hepato-Gastroenterology, Angers, France*
Email: paul.cales@univ-angers.fr

Background and Aims: The effects of non-selective beta-blockers (BBNS) on mortality of patients with cirrhosis are controversial. We evaluated the BBNS impact on mortality according to liver severity and cause of mortality. The present final results extend interim analysis performed in 2013 limited to overall mortality. Thus, the mean follow-up has been doubled to 5 years whereas all published studies have a short follow-up (<2 yr in most studies) and did not analyze the mortality cause.
Method: 259 patients with alcoholic cirrhosis were included in a retro-prospective cohort: 130 BBNS-treated and 129 as controls
Results: BBNS group had the following significant baseline differences: higher Child-Pugh and MELD score, more frequent previous gastro-intestinal bleeding and large esophageal varices, and lower heart rate. During an average follow-up of 5.3 ± 2.6 yr, MELD progression was: 2.7 ± 6.4 in the BBNS group vs 1.5 ± 7.4 in controls ($p = 0.017$). Kaplan-Meier estimates of overall survival did not significantly differ between BBNS and control groups ($p = 0.296$). However, in Cox analysis for overall mortality, baseline MELD score interacted with BBNS ($p = 0.065$). Liver related survival was decreased in the BBNS group ($p = 0.032$). In competing risk multivariate analysis for liver-related mortality, the MELD-BBNS interaction was significant ($p = 0.003$). Liver mortality was not related to BBNS in patients with Meld <12 (HR [95%CI]: 0.97 [0.26–3.68]) whereas BBNS was associated with an increase in liver-related mortality in patients with MELD ≥12 (HR [95%CI]: 3.32 [1.20–9.19]). Competing risk multivariate survival analysis in propensity risk score matched patients confirmed an interaction between baseline MELD and BBNS group ($p = 0.005$), HR for BBNS: 0.81 [0.22–2.96] in MELD <12 vs 3.41 [1.10–10.58] in MELD ≥12. In contrast, BBNS was associated with a decrease in non-liver-related mortality, especially in patients with baseline MELD ≥12 ($p = 0.142$ in whole study population).
Conclusion: In alcoholic cirrhosis, liver survival is improved by BBNS in MELD <12 but aggravated in MELD ≥12. This result extent other results observed in selected populations (refractory ascites, spontaneous bacterial peritonitis).

SAT-228

Men have higher mortality in cirrhosis: outcomes by gender and etiology in a large, diverse cohort

A. Yeluru[1], M.H. Le[1], C. Zhao[1,2], P. Nguyen[1], S. Trinh[1], H. Le[1], H. Dang[1], A. Pura[1], N. Dang[1], B. Alviar[1], S. Tran[1], T. Johnson[1], A. Le[1], J. Hoang[1], M. Nguyen[1]. *[1]Stanford University, Division of Gastroenterology and Hepatology, Palo Alto, United States; [2]Shanghai University, Department of Cirrhosis, Institute of Liver Disease, Shanghai, China*
Email: mindiehn@stanford.edu

Background and Aims: Cirrhosis results from a diverse group of etiologies, ranging from infectious to autoimmune to metabolic, which behave differently between the two genders. The purpose of this study is to explore differences in complications and mortality between men and women with cirrhosis of various etiologies.
Method: This is a retrospective analysis of 7254 patients (2905 female, 4349 male) with cirrhosis treated at a large academic tertiary care center in California, USA between 1998 and 2015. Data was collected via electronic and manual chart extraction. We report incidence of hepatic decompensation, HCC, and overall mortality over a follow-up period of up to 10 years in male vs. female patients with various etiologies of cirrhosis.
Results: Men and women had similar age at first presentation (54.9 *vs.* 55.5 years, $p = 0.084$), but women had higher rates of other

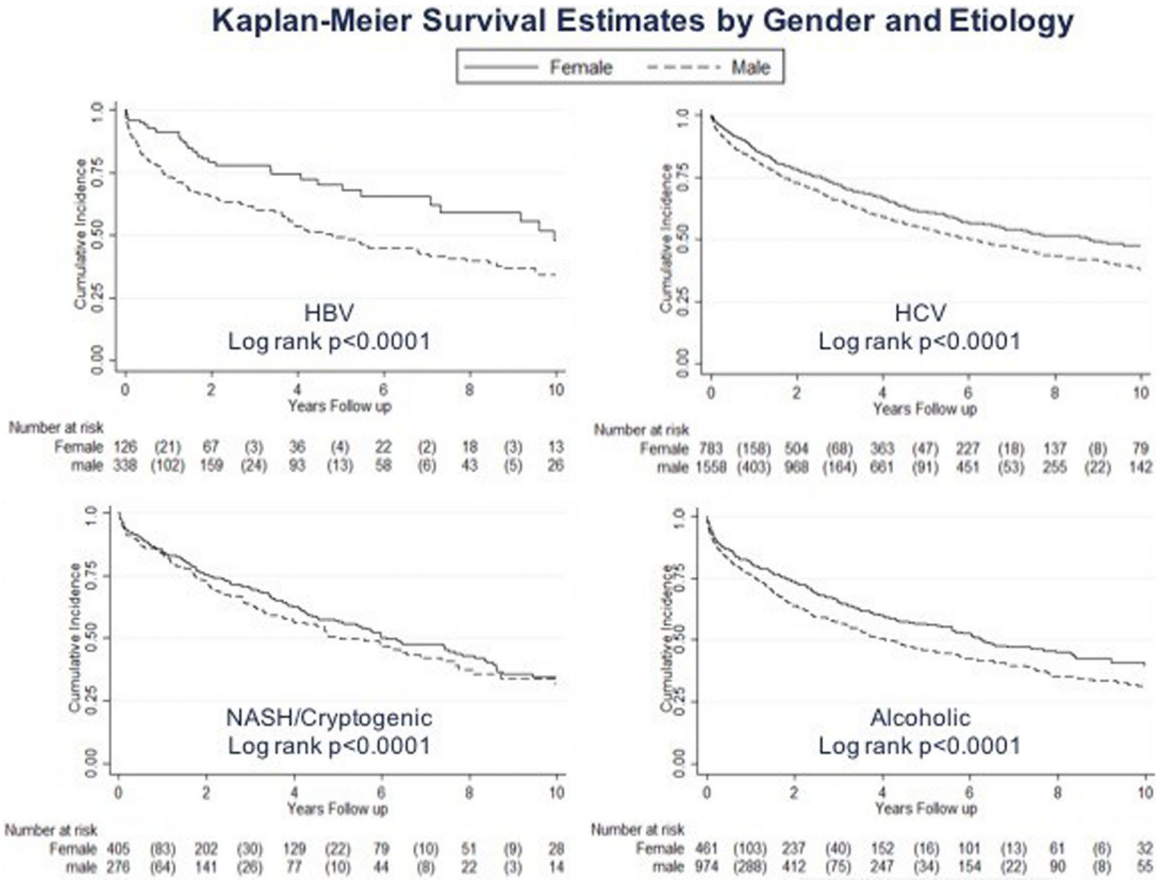


Figure: (abstract SAT-228)

medical comorbidities ($p < 0.01$). Women had lower median serum creatinine ($p < 0.0001$) and bilirubin levels ($p < 0.0001$) at baseline, correlating with lower median MELD scores (12 *vs.* 14, $p < 0.0001$). Men had higher rates of HCC (3.4% *vs.* 1.4%, $p < 0.0001$) and hepatic decompensation (48.9% *vs.* 46.5%, $p = 0.039$) at baseline. Male patients were more likely to have viral and alcoholic cirrhosis, whereas a much higher proportion of women had NASH, cryptogenic, biliary and autoimmune disease ($p < 0.001$). The rate of hepatic decompensation was significantly higher in male vs. female patients over 10- year follow-up (441 patients; $p = 0.03$), and similarly trended towards significance even at five years (1153 patients; $p = 0.09$). The cumulative incidence of HCC was significantly higher in men both at 5- and 10-year follow-up ($p < 0.0001$). Subgroup analysis showed that this was driven primarily by HCV patients: men with HCV had significantly higher annual incidence of HCC than women with HCV (5.5% *vs.* 3%, $p < 0.0001$). Looking at survival, in both male and female patients, those with viral etiologies (HBV, HCV) had significantly higher survival rates than those with NASH and cryptogenic cirrhosis ($p < 0.0001$). Men had worse mortality than women in all etiologies of cirrhosis ($p < 0.001$) except surprisingly in cryptogenic cirrhosis ($p = 0.28$).

Conclusion: To our knowledge, this is the largest cohort of cirrhotic patients studying gender differences in outcomes among etiologies. Men have significantly worse rates of decompensation, HCC, and mortality across diverse viral and nonviral etiologies. Incidence of HCC was highest in males with HCV.

SAT-229

Prior or on-treatment infection does not affect response to treatment or survival in patients with hepatorenal syndrome type 1

S. Pappas[1], F. Wong[2], K. Jamil[3]. [1]*Baylor College of Medicine, Houston, United States;* [2]*University of Toronto, Toronto, Canada;* [3]*Mallinckrodt Pharmaceuticals, Bridgewater, United States*
Email: spappas1@comcast.net

Background and Aims: The effect of prior infection or infection during treatment on response to terlipressin therapy and survival in patients with hepatorenal syndrome type 1 (HRS-1) remains unclear. Infection, particularly pneumonia and urinary tract infection (UTI), may impair response and decrease survival in these patients. To more clearly define the effects of infection on response and survival in patients with HRS-1, we examined outcomes in patients from a large randomized controlled trial of terlipressin in HRS-1.

Method: Subjects with prior infection (within 14 days of randomization) and infection reported as an adverse event, during the study period, from the REVERSE trial of terlipressin versus placebo in subjects with HRS-1 were identified. The incidence of HRS reversal and survival (defined as alive at day 90 and by Kaplan Meier estimates) were determined in these subjects. The full results of the REVERSE trial have been reported (Gastroenterology 2016;150:1579).

Results:

Conclusion: Overall, prior infection and infection reported as an AE did not appear to significantly affect response to therapy or survival in patients with HRS-1. In subjects with prior pneumonia, response was similar to the overall study group but survival was lower. In contrast, subjects with pneumonia reported as an AE and those with prior UTI showed a lower response rate but similar survival; subjects with prior UTI had a significantly lower response rate compared to those without prior UTI. In aggregate, these results suggest that prior or on-treatment infection should not discourage aggressive therapy for HRS-1.

SAT-230

Anticoagulant treatment for atrial fibrillation and decompensation rate in patients with liver cirrhosis

I. Girleanu[1], A. Trifan[1], O. Stoica[1], L. Huiban[1], C. Stanciu[2]. [1]*"Gr. T. Popa" University of Medicine and Pharmacy, Gastroenterology, Iasi, Romania;* [2]*Institute of Gastroenterology and Hepatology, Gastroenterology, Iasi, Romania*
Email: gilda_iri25@yahoo.com

Background and Aims: Anticoagulant treatment in patients with liver cirrhosis (LC) is still controversial. Recent studies demonstrated that anticoagulant treatment could reduce decompensation and mortality rates in cirrhotic patients. Our aim was to evaluate decompensation rate in patients with LC and atrial fibrillation treated with acenocoumarol for thrombotic events prophylaxis.

Method: The study group included patients diagnosed with compensated liver cirrhosis and atrial fibrillation treated with an oral anticoagulant (acenocoumarol), admitted in a tertiary center between January 2012 and December 2013. The control group included consecutive patients diagnosed with LC, matched by age, etiology and liver stage disease with the study group. All patients were regular follow-up since December 2016 or until first hepatic decompensation (ascites, hepatic encephalopathy, variceal bleeding) occurred.

Results: During the study period there were admitted 1151 cirrhotic patients of whom 118 patients (10.2%) were diagnosed with LC and atrial fibrillation of whom 76 and received an oral anticoagulant treatment with acenocoumarol, mean age 60.5 ± 11.2 years at diagnosis, 48 (61.53%) males, all of them with compensated liver cirrhosis. The majority of the patients were diagnosed with alcoholic LC- 46 patients (60.5%). There were no differences regarding baseline characteristics and LC severity between the patients with or without atrial fibrillation. Mean follow-up period was 32 ± 13.2 months. During the follow-up period 353 patients (30.6%) developed hepatic decompensation in both study groups of whom 102 died. The cumulative decompensation rate was 17.9% in the study group and 38.6% in the control group, respectively ($p < 0.0001$). The rate of decompensation was higher in the first year in both groups. There were 27 cases of epistaxis in the study group, and 34 cases of variceal bleeding in both groups, with no other major bleeding side effect to anticoagulant treatment.

Conclusion: Anticoagulant treatment in patients with LC is relatively safe, and may improve patient outcome and decrease decompensation rate, despite association of atrial fibrillation.

Table 1: (abstract: SAT-229).

	N	HRS reversal N	(%)	Alive at Day 90 N	(%)
Prior infection	86	12	**14%**	32	**37.2%**
No prior infection	109	20	**18%**	48	**44%**
Infection reported as an AE	49	6	**12.2%**	19	**38.8%**
No infection reported as an AE	147	26	**17.7%**	62	**42.2%**
Prior pneumonia	9	2	**22.2%**	2	**22.2%**
Pneumonia reported as an AE	12	1	**8.3% (p = N.S.prior vs. AE)**	5	**41.7%**
Prior UTI	43	2	**4.7%**	16	**37.2%**
No prior UTI	153	30	**19.6% (p = 0.019, prior vs. no prior UTI)**	65	**42.5% P = N.S. for all survival comparisons**

SAT-231

Decreased model for end-stage liver disease score after antiviral treatment predicts reduced risk of mortality and hepatic events in chronic hepatitis B related cirrhosis – a study of 1729 subjects

L.-H. Grace Wong[1], T.C. Yip[2], H. Chan[3], Y.-K. Tse[4], W. Sun, V. Wong[1].
[1]The Chinese University of Hong Kong, Dept of Medicine and Therapeutics, Hong Kong, Hong Kong; [2]The Chinese University of Hong Kong, Room 94020D, 7/F, Lui Che Woo Clinical Sciences Building, Hong Kong; [3]The Chinese University of Hong Kong, Hong Kong, Hong Kong, Hong Kong; [4]The Chinese University of Hong Kong, Room 94020D, 7/F, Lui Che Woo Clinical Sciences Building, Hong Kong, Hong Kong
Email: wonglaihung@cuhk.edu.hk

Background and Aims: The Model for End-Stage Liver Disease (MELD) is a scoring system for assessing the severity of chronic liver disease and to prioritize patients with liver cirrhosis for liver transplantation. Yet there has been scanty data on whether improvement in MELD score after antiviral treatment leads to improvement in clinical outcome and reduced hepatic events. We aimed to study the impact of baseline and on-treatment MELD score in patients with chronic hepatitis B (CHB) related cirrhosis.
Method: CHB patients with cirrhosis were identified from a territory-wide cohort of patients who were treated with entecavir (ETV) and/or tenofovir disoproxil fumarate (TDF) from January 2005 to December 2016 in Hong Kong. Patients with MELD scores available at baseline and one year after ETV/TDF were included in the final analysis. The primary and secondary outcome were all-cause mortality and hepatic event based on ICD-9-CM diagnosis codes. Patients with pre-existing hepatocellular carcinoma or at first year of antiviral treatment, and survival <1 year were excluded.
Results: 1,729 CHB patients (71.0% male, mean age 59.8 ± 11.5 years) with cirrhosis were identified and followed-up for a median (interquartile range) of 4.6 (2.6–6.0) years. The mean MELD score was 11.2 ± 4.5 at baseline and 9.9 ± 3.4 at one year; 238 (13.8%) patients died. Among 1,191 cirrhotic CHB patients without prior hepatic events, 99 (8.3%) patients developed hepatic events. The baseline and Year 1 MELD score had a time-dependent area under the receiver operating characteristic curve (td-AUROC; and 95% confidence interval[CI]) of 0.70 (0.67–0.74; $P < 0.001$) and 0.69 (0.65–0.73; $P < 0.001$) respectively to all-cause mortality. The td-AUROC of baseline and Year 1 MELD score was 0.73 (0.67–0.77; $P < 0.001$) and 0.71 (0.64–0.76; $P < 0.001$) respectively to predict hepatic event. Adjusted hazard ratio (aHR) with 95% CI for baseline MELD and decrease of MELD from baseline to Year 1 (DMELD) for all-cause mortality was 1.19 (1.16–1.22; $P < 0.001$) and 0.87 (0.85–0.89; $P < 0.001$) respectively; aHR of baseline and DMELD for hepatic event was 1.20 (1.15–1.25; $P < 0.001$) and 0.89 (0.85–0.93; $P < 0.001$) respectively.
Conclusion: MELD score at baseline and one year after antiviral treatment predicted all-cause mortality and hepatic events in CHB patients with cirrhosis. For each unit of improvement in MELD score at Year 1, there would be 13% reduction in all-cause mortality and 11% reduction in hepatic events in the next 5 years. Our findings support the current practice of delisting patients for liver transplantation after substantial improvement in MELD score after antiviral treatment.

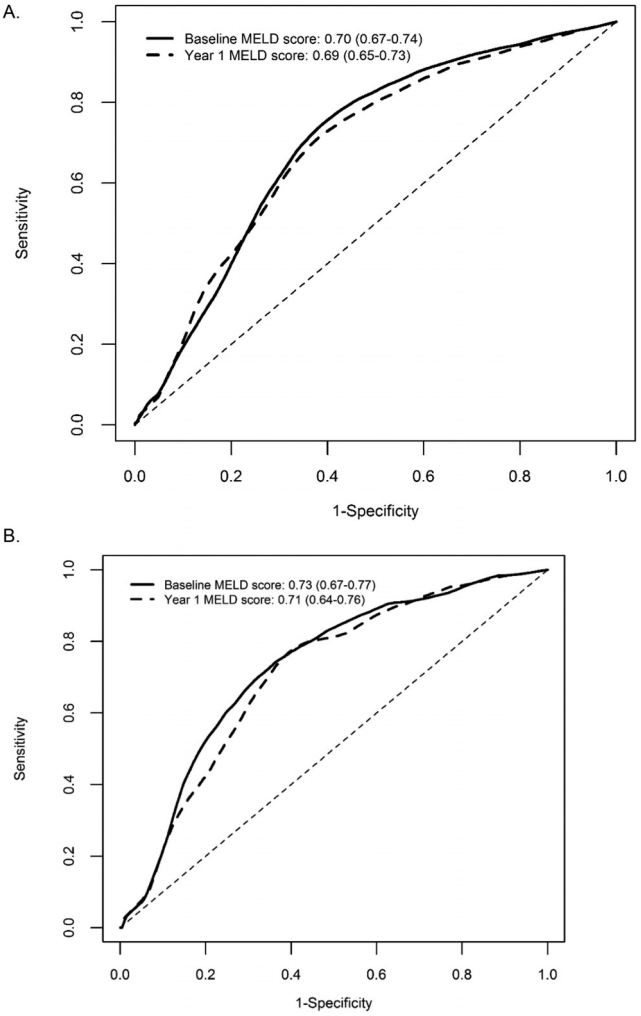


Figure: The receiver operating characteristic curves of baseline and Year 1 MELD score to predict A. all-cause mortality and B. hepatic events.

SAT-232

Propranolol treatment associated with better survival and reduced sepsis in cirrhotic patients with hepatic encephalopathy

P.-C. Lee[1], Y.-J. Chen[2], C.-W. Su[3], Y.-C. Cho[2], P.-H. Chen[1], W.-Y. Kao[4], Y.-H. Huang[1], H.-C. Lin[1], M.-C. Hou[1], J.-C. Wu[1]. *[1]Taipei Veterans General Hospital, Gastroenterology and Hepatology, Taipei; [2]Taipei Veterans General Hospital, Pharmacy, Taipei, Taiwan; [3]Division of Gastroenterology and Hepatology, Taipei Veterans General Hospital, Taipei, Taiwan; [4]Taipei Medical University Hospital, Gastroenterology and Hepatology, Taipei, Taiwan*
Email: tympanum3688@gmail.com

Background and Aims: Use of non-selective beta blockers (NSBBs) in cirrhotic patients with complications such as refractory ascites and spontaneous bacterial peritonitis is still controversial. Hepatic encephalopathy (HE) would impair survival of cirrhotic patients and is related to systemic inflammation and gut-liver disequilibrium. Considering the propranolol effects on gut permeability and inflammation, this study aims to investigate the association between propranolol treatment and the outcomes of cirrhotic patients with HE.
Method: By analyzing data from the Taiwan National Health Insurance Research Database, we identified 4,754 cirrhotic patients with newly diagnosed HE between January 2001 and December 2011. After excluding patients who had experience of liver transplantation,

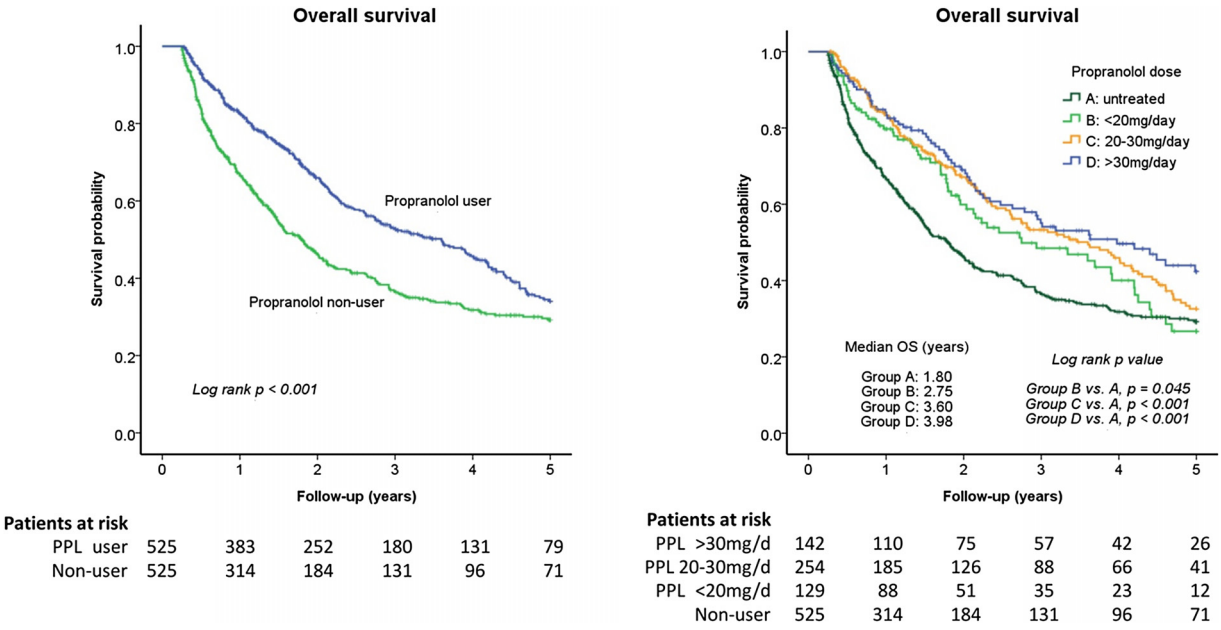


Figure: (abstract: SAT-232)

short follow-up duration, combined exposure to other NSBBs and short propranolol treatment, one-to-one matching by sex, age and propensity score was performed. Finally, 525 patients with and without propranolol treatment, respectively were enrolled for analyses. The Kaplan-Meier method and modified Cox proportional hazards models were employed for survival and multivariable, stratified analyses.

Results: The overall survival (OS) of cirrhotic patients with HE was significantly better in propranolol treated cohort than the untreated cohort (median OS: 3.60 versus 1.80 years, $p < 0.001$). Besides, dose dependent survival benefit was declared remarkably (median OS: 3.98, 3.60, and 2.75 years in patients treated with propranolol >30 mg/day, 20–30 mg/day, and <20 mg/day, respectively. [$p < 0.001$, $p < 0.001$, $p = 0.045$ versus untreated group, respectively]) Not only reduced the risk of overall mortality (adjusted hazard ratio, 0.60; $p < 0.001$), propranolol treatment also diminished the risk of sepsis related death (adjusted hazard ratio, 0.31; $p = 0.006$) in the multivariable analysis. However, risks of circulatory or hepatic failure were non-significantly altered.

Conclusion: Propranolol treatment was associated with a better overall survival in cirrhotic patients with hepatic encephalopathy in a dose-dependent manner. The risk of sepsis related death was reduced by propranolol treatment, but circulatory or hepatic failure was not significantly affected.

SAT-233

Six-minute walk test and sarcopenia in predicting mortality in patients with cirrhosis

T. Dang, M. Ebadi, A.J. Montano-Loza, P. Tandon. *University of Alberta, Gastroenterology, Edmonton, Canada*
Email: thucnhi@ualberta.ca

Background and Aims: Low muscle mass (sarcopenia) is associated with increased mortality in patients with cirrhosis. The association of functional performance with sarcopenia and its impact on mortality has not been well established in cirrhosis.

Objectives:

(1) Determine the association of functional performance assessed by the six-minute walk test (6MWT) and sarcopenia.
(2) Assess the prognostic value of the 6MWT in patients with cirrhosis.

Method: Patients who were assessed for liver transplant (LT) at the University of Alberta hospital were retrospectively enrolled in the study. Cross-sectional imaging within 1 year of assessment was used to determine sarcopenia. The third lumbar vertebra was used to quantify skeletal muscle cross sectional areas, which was then normalized to height to calculate the skeletal muscle index (SMI; cm2/m2). Sarcopenia was defined using pre-established cut-offs in patients with cirrhosis. Cut-offs for 6MWT to predict mortality (death or delisting for being too sick for LT) were determined using receiver-operating characteristic (ROC) curves. Cox proportional hazard models were conducted to assess associations between sarcopenia, functional performance assessed by the 6MWT, and mortality.

Results: There were a total of 180 cirrhotic patients who were evaluated for liver transplant who had a 6MWT test at the time of assessment and corresponding CT imaging (Table 1). There was a weak association between SMI and 6MWT observed as dimensional variables (r = 0.022; P = 0.003). A 6MWT < 489 m was independently associated with mortality, with AUC of 0.61 (95% CI, 0.51–0.71, P = 0.03) and subsequently defined as "poor physical performance." By univariate Cox analysis, both sarcopenia (HR 3.27; 95% CI 1.82–5.89; P < 0.001) and low 6MWT (HR 2.72; 95% CI 1.45–5.13; P < 0.001) were predictors of mortality. In a multivariate model, adjusted for MELD, sarcopenia (HR 2.96; 95% CI 1.59–5.51; P = 0.001) and low 6MWT (HR 2.33; 95% CI 1.21–4.51; P = 0.01) were independently associated with mortality. Poor physical performance was observed in 31 (60%) out of 52 sarcopenic patients. Sarcopenic patients with poor physical performance experienced a 6 times higher risk (HR 6.24; 95% CI 2.65–14.68; P < 0.001) of death. Sarcopenic patients with low 6MWT survived for 25 months (95%CI, 12–38) compared to 69 months (95% CI, 27–112) in sarcopenic patients with normal 6MWT (Log Rank = 0.04).

Conclusion: Sarcopenia and poor physical performance independently associate with mortality in patients with cirrhosis. Although poor physical performance was observed in more than half of the sarcopenic patients, its ability to discriminate mortality requires further investigation.

Baseline Characteristics (means or %)	
	Total Cohort (n = 180)
Male (%)	71
Age (years)	57 ± 7
MELD Score	12 ± 6
BMI (kg/m^2)	27 ± 6
Etiology of Liver Disease (%)	
• Alcohol	22
• Non-alcoholic steatohepatitis	24
• Hepatitis B	3
• Hepatitis C	44
• Autoimmune Liver Disease	7

SAT-234

The effect of primary prophylaxis therapy for large esophageal varices in patients with hepatocellular carcinoma

H.-S. Lu[1], C.-W. Su[1,2], M.-C. Hou[1,3], P.-H. Chen[4,5], P.-C. Lee[1,6], W.-Y. Kao[3,7], T.-I. Huo[1,6], Y.-H. Huang[1,2,8], H.-C. Lin[1,3], J.-C. Wu[8,9]. *[1]Taipei Veterans General Hospital, Divison of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [2]National Yang-Ming University, Faculty of Medicine, School of Medcine, Taipei, Taiwan; [3]National Yang-Ming University, Faculty of Medicine, School of Medicine, Taipei, Taiwan; [4]Taipei Veterans General Hospital, Endoscopy Center for Diagnosis and Treatment, Taipei, Taiwan; [5]National Yang-Ming University, Institute of Biophotonics, Taipei, Taiwan; [6]National Yang-Ming University, Institute of Pharmacology, Taipei, Taiwan; [7] Taipei Medical University Hospital, Divison of Gastroenterology and Hepatology, Department of Internal Medicine, Taipei, Taiwan; [8]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan; [9]Taipei Veterans General Hospital, Department of Medical Research, Taipei, Taiwan*
Email: cwsu2@vghtpe.gov.tw

Background and Aims: Whether or not primary prophylaxis therapy could improve the prognosis of patients with hepatocellular carcinoma (HCC) and with high risk esophageal varices (EVs) is not fully elucidated. We aimed to investigate the effect of primary prophylaxis therapy in determining the outcomes of patients with HCC and with large EV.

Method: We retrospectively enrolled 1157 HCC patients who received an esophagogastroduodenoscopy at the time of HCC diagnosis in Taipei Veterans General Hospital from October 2007 to May 2014. Among them, 352 patients had large EV (F2 and/or F3) indicated for primary prevention. A total of 127 patients received primary prevention therapy (37 patients received non-selective beta-blocker and 90 patients received endoscopic variceal ligation, respectively) and the remaining 225 patients did not receive primary prevention. Prognostic factors were analyzed in terms of overall survival and variceal bleeding-free survival.

Results: The median age and the model for end-stage liver disease (MELD) score of enrolled patients were 67 years (interquartile range IQR, 60–77.0 months) and 10.67 (IQR 8.7–14.06), respectively. Hepatitis B virus infection (54.9%) and hepatitis C virus infection (32.2%) were the major etiologies of HCC. Moreover, 186 (52.8%) patients had ascites. After a median follow-up of 8.7 months (interquartile range, 2.8–30.9 months), 299 patient dead and the remaining 53 patients were alive at their last visit. The cumulative 1- and 3-year overall survival rates were 52.8% vs. 36.2% and 31.5% vs. 20.4%, respectively ($p = 0.019$). The cumulative 1- and 3-year bleeding-free survival rates were 86.6% vs. 64.6% and 82.7% vs. 59.6%, respectively ($p < 0.001$). Multivariate analysis disclosed that serum bilirubin levels > 1.6 mg/dL (Hazard ratio HR 1.681, 95% confidence interval CI 1.317–2.145, $p = < 0.001$), aspartate aminotransferase > 40 U/L (HR 1.451, 95% CI 1.048–2.008, $p = 0.023$), presence of ascites (HR 1.964, 95% CI 1.488–2.591, $p = < 0.001$), serum alpha-fetoprotein level >20 ng/ml (HR 1.682, 95% CI 1.228–2.304, $p = 0.001$), tumor size > 3 cm (HR 2.000, 95% CI 1.462–2.734, $p < 0.001$), portal vein invasion (HR 2.491, 95% CI 1.852–3.351, $p < 0.001$), and without primary prevention (HR 1.368, 95% CI 1.037–1.804, $p = 0.027$) were the independent risk factors associated with 3-year overall mortality.

Conclusion: For HCC patients with large EVs, primary prevention therapy could decrease the risk of variceal bleeding and improve overall survival.

SAT-235

Characteristics of bone marrow drived mesenchymal stem cells in patients with liver cirrhosis

K.T. Suk[1], D.J. Kim[1], Y.L. Ham[2], D.B. Choi[1], S.J. Yoon[1]. *[1]Hallym University College of Medicine, Internal Medicine, Chuncheon, Korea, Rep. of South; [2]Daewon University, Emergency, Jaecheon, Rep. of South Korea*
Email: ktsuk@hallym.ac.kr

Background and Aims: Cirrhosis is the end stage of chronic liver disease, which may lead to severe hepatic dysfunction and even life-threatening conditions. The beneficial impact of mesenchymal stem cells (MSCs) transplantation on liver diseases has been confirmed on several studies include our previous clinical trial for autologous bone marrow-derived mesenchymal stem cells (BM MSCs) transplantation to patients with liver cirrhosis, which have shown the ability of MSCs to reduce liver cirrhosis and improve liver function. We aimed to identify secreted factors by undifferentiated BM-MSCs in order to describe related pathways potentially targeted gene by MSC in liver cirrhosis.

Method: Human BM-MSCs from normal and patients who had liver cirrhosis after autologous BM-MSCs transplanted and cultured specific medium condition for mesenchymal stem cells. We evaluated the potential of differentiation to osteoblast and adipocytes, morphological changes and cell proliferation depending on culture period, and immunophenotyping assay with flow cytometer with CD14, CD34, CD45, CD73 and CD105. At passage 4–5 of BM-MSCs were used for cDNA microarrays to identify secreted genes and related pathway that differentially expressed in specific stem cell population in liver cirrhosis and identified by biomathmatical analysis.

Results: On immunophenotyping analysis to determine mesenchymal function, CD14, CD34 and CD45 were 0.88%, 0.68% and 0.78%, respectively, however CD73 and CD105 for specific antigen of MSCs were 99.81% and 99.92%. BM MSCs secreted different factors in normal and patients with liver cirrhosis. We found 2968 genomes of 15 maps in KEGG pathway include Metabolic pathways, TGF-beta signaling pathway, Wnt signaling pathway, Cytokine-cytokine receptor interaction, HIF-1 signaling pathway, Ras signaling pathway and Natural killer cell mediated cytotoxicity. Within these pathways, functionally up-regulated genes were 7 genes and down-regulated genes were 9. In particular, we were able to identify potential specific genes might have typical function for regulation of liver cirrhosis and regeneration (FBN2, P4HA1 and STC1), and KIR3DL2, which is gene for regulation of immune system process.

Conclusion: Based on our previous clinical trial for autologous BM MSCs transplantation to patients with liver cirrhosis, the results have shown the ability of MSCs to reduce liver cirrhosis and improve liver function. Application of MSCs might target a widespread pattern of biological, cellular compositional and molecular functional event in the liver. MSC secreted genes and proteins can be differ depending on pathways and molecular mechanisms. Genes involved liver cirrhosis are able to release hepatotropic factors from transplanted MSCs, also potentially supporting liver regenerations.

SAT-236

Efficacy of L-ornithine L-aspartate for minimal hepatic encephalopathy in cirrhosis: A systematic review and meta-analysis of randomized controlled trials

R.F. Butterworth[1], N. Hilger[2], G. Kircheis[3], M.J.W. McPhail. [1]*University of Montreal, CHUM St-Luc Hospital, Montreal;* [2]*University of Bonn, Institute of Psychology, Methodology, Diagnostics and Evaluation, Bonn;* [3]*Medical University of Brandenburg Theodor Fontane, Clinic of Brandenburg, Brandenburg;* [4]*Kings College London, Liver Intensive Therapy Unit, Institute of Liver Studies, Division of Transplantation and Mucosal Biology, London, United Kingdom*
Email: rb@enceph.com

Background and Aims: Minimal hepatic encephalopathy (MHE) may seriously impact on reaction times, the ability to drive an automobile and on a patient's health-related quality of life. L-ornithine L-aspartate (LOLA) is an effective ammonia-lowering agent that is effective for the improvement of mental state in clinical hepatic encephalopathy (HE). However, its efficacy for the treatment of MHE remains the subject of debate. Published randomised controlled trials (RCTs) assessing the efficacy of LOLA in MHE are rare involving small numbers of patients and the results of these trials remain equivocal. Consequently, the aims of the present study were to meta-analyse the efficacy of LOLA in patients with cirrhosis and MHE. Efficacy was defined as the extent of improvement of mental state assessed by psychometric testing together with the lowering of blood ammonia.
Method: Appropriate keywords were used for searches of databases including The Cochrane Register, Medline, Google Search and Clinicaltrials.gov in order to identify RCTs for inclusion. Study quality and risk of bias were assessed using a novel combination of the established Jadad Composite Scale together with The Cochrane Scoring Tool. Group differences were assessed using the Random effects model and were expressed as pooled risk ratio (RR) or mean difference (MD) with associated 95% confidence intervals (CI).
Results: Seven RCTs with 332 patients satisfied inclusion criteria. Regression analysis revealed no evidence of publication bias or other small study effects. Five out of seven included RCTs had low risk of bias by Jadad/Cochrane criteria. Comparison with data from placebo/no intervention controls revealed that LOLA was significantly more effective for improvement of mental state (RR: 2.14, 95% CI: 1.62 to 2.83, $p < 0.01$) and for lowering of blood ammonia ($p < 0.01$) in MHE. The extent of improvement of mental state was greater in trials with low risk of bias and in trials using the oral formulation of LOLA ($p < 0.003$). Complete normalization of psychometric test scores occurred in 32/111 (28.8%) of MHE patients treated with LOLA compared to 14/120 (11.7%) in controls ($p < 0.02$).
Conclusion: Treatment with the oral formulation of LOLA resulted in significant improvement of mental state assessed by psychometric testing and lowering of blood ammonia in patients with cirrhosis and MHE.

SAT-237

Deleterious effect of proton pump inhibitors on the disease course of cirrhosis

Z. Vitális[1], T. Janka[1], T. Tornai[1], I. Tornai[1], D. Tornai[2], M. Papp[2]. [1]*University of Debrecen, Faculty of Medicine, Institute of Internal Medicine, Department of Gastroenterology, Debrecen, Hungary;* [2]*University of Debrecen, Faculty of Medicine, Department of Laboratory Medicine, Debrecen*
Email: drvitaliszs@gmail.com

Background and Aims: Proton pump inhibitors (PPIs) are widely used without rigorous indications in patients with cirrhosis. Association of PPI use with the occurrence of spontaneous bacterial peritonitis (SBP) has been the most extensively evaluated adverse outcome but a controversial issue so far. Long-standing PPI use might enhance pathologic bacterial translocation (BT) due to various reasons. Thus, we hypothesized that beyond SBP longstanding PPI use is associated with accelerated disease progression in cirrhosis (development of diseases-specific complications and/ or liver-related death).
Method: A 5-year follow-up observational cohort study was conducted to assess the impact of long-standing PPI use on the clinical course of cirrhosis in a large referral patient cohort. Three hundred and fifty patients with cirrhosis (male: 188, age: 56 ± 6 years, alcohol: 242 [69.1%], Child-Pugh stage A/B/C: 206/108/36) were included and assigned into two groups: regular PPI users (n = 154) and non-users (n = 196). Occurrence of SBP, decompensation events (development of ascites, hepatic encephalopathy and variceal bleeding) and liver-related death were assessed.
Results: Regular PPI use was associated with an increased cumulative probability of SBP [55.0% vs. 30.0%, pLogrank = 0.012] compared to non-users in patients with ascites (n = 113). Similar association was found with progressive disease course. First, the risk of the development of first decompensation event was higher in regular PPI users compared to non-users in patients with compensated clinical stage at enrollment (HR: 3.04, 95%CI: 1.56–5.92, p = 0.001, n = 163). Secondly, the risk of liver-related death was also significantly increased in case of regular PPI use ($p < 0.001$). In multi-variate Cox-regression analysis, regular PPI use (HR: 2.01, 95%CI: 1.38–2.93, $p < 0.001$), clinical stage (HR: 1.66, 95%CI: 1.12–2.45, p = 0.011) and MELD score (HR: 1.12, 95%CI: 1.08–1.55, $p < 0.001$) remained independent predictor of mortality.
Conclusion: In the present follow-up cohort, long-term PPI use was associated with the development of SBP and the progressive diseases course in patient with cirrhosis that might be caused by enhanced pathologic BT.

SAT-238

The impact of pulmonary arterial hypertension therapy in patients with portopulmonary hypertension: a single tertiary center cohort analysis

F. Nevens[1], H. Peeters[1], W. Laleman[1], C. Verslype[1], S. van der Merwe[2], D. Monbaliu[3], J. Pirenne[3], M. Delcroix[4]. [1]*UZ Leuven, Department of Gastroenterology and Hepatology, Leuven, Belgium;* [2]*UZ Leuven, Department of Gastroenterology and Hepatology, Belgium;* [3]*UZ Leuven, Department of Abdominal Transplant Surgery, Leuven, Belgium;* [4]*UZ Leuven, Department of Pneumology, Leuven, Belgium*
Email: frederik.nevens@uzleuven.be

Background and Aims: Portopulmonary hypertension (PoPH) has an ominous prognosis. Pulmonary arterial hypertension (PAH) specific medical therapy aims to improve hemodynamics to a threshold at which liver transplantation could safely be performed. However, currently there is limited long-term outcome data available. The aim of the present study was to evaluate efficacy of PAH therapy on cardiopulmonary hemodynamics, functional status, liver related complications and transplant outcome in patients with cirrhosis and PoPH in a single tertiary liver center with transplant facilities.
Method: In patients treated for PoPH the evolution of New York Heart Association (NYHA) classification, the six-minute walk distance (6MWD), MELD score, complications of portal hypertension and final outcome were prospectively monitored. Hemodynamic parameters were re-evaluated by serial right heart catheterization.
Results: Between 1997 and 2016, 31 patients were diagnosed with PoPH of which 29 received medical treatment and had long-term follow-up. All patients with PoPH subjected to PAH therapy responded to therapy with a significant improvement of mPAP (−15%, p = 008), PVR (−42%, p = 0.012), CO (+36%, p = 0.01), CI (+40%, p = 0.011) and functional capacity (NYHA functional class (-0.9 points, $p < 0.001$) and 6MWD (+65 m, $p < 0.001$)) at 6 months. In addition, PAH treatment was associated with an improvement of MELD score (10 ± 3.7 to 8.8 ± 4.6, p = 0.025) and a significant decrease in portal hypertensive complications. Of the 10 patients with advanced liver disease (mean MELD >12) that evolved to mild PoPH, and thus became eligible for LTx, 7 showed hepatic recompensation. Overall, the 5 years mortality due to liver

impairment in the absence of LTx was 8% and there was no difference in the 5-year survival in patients at baseline with or without advanced liver disease: 49% *vs.* 42%. Mortality was primarily driven by cardiopulmonary complications.
Conclusion: These data confirm the benefit and safety of PAH therapy also in patients with PoPH. Moreover, a favorable response to PAH therapy not only affected prognosis but also seems to hold the potential to improve liver dysfunction and reduce portal hypertensive complications. This combined impact therefore questions the need for LTx in patients with compensated liver disease and PoPH.

SAT-239

Non-selective beta-blockers reduce cardiac systolic function and impair renal function in patients with refractory ascites

L. Téllez[1], L. Ibañez[2], C. P. del Villar[3], E. Rodríguez-Santiago[1], R. Yotti[3], J. Martinez[1], M.Á. Rodríguez-Gandía[1], L. Carrión[2], M. Rivera[4], J. Bermejo[5], F. Gea[1], R. Bañares[2], A. Albillos[1]. *[1]Hospital Universitario Ramón y Cajal. IRYCIS. Universidad de Alcalá. CIBEREHD, Gastroenterology and Hepatology, Madrid, Spain; [2]IiSGM. CIBERehd. Universidad Complutense, Liver Unit. Hospital General Universitario Gregorio Marañón, Madrid, Spain; [3]IiSGM. Universidad Complutense., Cardiology. Hospital General Universitario Gregorio Marañón, Madrid, Spain; [4]IRYCIS. Universidad de Alcalá, Servicio de Nefrología. Hospital Universitario Ramón y Cajal, Madrid, Spain; [5]IiSGM. Universidad Complutense, Cardiology. Hospital General Universitario Gregorio Marañón*
Email: luis.tellez@salud.madrid.org

Background and Aims: Systolic dysfunction, a component of cirrhotic cardiomyopathy, is defined by an impaired cardiac contractile response to stress, and results in the inability of the heart to meet tissue perfusion demands. It has been related to renal dysfunction and prognosis in cirrhosis and could be at the root of the potential risk of beta-blockers in refractory ascites. In contrast to conventional echocardiography methods that depend on loading conditions, Doppler-derived intracardiac pressure differences, such as ejection intraventricular pressure difference (EIVPD), are highly sensitive and reliable to address systolic function independently of load conditions. Aims: To evaluate and compare systolic function by EIVPD in cirrhotic patients with diuretic-sensitive (DSA) and refractory ascites (RA), at baseline and after treatment with non-selective beta-blockers (NSBB).
Method: Muticentre, prospective, observational and controlled study in 25 patients with cirrhosis and ascites, 17 with RA and 8 with DSA. Patients underwent heart function assessment (pulmonary pressures and cardiac index by Swan-Ganz catheter, conventional echocardiographic measurements and EIVPD and EKG), renal function (renal Doppler US, blood and urine test) and hepatic hemodynamics were assessed at baseline and after 4 weeks on non-selective beta-blockers.
Results: (RA *vs.* DSA, mean ± SD) Child score (8.8 ± 1.7 *vs.* 9.2 ± 1.0), MELD (13.9 ± 3.3 *vs.* 14.1 ± 3.1) and HVPG (22.6 ± 3.9 *vs.* 23.6 ± 5.2 mmHg) were similar in both groups. Systolic function as measured by EIVPD was greater in DSA than in RA (5.56 ± 1.52 *vs.* 4.08 ± 1.39 mmHg, $p < 0.05$). In contrast, left-ventricular ejection fraction and cardiac index were similar in both groups (66.9 ± 4.93 *vs.* 67.9 ± 3.86%, and 4.3 ± 0.9 *vs.* 3.6 ± 0.9 l/min/m^2). Beta-blockade led to similar reductions in heart rate, cardiac index, mean arterial pressure and HVPG in both groups. Beta-blockade significantly reduced EIPVD in RA (4.08 ± 1.39 *vs.* 3.35 ± 0.91 mmHg, $p < 0.05$) but not in DSA (5.56 ± 1,53 *vs.* 5.24 ± 2.18 mmHg, NS). Absolute change in EIPVD (ΔEIPVD) directly correlated ($p < 0.01$) with worsening of renal function measured by cystatin C ($r = –0.69$) and creatinine ($r = –0.63$) in RA group. Changes in EIVPD after beta-blockade were similar in HVPG non- and responders (↓HVPG > 10%). ΔEIPVD was inversely correlated with baseline mean pressure in the whole group of patients ($r = 0.43$, $p < 0.05$).
Conclusion: Systolic function by robust Doppler derived indexes is reduced in cirrhosis with RA compared to DSA. Beta-blockade compromises systolic and renal function at short-term, especially in patients with lower arterial pressure

SAT-240

High risk of esophageal varices in patients with Fontan surgery: The VALDIG FONLIVER study

L. Téllez[1], E. Rodríguez-Santiago[1], E. Garrido[1], A. Baiges[2], V.L. Mura[3], E. Garrido-Lestache[4], R. Romera[5], J. Martinez[6], A. Clemente[7], L. Aguilera[1], E. Llop[8], D. Rincón[9], M.A. Fuente[10], I. Sánchez[10], F. Gea[1], D.M.J. Del Cerro[11], R. Bañares[7], G.P.J. Carlos[9], A. Albillos[1]. *[1]Hospital Universitario Ramón y Cajal. IRYCIS. Universidad de Alcalá. CIBEREHD, Gastroenterology and Hepatology, Madrid, Spain; [2]Liver Unit. Hospital Clínic., IDIBAPS. University of Barcelona., Barcelona, Spain; [3]San Donato, Internal Medicine, Milano, [4]Hospital Universitario Ramón y Cajal. IRYCIS., Pediatric Cardiology, Madrid, Spain; [5]Hospital Universitario Ramón y Cajal, Radiology; [6]Gastroenterology and Hepatology. Hospital Universitario Ramón y Cajal., IRYCIS. CIBERehd. Universidad de Alcalá, Madrid, Spain; [7]Liver Unit. Hospital General Universitario Gregorio Marañón, IiSGM, Madrid; [8]Hospital Universitario Puerta de Hierro, Gastroenterology and Hepatology, Madrid, Spain; [9]Liver Unit. Hospital Clínic., IDIBAPS. CIBERehd. University of Barcelona, Barcelona, Spain; [10]Hospital Universitario Ramón y Cajal. Universidad de Alcalá, Pediatric Cardiology, Madrid, Spain; [11]Hospital Universitario Ramón y Cajal. IRYCIS. Universidad de Alcalá., Pediatric Cardiology*
Email: luis.tellez@salud.madrid.org

Background and Aims: Fontan surgery (FS) allows the venous return to reach the pulmonary circulation bypassing the ventricle in patients with single ventricle. This results in sustained systemic venous hypertension and liver damage in long-term. Nevertheless, natural history of liver disease in these patients has been poorly studied; prevalence and features of esophageal varices (EV) are unknown. The AIM of this study is to estimate the prevalence and characterize EV in this population.
Method: Multicentre, observational, trans versal, prospective and analytical study. 32 patients with >5yr since FS underwent Doppler US, Fibroscan®, cardiac and hepatic catheterization, blood test and upper endoscopy. Haemorrhagic risk EV was defined according to Baveno VI criteria.
Results: 32 patients were included. Age: median 27.9 yr, IQR: 11; 34% were females. Time from FS was: median 21, IQR 8.3 yr. Prevalence of EV was 53% (17/32; CI95%:36–69%). 18% (6/32; CI95%:9–35%) had high-risk stigmata and 1 patient presented with variceal haemorrhage. The most frequent location was the mid-lower esophagus. There were not gastric varices. In the univariant analysis, inferior vena cava pressure > 16 mmHg ($p = 0.09$), platelets <125000/mm3 ($p = 0.06$) and Fibroscan® >30 kPa ($p = 0.04$) were associated with the presence of EV. The most relevant incidental finding was diffuse gastritis (16/32, 50%), followed by peptic ulcer in 4 patients (13%). Sedation conducted by experienced endoscopist had more sedation-related complications than expected (2/6, severe hypoxemia and sustained hypotension). Sedation guided by anaesthesiologists (22/32,69%) was safe.
Conclusion: Prevalence of EV is very high in patients after FS. Some of them have high-risk EV and haemorrhage may occur. Screening with upper endoscopy in patients with liver stiffness >30 kPa and platelets < 125000/ml is highly advisable.

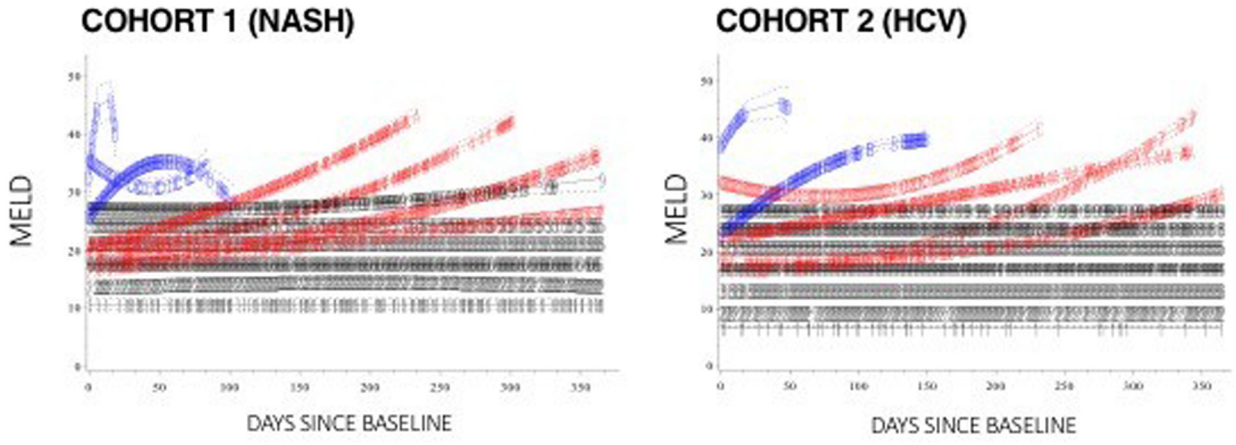
SAT-241

Distinct MELD trajectories in liver transplant candidates with hepatitis C and non-alcoholic steatohepatitis

A. Kwong, A. Mannalithara, W.R. Kim. *Stanford University, Gastroenterology and Hepatology, Stanford, United States*
Email: wrkim@stanford.edu

Background and Aims: Since its inception as a scale to determine priority for liver transplant (LT) candidates, the Model for End-stage Liver Disease (MELD) has been agnostic regarding the etiology of the underlying liver disease. The aim of this study was to identify and

Figure. Distinct MELD trajectories with 95% confidence intervals for LT candidates in 2016
1-year survival with LT censored, TFS = transplant-free survival.



	COHORT 1 (NASH)			COHORT 2 (HCV)		
Trajectory groups	N (%)	1-YR SURVIVAL	1-YR TFS	N (%)	1-YR SURVIVAL	1-YR TFS
1 (no change/linear trend)	883 (84.2)	83.0%	57.6%	1539 (90.1)	87.3%	62.7%
2 (late deterioration)	117 (11.2)	48.0%	12.8%	120 (7.1)	43.7%	8.6%
3 (early deterioration)	49 (4.7)	24.8%	0.0%	35 (2.1)	24.9%	0.0%

Figure: (abstract: SAT-241)

compare clusters of disease trajectory for LT candidates with HCV and non-alcoholic steatohepatitis (NASH).
Method: All adult primary LT candidates with end-stage liver disease who were on the waitlist as of February 1, 2016, were identified in the OPTN waitlist registry data. All patients, including those who met MELD exception criteria, with at least 1 recorded MELD within 1 year were included. Patients were censored at the time of LT. Latent subpopulations with heterogeneous disease trajectories were identified, using latent class growth mixture modeling to group individuals based on longitudinal changes in MELD over the 1 year of follow-up. Statistical fit was determined by Bayesian information criteria, and trajectories with similar patterns were categorized into separate groups for analysis.
Results: Three distinct trajectory groups were identified among 1049 patients with NASH and 1694 with HCV: (1) high MELD/early deterioration, (2) late deterioration, and (3) no change/linear trend (Figure). There was a greater proportion of patients with HCV exhibiting no change/linear trend (90.1%) compared to those with NASH (84.2%). In this trajectory group, HCV patients, in comparison to NASH patients, had better 1-year waitlist survival (87.3% v. 83.0%, respectively) and transplant-free survival (62.7% v. 57.6%, respectively). Of waitlist candidates belonging to the late deterioration trajectory group, HCV patients had a higher baseline MELD and a higher prevalence of ascites and hepatic encephalopathy compared to those with NASH ($p < 0.01$). Patients in the early deterioration trajectory group made up 4.7% of the NASH cohort and 2.1% of the HCV cohort, with 0% transplant-free survival at 1 year in both cohorts.
Conclusion: Using latent class trajectory modeling methods, distinct trajectory groups are identifiable for LT candidates with HCV and NASH. The reduced rate of disease progression among LT candidates with HCV compared to NASH may be related to the availability of antiviral therapy. Trajectory analysis may enable early identification of LT candidates at risk for deterioration on the waitlist and recognition of etiology-specific risk factors for clinical deterioration.

SAT-242

Natural history of patients with compensated cirrhosis and a hepatic venous pressure gradient >20 mmHg: A prospective longitudinal cohort study

A. Bhardwaj[1], A. Jindal[2], V. Arora[2], V. Rajan[2], A.S. Bhadoria[1], G. Kumar[1], L. Anand[2], A. Choudhury[3], S.M. Shasthry[2], R. Maiwall[2], M. Kumar[4], S.K. Sarin[5]. *[1]ILBS, Clinical Research, New Delhi, India; [2]ILBS, Hepatology, New Delhi, India; [3]Institute of Liver & Biliary Sciences, Hepatology, New Delhi, India; [4]Institute of Liver and Biliary Sciences, D1, NEW DELHI, India; [5]Institute of Liver and Biliary Sciences, Department of Hepatology, Vasant kunj, India*
Email: shivsarin@gmail.com

Background and Aims: HVPG >10 mm Hg predicts clinical decompensation (CD) in compensated cirrhotics. A proportion of cirrhotics have high HVPG (>20 mm Hg) despite no CD. The natural history, pattern of CD (ascites, hepatic encephalopathy, variceal bleed) and complications (HCC, mortality) in this group are largely unknown.
Method: Consecutive compensated cirrhosis patients with HVPG ≥6 mm Hg (n = 747) were followed-up every 3–6 months for any decompensation. Patients were classified based on HVPG (<12 mmHg (low HVPG group), 12–20 mmHg (Intermediate HVPG group) and >20 mmHg (High HVPG group). We analyzed only the low and high HVPG groups to identify predictors of new CD.
Results: 295(39.4%) patients developed CD at mean follow-up of 1.9 ± 0.3 years. In comparison to low HVPG group, first CD in high HVPG group developed early (1.4 ± 0.3 years *vs.* 2 ± 0.3 years, p = 0.02), more often (ascites- 27.1% *vs.* 13.2%, variceal bleed- 31.9% *vs.* 7.9%, AKI- 31% vs 12.8%, HCC- 12.4% *vs.* 3.9%; all $p < 0.05$) with higher mortality (15.9% *vs.* 1.9%; $p < 0.05$). There was no significant correlation between baseline HVPG level and grade of esophageal varices (p = 0.457). All patients in high HVPG group received carvedilol (maximum dose-25 mg/d, divided) and a repeat HVPG measured after a mean duration of 1.8 ± 0.4 years showed suboptimal HVPG

response (≥20% reduction in HVPG or <12 mmHg) in 26.6% patients (mean HVPG reduction, 3.3 ± 1.3 mm Hg). Etiology of cirrhosis and grade of varices were not significantly associated with CD or HVPG response. On multivariate analysis, baseline HVPG >20 mm Hg (hazard ratio [HR], 5.09; 95% confidence interval [CI], 2.909–8.926, p = 0.001) and high MELD score (HR, 1.125; 95% CI, 1.066–1.187, p = 0.001) were independent predictors of CD.
Conclusion: An HVPG of >20mm Hg independently predicts early and more frequent CD in compensated cirrhotics. Only a quarter of these patients respond to carvedilol and hence mandates us for careful HVPG monitoring and low threshold for additional drugs or interventions.

SAT-243

Effect of vardenafil on portal hemodynamics in patients with mild and moderate liver dysfunction: a randomized, placebo-controlled trial

R. Paternostro, B. Heinisch, R. Schwarzer, T. Reiberger, M. Wewalka, P. Schwabl, M. Ferlitsch, M. Mandorfer, M. Peck-Radosavljevic, M. Trauner, A. Ferlitsch. *Medical University of Vienna, Internal Medicine III, Gastroenterology and Hepatology*
Email: rafael.paternostro@meduniwien.ac.at

Background and Aims: Erectile Dysfunction (ED) is a frequent complication in patients with cirrhosis. Phosphodiesterase type 5 inhibitors (PDE5i) are effective to treat ED. Experimental studies have suggested beneficial effects of PDE5i on portal hypertension (PHT). We assessed the effects of 7 days treatment with vardenafil (10 mg o.d.; Bayer, Germany) or placebo on hepatic venous pressure gradient (HVPG) and safety in patients with cirrhosis and PHT.
Method: 20 male patients with stable cirrhosis and Child Pugh Score A and B were included. HVPG was assessed while under fasted conditions at baseline. After 7 days of treatment HVPG response (2 h after last dose) was recorded.
Results: 20 patients (age: 54 ± 13; etiology: 8 alcohol, 9 viral, 1 alcohol + viral and 2 others) were included. Three patients on vardenafil did not finish the HVPG study (n = 1 discontinuation due to headache, n = 2 failure to obtain second HVPG). Thus, n = 9 patients on vardenafil (Child A:4, B:5) and n = 8 on Placebo (Child A:4, B:4) were analyzed per protocol. Baseline HVPG (vardenafil: 18.1 ± 5.5; placebo: 18.3 ± 4.5; p = 0.952) was similar between groups. After 7 days of treatment HVPG was 17.8 ± 5 mmHg in the vardenafil group and 17.4 ± 3.9 mmHg in the placebo group; showing no significant decrease in HVPG in the vardenafil group (p = 0.724) and no statistical difference in on-treatment HVPG between groups (p = 0.858). Safety: One patient reported tinnitus and one patient reported fatigue and diffuse pain (foot, eyes) both on vardenafil. Considering the patient that discontinued the study medication due to headache, 30% of patients on vardenafil vs. 0% of patients in the placebo group reported side effects. Hence the study medication was not very well tolerated in our patient cohort.
Conclusion: Within this randomized control pilot study 30% of patients on Vardenafil reported side effects. Seven days of Vardenafil treatment did not decrease HVPG in patients with stable Child-Pugh A/B cirrhosis. These results do not support previous reports on portal pressure reduction with other PDE5i.

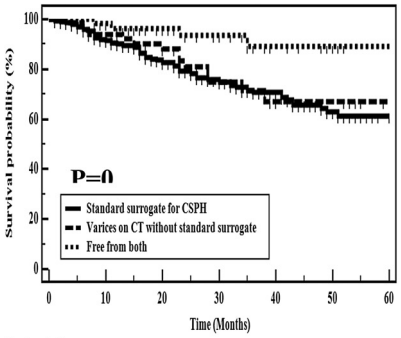
SAT-244

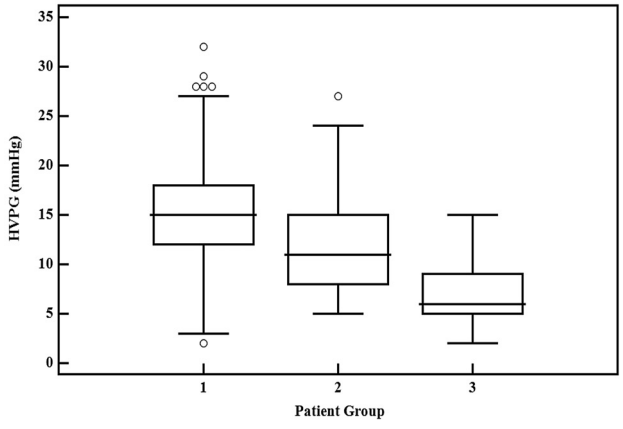
Varices on CT is the surrogate of clinically significant portal hypertension and can predict survival in patients with cirrhosis

D.H. Lee. *Seoul National University Hospital, Radiology, Seoul, Rep. of South Korea*
Email: dhlee.rad@gmail.com

Background and Aims: To investigate the prognostic value of varices on CT and redefine surrogate criteria for clinically significant portal hypertension (CSPH).

Method: We retrospectively enrolled 525 patients with cirrhosis who underwent hepatic venous pressure gradient (HVPG) measurement from 2008 to 2013. Using CT and upper endoscopy findings obtained within 3 months from HVPG measurement, patients were classified into three groups: presence of standard surrogate for CSPH, defined as presence of varices on upper endoscopy and/or splenomegaly associated with thrombocytopenia (Group 1, n = 375); varices on CT without standard surrogate for CSPH (Group 2, n = 76); and free from both (Group 3, n = 74). HVPG value and overall survival (OS) rates were compared among three patient groups. Revised surrogate for CSPH was defined as the presence of standard surrogate and/or presence of varices on CT (i.e., both group 1 and group 2).
Results: Mean HVPG value in Group 2 was significantly higher than that in Group 3 (11.5 mmHg vs. 6.8 mmHg, P < 0.001), but significantly lower than that in Group 1 (15.0 mmHg vs. 11.5 mmHg, P < 0.001). 5-year OS rates in Group 2 was similar to those in Group 1 (67.1% *vs.* 61.2%, P = 0.648), but significantly poorer than those in Group 3 (67.1% vs. 89.1%, P = 0.012). The presence of standard surrogate for CSPH was not a significant factor for OS (61.2% *vs.* 77.3%, P = 0.068). However, presence of revised surrogate for CSPH was a significant predictive factor for OS (61.9% *vs.* 89.1%, P = 0.017).





Conclusion: The presence of varices on CT was a significant sign for CSPH, predicting poor overall survival outcome in patients with cirrhosis.

SAT-245

Predictors of endoscopic high risk esophageal varices in compensated cirrhosis: Can we avoid Fibroscan?

G. Huard[1], J. Hercun[1], M. Bilodeau[2], J. Bissonnette[3], J.-M. Giard[1].
[1]*Centre Hospitalier de l'Université de Montréal, Montreal, Canada;* [2]*Centre Hospitalier de l'Université de Montréal, Montreal, Montreal, Canada;* [3]*Hôpital Beaujon, Centre Hospitalier de l'Université de Montréal, Paris, France*
Email: julianhercun@gmail.com

Background and Aims: Patients with cirrhosis are at risk of developing esophageal varices (EV). Recently, criteria based on elastography and platelet count (Baveno VI criteria) have been adopted and included in practice guidelines to circumvent screening endoscopy (EGD). However, elastography measurement is not widely available. The aim of the study was to determine predictive factors excluding liver stiffness in order to predict high-risk EV in patients with compensated cirrhosis.

Method: Retrospective chart review of all compensated cirrhotic adult patients who underwent screening EGD at Saint-Luc Hospital between 01/2014 and 12/2016. Patients with decompensated cirrhosis (ascites, hepatic encephalopathy, jaundice), past history of EV/TIPS or liver transplantation, acute upper gastrointestinal bleeding, acute alcoholic hepatitis were excluded. High-risk EV were defined as medium or large EV and/or presence of red wale signs. Splenomegaly was defined as a spleen ≥13 cm on imaging. Thrombopenia was defined as a platelet count $<150 \times 10^9$/L. Baseline characteristics, laboratory values and EGD findings were analyzed.

Results: A total of 463 patients were included. The median (IQR) age was 60.2 (13.4) years and the majority were males (n = 289; 62.4%). The most frequent causes of liver disease were chronic hepatitis C infection (n = 117; 25.3%) and non-alcoholic steatohepatitis (n = 112; 24.2%). At screening EGD, the median (IQR) MELD score was 7.5 (2.7), the median (IQR) platelet count was $154\ (87) \times 10^9$/L, and 203 (43.8%) patients had splenomegaly. A total of 45 (9.7%) patients had high-risk EV at screening EGD. In multivariate analysis adjusting for age and gender, the following variables were predictive of high-risk EV: thrombopenia (OR 4.7; p= 0.001) and splenomegaly (OR 3.8; p = 0.001). MELD >6 score was not predictive of high-risk EV (OR 1.7; p = 0.337). Among the 172 patients having normal spleen size and platelet count $\geq 150 \times 10^9$, only 2 (1.2%) patients had high-risk EV at screening EGD. The presence of splenomegaly and/or thrombopenia had a sensitivity of 95.6% and a negative predictive value of 98.8% for the presence of high-risk EV at screening endoscopy.

Conclusion: In compensated cirrhosis, the combination of normal spleen size and normal platelet count translates into a 98.8% chance of absence of high-risk EV at screening EGD. Using these criteria, 172 (37.1%) screening EGD could have been avoided in our population. Therefore, the use of elastography is not mandatory in the decision of recommending screening EGD in patients with compensated cirrhosis.

SAT-248

Uncontrolled diabetes increases all causes of mortality and particularly cardiovascular death in patients with cirrhosis

F.H.-d.L. Tijera[1], A. Servin-Caamaño[2], A.E. Navarro-Estrada[2], R. Rabago[3], A. Cruz-Estrada[4]. [1]*Hospital General de Mexico, Head of Gastroenterology Department, Mexico;* [2]*Hospital General de Mexico, Internal Medicine;* [3]*Hospital General de Mexico, Gastroenterology, Liver Clinic;* [4]*Hospital General de Mexico, Head of Internal Medicine Department*
Email: fatimahiguera@yahoo.com.mx

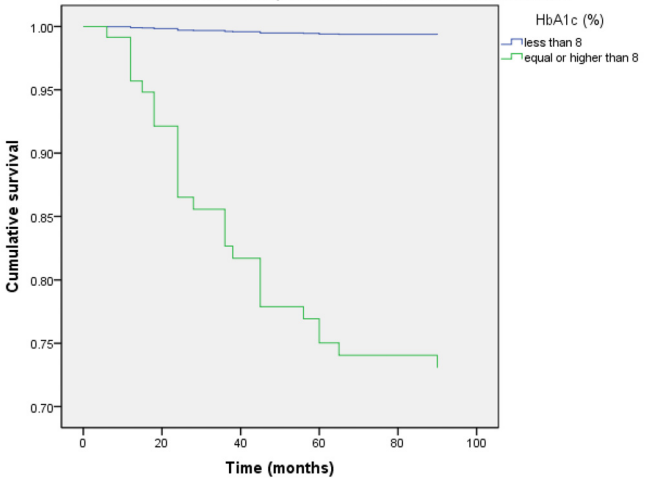
Background and Aims: Diabetes is a comorbidity that is increasing in patients with cirrhosis; nevertheless, there are not specific guidelines to treat diabetes in this population. The aim of this study was to investigate risk factors increasing all causes of mortality, with special attention on cardiovascular death in patients with cirrhosis with type 2 diabetes.

Method: A cohort study which included patients with cirrhosis and diabetes, seen at the Liver Clinic in the last 10 years. We excluded patients with other conditions potentially related to immunosuppression. Demographic, clinic, metabolic and biochemical data were collected; the date of diabetes and cirrhosis diagnosis was verified, during follow-up we specially search for all causes of mortality and cardiovascular death. Univariate analysis was performed using t Student's test or Mann-Whitney U test, or with X2 or Fisher's exact test. Cox regression model was used for the multivariate analysis. Kaplan-Meier curves was constructed to compare between those death or alive. A $p < 0.001$ value was considered significant.

Results: 380 patients with cirrhosis and diabetes were included, 193 (50.8%) were men. The mean of age was 62.6 + 9.0 year-old. Causes of cirrhosis were: alcohol 156 patients (41.1%), hepatitis C 76(20.0%), non-alcoholic steatohepatitis 111(29.2%), cryptogenic 37(9.7%). According to Child-Pugh: 141 patients (37.1%) were assessed as A, 170(44.7%) B, 69(18.2%) C. Thirty three (8.7%) died for liver-related causes, 29(7.6%) died for cardiovascular death.

Patients who died had higher fast serum glucose compared with those alive: 220 ± 85 mg/dL vs. 143 ± 62 mg/dL, $p < 0.0001$; and higher Hb_{A1c} serum levels: 8.4 ± 1.5% *vs.* 6.8 ± 1.1%, $p < 0.0001$. In the univariate analysis, hepatic encephalopathy (HE), ascites, spontaneous bacterial peritonitis (SBP), level of Hb_{A1c} >8.0%, and decompensated cirrhosis (Child B/C) were factors associated with all causes of mortality, ($p < 0.0001$). In the multivariate analysis, only Hb_{A1c} >8.0% was associated with all causes of mortality (HR = 6.3; 95%CI = 3.2–12.6; $p < 0.0001$). When we analysed specifically for cardiovascular death, those who died had higher serum glucose levels: 230 ± 92 mg/dL vs. 143 ± 62 mg/dL, $p < 0.0001$; and Hb_{A1c} serum levels: 8.8 ± 1.6% *vs.* 6.8 ± 1.1%, $p < 0.0001$. In the univariate analysis, ascites ($p = 0.001$), HE, SBP, level of Hb_{A1c} >8.0% were associated with cardiovascular death ($p < 0.0001$). Decompensated liver disease, variceal bleeding, sex were not significant. In the multivariate analysis Hb_{A1c} >8.0% was strongly associated with cardiovascular death (HR = 48.6; 95%CI = 10.6–222.4; $p < 0.0001$).

Kaplan Meier curves showing survival rate for cardiovascular death according to HbA1c serum levels in patients with cirrhosis and diabetes



Conclusion: When diabetes coexists with cirrhosis, uncontrolled glycaemia seems to be the most important risk factor predicting all causes of mortality, but specially is strongly associated with cardiovascular death.

SAT-249

TIPS placement improves sarcopenia and modifies fat distribution: A monocentric retrospective study

F. Artru[1], M. Xavier[1], A. Mustapha[1], N. Amelie[1], T. Pierre[1], E. Olivier[1], G. Lassailly[2], S. Dharancy[3], S. Geraldine[1], P. Mathurin[1], A. Louvet[1].
[1]CHRU Lille, Liver unit, Lille, France; [2]Liver unit, CHRU Lille, Lille, France; [3]Liver unit, CHRU Lille, Lille, France
Email: florent.artru@chru-lille.fr

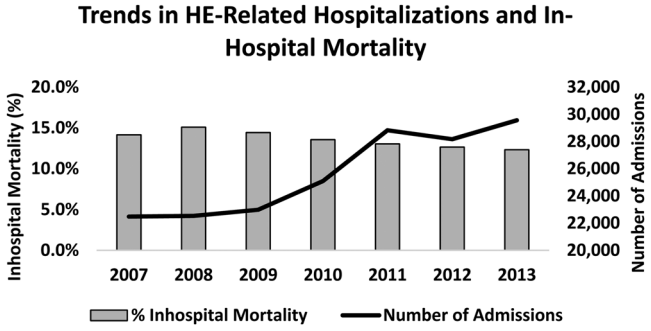
Background and Aims: Sarcopenia is associated with mortality in decompensated cirrhosis and has been suggested being reversible after TIPS placement based on the results of only one study. Computed tomography (CT) scan enables to assess body composition after TIPS placement. The aims of our study were to evaluate the impact of TIPS placement on body composition and to assess its changes by radiological sequential analysis.
Method: All patients who underwent TIPS insertion for elective indication (refractory ascites and secondary prophylaxis of portal hypertension related GI bleeding) between July 2011 and March 2017 have been retrospectively included. Clinical, biological and CT data have been recorded sequentially 1, 3 and 6 months after TIPS placement.
Results: 132 patients were included. 84.1% (n = 111) had alcohol-related cirrhosis. Median age was 58.5 (IQR 52.8–63.3) years, MELD score 10.7 (8.5–13.2) and Child-Pugh score 8 (7–8). TIPS indication was refractory ascites in 71.2% (n = 98) and secondary prophylaxis of GI bleeding in 28.8% (n = 38). 6-month survival was 84.8 and 97.3% respectively (p = NS). We observed a progressive improvement in sarcopenia at 3 and 6 months after TIPS as shown by an increase in umbilical level psoas axial diameter (AD) from 42.5 to 45.4 mm ($p < 0.0001$), psoas transverse diameter (TD) from 33.8 to 37.2 mm ($p < 0.0001$), and L3-L4 intervertebral level sum of psoas area from 2017.7 à 2249 mm² ($p < 0.0001$). Such improvement was not observed in patients who developed TIPS obstruction when compared to those who did not developed obstruction: TD 33.6 to 34.2 mm ($p = 0.63$) vs. 34.3 to 38.1 mm ($p < 0.0001$), AD 40.7 to 41 mm ($p = 0.86$) *vs.* 43.7 to 46.6 mm ($p < 0.0001$), sum of area 1868.9 to 1869.2 mm² ($p = 0.99$) vs. 2083.3 to 2333.8 ($p < 0.0001$). From baseline to 3 and 6 months, subcutaneous fat (SCF) increased from 163.8 cm² to 225.1 cm² ($p < 0.0001$) and visceral fat (VF) decreased from 158.6 cm² to 143.7 cm² ($p = 0.02$). At 6 months, we observed an increase of SCF from 174.8 to 225.2 cm² ($p < 0.0001$) and a decrease of VF from 152.5 to 130.8 cm² ($p = 0.002$) in patients without TIPS thrombosis. In the others, VF decreased from 207.3 to 180.3 cm² ($p = 0.03$) without significant increase of SCF from 207.4 to 231.5 cm² ($p = 0.13$). In univariate analysis, at time of TIPS placement, VF (RR 1.005 95% CI 1.005–1.1, $p = 0.05$), AD (RR 0.9, 0.83–0.96, $p = 0.005$), TD (RR 0.91, 0.85–0.98, $p = 0.01$) and MELD score (1.09, 1.02–1.2, $p < 0.04$) were associated with 6-month mortality. No multivariate analysis was performed because of a too small sample size.
Conclusion: Elective insertion of TIPS is followed by a rapid improvement of sarcopenia, an increase of SCF and a decrease of VF, which depends on the permeability of the stent. This confirms the role of portal hypertension on body composition of cirrhotic patients.

SAT-250

Increasing burden of hepatic encephalopathy among hospitalized adults, with significantly higher risk of in-hospital mortality in African Americans: An analysis of the 2007–2013 nationwide inpatient sample

G. Hirode, B. Liu, T. Bhuket, R. Wong. *Alameda Health System, Highland Hospital, United States*
Email: rowong@alamedahealthsystem.org

Background and Aims: Hepatic encephalopathy (HE) is a common complication associated with decompensated liver disease among patients with acute liver failure or advanced cirrhosis. Development of HE is associated with significant morbidity and mortality, contributing to significant burden on healthcare systems. We aim to evaluate trends in the burden of HE among hospitalized adults in the U.S.
Method: Using the 2007–2013 Nationwide Inpatient Sample, we identified HE-related hospitalizations using International Classification of Diseases, Ninth Revision codes. Annual trends in HE-related hospitalizations and in-hospital mortality were evaluated. Multivariable logistic regression was performed on weighted data to identify factors associated with in-hospital mortality adjusting for patient- and hospital-level characteristics. Variables that demonstrated statistically significant associations ($p < 0.05$) in univariable analysis, and with biological plausibility, were included.
Results: Among 179,604 HE-related hospitalizations (58.3% male, 67.4% non-Hispanic white, median age 58 IQR 51–67, 67.1% with cirrhosis diagnosis), overall hospital length of stay was 5 days (IQR 3–10) and in-hospital mortality was 13.5%. From 2007 to 2013, HE-related hospitalizations increased by 31.5% (22,471 to 29,559, $p < 0.001$). During this same period, in-hospital mortality rates among HE hospitalizations decreased from 14.1% in 2007 to 12.3% in 2013, $p < 0.001$. On multivariable regression, African Americans had significantly higher in-hospital mortality compared to non-Hispanic whites (OR, 1.21; 95% CI, 1.13–1.30; $p < 0.001$). Significantly higher risk of in-hospital mortality was also observed in patients with acute liver failure (OR, 3.73; 95% CI, 3.48–4.00; $p < 0.001$), hepatorenal syndrome (OR, 4.04; 95% CI, 3.79–4.30; $p < 0.001$), ascites (OR, 1.36; 95% CI, 1.30–1.42; $p < 0.001$), and hepatocellular carcinoma (OR, 1.58; 95% CI, 1.43–1.74; $p < 0.001$). Additionally, being admitted to an urban teaching hospital (relative to rural) was also associated with higher odds ($p < 0.05$).



Conclusion: The burden of HE-related hospitalizations in the U.S. continues to rise. While overall in-hospital mortality has declined, significant race/ethnicity-specific disparities are observed, with the significantly higher risk of mortality seen in African Americans with HE compared to non-Hispanic whites.

SAT-251

Health care costs are double for non-alcoholic fatty liver disease non-alcoholic steatohepatitis patients with compensated cirrhosis who progress to end-stage liver disease

R. Loomba[1], S. Li[2], Y. Peng[2], X. Wang[2], S. Harrison[3]. *[1]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States; [2]Chronic Disease Research Group, Minneapolis, United States; [3]Pinnacle Clinical Research, San Antonio, United States*
Email: roloomba@ucsd.edu

Background and Aims: NAFLD/NASH is one of the most common causes of CC in the United States. CC patients often develop complications and advance to ESLD which includes decompensated cirrhosis (DCC), hepatocellular carcinoma (HCC) and liver transplant (LT) which may lead to death. The study objective was to characterize long-term economic burden in compensated cirrhosis (CC) patients who progressed to end-stage liver disease (ESLD) compared to those who did not.

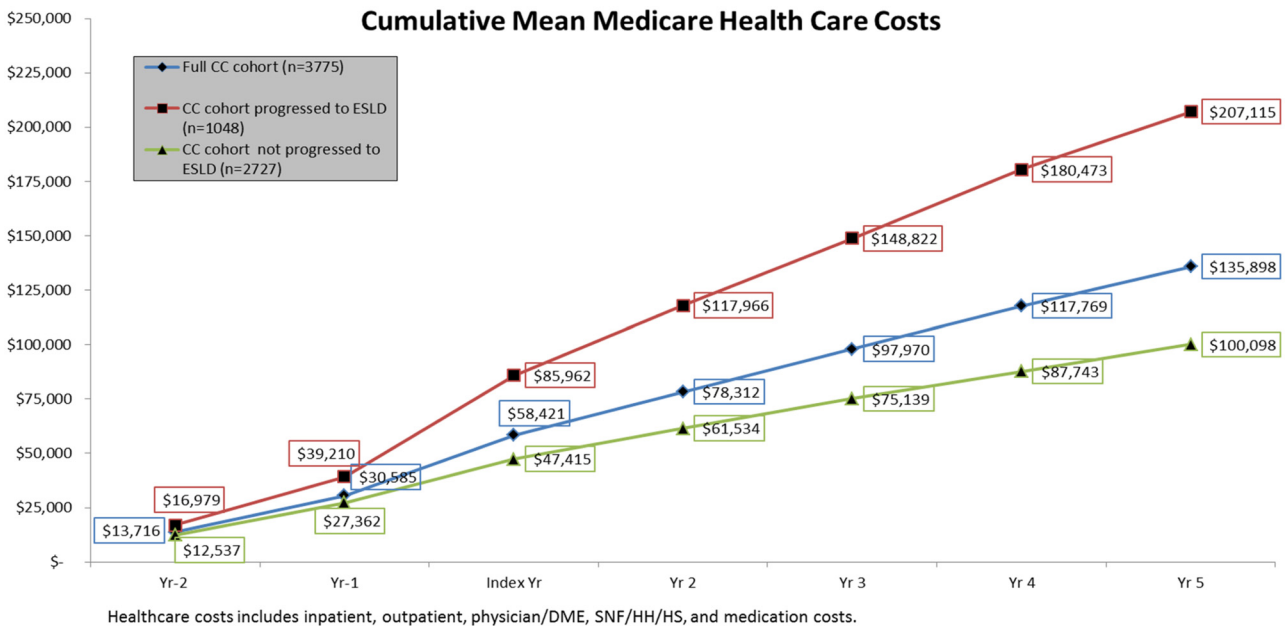


Figure: (abstract: SAT-251)

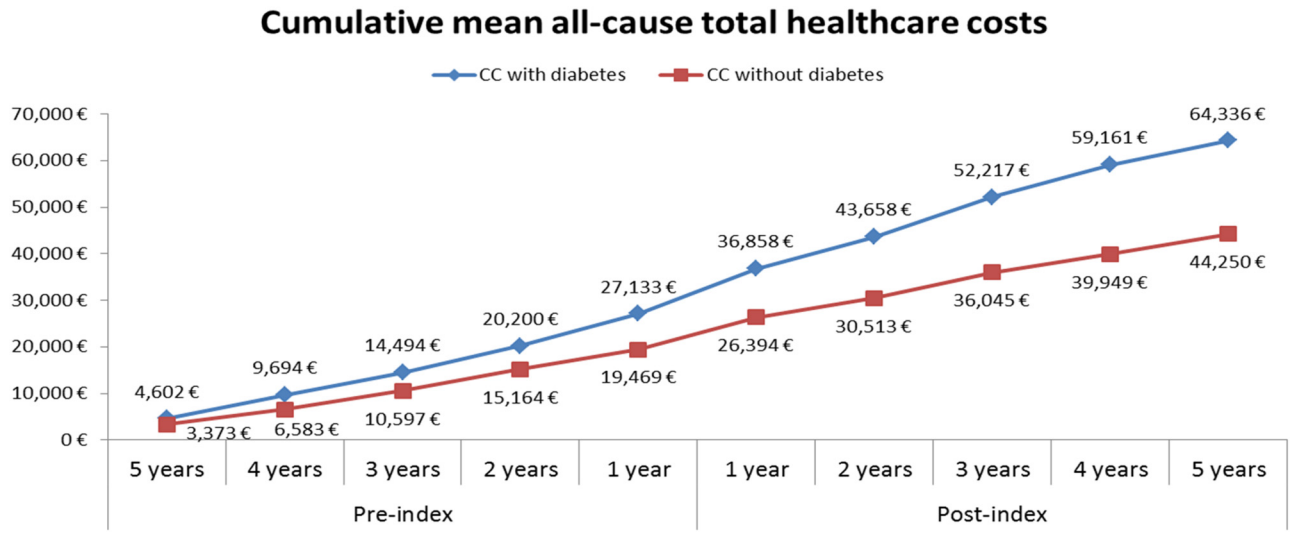
Method: The study population was extracted from the 2007–2015 US Medicare 20% sample data and included NAFLD/NASH patients with CC aged ≥18 years. The first CC diagnosis date was defined as the index date. Any patients with hepatitis B, hepatitis C, other viral hepatitis, HIV, alcoholism, toxic liver disease, Wilson's disease, autoimmune hepatitis, gaucher + LAL-D, biliary cirrhosis, primary sclerosing cholangitis, and hemochromatosis were excluded. Medicare costs were estimated during 2 year pre-index and 1 year pre-index along with 1 year, 2 years, 3 years, 4 years, and 5 years of follow-up post-index. Total 7-year cumulative costs were calculated per patient (PP) annually and adjusted for 2015 USD.
Results: The study identified 3,775 NAFLD/NASH patients with CC having 67 (10.9) years mean age, 63.3% females and a high comorbidity burden 74.8% with DM; 91.6% with hyperlipidemia; 93.9% with hypertension. Cumulative Medicare costs increased 890.8% over 7 years, from $13,716 (2 year pre-index) to $135,898 (5 year post-index). Of the total cohort, 27.8% (1,048) patients progressed to ESLD (progressors) and 72.2% (2727) remained in CC (non-progressors) during the study period. The comorbidity burden was high for both progressors and non-progressors – DM 79.1% (progressors) and 73.2% (non- progressors); hyperlipidemia 92.7% (progressors) and 91.3% (non-progressors); hypertension 96.4% (progressors) and 93.1% (non-progressors). The 7 year cumulative increase in Medicare costs was found to be 1120% for progressors [$16,979 (2 year pre-index) to $207,115 (5 year post-index)] and 698% for non-progressors [$12,537 (2 year pre-index) to $100,098 (5 year post-index)].
Conclusion: NASH/NAFLD patients upon progression to CC keep accumulating substantial costs over a long duration. Progressors experienced 1120% increase and the non-progressors experienced 698% increase in health care costs. This study underscores the need for effective treatments for patients with NAFLD/NASH with CC due to the significant morbidity and mortality, and the high economic burden.

SAT-252

High real-world healthcare costs in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis compensated cirrhosis patients with and without type-2 diabetes mellitus: A large German database study

A. Canbay[1], J. Altevers[2], S. Braun[2]. [1]*Department of Gastroenterology, Hepatology and Infectiology, University of Magdeburg Medical School, Magdeburg, Germany;* [2]*Xcenda GmbH, Hannover, Germany*
Email: ali.canbay@med.ovgu.de

Background and Aims: Comorbid type-2 diabetes mellitus (DM) in NAFLD/NASH patients is associated with an increased risk of progression and mortality leading to increased healthcare costs. This study examined the comorbidities and healthcare costs among German NALFD/NASH DM and non-DM patients once they were diagnosed with compensated cirrhosis (CC).
Method: Patients aged ≥18 years with a NAFLD/NASH diagnosis between 2011 and 2016 were identified retrospectively from the InGef research claims database with about 4 million insurees. CC diagnosis followed the NASH/NAFLD diagnosis, with the first CC diagnosis as the index date. Patients were stratified by DM or non-DM status. Patients were excluded if they had <1 year of continuous enrolment (CE) pre- and post-index, and other causes of liver disease. Progression to end-stage liver disease (ESLD; decompensated cirrhosis, hepatocellular carcinoma, liver transplant) in the post-index period was not allowed. All-cause mortality was evaluated within 1-year post index. Mean annual all-cause healthcare costs were examined for patients with 1–5 years of CE pre- and post-index.
Results: The study population included 555 NAFLD/NASH CC patients with 1 year of CE pre- and post-index — 307 with DM (mean age 68.1 ± 10.9; 56% male) and 248 non-DM (mean age 63.7 ± 13.9; 59% male). NAFLD/NASH CC DM and non-DM patients had a high prevalence of comorbidities: hypertension was 90% and 67%, obesity was 53% and 25%, and dyslipidemia was 61% and 42%, respectively. In the post-index period, 7.8% and 7.3% of DM and non-DM patients deceased. The 307 DM patients cumulated €2,985,320 and the 248 non-DM patients cumulated €1,717,607 all-cause annual healthcare costs in the 1-year post-index period. Prior to cirrhosis index, DM patients had mean annual all-cause healthcare costs of €6,934 and non-DM of €4,305 ($P < 0.001$). Following index, these costs increased for DM



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patients to €9,724 and non-DM to €6,926 (P < 0.001 for DM vs. non-DM and pre- and post-index). DM patients' cumulative mean annual all-cause total costs increased 137% over a five-year period, from €27,133 (pre-year 1) to €64,336 (year 5), while non-DM patients increased 127% from €19,469 (pre-year 1) to €44,250 (year 5) (Figure).

Conclusion: In the 5 years following cirrhosis diagnosis German NAFLD/NASH DM patients experienced an increase of over €37,000 in cumulative costs and non-DM patients a nearly €25,000 increase. Improved patient management and treatment options are needed to improve patient outcomes and reduce healthcare costs.

SAT-253

Functional polymorphisms of innate immunity receptors are not risk factors for non-SBP type bacterial infections in cirrhosis

T. Tornai[1], T. Dinya[2], Z. Vitális[1], I. Tornai[1], B. Balogh[1], D. Tornai[3], P. Antal-Szalmás[3], A. Sümegi[4], H. Andrikovics[5], A. Bors[5], A. Tordai[6], M. Papp[1]. [1]*University of Debrecen, Faculty of Medicine, Institute of Internal Medicine, Department of Gastroenterology, Debrecen, Hungary;* [2]*University of Debrecen, Faculty of Medicine, Department of Surgery;* [3]*University of Debrecen, Faculty of Medicine, Department of Laboratory Medicine;* [4]*Hungarian Academy of Sciences, Vascular Biology, Thrombosis and Haemostasis Research Group;* [5]*Hungarian National Blood Transfusion Service;* [6]*Semmelweiss University, Department of Pathophysiology, Budapest, Hungary*
Email: tornaitamas@gmail.com

Background and Aims: Innate immunity pattern recognition receptors (PRRs) recognize distinct pathogen-associated molecular patterns (PAMPs) on the cell surface or in the cytoplasm. Functional polymorphisms of various PRRs have been established to contribute to susceptibility to spontaneous bacterial peritonitis (SBP). However, their role in the development of cirrhosis-associated bacterial infections (BI) beyond SBP remains unknown. We aimed to investigate the link between PRR gene variants, pathological bacterial translocation (BT) and thus the development of cirrhosis-associated complications

Method: 349 patients with cirrhosis (stable outpatients: 243 and acute decompensation: 106) were genotyped for the common *NOD2* (p.R702W, p.G908R and c.3020 insC), *TLR2* (g.6686T/A), *TLR4* (D299G) and *CD14* (c. 159C/T) gene variants. In the stable outpatients (male: 116, age: 56 ± 11 yrs, alcohol: 62.6%, ascites: 36.2%, MELD score: 11) incidence of BI, decompensating events (ascites, variceal bleeding and hepatic encephalopathy) and liver-related death were prospectively assessed in a 5-year followup observational study. BT was assessed based on the presence of anti-microbial antibodies (anti-OMP Plus IgA and/or Endotoxin core IgA antibody [EndoCab]) or increased serum level of lipopolysaccharide-binding protein (LBP).

Results: Ninety-four (38.7%) patients encountered at least one episode of BI. Distribution of bacterial infections were as follows: urinary tract infection (39.4%), SBP (27.7%), pneumonia (13.8%) and miscellaneous (24.5%). 5.3% of the cases were multifocal. PRR genetic profile was not associated with prior BI episode and also not with the risk of overall BI or infection-related death during the follow-up. Decompensated clinical stage (HR,[95%CI]: 2.11 [1.38–3.25]) and prior history of a BI episode (HR: 2.42 [1.58–3.72]) were the major clinical risk factors of a subsequent BI. *NOD2* variants however, were associated with an increased cumulative probability of SBP in patients with ascites(n = 88) as compared to wild type (76.9 ± 19.9% *vs.* 30.9 ± 6.9%, $P_{LogRank} = 0.047$). Frequency of anti-microbial antibodies and LBP levels did not differ between various PRR genotypes. Correspondingly, PRR genetic profile was not able to predict the long-term disease course in cirrhosis.

Conclusion: In a Hungarian patient cohort with cirrhosis, common *NOD2* gene variants but not the other PRR polymorphisms enabled to improve identification of patients with high risk for SBP. None of the examined PRR gene variants influenced the risk of other types of BI or the long-term disease course. They were also not associated with serological markers of BT.

SAT-254

The prognosis following bacterascites is as poor as spontaneous bacterial peritonitis

J.J. King[1], N. Halliday[1], E. Wey[2], E. Tsochatzis[1], A. Gerussi[1,3], D. Patch[1], J. Ryan[4], J. Graff[1], R. Westbrook[5]. [1]*Royal Free London NHS Trust, UCL Institute for Liver and Digestive Health, The Royal Free Sheila Sherlock Centre, London, United Kingdom;* [2]*Royal Free London NHS Trust, Centre for Clinical Microbiology, Division of Infection & Immunity, London, United Kingdom;* [3]*University of Udine, Liver unit, Internal Medicine, Department of experimental and clinical medical sciences, Martignacco, Italy;* [4]*Royal Free London NHS Trust, UCL Institute of Liver and Digestive Health, The Royal Free Sheila Sherlock Centre, United Kingdom;* [5]*Royal Free Hospital, london, United Kingdom*
Email: jijadeking@gmail.com

Background and Aims: Spontaneous bacterial peritonitis (SBP) is defined as an ascitic PMN count >250 cells/mm³ and is associated with a significant morbidity and mortality. Bacterascites (BA) (the presence of organism on culture but ascitic WCC <250 cells/mm³)

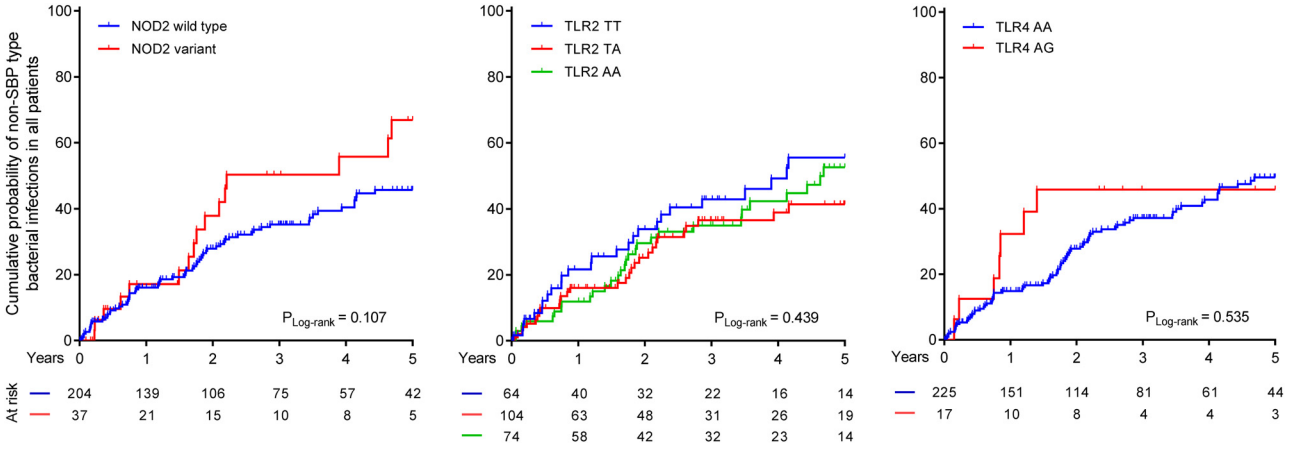


Figure: (abstract: SAT-253)

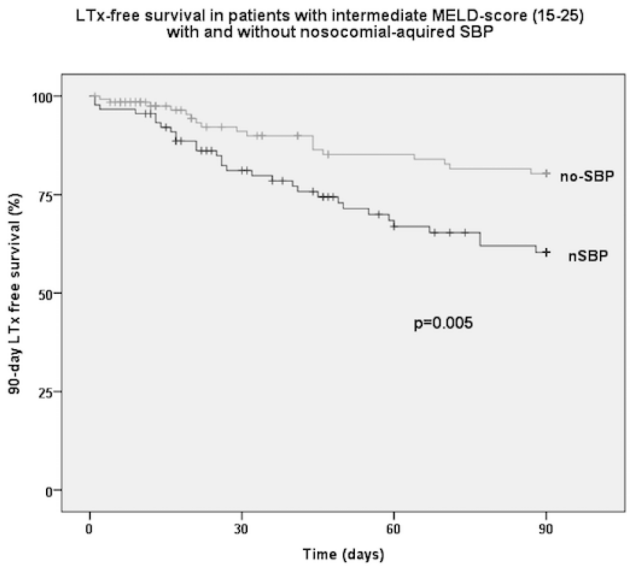
may progress to SBP or spontaneously resolve. The prognostic significance of a treated episode of BA on 2-year survival is undefined.
Method: Ascitic fluid cultures from consecutive cirrhotic patients from 2014 to 2016 were reviewed and patients assigned to SBP, BA or sterile culture groups. Baseline data on disease aetiology, laboratory parameters, MELD scores, pathogens and antimicrobial sensitivities were obtained. Clinical outcomes evaluated over a 2-year period and censored at the time of death or liver transplantation (LT). Patients with previous SBP/BA were excluded, and over the study period only the index case was recorded.
Results: 178 patients (71 female) were included. Median age was 56-years (IQR 48–64 years) and median MELD score 18 (IQR 12–21). 30 had BA, 18 SBP and 130 had sterile ascites. Alcohol related liver disease was the underlying aetiology in 53% of cases.
No differences were found in MELD scores between those with BA (19 *vs.* 17, p = 0.26) or SBP (20 vs. 17, p = 0.08), or the individual components, WCC or serum albumin when compared to sterile controls. Comparing those with BA to SBP, no significant differences in age (p = 0.4), MELD (p = 0.4), albumin (p = 0.3) or WCC (p = 0.5) existed.
Survival (without LT) at 2-years in the 3 groups were SBP 6/18 (33%), BA 9/30 (30%) and 69/130 (53%) in the sterile controls. Survival at 2 years (without LT) was significantly higher in the sterile controls when compared to those with BA/SBP (p = 0.01) and BA alone (p = 0.02), but equivalent in patients with SBP and BA (33 vs 30% NS).
The BA group had lower rates of pathogenic isolates (50%) when compared to the SBP group (100%) and Enterobacteriacae comprised a smaller proportion of isolates cultured (46 *vs.* 60%, NS). Resistance rates of Enterobacteriaceae were equivalent in both the BA and SBP groups (29% *vs.* 33%, NS).
Conclusion: Data from this study highlights bacterascites is a poor prognostic factor, independent of MELD score and synthetic parameters. The long-term impact on prognosis appears equivalent in SBP and BA (despite SBP cultured organisms being more likely pathogenic) and this needs to be acknowledged in patients with BA when management decisions regarding LT and antibiotic prophylaxis is being considered.

SAT-255

MELD-score underestimates mortality in patients with nosocomial spontaneous bacterial peritonitis

M. Kimmann[1], T. Tergast[1], H. Laser[2], M.P. Manns[1,3,4], M. Cornberg[1,3,4], B. Maasoumy[1,3,4]. [1]*Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany;* [2]*Centre for Information Management, Hannover, Germany;* [3]*German Centre for Infection Research, Braunschweig, Germany;* [4]*Centre for Individualised Infection Medicine (CIIM), Hannover, Germany*
Email: Kimmann.Markus@mh-hannover.de

Background and Aims: Spontaneous bacterial peritonitis (SBP) is a severe complication in patients with liver cirrhosis. Model of End-stage Liver Disease (MELD)-score is widely used to predict mortality and the main criteria for liver transplant allocation in several countries. However, only limited data exist regarding the prognostic value of the MELD-score in patients with SBP. The aim of this study was to investigate whether SBP affects the accuracy of the MELD-Score in patients with decompensated liver cirrhosis in predicting mortalilty.
Method: A number of 608 consecutive patients with liver cirrhosis and ascites who underwent a paracentesis at Hannover Medical School between January 2012 and June 2016 were included. Patients were divided into three groups: Patients without SBP within 90 days after baseline paracentesis (no-SBP) (n = 334), those with a community-acquired SBP (caSBP) (n = 59) and patients with a nosocomial-acquired SBP (nSBP) (n = 215). LTx-free survival (within 90 days) was analyzed using the log-rank test. Uni- and multivariate Cox-Regression was performed to identify risk factors for mortality.
Results: Survival was significantly lower in patients with nSBP compared to no-SBP patients (nSBP 60.5% *vs.* no-SBP 79.6%; p < 0.001). In the multivariate analysis MELD-score (p < 0.001; HR = 1.130) and nSBP (p = 0.006; HR = 1.567) were the only significant predictors of mortality. In contrast, survival was not different between caSBP and no-SBP patients (caSBP 86.4% *vs.* no-SBP 79.6% p = 0.16). To further investigate the impact of nSBP on mortality the no-SBP and nSBP cohorts were divided into a low (<15), an intermediate (15–25) and a high (>25) MELD group. In the low MELD group, there was no difference in survival between nSBP (n = 56) and no-SBP patients (n = 129) (nSBP 91.1% *vs.* no-SBP 93.8%; p = 0.55). Among the high MELD group survival was numerically lower in patients with nSBP (n = 69) compared to the no-SBP group (n = 75) (nSBP 27.5% vs. no-SBP 44.0%; p = 0.065). However, the most prominent difference was documented among patients in the intermediate MELD group. Survival was significantly impaired in the nSBP cohort (n = 90) in comparison to the no-SBP cohort (n = 130) (nSBP 66.7% *vs.* no-SBP 86.2%; p = 0.005; Figure). Importantly, mean MELD-score was not different between these two groups (nSBP 19.8 *vs.* no-SBP 19.9; p = 0.8). Furthermore, MELD-score was not a statistical significant risk factor for mortality in the group of patients with intermediate MELD-scores and nSBP (p = 0.102; HR = 1.104).



Conclusion: MELD-score seems to underestimate mortality in patients with nSBP, in particular in those with intermediate MELD-scores.

SAT-256

The role of transjugular intrahepatic portosystemic shunt in the management of portal vein thrombosis: A systematic review and meta-analysis

N. Valentin, P. Korrapati, J. Constantino, A. Young, I. Weisberg.
Mount Sinai Beth Israel, Division of Digestive Diseases, New York, United States
Email: ilan.weisberg@mountsinai.org

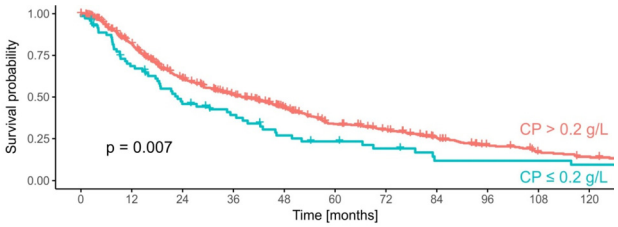
Background and Aims: The role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the management of Portal Vein Thrombosis (PVT) remains controversial. The aim of this study was to conduct a systematic review and meta-analysis to evaluate the role of TIPS for the management of PVT in adult patients with underlying liver disease.
Method: Multiple databases were searched through April 2017. Data were gathered to estimate the rates of technical success, portal vein recanalization, portal patency after shunt placement, hepatic encephalopathy (HE), and the mean change in portal pressure gradient (PPG) in patients with PVT who underwent TIPS. Estimates were pooled across studies using the random effects model.
Results: A comprehensive search of the literature identified 495 potential studies. Eighteen studies with 439 patients who underwent TIPS for the management of PVT were included in the analysis. The technical success rate of TIPS ranged between 60% and 99% with a pooled rate of 86.7% (95%CI = 78.6%–92.1%). The rate of portal vein recanalization ranged between 68% and 98% with a pooled rate of 84.4% (95%CI = 78.4%-89.0%). Complete recanalization ranged between 57% and 96% with a pooled rate of 73.7% (95%CI = 64.3%–81.3%). The rate of portal patency ranged between 72% and 96% with a pooled rate of 86.9% (95%CI = 79.7%-91.8%). The mean change in portal pressure gradient ranged between 12 mmHg and 19 mmHg with a pooled change of 14.5 mmHg (95%CI = 11.3 mmHg–17.7 mmHg). The rate of HE ranged between 5% and 41% with a pooled rate of 25.3% (95%CI = 19.2%–32.6%). In patients who successfully underwent TIPS placement, the number of major adverse events reported across studies was low. The majority of the analyses were not associated with substantial heterogeneity. Intervention analysis in comparison to a gold standard was unable to be estimated due to lack of comparative studies.
Conclusion: The use of TIPS in the management of PVT is feasible and effective in achieving a significant and sustainable reduction in clot burden with a low risk of major complications. TIPS should be considered as a viable treatment option in patients with PVT. Given the limited amount of randomized comparative studies reported, additional trials are warranted to assess the safety and efficacy of TIPS as treatment in PVT in comparison to other treatment options, such as anticoagulation.

SAT-257

Reduced serum ceruloplasmin concentration is common in patients with cirrhosis and a NaMELD independent predictor of transplantation or death

B. Schaefer, A. Viveiros, R. Al-Zoairy, M. Tobiasch, M. Effenberger, H. Tilg, H. Zoller. *Medical University of Innsbruck, Internal Medicine I, Innsbruck, Austria*
Email: benedikt.schaefer@i-med.ac.at

Background and Aims: Reduced concentrations of the copper-binding plasma ferroxidase ceruloplasmin (CP) are both indicative of Wilson disease, but also commonly found in patients with NASH cirrhosis. Not all patients with multiple metabolic risk factors for NASH cirrhosis and low CP receive full diagnostic workup for the confirmation or exclusion of Wilson disease. The aim of the present study was to determine the prevalence and prognostic relevance of CP concentration in an unselected cohort of patients with cirrhosis referred for PNPLA3 genotyping.
Method: Patients referred for PNPLA3 to the Hepatology Laboratory at the Medical University of Innsbruck were retrospectively assessed and included if the diagnosis cirrhosis was made. Demographic, clinical and biochemical parameters were extracted from patient records. PNPLA3 genotype was determined by an allelic discrimination PCR.
Results: Reduced CP concentration ≤ 0.2 g/L was present in 11.7% (72/613) of patients. The diagnosis Wilson disease had been made in 4 of 613 patients, only 3 of which had CP ≤ 0.2 g/L. The prevalence of low CP was 75% in Wilson disease patients and 23% (3/13) in hemochromatosis patients followed by 16% in alcoholic cirrhosis (24/142) and 13% (15/150) in patients with NAFLD/NASH. Median NaMELD score was significantly higher in the patient group with CP < 0.2 g/L (23 vs 17, p < 0.001) and a significant negative correlation between CP and INR but not with albumin was found. Correlation analysis further showed a significant association between CP and markers of iron metabolism/inflammation (transferrin, transferrin saturation, C-reactive protein). Median time to transplantation or death as combined endpoint was also significantly reduced in the group of patients with low CP concentration (log rank test p = 0.07, Figure 1). CP but not PNPLA3 genotype was an independent predictor of the time to transplantation or death in a Cox proportional hazards model including age, NaMELD and CP.



Number at risk

CP > 0.2 g/L:	541	414	283	223	168	118	98	73	52	38	31
CP ≤ 0.2 g/L:	72	47	30	23	15	12	9	5	5	5	4

Conclusion: Hypoceruloplasminemia is common in an unselected cohort of patients with liver cirrhosis with highest frequencies in Wilson disease followed by hemochromatosis and alcoholic or non-alcoholic liver cirrhosis. The negative association of CP with C-reactive protein and INR confirm its role as a marker of hepatic function and inflammation. CP is a NaMELD-independent predictor of survival indicating that ferroxidase activity is implicated in the progression of cirrhosis.

SAT-258

Development and predictive validity of the cirrhosis-associated ascites symptom scale: A cohort study of 103 patients

A. Riedel[1], N. Kimer[1], A.-S.H. Jensen[2], M. Israelsen[3], E. Dahl[4], L. Aamann[5], L.L. Gluud[4]. *[1]Copenhagen University Hospital Hvidovre, Gastro Unit, Medical Division, Hvidovre, Denmark; [2]University Hospital Zealand, Slagelse, Denmark; [3]Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; [4]Copenhagen University Hospital Hvidovre, Hvidovre, Denmark; [5]Aarhus University Hospital, Department of Hepatology, Aarhus, Denmark*
Email: agnete.nordheim.riedel.03@regionh.dk

Background and Aims: Cirrhosis is associated with a detrimental effect on health-related quality of life (HRQL). The Chronic Liver Disease Questionnaire (CLDQ) is used to evaluate HRQL in patients with all stages of liver disease. CLDQ correlates with the severity of liver disease and is associated with active medical and psychiatric comorbidity. No studies have specifically evaluated the association between the severity of ascites related symptoms and HRQL. We therefore aimed to develop and evaluate the predictive ability of a scale specifically designed to assess symptoms associated with cirrhosis-related ascites. We subsequently undertook a multicenter cohort study to evaluate the association between our scale and a disease specific scale (CLDQ) as well as a generic HRQOL questionnaire.
Method: We initially undertook literature searches and a qualitative study, which included assessment by patients and health-care professionals in order to design a Cirrhosis- Associated Symptom (CAS) scale. The final scale included 14 items describing symptoms with a potential detrimental impact on HRQL (the higher the score, the worse the symptoms). Discriminatory validity was assessed in a validation cohort including patients with I) tense/severe, II) moderate/mild or III) no ascites (controls). Patients also completed CLDQ and the EQ-5D-5L questionnaire evaluating HRQL. The relation between scale scores was analysed using Spearman correlations.
Results: The final CAS scale included 14 items. Equivalent reliability was high (Chronbach's alpha 0.88). The validation cohort included 103 patients (72% men, mean age 62.4 years). The mean scores for each question in the CAS scale were higher for patients with severe/tense ascites than for mild/moderate ascites and controls. Compared with controls (mean = 9.9), the total CAS scale score was higher for severe/tense ascites (mean = 23.8) as well as moderate/mild ascites (mean = 18.6) ($p < 0.001$ both groups). We found a strong correlation between the total CAS and CLDQ score (rho = 0.82, p= < 0.001) and a moderate correlation between the CAS and the EQ-5D-5L score (0.67, p= < 0.001).
Conclusion: The CAS addresses relevant questions of symptom burden of ascites and correlates strongly with CLDQ score in patients with cirrhosis and ascites.

SAT-259

Clinical, paraclinical and MR-spectroscopy profile in cirrhotic and non-cirrhotic portal hypertension patients with minimal hepatic encephalopathy

B. Hermann[1], N. Weiss[1], M. Rudler[2], D. Galanaud[3], M. Mallet[2], C. Duvoux[4], A. Coilly[5], C. Francoz[6], A. Plessier[7], D. Thabut[2]. *[1]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique – Hôpitaux de Paris, Unité de réanimation neurologique, département de neurologie, Pôle des Maladies du Système Nerveux, Paris, France; [2]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique – Hôpitaux de Paris, Unité de soins intensifs d'hépatologie, service d'hépatogastroentérologie, Paris, France; [3]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique – Hôpitaux de Paris, Service de Neuroradiologie, Paris, France; [4]European Liver Transplant Registry, Paul Brousse Hospital, France; [5]Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France; [6]Hopital Beaujon, Hépatologie, AP-HP, France; [7]Hôpital Beaujon, Service d'Hépatologie, Réanimation Hépatique et Transplantation, Clichy, France*
Email: bertrand.hermann@gmail.com

Background and Aims: Minimal hepatic encephalopathy (MHE) can be the result of either cirrhotic liver disease (CLD) or non-cirrhotic portal hypertension (NCPH). Whether the clinical and paraclinical profile of MHE is the same in these two conditions is unclear. We sought to compared the clinical, psychometric and paraclinical profile of MHE between CLD and NCPH.
Method: We conducted a retrospective study in a specific hepato-neurology out-patients consultation of a single tertiary university hospital in Paris, France. We included all the patients diagnosed as having MHE by the consensus of two experts and compared their clinical (complaints, neurological physical neurological examination), psychometric (Critical Flicker Frequency-CFF, Psychometric Hepatic Encephalopathy Score-PHES) and paraclinical (ammonemia, EEG and cerebral MRI with spectroscopy (MRS)) profile according to the underlying hepatopathy.
Results: Between February 2013 and April 2016, among the 56 patients referred to the consultation, 32 were diagnosed by the experts as having MHE. The underlying hepatopathy was a CLD in 22 patients (etiology: alcoholic 44%, NASH 9%, viral 19%, alcoholic and non-alcoholic steatohepatitis 24%, others 5%; median MELD of 11 [9–12]) and a NCPH in 10 patients (Budd-Chiari 40%, extra-hepatic portal hypertension 30%, idiopathic portal hypertension 10%, portal agenesia 10% and nodular regenerative hyperplasia 10%). Patients with CLD were older than patients with NCPH (median age 61 years [54–64] vs. 44 years [33–58], p = 0,018) and had less frequently a portosystemic shunt (either surgical or TIPS). No statistical differences were found in any of following variables between the two groups: patients' or family's complaints, neurological examination, CFF, PHES, ammonemia, EEG and MRI (T1 hyperintensity of the basal ganglia and MRS). Notably, no differences were found in the ammonemia levels (69 µmol/L [54–115] vs. 67 µmol/L [93–51], p = 0,56), the number of patients with ammonemia ≥ 50 µmol/L (with 14 patients (88%) vs. 7 (88%), p = 1,0), the MRS choline/creatine ratio (0,82 [0,78–0,85] vs. 0,86 [0,81–0,87], p = 0,18) nor the myoinositol/creatine ratio (0,58 [0,53–0,66], vs. 0,59 [0,58–0,64] p = 0,43) between CLD and NCPH respectively. During follow-up, six CLD patients developed at least one overt HE episode, but none in the NCPH group.

	CLD *n = 22*	NCPH *n = 10*	p
		MRI findings	
Basal ganglia T1 hypersignal	16 (80)	9 (100)	0,28
Typical HE profile on MRS	19 (95)	8 (100)	1,00
NAA/Cr	1,61 [1,52–1,68]	1,66 [1,58–1,77]	0,29
Glu/Cr	0,79 [0,72–0,85]	0,75 [0,80–0,85]	0,74
Glx/Cr	0,87 [0,82–1,01]	0,9 [0,86–1,05]	0,42
Cho/Cr	0,82 [0,78–0,85]	0,86 [0,81–0,87]	0,18
mIns/Cr	0,58 [0,53–0,66]	0,59 [0,58–0,64]	0,43

Conclusion: There seem to be no differences in the clinical, neuropsychological, and imaging profile of CLD and NCPH MHE.

SAT-260

Multimodal approach including MR-spectroscopy for the diagnosis of minimal hepatic encephalopathy

B. Hermann[1], N. Weiss[1], M. Rudler[2], D. Galanaud[3], M. Mallet[2], C. Duvoux[4], A. Coilly[5], C. Francoz[6], A. Plessier[6], D. Thabut[2]. *[1]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique – Hôpitaux de Paris, Unité de réanimation neurologique, département de neurologie, Pôle des Maladies du Système Nerveux, Paris, France; [2]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique – Hôpitaux de Paris, Unité de soins intensifs d'hépatologie, service*

d'hépatogastroentérologie, Paris, France; [3]Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Assistance Publique – Hôpitaux de Paris, Service de Neuroradiologie, Paris, France; [4]Hôpital Henri Mondor, Service d'hépato-gastro-entérologie, Créteil, France; [5]Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France; [6]Hôpital Beaujon, Unité de soins intensifs d'hépatologie, service d'hépatogastroentérologie, Clichy, France
Email: bertrand.hermann@gmail.com

Background and Aims: There is no gold-standard for the diagnosis of hepatic encephalopathy (HE) and especially in case of minimal HE (MHE) where the value of paraclinical examinations is debated. MR-spectroscopy has been proposed as a valuable diagnostic tool for the diagnosis of HE by showing increased glutamate/glutamine peak and decreased myoinositol and choline peaks. However, access to MRI is difficult and no real life experience has been reported. We studied the interest of a multimodal approach combining clinical, neuropsychological, biological and MR-spectroscopy in the diagnosis of MHE.
Method: We conducted a retrospective study in a single tertiary university hospital in Paris, France, where all out-patients referred to a specific hepato-neurology consultation dedicated to the diagnostic of MHE underwent a clinical examination, psychometric tests (Critical Flicker Frequency-CFF, Psychometric Hepatic Encephalopathy Score-PHES), ammonemia and cerebral MRI with spectroscopy (MRS). Patients were classified as having MHE or not by consensus between two experts.
Results: We included 56 patients between February 2013 and April 2016. Median age was 57 years [49–63]. Forty-four (79%) had a cirrhosis (alcoholic 35%, NASH 9%, viral 23%, alcoholic and non-alcoholic steatohepatitis 26%, other 7%) with a median MELD of 10 [7–12]. Twelve (21%) had non-cirrhotic portal hypertension (Budd-Chiari 33%, extra-hepatic portal hypertension 33%, idiopathic portal hypertension 16%, portal agenesia 9% and nodular regenerative hyperplasia 9%). According to the experts, 57% had an MHE, whereas 43% hadn't. Among the clinical informations, only the presence of a portosystemic shunt (TIPS or surgical) was associated with MHE. A venous ammonemia >50 μmol/l, MRI T1 hyperintensity of the basal ganglia and an MRS HE profile suggestive of HE were all statistically associated with the diagnosis of MHE ($p < 0{,}0001$). The best diagnostic performance was achieved by combining MRS with either MRI T1 hyperintensity (AUC = 0,93) or ammonemia (AUC = 0,91). Neither the CFF nor the PHES had good diagnostic performances in our setting.
Conclusion: A multimodal approach combining clinical data, ammonemia and cerebral MRI with MRS seems to have good accuracy for the diagnosis of MHE. Further prospective studies are mandatory.

SAT-261
Kinetics of polymorphonuclear count in ascitic fluid. Persistent spontaneous bacterial peritonitis

A. Amador[1,2,3], A. Cachero[1,3,4], E. Dueñas[1,2,3], F. Bas[1,2,3], L.C. De la Peña[1,2,3], S. Salord[1,2,3], C. Baliellas[1,2,3], J. Castellote[1,2,3]. *[1]IDIBELL; [2]Hospital Universitario de Bellvitge, Hepatology Unit; [3]Universidad de Barcelona; [4]Hospital Universitario de Bellvitge, Hepatology Unit, Hospitalet de Llobregat. Barcelona, Spain*
Email: aamadornavarrete@gmail.com

Background and Aims: the slow decrease of the polymorphonuclear count (PMN) in ascitic fluid is considered a sign of worse short-term prognosis in spontaneous bacterial peritonitis (SBP). The concept of persistent SBP is not well defined. The aims of our study are: 1. Study the relationship between the kinetics of PMN in ascitic fluid at 48h and the resolution of SBP at the 2nd and 5th day with the prognosis of the infection. 2. Systematically define the concept of persistent SBP.
Method: retrospective observational study of 293 episodes of spontaneous bacterial peritonitis diagnosed at universitary hospital between 2010 and 2017. Clinical, analytical, microbiological variables and the PMN delta have been collected at 48 h (PMN48) and resolution of SBP at 48 h and 5th day defined as ≤ 250 PMN/μL with negative culture. A univariate and multivariate analysis was performed to determine the predictive factors of mortality and resolution on the 5th day.
Results: 12.7% of the episodes showed an increase in PMN at 48 h over the baseline, and 20.4% of the episodes were not resolved at 5th day. In-hospital mortality was 17.4%. The AUC-ROC of the delta PMN48h was 0.598 for mortality (p 0.074) and 0.731 (p 0.000) for the resolution at the 5th day. In the multivariate analysis, the PMN increase at 48 h over the baseline (HR 10.91 [1.2–98.7]) and the absence of resolution at the 5th day (HR 4.84 [1.8–13.8]) were independent predictors of in-hospital mortality, as well as other classical parameters: SIRS at admission (HR 3.58 [1.22–10.5]), urea (HR 1.11 [1.03–1.17]), peripheral blood leukocytes (HR 1.07 [1.01–1.14]) and Child Pugh score (HR 2.02 [1.44–2.83]). Besides, SIRS (21.9 vs 34.2%, p 0.03), peritonism (19.2 vs 34.2%, p 0.024), MELD (20.5 ± 7.2 vs 23.2 ± 8.4, p 0.032) and hyponatremia (134.3 ± 5.8 vs 131.9 ± 6.6, p 0.01), proteins (11.5 ± 7.5 vs 15.6 ± 9.9, p 0.001) and LDH (1.3 ± 0.7 vs 2.7 ± 2.9, p 0.004) in ascitic fluid were associated with the absence of resolution at the 5th day, without differences in the culture of ascitic fluid, the gram negative origin, the resistance to cephalosporins or in the inadequate empirical treatment.
Conclusion: (1) The increase in PMN at 48h and the absence of resolution at the 5th day are independently associated with in-hospital mortality. (2) The paracentesis at 48h is justified given its prognostic value. (3) The absence of resolution the 5th day could be the best definition for persistent SBP.

SAT-262
Impact of an antimicrobial stewardship policy on the reduction of empirical antibiotic treatment failure and the spread of multidrug-resistant organisms in hospitalized cirrhotic patients

S. Incicco[1], V.D. Gregorio[1], C. Lucidi[1], B. Lattanzi[1], D. D'ambrosio[1], D. Tavano[1], S.D. Cola[1], G. Ceccarelli[2], M. Venditti[2], M. Merli[1]. *[1]Sapienza University of Rome, Department of Clinical Medicine, Rome, Italy; [2]Sapienza University of Rome, Department of Infectious Disease, Rome, Italy*
Email: simone.incicco@gmail.com

Background and Aims: Bacterial infections are among the most relevant complications of cirrhosis and are associated with poor outcomes. The application of antimicrobial stewardship (AMS) policies is the best strategy in the management of cirrhotic patients with infections, since they help to avoid inappropriate antibiotic use and development of multidrug-resistant organisms (MDRO). The aim of the study is to evaluate the effect of AMS on the empirical antibiotic treatment failure, the onset of infection-related complications and in-hospital mortality, and the spread of MDRO.
Method: This is an observational study performed in patients consecutively admitted to our department from 2009. The population was divided into two groups: the first (Group A) includes patients in which non-specific policies were adopted (until August 2014); the second (Group B) includes patients in which AMS policy was used. AMS policy consisted in addressing a dedicated infectious disease consultant.
Results: We enrolled 313 infected patients, 207 in Group A and 106 in Group B. The two groups were similar for demographic and severity of liver disease (Child Pugh score 8.6 ± 1.8 vs 8.9 ± 1.8). In both groups main sites of infection were urinary tract and pneumonia. The application of AMS resulted in a reduced use of fluoroquinolones (25% in Group A vs 10.4% in Group B, $p = 0.002$) and third-generation cephalosporins (25% in Group A vs 6.6% in Group B, $p < 0.001$) as empirical antibiotic treatment, and an increased use of Piperacillin-Tazobactam (17.4% in Group A vs 40.6% in Group B, $p < 0.001$). In group B: incidence of MDRO was reduced (59 vs 30.2%, $p < 0.001$), the rate of failure of empirical antibiotic treatment was decreased (44 vs 19%, $p < 0.001$), the prevalence of sepsis was lower (54 vs 24.5% $P < 0.001$), the infection-related mortality showed a trend of reduction (17.4 vs 8.5%). The multivariate analysis showed that the introduction of the

AMS policy was responsible for the reduced rate of empirical treatment failure (p = 0.005; OR 0.42; 95% CI 0.25–0.59).
Conclusion: Our results show that AMS policies, by optimizing the use of antimicrobial drugs, are able to reduce the rate of empirical antibiotic treatment failure. In our experience this strategy has been effective in reducing incidence of MDRO and sepsis in cirrhotic patients.

SAT-263
Outpatient terlipressin infusion increases dietary intake and functional muscle strength in patients awaiting liver transplant
B. Chapman[1], P. Gow[2], P. Angus[2], M. Sinclair[2], A. Testro[2]. [1]*Austin Health, Nutrition and Dietetics, Heidelberg, Australia;* [2]*Austin Health, Liver Transplant Unit, Heidelberg, Australia*
Email: Brooke.chapman@austin.org.au

Background and Aims: Portal hypertension has multiple negative effects on gastrointestinal function, including the development of ascites, reduced gastric reserve, slowed intestinal transit and malabsorption; thereby contributing to malnutrition and sarcopenia. Our centre offers outpatient continuous terlipressin infusion as a bridge to transplantation to patients with hepatorenal syndrome or refractory ascites. We describe for the first time the effect of terlipressin on nutritional and functional muscle parameters in this novel cohort.
Method: Nutritional (subjective global assessment) and functional muscle assessment (handgrip strength), dietary intake (energy and protein), volume and frequency of paracentesis, severity of liver disease (MELD, MELD-Na) and complications of therapy were prospectively recorded at commencement of terlipressin and again at follow up (transplantation, cessation of therapy or census date). Terlipressin non-responders and infusion duration <2 weeks were excluded.
Results: Thirteen of 19 patients treated with terlipressin (100% male, mean age 58 years, hepatorenal syndrome n = 9, ascites n = 4) met inclusion criteria. All patients were malnourished at commencement of therapy, 70% (n = 9) had poor muscle strength (grip strength <30 kg), and 70% required weekly large-volume paracentesis (>5 L). Median duration of treatment was 74 days (range 24–376). Terlipressin therapy resulted in a significant improvement in multiple biochemical, functional and nutritional parameters. Improvement in MELD was primarily driven by reduction in creatinine (Table 1). Paracentesis volume and frequency reduced by >50% in all patients. Seven patients (53%) were transplanted, 2 were delisted and 4 continue on terlipressin. There have been no clinical complications attributed directly to terlipressin therapy.

Table 1: Change in outcome measures following terlipressin

Parameter Median (range)	Pre-Terlipressin	Post-Terlipressin	p value
MELD	23 (14–34)	16 (12–26)	0.001
MELD-Na	26 (18–36)	19 (15–24)	<0.001
Creatinine, umol/L	176.5 (99–300)	123 (50–127)	<0.001
INR	1.5 (1.2–2.8)	1.6 (1.1–2.8)	0.611
Bilirubin, umol/L	28 (18–293)	26 (13–146)	0.109
Handgrip strength, kg	24.5 (12–39)	29.5 (16–40)	0.001
% energy requirements met	56 (25–75)	86 (60–100)	<0.001
% protein requirements met	60 (35–90)	89 (50–100)	<0.001

Conclusion: Continuous terlipressin infusion significantly improves both nutritional and functional muscle parameters in cirrhotic patients on the liver transplant waitlist, in whom such parameters usually demonstrate a progressive decline. Through sustained reduction in portal hypertension, we postulate that continuous terlipressin infusion reduces ascites and its associated protein losses; increases calorie and protein intake by improving gastric reserve; and may improve enteral absorption, with subsequent net gain of muscle strength.

SAT-264
Dynamic Visual Processing in Patients with Decompensated Cirrhosis
K. Wong[1], D. Liston[2], S. Papademetriou[2], A. Yeoh[3], A. Goel[1], P. Kwo[1], P. Okafor[1]. [1]*Stanford University School of Medicine, Medicine, Division of Gastroenterology and Hepatology, Stanford, CA, United States;* [2]*NeuroFit, Inc, Mountain View, CA, United States;* [3]*Stanford University School of Medicine, Medicine, Stanford, CA, United States*
Email: katherinew1@gmail.com

Background and Aims: Patients with decompensated cirrhosis are at increased risk of overt and covert hepatic encephalopathy (HE), falls, and motor vehicular accidents (MVA). Visual processing can reveal changes in cognitive function and remains understudied in cirrhosis. We hypothesize that decompensated cirrhotics have impairment in visual processing that negatively impacts aforementioned outcomes.
Methods: We utilized a validated, non-invasive, oculometric assessment tool to prospectively study adult patients with cirrhosis in the Stanford University liver clinic after informed consent. We excluded patients who had undergone liver transplantation. Baseline demographic and oculometric data were obtained. Oculomotor metrics included latency, acceleration, gain, proportion smooth pursuit, saccadic amplitude, direction noise, speed tuning responsiveness and noise. A composite visual processing score (nFit) was also generated. Results were compared to a historical control group of noncirrhotics.
Results: Results of the first 18 decompensated cirrhotic patients enrolled are presented. Median age was 59 (range 39–71) years and median BMI was 29.4 (range 25–42). Seventy-two percent of the cohort were male. Most common aetiologies for cirrhosis were hepatitis C (28%), NASH (28%), and alcohol (22%). The most common forms of decompensation were ascites (78%) and hepatic encephalopathy (78%). Seventy-eight percent of patients were on lactulose, 67% on rifaximin, 78% on diuretics, 33% on nonselective beta blockers, 22% on statins, and 22% were on antidepressants. No patient had been in a MVA while driving in the past year, but 6 (33%) patients had experienced falls. Median MELD-Na was 14, while median Child-Pugh score was 7. Median nFit z-score (compared to historical controls) was −2.9. Median z-scores for other domains were: latency (−1.8), acceleration (−1.4), saccadic amplitude (−0.99), gain (−2.3), proportion smooth pursuit (−2.4), direction noise (−5.5), speed tuning responsiveness (−3.3), and speed tuning noise (−1.3).
Conclusion: Compared to non-cirrhotics, patients with decompensated cirrhosis score lower for all domains of visual processing, most pronounced in the proportion of smooth tracking, speed tuning responsiveness, and direction noise. Further studies are needed to assess the utility of oculometric testing as a screening tool for HE, falls, and MVA in patients with advanced liver disease.

SAT-265
The physical component of the SF-36 Quality of Life tool is an independent predictor of mortality in patients with severe ascites
S. Macdonald[1], P. Jepsen[2,3], H. Watson[4], H. Vilstrup[2], R. Jalan[1]. [1]*University College London, Liver Failure Group, Institute for Liver and Digestive Health, London, United Kingdom;* [2]*Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark;* [3]*Aarhus University Hospital, Department of Clinical Epidemiology, Aarhus, Denmark;* [4]*Sanofi-Aventis R&D, Infectious Diseases Unit, Marcy l'Etoile, France*
Email: stewart.macdonald@ucl.ac.uk

Background and Aims: Severe ascites in cirrhosis is associated with increased mortality rates, which is not captured by conventional prognostic markers. These patients have a poor Health-related Quality of Life (HRQL), which has also been shown to be an independent predictor of mortality in a number of medical conditions. The aim of this study was to determine the prognostic value of HRQL in defining the outcome of patients with severe ascites.

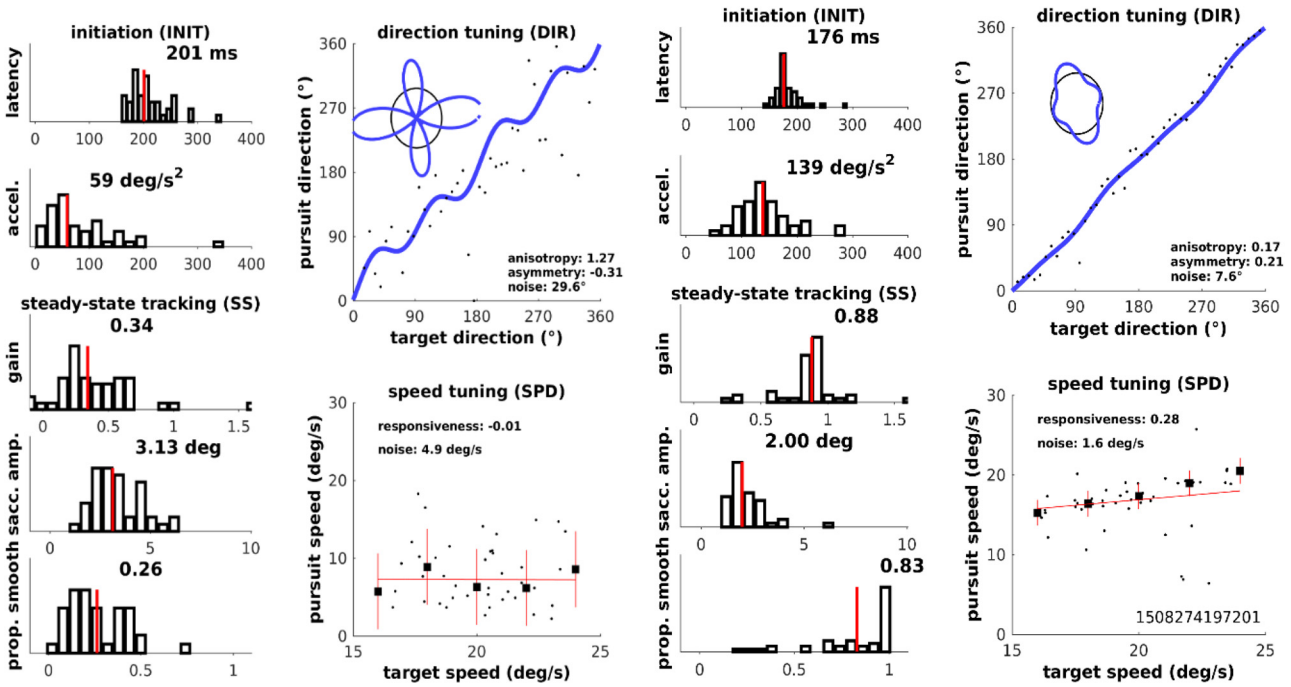


Figure: (abstract: SAT-264): Visual Processing Impairments in Decompensated Cirrhosis. A representative decompensated cirrhotic patient (left) shows sluggish and disorderly visual tracking as compared to a representative control subject (right).

Methods: 405 patients, as part of a randomised controlled trial testing the efficacy of satavaptan in ascites, were included. All patients had either difficult-to-treat ascites (2 paracentesis in 3 months prior to enrolment, n = 164) or refractory ascites (n = 241). Patients completed the SF-36 HRQL tool [a combination of physical component score (PCS) and mental component score (MCS) sub-scores] in addition to standard biochemical tests and were followed up for 52-weeks. Data were analysed to determine the role of factors associated with mortality.

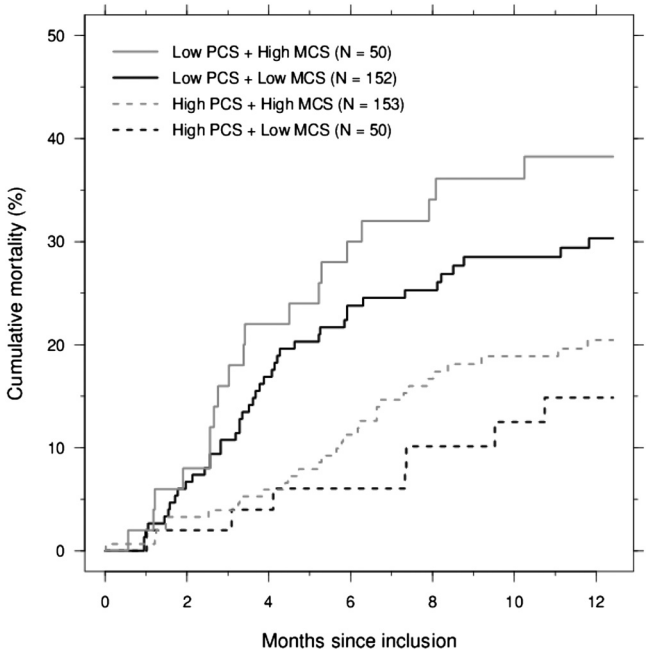


Figure 1: Cumulative all-cause mortality for all patients defined by below- or above-median physical component score (PCS) and mental component score (MCS). A high PCS or MCS indicates better quality of life, as measured by the SF-36 tool.

Results: The two ascites groups were combined for analysis as no significant difference in rate of liver-related complications or mortality was observed. Satavaptan therapy had no effect on clinical outcomes, PCS or MCS. MCS and PCS correlated with each other (0.68) but not with any other variables. 99 deaths occurred during follow up. Death was associated with markers of impaired hepatic function but also a poorer (lower) overall PCS [median (IQR) died: 34 (24–49), survived: 41 (29–53) p = 0.01]. This was not seen with MCS, and in several domains of the MCS higher scores were associated with increased mortality. A 10-point increase in PCS score was associated with a reduction in the Hazard ratio (0.87 95% CI 0.78 to 0.97), which remained statistically significant after adjustment for confounders (0.83 95% CI 0.72–0.97) and when mortality was restricted to only cirrhosis-related deaths (0.84 95% CI 0.71 to 0.99). PCS was highly significant when modeling cumulative risk of death over the study period (Figure 1).

Conclusion: The data demonstrated that patients with difficult to treat ascites had the same risk of death as those with refractory ascites and therefore this should be recognised in the management of their condition. The data also showed for the first time that in cirrhotic patients with severe ascites the PCS component of the SF-36 tool is predictive of mortality and this risk is independent of the traditional prognostic markers and scores.

SAT-266

Clinical frailty scale as a novel tool predicts unplanned hospitalisation and/or death in outpatients with cirrhosis

A.P. Singh, K. Devadas, K. Sandesh, G. Kapur. *Government Medical college, Medical gastroenterology, Thiruvananthapuram, India*
Email: doc.aniruddha85@gmail.com

Background and Aims: Hospitalizations in patients are the major cause of morbidity and healthcare expenditure in patients with cirrhosis. Predictive factors determining which outpatients with cirrhosis are at highest risk for unplanned admissions are lacking. We aimed to study factors predicting unplanned hospitalization or death at 3 months and study utility of Clinical Frailty scale in outpatients with cirrhosis.

Method: Prospective study with all the assessment carried out on the same day with study population comprising consecutive outpatients with cirrhosis in a single Tertiary care centre. Patients with active malignancy, ESRD and any condition requiring immediate admission were excluded. Frailty was defined as Clinical frailty scale (CFS) >4. Unplanned hospitalization was defined as any admission to acute care hospital that was not planned. Data on socioeconomic status, MELD, CHILD score, Burden of total comorbidity using Charlson comorbidity index were recorded. The outcome was defined as unplanned hospitalization or/and death at 1 and 3 months from study entry. Variables found to be significant with P < 0.05 on univariate analysis were used for Binary backward logistic regression.
Results: Overall 124 patients included, 52(41.9%) were frail, Etiology was predominantly alcohol 63/124 (51%) followed by HBV 30/124 (24%) then NASH 12/124(16.7%) related cirrhosis. Mean MELD was 20 and CTP score was 10.6 in frail patients.CFS mean value was 5.2 with CRP mean of 3.2 mg/dl in frail outpatients. 26/52 (50%) of frail patients as compared to 2/72 (2.8%) non-frail patients had unplanned hospitalization at 1 month whereas 44/52(84.6%) as compared to 11/72(15.3%) had unplanned hospitalization at 3 months. 9/52 (17.3%) frail patients died in comparison to only 1/72(1.46%) in the non-Frail group at 3 months. On Univariate regression analysis variables found to have p values <0.05 were considered for Multivariate cox regression analysis. Multivariate Binary logistic regression (Backward LR) patients taking B- blocker more than 20 mg with P < 0.07, OR 7.16(CI 1.73–29.6), Frail patients with CFS > 4 P < 0.01, OR:5.38(CI: 1.3–21.6), Presence of AKI with P < 0.006, OR:17.24 (CI:2.2–133.7), CRP >2 mg/dl with P < 0.001, OR:11.23 (CI:2.6–47) were found to independently predict unplanned admission at 1 month and unplanned admission/death at 3 months. We also observed that CRP with a cut-off of 2 mg/dl with sensitivity of 77.5% and specificity of 92.42% with AUC of 0.88 predicted unplanned hospitalization/death at 3 months.

Variable		Frail				Total		P
		Yes (N=52)		No (N=72)				
		N	%	N	%	N	%	
Admission at 1 month	Yes	26	50.0	2	2.8	28	22.6	<0.001
	No	26	50.0	70	97.2	96	77.4	
Admission at 3 month	Yes	44	84.6	11	15.3	55	44.4	<0.001
	No	8	15.4	61	84.7	69	55.6	
Death	Yes	9	17.3	1	1.4	10	8.1	.001
	No	43	82.7	71	98.6	114	91.9	

Multivariate Logistic Regression (Backward LR) for prediction of hospitalization/death at 3 months.

Variables	p-value	OR	CI
B-Blockers (>20 mg)	0.07	7.16	1.73-29.67
CFS > 4	0.01	5.38	1.3-21.6
AKI	0.006	17.24	2.2-133.7
CRP	0.001	11.23	2.6-47
Hosmer Lemeshow goodness-of-Fit test, X^2 (P-value)			9.32(0.15)

Conclusion: Clinical frailty scale as rapid 1-minute screen and Serum CRP with a cut-off 2 mg/dl predicts unplanned hospitalization and/or death at 3 months and can be utilized in outpatients with cirrhosis for stratifying patients at risk of adverse outcomes.

SAT-267

Relationship between visceral fat and portal vein thrombosis in patients with liver cirrhosis

M.H. Conde[1,2], E. Llop[1,3], M. López-Gómez[1], C. Perelló[1], C. Fernández-Carrillo[1], J.A. Guerra[1], J.L.M. Porras[1], N.F. Puga[1], M. Magaz[1], J.L.C. Panero[1]. *[1]Hospital Universitario Puerta de Hierro Majadahonda, Spain; [2]Co-autors; [3]co-autors*
Email: marta.hernandez.conde@gmail.com

Background and Aims: It has been shown that an increased waist circumference (WC) is important in the association between obesity and venous thrombosis. Therefore, central obesity, due to the accumulation of visceral fat (VF), is one of the main risk factors for the development of venous thrombosis. In addition, it has been shown that it could be the first risk factor for the development of non-cirrhotic portal vein thrombosis (PVT). The aim of this study was to determine if WC and VF could be risk factors in the development of PVT in patients with liver cirrhosis (LC).

Method: Between 2016 and 2017, outpatients with LC were prospectively included. Patients with active alcohol consumption, active viral hepatitis and those with hepatocellular carcinoma outside the Milan Criteria were excluded. All patients underwent a complete anthropometric evaluation, blood tests and bioimpedence (BIA) (TANITA DC430PMA).
Results: One hundred seventy-five patients were included (men 70.3%, mean age 63 years (SD 9.9)). The most frequent etiology was HCV (49.7%), followed by alcohol (32%). Child-Pugh classification A/B/C 75.3%/18.4%/6.3% and median MELD score 10.3 (SD 3.5). Eighty patients (45.7%) had prior liver decompensation and 62 patients (35.4%) had large esophageal varices. The mean spleen diameter measured by abdominal ultrasound was 135.2 mm (SD 30.9). The mean body mass index (BMI) was 28.7 Kg/m^2 (SD 4.5). 21.3% of the patients were normal weight, 37.9% were overweight and 40.8% were obese. The mean WC was 103.6 mm (SD 13.4), with an increase in WC (≥102 mm in men and ≥88 mm in women) in 119 patients (68%).
Fourteen patients (8%) had PVT at the time of inclusion. PVT was more frequent in patients with prior liver decompensation (78.6 vs. 21.4%, p = 0.01) and with large esophageal varices (64.3 vs. 35.7%, p = 0.02). WC and VF were higher in patients with PVT (113.6 vs. 102.9 mm, p = 0.01 and 17.4 vs. 14.3, p = 0.01). PVT was more frequent in patients with an increased WC (92.9% vs. 7.1%, p = 0.04). Patients with PVT also presented a larger diameter of the spleen (153.2 vs. 133.9 mm, p = 0.005).
In the multivariate analysis, the parameters associated with PVT in patients with LC were: the presence of prior liver decompensation (OR 6, 95%CI 1.22–29.1, p = 0.03), VF (OR 1.2, 95%CI 1.02–1.35, p = 0.02) and the presence of large esophageal varices (OR 3.8, 95%CI 1.03–13.77, p = 0.04).
Conclusion: VF has been independently associated with the presence of PVT in patients with LC. In our study, other previously proven factors such as previous liver decompensation and the presence of esophageal varices were confirmed.

SAT-268

Terlipressin for variceal bleeding induces severe plasma sodium disturbances in non-cirrhotic portal hypertension

P.L. Eriksen, A.L. Hartkopf-Mikkelsen, P. Ott, H. Vilstrup, N.K. Aagaard. *Aarhus University Hospital, Department of Hepatology and Gastroenterology, Aarhus, Denmark*
Email: ple@clin.au.dk

Background and Aims: Variceal bleeding is a severe complication of portal hypertension in patients with cirrhosis of the liver. While treatment with terlipressin is highly efficient, one side effect is a reduction of plasma sodium, which is usually not severe. In patients with variceal bleeding due to non-cirrhotic portal hypertension, terlipressin may also be used. Casuistic observations and theoretical considerations suggested that the latter patient group could be at special risk of terlipressin induced sodium disturbances. That question was studied in a retrospective cohort study.
Method: During a 39-month period, 134 patients with liver cirrhosis and 11 patients with non-cirrhotic prehepatic portal hypertension were treated for variceal bleeding and received a minimum cumulative terlipressin dose of 4 mg during at least 24 hours. Plasma sodium changes were compared between the groups.
Results: As compared to patients with cirrhosis, those with prehepatic portal hypertension displayed a greater reduction in plasma sodium [mean 8.3 mmol/l (95% confidence interval: 1.9–14.6) vs. 1.8 mmol/l (1.0–2.7); p = 0.048], a lower nadir plasma sodium during terlipressin treatment [129 mmol/l (123–135) vs. 133 mmol/l (132–134), p = 0.06], and a greater increase in plasma sodium within 48 hours after discontinuation of terlipressin [12.6 mmol/l (3.4–21.7) vs. 2.3 mmol/l (1.5–3.0); p = 0.03].

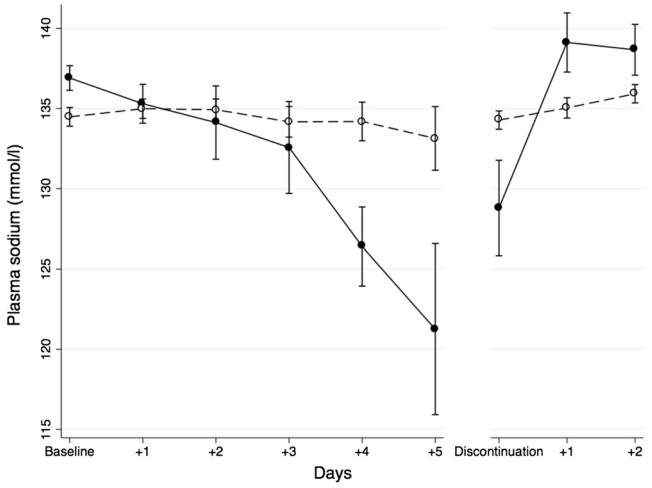


Figure: Plasma sodium profile during and after terlipressin treatment (mean ± SEM). •: Pre-hepatic portal hypertension ○: Cirrhotic portal hypertension

Conclusion: Patients with non-cirrhotic prehepatic portal hypertension constitute a group at particular risk of severe hyponatremia during terlipressin treatment for variceal bleeding, and of rapid normalisation of plasma sodium upon discontinuation. Special caution is warranted if terlipressin is used in these patients.

SAT-269

Outcome after the use of SX-ELLA Danis bleeding stents for refractory variceal bleeding- a Vienna Multicenter Experience

N. Pfisterer[1,2], W. Dolak[2], T. Pachofszky[1], M. Schoniger-Hekele[2], B. Schuster[1], B. Tribl[2], M. Mandorfer[2], L. Unger[2], F. Riedl[2], P. Schwabl[2], T. Bucsics[2], K. König[3], L. Kramer[3], M. Gschwantler[4], C. Madl[1], M. Trauner[2], T. Reiberger[2]. [1]*Krankenanstalt Rudolfstiftung, IV Medical Department of Gastroenterology and Hepatology;* [2]*Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III;* [3]*Krankenhaus Hietzing, I. Department of Gastroenterology;* [4]*Wilhelminenspital, IV Medical Department of Gastroenterology and Hepatology*
Email: nikolauspfisterer@hotmail.com

Background and Aims: Current guidelines favor the use of bleeding stents over balloon tamponade for refractory esophageal variceal bleeding (EVB). However, data on the efficacy of and outcomes after the placement of an SX-ELLA "Danis-stent" are limited.
Method: Retrospective multicenter study including cirrhotic patients receiving Danis-stents for massive/refractory EVB at 4 specialized bleeding/endoscopy units in Vienna. Rates of bleeding control (5 days), bleeding-related mortality (6 weeks) and overall mortality were assessed.
Results: Among 34 patients, 12 patients had an unsuccessful endoscopic band ligation (EBL) prior to Danis-stent placement. Danis-stent controlled EVB in 79.4% (27/34) of patients. In the remaining uncontrolled bleeders (n = 7), 3 patients had subsequent EBL, while in 3 patients the stent had to be replaced and 1 patient received a Linton-tube. Among these patients with initial Danis-stent failure, 3 died of uncontrollable EVB, 3 experienced early bleeding-related mortality, and only 1 patient achieved a successful long-term bleeding control.

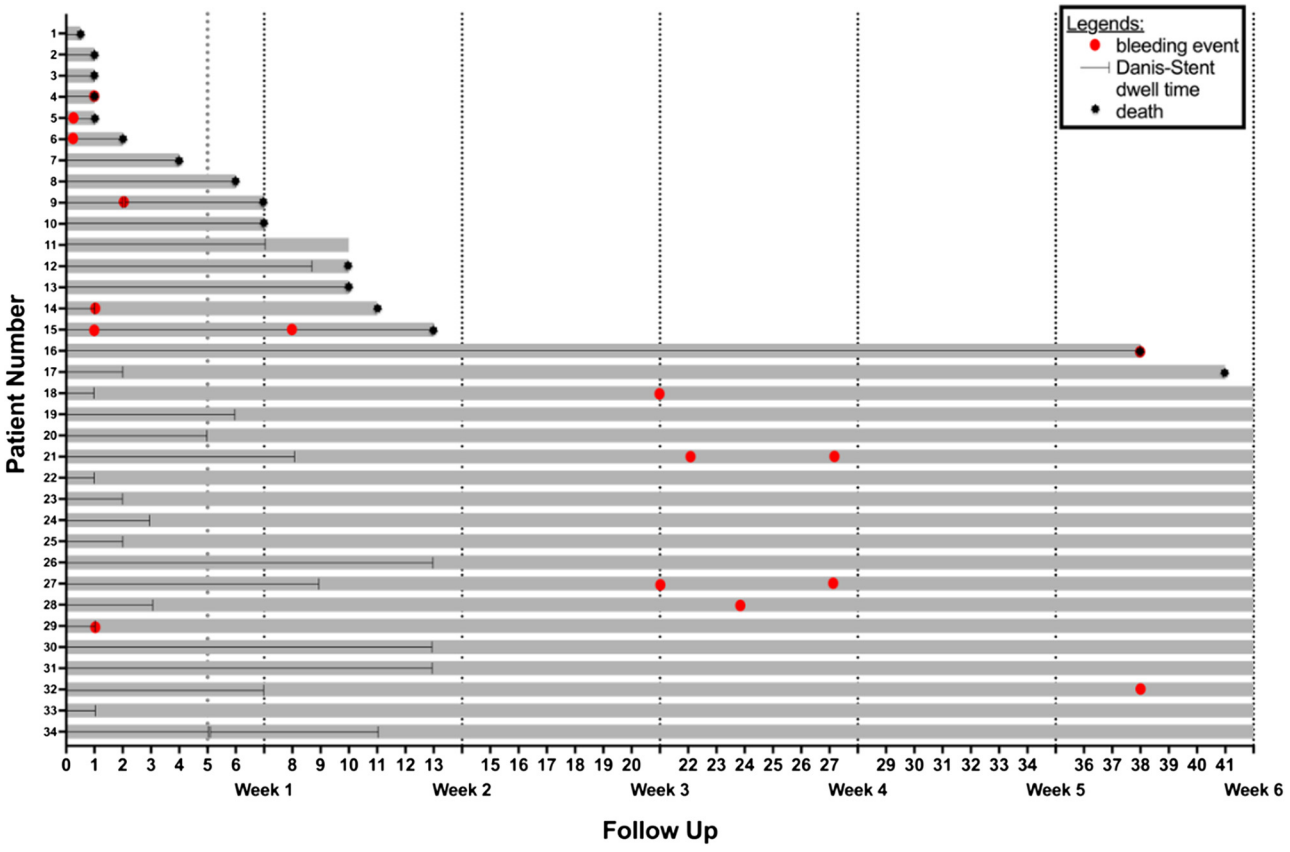


Figure: (abstract: SAT-269)

In total, early-rebleeding within 6 weeks occurred in n = 5 (14.7%): 3 underwent EBL, 1 received a subsequent Danis-stent, and 1 patient was treated with a Sengstaken tube.
Moreover, among n = 22 patients without early rebleeding within 6 weeks, only n = 3 (8.8%) showed rebleeding later during follow-up: n = 2 patients were treated with a Sengstaken-tube (both experienced bleeding-related death) and n = 1 had another Danis-stent placed (successful bleeding control).
Only n = 11 (32.4%) patients did not experience any rebleeding after Danis-stent removal, while n = 13 patients died with the Danis-stent in situ. Notably, no "early-TIPS" was performed in this study, but 4 (11.8%) received an elective TIPS during follow-up. Ultimately, n = 7 patients (20.6%) died due to uncontrolled bleeding (≤5days) and n = 9 died within 6 weeks (bleeding-related mortality: 26.5%). Overall, n = 22/35 (64.7%) patients died. The median survival was 62 (IQR538.5) days after Danis-stent placement.
Median Danis-stents dwell time was 5 (range: 0.5–38) days. The most common adverse events were stent dislocations (n = 13; 38.2%), while ulcers/necrosis of the esophageal mucosa were seen in only 4 (11.8%) patients.
Conclusion: Danis-stent controlled refractory/massive EVB in 79.4% of patients but bleeding-related mortality was still as high as 47.1%. While stent dislocations were frequent, esophageal ulcers/necrosis were rare with a median stent dwell time of 5 days. The implementation of an early-TIPS strategy might improve the overall outcome after Danis-stent placement.

SAT-270

The beneficial effects of non-selective betabockers in secondary prophylaxis are most pronounced in patients without refractory ascites

N. Pfisterer[1,2], C. Dexheimer[2], E.-M. Fuchs[1], T. Bucsics[2], M. Mandorfer[2], P. Schwabl[2], I. Gessl[2], L. Sandrieser[2], L. Baumann[2], F. Riedl[2], B. Scheiner[2], T. Pachofszky[1], W. Dolak[2], C. Schrutka-Kölbl[1], A. Ferlitsch[2], M. Schoniger-Hekele[2], M. Peck-Radosavljevic[3], M. Trauner[2], C. Madl[1], T. Reiberger[2]. *[1]Krankenanstalt Rudolfstiftung, IV Department of Gastroenterology and Hepatology; [2]Medical University of Vienna, Division of Gastroenterology and Hepatology, Department of Internal Medicine III; [3]Klinikum Klagenfurt am Wörthersee, Dept. of Gastroenterology/Hepatology, Endocrinology and Nephrology*
Email: nikolauspfisterer@hotmail.com

Background and Aims: Endoscopic band ligation (EBL) is used for primary (PP) and secondary prophylaxis (SP) of variceal bleeding. For SP, current guidelines recommend combined use of non-selective beta-blockers (NSBBs) and EBL for SP, while either NSBB or EBL should be used in PP.
Method: (Re-)bleeding rates and mortality were retrospectively assessed with and without concomitant NSBB therapy after first EBL in PP and SP.
Results: 766 patients with esophageal varices underwent EBL from 01/2005–06/2015. In PP, among 284 patients undergoing EBL, n = 101 (35.6%) received EBL only, while n = 180 (63.4%) received EBL + NSBBs. In 482 patients on SP, n = 163 (33.8%) received EBL only, while n = 299 (62%) received EBL + NSBBs.
In PP, concomitant NSBB therapy neither had an impact on bleeding rates (log-rank p = 0.353) nor on mortality (log-rank p = 0.497) as compared to EBL alone.
Patients in SP with EBL + NSBB showed similar rebleeding rates as compared EBL alone (log-rank p = 0.247). However, in SP, a

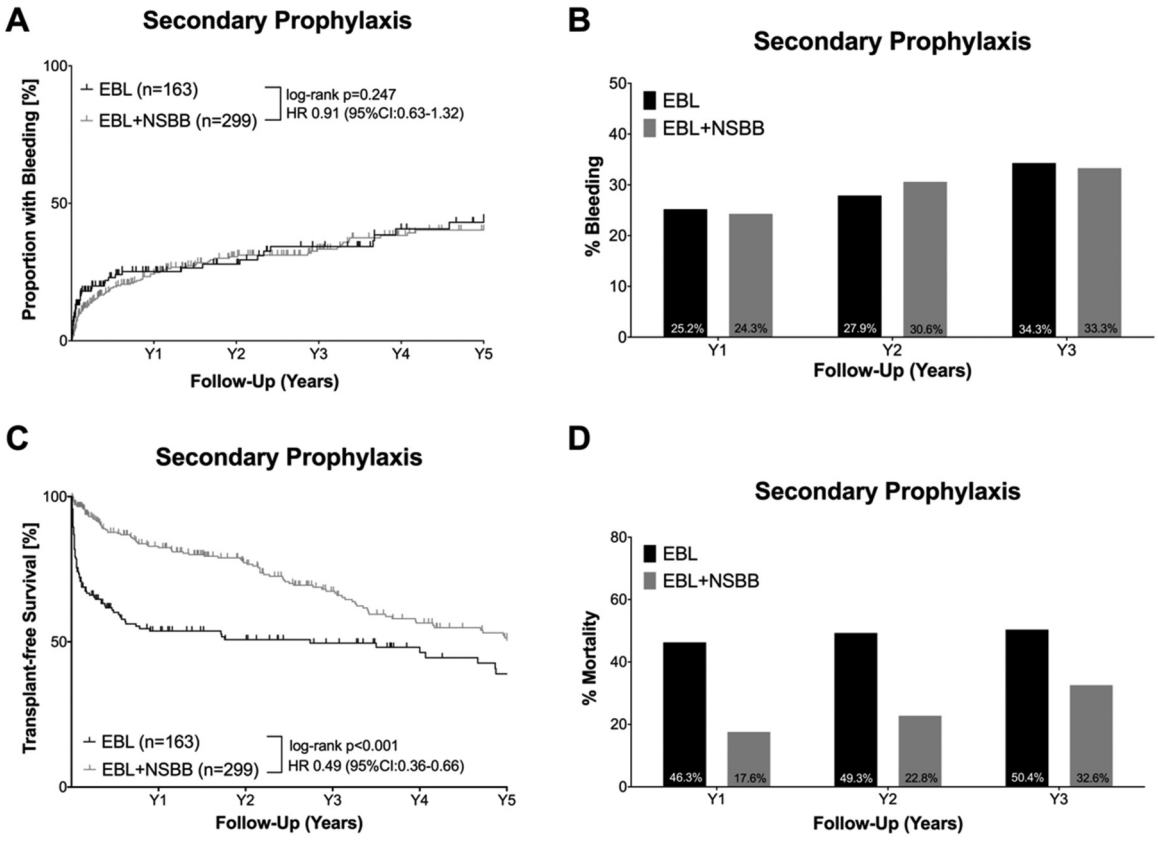


Figure: (abstract: SAT-270)

concomitant NSBB therapy resulted in a significantly lower mortality rate (log-rank $p < 0.001$) with fewer deaths related to liver failure, bleeding, and infections with EBL + NSBB combination therapy. A decreased risk of death with EBL + NSBB in SP (hazard ratio, HR:0.50; $p < 0.001$) but not of rebleeding, transplantation or further decompensation was confirmed by competing risk analysis. Interestingly, in SP, NSBB intake reduced 6-months mortality (HR:0.53, $p = 0.008$) in patients without severe/refractory ascites (HR:0.37; $p = 0.001$) only but this effect was not seen in patients with severe/refractory ascites (HR:0.80; $p = 0.567$).
Conclusion: EBL alone seemed to be sufficient for PP of variceal bleeding. In SP, concomitant NSBB to EBL improves survival within the first 6 months after EBL, as compared to EBL alone. In patients with severe/refractory ascites these beneficial effects of NSBB therapy have to be weighted against their potential side-effects.

SAT-271

The post-living donor liver transplantation survival-defining factor high tricuspid regurgitation pressure gradient in liver cirrhosis correlates with the diastolic heart failure and a high oxidative stress status

A. Takaki[1], T. Yasunaka[1], H. Okada[1]. [1]*Okayama University, Gastroenterology and Hepatology, Okayama, Japan*
Email: akitaka@md.okayama-u.ac.jp

Background and Aims: We previously reported that mild liver congestion as defined by a high tricuspid regurgitation pressure gradient (TRPG) measured by transthoracic echocardiography (TTE) is the survival-defining factor after living donor liver transplantation (LDLT), although such a condition is widely accepted as not critical after deceased donor OLT (DDLT). Given that left or right lobe LDLT grafts are smaller than DDLT grafts, even mild hepatic vein pressure might result in a strong congestive impact on the LDLT grafted liver. Although the mean pulmonary artery pressure (mPAP) is the standard method for diagnosing pulmonary hypertension and congestive pressure to the liver, TRPG but not mPAP was the survival-defining factor in our previous analysis. To determine the difference between a high mPAP and high TRPG status, we compared the clinical characteristics of these two conditions.
Method: The clinical characteristics and course post-LDLT of patients were investigated according to high mPAP and high-TRPG status. We recruited 84 LDLT candidates with liver cirrhosis. Patients exhibiting a TRPG $\geq$ 25 mmHg (median) on TTE were categorized as potentially having high TRPG (subclinical high-TRPG; n = 34). Patients exhibiting a high mPAP (>25 mmHg) measured after general anesthesia with $FIO_2$0.6 (mPAP-$FIO_2$0.6) were categorized as potentially having pulmonary hypertension (PH) (subclinical PH; n = 19). As oxidative stress is known to be correlated with the vascular function, the oxidative stress marker and anti-oxidative marker were also investigated.
Results: A subclinical high TRPG ($p = 0.012$) and older donor age ($p = 0.008$) were correlated with a poor 40-month survival. Subclinical high-TRPG but not subclinical PH was associated with a high E/e', indicating diastolic heart failure that could lead to heart failure with preserved ejection fraction. Levels of the oxidative stress-related marker dROM were not markedly different between the two conditions, but those of the anti-oxidative marker OXY were lower in the subclinical high-TRPG group. The staining pattern of the oxidative stress-related marker 4-HNE in the excised liver showed a larger stained area in the subclinical high-TRPG group but not in the subclinical PH group.
Conclusion: The post-LDLT survival-defining factor high TRPG was associated with a diastolic heart failure tendency and high oxidative stress status that should be controlled.

SAT-272

Hemodynamic disturbances across different stages of decompensated cirrhosis and influencie on outcomes

M.G. Guix[1], E. Alvarado[1], A. Ardevol[1], R. Montañés[1], B. Cuyas[1], M. Poca[1], X. Torras[1], C. Guarner[1], C. Aracil[2], C. Villanueva[1]. [1]*Hospital Santa Creu i Sant Pau, Spain;* [2]*Hospital Arnau de Vilanova, Spain*
Email: martagguix89@gmail.com

Background and Aims: Different stages can be identified in decompensated cirrhosis, such as bleeding without any other decompensation, ascites without bleeding or bleeding with other concomitant decompensation. Whether hemodynamic derangements change across these stages has not been clarified despite the potential clinical implications. This study aimed to assess systemic and hepatic hemodynamic changes across the different stages of decompensated cirrhosis
Methods: From January 2007 patients consecutively admitted due to variceal bleeding were included. All received secondary prophylaxis with non-selective β-blockers (NSBB) plus EVL. A baseline hemodynamic study was performed before starting therapy. Hemodynamic data were compared in patients with bleeding alone (BlAl) vs those with other decompensation in addition to bleeding (BlPlus). Mean arterial pressure (MAP), hearth rate (HR), cardiac output (CO), systemic vascular resistance (SvR) and HVPG were measured. Patients with ascites and varices without previous bleeding (AsAl) referred during the study period for primary prophylaxis, were also investigated to assess differences with the previous bleeding groups.
Results: 231 patients with variceal bleeding were included, 70 without any other decompensation. Patients with BlAl had better baseline liver function than those with BlPlus. Patients with BlAl had, as compared with those with BlPlus, lower risk of developing further decompensation of cirrhosis during follow-up and better survival (90% *vs.* 55% at 3 years, $p < 0.001$ by log-rank). Patients with BlAl were less hyperdynamic than those with BlPlus as indicated by a lower CO (7.2 ± 2.3 *vs.* 8.0 ± 2.6 L/min, $p = 0.05$) and higher SvR (990 ± 368 *vs.* 872 ± 309, $P = 0.01$), had lower HR (84 ± 16 vs 89 ± 15, $p = 0.04$) and lower HVPG (17.6 ± 4 vs 21.0 ± 4 mmHg, $P < 0.001$). MAP, CO and SvR were similar between patients BlAl and the cohort with AsAl, while HVPG was lower in those with BlAl (17.6 ± 4 *vs.* 19.4 ± 5, $p = 0.03$). Survival probability was better in patients with BlAl vs those with AsAl (90% *vs.* 73% at 3 y, $p = 0.3$). Patients with BlPlus had lower MAP ($p = 0.03$) and SvR ($p = 0.09$) than those with AsAl and had slightly higher CO ($p = 0.154$) and higher HVPG (21.1 ± 5 *vs.* 19.4 ± 5, $p = 0.01$). Survival was better in patients with AsAl than in those with BlPlus (73% *vs.* 55% at 3 y, $p < 0.001$).
Conclusion: Hyperdynamic circulation, portal pressure and survival are worse in patients with other decompensation in addition to bleeding than in those with bleeding alone. Patients with ascites alone have an intermediate situation

SAT-273

Prevalence and clinic impact of rectal colonization by multidrug-resistant bacteria in descompensated cirrhosis

M. Hernandez-Tejero, F.M. Reverte, F. Aziz, C. Pitart, I. Campo, A. Carpio, E. Reverter, A. Escorsell, P. Ginès, A. Soriano, J. Vila, J. Fernandez. *Clinic Hospital, Liver ICU, Liver Unit, Barcelona, Spain*
Email: mhdeztejero@hotmail.com

Background and Aims: Infections caused by multidrug-resistant (MDR) bacteria are increasingly reported in cirrhosis. Rate and clinical impact of rectal colonization by MDR strains in this population is poorly known.
Method: Prospective study in 119 patients admitted to our unit (86 in the regular ward and 33 in the ICU). Rectal swabs were obtained at admission and weekly thereafter until discharge and cultured for ESBL-producing *Enterobacteriaceae* and carbapenem-resistant bacteria. Patients were followed up for bacterial infections within the

next 3-months. MDR microbiological isolations were considered to guide antibiotic therapy and isolation strategies.
Results: Twenty-seven percent of patients (n = 32) were colonized by MDR strains at inclusion. Prevalence was slightly higher in patients admitted to the regular ward (30% *vs.* 18% in the ICU, p = ns). Twenty-one percent of the non-colonized patients became colonized during hospitalization, with similar rates between ICU and regular ward. Among the 40 MDROs isolated in rectal swabs, the most common strains were ESBL-producing *Klebsiella pneumoniae* (n = 16), ESBL-producing Escherichia Coli (n = 14), and carbapenem-resistant-*Enterobacteriaceae* (n = 5). Multivariate analysis identified MDR isolation in the previous 6 months (HR: 20.4; p = 0.009) and hospital and ICU admission within the last 3 months (HR 3.2 and HR 3.1; p = 0.02 and p = 0.047, respectively) as independent risk factors for MDR colonization at admission. Twenty-one percent of colonized patients developed an infection caused by MDR bacteria during follow-up compared to 1% in patients without colonization (p < 0.0001). Infections occurring in patients colonized by MDR bacteria were frequently caused by the same MDR strain.
Conclusion: Rectal colonization by MDR bacteria is frequent in patients with decompensated cirrhosis whether admitted or not to the ICU. MDROs carriage is associated to a higher risk of infection caused by the same MDRO. Studies assessing cost-effectiveness of epidemiological surveillance in cirrhosis are needed.

SAT-274
Improving assessment of hepatic encephalopathy in outpatient clinics
F. Hansa[1], A. Nicoll[1,2,3,4], S. Le[1,2,4], S. Knowles[5,6,7], J. Lubel[1,3], J. Halliday[2,4], P. Prichard[2,4], S. Bloom[1,3], S. Sood[2,4]. [1]*Monash University, Faculty of Medicine, Nursing and Health Sciences, Melbourne, Australia;* [2]*Royal Melbourne Hospital, Department of Gastroenterology and Hepatology, Melbourne, Australia;* [3]*Eastern Health, Department of Gastroenterology, Melbourne, Australia;* [4]*University of Melbourne, Department of Medicine, Melbourne, Australia;* [5]*Swinburne University of Technology, Faculty of Health, Arts and Design, Melbourne, Australia;* [6]*Royal Melbourne Hospital, Colorectal Medicine and Genetics, Melbourne, Australia;* [7]*University of Melbourne, Faculty of Medicine, Dentistry, & Health Sciences, Melbourne, Australia*
Email: fshan1@student.monash.edu

Background and Aims: Overt hepatic encephalopathy (OHE) is a simple diagnosis based on clinical signs; however, minimal hepatic encephalopathy (MHE) can only be diagnosed with special tests that are impractical in the clinic setting. MHE diagnosis is important as it is associated with impairment to quality of life and driving performance, yet the prevalence of MHE amongst cirrhotic patients in Australia remains unknown. A new app, *EncephalApp: Stroop Test*®, may be a practical alternative to diagnose MHE in an outpatient setting.
This study aimed to determine the prevalence of MHE in a cirrhotic outpatient population, assess the feasibility of *EncephalApp*® use in real-world clinic settings, and to identify factors independently associated with MHE.
Method: Patients with cirrhosis were recruited prior to their outpatients' appointment for a cross-sectional study at two Victorian public health services between March-July 2017. Participants performed EncephalApp® on an iPad® under supervision, and the time taken was documented to determine its feasibility as a diagnostic tool. EncephalApp® scores were blinded to clinicians until after initial clinical assessment had been undertaken. After the patient's appointment, the clinician's assessment of HE was documented, and patient demographics and cirrhosis features were collected from the patient's case file. Patients with factors affecting cognition, such as acquired brain injury and stroke were excluded, as were patients with hepatocellular carcinoma.
Results: A total of 1685 patients were screened, 433 had the diagnosis of cirrhosis. 125 patients (median age 56y (interquartile range 50–63), 65.6% male) were recruited of which 46 (36.8%) had MHE according to EncephalApp®. Of these participants, only 13 (28.3%) were also diagnosed with HE by the clinician. 5 patients were diagnosed with HE by the clinician but not EncephalApp®. The median times taken to explain and complete EncephalApp® were 1 and 7 minutes respectively. On multivariate logistic regression, increasing age (odds ratio (OR) 1.08, p = 0.002), and lactulose therapy (OR 22.5, p = 0.01) were strongly associated with MHE according to EncephalApp®, suggesting pre-existing suspicion of HE from the clinician commencing lactulose therapy. No other clinical factors were useful in identifying risk of MHE.
Conclusion: E*ncephalApp®* is a quick and easy to administer tool that could be employed in the real-world clinic setting to assess MHE. It may identify a significant number of cases that would otherwise remain undiagnosed yet may benefit from intervention.

SAT-275
Proton pump inhibitors increase the risk of minimal and overt hepatic encephalopathy and they are associated with high mortality in cirrhotic patients
S. Nardelli[1], S. Gioia[1], C. Pasquale[1], L. Ridola[2], O. Riggio[1]. [1]*Sapienza University of Rome, Gastroenterology, Rome, Italy;* [2]*Ospedale Santa Maria Goretti, Latina, Italy*
Email: nardelli.silvia@gmail.com

Background and Aims: Proton pump inhibitors (PPIs) can contribute to small-bowel bacterial overgrowth and are a risk factor for overt hepatic encephalopathy (HE). Minimal hepatic encephalopathy (MHE) is a subclinical cognitive dysfunction, frequently observed in cirrhotic patients, that can be detected only with psychometric tests; no study investigated the link between PPIs and MHE. The aim of this study was to investigate the incidence of minimal and overt HE in a cohort of cirrhotic patients treated with PPIs. Another aim was to evaluate if long term therapy with PPIs influenced survival in cirrhotic patients.
Method: 310 consecutive cirrhotic patients without overt HE were included in the study. All patients underwent a psychometric evaluation and MHE was diagnosed when the Psychometric Hepatic Encephalopathy Score (PHES) was ≤ –4. Demographic data, PPIs dosage as well as a number of clinical and laboratory variables collected in each patient were analysed. Logistic and Cox regression multivariable models were used to assess if PPIs therapy was independently associated with MHE, overt HE and survival. Survival curve was estimated with the Kaplan-Meier method.
Results: at inclusion, 125 patients (40%) used PPI; the comparison among patients with and without PPI is shown in the Table 1. Three outcomes were considered. The variables independently associated to the presence of MHE were: PPIs (p < 0.001), Child-Pugh score (p = 0.03), MELD score (p = 0.02), serum albumin level (p = 0.03) and history of overt HE (p = 0.002). The variables independently associated to the presence of overt HE were: PPIs (p = 0.008), MHE (p = 0.001), age (p = 0.03), serum albumin level (p < 0.001) and history of overt HE (p < 0.001). The variables independently associated to mortality were: PPIs (p = 0.05), MHE (p = 0.04), age (p = 0.002), serum albumin level (p = 0.01) and MELD score (p < 0.001). During a mean follow-up of 14.1 ± 12.3 months, overall survival was evaluated and among PPIs users' mortality was higher than in cirrhotic patients not treated with PPI (p < 0.001).
Conclusion: the chronic administration of PPIs is frequent in cirrhotic patients and seems to be associated with the presence of MHE and with the development of overt HE. Furthermore, the use of PPIs is associated to an increased mortality in cirrhosis.

Table 1:

	PPI – (n = 185)	PPI + (n = 125)	P value
Sex (M/F)	137/48	84/41	Ns
Age (y)	61.5 ± 11.9	63.3 ± 11.6	Ns
Aetiology (virus/alchol/other)	105/54/26	84/30/11	Ns
MELD	12.3 ± 4.5	13.3 ± 5.5	0.06
Child Pugh class (A/B/C)	87/82/16	55/51/19	Ns
Child Pugh score	6.9 ± 1.7	7.2 ± 1.8	Ns
Previous HE (no/yes)	144/41	89/36	Ns
Ascites (no/yes)	92/93	57/68	Ns
MHE (no/yes)	131/54	48/77	<0.001
HE post (no/yes)	138/47	57/68	<0.001
Hemoglobin (g/dl)	11.1 ± 2.3	11.5 ± 2.1	Ns
Bilirubin (mg/dl)	2.2 ± 3.2	3.3 ± 6.4	0.04
Albumin (g/dl)	3.4 ± 0.6	3.3 ± 0.6	<0.001
INR	1.3 ± 0.3	1.4 ± 0.3	Ns
Sodium (mEq/L)	137.6 ± 3.8	136.1 ± 5.1	0.005

SAT-276

The time trend of hospital admissions, inpatient mortality rate, and hospital cost of hospitalizations associated with cirrhosis in the United States: an analysis on the National Inpatient Sample

B. Zou[1], Y.H. Yeo[1], D. Jeong[1], E. Sheen[1], H. Park[2], D.H. Lee[1], G. Garcia[1], M. Nguyen[1]. *[1]Stanford University Medical Centre, Division of Gastroenterology and Hepatology, Palo Alto, United States; [2]University of Florida College of Pharmacy, Pharmaceutical Outcomes & Policy, United States*

Email: mindiehn@stanford.edu

Background and Aims: Liver cirrhosis carries high morbidity, mortality and economic burden and affects 6% of the U.S. population. The study aimed to investigate the time trend of the disease burden in terms of number of inpatient admissions, inpatient mortality rate and hospital cost of hospital admissions for cirrhotic patients.

Method: We used the National Inpatient Sample database which samples 20% of all discharges from U.S. community hospitals (excluding rehabilitation and long-term acute care hospitals) to determine the trend of cirrhosis associated hospitalizations and inpatient mortality rates from 2005 to 2011. Generalized linear model was used to compare the hospital cost per admission within different racial/ethnic groups and patients with different causes of cirrhosis, adjusting for age, sex, insurance type, region, income, severity of cirrhosis, and comorbidities. All cost was inflation (3%) adjusted to 2013 US dollars.

Results: A total of 880,005 hospitalizations associated with cirrhosis were identified during 2005 and 2011. The total number of cirrhotic admissions increased from 102,158 in 2005 to 160,246 in 2011. The total cost of cirrhotic admissions per year also showed an increasing trend from 1.55 billion dollars in 2005 to 2.56 billion dollars in 2011. In 2011, the inpatient mortality rate was significantly higher in Asians vs. Hispanics (7.87% *vs.* 5.82%, $p < 0.0001$). Moreover, the adjusted cost per admission for Hispanics was $1107 lower than that of the Whites ($16,219 *vs.* $17,326, $p < 0.0001$). The number of hospitalizations related to hepatitis C virus infection (HCV), alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) and other liver diseases all increased over time except for admissions for cirrhosis associated with hepatitis B virus (HBV) which remained stable (Figure 1a). In regards to the hospital cost per admission for cirrhotic patients, the cost was significantly lower in HCV, ALD and NAFLD-related cirrhosis compared to the cost on the HBV-associated cirrhotic admissions (Figure 1b).

Conclusion: The number of hospital admissions for cirrhosis and their total hospital cost witnessed an increasing trend from 2005 to 2011 for most liver diseases including HCV and NAFLD. Hepatitis B patients, in contrast, showed a stable number of admissions for cirrhosis but a higher cost per admission compared to HCV, ALD and NAFLD related cirrhosis admissions.

SAT-277

Validation and modification of Baveno criteria to rule out high-risk varices in patients with compensated cirrhosis

V. Tadkalkar, R. Gunjal, K. Devadas. *Govt Medical College, Department of Medical Gastroenterology, Thiruvananthapuram, India*

Email: kdas40@gmail.com

Background and Aims: Baveno VI criteria defines patients with compensated cirrhosis in whom endoscopy can be avoided as those with a liver stiffness (LSM) by TE <20 kPa and platelet count and >150,000/mm^3. The aim was to validate Baveno criteria in our cohort from India and to determine whether alternate parameters not including TE would be equal/more accurate in ruling out high risk varices (HRV).

Method: Cross-sectional study evaluating patients with liver stiffness >10 kPa who had endoscopy within 6 months of TE evaluation. Factors like Hemoglobin, Platelet, LFT, RFT, INR, etiology, LSM and

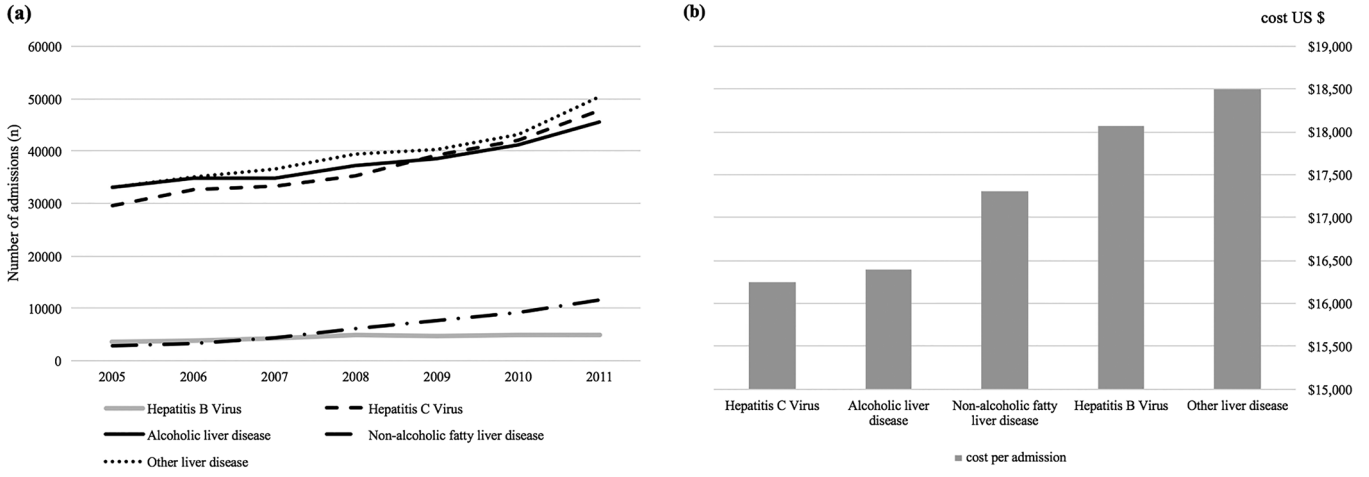


Figure: (abstract: SAT-276): (a) The time trend of number of hospital admissions associated with cirrhosis by aetiology from 2005 to 2011; (b) The cost per admission for hospital admissions associated with cirrhosis by aetiology in 2011. Other liver disease: Autoimmune hepatitis, alpha-1-antitrypsin deficiency, hereditary hemochromatosis, hemochromatosis due to repeated red blood cell transfusions, other hemochromatosis, disorders of copper metabolism, cholangitis.

MELD score were compared between the groups who had HRV and who did not have HRV.
Results: This study included 272 patients who underwent Transient elastography (TE) and upper GI endoscopy from September 2015 to August 2017 at our centre. 168 (61%) patients were male while 104 (38%) patients were female. Most common etiology was HCV (43%) followed by HBV, NASH and ethanol. Out of 192 patients satisfying Baveno criteria (LSM <20 kPa and platelet >150000/mm^3), 190 patients did not have HRV. Sensitivity, specificity, Positive predictive value (PPV) and Negative predictive value (NPV) was 98%, 78%, 91% and 97% respectively. (AUC = 0.89). In all patients, among the factors studied, Platelet count, S. Bilirubin, MELD and LSM significantly differed between patients who had HRV and those who did not have HRV by Mann Whitney U test. An alternative strategy excluding TE and including platelet count and MELD score was also used. No patients with MELD score 6 showed HRV irrespective of platelet count (Sensitivity and NPV = 100%), No patient with MELD score 7 and platelet >150000/mm^3 had varices (Sensitivity and NPV = 100%). One out of 147 patients with platelet >150000/mm^3 had HRV whose MELD was 8. By using MELD 6 or MELD <8 and platelet >150000/mm^3 criteria, 180 (66%) endoscopies could have been circumvented, while using Baveno criteria, 190 (70%) endoscopies could have been circumvented.
Conclusion: This study validates Baveno VI criteria defining patients in which screening endoscopy can be safely avoided. It also describes a new strategy with MELD 6 or MELD <8 and platelet >150000/mm^3 which can be used when TE is not available to screen patient who can safely avoid endoscopy in resource constrained settings.

SAT-278

Outcomes of intrahepatic porto-systemic shunt in the treatment of portal vein thrombosis: A systematic review and meta-analysis

S. Rodrigues[1], S. Sixt[2], A. De Gottardi[3], I. Baumgartner[2], A. Berzigotti[1]. *[1]Hepatology, UVCM, Inselspital, University of Bern, Switzerland; [2]Clinic for Angiology, Swiss Cardiovascular Center, Inselspital, University of Bern, Switzerland; [3]University hospital of Berne, Hepatology, Bern, Switzerland*
Email: susanagrodrigues@gmail.com

Background and Aims: In recent years, minimally-invasive endovascular therapy, and in particular intrahepatic porto-systemic shunts (IPS), (transjugular, transhepatic or transplenic), has been increasingly used to recanalize portal vein thrombosis (PVT). Data regarding the efficacy and safety of endovascular therapy in PVT are scarce, making evidenced-based decisions challenging. The aims of this systematic review and meta-analysis were to determine the feasibility and safety of IPS, and the 1-year shunt patency and PV recanalization rates in patients with PVT undergoing IPS.
Method: Relevant publications up to October 15, 2017 in English were searched in four electronic databases: PubMed, Web of Sciences, Scopus and Embase. Studies were screened and reviewed by two independent investigators for eligibility, according to the PRISMA-guided protocol. Disagreements were resolved by the senior authors. Studies including sufficient information on the characteristics of patients, of PVT, and on the outcomes of IPS were analysed. Data was extracted, and meta-analysis of the results was performed using a random effects model.
Results: The initial search yielded 709 candidate studies; among them 14 studies were included (397 patients). Most patients (93%) had cirrhosis. PVT was complete in 68%, chronic in 96%, cavernoma was present in 18% and superior mesenteric vein involvement in 40%. IPS was technically feasible in 92% (95% CI: 9–96%) with significant heterogeneity among studies (I^2 = 77%). Major complications occurred in 3.7% (95% CI: 1.3–6.1%), with no significant heterogeneity (I^2 = 13%). The mean follow-up after IPS was 19.8 + 8 months. Shunt patency was maintained at 1 year in 80% (95% CI: 72–87%) with significant heterogeneity (I^2 = 79%), largely explained by the use of uncovered stents in 24%. The one-year portal vein recanalization rate was 84% (95% CI: 78–91%), with significant heterogeneity (I^2 = 72%). Among the 3 studies that included non-cirrhotic patients, the 1-year recanalization rate was 64% (95% CI: 37–91%), with significant heterogeneity (I^2 = 64%). Recanalization rate correlated with a higher number of patients per study (r = 0.89). The overall one-year survival rate was 87%.
Conclusion: Endovascular therapy is highly feasible, effective and safe in recanalizing PVT. Experienced-centers achieve a higher PV recanalization rate.

SAT-279

Clinically significant portal hypertension in chronic liver disease: Always cirrhosis?

S. Rodrigues[1], A. Berzigotti[1], M. Montani[2], A. De Gottardi[1], J. Bosch[1]. *[1]Hepatology, UVCM, Inselspital, University of Bern, Switzerland; [2]Institute of Pathology, University of Bern, Inselspital, Bern, Switzerland*
Email: susanagrodrigues@gmail.com

Background and Aims: Clinically significant portal hypertension (CSPH) is defined by a hepatic venous pressure gradient (HVPG) ≥ 10 mmHg. In the setting of chronic liver disease, CSPH is highly correlated with the presence of cirrhosis, is used in the prognostic stratification of patients with cirrhosis and has been even proposed as a diagnostic surrogate of the presence of cirrhosis on histology. The aim of this study was to characterize patients showing HVPG ≥ 10mm Hg in whom histology did not confirm the presence of cirrhosis.
Method: A prospective database of 185 consecutive patients with liver diseases submitted to simultaneous HVPG measurements and transjugular liver biopsy (TJLB) between January 2015 and June 2017 was retrospectively analyzed. Patients with CSPH (HVPG ≥ 10 mmHg) and chronic liver disease were selected, and liver biopsies were reviewed to detect cases that were not showing a histological stage of cirrhosis.
Results: Among the 185 patients, 92 (50%) had CSPH defined by an HVPG ≥ 10 mmHg. After excluding 3 patients with haematological infiltration of the liver (lymphoma and amyloidosis), a HVPG ≥ 10 and a METAVIR score below F4 was found in 16% of the patients (14/89). All of the patients had representative biopsies with ≥ 10 portal tracts. The median HVPG in this group was 12 mmHg (10–16.5). METAVIR stages were F3 (n = 7), F2 (n = 1) and F1 (n = 6). The aetiologies included chronic hepatitis C (n = 2), non-alcoholic steatohepatitis (n = 4), portal sinusoidal disease (n = 5), cholestatic (n = 2) and autoimmune diseases (n = 1). The median spleen size was 13 cm (10.5–13.9) and median platelet count was 138 × 10^9/L (102–159). Perisinusoidal fibrosis (6/14, 43%) and hepatocyte ballooning (7/14, 50%) were common histological features of these patients.
Conclusion: CSPH in patients with chronic liver disease is not always synonymous of cirrhosis. Sixteen percent of patients with chronic liver disease had CSPH, although they did not have cirrhosis on histology. In these patients, perisinusoidal fibrosis and hepatocyte ballooning likely contribute to the increase in sinusoidal pressure beyond that expected from their histological stage of fibrosis.

SAT-280

Screening of esophagogastric varices: Performance of the "Expanded Baveno VI criteria" and the "platelet 150/MELD 6" strategy in all etiology compensated advanced chronic liver disease

G. Tosetti[1], V.L. Mura[1], R. D'ambrosio[1], E. Degasperi[1], N. Mezzina[2], M. Viganò[2], M.G. Rumi[2], A.L. Fracanzani[3], R. Lombardi[3], M. Fraquelli[4], A. Aghemo[5], P. Lampertico[1], M. Primignani[1]. *[1]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Università degli Studi di Milano, CRC A.M. and A. Migliavacca for Liver Disease, Division of Gastroenterology and Hepatology, Milan, Italy; [2]Ospedale San Giuseppe, Università degli Studi di Milano, Division of Hepatology, Milan, Italy; [3]Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, University of Milan, Internal Medicine, Department of pathophysiology and Transplantation, Italy; [4]Fondazione IRCCS Cà Granda Ospedale Maggiore*

Policlinico, Division of Gastroenterology and Endoscopy, Milan, Italy; [5]Humanitas University, Department of Biomedical Sciences, Rozzano, Italy
Email: pietro.lampertico@unimi.it

Background and Aims: Baveno VI criteria (liver stiffness measurement-LSM <20 kPa and/or platelet count >150,000/mm^3) in viral compensated advanced chronic liver disease (cACLD) patients allow to spare 20–25% variceal screening endoscopies. More recently, less conservative strategies to further reduce the number of unneeded endoscopies ("Expanded Baveno VI criteria": LSM <25 kPa and/or platelet count >110,000/mm^3) were proposed. Due to the limits/unavailibilty worldwide of LSM a "Plt >150,000/MELD 6 criteria" was also proposed. Both criteria proved accurate and effective but need external validation.
The aim is to assess the accuracy of the new "Baveno VI expanded criteria" and "Plt >150,000/MELD 6 criteria" in a large cohort of cACLD patients of any etiology, as compared to the original "Baveno VI" criteria.
Method: cACLD patients undergoing endoscopic screening for varices were evaluated. Laboratory data within 6 months and LSM within one year were retrospectively collected. Exclusion criteria were: LSM unavailable or unsuccessful, liver decompensation, previous variceal treatment, portal vein thrombosis, current hepatocellular carcinoma or other neoplasm and splenectomy.
Results: 471 of 1182 patients fulfilled inclusion criteria: 79% viral cACLD (316 HCV, 56 HBV), 21% metabolic/ETOH cACLD (ETOH 32, metabolic 50, mixed ETOH/metabolic 17), platelet count (PLT) was 124 (36–347) × 10^9/L, LSM 19,1 kPa (7,7–75,0). 144 (31%) had varices; of these, 31 (21%) had varices requiring prophylaxis. Baveno VI criteria had 100% sensitivity (Se) and 100% negative predictive value (NPV): according to these criteria 100 (21%) patients could have safely avoided endoscopy. The "expanded Baveno VI" criteria maintain the highest accuracy (Se 100% and NPV 100%) sparing 211 (45%) endoscopies (original "Baveno VI criteria" vs "expanded Baveno VI" criteria p <0.001, McNemar test). Conversely, the "platelet count >150,000/MELD 6 criteria" proved less accurate (Se 0,9; NPV 0,985), since, similarly to the expanded Baveno VI criteria, led to save up to 41% endoscopies, but would have lost 3 out of 31 patients (10%) of those with varices requiring prophylaxis.
Conclusion: The new "Expanded Baveno VI" criteria are valid and reproducible in all etiology cACLD patients and allow sparing screening endoscopies up to 45% without losing accuracy. The "Plt >150,000/MELD 6" strategy is less accurate.

SAT-281

Combined elastin and collagen proportionate area sub-classifies cirrhosis and predicts clinical outcomes

A. Majumdar[1,2], A. Hall[1], T.V. Luong[3], M. Pinzani[1], E. Tsochatzis[1]. *[1]UCL Institute for Liver and Digestive Health and Sheila Sherlock Liver Centre, Royal Free Hospital, London, United Kingdom; [2]AW Morrow Gastroenterology and Liver Centre, Australian National Liver Transplant Unit, Royal Prince Alfred Hospital, Sydney, Australia; [3]Department of Histopathology, UCL Medical School, Royal Free Campus, London, United Kingdom*
Email: avikmajumdar@me.com

Background and Aims: Hepatic fibrosis comprises both collagen and elastic fibres. Morphometric quantification of fibrosis with collagen proportionate area (CPA) can sub-classify cirrhosis and is a validated histological predictor of clinical outcomes. We aimed to explore the role of elastin quantification in this context.
Method: A historical CPA validation cohort of 69 patients with cirrhosis was investigated. Slides were re-cut and stained from paraffin blocks using modified Elastic Van-Gieson (EVG). After digital image acquisition at x4 objective magnification, semi-automated quantification of elastin was performed using a purpose built MATLAB script. Elastin proportionate area (EPA), CPA and ECPA were compared to existing semi-quantitative histological criteria (Laennec, Kumar, Nagula, Sethasine) and clinical scores. The outcomes of interest were decompensation at baseline and future decompensation. Standard statistical methods were employed using STATA v14.0.
Results: 59 patients (59% male) with a mean age of 51 ± 11 had complete EPA and CPA measurements. Cirrhosis was mostly due to alcohol (37%), hepatitis C (25%) and hepatitis B (10%). At biopsy, 21 (36%) were decompensated, while 9/38 (24%) of the compensated patients decompensated during a median follow-up of 57 months (IQR 16–92). Mean MELD score was 12 (± 6). Mean biopsy length was 22.1 mm(± 11). Mean EPA, CPA and ECPA were 3 (± 3.40), 22.6 (± 12.2) and 25.7 (± 14.8) respectively. At baseline, CPA (cut-off 26.1) correctly classified 88% as decompensated (sensitivity 88%, specificity 89%) compared to ECPA (cut-off 25.8), which correctly classified 92% (sensitivity 96%, specificity 90%). The AUC for prior decompensation for CPA and ECPA were similar (both 0.91, p = 0.07). On multivariate analysis, only the models containing ECPA (OR 1.16 [1.03–1.30]) or CPA (OR 1.20 [1.05–1.36]) in combination with MELD were significant. The AUC for predicting future decompensation was 0.75 for ECPA and 0.76 for CPA (p = NS). On Cox regression, only ECPA (HR 1.04 [1.01–1.08], p = 0.02) and CPA (HR 1.05 [1.00–1.10], p = 0.03) predicted future decompensation when compared to other scores.
Conclusion: We provide a proof of concept study for the measurement of elastin using digital image analysis and its relation to clinically relevant outcomes. The combination of EPA and CPA should be further explored in larger cohorts.

SAT-282

Transjugular intrahepatic portosystemic shunt is highly effective in patients with a MELD score <20 and does not require routine Doppler ultrasound follow-up

K. de Wit[1], O. van Delden[2], U. Beuers[1], B. Takkenberg[1]. *[1]Academic Medical Centre, Gastroenterology and Hepatology, Amsterdam, Netherlands; [2]Academic Medical Centre, Radiology, Amsterdam, Netherlands*
Email: k.dewit@amc.uva.nl

Background and Aims: A transjugular intrahepatic portosystemic shunt (TIPS) is a highly effective intervention to treat complications of portal hypertension. Since the introduction of polytetrafluoroethylene (PTFE)-covered stents patency rates have improved. Nevertheless, TIPS is still a second line treatment. The aims of this study were to assess the indications, overall response, clinical outcome and yield of ultrasound follow-up in patients receiving PTFE-covered TIPS in an academic centre.
Method: A retrospective cohort study of all consecutive patients (aged 18 years or older) who underwent PTFE-covered TIPS placement between 2001 and 2016. Imaging, laboratory and clinical parameters were reviewed and analysed.
Results: A total of 120 patients were included, of whom 47% had alcoholic liver cirrhosis. Main indications for TIPS were variceal bleeding (42%) and refractory ascites (38%). At 1-year follow-up control of bleeding was successful in 94%, and control of refractory ascites was successful in 82%. Within 30 days post TIPS-placement, 33% developed hepatic encephalopathy (HE). Overall one-year transplant free (TF)-survival was 58%. Irrespective of TIPS indication patients with MELD score <20 had a significantly better TF-survival compared to patients with a MELD >20 (p < 0.001; Figure). In patients with Child Pugh-B cirrhosis, one-year TF-survival significantly differed between patients with variceal bleeding (94%) and refractory ascites (36%) (p = 0.001). Predictors of mortality in patients with variceal bleeding were INR > 1.4 and a serum bilirubin level >43 µmol/L. In patients with refractory ascites, a serum albumin level <34 g/L was a predictor of mortality. Doppler ultrasound investigations during regular follow-up at the outpatient clinic revealed abnormalities in 3%, which were all associated with clinical deterioration, while abnormalities were detected in 13% of patients who presented at the emergency ward with clinical symptoms of TIPS-dysfunction.

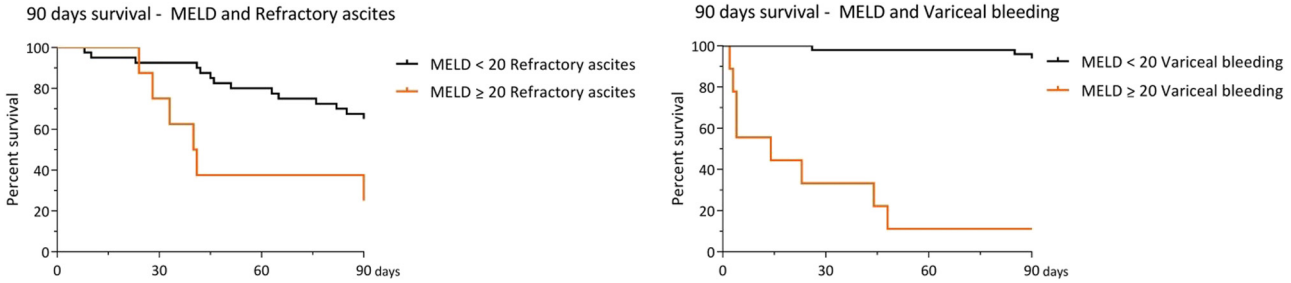


Figure: (abstract: SAT-282): Kaplan-Meier survival curves of 90 days survival, divided by MELD score lower than 20 and greater or equal to 20, for refractory ascites ($p < 0.001$) and variceal bleeding ($p < 0.001$).

Conclusion: In selected patients TIPS is a highly effective treatment for variceal bleeding and refractory ascites, but patients with a MELD score greater or equal to 20 have a poor survival asking for most critical judgement before decision for TIPS placement. The use of routine Doppler ultrasound follow-up after PTFE-covered TIPS placement seems unnecessary as abnormal Doppler findings are almost always associated with clinical symptoms of TIPS-dysfunction.

SAT-283

Efficacy of liver stiffness measurement and platelet count in screening for high grade varies in patients with cirrhosis

A. Agarwal, G. Rout, S.K. Vuyyuru, D. Gunjan, S. Kedia, B. Nayak, Shalimar. *All India Institute of Medical Sciences, Gastroenterology and Human Nutrition Unit, New Delhi, India*
Email: drshalimar@yahoo.com

Background and Aims: Endoscopy is the gold standard for detection and staging of varices; guidelines recommend screening endoscopy in newly diagnosed cirrhosis. The aim of this study was to validate the recently published Baveno VI guidelines which recommend avoiding endoscopy in patients with compensated cirrhosis with liver stiffness measurement (LSM) ≤20 kPa and platelet count ≥150,000/mm^3.
Method: Consecutive cirrhosis patients of viral etiologies- hepatitis B virus (HBV) and hepatitis C virus (HCV) evaluated from Jan 2015 to May 2017 were included. High grade varices (HGVs) were defined as grade III and grade IV varices or lower grade varices with red color signs on endoscopy. Receiver operator characteristic (ROC) curves were computed for LSM and platelet count and presence of HGVs. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy (DA) were reported.
Results: In this analysis from an ongoing prospective study- 295 patients (HBV 154 and HCV 141); mean age 43.1 ± 13.2 years; 127 (43.1%) males were included. The median LSM (IQR) and platelet counts (IQR) were 19.7 (14.8–28.8) kPa and 119000/mm^3 (80000–160000/mm^3), respectively. The area under ROC (AUROC) curve for LSM, platelet count and both combined as predictors for presence of HGVs were 0.58 (95% CI, 0.48–0.67), 0.68 (0.60–0.76) and 0.63 (0.54–0.71), respectively. LSM (at a cut-off of 21.4 kPa) had sensitivity, specificity, NPV, PPV and DA of 58.3%, 58.7%, 87.9%, 27.5% and 0.58, respectively. Platelet count (at a cut-off of 106500/mm^3) had a sensitivity, specificity, NPV, PPV and DA of 62.5%, 61.1%, 86.6%, 19.4%, and 0.61, respectively. The use of LSM and CAP in conjunction did not significantly improve the overall diagnostic accuracy over individual values. Using the Baveno VI cut-offs (LSM 20 kPa and platelet count 150000/mm^3), the sensitivity, specificity, NPV, PPV and DA for prediction of HGVs for LSM and platelet count were 60.4%, 53.4%, 20.1%, 87.4%, 0.54 and 85.4%, 32.4%, 19.7%, 91.9%, 0.41 respectively. There were no differences in predictive values of LSM and platelet in patients with hepatitis B and C etiologies.
Conclusion: The diagnostic performance of liver stiffness measurement and platelet count for prediction of high grade varices is modest and more data is required before it can replace screening endoscopy.

SAT-284

Correlation and prognostic accuracy between noninvasive liver reserve markers and portal pressure in cirrhosis: Role of ALBI score

Y.-C. Hsieh, H.-C. Lin, K.-C. Lee, Y.-Y. Yang, M.-C. Hou, T.-I. Huo. *Taipei Veterans General Hospital, Department of Gastroenterology and Hepatology, Taipei, Taiwan*
Email: hclin@vghtpe.gov.tw

Background and Aims: The role of non-invasive liver reserve markers which developed to evaluate the severity of chronic liver disease remained unclear in cirrhosis. We aimed to evaluate the correlation between noninvasive liver reserve markers and hemodynamic parameters and their prognostic performance in cirrhotic patients.
Method: A total of 242 cirrhotic patients undergoing hemodynamic study were analyzed. The correlations between noninvasive models, including the FIB-4, aspartate aminotransferase to platelet ratio index, cirrhosis discriminant score, Lok index, Goteborg University Cirrhosis Index, and albumin-bilirubin (ALBI) score and hemodynamic parameters were investigated, along with their predictive accuracy in short-term and long-term survival.
Results: There was a significant correlation between all noninvasive markers and hepatic venous pressure gradient (HVPG), and ALBI score had the best correlation ($r = 0.307$, $p < 0.001$). For the prediction of 3-month and 6-month mortality, serum sodium (sNa) levels had the highest area under curve (AUC; 0.799 and 0.818, respectively) among all parameters, and ALBI score showed the best performance (AUC = 0.691 and 0.740, respectively) compared with other 5 noninvasive models. Of 159 patients with low MELD scores (<14), high ALBI score (>−1.4) and low sNa (<135 mmol/L) predicted early mortality. In the Cox multivariate model, ALBI, MELD, HVPG and sNa were independent predictors of long-term survival.
Conclusion: Among noninvasive markers, ALBI score is best correlated with HVPG and associated with short-term outcome in cirrhotic patients. A high ALBI score and low sNa identify high-risk patients with low MELD scores. High MELD, HVPG, ALBI and low sNa levels are independent predictors of decreased long-term survival.

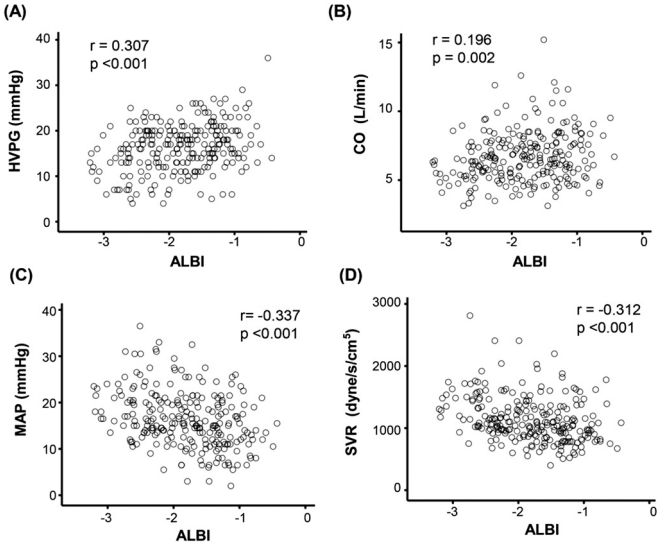


Figure 1. Correlation between the albumin-bilirubin (ALBI) scores and hemodynamic parameters in cirrhotic patients. The correlation between the ALBI scores and hepatic venous pressure gradient (HVPG, panel A), cardiac output (CO, panel B), mean arterial pressure (MAP, panel C), and systemic vascular resistance (panel D).

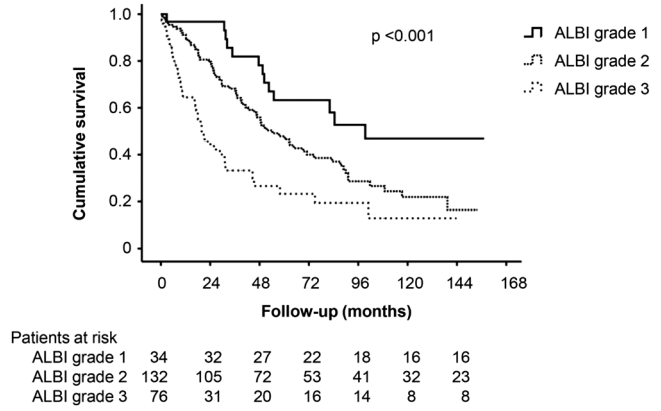


Figure 2. Comparison of long-term survival according to different ALBI grades.

SAT-285

Tolerability and kinetics of SYNB1020 in a Phase 1, first-in-Human, healthy adult volunteer study

M. Puurunen[1], W.S. Denney[2], L. Blankstein[1], R. Goldwater[3], T. Parsons[1], Y. Millet[1], C. Kurtz[1], A. Brennan[1]. *[1]Synlogic Inc.; [2]Human Predictions; [3]Parexel*
Email: marja@synlogictx.com

Background and Aims: Patients with impaired liver function accumulate toxins in the blood stream, which presents as hepatic encephalopathy (HE) in approximately 55% of patients with chronic liver disease. The pathogenesis of HE is believed to be largely attributable to hyperammonia. Current standard of care for HE aims at reducing blood ammonia levels using lactulose or rifaximin. SYNB1020 is an orally administered live biotherapeutic product that is a genetically modified strain of *Escherichia coli* Nissle 1917 (EcN) designed to consume ammonia and produce arginine in the intestinal tract. To prevent gut colonization, additional modifications were performed to make SYNB1020 a thymidine auxotroph (Figure 1). The rationale for development of SYNB1020 was to create a commensal strain of EcN that would produce excess arginine and continuously consume excess ammonia where it is naturally produced, in the colon, before it can be absorbed into the blood.
Method: A Phase 1, first-in-human, oral single and multiple dose-escalation, randomized, double-blinded, placebo (PBO)-controlled Study of SYNB1020 in healthy adult volunteers (HV) was conducted to evaluate safety and tolerability of SYNB1020 following single (SAD) and multiple (MAD) ascending doses (NCT03179878). Secondary objectives were assessment of gastrointestinal (GI) tolerability using the Gastrointestinal Symptom Rating Scale (GSRS), and SYNB1020 microbial kinetics in feces.
Results: 52 HV received SYNB1020 or PBO (ratio 3:1). SYNB1020 was well tolerated at total daily doses up to 1.5×10^{12} CFU for 14 days. Higher doses were associated with mild to moderate nausea and vomiting during the first 1–2 days of dosing. There were no SAEs or deaths. No clinically significant change in total GSRS was observed in the MAD cohorts. qPCR revealed rapid clearance of the strain following discontinuation of dosing. There was no evidence of colonization in any subject. Strain activity was demonstrated in feces from subjects who received SYNB1020 but not PBO.
Conclusion: This first in human trial demonstrated safety and tolerability of SYNB1020 in healthy volunteers. Tolerability and microbial kinetic data will guide future clinical studies in patients with liver disease and hyperammonemia.

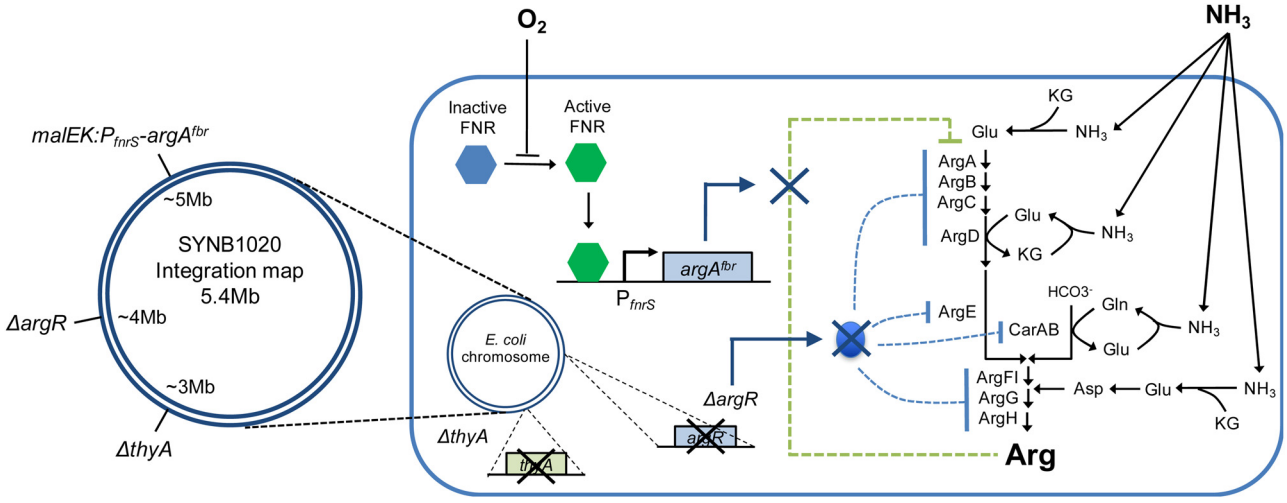


Figure 1: (abstract: SAT-285): SYNB1020 genetic modifications. (1) argR repressor gene deleted, (2) argA gene replaced with a feedback-resistant version, (3) Control of argA gene by anaerobic promoter (fnr), (4) thyA gene deleted to confer auxotrophy.

SAT-286

Cardiac fibrosis and coronary atherosclerosis in cirrhosis. Indications of cirrhotic cardiomyopathy?

S. Wiese[1,2,3], J. Hove[2,4], S. Mo[5], F. Bendtsen[2,5], S. Møller[2,3]. [1]*Hvidovre Hospital, Gastro Unit, medicial division, Denmark;* [2]*University of Copenhagen, Faculty of health and medical sciences, Denmark;* [3]*Hvidovre Hospital, Dept. Clinical Physiology, Denmark;* [4]*Hvidovre Hospital, Dept. Cardiology, Denmark;* [5]*Hvidovre Hospital, Gastro Unit, medical division, Denmark*
Email: signeswiese@gmail.com

Background and Aims: The underlying etiology of cirrhotic cardiomyopathy remains partly unknown. Quantification of the extracellular volume fraction (ECV) by cardiac MRI (CMR) is a new method to assess structural myocardial changes, including diffuse myocardial fibrosis. Patients with cardiac failure have increased myocardial ECV and we have recently shown in cirrhosis, that ECV is related to disease severity and poor outcome. In patients with cirrhosis the relation between coronary artery sclerosis, cardiac fibrosis, and cirrhotic cardiomyopathy has not been explored. Our aim was therefore to investigate if the degree of myocardial fibrosis as assessed by CMR-derived myocardial ECV was related to well-established cardiovascular risk factors and coronary artery atherosclerosis.
Method: 52 patients with cirrhosis and 10 healthy controls were included. All patients underwent CMR with ECV quantification, coronary-CT angiography including coronary artery calcium (CAC)-score, tissue Doppler echocardiography, clinical and biochemical assessments. In the controls, contrast-enhanced CMR alone was performed.
Results: Myocardial ECV was higher in patients compared with healthy controls (31.2 ± 6 *vs.* 27.4 ± 3%, $p = 0.04$). Moreover, ECV increased across Child Pugh A/B/C classes (26.9 ± 4/ 31.5 ± 5/ 34.4 ± 6%, $p = 0.02$). There were no differences between patients with a high ECV (>31.2%) versus a low ECV (≤31.2%) with respect to prevalence of smoking (46% vs. 55%), hypercholesterolemia (22% *vs.* 78%), arterial hypertension (48 *vs.* 52%) or type II diabetes (40 vs. 60%) (P = NS). Even though the median CAC-score (289 HU (26; 645)) was increased in the patients we found no association between myocardial ECV and CAC-score ($r = -0.18$; $P = 0.22$). Myocardial ECV correlated with cardiac index ($r = 0.35$, $p = 0.015$), CRP ($r = 0.47$, $p = 0.001$), and proANP ($r = 0.4$, $p < 0.001$). No associations to age, etiology or portal hypertension (P = NS).
Conclusion: Myocardial fibrosis in cirrhosis is related to disease severity, but not to well-established cardiovascular risk factors or presence of coronary artery atherosclerosis. Since ischemic heart disease does not seem to be involved in the development of structural myocardial changes in cirrhosis, increased myocardial fibrosis may represent an early manifestation of cirrhotic cardiomyopathy.

SAT-287

The role of bile acids in the development of structural myocardial changes and cardiac dysfunction in patients with cirrhosis

S. Wiese[1,2,3], J. Hove[3,4], S. Mo[2], F. Bendtsen[2,5], S. Møller[5,6]. [1]*Hvidovre Hospital, Dept. Clinical Physiology, Denmark;* [2]*Hvidovre Hospital, Gastro Unit, Medical Division, Denmark;* [3]*University of Copenhagen, Faculty of Health and Medical sciences, Denmark;* [4]*Hvidovre Hospital, Dept. Cardiology;* [5]*University of Copenhagen, Denmark; Faculty of Health and Medical sciences;* [6]*Hvidovre Hospital, Dept. Clinical Physiology, Copenhagen, Denmark*
Email: signeswiese@gmail.com

Background and Aims: Bile acids (BA) suppress cardiac function in experimental models of cirrhosis. However, the potential deleterious cardiac effects of BA in patients with cirrhosis have only been sparsely investigated. Cardiac MRI (CMR) with quantification of the extracellular volume fraction (ECV) is a new method that allows for noninvasive assessment of structural myocardial changes, in particular diffuse myocardial fibrosis. Our aim was to investigate if abnormal levels of circulating BA contribute to the development of structural myocardial changes and cardiac dysfunction in patients with cirrhosis.
Method: 52 patients with cirrhosis and 10 healthy controls were included. All patients underwent CMR with ECV quantification, coronary-CT angiography including coronary artery calcium (CAC)-score, tissue Doppler echocardiography, clinical and biochemical assessments including total bile acid (tBA) concentrations. In the controls, contrast-enhanced CMR alone was performed.
Results: Patients with cirrhosis had increased circulating levels of tBA, median 42 µmol/L (19;86) with the highest levels in patients with advanced disease (86 µmol/L (37;116) *vs.* 24 µmol/L (17;46), $p < 0.001$). When patients were divided into two groups based on a tBA cut-off of 42 µmol/L those with high levels of tBA had an increased myocardial ECV in comparison with those with lower levels of tBA (33.2 *vs.* 29.6%, $p = 0.011$). Patients with high tBA levels also had increases in cardiac index ($p = 0.02$), left atrial volume ($p = 0.047$), left ventricle end diastolic volume ($p = 0.01$) and right ventricle end diastolic volume ($p = 0.013$). Additionally, tBA correlated with MELD ($r = 0.67$, $p = 0.000$), lateral e' ($r = 0.30$, $p = 0.02$) and hepatic venous pressure gradient ($r = 0.39$, $p = 0.006$). No correlations were seen to natriuretic peptides (p = NS).
Conclusion: Circulating levels of tBA are increased and related to disease severity, portal pressure and cardiac dimensions in patients with cirrhosis. Moreover, increases in tBA levels are associated with an increased myocardial ECV reflecting myocardial fibrosis. This may indicate that BAs are involved in the development of structural myocardial changes in cirrhosis and that BAs most likely play a contributing role in cardiac changes relating to cirrhotic cardiomyopathy.

SAT-288

Hepatopulmonary syndrome: a spontaneously reversible condition? Variability in prevalence in a prospective follow-up study of cirrhotic patients

A. Chiricuta[1], T. Voiosu[1,2], B. Mateescu[1,2], A. Voiosu[1]. [1]*Colentina Clinical Hospital, Gastroenterology, Bucharest, Romania;* [2]*UMF Carol Davila*
Email: radoiaurelia@yahoo.com

Background and Aims: Hepatopulmonary syndrome (HPS) is a pulmonary vascular complication of liver disease associated with increased mortality in patients awaiting liver transplantation. Repeating arterial blood gas analysis may lead to reclassification in some cases. We aimed to assess the variability in prevalence of HPS at different timepoints in a cohort of cirrhotic patients.
Method: This is a prospective observational study of 87 consecutive patients with cirrhosis. Patients with significant pulmonary or cardiovascular disease were excluded. Routine blood tests, pulse oxymetry and blood gas measurements were performed at baseline and at 1 and 2 years of follow-up. Contrast enhanced echocardiography examination for detecting intrapulmonary vascular dilations was performed at baseline. The main outcomes were prevalence of HPS and cirrhosis-related complications and death during follow-up.
Results: Patients were followed up for a mean of 19 months. Of the 87 patients enrolled, 19 had HPS at baseline, but during follow-up visits only 6 (after 1 year) respectively 3 (after 2 years) fulfilled the oxygenation criteria for HPS. After one year there were 2 new and 6 persistent cases of HPS and after 2 years there were 5 HPS cases (2 new). One patient had a variable oxygenation gradient compatible with the HPS criterion at baseline and at 2 years, but not at the 1 year visit. HPS at baseline was associated with decreased survival: 18.7 vs. 21 months ($p = 0.021$ log rank). Of the initial 19 HPS patients 10 died during follow-up and there were 8 cases of new onset ascites, 4 of gastrointestinal bleeding, 8 of hepatic encephalopathy, 2 severe infections and 1 hepatorenal syndrome recorded in this group.
Conclusion: Oxygenation abnormalities diagnostic for HPS fluctuate in time and may lead to reclassification of patients with HPS but an initial diagnosis is associated with adverse outcome at 2 years.

Periodic reassessment of arterial oxygen concentrations may be advisable when monitoring cirrhotic patients.

SAT-289

Is obesity an additional negative factor in sarcopenic cirrhotic patients?

D. D'ambrosio, B. Lattanzi, V. Di Gregorio, V. Fedele, S. Incicco, M. Merli. *Clinical Medicine, Rome, Italy*
Email: daria.damb@gmail.com

Background and Aims: Sarcopenia is an important burden in cirrhotic patients and is recognized as a negative prognostic factor in these patients. Nowadays, non-alcoholic steatohepatitis (NASH) is among the most common causes of cirrhosis also leading to liver transplantation. These patients may present obesity and sarcopenia at the same time, a condition known as sarcopenic obesity. Obesity is associated with a proinflammatory state caused by the increase in inflammatory cytokines and has been shown to increase the rate of decompensation in patients with liver cirrhosis. The aim of the study was to analyze the role of sarcopenic obesity in hospitalized cirrhotic patients.
Method: All consecutive cirrhotic patients hospitalized from 2012 to 2015 at our tertiary care center were enrolled in the study. In each patient, we performed anthropometric evaluation. Sarcopenia was diagnosed according to mid-arm muscle circumference (MAMC), body mass index (BMI) was corrected for ascites. Sarcopenic obesity was diagnosed in presence of sarcopenia and BMI ≥ 30.
Results: We analyzed 466 cirrhotic patients. Sarcopenia was present in 306 patients (66%). Concomitant obesity was present in 139 patients with sarcopenia (45%). Cirrhotic patients with sarcopenic obesity presented a higher rate of complications linked to portal hypertension (85% *vs.* 62% $p < 0.001$), an increased prevalence of variceal bleeding (34% *vs.* 18%; $p = 0.008$) and hepatic encephalopathy (38% *vs.* 25% $p = 0.03$) vs cirrhotic patients with sarcopenia and not obese. No difference was found for in-hospital mortality ($p = 0.17$).
Conclusion: Sarcopenic obesity is a condition often underestimated that may increase morbidity in patients with cirrhosis leading to a higher frequency of complication in comparison with sarcopenic cirrhotic patients with normal/low weight.

SAT-290

Liver cirrhosis and wound healing: Activation of von Willebrand factor and platelets

L. Langholm[1], M. Karsdal[1], F. Bendtsen[2], D. Leeming[3], T. Manon-Jensen[1], S. Møller[4]. *[1]Nordic Bioscience A/S, Biomarkers & Research, Herlev, Denmark; [2]Hvidovre Hospital, Gastro Unit, medical division, Hvidovre, Denmark; [3]Nordic Bioscience, Biomarkers & Research, Herlev, Denmark; [4]Hvidovre Hospital, Department of Clinical Physiology, Hvidovre, Denmark*
Email: lla@nordicbio.com

Background and Aims: Portal hypertension (PHT) is closely related to development of complications to liver cirrhosis. PHT is often accompanied by endothelial dysfunction leading to an impaired wound healing response and decreased platelet count and activity. Increased Von Willebrand Factor (VWF) formation in cirrhosis has been suggested as a compensatory mechanism for low platelet count. The ADAMTS13-processing yields a VWF form that efficiently binds and activates platelets, and consequently is considered a platelet activation factor. VWF antigen and ADAMTS13 levels and activity have previously been assessed in cirrhosis, thus only indirectly assessing the role of VWF processing. The aim of this study was to measure the true ADAMTS13 cleaved VWF form (VWF-A) in addition to VWF formation (VWF-N) to investigate the association of platelet activation and would healing in relation to PHT in liver cirrhosis.
Method: Plasma samples from 105 participants undergoing liver vein catheterization and with liver cirrhosis of varying severity were included in the study together with 20 controls without liver disease. A competitive ELISA format was used to estimate biomarkers of VWF formation (VWF-N) and ADAMTS13-processing (VWF-A) using neo-epitope specific monoclonal antibodies.
Results: VWF-N levels and VWF-A levels were significantly elevated in cirrhotic patients compared to controls ($p < 0.001$) and both markers could discriminate mild from severe cirrhosis (Child-Pugh score A vs C) (VWF-N, $p < 0.0001$; VWF-A, $p = 0.0061$). Discriminating patients with cirrhosis from controls using AUROC analysis showed equally good diagnostic accuracy for both markers (AUC 0.87, $p < 0.0001$). When stratifying the patients based on PHT, the biomarkers were capable of separating cirrhotic patients with from patients without clinically significant/severe PHT as defined by a HVPG cutoff of ≥10 (VWF-N, $p = 0.0003$; VWF-A, $p = 0.028$).
Conclusion: The data clearly indicate that not only is VWF formation increased in cirrhosis, but more importantly VWF activation which is a surrogate of active wound healing. Total VWF-N and activated VWF-A identified subjects with cirrhosis and discriminated between those with and without PHT and may therefore contain additional information to assess the presence and severity of PHT as an early indicator of cirrhosis. Whether the increased would healing has impact on long-term outcome needs to be addressed in future studies.

SAT-291

The incidence of ulcer bleeding post endoscopic band ligation of esophageal varices

S. Machlab[1], J. Da Costa[1], D. Horta[2], P. Ruiz[2], J. Profitós[3], M.V. Gómez[1,4], M. Miquel[1,4], M. Casas[1], B. Dalmau[1], R. Campo[1], E. Brullet[1], F. Junquera[1], V. Puig-Diví[1], E. Martínez-Bauer[1], P. García-Iglesias[1], A. Villoria[1], M. Gallach[1], L. Melcarne[1], X. Calvet[1,4], J. Sánchez-Delgado[1,4]. *[1]Parc Taulí Hospital Universitari. Institut d' Investigació i Innovació Parc Taulí I3PT, Universitat Autònoma de Barcelona, Digestive Diseases Department, Sabadell; [2]Hospital Universitario Mútua de Terrassa, Digestive Diseases Department, Terrassa, Spain; [3]Consorci Sanitari de Terrassa (CST), Digestive Diseases Department, Terrassa, Spain; [4]Instituto Carlos III, CIBERehd, Madrid, Spain*
Email: machlab@gmail.com

Background and Aims: Endoscopic esophageal varices band ligation can be complicated by bleeding from post-ligation ulcers. Most published studies on prophylaxis with this procedure do not report the incidence of this event. Our aim is to assess the incidence and risk factors of post-ligation early hemorrhage.
Method: Retrospective multicenter study. Patients treated with elective band ligation between January 2013 and December 2015 in three centers were included. Clinical, endoscopic and analytical variables were collected
Results: 297 banding sessions in 133 patients were included. The average number of sessions were 3 per patient with an average of 5 bands. Twelve patients developed eschar bleeding, which represents an incidence of 4% and that 9% of the patients bled. Three patients required endoscopic treatment with adrenaline and/or sclerosis injection and another patient also required combined treatment with hemoclips and Endoclot. The 90% required transfusion of 1.3 ± 0.8 red blood cell concentrates. We found no statistically significant differences. The patients who bled had a mean age of 59 years, 10 patients (83.3%) were males, with cirrhosis due to alcohol (33.3%), HCV (25%), cryptogenic (16.7%), OH + HCV (16.7%) and NASH (8.3%). 5 of the 12 patients (41.7%) presented bleeding after the second banding session. 66.7% had signs of hypertensive gastropathy and 41.7% red spots on varicose veins. Regarding the Child-Pugh stage, 41.7% were Child A and B and 16.7% C. 25% had portal thrombosis and 41.7% had ascites at the time of endoscopy. 58.3% were in treatment with PPI and 50% with beta-blockers. An average 4 ± 2 band were placed. The mean platelet count was $81 \pm 40 \times 10^9$ / L, albumin 38 ± 5 g/L and INR of 1.2 ± 0.2 ratio.
Conclusion: Endoscopic esophageal varices band ligation has a 4% incidence of bleeding from eschar. A 33% of the bleeding patients

required endoscopic treatment, a 90% transfusion of packed red blood cells and there was no death. No clinical, analytical or endoscopic factors have been associated with an increased risk of bleeding from eschar.

SAT-292

Association between hospital type and transplant-free survival in patients with cirrhosis receiving transjugular intrahepatic portosystemic shunts: A population-based study

J. Mah[1], Y. Dewit[2], C. Booth[1,2], A. Menard[3], J. Flemming[1,2]. [1]*Queen's University, Medicine, Canada;* [2]*Institute for Clinical Evaluative Sciences, Canada;* [3]*Queen's University, Radiology, Canada*
Email: flemmij@hdh.kari.net

Background and Aims: The transjugular intrahepatic portosystemic shunt (TIPS) procedure is designed to reduce portal pressure in patients with cirrhosis, thereby treating complications of portal hypertension. It has been recently suggested that TIPS performed at high volume centres are associated with improved in-hospital survival. Whether this association persists over the long-term following discharge from hospital has yet to be studied. The aim of this study was to determine the association between the type of hospital (academic vs. community) where the TIPS was performed and long-term survival in the general population of patients with cirrhosis.

Method: We conducted a population-based retrospective cohort study utilizing administrative health care data from Ontario, Canada accessed through the Institute of Comparative Evaluative Sciences. All adult patients with cirrhosis who received a TIPS between January 1, 1998 and December 31, 2015 were included, with follow-up until December 31, 2016. Our primary exposure was hospital type based on whether the TIPS was performed at an academic or community hospital. Liver transplant-free (LTF) survival was described using Kaplan-Meier curves and the log-rank test. The association between hospital type and LTF survival was evaluated using multivariate Cox proportional hazards regression.

Results: Our study cohort consisted of 837 unique patients and was 62% (n = 579) male with a mean age of 57.2 years (SD 10.4). TIPS was performed at an academic hospital for 84.6% (n = 708) and at a community hospital for the remaining 15.4% (n = 129). LTF survival post-TIPS was lower in community hospitals compared to academic hospitals (1 year 48.4% *vs.* 58.9%; 5 years 23.9% *vs.* 32.6%; P < 0.001). Using multivariate Cox regression adjusting for age, sex, comorbidity, and indication for TIPS, patients had a higher hazard of death if their procedure was performed at a community hospital compared to at an academic centre (HR 1.36, 95% CI 1.09–1.69, p = 0.006). Other factors independently associated with mortality included older age (HR 1.03 per year increase, 95% CI 1.02–1.04, p < 0.001), Charlson-Deyo Comorbidity Index ≥4 (HR 1.32, 95% CI 1.08–1.63, p = 0.008), and indication for TIPS related to variceal haemorrhage (HR 1.33, 95% CI 1.11–1.61, p = 0.002).

Conclusion: TIPS performed in a non-academic centres are associated with a higher risk of death following the procedure. These results suggest that patients who require a TIPS may be best served by transferring to an academic centre, if possible. Future research focusing on centralization of TIPS to high-volume academic centres is warranted.

SAT-293

A simple patient-reported instrument can predict development of overt hepatic encephalopathy

M.M. Lauridsen[1], C. Wernberg[1], H. Vilstrup[2], O.B.S. de Muckadell[3], D.M. Heuman[4], J.S. Bajaj[4]. [1]*Hospital of South West Jutland, Department of Gastroenterology and Hepatology, Esbjerg, Denmark;* [2]*Aarhus University Hopsital, Department of Gastroenterology and Hepatology, Aarhus, Denmark;* [3]*Odense Universitetshospital, Department of Gastroenterology and Hepatology, Odense;* [4]*Virginia Commonwealth University Medical Center, Division of Gastroenterology, Hepatology and Nutrition, Richmond, United States*
Email: mettelauridsen@gmail.com

Background and Aims: Minimal hepatic encephalopathy (MHE) impinges on health-related quality of life (HRQoL) and prognosticates overt HE (OHE). However, MHE is rarely diagnosed in practice due to the need for specialized tests. Simple, patient-administered HRQoL questionnaires e.g. sickness impact profile (SIP), could aid in identifying patients with MHE without requiring specialized testing. This approach was tested in a US-based study introducing the SIPCHE score (formula of 4 SIP statements, gender and age; score >0 = abnormal) and was validated in a separate Danish population with a sensitivity of >80% cross-sectionally. However, the utility of a positive SIPCHE score in predicting OHE is unclear. Our aim was to determine the value of a positive SIPCHE score in the prediction of OHE development.

Method: Cirrhotic outpatients without OHE completed specialized cognitive testing with Continuous Reaction Time (CRT) and Portosystemic Hepatic Encephalopathy Score (PHES) and SIP at baseline. Abnormal CRT and/or PHES diagnosed MHE. SIP consists of 136 yes/no questions inquiring about HRQoL. The SIPCHE score was calculated from gender, age and the answer to 4 specific SIP statements related to balance problems, loss of appetite and irritable, impatient or passive behaviour. The patients were followed subsequently for OHE defined as grade 2 or higher on West Haven Criteria requiring hospitalizations.

Results: We included 110 patients (age 60 years on average, mean MELD 11.4, 80% blue-collar workers, 95% alcohol aetiology) and 64% were diagnosed with MHE on specialized tests. These patients had a worse HRQoL in SIP categories and statements addressing balance problems, vegetative symptoms and the need for assistance in daily activities. Mean follow up time was 2.7 years (SD 40 days). 33/110 (30%) of patients developed OHE during follow up – 8 experienced more than 1 episode. Patients with abnormal SIPCHE experienced HE episodes more frequently during follow up (35% vs. 14%, p = 0.05). On multivariate analysis including Child Pugh score (OR 1.6, 95% CI 1.2–2.1), CRT index (0.98, 95% CI 0.4–2.2), PHES (OR 1.02, 95% CI 0.9–1.1), and years of education (OR 1.1, 95% CI 0.9–1.3), SIPCHE (OR 3.5 95% CI 1.0–12), remained a significant predictive factor for OHE development along with Child Pugh Score.

Conclusion: The SIPCHE, a tool based on patient-reported instruments and demographics, can predict the development of future OHE in cirrhotic outpatients while avoiding the need for specialized tests. Patient-reported instruments such as SIPCHE could increase the diagnosis of MHE and improve prediction for OHE in cirrhotic patients.

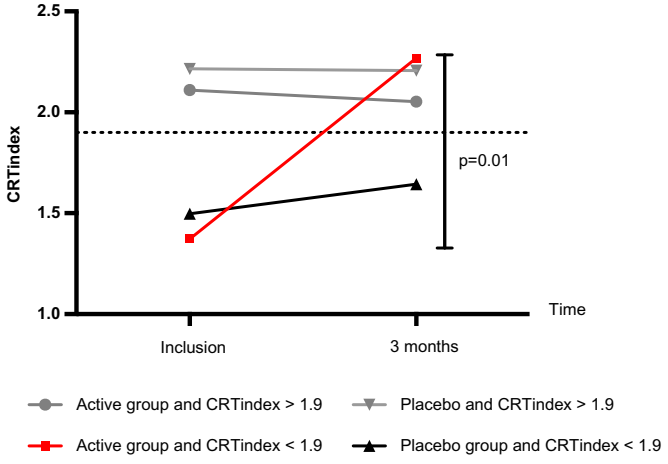
SAT-294

The continuous reaction time test for minimal hepatic encephalopathy validated by a randomized controlled multimodal intervention

M.M. Lauridsen[1], J. Gram[2], O.B.S. de Muckadell[3], H. Vilstrup[4]. [1]*Hospital of South West Jutland, Department of Gastroenterology and Hepatology, Denmark;* [2]*Hospital of South West Jutland, Department of Endocrinology, Denmark;* [3]*Odense Universitetshospital, Department of Gastroenterology and Hepatology, Denmark;* [4]*Aarhus University Hopsital, Department of Gastroenterology and Hepatology, Denmark*
Email: mettelauridsen@gmail.com

Background and Aims: Minimal hepatic encephalopathy (MHE) is clinically undetectable and the diagnosis requires psychometric tests. However, a lack of clarity exists as to whether the tests are in fact able to detect changes in cognition. Our aim was to examine if the continuous reaction time test (CRT) can detect changes in cognition with anti-HE intervention in patients with cirrhosis and without clinically manifest hepatic encephalopathy (HE).

Method: Firstly, we conducted a reproducibility analysis and secondly measured change in CRT induced by anti-HE treatment in a randomized controlled pilot study: We stratified 44 patients with liver cirrhosis and without clinically manifest HE according to a normal (n = 22) or abnormal (n = 22) CRT. Each stratum was then block randomized to receive multimodal anti-HE intervention (lactulose + branched-chain amino acids + rifaximin) or triple placebos for 3 months in a double-blinded fashion. The CRT is a simple PC-based test and the test result, the CRT index (normal threshold >1.9), describes the patient's stability of alertness during the 10–minute test. Our study outcome was the change in CRT index in each group at study exit. The portosystemic encephalopathy (PSE) test, a paper-and-pencil test battery (normal threshold above -5), was used as a comparator test according to international guidelines.
Results: The patients with an abnormal CRT index who were randomized to receive the active intervention normalized or improved their CRT index (mean change 0.92 ± 0.29, p = 0.01). Additionally, their PSE improved (change 3.85 ± 1.83, p = 0.03). There was no such effect in any of the other study groups



Conclusion: In this cohort of patients with liver cirrhosis and no manifest HE, the CRT identified a group in whom cognition improved with intensive anti-HE intervention. This finding infers that the CRT can detect a response to treatment and might help in selecting patients for treatment.

SAT-295

Transjugular intrahepatic portosystemic shunt versus beta-blocker and/or endotherapy for prevention of variceal rebleeding in adults with EHPVO

H. Chen, J. Fan, S. Tang, C. He, Y. Lv, Q. Wang, H. Liu, J. Yuan, B. Luo, T. Yu, X. Yuan, Z. Yin, G. Han. *National clinical research center for Digestive Diseases and Xijing Hospital of Digestive Diseases, Fourth Military Medical University, Department of liver Diseases and Digestive interventional radiology, Xi'an, China*
Email: qychenhui@163.com

Background and Aims: Optimal strategy for the prevention of variceal rebleeding in adults with extrahepatic portal vein obstruction (EHPVO) has never been established due to extremely insufficient comparative studies between different modalities. The present study aimed to compare transjugular intrahepatic portosystemic shunt (TIPS) versus non-selective β-blocker and/or endoscopic therapy for the prevention of variceal rebleeding among patients with EHPVO.
Method: Between March 2002 and June 2016, 127 consecutive adult patients with EHPVO and a recent variceal bleeding were included. We compared the clinically significant variceal rebleeding, recanalization of the portal venous system, hepatic encephalopathy (HE) and survival between successful TIPS (group A, n = 27), failed TIPS (group B, n = 27) and NSBB and/or endoscopic (group C, n = 73).
Results: During a median follow-up of 35.3 months, cumulative incidence of clinically significant variceal rebleeding was similar between the groups (34.6%, 39.5% and 29.3% at 5-years for group A, B and C, respectively). Group A has a signifcantly higher portal vein recanalization rate (65.2% *vs* 0% and 0%) and a relatively lower recurrence rate (8.7% *vs* 34.8% and 14.3%) compared with group B and C (p < 0.001). There were no statistically signifcant differences in spontaneous overt HE (3.7% *vs.* 0% and 1.4%; p = 0.54) and survival (83.0%, 88% and 94.3% at 5-years, respectively, p = 0.50).

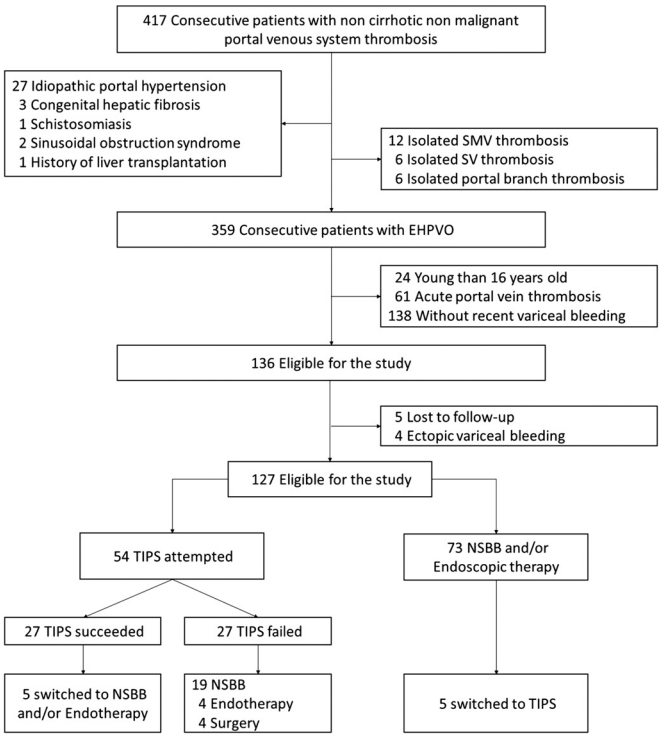


Figure 1: Flow chart showing patients' enrollment and its distribution between groups. EHPVO, extrahepatic portal vein obstruction; NSBB, non-selective beta-blockers; SMV, superior mesenteric vein; SV, splenic vein; TIPS, transjugular intrahepatic portosystemic shunt.

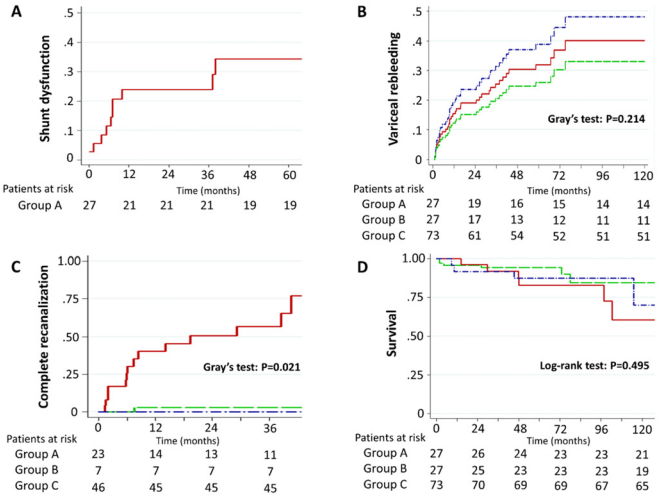


Figure 2: Cumulative incidence of (*A*) shunt dysfunction, (*B*) clinically significant variceal rebleeding, (*C*) complete Recanalization of portal venous system and (*D*) survival in Group A (continuous red line), Group B (dash dot blue line) and Group C (long dash green line). Note: Group A, successful TIPS; Group B, failed TIPS; Group C, NSBB and/or endotherapy.

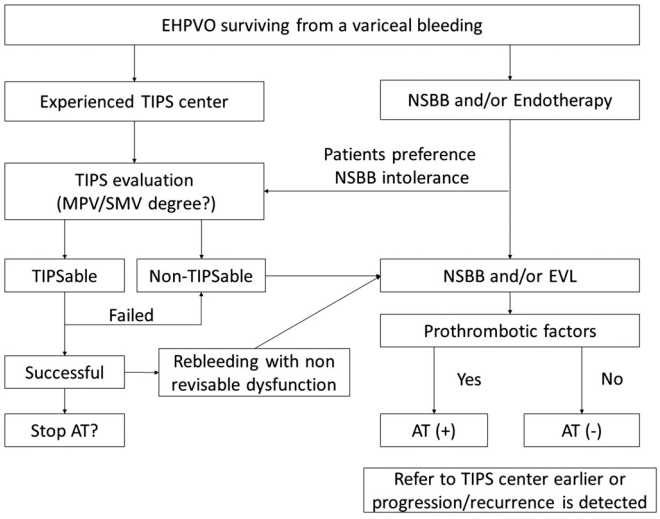


Figure 3: Proposed algorithm for the prophylaxis of variceal rebleeding in adults with EHPVO. AT, anticoagulation; EHPVO, extrahepatic portal vein obstruction; NSBB, non-selective beta-blockers; MPV, main portal vein; SMV, superior mesenteric vein; TIPS, transjugular intrahepatic portosystemic shunt.

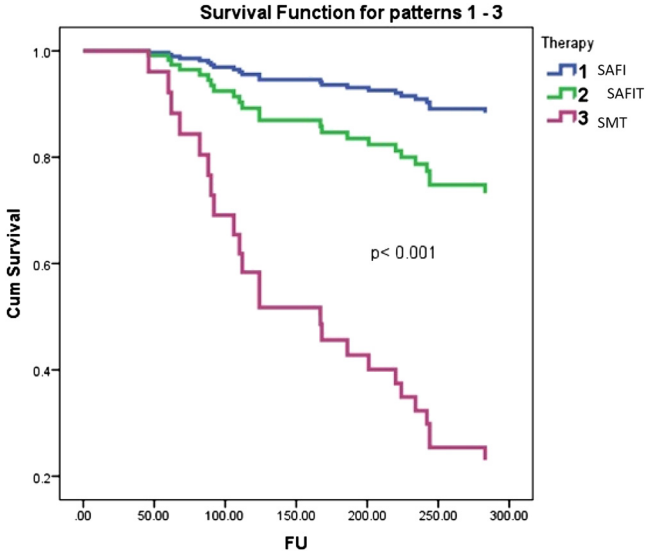
Conclusion: TIPS is as effective as NSBB and/or endoscopic therapy for the prevention of variceal rebleeding without increasing the risk of spontaneous overt HE and mortality in adults with EHPVO. Furthermore, TIPS has unique role in recanalizing obstructed portal vein and prevent progression and additional portal hypertensive complications.

SAT-296

Slow continuous albumin Infusion with furosemide with or without terlipressin in cirrhotic patients with refractory ascites

G. Pandey[1], M. Durgappa[2], A. Kumar[2], A. Singh[2], A. Nehra[2], K. Vp[2], P. Mishra[3], S. Mohindra[2], V. Saraswat[2]. *[1]Sanjay Gandhi Institute of Medical S, Hepatology and Gastroenterology, Lucknow, India; [2]Sanjay Gandhi Institute of Medical S, Gastroenterology, Lucknow, India; [3]Sanjay Gandhi Institute of Medical S, Biostatics, Lucknow, India*
Email: drgauravpandey@yahoo.com

Background and Aims: Mobilization of refractory ascites (RA)is challenging in decompensated cirrhosis. To study efficacy and safety of low-dose furosemide with albumin ± Terlipressin (SAFI ± T) to a response-guided protocol to achieve urinary sodium (UNa+) >80 mmol/L and continued till clinically complete mobilisation in RA
Method: Patients with RA (diuretic intractable or resistant) undergoing multiple sessions of large volume paracentesis (LVP) in the previous 3 months were enrolled in a 5:1 ratio. Arm 1 received SAFI ± T. Central line was placed in oliguric patients and infusions of Furosemide at 2 mg/hour and albumin at 2 g/hour (20 g/d) were started. Urine samples were collected 12 hourly for electrolytes. Furosemide infusion rate was increased by 1 mg/h, (maximum 5 mg/h), if UNa+ excretion was < 80 mmol at 24 hours. All patients received aggressive potassium supplementation. If, after 48 hours UNa+ < 80 mmol/L, terlipressin infusion at 2 mg/24 hours was started after correcting anemia and ECG monitoring. Terlipressin was increased by 1 mg/12th hourly in a response guided manner to a maximum of 6 mg/24 hours. Arm 2 received LVP and oral diuretics. After clinically complete mobilization, patients were stepped down to oral diuretics for discharge with dose adjusted to maintain UNa+ > 80 mmol/24 hours.
Results: 87 patients (intractable 58, resistant 29; arm 1: arm 2 = 73:14; M:F-60:30) were enrolled between 2013 and 2016. Mean age (46.7 ± 11.7 years *vs.* 49 ± 9.4 years), baseline mean CTP score (11.4 ± 1.4 *vs.* 12 ± 0.9), MELD (23 ± 5.7 *vs.* 24.3 ± 5.6) were similar in the two arms, as was the etiology. Arm 1 included 8 patients with hepatic hydrothorax (HH), 18 with spontaneous bacterial peritonitis (SBP) and 13 with hepatic encephalopathy grades 1–2 (HE). All patients in arm 1, but none in arm 2, were clinically dry in a median period of 10.8 ± 2.5 days. Only in Arm Imean urinary sodium excretion in increased from 17.2 ± 5.9 mmol/d to 171.2 ± 61.3 (p = 0.001), urine output from baseline of 563 ± 275 ml to maximal volume of 2972.08 ± 803 ml/day (p = 0.001). Weight decreased by mean of 14.8 ± 3.7 kgs. At end of treatment (EOT), serum sodium (130 ± 7 to 131.8 ± 4.7 meq/l; p = 0.00) and serum creatinine improved (1.6 ± 1.2 to 0.94 ± 0.43 mg/dl), as did e-GFR from 63.4 ± 50 ml/min to 93.9 ± 43.7 ml/min (p = 0.023). At mean follow up of 287 ± 83 days survival in Arm 1 was 88% for SAFI, 72% for SAFIT and 33% in Arm 2. In Arm 1 survival with and without HH was 82.8% *vs.* 62.5% and with and without SBP was 81.3% *vs.* 75%.



Conclusion: SAFI ± T is a safe and effective treatment was LVP-dependent RA, even in difficult –to-treat subsets such as those with HH, SBP and HE.

SAT-297

A prospective evaluation of symptom burden, opioid risk in cirrhosis patients

M. Niazi[1], S. Chavda[2], E. Hjartarson[2], R. Bailey[3], A. Brisebois[2], P. Tandon[1]. *[1]University of Alberta Hospital, Gastroenterology and Hepatology; [2]University of Alberta Hospital, Medicine; [3]Royal Alexandra Hospital, Gastroenterology and hepatology*
Email: ptandon@ualberta.ca

Background and Aims: Cirrhosis is associated with magnitude of symptoms leading to disability and poor quality of life. In literature it has been shown that significant number of cirrhotic patients experience chronic pain and pain-related disability. Although opioids are effective in many cases, opioid use has been associated with increased frequency of hepatic encephalopathy, cost related to hospital admission and longer hospital stay. In other chronic disease population including cancer, non-pharmacological therapies such as mindfulness-based stress reduction therapy (MBSR) have been efficacious for reducing pain, emotional distress, and fatigue. Patient interest, current use as well as perceived benefit and barriers for utilization of non-pharmacological therapies are unclear in cirrhosis patients. Within a population of patients with cirrhosis, we aimed to: (1) assess symptom burden; (2) risk of opioid dependency; (3) willingness to consider non-pharmacological therapy for symptom management.
Method: In a prospective study, we recruited 135 patients with chronic liver disease attending Cirrhosis Care Clinic at the University

of Alberta Hospital and Royal Alexandra Hospital. Our inclusion criterion for the study was documented cirrhosis on imaging in individuals 18 years of age and older. We collected data on patient demographics, symptom burden using the Edmonton Symptoms Assessment Scale (ESAS-r), perceived overall wellbeing using Euroquol Visual Analogue Scale (EQ-VAS), and risk of opioid dependency using Opioid Risk Tool Calculator. In addition, we assessed patients' familiarity with non-pharmacological therapy, willingness to try these therapies and any barriers preventing them from utilizing non-pharmacological treatment modalities.

Results: 135 patients were prospectively recruited, mean age of 60 years with 62% male patients, Child Pugh Class: A (58%), B (36%), and C (6%). Overall health status using EQ-VAS (EQ-VAS 0–100 Scale) was rated at 63.9 ± 22. Most commonly reported symptoms included: tiredness (52%), mood disorder (40%), drowsiness (36%), and pain (22%). In our study, 33% of the patients had moderate and 24% had severe opioid risk score, with higher scores being correlated with increased risk for opioid dependency and future opioid abuse. Eighty-five percent (85%) of patients were willing to learn about non-pharmacological approaches for their symptoms.

Conclusion: Despite the relatively well-compensated status of our cirrhosis cohort, symptom burden was significant, and quality of life was low. In our study, we observed significant risk of opioid dependency. Patients have a high willingness to proceed with non-pharmacological therapy, with only few noted barriers. Therefore, more research is needed surrounding non-pharmacological therapeutic options in cirrhosis patients.

SAT-298

Critical flicker frequency improves its diagnostic and predictive accuracy of hepatic encephalopathy by decreasing the dispersion between measures

C. Sendra[1], V. Aguilera[2], M.C. Rico[1,3], R. Millan[1,3], A. Gil-Gomez[1,3], J. Ampuero[1,3,4], M.R. Gomez[1,3,4]. *[1]Digestive Diseases Unit. Virgen del Rocío University Hospital; [2]Huelva Hospital Complex. Digestive Diseases Unit, Spain; [3]Institute of Biomedicine of Seville (IBIS); [4]CIBERehd, Spain*
Email: csendra.fernandez@gmail.com

Background and Aims: To determine the utility of using quality criteria to improve the ability of critical flicker frequency (CFF) to detect minimal hepatic encephalopathy (MHE) and predict overt hepatic encephalopathy (OHE).

Method: Prospective study including 115 patients with liver cirrhosis. CFF resulted from averaging ten consecutive measurements (pathological <=39 Hz). MHE was detected by the psychometrical hepatic encephalopathy score (PHES) (pathological <–4 points). We analyzed some quality criteria of CFF related to dispersion values: (a) median; (b) interquartile range (IQR); and (c) standard deviation (SD). Sensitivity (Se), specificity (Sp), positive (PPV) and negative predicted values (NPV) of CFF were calculated to detect MHE according to the presence of quality criteria. OHE was predicted by CFF (according to the best quality criteria) during a follow-up of 1.6 ± 1.1 years.

Results: MHE was detected in 40.9% of patients and 16.8% developed an episode of OHE. A lack of concordance between CFF and PHES was observed in 36.5% (42/115) of patients. The SD was the dispersion value associated with the greater discordance. MHE was correctly classified by CFF in 62.6% (72/115) of patients in the absence of any quality criteria (Se 51%; Sp 70.6%; PPV 54.5%; NPV 67.6%). If CFF was adjusted by SD < 2, the percentage of patients properly classified increased to 69.6% (55/79) (Se 71.9%; Sp 68.1%; PPV 60.5%; VPN 78%). However, the number of well-classified patients was 47.2% (11/36) (Se 6.7%; Sp 76.2%; VPP 16.7%; VPN 53.5%) when SD was >=2. CFF <= 39 Hz was associated to the development of OHE during the follow-up in patients with SD < 2 (28.2% (11/39) *vs.* FCP > 39 Hz 8,7% (4/46); logRank 8.301, p = 0.004), but did not in those with SD >= 2 (14.3% (1/7) *vs.* FCP > 39 Hz 10% (3/30); logRank 0.007, p = 0.935) (Figure).

Conclusion: CFF accuracy to detect MHE and predict OHE was superior when the dispersion between measures was low, obtaining a greater diagnostic accuracy and higher quality results when the standard deviation was lower than 2. CFF assessment, adjusted by standard deviation, will allow solving some of the limitations of this technique.

SAT-299

Four years outcomes of Baveno VI low risk cirrhotic patients

P. Pollo-Flores[1], M. Rudler[2], M. Munteanu[3], A. Ngo[4], Y. Ngo[4], D. Thabut[5], T. Poynard[6]. *[1]CAPES, UFF Internal Medicine, Niteroi, Brazil; [2]Hôpital Pitié Salpétrière, UPMC, Paris, France; [3]Hôpital Pitié Salpétrière, Biopredictive, Paris, France; [4]Biopredictive, Paris, France; [5]UPMC, Université Pierre et Marie Curie, Hôpital Pitié-Salpétrière, Paris, France; [6]UPMC Université Pierre et Marie Curie, Hôpital Pitié-Salpétrière, Paris, France*
Email: priscilapollo96@gmail.com

Background and Aims: Baveno VI statement established that screening endoscopy can be avoided in patients with compensated chronic liver disease, platelet count >150.000/mm^3 and liver stiffness measurement <20 kPa. However, there is few data regarding further development of complications of cirrhosis and survival in patients at low risk. The aim of this study was to evaluate 4 years survival and complications in patients at low risk according to Baveno VI criteria.

Method: Retrospective study was conducted in cirrhotic patients consecutively evaluated in a tertiary center between 2012 and 2017. Patients with compensated cirrhosis (defined by an applicable liver

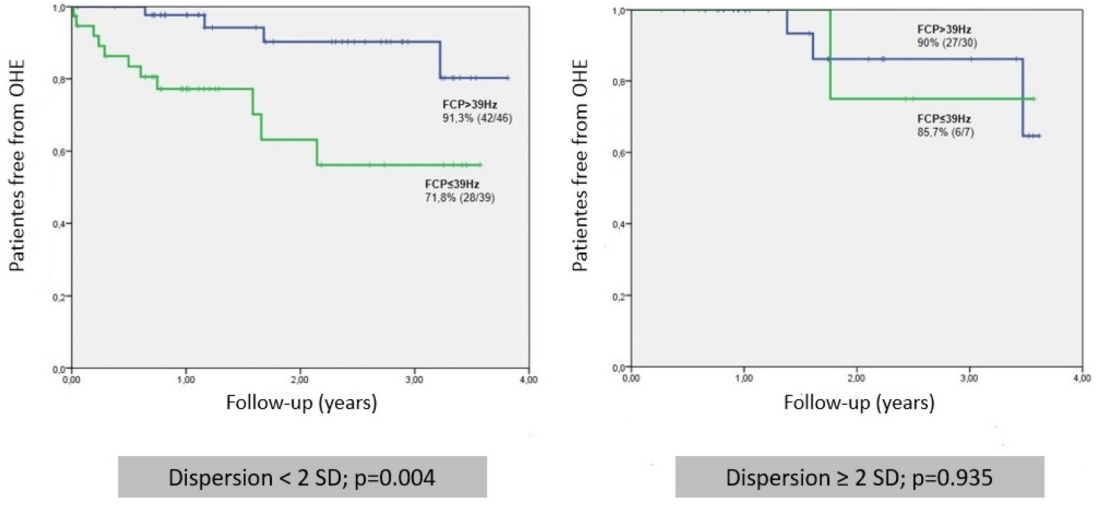


Figure: (abstract: SAT-298)

stiffness measure (LS) >12.5 kPa) were included. They were divided into two groups according to BAVENO VI criteria: Baveno VI positive (Bav+) with platelet count <150.000/mm^3 and FS >20 kpa, Baveno VI negative (Bav-) with platelet count >150.000 mm^3 or FS <20 kPa. Complications of cirrhosis including ascites, hepatic encephalopathy, jaundice, variceal bleeding and hepatocellular carcinoma were recorded. Survival was compared between groups.

Results: 241 patients with mean age of 57 yrs, male gender 70,5% and Child-Pugh(CP) score 5. Etiologies were 52% HCV, 18% NASH, 11% alcohol, 10% HBV and 9% other causes. One hundred and fifty-six patients (65%) were classified in group Bav+ and 85 (35%) in Bav- with mean age of 57 years in Bav+ and in Bav-; Preponderance of male gender was observed in both groups, 70,5%, Bav+ and Bav-; Etiologies HCV and alcohol were significantly more frequently in Bav+ than Bav-. High risk varices were observed in 14% of patients:1 patient in Bav- (1,2%) and 33 patients in Bav+ (21%), p = 0,004. In Bav+ CP median was 5.2 *vs.* 5.1 in Bav– (p = 0,12). Bav+ vs Bav– showed Platelet count (137.000 U/mm^3 *vs.* 214. 000 U/mm^3, p = 0.004) and LS measure (23.7 *vs.* 14.5 kPa, respectively, p = 0,0004) different; sixty-one (25%) patients were submitted to HCV treatment and 50 (21%) acquired sustained virological response (82%SVR). During follow-up, in Bav + group 5 patients developed encephalopathy, 4 variceal bleeding, 12 ascites and 14 CHC; in Bav- nobody developed encephalopathy (p = 0.09) or variceal bleeding (p = 0.13), 3 patients developed ascites (p = 0,27) and 5 CHC (p = 0,39) All portal hypertension complications considered, excluding hepatocellular carcinoma, tended to be more common in Bav+ patients (p = 0.06); In HCV patients PH complications were also more common in Bav+ (p = 0,05); In Bav+, 2 deaths (1%) were observed and no deaths were observed in Bav- group (p = 0.29).

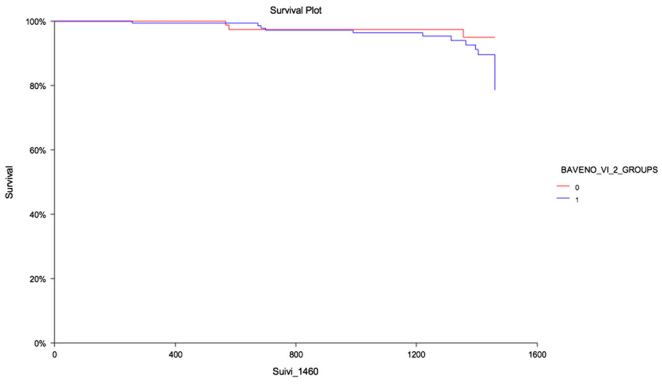


Figure: Portal Hypertension complications (follow-up of 4 years)

Conclusion: In this study, followed for 4 years, Bav- patients did not presented variceal bleeding, liver encephalopathy or death. All portal hypertension complications tended to be less often observed in Bav- group. Therefore, Baveno's criteria seems to be a reliable tool for predicting cirrhosis complications.

SAT-300

A novel sonographic parameter for the quantification of muscle mass in cirrhosis

K. Kobayashi, H. Maruyama, S. Kiyono, S. Ogasawara, E. Suzuki, Y. Ooka, T. Chiba, N. Kato. *Chiba University Graduate School of Medicine, Department of Gastroenterology, Japan*
Email: maru-cib@umin.ac.jp

Background and Aims: Sarcopenia is the common complication in patients with cirrhosis. As it is a significant prognostic factor, muscle mass quantification is an important issue in their practical care. Computed tomography (CT) is frequently used as a standard tool to evaluate the muscle volume. However, repeatedly available less-invasive procedure without radiation exposure may be preferred for the long-term clinical course. The aim of this study was to propose ultrasound-based parameter for the diagnosis of muscle mass loss (MML) in Japanese cirrhosis patients.

Method: This is an IRB-approved cross-sectional study (October 2013 to March 2017) after obtaining written informed consent. Consecutive cirrhosis patients who underwent both ultrasound (US) and CT were participated in our University Hospital. The study used the skeletal muscle index at the L3 level (L3-SMI) on CT as a standard to diagnose MML with the cut-off values of 42 cm^2/m^2 for males and 38 cm^2/m^2 for females according to the recent previous report from Japan [Nishikawa et al. Hepatol Res 2016]. Transcutaneous US was used to demonstrate a cross-section of the right iliopsoas muscle, and the iliopsoas muscle index (IP index) was defined by the iliopsoas muscle area/height^2 (mm^2/m^2).

Results: There were 248 patients with cirrhosis (150 males and 98 females), and 83 patients (33.5%; 41 males and 42 females) were diagnosed as having MML. The iliopsoas muscle was successfully detected in all subjects by US. The iliopsoas muscle area showed correlations between US and CT in males (r = 0.905, $P < 0.0001$) and in females (r = 0.905, $P < 0.0001$). Also, the L3-SMI and the IP index showed correlations in males (r = 0.707, $P < 0.0001$) and in females (r = 0.714, $P < 0.0001$). The IP index was lower in patients with MML than in those without: males (154.0 ± 42.8 *vs.* 234.7 ± 70.7, $P < 0.0001$) and females (150.3 ± 35.7 *vs.* 239.7 ± 70.6, $P < 0.0001$). Multivariate analysis detected body mass index and IP index as independent factors for MML, in both males and females. Sensitivity, specificity, and area under the receiver operating characteristic curve by IP index to detect MML were 78.1%, 76.2%, and 0.851, respectively, with the best cut-off value of 189.2 for males, and 83.3%, 80.4%, and 0.882, respectively, with the best cut-off value of 180.6 for females.

Conclusion: The study clearly reported the clinical value of the IP index by transcutaneous US as a novel diagnostic parameter for MML in cirrhosis.

SAT-301

Repeated episodes of acute kidney injury on the transplant waiting list: Impact on post-liver transplantation renal and patient outcomes

S. Neong[1], R. Rajakumar[1], N. Selzner[1], F. Wong[2]. [1]*Toronto General Hospital, Multi-Organ Transplant, Toronto, Canada;* [2]*Toronto General Hospital, Division of Gastroenterology, Dept of Medicine, Toronto, Canada*
Email: sagigal314@hotmail.com

Background and Aims: It is unclear whether repeated episodes of AKI pre-transplant, defined as an increase in serum creatinine (sCr) of >26.5 µmol/L in ≤48 hours or >50% increase from known baseline, will cumulatively & negatively impact patient and renal outcomes post-transplant. We aim to evaluate impact of repeated AKI episodes in the 18 months prior to liver transplantation on renal and patient outcomes post-transplant.

Method: Single-centre retrospective study of prospectively collected data on consecutive adults receiving single organ liver transplant between 01/01/2007 to 31/12/2014 was conducted. Data retrieved included demographics, every laboratory tests ever performed, co-morbidities, hospital admissions and pre-and post-transplant course.

Results: 194/402 cirrhotics with ascites wait-listed for liver transplantation with AKI were included. They were mostly middle-aged men [aged 54 (49–60)] (70%) with alcoholic cirrhosis (61%) with similar baseline demographics divided into groups of 1, 2, 3, ≥4 AKI episodes. Patients with ≥4 episodes of AKI have significantly higher MELD score at listing [23 (17–34)] (p = 0.039) and at transplant [31 (25–37)] (p < 0.001) with shorter time to transplant [42 days (7–162)] (p = 0.089). Infection was not statistically more common amongst the higher number of AKI groups. Patients with higher number of AKI episodes had significantly higher AKI stages, with higher peak and delta sCr within 48 hours (all p < 0.001), and more likely to have AKI progression and less likely to reverse their AKI with

Table 1: (abstract: SAT-301).

	AKI episodes				
Median (IQR)	1 (n = 85)	2 (n = 41)	3 (n = 20)	>= 4 (n = 48)	p-value
AKI stage					
1	71 (83.5%)	32 (78.0%)	17 (85.0%)	42 (87.5%)	0.69
2	10 (11.8%)	14 (34.1%)	14 (70.0%)	30 (62.5%)	<0.001
3	4 (4.7%)	8 (19.5%)	8 (40.0%)	29 (60.4%)	<0.001
Peak sCr	133 (115–167)	196 (148–262)	286 (183–379)	360 (250–479)	<0.001
Delta sCr in 48h	49 (38–63)	73 (49–142)	103 (74–174)	138 (98–273)	<0.001
AKI stage progression	0 (0.0%)	7 (17.1%)	13 (65.0%)	26 (54.2%)	<0.001
Response					
Full	65 (76.5%)	29 (70.7%)	15 (75.0%)	38 (79.2%)	0.83
Partial	10 (11.8%)	18 (43.9%)	7 (35.0%)	29 (60.4%)	<0.001
No	10 (11.8%)	17 (41.5%)	17 (85.0%)	42 (87.5%)	<0.001
Need for RRT					
Pre-transplant	1 (1.2%)	6 (14.6%)	4 (20.0%)	16 (33.3%)	<0.001
Post-transplant	2 (2.4%)	6 (14.6%)	5 (25.0%)	15 (31.3%)	<0.001
Survival					
12-month	94%	88%	80%	77%	0.030

treatment (all p < 0.001), associated with reduced post-transplant survival at 12 months.

Conclusion: Repeated episodes of AKI are detrimental to patients wait-listed for liver transplant. Greater efforts should be made to prevent recurrent episodes of AKI on the transplant waiting list.

SAT-302

Eradication of hepatitis C virus in patients with decompensated cirrhosis does not improve the management of ascites after one year of follow-up

A. Juanola[1,2,3,4], I. Graupera[1,2,3,4], A. Risso[1,2,3], G. Mezzano[1,2], S. Lens[1,2,3,4], Z. Mariño[1,2,4], X. Ariza[1,2,3,4], E. Solà[1,2,3], V. Hernandez-Gea[1,2,3,4], X. Forns[1,2,3,4], P. Ginès[1,2,3,4]. *[1]Hospital Clinic de Barcelona, Liver Unit, BARCELONA, Spain; [2]University of Barcelona, Faculty of Medicine and Health Sciences, BARCELONA, Spain; [3]IDIBAPS, BARCELONA, Spain; [4]CIBEReHD, BARCELONA, Spain*
Email: pgines@clinic.ub.es

Background and Aim: Treatment of HCV infection is effective in compensated cirrhosis and prevents decompensation in most patients. However, the effects of HCV eradication in decompensated cirrhosis, particularly the impact on the management of ascites, is less defined. We investigated whether treatment with oral antiviral drugs improves the management of ascites in decompensated cirrhotic patients.

Methods: A cohort of 42 consecutive patients with HCV cirrhosis and ascites treated with interferon-free regimes was analyzed. Patients with Child A or B cirrhosis were included. Primary endpoints were average dose of diuretics required, proportion of patients in whom diuretics could be withdrawn, and need for large-volume paracentesis (LVP). Secondary endpoints were hepatic venous pressure gradient (HVPG), which was measured in 18 patients before and after 6 months, and liver function. Endpoints were analyzed within 6 months before therapy and for two consecutive periods of 6 months (0–6 and 7–12) after SVR12.

Results: SVR12 was achieved in all patients. Two patients died (months 0–6) and 2 were lost to follow-up (months 7–12). HCV eradication was neither associated with reduction in the mean dose of diuretics required (furosemide: 20 ± 29, 30 ± 30 and 31 ± 35 mg/day; spironolactone: 53 ± 43, 70 ± 58 and 73 ± 57 mg/day at 6 months before therapy and 0–6 and 7–12 months after SVR12, respectively; p = NS for both) nor in the need for LVP. Diuretics could be withdrawn only in 3 of the 42 (7%) patients. HVPG did not change significantly (18.6 ± 4.8 vs 19.4 ± 5.3 mmHg; p = 0.84) and decreased below the threshold value of 10 mmHg in only one patient. Child-Pugh score decreased slightly but significantly during follow-up (7.3 ± 1.1, 6.6 ± 1.3 and 6.6 ± 1.3, respectively; p = 0.02), due to a significant reduction in serum bilirubin and a significant increase in serum albumin. By contrast, MELD score did not change significantly (12.9 ± 3, 12.2 ± 2.9, 12.3 ± 3, respectively, p = 0.12).

Conclusions: Eradication of HCV in patients with decompensated cirrhosis improves liver function but this is not associated with better management of ascites within 1-yr period after SVR12. The latter may be related to pathophysiology of ascites, which is related to portal hypertension (and thus severe architectural changes in the liver). Nonetheless, further studies are needed to investigate whether ascites management improves after a longer follow-up.

SAT-303

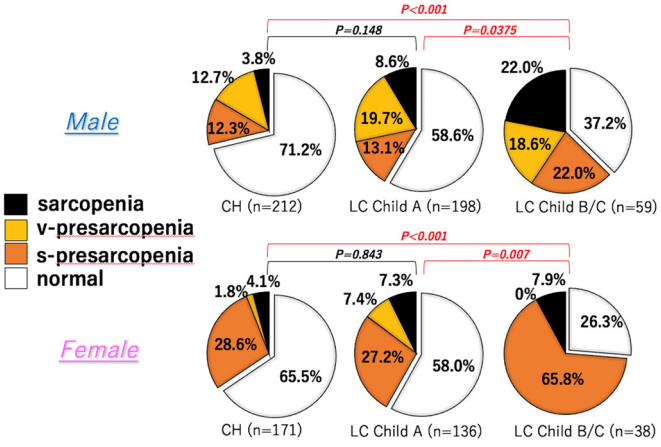
Gender differences regarding sarcopenia development in chronic liver disease

A. Hiraoka[1], K. Michitaka[2], T. Ninomiya[3], H. Masashi[4], B. Matsuura[5], M. Abe[5], Y. Hiasa[6]. *[1]Ehime Prefectural Central Hospital, Gastroenterology Center, Matsuyama, Japan; [2]Ehime Prefectural Central Hospital, Gastroenterology enter, Japan; [3]Ehime Prefectural Central Hospital, Gastroenterology Center, Japan; [4]Ehime University Graduate School of Medicine, Touon, Japan; [5]Ehime University Graduate School of Medicine, Departments of Gastroenterology and Metabology, Japan; [6]Ehime University, Gastroenterology and Metabology, Toon, Ehime, Japan*
Email: hirage@gmail.com

Background and Aims: In chronic liver disease (CLD) patients, sarcopenia is defined by decreased muscle strength and muscle volume loss according to the European and Asian diagnostic criteria for sarcopenia (EWGSOP/AWGS) and Japanese Society of Hepatology (JSH) for patients with CLD. However, few studies have investigated gender differences in regard to sarcopenia. We aimed to elucidate clinical features in male and female CLD patients with muscle volume loss and decreased muscle strength.

Method: From April to September 2015, 807 Japanese patients with CLD were enrolled (males 466, females 341). Muscle volume loss (v-presarcopenia) was evaluated by a previously reported method using psoas muscle area and height [psoas index (PSI): psoas muscle area (cm^2)/height $(m)^2$] based on computed tomography findings (cut-off value: males 4.24, females 2.50 cm^2/m^2). Decreased muscle strength (s-presarcopenia) was determined using the criteria for handgrip strength of the JSH for CLD (males 26, females 18 kg). When patients had findings indicating both v- and s-presarcopenia, they were diagnosed with sarcopenia in the present study. Clinical features for each gender were then investigated.

Results: The median age for males was 67 years [interquartile range (IQR): 59–73] and for females was 69 years (IQR: 64–76). The proportions of male patients with chronic hepatitis (CH), and liver cirrhosis (LC) Child-Pugh class A and B/C were 45.5%, 41.8%, and 12.7%, respectively, while those of female patients were 49.9%, 39.3%, and 10.9%, respectively. The frequency of sarcopenia, and s- and v-presarcopenia regardless of CLD grade was 7.9%, 13.5%, and 16.5%, respectively, for males, and 5.6%, 32.3%, and 3.8%, respectively, for females. The frequency of s-presarcopenia was higher in females ($P < 0.001$), whereas that of v-presarcopenia was higher in males ($P < 0.001$). The relationship between PSI and handgrip strength was more significant in males ($r = 0.284$, $P < 0.001$) as compared to females ($r = 0.127$, $P = 0.019$), while that between CT value and handgrip strength was similar between males ($r = 0.236$, $P < 0.001$) and females ($r = 0.274$, $P < 0.001$).



Conclusion: In CLD patients, the 2 types of pre-sarcopenia were not rare regardless of gender, though differences between males and females may exist in regard to ratios of pre-sarcopenia type.

SAT-304

Assessment of subclinical hepatic encephalopathy by using EncephalApp Stroop test and brain MRI

I.-C. Lupescu[1], S. Iacob[2,3], L. Gheorghe[2,3]. [1]*Fundeni Clinical Institute, Neurology, Bucharest, Sector 2, Romania;* [2]*Fundeni Clinical Institute, Gastroenterology and Hepatology, Bucharest, Sector 2, Romania;* [3]*Carol Davila University of Medicine and Pharmacy, Gastroenterology and Hepatology, București, Romania*
Email: ioan.cristian.lupescu@gmail.com

Background and Aims: Subclinical hepatic encephalopathy remains difficult to assess, despite numerous psychometric and paraclinical tests available. New possibilities can emerge with advancement in portable devices, through the development of applications that allow rapid testing of cognitive functions.
Method: We evaluated 65 cirrhotic patients and 15 controls using the new EncephalApp Stroop test on an Apple iPad Mini 4. All participants had a MMSE ≥24 and presented neither overt hepatic encephalopathy nor other neurologic/psychiatric conditions at the time of testing. Brain MRI (including MR-spectroscopy) was also performed in 25 of the patients.
Results: Mean age for cirrhotic group was 51.8 ± 10.4 years and 69.2% were males; mean age for controls was 47.3 ± 13.9 years. Mean Stroop result (On + Off) was 170.54 ± 30.6 seconds. Mean MELD score was 14 ± 6. Stroop results correlated positively with age ($p < 0.0001$) and MELD score ($p = 0.01$); there was a negative association with haemoglobin ($p = 0.029$) and cholesterol levels ($p = 0.026$). Mean Stroop results varied significantly ($p = 0.0003$) between age groups: patients ≤45 years scored 155.97 ± 23.42 seconds, those between 46 and 55 years scored 159.01 ± 21.22 and patients with 56–65 years scored 189.35 ± 34.89. Stroop results varied significantly ($p = 0.01$) between Child A (156.81 sec) and Child B/C patients (173.86 sec). There was a statistically significant difference ($p = 0.00006$) between mean Stroop result of controls (138.85 ± 17.84 seconds) and that of cirrhotic patients. Brain MRI revealed Globus pallidus abnormalities in the form of T1 hyperintensities ± SWI hypointensities, with raised glutamate and lowered myo-inositol peaks in 84% (n = 21). Mean Stroop result for these 21 patients was 170 ± 24.1 seconds and mean MELD 16 ± 4. Child B cirrhosis was present in 67% (n = 14), Child C in 19% (n = 4) and Child A in 14% (n = 3). Discrete-to-moderate cerebellar and cortical atrophy was present in 10 of 25, but no differences were found between patients with and without atrophy.
Conclusion: Stroop results correlated with increasing age and severity of cirrhosis measured by both MELD and Child-Pugh scores. Brain MRI can be a helpful examination in revealing changes compatible with hepatic encephalopathy, thus confirming the value of EncephalApp Stroop test.

SAT-305

Impact of antibiotic prophylaxis of spontaneous bacterial peritonitis on colonization and infections with multidrug-resistant bacteria

M. Mücke[1], A. Mayer[1], J. Kessel[2], V.T. Mücke[1], K. Schwarzkopf[1], A. Vermehren[1], N. Weiler[1], M.W. Welker[1], J. Vermehren[1], V.A.J. Kempf[3], S. Zeuzem[4], C. Lange[2]. [1]*J.W. Goethe University Hospital, Department of Internal Medicine 1, Frankfurt am Main, Germany;* [2]*J.W. Goethe University Hospital, Department of Internal Medicine 2, Frankfurt am Main, Germany;* [3]*J.W. Goethe University Hospital, Institute of Medical Microbiology and Infection Control, Frankfurt am Main, Germany;* [4]*University of Frankfurt, Department of Medicine, Frankfurt, Germany*
Email: marcus.m.muecke@gmail.com

Background and Aims: Spontaneous bacterial peritonitis (SBP) is the most frequent infection in patients with liver cirrhosis. Current guidelines recommend primary antibiotic prophylaxis of SBP for patients with liver cirrhosis and ascites who are at risk for the development of SBP and secondary prophylaxis for all patients with resolved SBP. However, little is known about the efficacy and safety of SBP prophylaxis in patient populations with high prevalence of multidrug-resistant bacteria.
Method: This is an ongoing prospective observational study in patients with liver cirrhosis and indication for primary or secondary prophylaxis of SBP in a large German tertiary liver transplant center. All patients underwent scheduled microbial and clinical monitoring at baseline and after 4, 8, 12 and 24 weeks of SBP prophylaxis with norfloxacin or ciprofloxacin. Uni- and multivariate analyses were performed to identify predictors of infection or de-novo colonization with multidrug-resistant organisms (MDROs) during antibiotic prophylaxis.
Results: To date, 53 patients were included and followed for an average of 12.4 weeks. Most patients had Child-Pugh C cirrhosis and the mean MELD score was 16. Overall, 21 (39.6%) and 32 patients (60.4%) received primary and secondary SBP prophylaxis, respectively, with ciprofloxacin (n = 26) or norfloxacin (n = 27). At baseline, 24 patients (45%) were colonized with MDROs, and 14 patients (26%) obtained de-novo colonization with MDROs during antibiotic prophylaxis. Secondary infections during SBP prophylaxis were frequent (41.5%), including infections with MDRO in 9 patients (17%). Overall, 17 patients (32%) died. In multivariate analysis, MELD score ($p = 0.01$, OR 1.12) and any known MDRO colonization prior to SBP prophylaxis ($p = 0.02$, OR 6.55) were the only independent predictors of mortality. SBP during antibiotic prophylaxis occurred significantly more frequent in patients who acquired new MDROs ($p = 0.02$, OR 18.00).
Conclusion: Our study reveals a substantial risk of de-novo colonization and infection with MDRO during antibiotic prophylaxis

of SBP with fluoroquinolones, which – however – did not adversely affect short-term survival.

SAT-306

The Indication, dosage and duration of proton pump inhibitors in liver cirrhosis

M. De Roza, J.H. Chen. *Singhealth, Department of Gastroenterology and Hepatology, Singapore, Singapore*
Email: marianneanastasia.deroza@mohh.com.sg

Background and Aims: There are increasing concerns about Proton Pump Inhibitor (PPI) use in liver cirrhosis. Yet, it is still widely prescribed in this population and sometimes with no indication. However, PPI users are not well defined and there is little data on the cumulative dosage of PPI in the cirrhotic population. This study aims to review the indication, cumulative dosage and duration of PPI use in liver cirrhosis

Method: Patients admitted to a tertiary hospital with a confirmed diagnosis of liver cirrhosis by histology or transient elastography from January 2016 to June 2017 were identified. Only the following were included: those on follow up with a hepatologist and with complete inpatient records including: Baseline blood tests, previous medical records, medication lists and recent liver imaging. For patients prescribed with PPIs, the indication, dosage and duration were reviewed. We used the cumulative defined daily dose (cDDD) as recommended by the WHO to describe both inpatient and discharge PPI prescriptions and stratified them into 4 groups: cDDD <28 (<1-month use), cDDD 28–56 (1 to 2 months use), cDDD 57–84 (2–3 months use) and cDDD >84 (>3 months use).

Results: A total of 100 patients were included into the study. 32% were female and 68% were male. 46% were Chinese, 35% Malay, 17% Indian and 2% Eurasian. Mean age was 62.6 ± 10.9 years. Hepatitis C was the most common etiology of cirrhosis (25%). 42% of patients were child-pugh B and 41% were child-pugh A. A total of 64 patients were prescribed with PPI of which 37 (57.8%) had unclear or no indication. Of these 64 patients, 42(65.6%) were overprescribed in terms of dose and duration. On discharge, up to 31 (48.4%) were prescribed a cDDD > 3 months of which 16 (51.6%) had unclear or no indication. Interestingly, using logistic regression analysis, those >75 years old (OR-8.22, (1.24–54.78); p = 0.029) and with history of hepatic encephalopathy (OR-7.03, (1.11–44.49); p = 0.038) were more likely to be PPI users after adjustment.

Conclusion: A majority of inpatients with liver cirrhosis are on PPIs of which 57.8% had unclear or no indications and 65.6% were over-prescribed in terms of dose and duration. This continued even on discharge where 48.4% were prescribed 3 months of PPI and 51.6% had no clear indication. PPI users were also more likely to be older and have hepatic encephalopathy at baseline.

SAT-307

The effect of new infection control measures for the prevention of hospital acquired infections in cirrhotic patients

V. Di Gregorio[1], S. Incicco[1], C. Lucidi[1], B. Lattanzi[1], D. D'ambrosio[1], D. Tavano[1], G. Ceccarelli[2], M. Venditti[2], M. Merli[1]. *[1]Sapienza University of Rome, Department of Clinical Medicine, Rome, Italy; [2]Sapienza University of Rome, Department of Infectious Disease, Rome, Italy*
Email: vincenzadg@yahoo.it

Background and Aims: Healthcare-related infections are a matter of great relevance in cirrhosis. The prevalence of multidrug-resistant organisms (MDRO) has dramatically increased worldwide, especially in hospital setting. Although a number of measures used to control the spread of Hospital Acquired Infections (HAIs), especially in intensive care setting (ICS), the relevance of more stringent precautions in cirrhotic patients hospitalized in a non-ICS have not been studied so far. The aim of the study was to evaluate the effects of the introduction of stringent control measures for the prevention of HAIs in cirrhotic patients in a non-ICS.

Method: This is an observational study performed in patients consecutively admitted to our department from 2009. The population was divided into two groups: the first (Group A) includes patients in which "basic practices" were adopted (from 2009 to August 2014); the second (Group B) includes patients in which "additional special approaches" were used. These approaches consist in the reduction of the number of beds per room, the single-site placement of patients with MDRO and the use of dedicated medical instruments, the careful disinfection of the room after discharge of patients with MDRO, the implementation of hand hygiene and positioning within each room of antiseptic gel dispensers.

Results: We enrolled 799 patients, 442 in Group A and 357 in Group B. The two groups were similar for age, (61.4 ± 12.7 vs. 60.6 ± 10.9 yrs, NS), gender (71.5 *vs.* 79.8% males) and severity of liver disease (MELD 13.8 ± 5.5 *vs.* 13.5 ± 5, NS). Group B showed a significantly lower incidence of HAIs (39.1 vs. 28.3%, p = 0.03). Main site of HAIs were similar being urinary tract infections (40.7 *vs.* 26.7%) and pneumonia (21 *vs.* 26.7%) the more frequent. In Group B a trend in reducing MDRO (57.1 *vs.* 36.8%) was observed. At multivariate analysis, the introduction of the "additional special approaches" was selected as a protective factor in the development of HAIs (OR 0.56; 95% CI 0.32–0.8; p = 0.04). As a result, the infection-related mortality was significantly lower in Group B (8.1 *vs.* 2.5; p = 0.05).

Conclusion: Our results underline the need of "additional special approaches" measures for the control of infectious risk to reduce morbidity and mortality in cirrhotic patients hospitalized in non-ICS. The control of HAIs infections may also limit the spread of MDRO infections.

SAT-308

Presepsin, C reactive protein and procalcitonin have similar accuracy for bacterial infection and sepsis in decompensated cirrhosis

P. Fischer[1], C. Grigoras[1], A. Bugariu[2], O. Farcau[1], A. Benea[2], H. Stefanescu[2], I.M. Gabriela[1], S. Pascalau[1], D. Matei[1], D. Ionescu[2], M. Tantau[1], B. Procopet[1]. *[1]University of Medicine and Pharmacy "Iuliu Hatieganu", 3rd Medical Clinic, Gastroenterology Department; [2]Regional Institute of Gastroenterology and Hepatology "O Fodor", Regional Institute of Gastroenterology and Hepatology "O Fodor"*
Email: bogdanprocopet@gmail.com

Background and Aims: Bacterial infections may precipitate decompensation in cirrhosis. Rapid diagnosis for appropriate empiric treatment is essential but frequently patients do not exhibit specific signs of infection. Therefore, surrogate infection markers are needed but validation in cirrhosis is still warranting. Recently, presepsin, the soluble fraction of CD14, has been described as biologic marker for early diagnosis of severe bacterial infections. The aim of the study is to compare presepsin, C relative protein (CRP) and procalcitonin (PCT) as early infection markers in patients with decompensated cirrhosis and their association with 28-days mortality.

Method: 110 consecutive patients (75% males) with decompensated cirrhosis due to alcohol (69%), B or C viral infection (27%) and other (4%) were enrolled. A complete infection workup was performed at admission. CRP, procalcitonin and presepsin levels were measured within the first 6 hours from admission. Patients were followed-up for 28 days. To assess the performance of presepsin, CRP and PCT in diagnosis of bacterial infection and sepsis, receiver operating characteristic (ROC) curves and accuracy were calculated.

Results: Fifty-six (50.4%) patients were infected at admission and among them 24 (43%) had sepsis. The most frequent types of infections were: spontaneous bacterial peritonitis (34%), urinary tract infections and spontaneous bacteremia (18%) and respiratory tract infections (12.5%). Eleven (20%) patients had multiple infections. For diagnosis of infection the AUROCs for presepsin, CRP and PCT were 0.71 (95%CI: 0.62–0.81) (p < 0.001), 0.71 (95%CI: 0.60–0.82) (p = 0.002) and 0.70 (95%CI: 0.60–0.80) (p < 0.001) respectively. For sepsis the AUROCs were superior for all the tests, 0.85 (95%CI: 0.77–0.94) (p

< 0.001) for presepsin, 0.82 (95%CI: 0.71–0.93) (p < 0.001) for CRP and AUROC 0.84 (95%CI: 0.74–0.94) (p < 0.001) for PCT. The recommended cut-offs for presepsin (1000 pg/ml) had 62% accuracy and for PCT (0.5 ng/ml) had 66% accuracy. For CRP the best cut-off in our population was 3.4 mg/dl, with 66.2% accuracy. Combining a high sensitivity cut-off for CRP (2 mg/dl) and high specificity cut-off for presepsin (1000 pg/ml) the accuracy was increased to 72%. During follow-up 26 patients died. Only presepsin and CRP were significantly associated with 28-day mortality.
Conclusion: Presepsin, CRP and PCT have similar diagnostic performances for bacterial infection and sepsis in cirrhosis. Combining presepsin and CRP the accuracy may increase.
This work was supported by a national grant (PN-II-RU-TE-2014-4-0709)

SAT-309
Predictive factors of esophageal varices recurrence after prophylactic endoscopic band ligation
J. Rodrigues[1], S. Fernandes[1], L. Proença[1], M. Sousa[1], J.C. Silva[1], S.A. Leite[1], A.P. Silva[1], T. Freitas[1], J. Carvalho[1]. [1]*Centro Hospitalar Vila Nova de Gaia/Espinho, Gastroenterology, Vila Nova de Gaia, Portugal*
Email: jaimepereirarodrigues@gmail.com

Background and Aims: Eradication of esophageal varices (EV) by endoscopic band ligation (EBL) is an effective variceal bleeding prophylactic therapy. However variceal recurrence following EBL is common and frequently associated with severe outcomes. We aimed to determine the outcome of prophylactic EBL and understand factors related to EV recurrence following successful eradication.
Method: We included all patients with cirrhosis who entered a protocol of EBL between 2010 and 2015, for primary or secondary variceal bleeding prophylaxis, with ≥24-month follow-up. EBL was regularly performed until EV were eradicated, then at 3 and 9 months and thereafter annually. Eradication was defined as absence of EV or identification of small EV with no EBL indication. Recurrence corresponded to large EV with additional EBL need or variceal bleeding, in patients with previous successful variceal eradication. Demographic, clinical, analytical and technical data were collected.
Results: 101 patients were selected, 75.2% (n = 76) male, mean age = 57.2 ± 10.9 years. Child-Pugh class distribution was A (52.5%, n = 53), B (41.6%, n = 42) and C (6.0%, n = 6). MELD ranged between 6 and 27 (mean 12.3 ± 4.2). Mean follow-up was 45.8 ± 21.5 months. Mortality rate was 50.5% (n = 51), 38.6% (n = 39) directly related to cirrhosis complications. Successful eradication of EV was achieved in 89.1% (n = 90) of patients, with 2.8 ± 1.6 endoscopic sessions and 13.7 ± 8.6 total bands applied over 17.0 ± 14.5 weeks. Recurrence rate was 61.1% (n = 55), including 5.6% (n = 5) variceal rebleeding episodes. Recurrence occurred 16.9 ± 16.4 months after eradication. Concomitant non-selective beta-blocker therapy (≥40 mg propranolol or carvedilol) reduced recurrence rate (p = 0.017). Variceal bleeding *stigmata* (p = 0.023), portal hypertensive gastropathy (p = 0.031), interbanding interval ≥6 weeks (p = 0.023) and higher total number of bands used (p = 0.017) were associated with recurrence. On multivariate analysis adjusted for age, gender, MELD, primary/secondary prophylaxis and cirrhosis etiology, beta-blocker therapy was independently associated with less recurrence (OR = 3.72; 95%CI: 1.09–15.54). Variceal bleeding *stigmata* (OR = 9.94; 95%CI: 1.74–56.93) and a higher number of bands necessary for eradication (OR = 1.13; 95%CI: 1.02–1.25) were independently associated with recurrence (r^2 = 0.45).
Conclusion: EBL was an effective therapy for EV eradication however recurrence was high (61.1%). Concomitant beta-blocker therapy diminished recurrence rate. Variceal bleeding *stigmata* at index endoscopy and a higher need of bands for eradication predicted higher recurrence.

SAT-310
A study evaluating outcomes of cirrhotic patients managed in a dedicated liver cirrhosis clinic and factors influencing survival
D. Kockerling[1], R. Nathwani[1], S. Balarajah[1], P. Manousou[1], H. Antoniades[1], A. Dhar[1]. [1]*St. Mary's Hospital, Hepatology, London, United Kingdom*
Email: rooshi_n@hotmail.com

Background and Aims: Liver cirrhosis results in increased morbidity and mortality and treating patients in a dedicated cirrhosis clinic may improve outcomes. The aim of this study was to demonstrate whether survival was improved by managing cirrhotics in a specialist clinic and factors that influenced survival, admission and infection rates in this patient cohort.
Method: A retrospective analysis was performed on patients attending specialist cirrhosis clinics, in a UK based university teaching hospital between November 2015 and March 2017. Data was collected for demographic details, aetiology of disease, biochemical and clinical parameters and pharmacological agents at baseline, 6-months and 12-months from clinic attendance to evaluate factors influencing survival. One-year mortality was stratified by Childs-Pugh (CP) grade and compared to historical published values.
Results: 174 patients were eligible for analysis (M:F;114:60). Alcohol-related cirrhosis was the commonest aetiology (80/174;46%). 149/174 (86%) patients survived at one-year post attendance to clinic. 25/174 (14%) died. One-year mortality was significantly lower than predicted values in CPC patients (n = 30; 33.3% vs 55.0%, 95% CI 17.3–52.8%). No significant difference was observed for CPA (n = 73;2.7% vs 5.0%) and CPB (n = 71;18.3% *vs.* 20.0%) patients. In CPB and CPC patients (n = 101) univariate analysis demonstrated increased survival with rifaximin (survivors *vs.* non-survivors: 42/78 *vs.* 6/23; p = 0.03) and Non-Selective Beta-Blockers (NSBB) use (survivors *vs.* non-survivors: 55/78 *vs.* 10/23; p = 0.02). Of these, on restricted multivariate analysis only NSBB demonstrated significant survival benefit (p = 0.018; OR 3.5). On univariate analysis NSBB use resulted in a significant reduction in incidence of infection (p = 0.03) and a reduction in admission rates in (p = 0.04) in CPB patients alone. Rifaximin use was associated with a borderline reduction in incidence of infection (p = 0.05).
Conclusion: Managing patients in a dedicated cirrhosis clinic improves survival in CPC patients when compared to historical published values. Admission and infection rates and survival were positively influenced by the use of NSBB. Rifaximin use was associated with a borderline reduction in incidence of infection. Further studies are required to delineate the mechanisms of these effects.

SAT-311
Frialty is an independent predictive factor of hospital admissions and falls in patients with cirrhosis
E. Roman[1,2,3], M. Parramon[4], M. Flavià[5], C. Gely[6], M. Poca[7,8], R. Santesmases[1,2], E. Hernández[1,2], J.C. Nieto[9], E. Urgell[10], E. Alvarado[11], S. Vidal[9], V.M.V. Blasco[12], C. Guarner[2,11,13], G. Soriano[2,11,13]. [1]*School of Nursing EUI-Sant Pau;* [2]*Universitat Autònoma de Barcelona;* [3]*Hospital de la Santa Creu i Sant Pau;* [4]*CAP Passeig de Maragall, Barcelona, Spain;* [5]*Hospital Universitari Vall d'Hebron, Department of Internal Medicine-Hepatology, Barcelona, Spain;* [6]*Institut de Recerca Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [7]*Hospital de la Santa Creu i Sant Pau, Department of Gastroenterology, Barcelona, Spain;* [8]*Instituto de Salud Carlos III, Majadahonda, Spain;* [9]*Hospital de la Santa Creu i Sant Pau, Department of Immunology;* [10]*Hospital de la Santa Creu i Sant Pau, Department of Biochemistry;* [11]*Hospital de la Santa Creu i Sant Pau, Department of Gastroenterology;* [12]*Hospital Universitari Vall d'Hebron, Department of Internal Medicine-Hepatology;* [13]*Instituto de Salud Carlos III*
Email: eroman@santpau.cat

Background and Aims: Frailty associated with chronic diseases could have important consequences on the prognosis of patients with

cirrhosis. The aim was to analyze the prevalence and characteristics of frailty, and its prognostic value to predict hospital admissions, falls and mortality in patients with cirrhosis.
Method: Outpatients with cirrhosis and primary care non-cirrhotic controls matched by age and gender were included. Patients with MELD >25, hepatocellular carcinoma, overt or covert hepatic encephalopathy (Psychometric Hepatic Encephalopathy Score [PHES] <−4), or active alcohol intake (<3 months) were excluded. Frailty was defined according to the five Fried's criteria (unintentional weight loss, reduced handgrip strength, slow walking speed, self-reported exhaustion, and low physical activity): frail ≥3 criteria, pre-frail 1–2 criteria, and robust 0 criteria. In addition to the Fried index, other parameters of frailty were evaluated in patients with cirrhosis (risk of falls, cognitive function, biomarkers), and their ability to predict hospital admissions, falls and mortality.
Results: One hundred and thirty-five patients with cirrhosis (age 62.7 ± 8.8, 72% men and MELD 9.4 ± 2.9) and 135 controls were included. The prevalence of frailty was higher among patients with cirrhosis: 37 (27.4%) frail, 72 (53.3%) pre-frail and 26 (19.2%) robust *vs* 14 (10.4%) frail, 67 (49.6%) pre-frail and 54 (40%) robust in the control group ($p < 0.001$), mainly due to decreased muscle strength in cirrhotic patients. During 2-year follow-up, frail patients with cirrhosis showed a higher incidence of hospital admissions and falls compared to pre-frail and robust cirrhotic patients (35%, 13.9% and 3.8%, p = 0.001, and 18.9%, 8.3% and 3.8%, p = 0.04, respectively), with similar mortality. MELD score (HR 1.232, 95%CI 1.095–1.387, p = 0.001) and frailty (HR 2.453, 95%CI 1.050–5.732, p = 0.03) were independent predictive factors of hospital admissions, and frailty for falls (HR 3.199, 95%CI 1.075–9.513, p = 0.03). Among biomarkers, vitamin D deficiency (p = 0.02) and the increase in cystatin (p = 0.007) were associated with frailty.
Conclusion: Frailty is more frequent in patients with cirrhosis than in controls, mainly due to decrease in muscle strength, and is an independent predictive factor of hospitalization and falls in these patients. Detection of frailty and pre-frailty in cirrhotic patients will allow the implementation of preventive measures to reduce hospital admissions and falls.

SAT-312
Cardiac assessment in children with chronic liver disease: cholestatic and non-cholestatic

T.Y.A. Ghaffar[1,2], W.A.I. Ahmed[2], W.M.E. Guindy[2], M. Moafy[2], S.M.M. Hassan[1]. [1]*Yassin Abdel Ghaffar charity center for liver disease and research, Cairo;* [2]*Ain Shams University, pediatric department, Cairo, Egypt*
Email: tyghaffar@gmail.com

Background and Aims: Chronic liver disease (CLD) may affect cardiac performance. We aimed to study the effects of CLD on cardiac electrical activity, structure and function in children.
Method: 32 patients (20 males & 16 females; mean age = 7.39 years) with various causes of CLD (free from any primary cardiac disease) and 15 age and sex matched controls were studied. For all, blood pressure (BP) was measured and: ECG, 2D, M-mode and Doppler echocardiography were done. Patients were divided into 2 groups: cholestatic (C) (n = 16) and non-cholestatic (NC) (n = 16).
Results: The median Z score of systolic BP (−0.01), diastolic BP (−0.11) and mean BP (0.122) was not significantly different from controls. There was no significant difference between C verses NC patients as well.
40.6% of CLD children had a prolonged QTc (mean = 0.44 sec). C had a prolonged QTc than NC (62.5% v 18.8%, mean = 0.46 sec ± 0.06 v 0.42 sec ± 0.04, p = 0.034). Cardiac geometry was normal in 37.5% of CLD children. Concentric hypertrophy was more common in C (18.8% v 6.3%).
CLD patients compared to controls showed cardiac functional and structural derangement on 2D echo with statistically higher pulmonary arterial pressure (28.3 mmHg + 8; p = 0.000) and left ventricle mass index (79 g/m2 + 35; p = 0.00), with no statistical difference between C and NC. Yet compared to controls, C children showed impaired diastolic filling properties (mean E/A ratio 2.4 v 1.5; p = 0.001), as well as LV structural changes (p < 0.05 for (mean values): LV mass (70.3 v 46.4 g), LVMI (86 v 37 g/m2), relative wall thickness (0.49 v 0.31 cm), interventricular septal thickness dimension (0.68 v 0.6 cm) and LV posterior wall in diastole (0.7 cm v 0.6 cm)). Compared to controls, a hyperdynamic status evidenced by higher mean values of FS% (40 v 33%; p = 0.001), stroke volume (50 v 39 ml; p = 0.025) & cardiac output (5 v 3.6 L/min; p = 0.023) was found in C but not NC children.
Child score correlated positively with QTc interval (r = 0.403, p = 0.022) and cardiac index (r = 0.49, p = 0.004), while the duration of the cholestatic disease correlated positively with structural abnormalities: end diastolic volume (r = 0.299, p = 0.028), left ventricle internal diastolic diameter (r = 0.274, p = 0.037), LVM (r = 0.23, p = 0.035) and LVMI (r = 0.094, p = 0.001).
Conclusion: CLD affects cardiac performance in children. C children are specifically liable to QTc prolongation, structural changes, hyperdynamic status, and diastolic dysfunction.

SAT-313
Non-invasive predictors of varices in non-cirrhotic portal hypertension

M. Cunningham, G.P. Chehr, O. Cerocchi, D. Wong, K. Patel. *University Health Network, Centre for Liver Disease, Toronto, Canada*
Email: morven_c@hotmail.com

Background and Aims: Non-cirrhotic portal hypertension (NCPH) comprises a heterogenous group of liver disorders causing portal hypertension in the absence of cirrhosis, and carries a high risk of variceal bleeding. Recent guidelines, based largely on patients with viral cirrhosis, suggest that a combination of liver stiffness measurement and platelet count can predict low risk of clinically significant varices and select patients in whom screening gastroscopy can be deferred. In NCPH, LSM is often higher than healthy controls but lower than matched cirrhotic patients. LSM correlates with early portal hypertension in cirrhosis, but data in NCPH are lacking. The aim of this study was to assess whether LSM or other non-invasive assessments of portal hypertension could be used to predict varices in patients with NCPH.
Method: Records of patients with NCPH seen at a single centre between 2007 and 2017 were reviewed retrospectively. Outcome measures were presence or absence of varices at screening gastroscopy and history of variceal bleed. As well as LSM, platelet count/spleen length ratio (PSL) and liver stiffness-spleen length/platelet count ratio (LSP) were calculated for each patient. The association of these variables with presence of varices or on history of variceal bleed was analysed by univariate and multivariate analyses.
Results: 51 patients with NCPH were identified. 73% (37/51) had varices on most recent screening gastroscopy and 27% (14/51) had a history of variceal bleeding. There were no significant differences in age, BMI, liver biopsy fibrosis stage (all F0-3, n = 36), MELD, Childs-Pugh, FIB4 or APRI between those with and without varices. On univariate analysis, spleen size (17.8 ± 3.7 vs 13.8 ± 3.7 cm, p = 0.002), platelet count (95 ± 55 vs 124 ± 47 x10^9/L, p = 0.046), PSL (5.24 ± 3.34 vs 10.38 ± 6.26, p = 0.003) and LSP (3.08 ± 3.89 vs 1.18 ± 0.98, p = 0.018) correlated with presence of varices but LSM alone did not. No variable correlated with variceal bleeding. In a multivariate model, LSP was an independent variable associated with the presence of varices in this cohort (β = 2.22, p = 0.02; OR 9.23, 95% CI 1.4–60.7).
Conclusion: In patients with NCPH, LSM alone does not help to differentiate between patients with and without varices but combining LSM with spleen size and platelet count does predict the presence of varices. LSP warrants further evaluation as a non-invasive tool to identify patients with NCPH at low risk of varices who could defer gastroscopy.

SAT-314

Impact of adrenal dysfunction on psoas muscle thickness assessed by computed tomography in patients with liver cirrhosis

G. Privitera[1], L. Spadaro[2], D. Russo[3], S. Marchisello[3], F. Purrello[3].
[1]*University of Catania, Department of Clinical and Experimental Medicine, Catania, Italy;* [2]*University of Catania, Department of Clinical and Experimental Medicine, Catania, Italy;* [3]*University of Catania, Department of Clinical and Experimental Medicine, Catania, Italy*
Email: graziella.privi@gmail.com

Background and Aims: Sarcopenia is a feature of cirrhosis and contributes to mortality, but its pathogenesis is still poorly understood. Adrenal insufficiency (AI) is also common in cirrhosis. Nausea and weight loss are common symptoms of AI and could contribute to muscle waste. Therefore, the aim of our study was to evaluate the role of adrenal dysfunction on psoas muscle thickness assessed by CT scan in a cohort of cirrhotic patients.
Method: A study population of 74 cirrhotic patients was examined. Laboratory parameters of malnutrition (albumin, pre-albumin, transferrin and lymphocytes count) were assessed in all patients. Axial (APMT) and Transversal psoas muscle thickness (TPMT) were measured on a computed tomography (CT) image at the level of the umbilicus. Psoas muscle thickness was normalized to stature by division by height (APMT/h and TPMT/h). Adrenal function was assessed using the Standard-Dose short synacthen test. Normal adrenal response was defined as a peak cortisol >18 µg/dl.
Results: A significant reduction of TPMT values was observed in female compared to male (23.5 ± 6 vs 31 ± 8; p = 0.002), while no significant correlation was found between the radiologic parameters of sarcopenia and the severity and etiology of liver disease. Indeed, when we stratified our population according to the presence of ascites, we observed a significant reduction of APMT and APMT/h values in patients with ascites (37 ± 5 vs 43 ± 7; p = 0.02 and 23 ± 3 vs 26 ± 4; p = 0.02 respectively). In contrast TPMT and TPMT/h were not influenced by the presence of ascites. Adrenal insufficiency was present in 23 patients. The severity of cirrhosis graded by Child and MELD score was significantly increased in patients with AI compared to normal adrenal function (NAF) patients (p = 0.001). AI patients exhibited lower values of pre-albumin (6 ± 3 vs 10 ± 8 mg/dl; p = 0.03) and transferrin (150 ± 84 vs 220 ± 76 mg/dl; p = 0.003) compared to NAF independently to Child class. In contrast, cirrhotic patients with AI showed increased levels of both APMT (44 ± 6 vs 20 ± 5; p = 0.02) and TPMT (32 ± 8 vs 27 ± 7; p = 0.03) compared to NAF. A significant correlation was found between TPMT/h and peak cortisol (r = 0.38; p = 0.01).
Conclusion: Our data suggest that AI is associated with biochemical parameters of malnutrition but does not contribute to sarcopenia. Cortisol is one of the most important catabolic hormone, and its deficiency seems to play a protective role on muscle waste in cirrhotic patients.

SAT-315

Drug-induced encephalopathy in cirrhotic patients with neurological symptoms: A metabolomic study

N. Weiss[1], P.B.S. Hilaire[2], A. Schaefer[1], M. Rudler[1], S. Mouri[1], F. Sedel[3], F. Fenaille[2], B. Colsch[2], C. Junot[2], D. Thabut[1]. [1]*La Pitie Salpetriere University Hospital, Brain Liver Pitie Salpetriere Study Group, France;* [2]*CEA, CEA, iBiTec-S, Service de Pharmacologie et d'Immunoanalyse, Laboratoire d'Etude du Métabolisme des Médicaments, MetaboHUB-Paris, France;* [3]*Medday Pharmaceuticals, PARIS, France*
Email: nicolas.weiss@aphp.fr

Background and Aims: Encephalopathy is a classical complication of liver disease and/or portosystemic shunts. Its pathophysiology is not completely elucidated; mechanisms include the role of elevated ammonia levels in association with systemic inflammation. An impairment of blood-brain barrier (BBB) permeability is also hypothetised. Metabolomics enables to detect a wide range of metabolites without any a priori. In a recent metabolomic study including patients who underwent cerebrospinal fluid (CSF) collection, our group outlined that xenobiotics/drugs that usually don't cross BBB were retrieved in the CSF, suggesting a potential neurological toxicity of drugs. CSF collection is invasive. Hence, we aimed to describe the xenobiotics present in the plasma of cirrhotic patients, using the same metabolomic approach.
Method: We conducted a retrospective study of plasma samples in the Hepatological ICU. Plasma samples from cirrhotic patients displaying encephalopathy were compared to plasma from cirrhotic patients without neurological symptoms, and to plasma from healthy controls. Liquid chromatography coupled to high-resolution mass spectrometry was performed and thenafter the metabolic fingerprints were compared to database and between the different groups.
Results: Plasma samples were obtained from 12 cirrhotic patients with encephalopathy (age 59 [40–68], MELD 20 [16–31], alcohol 58%), 13 cirrhotic patients without encephalopathy (age 56 [55–64], MELD 17 [14–29], alcohol 38%) and 9 healthy controls. Among 495 identified metabolites, 25 corresponded to xenobiotics or its derivatives. Fluoxetine was detected with a more than 200-fold increase, aminosalicylic acid with a more than 10-fold increase and benzyl alcohol (present in cough pills and antiseptics) with a 3 fold increase in cirrhotic patients with encephalopathy as compared to cirrhotic patients. In cirrhotic patients with or without encephalopathy, propranolol was detected with a more than 8500-fold increase, acetaminophen with a 40-fold increase, penicillamine and ampicillin both with a 2 fold increase as compared to healthy controls. Interestingly, several substances which were not expected to have systemic diffusion were detected in cirrhotic patients and in healthy controls: eugenol, isoeugenol (used in mouth bathing solution), triethanolamine (trolamin, used in cutaneous creams) and resorcinol monoacetate (used in mouth bathing solution and in cutaneous creams).
Conclusion: Cirrhotic patients, especially those with neurological symptoms, display dramatically increased levels of several xenobiotics in plasma. These results confirm that PK/PD parameters of commonly used drugs are highly modified in those patients. This suggests a potential role of xenobiotics in the pathophysiology of encephalopathy in patients with liver diseases.

SAT-316

Endoscopic radiofrequency ablation for the treatment of gastric antral vascular ectasia in cirrhotic patients: A bi-centric clinical and economical cost-effective analysis

M. Senzolo[1], S. Realdon[2], B. Simoncin[1], A. Zanetto[1], S. Caronna[3], G.M. Saracco[4], C. De Angelis[3], W. Debernardi-Venon[5]. [1]*Multivisceral Transplant Unit, Surgery, Oncology and Gastroenterology, Padova, Italy;* [2]*Digestive Endoscopy Unit, Veneto Institute of Oncology IOV, Padova, Italy;* [3]*Gastroenterology and Hepatology Unit, Città della Salute e della Scienza, Turin, Italy;* [4]*Gastroenterology Unit, Department of Medical Sciences, AOU Città della Salute e della Scienza di Torino, University of Turin, Torino, Italy;* [5]*Gastro-Hepatology Unit, San Giovanni Battista Hospital, University of Turin, Italy*
Email: marcosenzolo@hotmail.com

Background and Aims: Gastric Antral Vascular Ectasia (GAVE) represents a rare, but clinically significant cause of GI bleeding and transfusion dependent chronic anaemia in cirrhotic patients. In approximately one third of cases it is refractory to argon plasma (APC) treatment and radiofrequency ablation (RFA) have been described to be potentially useful in heterogeneous cohorts of patients. To prospectively evaluate the safety and efficacy of RFA for the treatment of GAVE in cirrhotic patients with severe transfusion dependent anaemia (including patients without APC response) as well as to compare the cost and the advantage of the RFA treatment.
Method: cirrhotic patients with GAVE, recurrent GI bleeding and/or severe chronic anemia were enrolled at Padua and Turin University Hospital Gastroenterology Units. RFA treatment was performed by HALO90ULTRA – Ablation System. All the clinical data (levels of

haemoglobin, number of transfusions, need of re-treatment), the GAVE endoscopic grade and the GI bleeding related hospitalizations were collected over a 6 months follow-up. An economic cost-effective analysis was also performed in the same interval time.
Results: 25 patients (mean age 70 years; 50% Child B) were enrolled. Eighty-four per cent (21/25) of them didn't respond to conventional APC. RFA obtained eradication of GAVE in 100% and 13/25 patients received 2 sessions. During the 6 months of follow up, median Hb increased from 8 ± 0.7 g/dL to 11 ± 1 g/dL ($p < 0.001$) and most of patients (15/25) were free from transfusion. After RF therapy, there was a significant reduction in the median number of red blood cells transfusion (25 ± 14 to 1 ± 1.7; $p < 0.001$) as well as a significant reduction in GI bleeding related hospitalizations (1.6 ± 0.4 to 0.3 ± 0.1; $p < 0.001$). The economic analysis showed a significant reduction of total cost (€ 13.933 to € 6.233), packed red blood related cost (€ 10.048 vs € 2448) and hospitalizations for GI bleeding related cost (€ 3407 vs € 648), after RFA procedure.
Conclusion: RFA is safe and effective procedure for cirrhotic patients with GAVE, in particular if refractory to APC. Although the cost of RF is high, cost analysis shows a significant overall economic savings. RF could be considered as a first line treatment in severe form of GAVE in cirrhotics.

SAT-317
Avatrombopag decreases need for platelet transfusion in patients chronic liver disease and thrombocytopenia undergoing medical procedures with low to high associated bleeding risks

N.S. Reau[1], S. Sammy[2], L.F. Allen[3], K. Aggarwal[4], M. Vredenburg[3], W.R. Kim[5]. [1]*Rush University;* [2]*UCLA;* [3]*Dova Pharmaceuticals;* [4]*Dova Pharmaceuticals, Durham, United Kingdom;* [5]*Stanford, United States*
Email: kaggarwal@dova.com

Background and Aims: Thrombocytopenia (TCP) is common in patients with chronic liver disease (CLD). Because of the associated bleeding risks, patients may require prophylactic platelet transfusions before invasive procedures. Avatrombopag (AVA) is an oral thrombopoietin receptor agonist being developed as an alternative to platelet transfusions. Two randomized, double-blind, placebo (PBO)-controlled Phase 3 trials evaluated the efficacy of AVA to increase platelet counts (PC) and reduce platelet transfusions in patients with TCP and CLD undergoing scheduled procedures.
Method: Two randomized, double-blind, placebo (PBO)-controlled Phase 3 trials (ADAPT-1 and ADAPT-2) enrolled adults with CLD and PC < 50×10^9/L, scheduled to undergo a procedure. Patients were divided into 2 cohorts by baseline PC (**Cohort 1**- <40×10^9/L; **Cohort 2**- 40 to <50×10^9/L) and were randomized 2:1 to once-daily oral AVA (**Cohort 1**- 60 mg; **Cohort 2**- 40 mg) or PBO for 5 days, with the procedure scheduled 5 to 8 days after the last dose. Patients were stratified by procedure bleeding risk (low, moderate, high). The primary efficacy endpoint was the proportion of patients not requiring platelet transfusion or any bleeding rescue procedure up to 7 days post-procedure.
Results: Overall, 435 patients were randomized. The primary endpoint was met by 66.9% of AVA-treated vs 28.6% of PBO-treated in **Cohort 1** ($p < 0.0001$), and 88.0% of AVA-treated vs 35.8% of PBO-treated patients in **Cohort 2** ($p < 0.0001$). The proportion of patients across all the pooled treatment groups in each bleeding risk category was: 60.8% in the low, 17.2% in the moderate, and 22.1% in the high bleeding risk categories, and was balanced across treatment groups. The primary efficacy endpoints in the low, moderate, and high risk of bleeding categories all favored AVA and were consistent with the overall study results. A positive AVA treatment effect was noted across the various bleeding risk subgroups in both **Cohort 1** (AVA vs PBO: low risk- 78.1% vs 45.8%, moderate risk- 61.9% vs 17.6%, and high risk- 55.9% vs 6.7%, respectively), and **Cohort 2** (AVA vs PBO: low risk- 92.4% vs 34.2%, moderate risk- 90.0% vs 50.0%, and high risk- 88.9% vs 35.7%, respectively).
Conclusion: Subgroup analyses indicated that neither the type of procedure nor associated bleeding risk impacted the superiority of AVA to PBO in increasing PC and reducing platelet transfusions in patients with TCP and CLD undergoing a medical procedure.

SAT-318
Efficacy of avatrombopag compared with placebo across various mean baseline platelet count subgroups- pooled data from 2 Phase 3 studies

S. Sammy[1], N. Alkhouri[2], L.F. Allen[3], K. Aggarwal[3], M. Vredenburg[3], W. Tian[3], N. Terrault[4]. [1]*UCLA;* [2]*Texas Liver Institute;* [3]*Dova Pharmaceuticals;* [4]*UCSF*
Email: kaggarwal@dova.com

Background and Aims: Thrombocytopenia (TCP) is common in patients with chronic liver disease (CLD), increasing in severity with worsening liver disease. TCP presents a significant challenge in these patients who require multiple invasive procedures. Prophylactic platelet transfusions to reduce bleeding risk expose patients to the safety risks associated with transfusions. Avatrombopag (AVA) is an oral thrombopoietin receptor agonist that has completed Phase 3 development as an alternative to platelet transfusions. This analysis evaluated the efficacy of AVA in increasing platelet count (PC) in various subgroups based on their pre-treatment PC at Baseline.
Method: Two randomized, double-blind, placebo (PBO)-controlled Phase 3 trials (ADAPT-1 and ADAPT-2) enrolled adults with CLD and PC <50×10^9/L scheduled to undergo a procedure. Patients were randomized 2:1 to AVA or PBO and dosed orally for 5 days based on Baseline PC. Those with PC <40×10^9/L received 60 mg AVA and those with PC 40 to <50×10^9/L received 40 mg AVA; Procedure Day was scheduled 5 to 8 days after the last dose (Day 10 to 13). For analysis, patients were pooled by treatment group and then divided into subgroups by Baseline PC. The mean change in PC from Baseline to Procedure Day was a pre-defined secondary efficacy endpoint.
Results: In a preliminary analysis (Table 1), AVA was shown to increase Baseline PC 1.6 to 2.3-fold across all Baseline PC subgroups with the mean change in PC ranging from ~10 to 41 × 10^9/L, and larger AVA-induced increase in the 20 to <30, 30 to <40; and 40 to <50×10^9/L Baseline PC subgroups. There were few patients enrolled in the 10 to <20×10^9 Baseline PC subgroup, limiting the interpretation, and the smaller change in PC may have resulted from bone marrow toxicity or suppression, increased platelet destruction and/or splenic sequestration.

Table 1: Mean Change in Platelet Count from Baseline to Procedure Day

	Avatrombopag		Placebo	
Baseline Platelet Count Group ($x10^9$/L)	Number of Subjects n	Mean Change from Baseline n (+/–SD) $x10^9$/L	Number of Subjects n	Mean Change from Baseline n (+/–SD) $x10^9$/L
10 to <20*	9	9.6 (10.0)	6	–0.2 (2.2)
20 to <30*	41	33.2 (25.8)	23	–0.6 (5.4)
30 to <40*	106	33.1 (24.7)	61	3.1 (9.3)
40 to <50**	113	41.1 (30.7)	64	3.7 (12.6)

*60 mg AVA;
**40 mg AVA

Conclusion: Administration of AVA to patients with TCP and CLD resulted in measured increases in PC across the various Baseline PC subgroups.

SAT-319

Consistent efficacy of avatrombopag compared to placebo in patients with thrombocytopenia and chronic liver disease undergoing procedures across various disease severities and etiologies

S. Sammy[1], L.F. Allen[2], K. Aggarwal[3], M. Vredenburg[2], N. Terrault[4].
[1]*UCLA;* [2]*Dova Pharmaceuticals;* [3]*Dova Pharmaceuticals, Dova Pharmaceuticals, Durham, United States;* [4]*UCSF*
Email: kaggarwal@dova.com

Background and Aims: Thrombocytopenia (TCP) is common in patients with chronic liver disease (CLD) and known to increase in severity with worsening liver disease. It presents a significant challenge in the management of these patients who require multiple invasive procedures. Avatrombopag (AVA) is an oral thrombopoietin receptor agonist being developed as an alternative to platelet transfusions. This analysis evaluated the efficacy of AVA compared to placebo (PBO) in increasing platelet counts (PC) and reducing the need for platelet transfusion in patients with TCP and CLD undergoing scheduled procedures based on Baseline MELD score, CTP score, and liver disease etiologies.
Method: Two randomized, double-blind, placebo (PBO)-controlled Phase 3 trials (ADAPT-1 and ADAPT-2) enrolled adults with CLD and PC $<50 \times 10^9$/L who were scheduled to undergo a procedure. Patients were divided into 2 cohorts by Baseline PC (Cohort 1- PC $<40 \times 10^9$/L; Cohort 2- PC 40 to $<50 \times 10^9$/L) and randomized 2:1 to receive once-daily oral AVA (Cohort 1- 60 mg; Cohort 2- 40 mg) or PBO for 5 days, with Procedure Day scheduled 5 to 8 days after the last dose. The primary efficacy endpoint was the proportion of patients not requiring platelet transfusion or any bleeding rescue procedure up to 7 days post-procedure; subgroup analyses were done based on MELD, CTP, and liver disease etiology.
Results: Overall, 435 patients were randomized. AVA was superior to placebo with 66.9% of AVA-treated patients vs 28.6% of PBO-treated patients in Cohort 1 meeting the primary efficacy endpoint ($p < 0.0001$), and in Cohort 2, 88.0% of AVA-treated patients vs 35.8% PBO-treated patients ($p < 0.0001$). In a combined cohort analysis (Figure 1), consistently more AVA-treated patients met the primary efficacy endpoint compared with PBO-treated patients across the various Baseline MELD, CTP and disease etiology subgroups. As expected, subgroups with the smallest number of subjects had wide confidence intervals, e.g., CTP Grade C and Nonalcoholic Steatohepatitis and Other disease etiologies, although the point estimates of the treatment difference remained positive in favor of AVA-treated patients.

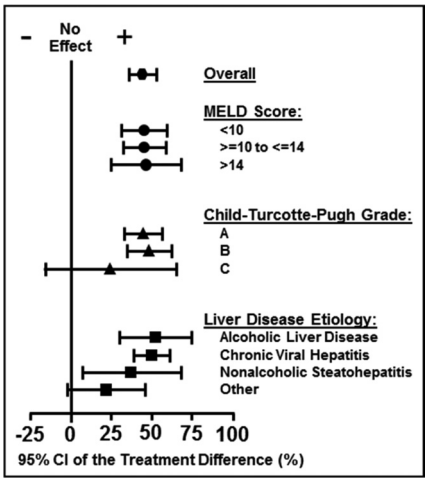


Figure 1: Proportion of Subjects Not Requiring a Platelet Transfusion or Rescue Procedure for Bleeding Results: Across Subgroups in the Combined Baseline Platelet Count Cohorts - Pooled Phase 3 ADAPT-1 & ADAPT-2 Studies

Conclusion: Baseline liver disease severity or etiology did not impact the efficacy of AVA in increasing PC or reducing platelet transfusions in patients with TCP and CLD scheduled for a procedure compared with PBO.

SAT-320

Rifaximin ameliorates hepatic encephalopathy and endotoxemia without affecting the gut microbiome diversity

H. Takaya, K. Kaji, S. Saikawa, M. Furukawa, S. Sato, Y. Sawada, H. Kawaratani, M. Kitade, K. Moriya, T. Namisaki, T. Akahane, A. Mitoro, H. Yoshiji. *Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan*
Email: htky@naramed-u.ac.jp

Background and Aims: Hepatic encephalopathy (HE) is characterized by deficits in cognitive, psychiatric, and motor function and ranges in severity from minimal to overt HE and coma. Rifaximin is used for standard treatment of HE, targeting reduction of ammonia and gut bacterial translocation. We examined the efficacy of rifaximin for HE with the linkage of endotoxin activity and gut microbiome in patients with decompensated cirrhosis.
Method: Twenty patients (12 men and 8 women; median age, 66.8 years; range, 46–81 years) with decompensated cirrhosis (Child-pugh score >7) underwent cognitive neuropsychological testing, endotoxin analysis, and fecal microbiome assessment at baseline and after 4 weeks of treatment with rifaximin 400 mg thrice a day. Changes in cognition, endotoxin, and microbiome were analyzed by the number connection test (NCT)-A, endotoxin activity assay, and 16S ribosome RNA gene sequencing, respectively. HE was determined by serum ammonia level and NCT-A.
Results: Treatment with rifaximin for 4 weeks improved hyperammonemia (from 90.6 ± 23.9 [mean ± SD] to 73.1 ± 33.1 μg/dL; $p < 0.05$) and time required for NCT-A (from 68.2 ± 17.4 to 54.9 ± 20.3 sec; $p < 0.05$) in patients who had higher levels at baseline. Endotoxin activity was reduced (from 0.43 ± 0.03 to 0.32 ± 0.09; $p < 0.05$) in direct correlation with decrease in serum ammonia levels ($r = 0.5886$, $p < 0.05$). No statistically significant differences were observed in the diversity estimator and major components of the gut microbiome between the baseline and after treatment groups (Shannon diversity index:3.948 ± 0.548 at baseline vs. 3.980 ± 0.968 after treatment; $p = 0.544$), but the relative abundances of genus Veillonella and Streptococcus were lowered.
Conclusion: Rifaximin significantly improved cognition and reduced endotoxin activity without significantly affecting the composition of the gut microbiome in patients with decompensated cirrhosis.

SAT-321

Sustained long-term improvement in clinical and cognitive outcomes after fecal microbiota transplantation in cirrhosis

J.S. Bajaj[1], A. Fagan[1], D. Heuman[1], E. Gavis[1], M. Fuchs[1], B. John[1], Z. Kassam[2], M. Sikaroodi[3], P. Gillevet[3]. [1]*Virginia Commonwealth University and McGuire VAMC, Richmond, United States;* [2]*OpenBiome, Boston, United States;* [3]*George Mason University, Manassas, United States*
Email: jasmohan.bajaj@vcuhealth.org

Background and Aims: In a randomized clinical trial (RCT), fecal microbial transplantation (FMT) prevented short-term hospitalizations and improved brain function in cirrhotic patients with hepatic encephalopathy (HE). However, the long-term consequences of FMT in this population are unclear. We aimed to determine the long-term (>1 year) impact of FMT on cognition, hospitalizations and HE episodes.
Method: In a previously described RCT, HE patients on rifaximin were randomized to pre-treatment broad-spectrum antibiotics and FMT or standard of care (SOC) with follow-up at month 6. Cognitive function was tested at baseline, day 5 and 20 with Psychometric hepatic encephalopathy score (PHES; higher score indicates good cognition) and EncephalApp (low score indicates good cognition). Subsequently, we followed participants who were alive and without liver transplant

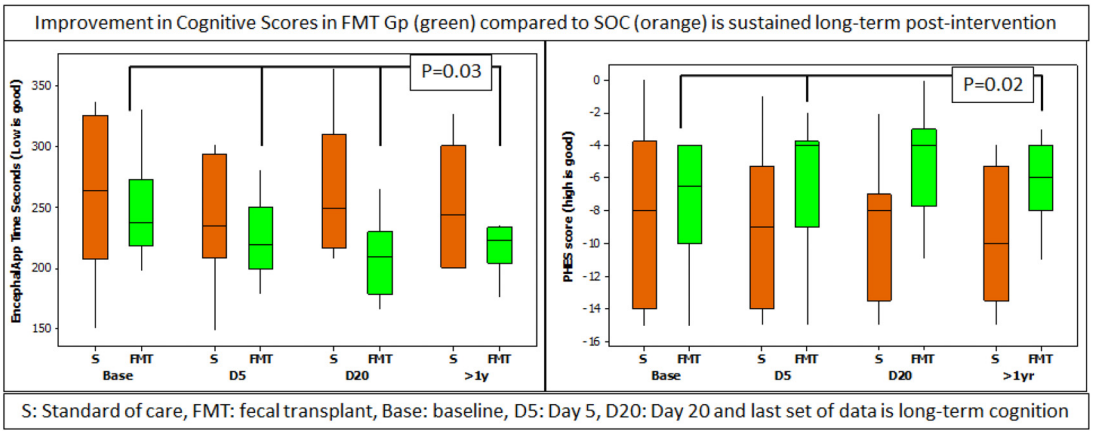


Figure: (abstract: SAT-321)

for 6 additional months (total 1 year after randomization) and assessed cognitive function and hepatic outcomes.
Results: 20 HE subjects (mean age: 58 years, 20 males, mean MELD 12.5) were randomized 1:1 into the FMT or SOC arm, and the RCT demonstrated that FMT reduced hospitalizations and HE episodes over 6 months and improved PHES and EncephalApp scores at day 20. *Long-term clinical outcomes*: One year after randomization, 1 participant in FMT arm (end-stage organ failures unrelated to FMT) and 3 in SOC arm died or underwent liver transplant. There was no related SAE in the FMT arm. Overall, there were persistently higher HE episodes/hospitalizations in SOC arm compared to FMT arm ($p = 0.02$) (Table), while MELD score was similar statistically. *Long-term cognitive outcomes*: The FMT arm showed sustained, statistically significant improvement post-FMT compared to baseline and SOC (Figure).

Long-term outcomes (>1 year)	FMT arm	SOC arm	P-value
MELD score delta	2.8 ± 4.5	2.78 ± 4.7	0.9
Hospitalizations	0 (0–1.50)	3 (0.75–5.75)	0.02
HE episodes	0 (0–1.00)	1.5 (0.75–2.75)	0.05
Death/liver transplant	3	1	0.4

Conclusion: FMT is associated with long-term improvements in hospitalizations, HE episodes and cognitive performance in patients with HE compared to standard of care.

Viral hepatitis A/E: Clinical aspects

SAT-325
High mortality rate in HBV-related cirrhosis patients with HEV superinfection

T.-C. Tseng[1], C.-J. Liu[1], T.-H. Su[1], W. Yang[2], C.-L. Chen[3], H.-C. Yang[1], C.-H. Liu[1], P.-J. Chen[1], D.-S. Chen[4], J.-H. Kao[1]. *[1]National Taiwan University Hospital, Division of Gastroenterology, Department of Internal Medicine, Taipei, Taiwan; [2]National Taiwan University Hospital, Hepatitis Research Center, Taipei, Taiwan; [3]National Taiwan University College of Medicine, Graduate Institute of Clinical Medicine, Taipei, Taiwan; [4]Academia Sinica, Taiwan, Genomics Research Center, Taipei, Taiwan*
Email: cjliu@ntu.edu.tw

Background and Aims: Hepatitis E virus (HEV) infection causes acute hepatitis, which is usually a self-limiting disease. However, it is unclear whether superinfection with HEV is associated with worse prognosis in patients with chronic hepatitis B virus (HBV) infection.
Method: A total of 2123 Taiwanese HBV patients who were negative for IgG-HEV at baseline were enrolled. IgG-HEV seroconversion was used to define HEV infection. We explored whether IgG-HEV seroconversion was associated with liver-related mortality in HBV patients after a long-term follow-up.
Results: With a mean follow-up of 12.08 years, there were 46 patients experienced IgG-HEV seroconversion and the annual incidence was 0.18%. Patients with HEV exposure had a higher liver-related mortality than those without, and the adjusted hazard ratio was 4.39 (95% confidence interval: 1.33–14.46). To be noted, 2 of 4 compensated liver cirrhosis patients (50%) had liver-related mortality within 3 months after IgG-HEV seroconversion. In contrast, only 1 of 42 non-cirrhotic IgG-HEV seroconverters (2.3%) had liver-related mortality after HEV exposure. Thus pre-existing liver cirrhosis was significantly associated with liver-related mortality in HBV patients with HEV superinfection ($p < 0.001$).
Conclusion: Superinfection with HEV is not rare in Taiwanese HBV patients, and may cause liver-related mortality in those with liver cirrhosis.

SAT-326
Clinical features and outcomes of hepatitis E in patients with underlying chronic liver disease: a respective case-control study

Y. Wang[1], H. Tang[1], C. Yang[1], Q. Pan[2], J. Zhao[1]. *[1]302 hospital, Department of Pathology and Hepatology, Beijing, China; [2]Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: yijinwang927015@163.com

Background and Aims: Although hepatitis E virus (HEV) infection generally causes acute and self-limiting disease, fulminant hepatitis are frequently reported in HEV patients with underlying chronic liver disease (CLD). However, the differences of clinical features upon HEV infection in individuals with or without existing chronic liver disease haven't been comprehensively understood. This study aims to investigate the clinical symptoms, manifestations and outcomes of HEV infection in presence or absence of CLD.
Method: From January 2015 to October 2017, 124 patients diagnosed with solely HEV infection and 103 patients diagnosed with HEV infection combining pre-existing CLD, including chronic hepatitis B, C, alcoholic liver disease, moderate/severe fatty liver and cirrhosis by presence of anti-HEV immunoglobulin (Ig) M, were enrolled. Epidemiological and clinical features were collected. Chi-squared or Fisher's exact tests were performed to compare proportions. The results based on two-sided tests and $p < 0.05$ was defined as statistically significant.

Results: Analysis of total 227 patients with positive anti-HEV IgM showed an overall high median age (54 years) and overwhelming proportion of males (189/227, 83%). Compared with patients of solely HEV infection, HEV infected patients with pre-existing CLD were more commonly to present abdominal pain/distension (35.92% vs. 20.97%, p = 0.017), but less likely to present nausea/vomiting (63.11% vs. 78.23%, p = 0.013). Higher level of procalcitonin (0.91 ± 0.92 μg/l vs 0.61 ± 0.52 μg/l; p = 0.047) and alkaline phosphatase (ALP) (205.54 ± 97.78U/l vs 176.20 ± 63.41U/l; p = 0.005) were demonstrated to associate with solely HEV infection than CLD combined HEV infection. While the presence of anti-HEV IgM in CLD patients had higher proportion of seroperitoneum (37.86% vs. 20.97%, p = 0.005), pleural effusion (17.48% vs. 4.84%, p = 0.002) and peritonitis (14.56% vs. 4.84%, p = 0.02). In addition, HEV patients with pre-existing CLD were more likely to develop liver failure (22.33% vs. 12.1%, p = 0.049) and shock (3.88% vs. 0.81%, p = 0.263).

Table 1: Characteristics in HEV patients with or without CLD

Characteristic	HEV infection with CLD (n = 103) No. (%)	HEV infection alone (n = 124) No. (%)	p value
Abdominal pain/distension	37 (35.92%)	26 (20.97%)	0.017
Nausea/vomiting	65 (63.11%)	97 (78.23%)	0.013
Electrolyte disturbance	44 (42.72%)	40 (32.26%)	0.129
Seroperitoneum	39 (37.86%)	26 (20.97%)	0.005
Pleural effusion	18 (17.48%)	6 (4.84%)	0.002
Peritonitis	15 (14.56%)	6 (4.84%)	0.02
Anemia	28 (27.18%)	26 (20.97%)	0.348
Shock	4 (3.88%)	1 (0.81%)	0.263
Liver failure	23 (22.33%)	15 (12.1%)	0.049

Conclusion: HEV infection in absence of pre-existing CLD presented typical clinical symptoms of acute hepatitis. However, HEV infection with underlying CLD showed more clinical manifestations and severe outcomes than HEV infection alone.

SAT-327

Risk factors of hepatitis E related liver failure: a restrospective case-control study

Y. Wang[1], H. Liu[1], Q. Pan[2], J. Zhao[1]. *[1]302 hospital, Department of Pathology and Hepatology, Beijing, China; [2]Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: yijinwang927015@163.com

Background and Aims: Hepatitis E virus (HEV) is one of the most common causes of non-chronic liver failure (NCLF) in developing countries. However, the risk factors for HEV patients developing liver failure have not been comprehensively investigated. The aim of this study was to understand the risk factors of HEV complicating with ALF.
Methods: 62 patients diagnosed with HEV who developed to NCLF (acute/subacute/acute-on-chronic liver failure) and 210 non-NCLF HEV infected patients as control were enrolled from November 2011 through September 2017. Clinical index and epidemiological records were analyzed. Differences were tested using Student's t test for continuous measures, and Chi-square or Fisher's exact test for categorical measures. The results based on two-sided tests and $P < 0.05$ was defined as statistically significant.
Results: Median age of HEV infected patients with or without NCLF were 54.55 ± 9.33 years vs 52.87 ± 13.58 years (p = 0.360), respectively. Development of NCLF upon HEV infection were more common in male (98.39% vs 79.52%; p < 0.001). Compared with solely HEV infected patients, HEV complicating NCLF presented a lower level of γ-glutamyltransferase (GGT) (123.36 ± 105.97U/l vs 236.91 ± 299.93U/l; p < 0.001), and prealbumin (PA) (50.93 ± 34.41 mg/l vs 99.04 ± 64.38 mg/l; p < 0.001), choline esterase (3450.25 ± 1471.04U/l vs 4925.83 ± 1958.22U/l; p < 0.001), leucine aminopeptidase (87.17 ± 25.95 U/L vs 104.15 ± 47.50U/l; p < 0.001), triglyceride (1.79 ± 0.72 mmol/l vs 2.36 ± 1.16 mmol/l; p < 0.001), low density lipoprotein cholesterol (1.92 ± 0.59 mmol/l vs 2.80 ± 1.13 mmol/l; p < 0.001) and γ1-globulin (3.56 ± 0.94 vs 4.88 ± 1.01, p < 0.001). While a higher value of aspartate aminotransferase (AST) (679.70 ± 1018.39U/l vs 394.07 ± 475.03U/l; p = 0.038), lactate dehydrogenase (317.23 ± 220.59U/l vs 252.89 ± 115.27U/l; p = 0.040) and alpha-fetoprotein (114.96 ± 201.01 ng/ml vs 54.43 ± 111.32ng/ml; p = 0.029) were significantly associated with NCLF development in HEV infected patients. Furthermore, a multivariate logistic regression model was constructed to identify independent risk factors of NCLF due to HEV. HEV infected patients with underlying chronic liver disease (CLD) (odds ratio, 2.640; 95%CI, 1.254, 5.559), including alcoholic liver disease, cirrhosis, hepatitis B virus (HBV) and autoimmune liver disease, high level of AST (odds ratio, 1.002; 95%CI, 1.001,1.003), lower level of GGT (odds ratio, 0.994; 95%CI, 0.990,0.998), low level of PA (odds ratio, 0.985; 95%CI, 0.973,0.997) were more likely to associate with NCLF. Furthermore, of the 62 HEV related NCLF patients, there is no difference between the improvement rate of NCLF in patients with or without underlying CLD (63.63% vs 66.67%, p = 1.000).
Conclusions: HEV infected patients with male gender, underlying CLD, higher level of AST, lower level of GGT and lower level of PA are more likely to develop non-chronic liver failure.

SAT-328

The role of hepatitis E in acute non-traumatic neuropathy in China: a prospective case-control study

Y. Wang[1], S. Wang[1], Y. Jiang[1], J. Wu[2], H. Liu[1], Q. Pan[3], J. Zhao[1]. *[1]302 Hospital, Department of Pathology and Hepatology, Beijing, China; [2]First People's Hospital, Yancheng, Department of Laboratory, Yancheng, China; [3]Erasmus MC-University Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: yijinwang927015@163.com

Background and Aims: Neurological complications have been increasingly reported in hepatitis E virus (HEV) infected patients in western countries and mainly due to genotype 3 HEV. Whether other genotypes of HEV are also related to neurological injury is largely unknown. The aim of this study is to determine the frequency of hepatitis E in patients with acute non-traumatic neurological disorder in China, where genotype 4 HEV is prevalent.
Method: From September through November 2017, 765 patients consecutively diagnosed with acute non-traumatic neurological injury, including posterior circulation ischemia (n = 210), cerebral infarction (n = 171), stroke (n = 133), neurodegenerative diseases (n = 108), central nervous system infections (n = 31), and others (n = 112) were enrolled, matched with 1,171 healthy controls. Serum samples were collected for testing anti-HEV immunoglobulin (Ig) M and IgG by ELISA. Subjects with detectable anti-HEV IgM were also tested for HEV RNA. All patients' demographic and clinical data are documented. Differences were tested using Student's t test for continuous measures, and Chi-square or Fisher's exact test for categorical measures. The results based on two-sided tests and $P < 0.05$ was defined as statistically significant.
Results: Anti-HEV IgM were positive in only 1 encephalitis (0.13%) of the neurological injured patients, and 8 (0.68%) in healthy controls. The 1 patient and 4 of the 8 controls with positive anti-HEV IgM were also positive for anti-HEV IgG. Overall, 290 of the 764 patients (37.96%) and 409 of the 1163 controls (35.2%) without anti-HEV IgM were detectable for anti-HEV IgG. Further study in our patients' cohort revealed that anti-HEV IgG positivity was more common in male (181/290, 62.41% vs 109/290, 37.59%, p = 0.006) and older patients (67.17 ± 12.65 vs 64.03 ± 13.69, p = 0.002). Of note, stratification analysis showed that central nervous system infections were less likely to be in patients with detectable anti-HEV IgG, compared with of ant-HEV IgG negative patients, although not statistically significant (2.41%, 7/290 vs 4.85%, 23/474, p = 0.124).

Table 1: Features of non-traumatic neurological injury patients with detectable versus undetectable anti-HEV IgG at enrollment

	HEV IgG+ (n = 290)	HEV IgG– (n = 474)	t	χ^2	p Value
Age, years	67.17 ± 2.65	64.03 ± 13.69	3.163		0.002
Sex					
Male	62.41%	52.11%		7.754	0.006
Female	37.59%	47.89%			
Posterior circulation ischemia	29.66%	26.16%		1.103	0.317
Cerebral infarction	23.10%	21.94%		0.140	0.721
Stroke	17.59%	17.30%		0.010	0.922
Neurodegenerative diseases	13.45%	14.56%		0.182	0.748
Central nervous system infections	2.41%	4.85%		2.807	0.124
Other diseases	13.79%	15.19%		0.281	0.601

Conclusion: Non-traumatic neurological injury is rarely associated with current/recent HEV infection in China. Past exposure to HEV seems a protective factor for central nervous system infections.

SAT-329

Clinical impact, morbidity and mortality of Hepatitis E at tertiary referral centres in central Europe

J. Hartl[1], P. Behrendt[2], M. Cornberg[2], K. Deterding[2], D. Westhölter[3], M. Luetgehetmann[4,5], A. Lohse[3], M.P. Manns[2], S. Pischke[3], H. Wedemeyer[2]. *[1]University Hospital Hamburg-Eppendorf (UKE), First Medial Centre, Hamburg, Germany; [2]Hannover Medical School, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [3]University Hospital Hamburg-Eppendorf (UKE), First Medical Centre, Hamburg, Germany; [4]University Hospital Hamburg-Eppendorf (UKE), Microbiology and Virology, Hamburg, Germany; [5]university Hospital Hamburg-Eppendorf (UKE), Microbiology and Virology, Hamburg*
Email: j.hartl@uke.de

Background and Aims: It has become increasingly evident that infection with the hepatitis E virus (HEV) is a frequent cause of viral hepatitis in Europe. Nevertheless, HEV-infections are mainly considered as a self-limiting and benign, however, this might not hold true for patient-groups treated at tertiary centres with comorbidities and immunosuppressive medications.
Methods: This retrospective study was conducted at two major tertiary referral hospitals and transplant-centres in Northern Germany. Medical charts of all consecutive patients were reviewed testing positive for HEV-RNA in serum between May 2011 and June 2017 were reviewed.
Results: In total, 150 HEV-RNA positive patients were identified. The vast majority (92%) had a locally-acquired HEV-infection and more than half of the patients were immunocompromised (54%).
53% of the immune-competent individuals with autochthonous HEV-infection were treated as inpatients (53%), which resulted in a total of 74 hospital days. 77% of patients had ALT values of >10x the upper limit of normal (ULN) and 20% presented with jaundice. Nine patients had a pre-existing liver disease, including 4 patients presenting with severe hepatitis (ALT > 1200U/l, INR > 1.2) and two with a fulminant course of hepatitis (INR > 2.5; ALT > 6635U/l). Both patients developed acute-on-chronic liver failure with jaundice, ascites and hepatic encephalopathy. Liver transplantation was not feasible due to infectious complications and both patients died.
In immunocompromised individuals, HEV-infection took a chronic course in 32/81 patients (40%), even though anti-viral treatment with ribavirin had been initiated in 17 patients within 2 months after diagnosis. Overall, 50/81 patients (61%) received treatment with ribavirin, which led to viral clearance in 42/50 (82%) after a median treatment time of 133 days (range 35–295). Eight (10%) immunosuppressed individuals died within 5 years after diagnosis of HEV-infection including three fatal outcomes being related to HEV infection.
Conclusions: HEV-infection is associated with significant morbidity and even mortality in patients treated at tertiary centres in central Europe. Severe courses of HEV infection are not limited to immunocompromised individuals. Hepatitis E should be considered as differential diagnosis in patients with acute-on-chronic liver failure.

SAT-330

Dynamics of HBsAg clearance in a UK cohort of chronic HBV infection

L. Downs[1], M. Patel[2], M.A. Ansari[3], A. Mcnaughton[3], M. Andersson[1], E. Barnes[2,3], K. Jeffery[1], P. Matthews[1,3]. *[1]Oxford University Hospitals NHS Foundation Trust, Department of Infectious Diseases and Microbiology, Oxford, United Kingdom; [2]Oxford University Hospitals NHS Foundation Trust, Department of Hepatology, Oxford, United Kingdom; [3]University of Oxford, Nuffield Department of Medicine, Oxford, United Kingdom*
Email: p.matthews@doctors.org.uk

Background and Aims: Hepatitis B surface antigen (HBsAg) has recently gained traction as a biomarker that may provide prognostic information and inform treatment decisions in chronic hepatitis B virus (HBV) infection. It may be particularly useful when HBV DNA levels are low and therefore difficult to quantify accurately, either as a result of treatment or natural immune control of the virus. There are few published descriptions of the kinetics of HBV clearance, and most existing data come from Asia. We therefore set out to identify adults who cleared HBsAg in a UK cohort, to characterise those who clear, and to describe the dynamics of HBsAg clearance.
Methods: Our cohort was collected from the records of a large UK teaching hospital that provides >1 million patient contacts per year. We measured serum HBsAg levels using the semi-quantitative Abbott Architect i2000SR, and HBV DNA levels using the Cobas taqman assay (Roche). We identified individuals with HBV infection confirmed between 2011 and 2016 (n = 442), but in whom HBsAg levels fell consistently (serial decline and two or more consecutive readings <1000 IU/ml) or became completely undetectable.
Results: HBsAg clearance occurred in 21 of 442 individuals (4.8%), and a further 43 (9.7%) progressed towards HBsAg clearance but did not clear completely during the time period under review (total n = 64). In this group of 64, the median age was 46 years (IQR 37–56), and males predominated (39/64, 61%). The majority were HBeAg negative (61/64, 95%) and had HBV DNA <20 IU/ml (42/64, 66%). The majority of patients were treatment naïve (45/64, 70%). In individuals with an elastography score recorded, most were <10 kPa (45/50, 90%). In this clearance phase, there was no correlation between HBsAg and HBV DNA viral load (p = 0.4). For individuals starting with HBsAg ≥1000 IU/ml, the median time to clearance was 46 months (IQR 29–58 months) (Figure). There was no difference in time to clearance between patients on and off treatment (p = 0.6).
Conclusions: The majority of clearance events occurred in untreated patients, suggesting an underlying immunological mechanism. In the longer term, developing a robust understanding of the interplay between host and virus that leads to HBsAg clearance could provide insights into natural immunological control, and therefore underpin new approaches to immunotherapy. Developing insights into the use of HBsAg as a biomarker could be influential in informing prognosis and treatment of HBV, particularly in resource-limited settings in which HBV DNA measurements are not accessible.

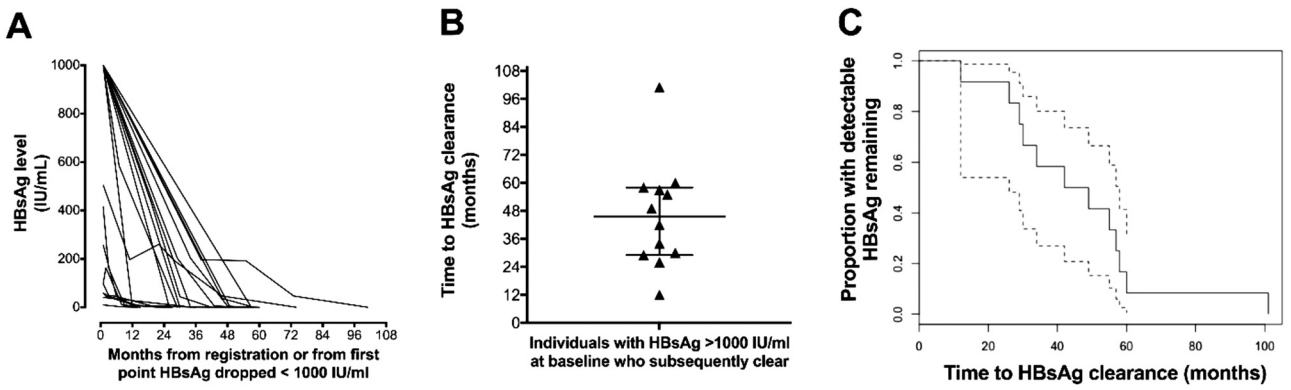


Figure: (abstract: SAT-330): Trends in HBsAg clearance. A: Longitudinal decline in HBsAg levels in 21 adults who cleared infection. B: Time taken to clear HBsAg in 12 individuals who started with HBsAg > 1000IU/ml (median and 95%CI in solid lines). C: Kaplan-Meier curve showing loss of HBsAg over time (95% CI in dashed lines).

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Blood products as source of HEV transmission? 1-year experience with routine HEV screening at a tertiary center

T. Horvatits[1], D. Westhölter[1], J. Hiller[2], U. Denzer[2], P. Sven[2], S. Polywka[3], A. Lohse[1], S. Pischke[1], M. Luetgehmann[3]. *[1]University Medical Center Hamburg-Eppendorf, Internal Medicine, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Transfusion Medicine, Hamburg, Germany; [3]University Medical Center Hamburg-Eppendorf, Microbiology, Hamburg, Germany*
Email: t.horvatits@uke.de

Background and Aims: Hepatitis E virus (HEV) infection has become a relevant topic with increasing attention. Routine HEV testing of blood products has recently been implemented in Great-Britain and the Netherlands. The relevance of bloodborne HEV-transmission is still controversially discussed in numerous countries. Hereby we report an update of our experience at a tertiary center in Germany covering one year routine HEV testing of blood products.
Methods: From 10/2016 onwards all blood donors at the University Hospital Hamburg-Eppendorf were routinely screened for HEV RNA by PCR using the Roche cobas 6800® (LLOD single: 19 IU/ml, 24 pool: 456 IU/ml). Pools of 24 donations were tested, whereas reactive pools were tested individually to identify HEV RNA positive donors. HEV RNA positive blood products were not transfused. HEV-PCR positive donors and a control cohort (n = 256) were asked to answer a questionnaire.
Results: We identified 0.1% (30/28981) HEV-RNA-positive donors with a median viral load of 960 IU/ml. Only three of them (10%) presented with increased serum transaminases at time of donation (ALT: 83U/l, 192U/l and 101U/l). Retrospective analysis of all HEV-positive donors revealed that four donors (asymptomatic infection) had been HEV-viraemic for up to three months and the longest duration of HEV-viraemia exceeded four months. Despite the HEV testing efforts, 2 cases of clinical relevant blood borne hepatitis E occurred. Out of those one recipient developed fatal acute-on-chronic liver failure complicated by pseudomonas septicemia. The questionnaire revealed that HEV-viraemic donors significantly more often consumed raw pork meat (12/19; 63%) than controls (89/256, 35%, p < 0.01). In two donors undercooked pork liver dishes were identified as the source of infection.
Conclusions: Incidence of HEV RNA in asymptomatic blood donors in our cohort is higher than previously reported although most donors have low viral load. Since prolonged viraemia (more than 3 months) can be observed, a single HEV-positive blood donor can cause HEV infections in several patients with possible fatal clinical outcome. Uncooked or undercooked pork meat is a relevant risk factor for HEV infection.

SAT-332

Poor outcome of acute hepatitis E in liver cirrhosis and transplant recipients

M.R. Barciela[1,2], A. Barreira[1], M. Bermúdez[3], J. Llaneras[4], E. Mena[4], S. Romero[4], M.V. Cots[4], F. Sanpedro[4], M.B. Ferret[1,2], R. Esteban[1,2]. *[1]Hospital Universitari Vall de Hebrón, Liver Unit, Department of Internal Medicine; [2]CIBERehd; [3]Hospital Universitari Vall de Hebrón, Gastroenterology Department; [4]Hospital Universitari Vall de Hebrón, Emergency department*
Email: mar.riveiro@gmail.com

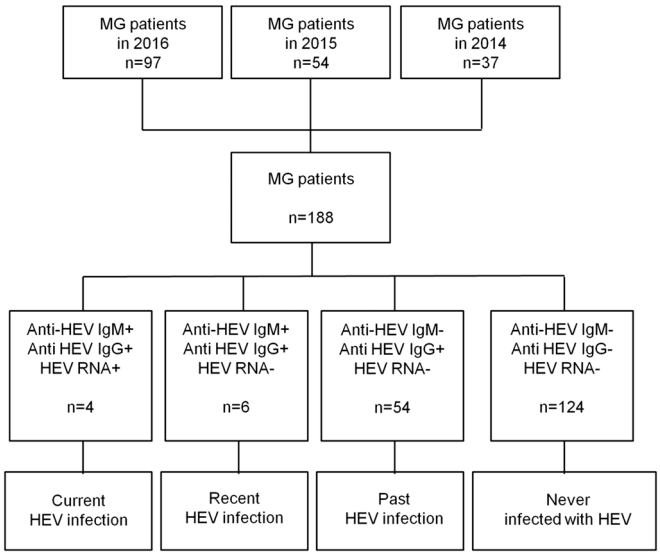
Background and Aims: Acute hepatitis E (AHE) is the most common cause of acute viral hepatitis in some Western countries, though there is scarce data concerning the outcome and associated complications.
Method: Prospective study including all consecutive AHE in subjects aged over 16 years attended at our hospital from October 2014 to October 2017. Diagnosis of AHE was based on the presence of positive HEV Ig M and abnormal liver function tests (ALT > 5xULN).
Results: 239 cases of acute hepatitis were recorded during the 3 years period. 60 (25%) were AHE: 53% female, median age 52 years (IQR 38–71). 15 (25%) were undergoing immunosuppressant therapy, 7 (12%) were transplant recipients and 6 (10%) with liver cirrhosis (1 HBV, 2 HCV, 3 alcohol). Epidemiology of AHE: 13% subjects lived in rural areas, 13% usually eat raw or undercooked meat or game meat, 7% had received blood products during the previous 3 months, 5% had travelled to an endemic HEV area within the previous year. At diagnosis of AHE 40 (67%) patients presented mild symptoms and 19 (32%) jaundice. Baseline median ALT value was 443 IU/ml (IQR 238–840), platelets 217 × 10E9/ml (IQR150–268) and albumin 3.9mg/dl (3.4–4.3). HEV RNA was carried out in 29 (48%) cases of AHE and it was positive in 9 (31%). HEV RNA remained positive more than 1 month in 5 (17%) cases and infection became chronic (positive HEV RNA for more than 6 months) in 3/7 (43%) transplant recipients with AHE. Previous solid organ transplant was the only factor associated with chronic hepatitis E (OR 1.9, p < 0.001). 6 (10%) presented extrahepatic manifestations associated with AHE: 1 neuralgic amyotrophy, 1 red cell aplasia, 4 thrombocytopenia.
3 (5%) subjects died. Mortality rate was higher in patients with liver cirrhosis (33% vs 2%, p = 0.025) due to the development of acute-on-chronic liver failure. The only dependent factor associated with higher mortality rate was platelet count <150 × 10E9/ml (OR 1.7, p = 0.001), regardless of the presence of liver cirrhosis.
Conclusion: Acute hepatitis E presented a high risk of chronic infection development in transplant patients and high mortality rate in patients with cirrhosis or low platelets account.

SAT-333

Preceding hepatitis E virus infection in patients with myasthenia gravis

L. Wang, L. Wang. *Peking University Health Science Center, Microbiology and Infectious Disease Center, Beijing, China*
Email: lingwang@bjmu.edu.cn

Background and Aims: Hepatitis E virus (HEV) is the commonest cause of acute viral hepatitis worldwide. HEV infection is associated with a broad spectrum of neurological injuries. Recently, one study described an immunocompetent woman suffered with muscle-specific kinase (MuSK) antibody–positive myasthenia gravis (MG) as a complication of acute HEV infection. However, this potential relationship between HEV and MG patients has not been systematically investigated in a larger MG patient cohort.
Methods: MG patients seen within the Department of Neurology of Peking University First Hospital between Jan. 2014 and Dec. 2016 were enrolled. A total number of 188 patients fulfilled the study criteria of a definitive MG diagnosis and serum samples being available at the time of diagnosis. All samples were tested for the presence of anti-HEV IgM and IgG using commercial EIA assays (Wantai, Beijing), according to the manufacturer's instructions. Nested reverse transcriptase polymerase chain reaction (RT-nPCR) was performed to detect HEV genome in all samples.
Results: Demographic analysis showed that 51.1% (96/188) of the patients were male and 48.9% (92/188) were female. The median onset age of the study cohort was 51 years, but ranged from 1 to 85. When assessing possible acute HEV infection preceding MG, positive anti-HEV IgM was found in 10 patients (~5%, 10/188). Anti-HEV IgG was detected in 64 patients (34%, 64/188). The 10 anti-HEV IgM-positive patients were all anti-HEV IgG-positive (Figure). Four of the anti-HEV IgM-positive samples (2.1%, 4/188) were also positive for HEV RNA (Figure). Phylogenetic analysis showed that the four HEV isolates were genotype 4. Of the 10 patients who had a current/recent HEV infection (HEV+), six were male and four female. They had a median age of 51, and ranged from 22 to 79. Their maximum Myasthenia Gravis Foundation of America Grade was obtained and compared to HEV- MG patients but this revealed no statistically significant difference. There was also no statistical difference between HEV+ and HEV- patients regarding age at onset, sex, MG antibodies and preceding thymic hyperplasia. However, HEV+ MG patients did have a significantly higher rate of preceding thymoma than HEV- MG patients (40.0% versus 9.6%, p = 0.02).



Conclusions: The current study, conducted on a large well-defined cohort of Chinese patients with MG, indicates that approximately 5% of the patients have acute HEV infection at the start of their neurological illness. HEV viraemia was detected in 4/188 MG patients (2.1%, 1:47), a prevalence that is at least 20 times greater than that reported for Chinese blood donors (0.09%, 1:1094). In addition, the four HEV strains detected were all HEV-4 and closely related to strains isolated from swine in China. Additional studies conducted in other geographical areas are warranted and patients with MG should be screened for HEV infection.

SAT-334

Hepatitis A affecting men having sex with men: ongoing outbreak in Israel, December 2016–September 2017

Y. Gozlan[1], I. Bar-Or[1], A. Rakovsky[1], M. Savion[2], N. Cider[3], E. Mendelson[1], Z.B. Ari[4], O. Mor[1]. *[1]Chaim Sheba Medical Center, Central Virology Laboratory, Ramat Gan, Israel; [2]Ministry of Health, Tel Aviv, Israel; [3]Ministry of Health, Jerusalem, Israel; [4]Sheba Medical Center at Tel Hashomer, Center of Liver Diseases, Tel Aviv, Israel*
Email: orna.mor@sheba.health.gov.il

Background and Aims: Since June 2016, a hepatitis A virus (HAV) outbreak mainly affecting men having sex with men (MSM) in multiple European countries has been reported. The first cases in Israel were identified at the end of December 2016, despite infant HAV vaccination program implemented since 1999, which have brought to a 90% decline in disease incidence. Here, we report the clinical and environmental surveillance of the current ongoing HAV outbreak, spanning January 2017–September 2017.
Methods: Blood samples from acute viral hepatitis cases (HAV immunoglobulin M positive) and 113 sewage samples, collected monthly from 14 facilities around the country, were analyzed. Total nucleic acids were extracted with NucliSENS EasyMag (bioMérieu, France). Real-time PCR (RT-PCR) and sequencing of the VP1-2a region were performed according to national protocols. Phylogenetic analysis included the current three 1a European outbreak strains (RIVM_HAV16-90 (EUROPRIDE), VRD_521_2016 (UK/SPAIN) and V16-25801_VP1). Demographic and clinical information from all affected cases was also collected.
Results: Reports of 56 HAV infections were filed in the study period, affecting patients with median age of 34 (range 15–62). Among these, 94.6% (53/56) were male, 29 of whom were self-identified as MSM, of whom 86.5% (25/29) were from the Tel Aviv area. Only 22.7% (5/22) of those identified as non-MSM were from the Tel Aviv area. Information on HAV vaccination was available for 43 of the patients; most (93%, 40/43) were unvaccinated. In parallel, HAV positivity was measured in 20.4% (23/113) of all sewage samples, with a high prevalence (70%, 16/23) in facilities in the Tel-Aviv area. The rate of HAV-positive samples increased between Q1 2017 (8.1%, 3/37) and Q3 2017 (28.9%, 11/38) (Figure 1a). Most (94.2%) HAV-positive clinical samples and all sewage-derived HAV sequences clustered with RIVM_HAV16-90 (EUROPRIDE) or VRD_521_2016 (UK/SPAIN) 1a subtypes (Figure 1b).
Conclusions: These observations confirm an ongoing HAV 1a outbreak in Israel. In addition, the parallel seen between sewage and clinical results, demonstrates the value of enviormomental sampling in disease surveillance. As all clinical cases occurred in individuals older than 24 years of age, and many of the infections were in the MSM population, this study further demonstrates that despite efficient vaccination program, HAV can still be transmitted to the unvaccinated, high-risk population.

SAT-335

Incidence of hepatitis E infection in renal transplant patients in The Netherlands

R. Erken, S. Willemse, M. Sinnige, H. Reesink, F. Bemelman, H. Zaaijer. *Academic Medical Center, Hepatology, Amsterdam, Netherlands*
Email: h.w.reesink@amc.uva.nl

Background and Aims: Hepatitis E virus (HEV) infection is a major cause of hepatitis worldwide. HEV genotype (gt) 1 and 2 are endemic

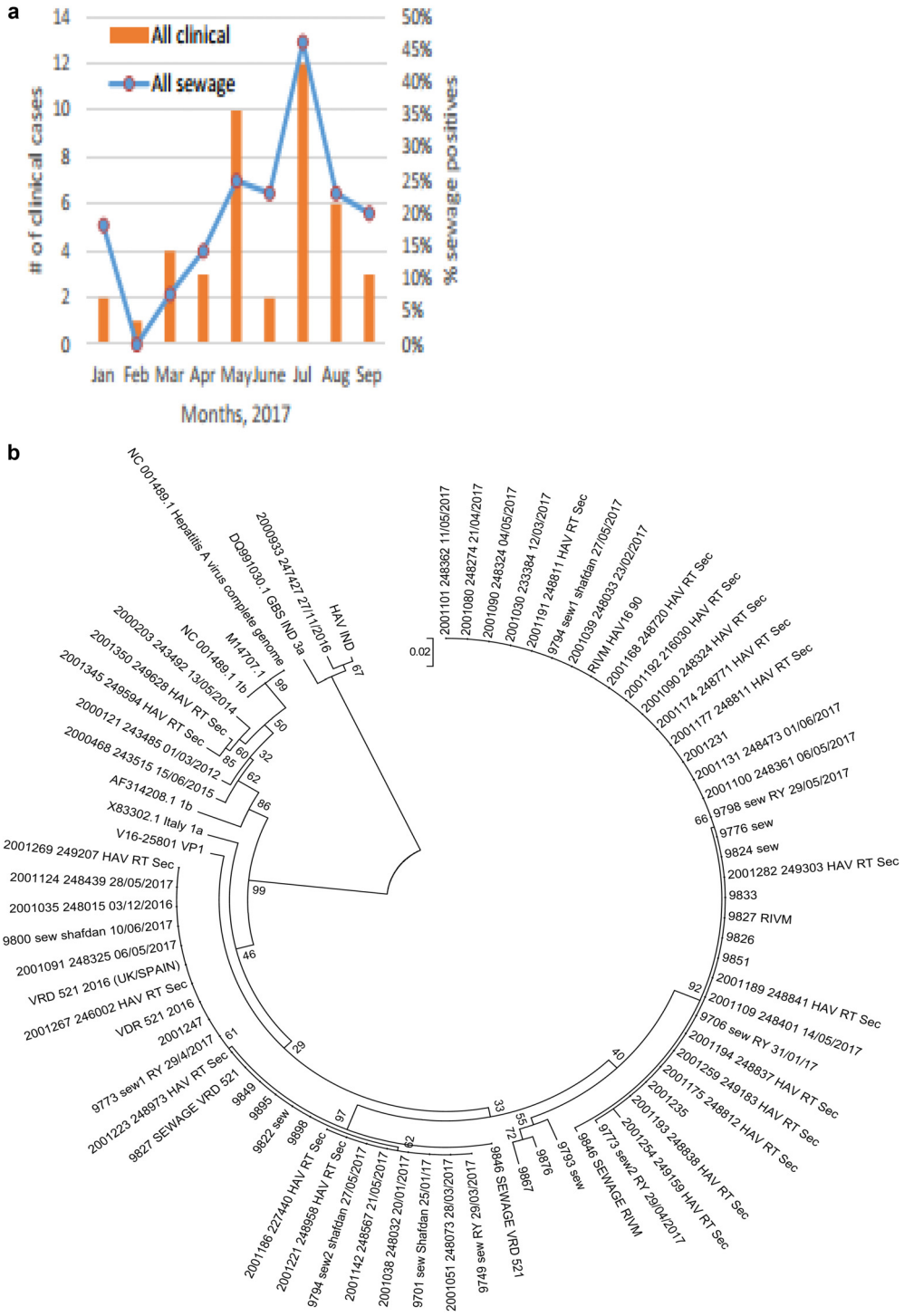


Figure: (abstract: SAT-334)

in developing countries where they cause self-limiting acute hepatitis. The zoonotic genotypes 3 and 4 mainly cause asymptomatic infections and are endemic in developed countries such as in Western Europe. HEV gt3 infection in immunocompromised patients can persist and patients may develop chronic hepatitis. Subsequently, chronic hepatitis E can result in rapid development of liver cirrhosis and liver failure. In this retrospective study, we aimed to identify HEV infections in immunocompromised kidney transplant recipients in a transplantation center in The Netherlands.

Methods: Between 2001 and 2012, serum samples of 677 kidney transplant recipients were prospectively collected and cryopreserved for research purposes. Patients who had elevated alanine transferase (ALT) levels at some time point after kidney transplantation were selected for HEV testing. Samples for HEV measurement were selected in time, in the period of an ALT elevation. Samples were pooled per 10 and HEV RNA was determined using an in-house made polymerase chain reaction (PCR) (lower limit of detection (LLD)10 IU/ml). Consequently, the LLD in these pools corresponded with 100 IU/ml.

Results: Of the total of 677 patients, 359 had at least one episode of elevated ALT levels. Of these patients, there were 300 patients with available samples for testing. Furthermore, 73 of these 300 patients had two or more episodes with ALT elevations after transplantation. Of all of these 73 patients, samples were available for testing. In total, two out of 300 patients (0.7%) with ALT elevations tested positive for HEV RNA while in these patients, no HEV RNA could be detected around the time of transplantation. Both patients developed chronic HEV infection, one of which was successfully treated with ribavirin. The other patient cleared the infection spontaneously after 3 years without treatment. After clearance of the HEV-infection, both patients developed anti-HEV IgG antibodies.
Conclusions: In this cohort of 677 immunocompromised kidney transplant recipients, 300 (44.3%) patients had one or more ALT elevations post -transplantation. With 0.7%, the incidence of chronic HEV infection in renal transplant recipients with elevated transaminases in our center is low.

SAT-336
Hepatitis E Virus adapts to cell culture, but shows limited mutagenesis in immune compromised hosts
M. Van de Garde[1], A. van Schoonhoven[1], G.S. Kaplan[1], R.D. Man[1], A. Boonstra[1], S. Pas[2,#], T. Vanwolleghem[1,2,#]. *[1]Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Laboratory of Experimental Medicine and Pediatrics, Faculty of Medicine and Health Sciences, University of Antwerp and Department of Gastroenterology and Hepatology, Antwerp University Hospital, Antwerp, Belgium; [3]Department of Viroscience, Erasmus University Medical Center, Rotterdam, The Netherlands*
Email: t.vanwolleghem@erasmusmc.nl

Background and Aims: Hepatitis E viruses (HEV) in patient blood, feces or liver have different in vivo and in vitro infectivities, which has been ascribed to biophysical differences of the virions. Less is known about the selection of viral quasispecies in these different body compartments. Since single nucleotide variants have been suggested to alter HEV virulence, we examined the genomic stability of HEV virions in different clinical samples and experimental conditions
Methods: Near full HEV genome Sanger sequences of untreated chronic phase serum- and feces samples from two immunocompromised chronic HEV gt3 patients were obtained. In vitro derived HEV was obtained from A549 cell culture supernatant after seven passages of patient feces-derived HEV, showing increased replication capacity over other passages. In vivo derived HEV was obtained from a human-chimeric mouse infected with patient feces derived HEV.
Results: After prolonged in vitro culture, a clinical HEV gt3 strain acquired 19 nucleotide mutations, leading to 7 non-synonymous amino acids changes in the papain-like cystein protease, variable, viroporin and capsid regions. The same clinical HEV gt3 strain showed only 4 nucleotide mutations without alterations in the amino acid sequence after prolonged infection in a human liver-chimeric mouse model with impaired adaptive and innate immune responses. Similarly, intra-patient comparison of feces- and serum-derived HEV gt3 showed 7 and 2 nucleotide mutations with 2 and 0 amino acid changes, in two patients respectively.
Conclusion: Overall, our data suggest that in vivo selection pressure in immunodeficient hosts is minimal, but adaptation to in vitro culture occurs.

Viral Hepatitis A, B, C, D, E: Virology

SAT-339
Longitudinal analysis of HCV full genomes in patients failing NS5A inhibitors reveals the selection of novel amino acid substitutions outside NS5A
S. Fourati[1,2], C. Rodriguez[1,2], A. Soulier[1,2], L. Poiteau[1,2], D. Vanessa[1,2], I. Ruiz[2], C. Hezode[2,3], S. Chevaliez[1,2], J.-M. Pawlotsky[1,2]. *[1]National Reference Center for Viral Hepatitis B, C and delta, Department of Virology; [2]INSERM, INSERM U955 equipe 18; [3]Henri Mondor Hospital, Hepatology*
Email: slim.fourati@aphp.fr

Background and Aims: When treatment fails, HCV NS5A inhibitors select Resistance Associated substitutions (RASs) located in domain I of the NS5A protein. NS5A RASs persist for many years, probably forever, after DAA-containing treatment failure. By analogy to HIV or HBV resistance, it is thought that compensatory or fitness-associated substitutions are also selected during treatment and could at least partly explain the long-term persistence of NS5A RASs. However, very limited information on compensatory mutations selected under antiviral therapy has been generated thus far, principally due to the sequencing methods available that characterize short genome fragments only. Here, we used an original shotgun metagenomics method based on deep sequencing of full-length HCV genomes to characterize amino acid substitutions selected by DAA therapy in regions targeted or not targeted by the NS5A inhibitors in patients who fail to achieve SVR.
Method: Using shotgun metagenomics, we generated the full-length HCV genome sequences at treatment initiation and at virological relapse in 12 patients who failed to achieve SVR on an NS5A-containing regimen (sofosbuvir + daclatasvir or sofosbuvir + ledipasvir). Briefly, universal DNA/RNA extraction was performed followed by library preparation using Total RNA and Nextera XT kit (Illumina). Deep sequencing was performed by means of NextSeq500 (Illumina). Full-length HCV sequences at baseline and at virological relapse were analyzed using our original in-house MetaMIC® software (quality, filtering, identification, genome reconstruction and comparison) and the sequences were analyzed using a 15% cutoff, according to EASL guidelines.
Results: A significant relationship was found between the HCV RNA levels and the number of equivalent HCV genome sequences generated ($p < 0.01$; $r^2 = 0.91$). Sequential analysis of full-length genome sequences identified selection of known RASs in NS5A domain I targeted by the inhibitors, but also of a number of substitutions in other genomic regions (core, E1, E2, NS3, NS4B, NS5A domain III). The majority of failures occurred in patients infected with genotype 3 ($n = 5$) and genotype 4 ($n = 4$). In genotype-3 infected patients, the following amino acid substitutions were selected together with NS5A RASs: in NS3 T98S or T98A, NS4B T48A and G114S, NS5A N448S and NS5B K114R.
Conclusion: Using an original shotgun metagenomics method based on deep sequencing that generates full-length HCV sequences, we could detect amino acid substitutions independently selected in the NS3, NS4B, NS5A (domain III) or NS5B regions in patients failing sofosbuvir plus an NS5A inhibitors. Some mutated residues were known to influence viral replication. These changes could increase RAS-related reduced drug susceptibility and/or compensate for losses of viral replication capacity they confer (e.g. Y93H). Phenotypic characterization is underway.

SAT-340

Efficient, reproducible, and long-term hepatitis B virus infection in cryopreserved primary human hepatocytes

M. Yu, L. Gamelin, S. Xu, X. Xie, J.J. Chia, T. Cheung, J. Song, D. Burdette, C. Niu, S. Daffis, R. Choy, H. Yang, B. Delaney, G. Cheng. *Gilead Sciences, Inc, Biology, Foster City, United States*
Email: mei.yu@gilead.com

Background and Aims: HepG2 cells expressing NTCP support HBV infection; however, the infection remains inefficient and HepG2 is a transformed cell line. Freshly isolated primary human hepatocytes (PHHs) support efficient HBV infection, but have limited availability. The use of cryopreserved PHHs can avoid these limitations but historically has not yielded efficient and reproducible HBV infection. Here, we report establishment of an efficient and reproducible HBV infection model using cryopreserved PHHs.
Method: Cryopreserved PHHs and culture media were purchased from Thermo Fisher Scientific or other commercial suppliers. In vitro HBV inocula were produced by HepAD38 cells. HBV patient viruses were purchased from various clinical contract research organizations. HBV DNA and RNA were quantified by qPCR. HBe and HBs antigens were measured by ELISA. HBV cccDNA was quantified by Southern Blot and qPCR. NTCP knockdown was achieved using siRNA (Thermo Fisher).
Results: Under culture conditions recommended by suppliers, cryopreserved PHH from two donors did not produce significant HBsAg (<1 ng/ml) following infection with Hep-AD38-derived HBV (500 genome equivalents/cell). However, optimization of culture medium to include 4% PEG8000 and 1.5% DMSO resulted in >100-fold higher HBsAg levels within 13 days of infection. Using these modifications, cultured PHHs also supported robust infection by plasma-derived patient viruses of multiple genotypes. To achieve similar infection in HepG2-NTCP cells, at least 10 times more viruses were needed. In infected PHH, HBV cccDNA was detected by Southern Blot as early as day 1 post infection and reached a steady level at day 3–4 post infection. Addition of the HBV entry inhibitor Myrcludex B or knockdown of NTCP by siRNA inhibited >90% HBV infection. Importantly, these culture conditions have been successfully applied to 20 cryopreserved PHHs donors, although not all donors tested support efficient infection. These infection and culture conditions have also permitted effective passage of infection to naïve PHH cultures and supported persistent HBV infection for >40 days. Treatment with nucleoside inhibitors or capsid assembly modulators inhibited viral DNA replication but had minimal effect on antigen production. Finally, IFN-α inhibited both viral DNA and antigens with >10-fold higher potency than in HepG2-NTCP, but had no effect on cccDNA level.
Conclusion: An efficient HBV infection model has been established using cryopreserved PHHs. Its high efficiency, reproducibility, and ability to support long-term infection will facilitate a better understanding of HBV life cycle and discovery of novel therapeutics.

SAT-341

NLRX1 and the p.Arg707Cys variant in NLRX1 affect host susceptibility of hepatitis B virus infection in Huh7-NTCP cells

L. Peng, J. Qian. *3rd Affiliated Hospital of Sun Yat-sen University, Department of Infectious Diseases, Guangzhou, China*
Email: pliang@mail.sysu.edu.cn

Background and Aims: NLRX1 is a negative regulator of mitochondrial antiviral immunity. Expression of NLRX1 results in the potent inhibition of RLH- and MAVS-mediated interferon-β promoter activity and in the disruption of virus-induced RLH- MAVS interactions. How NLRX1 affects the individual susceptibility to HBV is not clear. Our previous study found that a rare genetic mutation NLRX1 p.Arg707Cys affects the structure of NLRX1 and contributes to influence host susceptibility of CHB.
The purpose of this research was to investigate the effects and mechanisms of NLRX1 and the p.Arg707Cys Variant in NLRX1 on the individual susceptibility to HBV.
Method: The Huh7- NTCP model was established. In the same way, lentiviral vectors were used to establish both stable wild type NLRX1 (WT)- overexpressing and p.Arg707Cys NLRX1 (MT)- overexpressing Huh7- NTCP cell lines. Western blot and real time quantitative PCR were used to confirm the overexpressing of WT NLRX1 and MT NLRX1 in Huh7- NTCP cells. The susceptibility to HBV of MT and WT were tested on Huh7- NTCP infected cells with HBV, HBsAg, HBcAg, HBV DNA and HBV cccDNA were detected.
Results: WT NLRX1 and MT NLRX1 in Huh7- NTCP cells were demonstrated significantly increased. Cell model experiments confirmed that NLRX1 reduced HBV infection and p.Arg707Cys impairs the individual susceptibility to HBV of NLRX1. HBsAg, HBcAg, HBV cccDNA and HBV DNA levels were significantly increased in both WT and MT NLRX1-overexpressing Huh7- NTCP cells compared with naive Huh7- NTCP cells. While the levels in MT NLRX1-overexpressing Huh7- NTCP cells was significantly lower than the WT ones.
Conclusion: NLRX1 is a negative regulator of host response to HBV, and its coding gene mutation NLRX1p.Arg707Cys will weaken the negative regulation function, enhances the ability of host resistance to HBV infection. Therefore, this means that the p.Arg707Cys Variant in NLRX1 is a new target for HBV antiviral therapy.

SAT-342

The stapled peptides derived from hepatitis B virus core protein hijack viral replication

J. Han, X. Cong. *Peking university people's hospital, Peking university hepatology*
Email: hjcaizhh@126.com

Background and Aims: Protein-protein interactions (PPI) are involved in all aspects of the viral lifecycle, including genome packaging, reverse transcription, intracellular trafficking and cccDNA epigenetic regulation. Those processes depend on the correct function and conformation of HBV core protein. To develop PPI inhibitors targeting core protein is attractive for HBV therapy. Here we designed a series of stapled peptides based on α-helix domains of core protein, and completed antiviral activity assay.
Method: Helical peptides with hydrocarbon staples were synthesized, uptake of peptide by cell and stabilization were assayed. Antiviral activity was measured by qPCR from HepG2 cells transiently transfected with four genotype expressing vectors (A~D). HBsAg and HBeAg were measured by ELISA in HepDes19 cells. HBV replicative DNA intermediates and viral RNA were detected by southern and northern blot analysis. The interaction of stapled peptides with core protein was determined by co-immunoprecipitation.
Results: Those stapled had more highly levels of cell penetration, proteolytic resistance, and target affinity than natural α-helix peptides. Several stapled peptides derived from core protein intra-dimmer interface exhibited potent viral load reduction in vitro. Surprised, Stapled peptides inhibited HBsAg and HBeAg expression (EC50 50~100 mM). HBV cccDNA was reduced in HepDeS19 cells treated with stapled peptides.
Conclusion: Hydrocarbon stapled α-helix peptides derived from core protein interfere HBV replication, which could be attractive tools for HBV therapy.

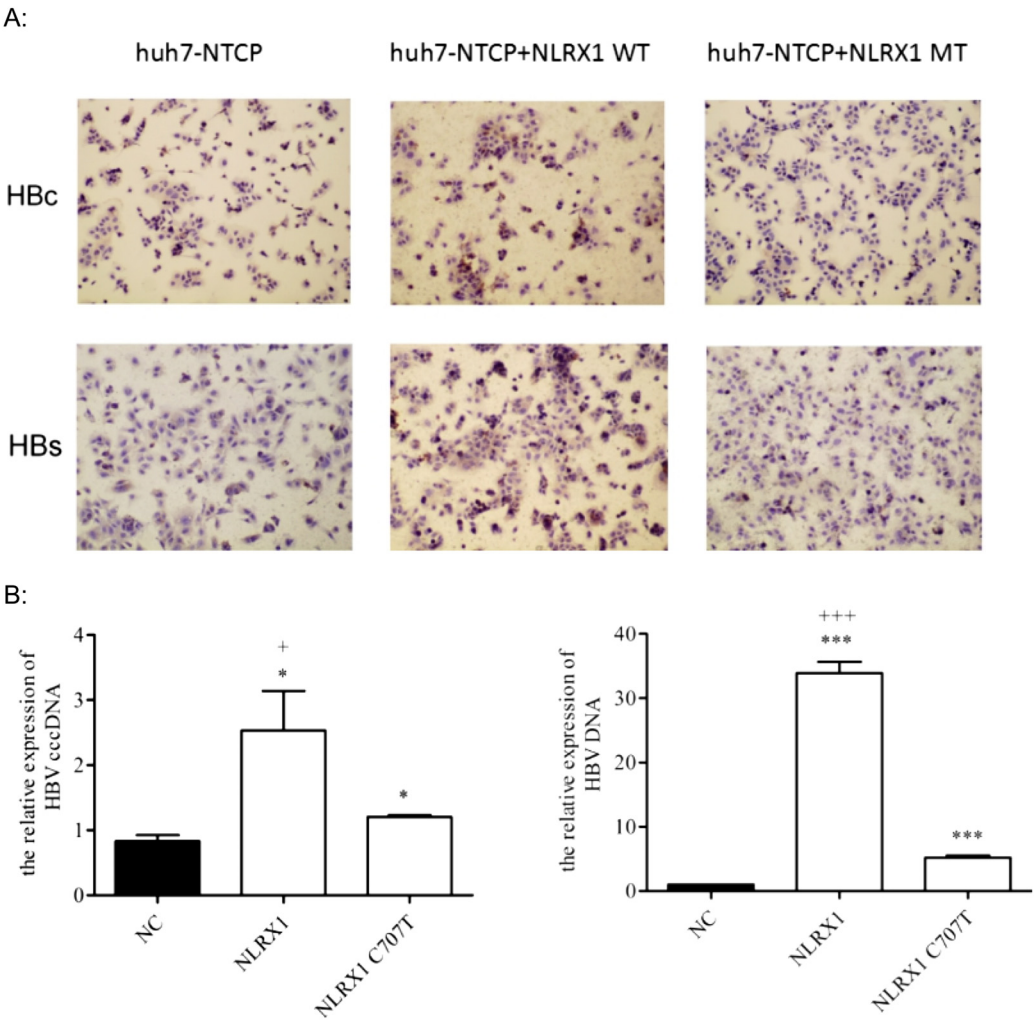


Figure: (abstract: SAT-341): Figure legend: Levels of HBcAg, HBsAg, HBV cccDNA, and HBV DNA in HBV-infected Huh7- NTCP cells with NLRX1 WT and MT overexpression. (A) IHC results showed higher levels of HBcAg and HBsAg in NLRX1 WT and MT overexpression Huh7- NTCP cells than in naive Huh7- NTCP cells. While the levels of HBcAg and HBsAg were lower in NLRX1 MT than WT overexpression Huh7- NTCP cells. (B) Quantitative analysis of HBV cccDNA and HBV DNA levels in HBV-infected Huh7- NTCP cells with NLRX1 WT and MT overexpression. After HBV infection, the level of HBV cccDNA ($^{*}p < 0.05$) and HBV DNA ($^{***}p < 0.001$) in Huh7- NTCP cells with NLRX1 WT and MT overexpression were higher than in naive Huh7- NTCP cells. While the levels of HBV cccDNA ($^{+}p < 0.05$) and HBV DNA ($^{+++}p < 0.001$) were lower in NLRX1 MT than WT overexpression Huh7- NTCP cells.

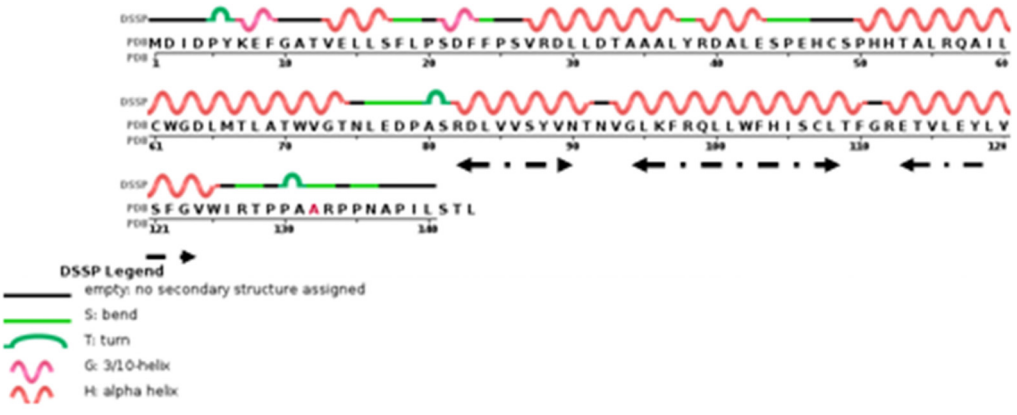


Figure: core protein sequence and secondary structure

← · — ▸ a-helix domains for stapled peptides design

Figure: (abstract: SAT-342)

SAT-343

DEAD-box helicases DDX5 and DDX17 areinvolved in the fine tuning of hepatitis B virus minichromosome transcriptional regulation

F. Chapus[1,2], M. Locatelli[1,2], J. Fresquet[1], B. Testoni[1,2], F. Zoulim[1,2,3].
[1]*CRCL, Inserm U1052, LYON, France;* [2]*Université de Lyon 1, LYON, France;* [3]*Hospices Civiles de Lyon, LYON, France*
Email: fabien.zoulim@inserm.fr

Background and Aims: Hepatitis B virus (HBV) minichromosome, the covalently-closed-circular (ccc)DNA, is responsible for HBV chronicity and reactivation. Current antiviral treatments inhibit viral replication, but do not significantly affect cccDNA reservoir in the hepatocyte nuclei. cccDNA is a stable episome with a dynamic chromatin structure regulated by epigenetic mechanisms. It is the template for all viral subgenomic transcripts and for the pre-genomic RNA (pgRNA), which is retrotranscribed and encapsidated to ensure both newly synthesized viral progeny and cccDNA pool replenishment via intracellular nucleocapsid recycling. Overlapping open reading frames and regulatory elements on HBV genome have to be precisely and timely controlled to ensure correct cccDNA transcription and viral mRNA processing. To better understand the mechanisms orchestrating cccDNA transcriptional regulation, we investigated the role of DDX5 and its highly related paralog DDX17, two DEAD-box helicases known to play a driving role in connecting cellular chromatin topology to correct transcriptional initiation and termination in concert with the architectural proteins CCCTC-binding Factor (CTCF) and Matrin-3.
Method: Chromatin Immunoprecipitation (ChIP), RNA-IP, protein co-immunoprecipitation (co-IP) and knockdown by RNAi were performed in HepG2-NTCP cells and Primary Human Hepatocytes one week after HBV infection, when cccDNA pool is stable.
Results: ChIP analysis demonstrated that DDX5/17, CTCF and Matrin-3 bind to cccDNA in both HepG2-NTCP cells and PHH, together with the HBV core protein (HBc). Protein co-IP in a HepaRG cell line overexpressing HBc in an inducible manner, demonstrated that HBc, DDX5/17, CTCF and Matrin-3 belong to the same complex. In particular, sequential ChIP with an anti-HBc and then an anti-CTCF antibody confirmed the simultaneous presence of both proteins on the same cccDNA molecule. RNA-IP also showed the binding of DDX5/17, CTCF and Matrin-3 to viral RNAs and to preC/pgRNA in particular. DDX5/17 knockdown by small interfering RNA (siRNA) induced a strong decrease of preC/pgRNA levels and viral HBe antigen secretion, without affecting global cccDNA levels.
Conclusion: These data highlight the presence of a complex formed by HBc, DDX5/17, CTCF and Matrin-3 at the interface between cccDNA and viral RNAs and suggest a functional role for the helicases DDX5/17 on cccDNA transcriptional regulation and/or mRNA processing.

SAT-344

Rolling circle amplification and nanopore-based deep sequencing of full-length HBV genomes

A. Mcnaughton[1], D. Bonsall[2], M.D. Cesare[2], A. Brown[1], D. Parkes[3], R. Bowden[3], E. Barnes[1,4], P. Matthews[1,5]. [1]*University of Oxford, Nuffield Department of Medicine, Oxford, United Kingdom;* [2]*Wellcome Centre for Human Genetics, Nuffield Department of Medicine, Oxford, United Kingdom;* [3]*University of Oxford, Wellcome Centre for Human Genetics, Oxford, United Kingdom;* [4]*Oxford University Hospitals NHS Foundation Trust, Department of Hepatology, Oxford, United Kingdom;* [5]*Oxford University Hospitals NHS Foundation Trust, Department of Infectious Diseases and Microbiology, Oxford, United Kingdom*
Email: p.matthews@doctors.org.uk

Background and Aims: The optimisation of unbiased deep-sequencing methods for full-length HBV genomes will inform detailed insights into the evolution and diversity of this pathogen. Nanopore-based sequencing technologies offer the potential for real-time detection and sequencing of blood-borne viruses, useful for clinical diagnosis, drug-resistance calling and high-resolution molecular epidemiology. To date, sequencing accuracy has limited the full potential of Oxford Nanopore's long-read capabilities. We here describe use of an isothermal rolling-circle amplification (RCA) method, (i) to amplify HBV DNA and (ii) to derive concatemers of whole HBV genomes thus providing a mechanism to correct sequencing errors.
Method: DNA was extracted from plasma samples from patients with chronic HBV infection using the NucliSENS magnetic extraction system. Partially double-stranded HBV DNA genomes were converted into fully double-stranded, covalently closed circular DNA using T4 polymerase followed by T4 ligase. RCA was undertaken by incubation with a panel of 8 HBV-specific primers (complementary to both strands) and phi29 DNA polymerase at 30°C for 22 hours. Products were "debranched" using T7 endonuclease and sequenced on the Nanopore MinION device using the 1d ligation sequencing kit and R9.4 flowcell (SQK-LSK108; Oxford Nanopore technologies). On-target HBV sequences were filtered from base-called fastq files using Kraken and BLAST; consensus sequences were derived from multiple concatenations to correct error.
Results: We successfully sequenced individual whole HBV genomes as single reads. The highest-yield sample produced 1,296,131 reads, of which 87% contained human sequence. BLAST identified 16,297 HBV reads, of which 2,738 contained at least one contiguous, complete HBV genome. Consensus averaging of concatenated genomes facilitated error correction of complete viral haplotypes. Based on BLAST analysis with a database of reference sequences for subtypes A-H, this sample genotyped as E.
Conclusion: We have demonstrated that an isothermal RCA method can provide enrichment of HBV DNA and concatenation of the HBV genome. This is the first example of a deep-sequencing method for characterising HBV variants that takes full advantage of Nanopore's ability to sequence whole genomes within single reads, and also facilitating correction of sequencing error. There is exciting potential for these tools to be refined for full-length, high-resolution sequencing analysis of HBV (and other viruses), impacting both clinical and research settings.

SAT-345

LTPprodrug technology offers new generation nucleotide antiviral agents

L. Zhi[1], E. Vajda[2]. [1]*Nucorion Pharmaceuticals, Suite 110, San Diego, United States;* [2]*Ligand Pharmaceuticals, Ligand Pharmaceuticals, San Diego, United States*
Email: lzhi@ligand.com

Background and Aims: Nucleotide analog reverse-transcriptase inhibitors (NtRTI) have been one of the major antiviral arsenals in combating HBV and HIV. Improving prodrug efficiency over clinically validated nucleotide molecules has demonstrated to be a cost-effective new drug development strategy to offer more effective and safer medicines, e.g. tenofovir alafenamide fumarate (TAF) offers significant advantages over tenofovir disoproxil fumarate (TDF). We report that LTP technology improves prodrug delivery efficiency to a new level over the HepDirect(HD) technology and ProTide technology.
Method: Three types of tenoforvir prodrugs were orally administered to Sprague-Dawley rats at the same doses. Blood and tissues were harvested and snap-frozen in liquid nitrogen. Tenofovir and tenofovir-diphosphate (TDP) concentrations were measured by LC-MS/MS to compare oral delivery and liver-targeting efficiency.
Results: At 5 mg/kg doses, NCO-8548 (LTP-tenofovir) achieved TDP levels in the liver at 1 and 5 hours after dosing over 92- and 21-fold higher than that of NCO-8429 (HD-tenofovir) and over 15- and 7-fold higher than TAF-base (ProTide-tenofovir) (see Table 1 below). Since NCO-8429 and NCO-8548 are mainly metabolized by CYP3A4 and phosphoramide bond of TAF-base was cleaved by histidine triad nucleotide-binding protein 1 (HINT1), one can expect that exposure levels of the nucleotides in other target tissues will be largely dependent on the tissue expression levels of these enzymes. CYP3A4

is expressed at particularly high levels in the liver, making it ideal for enhanced liver targeting of NCO- compounds.

Table: Liver TDP and blood tenofovir levels after oral dosing of TAF-base, NCO-8429, and NCO-8548 in male Sprague Dawley rats

Compound	TAF-base (ProTide prodrug)	NCO-8429* (HD prodrug)	NCO-8548* (LTP prodrug)
TDP_{liver} at 1, 5 h(nmol/g)	0.86 ± 0.91	0.14 ± 0.06	13.0 ± 9.5
	2.16 ± 1.06	0.75 ± 0.30	16.1 ± 8.2
$Tenofovir_{blood}$ at 1, 5 h (nmol/mL)	0.22 ± 0.13	<0.007	0.11 ± 0.03
	0.030 ± 0.007	<0.007	0.051 ± 0.007
TDP_{liver}/ $Tenofovir_{blood}$ at 1, 5 h	3.9, 72	>20, >107	118, 316
$Drug_{liver}$ at 1, 5 h(nmol/g)	<0.02	0.074 ± 0.014	0.32 ± 0.10
	<0.02	0.026 ± ND	<0.01
$Drug_{blood}$ at 1, 5 h(nmol/g)	<0.003	0.015 ± 0.002	0.016 ± 0.006
	<0.003	0.005 ± 0.002	<0.003

*Results are adjusted to the doses that are nucleotide equivalent.

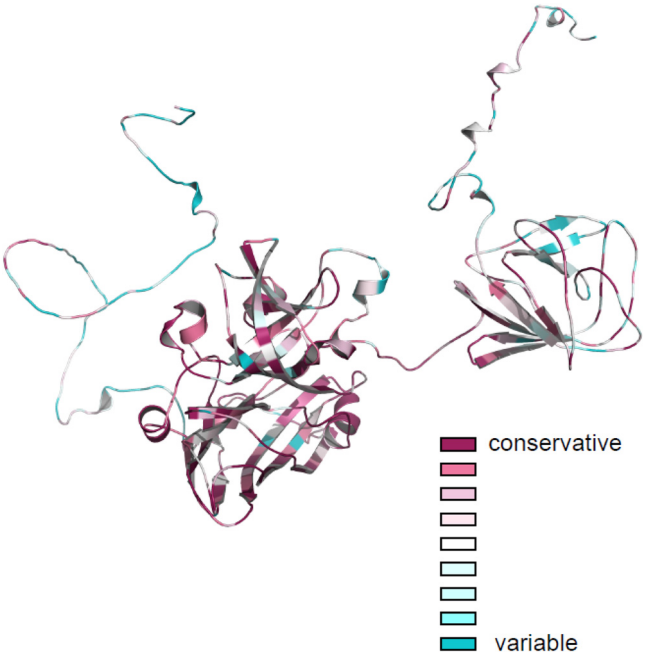
Conclusion: LTP-tenofovir compound demonstrated higher level of TDP in the liver and enhanced liver-targeting relative to the HD-tenofovir and ProTide prodrugs. LTP technology can be an effective method to increase the antiviral therapeutic index of nucleotides.

SAT-346

Conservation and variation of the hepatitis E virus open reading frame 2 proteome

S. Zhang[1], C. Qu[2], M. Peppelenbosch[2], Q. Pan[2]. [1]*Gastraenterology and hepatology, Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Erasmus University Medical Center, Gastroenterology and Hepatology*
Email: s.zhang@erasmusmc.nl

Background and Aims: Hepatitis E virus (HEV) infection is emerging as a global health issue. HEV particles are made up of capsid proteins and viral genomic RNA. As the major protein component of mature viral particle, capsid carries almost all the information of viral assembly and interactions with hosts. With tremendous advances in computing technology and algorithm, bioinformatics has allowed us to map the evolutionary features and model high-accuracy structures of the open reading frame 2 (ORF2) proteome across different strains. Importantly, we were able to model the binding affinity of ORF2 from different strains towards neutralizing antibody.
Method: We systematically retrieved 307 high quality ORF2 sequence from more than 30 countries with collection date cover three decades and performed conservation analysis. We have also modelled up to 41 ORF2 structures across the defined reference sequences and subtypes. Structure alignment and docking with neutralizing antibodies were accomplished.
Results: HEV ORF2 has a conservative length, 660 is typical and 674 is the longest. With conservation analysis, we confirmed up 138 evolutionary conservative sites of ORF2, some of which are consistent with protein modification in experimentation. Systematically modelling of reference sequences revealed five functional regions of ORF2 and we found P domain more variable than S and M domains. Despite known S, M and P domains, we also find chain structures of N and C termination which possibly are cleaved during viral assembly. Docking with neutralizing mouse monoclonal antibodies shows that there is no clear association with viral evolution and binding affinity with antibody.
Conclusion: ORF2 is evolutionary conservative and can be important clue to biology of HEV. As building blocks in viral assembly, S and M domain are conservative while P domain is more variable. Therefore, the effectiveness of neutralizing with antibody is significantly different across subtypes.



SAT-347

Mutations in HCV NS3 but no Sec14L2 variants alter HCV RNA replication of natural occuring viruses in cell culture

R. Costa[1], D. Todt[2], F. Belinchon[1], A. Walker[3], C. Schenk[4], J. Timm[3], V. Lohmann[4], V.H. Thomas[1], S. Ciesek[5]. [1]*Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany;* [2]*Experimental Virology, Twincore, Hannover, Germany;* [3]*Institute of Virology, Düsseldorf, Germany;* [4]*Molecular Virology, Heidelberg, Germany;* [5]*Institute of Virology, Essen, Germany*
Email: Sandra.ciesek@uk-essen.de

Background and Aims: With 71 million chronically infected patients worldwide, HCV remains an important element in the aetiology of chronic liver disease. Since the discovery of the virus several breakthroughs allowed the development of effective therapies to combat the infection, nonetheless, important elements of the viral life cycle remained elusive. Chief among them, the inability to consistently replicate pan-genotype virus samples in cell culture. This changed in 2015 with the discovery of SEC14L2 as a necessary factor for viral replication. In this study we aim to broaden the understanding of the role of SEC14L2 and its variants.
Method: We employed the model reported by Saeed et al to enable HCV viral replication in cell culture. Following model validation we introduced single nucleotide polymorphisms of SEC14L2 in cell culture populations and characterized relevant phenotypes such as cytosolic vitamin E abundance, cellular cholesterol abundance and variant expression levels. Following characterization we infected the cells with patient isolates to compare replication enhancement effects among variants. Finally we selected two variants and screened a cohort of 35 HCV infected patient sera, containing genotypes 1a, 1b, 2a, 2b, 3a, 3c, 4a, 4d and 5 to validate our observations in an extensive virus panel and identify genotype specific dependencies.
Results: We were able to reproduce SEC14L2 dependent HCV replication in our cell model yet, not all isolates exhibited the same levels of replication in cell culture. When testing SEC14L2 variants, we observed no statistically significant differences in the analyzed phenotypic traits; nonetheless only 7 out of 13 Sec14L2 variants enabled HCV replication in cell culture. Isolates from genotypes 1 and 3 exhibited a marked enhancement from the expression of SEC14L2 whereas genotypes 2, 4 and 5 remained largely unaffected. Furthermore, after isolate sequencing, we were able to identify

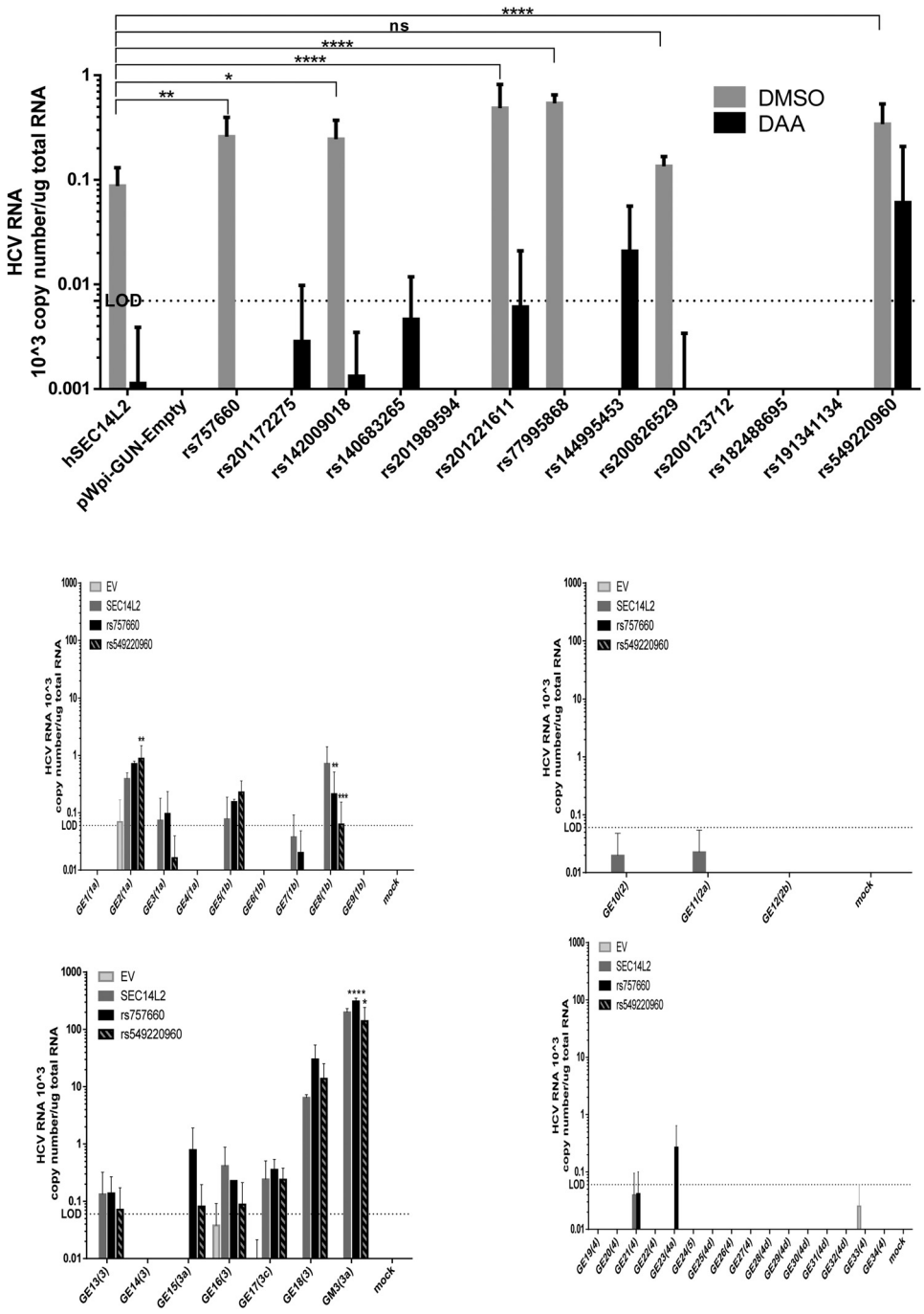


Figure: (abstract: SAT-347)

several candidate mutations mapped to NS3 and NS5A that were present in the replicating isolates and not the non-replicating, these may impact the replication phenotype.

Conclusion: SEC14L2 is an important factor for HCV viral replication. In this work we set out to report the effect of SEC14L2 variants in viral replication in cell culture and possible viral determinants that mediate dependency of SCE14L2. Interestingly, in our observations, only 7 of the 13 SEC14L2 enabled replication although the vitamin E phenotype did not vary in a statistically significant way among them which argues in favor of a further mechanism that is yet to be described. Furthermore the pattern of replication among isolates suggests the level of SEC14L2 dependency may be genotype specific. Here, we identified several mutations that may provide new insights in the mechanism behind the HCV SEC14L2 dichotomy.

SAT-348

Expanding the donor pool-decontamination of HCV RNA positive kidneys with methylene blue

F. Helfritz[1], D. Bojkova[2], S. Westhaus[2], E. Steinmann[3], T. Minor[1], P. Meuleman[4], A. Paul[1], S. Ciesek[2]. *[1]General, Visceral and Transplantation Surgery; [2]Institute of Virology, Essen, Germany; [3]Twincore, Hannover, Germany; [4]Dept. Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium*
Email: Sandra.ciesek@uk-essen.de

Background and Aims: Although organ shortage is a rising problem, organs from HCV RNA positive donors are not routinely transplanted in HCV negative individuals. Since HCV can only infect hepatocytes, other organs such as kidneys are merely contaminated with HCV.

Consequently, we established an HCV decontamination protocol for kidneys making them available for transfer into HCV negative recipients.
Method: Standard virological assays were used to investigate the effect of preservation solutions on the HCV replication cycle and to examine several antivirals, including methylene blue (MB), in preservation solutions. Kidneys from mini pigs were contaminated with Jc1 or HCV RNA positive human serum. Afterwards, organs were flushed with MB. Hypothermic machine perfusion was used to optimize inactivation of HCV.
Results: All preservation solutions enhanced HCV infectivity: while IGL-1 increased HCV attachment, UW and Perfadex boosted HCV entry. In HTK HCV was significantly more stable. Investigation of different antivirals for their ability to inactivate HCV revealed that MB completely inactivates HCV in the presence of all perfusion solutions. HCV contaminated kidneys from mini pigs were successfully decontaminated from HCV by hypothermic machine perfusion treatment with MB without any negative effect on the graft. In addition, human liver-uPA-SCID mice did not establish HCV infection after inoculation with flow through from these kidneys.
Conclusion: While several perfusion solutions enhance HCV infectivity, MB treatment reduces HCV infectivity efficiently. Flushing of an HCV contaminated kidney with MB inactivates all HCV genotypes. Finally, kidneys from HCV RNA positive donors might serve as a useful extension of the donor pool after treatment with MB.

SAT-349

Seeking genetic determinants of resistance to hepatitis C virus infection in a highly resistant cohort

D. Felmlee, P. Redondo, M. Ow, M. Cramp. *Peninsula Schools of Medicine and Dentistry*
Email: Daniel.Felmlee@plymouth.ac.uk

Background and Aims: We have studied a very rare cohort of individuals with evidence of high-level resistance to HCV infection to better understand how HCV interacts with hepatocytes. We seek to use this knowledge to translate into new approaches to deal with HCV and other related viral illnesses. Historically the major mode of transmission of HCV infection was from infected blood and blood products prior to routine screens for HCV in 1991. The blood transfusion service in England instigated a Lookback Programme in 1995 to identify individuals who had received HCV contaminated blood or blood products from donors before 1991, who tested positive.
Method: We have painstakingly gone over the records of 1340 recipients of blood/blood products from HCV infected donors and from these identified 13 individuals with confirmed HCV exposure but without any evidence of HCV infection testing negative for HCV antibody and HCV RNA. These 13 remained uninfected despite high level exposure to HCV and appear to be highly resistant to HCV infection. 8 of the 13 patients were traced, still alive, and consented to contribute to this study. We sought to determine genetic contributions to resistance to HCV infection by whole-exome sequencing of the genomes of these individuals, with 96% coverage of all exomes. We studied the genes of 11 known host entry factors for HCV, including CD81, scavenger receptor B-1 (SRB1), occludin (OCLN) claudin-1 (CLDN1), epidermal growth factor receptor (EGFR), Cideb, Ldlr, Epha2, for allelic changes.
Results: The primary screen revealed no significantly over-represented SNPs present in the gene transcripts of any HCV entry host factors within the EU cohort. One EU individual showed a single synonymous allele change in the OCLN gene (MAF = 0.023) and two had a heterozygous serine to phenylalanine change in epidermal growth factor receptor (EGFR), however no trends in the known host entry factors could be attributed to resistance to infection.
Conclusion: The findings to date suggest that variation in canonical HCV host entry factors is not the cause of the high level of resistance to HCV. We are undertaking further analysis of the sequencing data and speculate that there could be novel genes involved in the HCV lifecycle, that with a specific mutation could confer high-level resistance to HCV infection. Much remains to be learnt from this interesting cohort and our future work will include a secondary screen of the SNP output to identify novel gene targets.

SAT-350

A hyper-glycosylation of HBV surface antigen characterizes immunosuppression-driven HBV reactivation and hinders HBsAg recognition in vitro

R. Salpini[1], L. Piermatteo[1], A. Battisti[1], L. Colagrossi[1], M. Aragri[1], L. Fabeni[2], A. Bertoli[1], C.M. Mastroianni[3], M. Marignani[4], S. Maylin[5], C. Delaugerre[5], F. Morisco[6], C. Nicola[7], A. Marrone[8], N. Iapadre[9], A. Mario[10], L. Sarmati[11], M. Andreoni[11], J. Verheyen[12], F.C. Silberstein[1], M. Levrero[13,14,15], C.F. Perno[1], L. Belloni[15], V. Svicher[1]. *[1]University of Rome Tor Vergata, Experimental Medicine and Surgery, Rome, Italy; [2]National Institute for Infectious Diseases L. Spallanzani, IRCCS, Rome, Italy; [3]"Sapienza" University, Public Health and Infectious Disease, Rome, Italy; [4]"S. Andrea Hospital", Gastroenterology, Rome, Italy; [5]Saint Louis Hospital & University, Laboratory of Virology, Paris, France; [6]University of Naples "Federico II", Clinical Medicine and Surgery, Gastroenterology Unit, Naples, Italy; [7]Second University of Naples, Mental Health and Public Medicine, Naples; [8]University of Campania "Luigi Vanvitelli", Medical, Surgical, Neurological, Metabolic and Aging Sciences, Naples, Italy; [9]"San Salvatore" Hospital, Infectious Diseases Unit, L'Aquila, Italy; [10]Tor Vergata University Hospital, Hepatology Unit, Rome, Italy; [11]Tor Vergata University Hospital, Infectious Diseases Unit, Rome, Italy; [12]University Hospital of Essen, University of Duisburg-Essen, Institute of Virology, Essen, Germany; [13]Cancer Research Center of Lyon (CRCL) – INSERM U1052, Lyon, France; [14]Service d'Hepatologie, Hopital de la Croix-Rousse, HCL, Lyon, France; [15]IIT, Center for Life Nanosciences (CLNS) – Sapienza, Rome, Italy*
Email: piermatteolorenzo@gmail.com

Background and Aims: The aim of the study was to investigate N-linked glycosylation (N-glyc) patterns of HBsAg in immunosuppression-driven HBV-reactivation *in vivo* and to evaluate their impact on HBsAg antigenicity and HBV replication *in vitro.*
Method: Mutations associated with acquisition of N-glyc site are investigated in HBsAg genotype-D sequences from 55 patients with immunosuppression-driven HBV-reactivation (defined as Hwang, 2014). The impact of N-glyc sites on pgRNA, core particle-associated HBV-DNA, and extracellular HBsAg is assessed by transfecting Huh7 cells with a plasmid containing wt or mutated HBV genotype D full-length genome. The impact of N-glyc sites on HBsAg antigenicity is analyzed by transfecting Huh7 cells with a plasmid encoding WT and mutated HBsAg-linked to a streptavidin-tag (strep-tag). The strep-tagged HBsAg amount in supernatants is quantified by a specifically-designed ELISA recognizing the Strep region (thus, not affected by HBsAg mutations) and also by an ELISA directly targeting the HBsAg. Tunicamycin, an inhibitor of N-glyc, is used on cells transfected with the strep-tagged HBsAg to confirm the role of N-glyc in altering HBsAg recognition by antibodies.
Results: At HBV reactivation, median [IQR] serum HBV-DNA and ALT are 6.7[5.3–8.0]logIU/ml and 149[42–630]U/l, respectively. Notably, 12.7% (7/55) of pts remains HBsAg-negative despite HBV reactivation (serum HBV-DNA range:2.9–7.6 logIU/ml). >1 additional N-glyc site in HBsAg is detected in 5/7 HBsAg-negative pts. I*n-vitro*, compared to wt, N-glyc sites strongly reduce extracellular HBsAg titer without affecting viral replication parameters. In particular, S113N + T131N + M133T determines 80% decrease in HBsAg titer, while ins114 + T115N, T115N and T123N cause a 68%, 62% and 32% reduction, respectively. Similarly, N-glyc sites decrease strep-tagged HBsAg titer by using the ELISA targeting the HBsAg (% reduction: 20% to 94%). Conversely, no decrease of strep-tagged HBsAg is revealed by ELISA targeting the Strep-tag, suggesting that N-glyc sites hamper HBsAg-recognition by antibodies without affecting HBsAg-release. Notably, in presence of

N-glyc sites, tunicamycin restores HBsAg titers observed in wt, confirming the direct role of N-glyc in hampering HBsAg recognition.
Conclusion: Additional N-glyc sites correlate with HBsAg-negativity despite HBV-reactivation, and profoundly alter HBsAg-antigenicity *in-vitro*. This supports the role of N-glyc in immune-escape and the importance of HBV-DNA (more than HBsAg) for a proper diagnosis of HBV-reactivation.

SAT-351

Palmitoylation determines the subcellular localization of the hepatitis E virus ORF3 protein

J. Gouttenoire[1], P. Angela[1], A. Laurence[2], M. Maxime[1], D.T.V. Loan[1], S. Dagmara[1], O. Joël[1], M. Johann[1], G. van der Goot[2], D. Moradpour[1]. *[1]Lausanne University Hospital, University of Lausanne, Service of Gastroenterology and Hepatology, Lausanne, Switzerland; [2]Ecole Polytechnique Fédérale de Lausanne, Global Health Institute, School of Life Sciences, Lausanne, Switzerland*
Email: darius.moradpour@chuv.ch

Background and Aims: Hepatitis E virus (HEV) is a positive-strand RNA virus encoding 3 open reading frames (ORF), namely ORF1, ORF2 and ORF3. HEV ORF3 protein is a small, hitherto poorly characterized protein involved in viral particle secretion and possibly other functions. Here, we investigate the structure and function of this essential viral protein.
Method: A panel of ORF3 constructs and the full-length protein expressed by infectious HEV were investigated by confocal laser scanning microscopy and immunoblot using GFP fusion proteins and newly established recombinant antibodies. Oligomerization was studied by coimmunoprecipitation and fluorescence resonance energy transfer. A wheat germ-based system was used for the cell-free expression of ORF3 protein. Posttranslational modifications were probed by site-directed mutagenesis and different biochemical assays.
Results: HEV ORF3 protein forms membrane-associated oligomers. HEV ORF3 proteins produced in cell-free and mammalian cell expression systems displayed different apparent molecular weight. Sequence analyses revealed the presence of 8 conserved cysteine residues within the first 21 amino acids which were found to be palmitoylated, as corroborated by ^{3}H-palmitate labeling, the investigation of cysteine-to-alanine substitution mutants and treatment with the palmitoylation inhibitor 2-bromopalmitate (2-BP). Abrogation of palmitoylation by site-directed mutagenesis or 2-BP treatment relocalized ORF3 protein from the plasma membrane to the cytoplasm and decreased stability of the protein. Moreover, we found, using selective permeabilization conditions coupled to immunofluorescence, that HEV ORF3 protein is entirely exposed to the cytosolic side of the membrane. The functional consequences of palmitoylation are currently being investigated using cell-culture derived infectious HEV.
Conclusion: HEV ORF3 protein forms membrane-associated oligomers and is palmitoylated at conserved N-terminal cysteine residues. This posttranslational modification determines the subcellular localization, stability and likely also the function of HEV ORF3 protein. These findings provide new insights into the life cycle of HEV and may yield new angles for therapeutic intervention.

SAT-352

Identification of hepatitis B virus core protein nuclear interacting factors points to RNA binding proteins as major regulators of HBV replication

H. Chabrolles[1], S. Vegna[1], A. Héloïse[1], Y. Couté[2], L. Belmudes[2], Y. Kim[1], L. Arnold[3], D. Grierson[4], B. Chabot[5], C. Combet[1], F. Zoulim[1], J. Lucifora[1], D. Durantel[1], A. Salvetti[1]. *[1]INSERM U1052, Research Center of Lyon (CRCL), Université de Lyon (UCBL1), CNRS UMR_5286, Centre Léon Bérard, Lyon, Lyon, France; [2]INSERM U1038, Université Grenoble Alpes, BIG-BGE, Grenoble; [3]DiscoverElucidations, LLC, Bloomington; [4]University of British Columbia, Faculty of Pharmaceutical Sciences, Vancouver, Canada; [5]Faculty of Medicine and Health Sciences, Université de Sherbrooke, Department of Microbiology and Infectious Diseases, Sherbrooke, Canada*
Email: anna.salvetti@inserm.fr

Background and Aims: Converging evidences suggest that the Hepatitis B virus core protein (HBc), beside its well-known structural role to form nucleocapsids around pregenomic RNA in the cytoplasm, could have important regulatory functions in the hepatocyte nucleus, in particular by binding to the HBV genome (cccDNA) and to cellular DNA and possibly regulate their expression. However, HBc nuclear functions and mode of action still remain undefined. The aim of this project was to decipher HBc regulatory functions, by identifying its cellular partners in the nucleus of human hepatocytes.
Method: Nuclear HBc-protein complexes, treated or not with Benzonase, were purified on Strep-Tactin® columns from differentiated HepaRG cells expressing an inducible Strep-tagged HBc protein (ST-HBc), analyzed by Mass Spectrometry (LC-MS/MS), and data processed using the MaxQuant and ProStaR softwares. Functional validation were performed in HBV-infected primary human hepatocytes (PHH) and HepaRG in which selected factors were invalidated by RNA interference, or using biochemical inhibition of their functions.
Results: This analysis identified more than 200 proteins, 1/5 of which were significantly enriched in ST-HBc versus control samples. Functional annotation revealed that approximately 50% of these factors were RNA binding proteins (RBPs), and in particular SR proteins, with the most relevant functional category corresponding to factors involved in RNA splicing which were highly interconnected. Functional analyses identified SRSF10 and RBMX as able to strongly and differentially modulate HBV replication. In addition, small compounds targeting the activity of selected SR proteins induced a strong decrease of viral replication suggesting that they could be used as host-targeting agents (HTA).
Conclusion: These data reveal that HBc interacts with a highly interconnected network of RBPs, in particular SRSF10 and RBMX which are involved in several post-transcriptional processes, in particular pre-mRNA splicing and associated trafficking, strongly suggesting that HBc might interfere with these processes to control the fate of viral and/or cellular mRNAs. Current studies are being performed to precisely evaluate the impact of these interactions on viral replication, as well as on viral or/and cellular RNA splicing. The former is important for the potential development of HTA, whereas the latter may lead us to better understand the role of HBc in HBV-induced pathogenesis.

SAT-353

Potential contribution of more sensitive hepatitis B surface antigen assays to detect and monitor hepatitis B infection

C. Pronier[1,2], L. Boizeau[3], D. Candotti[3], B. Jeremy[2], S. Laperche[3], V. Thibault[1,2]. *[1]CHU Pontchaillou, Virology, RENNES, France; [2]IRSET – INSERM UMR 1085 – University Rennes 1, Infection, immunité, facteurs environnementaux et foie (2IFEF), RENNES, France; [3]Institut National de la Transfusion Sanguine, Département d'étude des agents transmissibles par le sang/Centre National de Référence Risques Infectieux Transfusionnels, PARIS, France*
Email: charlotte.pronier@chu-rennes.fr

Background and Aims: Hepatitis B surface antigen (HBsAg) remains the main viral marker for screening and monitoring hepatitis B virus (HBV) infection. The limit of quantification (LoQ) of most current HBsAg quantification assays is around 0.05 IU/mL. The new Lumipulse G HBsAg-Quant assay (Fujirebio) claims a 10-time improved sensitivity. This study aims to assess the performance of this assay in detecting low HBsAg levels in clinical samples.
Method: Plasma or serum samples were selected among individuals with HBV DNA+ and undetectable HBsAg levels (n = 46): 10 samples collected during the early infection ramping phase (panel 1) and 36 from occult HBV carriers (panel 2). An additional panel 3 was composed of 22 samples with low or previously tested discrepant

HBsAg levels. Samples were retrospectively tested with Lumipulse and HBsAg Liaison-XL (DiaSorin; LoQ: 0.05 IU/ml) assays according to manufacturer's instructions. Samples (n = 38), with an initially HBsAg value ≥0.005 IU/ml with the Lumipulse assay, with values just below the threshold, or with an inconclusive result were tested twice to ascertain sensitivity and specificity of the assay.

Results: Overall, 8 of 46 samples (17%), initially screened HBsAg-negative, were tested Lumipulse reactive with mean HBsAg values ranging between 0.010 and 0.054 IU/ml, mostly below the Liaison-XL assay LoQ. Upon initial testing with Lumipulse, 5 (13%) positive results, ranging from 0.006 to 0.051 IU/ml (panel 1–2), were challenged on a second aliquot and were finally concluded as negative. The remaining 33 were confirmed as negative (n = 8) or positive (n = 25). From panel 1, only 1 sample was found positive with a concentration of 0.017 IU/ml. On panel 2, 7 (19%) samples were positive. On panel 3, 21 (95%) samples could be quantified by Lumipulse with a median value of 0.24 IU/ml and 17 (77%) with the Liaison-XL (med. 0.20 IU/ml). Quantification values obtained with the two assays were correlated (r = 0.944, Spearman) with a mean bias of 0.19I U/ml. Most HBsAg quantified samples had detectable viral loads.

Table: Comparison of HBsAg testing in 68 samples using Lumipulse and Liaison-XL assays

Samples	N	Lumipulse		Liaison-XL	
		Reactive	Non-reactive	Reactive	Non-reactive
Panel 1: early infection ramping phase HBV DNA+/HBsAg–/anti-HBcAb–	10	1	9	0	10
Panel 2: occult HBV carriers HBV DNA+/HBsAg–/anti-HBcAb+	36	7	29	0	32*
Panel 3: low or previously tested discrepant HBsAg levels HBV DNA ± /HBsAg+	22	21	1	17	5

*4 not tested because of insufficient volume but non-reactive with the Roche HBsAg qualitative assay.

Conclusion: This study confirms the high sensitivity of the Lumipulse assay allowing the detection of HBsAg in 17% of samples previously classified as negative by current assays. Assays with improved sensitivity will likely modify the clinical interpretation of HBV serological profiles as defined with lower sensitivity assays.

SAT-354

Compare HBsAg retention in the endoplasmic reticulum and the ER stress between the cells transfected or infected by the wild type and pre-S HBV mutants using in vitro transfection and in vivo infection of FRG mice

J.Y.-J. Liang[1], J.-C. Wu[1,2], Y. Chi[1], C.-P. Sun[3], C.-W. Su[4,5], M.-H. Tao[3].
[1]Taipei Veterans General Hospital, Department of Medical Research, Taipei, Taiwan; [2]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan; [3]Academia Sinica, Institute of Biomedical Science, Taipei, Taiwan; [4]Taipei Veterans General Hospital, Divison of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [5]National Yang-Ming University, Faculty of Medicine, School of Medicine, Taipei, Taiwan
Email: jcwu@vghtpe.gov.tw

Background and Aims: In the natural history of chronic hepatitis B virus (HBV) infection, pre-S deletion HBV mutants are more frequently found in cirrhosis and HCC patients. It is hypothesized that the HBV mutants escape the host`s immune attack due to the deletion of the pre-S segment containing immune epitopes. And the persistent replication of mutants account for hepatocarcinogenesis. In this study, we compare the HBV surface antigen (HBsAg) retention in endoplasmic reticulum (ER) and the subsequent ER stress between the Huh-7 cells transfected or hepatocytes in FRG mice infected by the wild type and various pre-S HBV mutants.

Method: Huh-7 cells were transfected by the wild type and the paired pre-S2 deletion HBV mutants. In addition, several pre-S2 deletion mutants were further generated by the substitution of Proline 142 by histidine or alanine, or deletion of Proline 142. Also, pCDNA3.1 was also transfected as a negative control. HBV DNA and HBsAg in transfected cells and culture media were measured. ER stress markers were analysed by Western blot analysis. HBV virions from culture media of transfected cells were purified and used as inoculum to infect the FRG mice that contain implanted human hepatocytes.

Results: The HBsAg in cells/HBsAg in media (retention ratio) was the lowest in the wild type, followed by the pre-S2 deletion HBV mutant with proline 142, and were the highest in the pre-S deletion HBV mutants without proline. The secretion of pre-S deletion mutants was rescued by the co-transfection with the wild type HBV, but the secretion gradually decreased as the wild type HBV decreased. ER stress markers (pIRE1α, XBP1, CHOP) were significantly higher in pre-S mutants without proline. The serum HBV DNA levels of FRG mice infected by the pre-S deletion HBV mutant were 2 logs lower than those infected by the wild type, consistent with the in vitro findings.

Conclusion: Pre-S deletion HBV mutants were impaired in secretion which resulted in the retention of HBsAg and generation of ER stress were verified both in vitro and in vivo systems. The secretion of pre-S deletion HBV mutants was rescued by the coexistence of the wild type HBsAg, but the secretion was further impaired and the retention gradually increased as the wild type HBV was reduced. Although circulating HBV DNA and HBsAg may decrease in late stage of infection, antiviral therapy may better be extended to assure the reduction of HBV DNA replication and HBsAg retention in ER and further decrease of HCC development.

SAT-355

HBV peptide array demonstrates candidate mechanisms of CRV431 anti-HBV activity

R. Foster[1], A. Levin[2], C. Le[2], D. Ure[1], D. Trepanier[1], L. Tyrrell[2]. *[1]ContraVir Pharmaceuticals, Inc., Drug Development, Edison, United States; [2]Li Ka Shing Institute of Virology, Department of Medical Microbiology and Immunology, Edmonton, Canada*
Email: ltyrrell@ualberta.ca

Background and Aims: CRV431 is a cyclosporine A analog that reduces HBsAg, HBV DNA, and other HBV markers. Most of the CRV431 activities are thought to occur by blocking participation of cellular cyclophilins, the primary molecular target of CRV431, in the HBV life cycle. However, the specific cyclophilin interactions that influence HBV have not yet been identified. The aims of the current study were to determine whether cyclophilin A can bind directly to HBV proteins, whether CRV431 blocks the interactions, and to identify the specific HBV protein sequences to which cyclophilin binds.

Method: Soluble, recombinant cyclophilin A was applied to immobilized, 15-amino acid, overlapping peptides representing the entire HBV proteome, and cyclophilin A binding to the peptides was detected with cyclophilin A antibody. CRV431 was additionally applied in some experiments to block the binding. The sequences of the peptides that bound to cyclophilin A were analyzed in detail, and soluble peptides were used in competition experiments to validate cyclophilin A binding to the HBV proteins.

Results: Cyclophilin A bound to 10 HBV-derived peptides, and all 10 binding events were inhibited by CRV431. The peptides that bound cyclophilin A were derived from preS1 HBsAg, HBV polymerase, precore, and core antigen. Furthermore, the peptides overlapped with sequences implicated in regulation of polymerase nuclear import, HBsAg transport and secretion, and capsid formation. One additional interaction between cyclophilin A and a polymerase-derived peptide was found but only in the presence of CRV431. Current studies are

investigating the physiological relevance of the cyclophilin A binding events observed in the peptide arrays.
Conclusion: These studies identified multiple cyclophilin-HBV interactions that may be the target(s) of CRV431 action.

SAT-356

Assessing the in vitro anti-HBV activity of combinations including CRV431, TXL, and prototype capsid assembly modulators

R. Foster[1], J. Greytok[1], D. Ure[1], D. Trepanier[1], J. Kulp[2], P. Gallay[3].
[1]ContraVir Pharmaceuticals, Inc., Research and Development, Edmonton, Canada; [2]Barach S. Blumberg Institute, Research, Doylestown, United States; [3]The Scripps Research Institute, Department of Immunology & Microbial Science, San Diego, United States
Email: jgreytok@contravir.com

Background and Aims: It is expected that a functional cure for chronic HBV infection will require drug combinations targeting the viral life cycle at multiple, complementary stages. CRV431, a cyclophilin inhibitor, blocks HBV interactions with host cyclophilins (cyp) essential for viral replication and chronicity. CRV431 reduces HBV DNA, suppresses HBsAg, inhibits viral uptake via NTCP and blocks HBx-cypA and HBsAg-cypA binding, as shown *in vitro* and in mouse models. TXL, a novel tenofovir (TFV) prodrug in Phase 2 clinical development, inhibits HBV polymerase and is designed to deliver high intra-hepatic tenofovir (TFV) concentrations, while minimizing off-target effects of high circulating TFV blood levels. Capsid assembly modulators (CAMs) block several HBV replication steps, including pre-genomic RNA packaging and cccDNA formation. The aim of our current studies was to investigate the antiviral activity of combinations of TXL, CRV431, and prototype CAMs (BAY41-4109, DVR-56).
Method: Combinations of TXL and CRV431, TXL and CAMs, as well as CRV and CAMs were tested in cell lines supporting HBV replication: AD38, DE19, and DES19. Drug concentrations tested bracketed the EC_{50} of the individual drugs. The endpoints measured for antiviral effect varied according to the cell lines and included intracellular HBV DNA, extracellular HBV DNA, extracellular HBsAg and HBeAg. Endpoints were quantitated according to published methods. Drug concentrations versus antiviral effect were evaluated using Prichard-Shipman MacSynergy and Chalice.
Results: As measured by the suppression of HBV DNA, synergy scores for combinations of CRV431 and TXL, CRV431 and CAMs, TXL and CAMs, ranged from additive to synergistic. None of the combinations tested showed any evidence of antagonism. Cells were viable within the ranges of drug concentrations tested.
Conclusion: These studies extend previous observations of synergy between CRV431 and TXL. Our data demonstrate that novel combinations of antivirals interrupting the HBV life cycle at multiple, previously untested, targets, were additive to synergistic. Importantly, none of the combinations showed antagonism. Two drug classes are currently approved for chronic HBV treatment, nucleoside analogs and alpha interferons. Innovative drugs and treatment strategies will be essential for achieving the HBV functional cure. These results lay the foundation for therapeutic strategies including TXL and/or CRV431 as the basis of drug combinations for the functional cure.

SAT-357

Establishment of a method to compare antiviral effect of drug products by human hepatitis B virus infected humanized chimeric mice

H. Enomoto[1], H. Tachiki[1], M. Moriyama[2]. *[1]Towa Pharmaceutical Co., Ltd., Scientific Research and Business Development Department, Kyoto; [2]Nihon University School of Medicine, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokyo, Japan*
Email: h-tachiki@towayakuhin.co.jp

Background and Aims: There are few reports on evaluation models that can compare the antiviral effects of drug products against hepatitis B virus without clinical trials, and the establishment of the evaluation model is considered to be useful for determining treatment strategies. In this study, for the purpose of establishing a comparative model of antiviral effect in drug products, we evaluated the antiviral effect when using two entecavir (ETV) formulations and pegylated interferon- alfa (PegIFN-α) plus ETV formulation.
Method: The human liver-chimeric mice (PXB-mice) were inoculated with HBV genotype C. After for 8 weeks, animals were treated with saline (p.o.), brand name ETV (bETV: 30 μg/kg p.o./daily), generic drug ETV (gETV: 30 μg/kg p.o./daily), gETV + PegIFN-α (30 μg/kg p.o./daily, 30 μg/kg i.p./two times week) for 2 weeks. Serum HBsAg, HBeAg and HBcrAg were evaluated chemiluminescence immunoassay (CLIA) or chemiluminescence enzyme immunoassay (CLEIA) method. The levels of HBV DNA and intrahepatic HBV covalently closed circular DNA (cccDNA) were quantified by RT-PCR. Intrahepatic HBsAg, HBcAg and HBV DNA localization were evaluated using an immunohistochemical procedure or fluorescence in situ hybridization (FISH). Statistical tests were two-sided; $p < 0.05$ was considered statistically significant.
Results: Among the two treated groups, significant decrease in the serum HBV DNA level were observed in bETV and gETV, and no significant different between bETV and gETV ($p = 0.997$). There were no significant differences in the HBsAg, HBeAg, HBcrAg and HBV cccDNA levels between bETV and gETV. Thus, antiviral effects of bETV and gETV was shown equivalent by this method. In addition, compared to the gETV group, several parameters reduced in the gETV + PegIFN-α group (serum HBV DNA: >1 logIU/ml, serum HBeAg: >0.5 log S/CO, intrahepatic HBsAg and HBcAg: $p < 0.05$). These results were considered to enhance the antiviral effect of gETV + PegIFN-α treatment.
Conclusion: This method was shown equivalence or enhancement of the antiviral effect depending on the type and combination of drugs, it was considered that antiviral effects of drug products can be compared. The present model system using humanized PXB-mice is promising to evaluate the antiviral effects of various drug formulations.

SAT-358

Identification of HBV genotypes and mutations associated to antiviral resistance and vaccine escape in serum and oral fluid samples from chronic hepatitis B patients

M.M. Portilho[1], A.C.D.F. Mendonça[1], B. Lago[1], C. Villela-Nogueira[2], L. Nabuco[2], C.A.P. Ivantes[3], L.L. Lewis-Ximenez[1], E. Lampe[1], L. Villar[1].
[1]Oswaldo Cruz Institute, Laboratory of Viral Hepatitis, Rio de Janeiro, Brazil; [2]Federal University of Rio de Janeiro, Clementino Fraga Filho University Hospital, Rio de Janeiro, Brazil; [3]Center of Orientation and Guidance (COA), Curitiba, Brazil
Email: moyramp@gmail.com

Background and Aims: HBV genotyping and identification of antiviral resistance and vaccine escape mutants are performed using serum samples. However oral fluid samples could be a non-invasive sample to increase the access of diagnosis, particularly, in low resource areas. This study aims to investigate the usefulness of oral fluid samples for identification of HBV genotypes and mutations associated to antiviral resistance and vaccine escape.
Method: Paired samples of serum and oral fluid from 10 chronic hepatitis B patients were submitted to PCR for amplification of HBV polymerase(RT)/surface gene. Biochemical and serological data were also obtained in serum samples. PCR products were purified with a QIAquick PCR Purification Kit (Qiagen, Netherlands) and sequenced with forward and reverse primers using a BigDye Terminator 3.1 Cycle Sequencing kit (Thermo Fisher Scientific). The reactions were performed in an automatic ABI PRISM 3100 Genetic Analyzer Sequencer (Thermo Fisher Scientific). Sequences were analyzed using Mega Software v7.0 and submitted to web-based software (Geno2pheno) for subtyping and prediction of phenotypic resistance

to genotype-specific mutations in the polymerase gene (RT mutation) and escape mutation (HBs mutation).

Results: Among 10 patients, all presented detectable HBV DNA in both types of samples. All individuals presented the same genotypes and subgenotypes in each serum and oral fluid (4 pairs of A1, 2 pairs of A2, 2 pairs of D3, 1 pair of F2 and 1 pair of E) and five pairs presented 100% of homology between HBV sequences in serum and oral fluid. A total of 51 and 57 described RT mutations were found in serum and oral fluid, respectively, but none of them confers resistance to antiviral treatment with lamivudine, Tenofovir, Entecavir or Adefovir, with exception of V173L that is a compensatory mutation for Lamivudine found in an oral fluid sample. The HBs mutation 144A was identified in a pair of samples and three secondary HBs mutations were found in some oral fluid samples (Table 1).

Conclusion: Oral fluid samples demonstrated to be efficient in genotyping HBV since all samples presented the same genotype and subgenotype classification and homology to paired serum sequence. A high number of mutations of RT domain could be identified in paired samples and mutation 144A, which is related to vaccine escape, was detected in a pair.

SAT-359

Identification of a stable HBV inter-genotype (A/G) recombinant strain in a guinean patient in "grey zone" of treatment

A.I. Gil[1,2,3], A. Madejón[1,2,3], I. Francisco-Recuero[1,2,3], E. Villafranca[1], M. Romero[1,2,3], A. García-Sánchez[1], A.O. Martin[1,3], J.C. Erdozaín[1], P. Castillo[1], R. Mena[2,4], F.J.G.-S. Rey[1,2,3]. *[1]Hospital Universitario La Paz, Hepatology Unit, Madrid, Spain; [2]IdiPAZ, Madrid, Spain; [3]CIBERehd, Madrid, Spain; [4]Instituto de Genética Médica y Molecular (INGEMM), Madrid, Spain*

Email: javiersamaniego@telefonica.net

Background and Aims: There are scarce data about the prevalence of hepatitis B virus (HBV) inter-genotype recombination and its effect on the progression of HBV liver disease. The aim of this project was to analyze the presence of recombinant HBV strains in patients with HBV active replication and no treatment (grey zone).

Method: We included plasma samples from 28 HBeAg-negative patients in the grey zone of treatment (HBV DNA titers between 2,000–20,000 IU/ml and mild or moderate necroinflammatory activity). In all cases the HBV genotype was determined by sequencing of the PreS1/PreS2/S and Precore/core coding regions, and subsequent phylogenetic analysis using the MEGA5 program.

Table: (abstract: SAT-358): Clinical, biochemical, molecular aspects and mutations profile of serum and oral fluid samples

Patient	Age (years)	Gender	AST/ALT (IU)	HBeAg status	Previous treatment	Genotype/ Subgenotype	Nucleotide divergence between serum and OF sequences	rt(HBV) mutations (pair)	rt(HBV) mutations (only in serum)	rt(HBV) mutations (only in OF)	s(HBV) mutation (pair)	s(HBV) mutations (only in OF)
1	42	M	11/12	Reagent	No	A1	0.001%	V112I, N122H, Y126C, M129L, V142A, V163I, Q215H, I253V	I53L,	I53H	144*	-
2	52	F	19/42	No reagent	No	D3	0.001%	L91I, F122L, Q130P, N131H, Y135S, C256S, D263E, I266V, V278I	-	V173L	-	-
3	51	M	17/20	No reagent	No	F2	0.007%	M129L, N131D, S137T, S213T, N246S,	N123D, L151F, L220I, T259S, D271E	S74P, D271E, Q288HQ	-	101H
4	31	F	19/9	Reagent	Yes (LMV+TNF)	A2	0.000%	L217R	-	-	-	-
5	24	M	31/12	Reagent	No	A1	0.001%	N122H, M129L, V163I	-	I53N,	-	-
6	40	F	36/18	Reagent	No	A2	0.000%	L217R	-	-	-	-
7	26	M	19/14	Reagent	No	E	0.000%	M267L	-	-	-	-
8	25	F	42/26	Reagent		A1	0.000%	N122H, M129L, W153R, V163I, I253V, V278I	-	-	-	101H
9	64	F	14/12	No reagent	No	A1	0.023%	N122H, M129L, V163I, I253V	-	I53V, W153R, S159T, S219A	-	100C
10	46	M	13/12	Reagent	Yes (TNF)	D3	0.000%	N53K, F122L, Q130P, Y135S, D263E, I266V, V278I	-	-	-	-

Abbreviations: M (Male); F (female); rtHBV (reverse transcriptas of HBV); sHBV (escape mutants of HBV); OF (oral fluid); TNF (Tenofovir); LAM (lamivudine).

Results: Only 2 (7%) patients showed discrepancies among the genotyping results. One of them, Caucasian, did not present evidence of recombination. By contrary, a Guinean patient, previously typed as a mixed infection A + E by LIPA, was typed as HBV-A in the HBsAg region and as a recombinant A/G in the PreC/C region. Structurally, this region had a fragment of 91 bases (nucleotides 1814-1905) with homology with genotypes no-A (D or E), an insertion of 36 nucleotides characteristic of the genotype G and the rest of the coding region of genotype A. In addition, this strain presented the mutation in position 1896, characteristic of genotype G, which induces a stop codon that prevents the synthesis of HBeAg. Of the 14 recombinant A/G sequences described in the literature, only 3 of them showed recombination points in the coding region of the core, and the maximum homology (94%) was found with a Nigerian patient (access number: AM110794) diagnosed as triple recombinant E/G/A. In addition to the high rate of homology, the structure of the recombination zone was identical between the sequence described here and the Nigerian isolate. The patient showed detectable HBV-DNA levels for 11 years [HBV-DNA levels (mean ± SD): 2,594 ± 2,920 IU/ml; range: 52-9,554 IU/ml]. The presence of the recombinant sequence as the major viral species was confirmed in the three samples analyzed, separate for a maximum period of 4 years. The ALT and AST figures were normal throughout the follow-up and the hepatic fibrosis stage (fibroscan) was F2.
Conclusion: The first identification of HBV A/G recombinants sequences with an identical structure in the recombination zone and a 95% homology rate in two patients from West Africa (Nigeria and Guinea) suggests the possibility of transmission of a recombinant A/G strain in this population. Supporting this hypothesis the stability in time of the recombinant in the Guinean patient, the extremely low prevalence of the G genotype in West Africa and the absence of previous reports of A/G strains with conserved recombination structure, even in patients from the same region geographical.

SAT-360

In vitro and in vivo antiviral characterization of RO7049389, a novel small molecule capsid assembly modulator for the treatment of chronic hepatitis B

X. Zhou[1], Y. Zhou[1], X. Tian[1], F. Shen[1], G. Yang[1], W. Zhu[1], G. Ottaviani[2], J. Xie[1], H. Shen[1], J. Young[2], L. Gao[1]. *[1]Roche Innovation Center Shanghai, China; [2]Roche Innovation Center Basel*
Email: lu.gao@roche.com

Background and Aims: The hepatitis B virus (HBV) core protein plays critical roles in multiple steps of the HBV life cycle. The proper assembly of HBV core proteins into capsids around viral pregenomic RNA is essential for HBV replication and maintenance of the nuclear cccDNA pool, thus representing an attractive direct antiviral target. RO7049389 is a small molecule HBV capsid assembly modulator in Phase I clinical development for the treatment of chronic hepatitis B. It is a new generation heteroaryldihydropyrimidine analogue that differentiates from earlier generation by demonstrating no induction potential for major CYP isoforms or UGTs, thus causing less concern on drug–drug interaction liabilities. Here we report *in vitro* and *in vivo* antiviral activities of RO7049389.
Method: In vitro assessments of the antiviral potency, cytotoxicity, HBV genotype coverage, and potential cross-resistance with approved HBV drugs were performed using appropriate cell culture models including HBV-producing stable cell line HepG2.2.15, HepG2 cells transiently transfected with HBV variants construct, and HBV-infected primary human hepatocytes (PHH). In vivo efficacy of RO7049389 was studied in a mouse model with a recombinant adeno–associated virus carrying hepatitis B virus genome (AAV–HBV). HBV DNA was quantified by quantitative real-time PCR. HBsAg and HBeAg were quantified using commercial chemiluminescence immunoassay kits.
Results: RO7049389 exhibited potent inhibition of HBV DNA in HepG2.2.15 cells with an average EC_{50}(± SD) of 6 ± 1 nM and CC_{50} > 100 µM. The molecule demonstrated activity against prevalent HBV genotypes (A, B, C, D) and against a panel of nucleos(t)ide analogues-resistant HBV variants. When RO7049389 was added together with the HBV inoculum in PHH, it prevented cccDNA establishment, leading to a reduction of HBsAg and HBeAg levels. RO7049389 demonstrated *in vivo* efficacy in the AAV-HBV mouse model when orally administered, by not only reducing serum HBV DNA as expected but also HBsAg and HBeAg levels. Once daily dosing of RO7049389 at 20 mg/kg for 8 weeks reduced HBV DNA by 3.0-log, HBsAg by 2.4-log, and HBeAg by 1.5-log. Remarkably, reductions in all of these viral markers, including HBsAg were maintained with no rebound observed within the 3-weeks off-treatment follow-up period.
Conclusion: RO7049389 is a promising anti-HBV agent that exhibited potent antiviral activity in cell culture systems and sustained suppression of HBV DNA, as well as HBsAg and HBeAg in the AAV-HBV mouse model. These effects have clearly differentiated RO7049389 from approved HBV drugs and may translate into higher functional cure rates in a clinical setting.

SAT-361

HBV reactivation and changes in interferon-stimulated gene expression during treatment of direct-acting antivirals for HCV: Analyses in a novel in vitro model for HBV-HCV coinfection using human induced pluripotent stem cell–derived hepatic cells

Y. Asahina[1,2], S. Kaneko[1], S. Kakinuma[1,2], A. Kamiya[3], M. Miyoshi[1], T. Tsunoda[1], E. Inoue[1], S. Nitta[1], A. Sato[1], H. Nagata[1], F. Kawai-Kitahata[1], M. Murakawa[1], Y. Itsui[1], M. Nakagawa[1], S. Azuma[1], M. Watanabe[2]. *[1]Tokyo Medical and Dental University, Department of Gastroenterology and Hepatology, Tokyo, Japan; [2]Tokyo Medical and Dental University, Department of Liver Disease Control, Tokyo, Japan; [3]Tokai University, Institute of Innovative Science and Technology, Japan*
Email: asahina.gast@tmd.ac.jp

Background and Aims: Reactivation of hepatitis B virus (HBV) during direct acting antivirals (DAAs) treatment against hepatitis C virus (HCV) have been reported in patients coinfected with HBV and HCV. However, mechanism responsible for HBV reactivation in such cases remains unknown. As an *in vitro* model, we have recently demonstrated that human induced pluripotent stem (iPS) cell-derived hepatocyte-like cells (iPS-Heps) are susceptible to HBV infection, and exhibit innate immune responses in host cells against HBV. The aim of this study is to investigate the mechanisms associated with HBV reactivation during DAAs treatment for HCV in coinfection with HBV and HCV.
Method: Several human iPS cell lines were differentiated into hepatic lineage using modified 4-step protocol as previously described (Kamiya, 2013). HBV and HCV were obtained from the culture supernatant of HepG2.2.15.7 and Huh7.5.1 transfected with HCV-RNA (JFH1 clone), respectively. HBV-related products and responses of interferon-stimulated genes (ISGs) were analysed using the culture system of iPS-Heps coinfected with HBV and HCV under the culture condition with or without sofosbuvir (SOF).
Results: Quantitative RT-PCR analyses demonstrated that the expression levels of host factors related to HCV life cycle in iPS-Heps were significantly higher than those in Huh7.5.1. The concentrations of HBe-antigen (Ag) and HCV-core Ag in culture supernatant of coinfected iPS-Heps were increased in a time-dependent manner after HBV and HCV coinfection. HCV infection induced the expression of ISGs in host cells, whereas the expression levels of ISGs were relatively lower in HBV-infected host cells. Expression levels of intracellular ISGs were significantly lower in the coinfected host cells than those in cells infected with HCV alone. HCV-core Ag in the culture supernatant was significantly decreased in the coinfected iPS-Heps after SOF treatment. On the other hand, HBeAg in the supernatant, intracellular HBV pregenomic RNA and total HBV transcripts were significantly increased in such cells compared to vehicle-treated cells. Furthermore, the expression levels of

intracellular ISGs were significantly decreased in SOF-treated cells compared to vehicle-treated cells.
Conclusion: Our data demonstrated that our *in vitro* system of iPS-Heps could be a novel research model for coinfection of HBV and HCV, and suggested that HBV reactivation during DAAs treatment for HCV is induced by suppression of ISGs.

SAT-362

Post transcriptional regulation of Hepatitis B virus in a prospective cohort of chronically infected patients

A. Schnuriger[1,2,3], M. Yassmina[2], S. Gourari[4], B. Lekbaby[1,2], T. Attout[1,2], H. Wang[1,2], J. Augustin[2], D. Kremsdorf[1,2], N. Debzi[4], P. Soussan[1,2,5].
[1]Université Pierre et Marie Curie Paris 6, Paris, France; [2]INSERM, U1135, Centre d'immunologie et des maladies infectieuses, Paris, France; [3]APHP, Laboratoire de Virologie Hôpital Trousseau, Paris, France; [4]Hopital Mustapha, Algiers, Algeria; [5]APHP, Laboratoire de Virologie Hôpital Tenon, Paris, France
Email: patrick.soussan@inserm.fr

Background and Aims: Hepatitis B virus transcription leads to expression of several transcripts, namely pregenomic, subgenomic and spliced RNAs. Epigenetic studies showed that its regulation depends on the amount and status of viral DNA. However, post-transcriptional regulation and impact on viral lifecycle remains elusive. Our aim was to investigate the different forms of HBV transcripts in liver tissue and correlate them to the circulating viral particles.
Method: A prospective cohort of 50 HBV chronically monoinfected, treatment naïve patients was constituted. Concomitant serum DNA and liver RNA samples were analyzed. HBs and HBe antigens, ALT levels and Metavir score were measured. Viral DNA and RNA were quantified by Abbott and in-house PCR, expressed in IU/ml and copies/µg RNA respectively. Selected serum samples were used for infection of differentiated HepG2-NTCP cells.
Results: Patients were split in high (n = 24) or low (n = 26) viral load using a cut-off value of 10^4 IU/ml. Despite highest serum ALT levels in highly replicative patients, liver histology was similar in both groups with mainly moderate liver damage. Quantitative HBsAg was not related to the level of replication. In liver samples, HBV pregenomic RNA (pgRNA) was reduced in low viral load group while the level of subgenomic RNAs was similar. We defined a "viral production marker" as the ratio of serum viral load/liver pgRNA. Surprisingly, this marker showed a viral synthesis 100 fold less efficient in low compared to high replicative patients, suggesting that post-transcriptional regulation of pgRNA differed in both groups. Thus, the level of spliced forms of HBV RNA (spRNAs) and subsequent HBV defective particles (dHBV), in serum and liver samples was compared in both groups. The ratio spRNA/pgRNA did not show an increase of the splicing efficiency in low replicative group, suggesting a preferential orientation of pgRNA towards the translation machinery. In accordance with this result, dHBV particles in sera were only detected in the high replicative group. However, our data revealed an alteration of the post-transcriptional machinery in liver tissues. Indeed, despite an overall correlation between pgRNA and spRNAs, spRNAs were unexpectedly detected in 1/3 of low and only in 2/3 of high replicative patients. Viral production and HBV splicing regulation were assessed *in vitro* with serum samples from 4 selected highly replicative patients (3 spRNAs positive and 1 spRNAs negative). Ten days post-infection, efficiencies of viral particles synthesis related to the intracellular pgRNA expression were weak and included in the range of those observed in low replicative patients. In contrast, spRNAs were detected in all infected cells.
Conclusion: Our data showed a dynamic process of the pgRNA outcome toward viral production, translation or splicing and highlighted a role of the liver microenvironment in the viral lifecycle.

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Statin inhibits HDV assembly, secretion, and large hepatitis delta antigen-Smad3-Twist mediated epithelial-mesenchymal transition

J.-C. Wu[1,2], Y.-C. Hsu[2], J.Y.-J. Liang[2], C.-W. Su[3,4]. *[1]National Yang-Ming University, Institute of Clinical Medicine, Taipei, Taiwan; [2]Taipei Veterans General Hospital, Department of Medical Research, Taipei, Taiwan; [3]Taipei Veterans General Hospital, Divison of Gastroenterology and Hepatology, Department of Medicine, Taipei, Taiwan; [4]National Yang-Ming University, Faculty of Medicine, School of Medicine, Taipei, Taiwan*
Email: jcwu@vghtpe.gov.tw

Background and Aims: Hepatitis D virus (HDV) infection is one of the important causes of fulminant hepatitis. In addition, HDV superinfection in chronic hepatitis B (CHB) patients may accelerate CHB to cirrhosis or hepatocellular carcinoma (HCC). Currently, there is no effective treatment. HDV encodes small delta antigens (S-HDAg) and large form HDAg (L-HDAg). S-HDAg is essential for HDV RNA replication, while L-HDAg needs to be isoprenylated to perform HDV virions assembly. In our previous reports, L-HDAg transactivated TGF-β and induced epithelial-mesenchymal transition (EMT) which may contribute to liver fibrosis. However, the mechanism is unclear. In this study, we hypothesized that L-HDAg can activate *twist*, the major regulator of EMT, expression which induces TGF-β, EMT, and may further lead to liver fibrosis. On the contrary, statin treatment may indirectly decrease isoprenylation of L-HDAg. As a result, expression of *twist* and TGF-β may be down-regulated, which may lead to the decrease of EMT.
Method: In this study, human HCC cell line HuH7 was transfected in vitro with three genotypes of S-HDAg, L-HDAg and vector. HBsAg or HBV expression plasmids were also co-transfected to evaluate if stain treatment could reduce secretion of L-HDAg.
Results: Using luciferase reporter, chromatin immunoprecipitation and co-immunoprecipitation assays, we confirmed that L-HDAg specifically activated *twist* promoter through interaction with Smad3. Furthermore, mutation of Smad-binding element in *twist* promoter significantly repressed *twist* promoter expression. Six types of statin were used in the treatment of HuH7 cells which transfected with L-HDAg or S-HDAg at a concentration of 5µM and 25µM. The results showed that all six statins indirectly decrease isoprenylation of L-HDAg and further reduced *twist* expression. In addition, we also observed that a dose-dependent negative correlation between Atrovastatin/Simvastatin treatment and *twist* promoter activity. Furthermore, statin treatment lead to the reduction of EMT and EMT markers expression. Interestingly, statin treatment reduced secretion of L-HDAg and TGF-β in culture medium.
Conclusion: L-HDAg interacted with Smad3 and activated twist promoter. Activated twist promoter increased the expression of TGF-β, which lead to the induction of EMT and EMT markers expression. On the contrary, L-HDAg secretion, TGF-β expression and the properties of EMT are decreased after statin treatment. This study demonstrated that in addition to decrease cholesterol biosynthesis, statin also showed great potential as a novel therapy for the treatment of chronic hepatitis D

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Murine hepatocytes with humanized sodium taurocholat polypeptide (NTCP) limit HDV infection in vivo independent of adaptive immune responses

M. Luetgehmann[1], K. Giersch[2], T. Volz[2], J. Kah[2], L. Allweiss[2], A. Lohse[2], J. Petersen[3], J. Casey[4], C. Sureau[5], M. Dandri[2]. *[1]University Medical Center Hamburg-Eppendorf, Department of Medical Microbiology, Virology and Hygiene, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany; [3]Asklepios Clinic St. Georg, ifi – Institut for Interdisciplinary Medicine, Hamburg, Germany; [4]Georgetown University Medical Center,*

Department of Microbiology and Immunology, Washington D.C, United States; [5]Institut National de la Transfusion Sanguine, Virologie Moléculaire, Paris, France
Email: mluetgeh@uke.de

Background and Aims: NTCP is the functional entry receptor for HBV and HDV and infection. Aim was to establish HDV mono-infection in immunocompetent mice expressing humanized NTCP and to compare efficiency and fate of infection with immunodeficient human liver chimeric mice.
Method: Murine NTCP in C57BL/6J mice was humanized by altering the residues 84–87 using the CRISPR/Cas technology (hNTCP mice). HDV virions of genotype (GT) 1 or 3 were injected i.p. or i.v. into adult hNTCP mice. 5 to 21 days post inoculation (p.i.) viral loads in livers were analysed by qRT-PCR, immunofluorescence staining and RNA in situ hybridisation. Human liver chimeric mice were generated by transplanting human hepatocytes into uPA/SCID/beige mice (USB mice) and were infected similarly. Murine hepatocytes of hNTCP mice were also isolated and transplanted into USB mice.
Results: In hNTCP mice, i.v. administration and HDV GT3 resulted in higher intrahepatic infection levels than i.p. administration and HDV GT1 inoculation, respectively (median copies HDV RNA/ng liver RNA in GT1 i.p.: undetectable, GT1 i.v.: 0.4, GT3 i.p.: 7.5; GT3 i.v.: 3.8). Although less than 0.1% of cells were HDAg-positive in livers of HDV GT3-infected hNTCP mice, the presence of antigenomic HDV RNA, demonstrated intracellular viral replication. Compared to hNTCP mice, HDV GT3-infected USB mice showed substantially higher amounts of intrahepatic HDV RNA (36-fold) and of HDAg-positive cells (0.4%). Infection kinetic studies in hNCTP mice showed detectable intrahepatic HDV RNA levels till day 14 p.i.. At day 21, HDV RNA levels were below detection limit, suggesting virus clearance or death of HDV-infected hepatocytes. Strikingly, intrahepatic HDV infection was also cleared by day 21 p.i. in murine hepatocytes of hNTCP mice which were transplanted into immunodeficient USB mice, while no reduction of intrahepatic infection was observed for at least 42 days in human hepatocytes in humanized USB mice.
Conclusion: HDV mono-infection can successfully be established in hNTCP mice, although intrahepatic HDV loads are higher in human liver chimeric mice. Moreover, HDV infection was cleared within 21 days both in immune competent (hNTCP mice) and in immune deficient systems (after transplantation of hNTCP murine hepatocytes in USB mice), suggesting that additional restriction factors exist in murine hepatocytes that limit HDV persistence. Better understanding of these factors might be important to develop novel antiviral strategies.

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Antiviral properties and liver specific delivery of a TLR1/2 ligand in HBV-infected in vitro and in vivo models

J. Lucifora[1], F. Fusil[2], L. Myriam[3], P. Capucine[3], M. Maud[1], D. Laura[1], A. Ludovic[1], B. Maud[1], F.-D. Suzanne[1], R. Michel[4], S. Daffis[5], S. Fletcher[5], F. Zoulim[1], A. Salvetti[1], F.L. Cosset[6], V. Bernard[7], D. Durantel[1]. *[1]INSERM U1052, Cancer Research Center of Lyon, Lyon, France; [2]Centre International de Recherche en Infectiologie, Lyon, France; [3]Institut de Biologie et Chimie des Protéines (IBCP), Lyon, France; [4]Centre Léon Bérard, Lyon, France; [5]Gilead Sciences, Foster City, United States; [6]Centre International de Recherche en Infectiologie (CIRI), LYON, France; [7]Institut de Biologie et Chimie des Protéines (IBCP), Laboratoire de Biologie Tissulaire et d'Ingénierie Thérapeutique (LBTI), Lyon, France*
Email: julie.lucifora@inserm.fr

Background and Aims: Current therapies for hepatitis B virus (HBV) chronic infections are effective at decreasing viremia in long-life treatment regimen, but do not lead to viral eradication. Recent studies highlighted the therapeutic potential of immune-stimulators to restore immune responses to HBV in various animal models as well as in early clinical trials. Our overall aim was to explore the anti-HBV effect of free or particulated TLR1/2 agonists *in vitro* and *in vivo* in monotherapy approaches.
Method: HBV-infected primary human hepatocytes (PHH), HBV-infected differentiated HepaRG cells (dHepaRG), as well as HBV-infected liver-humanized (HuHep) mice or AAV-HBV transduced mice were treated with TLR1/2 agonist. HBV replication and immune markers/correlates were followed by ELISA, qPCR, qRT-PCR, Southern Blot, and IHS.
Results: Pam3CSK4 (TLR1/2-ligand) was amongst the best TLR agonists tested that reduced viremia and antigenemia in HBV-infected models. Importantly, its antiviral effect was long-lasting *in vitro*, as a result of a strong transcriptional/post-transcriptional inhibition of cccDNA and a slight, but significant, decrease in its level. This effect was associated with an activation of the NFkB pathways in hepatocytes and immune cells, as demonstrated by analyses of mRNA and cytokines production as well as knock down experiments. To prevent systemic immune activation and improve its efficacy, Pam3CSK4 was encapsulated in either "naked or functionalized" nanoparticles that mostly accumulate in the liver of injected mice. Interestingly, nano-Pam3CSK4 led to a stronger antiviral activity as compared to free Pam3CK4 in HBV-infected models, without any toxicological issues.
Conclusion: Our data highlight the potential of innate immunity stimulators, such as TLR1/2 agonists, as direct antiviral effectors in hepatocytes and overall modulators of immune responses. This work further supports the clinical evaluation of TLR agonists as immune adjuvants in more complex immune-therapeutic strategies, based on either prime-boost vaccination or T-cell adoption to cure HBV infections.

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Inhibition of hepatitis B virus X protein in HBV-infected primary human hepatocytes leads to the reappearance of the Smc5/6 complex

R. Beran, C. Voitenleitner, D. Kornyeyev, C. Livingston, W. Xing, H. Kwon, S. Fletcher. *Gilead Sciences, Biology, Foster City, United States*
Email: simon.fletcher@gilead.com

Background and Aims: The host structural maintenance of chromosome 5/6 complex (Smc5/6) suppresses cccDNA transcription. HBV counters this restriction by expressing hepatitis virus X protein (HBx), which redirects the cellular DDB1-containing E3 ubiquitin ligase to target Smc5/6 for degradation. HBx is an attractive therapeutic target because inhibition of this key viral protein has the potential to transcriptionally silence cccDNA. However, it is challenging to evaluate the impact of different therapeutic approaches on this important viral protein due to the lack of a highly specific HBx antibody. Here we describe spatiotemporal analysis of HBx in HBV-infected primary human hepatocytes (PHH) using a novel monoclonal antibody.
Methods: Recombinant proteins and HepG2 cells transduced with a lentivirus expressing HBx were analyzed by Western blot. PHH were infected with wild-type HBV, HBx-negative HBV (HBVΔX), or were mock-infected. In certain experiments, PHH were transfected with siRNA targeting DDB1 (siDDB1), the HBx region of HBV RNA (siHBV) or a non-targeting control at day 3 post-infection. HBx, HBV core, HBsAg and Smc6 were measured by confocal microscopy at various times post-infection.
Results: An antibody that selectively detects recombinant HBx as well as HBx over-expressed in HepG2 cells was selected for confocal imaging studies. HBx exhibited a diffuse nuclear staining pattern in HBV-infected PHH and was not detected in the cytoplasm. Nuclear HBx positively correlated with HBV core and HBsAg and inversely correlated with the presence of Smc6. HBx was not detected in PHH infected with HBVΔX. Consistent with a previous study that characterized the kinetics of Smc6 degradation in HBV-infected PHH, HBx was expressed 1-2 days after infection. Treatment with siDDB1 (which blocks HBx function) and siHBV (which reduces all HBV RNAs, including HBx mRNA) decreased HBx levels and was associated with the reappearance of Smc6 in the nuclei of most HBV-infected PHH by day 18 post-infection.

Conclusions: Using a novel monoclonal antibody, we demonstrated that HBx is localized to the nucleus and is expressed early after HBV infection of PHH. We also determined that inhibition of HBx function or reduction of HBx mRNA levels in HBV-infected PHH leads to the reappearance of Smc6. These data suggest that cccDNA transcriptional silencing by the Smc5/6 complex may be restored by therapeutic targeting of HBx.

SAT-367

FXR is a proviral factor whose binding to HBV genome is modulated by FXR agonist and correlates with presence of the activated chromatin mark H3K4me3 in an HBx dependant manner

B. Lacombe, K. Mouzzanar, C. Ménard, V. Lotteau, C. Ramière, P. Andre.
INSERM U 1111 – CNRS UMR5308 Université Lyon 1, ENS de Lyon, Centre de Recherche International en Infectiologie, Lyon, France
Email: patrice.andre@inserm.fr

Background and Aims: HBV infection, bile acids (BA), and BA nuclear receptor FXR activity are intertwined. HBV compete for binding to the BA receptor NTCP and entry into hepatocytes. FXR response elements have been identified in the Enh2/Cp regulatory region. HBV infection modulates FXR activity in vivo and in HepaRG and PHH cellular models. Reciprocally, FXR agonists repress HBV replication in these models. HBx is known to be a major proviral factor and to bind to and affect FXR dependent expression of cellular genes. We aimed at further deciphering the role of FXR in HBV replication and that of HBx in this regulation.
Methods: An FXR KO HepaRG cell line was generated with shFXR lentiviral vector without affecting its differentiation or NTCP expression. ChIP were performed in Huh7 cells transfected with 1.3xHBV wild type plasmid or 1.3xHBV carrying a premature stop codon in HBx (1.3HBV-ΔHBx). HBV was produced by HepAD38 cells. FXR agonist GW4064 (GW) was used at 10μM.
Results: Permissiveness to HBV infection was dramatically reduced in shFXR-HepaRG cells and was further repressed by GW4064 treatment (GW-txt). In HepaRG, short 4-hour GW-txt quickly and transiently repressed FXR expression. During a single HBV replication cycle in HepaRG, 4-h GW-txt at day 2 p.i. decreased the cccDNA pool and all subsequent viral markers assessed at day 11 p.i. while same txt at day 6 reduced only the expression of the viral mRNA and proteins controlled by the Enh2/Cp. ChIP analysis in presence of 1.3xHBV showed moderate presence of FXR on BSEP and SHP promoters (BSEPp, SHPp), 2 genes up-regulated by FXR activation, and at a higher level on Enh2/Cp, preS1p, and ApoA1p, a gene down-regulated by FXR activation. GW-txt increased FXR binding to BSEPp and SHPp while it decreased FXR binding to Enh2/Cp and preS1p, and ApoA1p. Presence of HEK4me3 followed variations of FXR binding in similar proportions. Absence of HBx, in cells transfected with 1.3HBV-ΔHBx, did not significantly modify the variations of FXR binding and H3K4ME3 presence on BSEPp and SHPp in response to GW-txt. On the opposite, in HBx absence, FXR binding to Enh2/Cp and preS1 promoter, and ApoA1p was decreased and surprisingly, FXR binding to these regions was increased in response to GW-txt.
Conclusion: FXR is a proviral factor that plays an important role in cccDNA formation and maintenance as well as, later, on viral mRNA transcription. Presence of FXR on HBV DNA seems to be critical for both effects. FXR agonist, in addition to the feed-back repression of FXR expression, dramatically releases FXR from viral DNA, an effect that correlates with reduction of cccDNA formation and expression. Activity of Enh2/Cp region seems negatively regulated by FXR agonist as it is for ApoA1. Interestingly, HBx tends to increase FXR and H3K4me3 presence on HBV and ApoA1 promoters in absence of FXR agonist and to favor the release of these factors from the DNA after agonist treatment.

SAT-368

Developing a new world monkey model of chronic HBV infection in the post-chimpanzee era

C. Chen[1], D. Chavez[1], E. Salas[2], D. Tam[2], S. Eng[2], B. Delaney[2], R. Lanford[1], C. Voitenleitner[2]. [1]*Texas Biomedical Research Insitute;* [2]*Gilead Sciences, Biology, Foster City*
Email: christian.voitenleitner@gilead.com

Background and Aims: Hepatitis B virus (HBV), remains a global epidemic in urgent need of curative therapeutics. Scientific progress has been hampered by the lack of an immune-competent non-human primate model for chronic HBV infection. While woolly monkeys can be infected with woolly monkey HBV (WMHBV) they are an endangered species. However, WMHBV has been shown to infect spider monkeys, resulting in low titer viremia. Macaques are readily available research animals but significant differences in the sequence of their viral receptor, sodium taurocholate co-transporting polypeptide (NTCP), render these animals non-susceptible to HBV infection. Comparing NTCP amino acid sequences in the HBV binding region of alternative new world monkeys identified the Bolivian Squirrel Monkey (Saimiri boliviensis) as a potential candidate for infection.
Method: HepG2 cells were transfected with a plasmid expressing the Saimiri NTCP sequence and treated with fluorescently labeled Myrcludex B, a peptide spanning the preS1 region of HBV. Adult animals were inoculated with either HBV or WMHBV and viral DNA in the serum was determined by qPCR. A second cohort of animals was infected with an intravenous injection of either AAV-HBV or AAV8-WMHBV, a recombinant AAV8 carrying an infectious construct of HBV and WMHBV, respectively. Weekly bleeds and liver biopsies were

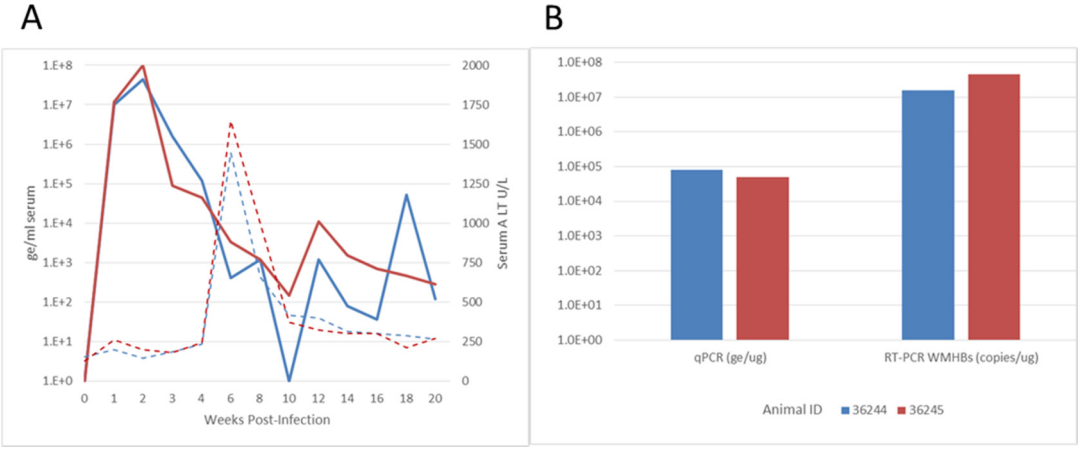


Figure: (abstract: SAT-368)

performed and DNA and WMHBV surface antigen (WMHBs) were analysed by ELISA and qPCR.
Results: HepG2 cells expressing the Saimiri NTCP bind fluorescently labeled Myrcludex B, suggesting that HBV should bind to Saimiri hepatocytes. Preliminary studies with viral inoculation of adult Saimiri with HBV and WMHBV low viremia with titers up to 6.6×10^4GE/μg but provided encouraging results, so we designed a study involving an AAV vector. Squirrel monkeys were injected with AAV8-HBV or AAV8-WMHBV virions. Viral genomes were monitored in serum after injection. A maximum viral titer of 9.9×10^7GE/ml serum for AAV8-WMHBV was observed two weeks after injection followed by an ALT spike (Figure 1A). ALT is a biomarker indicating immune-mediated inflammation and potential removal of infected hepatocytes. We observed a maximum viral titer of 8.2×10^4GE/μg tissue in the liver at week 4. In addition, WMHBs RNA expression was determined to be over 10^7 copies/μg by qPCR (Figure 1B).
Conclusion: Our data suggest that Squirrel monkeys may be a viable alternative to chimpanzees for modelling chronic HBV infection.

SAT-369
Reduction of serum infectivity of hepatitis Delta virus-infected patients treated with Myrcludex B: An in vitro assay to determine infectious units

K. Schöneweis[1], F. Lempp[1], M. Bock[1], F. Schlund[1], B. Bremer[2,3], A. Alexandrov[4], H. Wedemeyer[3], S. Urban[1,5]. *[1]Molecular Virology, Department of Infectious Diseases, Heidelberg, Germany; [2]Gastroenterologie, Hepatologie und Endokrinologie, Medizinische Hochschule Hannover, Hannover, Germany; [3]Hannover Medical School, Department of Gastroenterology, Hepatology and Endocrinology, Hannover, Germany; [4]MYR GmbH, Bad Homburg, Germany; [5]German Center for Infectious Diseases, TTU hepatitis, Heidelberg, Germany*
Email: stephan.urban@med.uni-heidelberg.de

Background and Aims: The entry inhibitor Myrcludex B (MyrB) blocks the HBV/HDV receptor NTCP. In a phase II clinical trial (MYR202), MyrB profoundly reduces HDV serum RNA levels as determined by RT-PCR diagnostics. It is presently unknown HDV serum levels reflect fully infectious virions. Moreover, it is unclear if MyrB treatment induces resistance. We therefore, developed an in vitro cell culture assay to analyze HDV infectivity and MyrB resistance in patient serum.
Method: HuH7-hNTCP cells were inoculated with sera from patients obtained at baseline (BL) or week 12 (w12) on treatment with MyrB/TDF or TDF alone. At day 3 post infection medium was exchanged and Hepatitis Delta antigen-specific immunofluorescence and automated cell quantification was performed (day 5).
Results: Infection rates obtained with sera from w12 during MyrB/TDF treatment were reduced by 43-fold in 100% of the 32 analyzed patients. In comparison serum infectivity at w12 from patients on TDF alone remained unchanged (n = 11). To quantitatively correlate serum infectivity with serum HDV RNA levels, we developed a TCID50 assay to define infectious units. In most of the cases, we found a remarkable correlation of the TCID50 values with HDV RNA quantified by RT-PCR. Interestingly, we identified patient sera from BL and week 12 with lower (>1 log10) TCID50 values compared to the respective serum HDV RNA level. This indicates the presence of defective HDV RNA containing particles. Vice versa, we identified sera (n = 3) with a higher infectivity (>1 log10) than predicted by the RT PCR values, indicting a reduced sensitivity of the PCR towards this HDV sub genotype. We finally applied our assay to test for MyrB resistance. All of the 120 patients were still sensitive to MyrB indicating no development of resistance within 12 weeks of treatment.
Conclusion: Our assay highlights HDV serum infectivity tests as a novel parameter to monitor HDV patients. The identification of poorly infectious HDV particles requires subsequent studies to characterize whether these defective particles have defects in the HBV envelope and/or carry HDV replication-deficient genomes. As expected for a drug that targets a cellular receptor no short term resistance against MyrB was observed.

SAT-370
The protein complex structural maintenance of chromosomes reappears after interferon alpha treatment in hepatitis B virus infected humanized mice but its presence does not hinder viral rebound

K. Giersch[1], T. Volz[1], L. Allweiss[1], A. Lohse[1], S. Urban[2], J. Petersen[3], M. Lütgehetmann[1], M. Dandri[1]. *[1]University Medical Center Hamburg Eppendorf, Department of Medicine, Germany; [2]University of Heidelberg, Department of Infectious Diseases, Germany; [3]IFI Institute Hamburg, Liver Center, Germany*
Email: m.dandri@uke.de

Background and Aims: The hepatitis B virus (HBV) X protein (HBx) is essential to initiate cccDNA transcription and HBx was shown to mediate the degradation of the structural maintenance of chromosomes (Smc) 5/6 complex, suggesting that Smc5/6 acts as a host restriction factor by inhibiting cccDNA transcription. **Aim** of this study was to investigate (1) whether interferon-mediated suppression of cccDNA transcription, which should lower also HBx expression, leads to smc5/6 reappearance in infected cells and (2) whether viral rebound is hindered by the presence of this host factor in cells already harboring an established cccDNA.
Method: We treated HBV infected human liver chimeric mice with pegylated interferon alpha (peg-IFNα) for 6 weeks. After that mice were either sacrificed, or left untreated to assess viral rebound or received the entry inhibitor Myrcludex-B (MyrB) to prevent occurrence of new infection events. HBV loads in serum and liver were analyzed by qRT-PCR. HBcAg and Smc6 protein were visualized by immunofluorescence. RNA in situ hybridization was combined to immunofluorescence to detect Smc6 and pgRNA at single cell level.
Results: Peg-IFNα treatment reduced viremia by 1.7 log and compared to untreated controls lowered intrahepatic pgRNA, total HBV DNA and cccDNA 7.3-, 16- and 5.3-fold, respectively. Smc6 protein appeared degraded in almost all human hepatocytes in HBV-infected mice, while Smc6 was clearly detected in uninfected mice and in HBcAg- and pgRNA-negative human hepatocytes (around 50%) in livers of peg-IFNα treated mice. After stopping IFN-treatment, viremia rebounded to BL within 3 weeks and intrahepatic HBV markers were comparable to those obtained in HBV-infected untreated controls. Viremia rebound was associated with renewed degradation of Smc6 and reappearance of HBcAg and pgRNA in nearly all human hepatocytes. Interestingly, HBV rebound was delayed in MyrB-treated mice, which also displayed higher amounts of Smc6 positive cells.
Conclusion: Peg-IFNα treatment is accompanied by the reappearance of Smc5/6 complex in human hepatocytes in vivo, indicating that drugs lowering HBV RNA levels promote Smc5/6 rebound. While Smc6 appears to be a reliable marker of infection and cccDNA activity, these results suggest that the presence of Smc6 does not hinder viral rebound in the setting of established HBV infection. Notably, MyrB delayed viral rebound by blocking reinfection of cells that may have cleared the cccDNA during IFN treatment.

SAT-371
Hepatitis B virus escapes non-canonical CTL effector function

K. Sandra[1], K. Steiger[2], U. Protzer[3], P.A. Knolle[1], D. Wohlleber[1]. *[1]Technische Universität München, Institute of Molecular Immunology, Munich, Germany; [2]Technische Universität München, Institute of Pathology, Munich, Germany; [3]Technische Universität München, Institute of Virology, Munich, Germany*
Email: dirk.wohlleber@gmail.com

Background and Aims: The effector molecule of the non-canonical CTL effector function, Tumor necrosis factor (TNF), induces apoptosis selectively in adenovirus- or lymphocytic choriomeningitis virus-infected hepatocytes but not in non-infected hepatocytes. Therefore,

viral infection sensitizes virus-infected hepatocytes towards TNF-mediated death-inducing signaling processes. Mitochondria serve as central integrators of death signaling in hepatocytes and alterations in mitochondrial functionality influence TNF-induced signaling that can either promote death or cell survival. Here we aimed to elucidate whether a Hepatitis B virus (HBV) infection also induces changes in mitochondria functionality and thereby sensitizes infected hepatocytes towards TNF-induced apoptosis.

Method: To investigate the non-canonical CTL effector function in clearing HBV infection we used an adenovirus as a model for liver infection in mice. We transferred 1.3 overlengh HBV genomes via an adenoviral virus (AdHBV) into mice and compared this to an adenoviruses encoding for GFP (AdGFP), known to sensitize hepatocytes towards TNF induced apoptosis. To investigate only the non-canonical CTL effector function we applied recombinant TNF systemically in the mice and checked for apoptosis induction in virus infected hepatocytes. In addition, we isolated mitochondria from AdHBV and AdGFP infected murine livers and analyzed mitochondrial functionality.

Results: We found that Hepatitis B virus escapes the TNF-induced apoptosis signaling in hepatocytes. Systemically applied TNF in mice infected with AdHBV did not cause liver damage detected by a lack of elevated serum ALT levels. In contrast, high levels of serum ALT could be detected in TNF treated mice that were infected with AdGFP. The responsible factor for the inhibition of the TNF induced apoptosis in AdHBV infected hepatocytes could so far not be identified, but the HBV core proteins, the X-protein and S-antigens could be excluded as inhibitors of apoptosis, shown by using AdHBV with selective mutations in these proteins. Moreover, the altered mitochondrial functionality, namely lack of stable energy production, decreased mitochondrial membrane potential, increased calcium sensitivity and enhanced cytochrome C release detected after AdGFP infection, which is most likely the cause for sensitization of virus-infected hepatocytes is absent in AdHBV infection.

Conclusion: Our observations for the first time identify an immune escape of HBV in infected hepatocytes that circumvents the non-canonical CTL effector function at the level of mitochondrial functionality. These results may be helpful for the development of therapies against chronic HBV infection, by restoring the mitochondrial sensitivity in HBV-infected hepatocytes.

SAT-372

HBsAg transcomplementation of defective HBV genomes in HBeAg negative chronic HBV infected patients

K.-H. Peiffer[1,2], L. Kuhnhenn[1,2], B. Jiang[2], J. Vermehren[1], V. Knop[1], S. Zeuzem[1], C. Sarrazin[1,3], E. Hildt[4]. *[1]J.W. Goethe University Hospital, Medical Clinic 1, Frankfurt am Main, Germany; [2]Paul-Ehrlich-Institut, Department of Virology, Langen (Hessen), Germany; [3]St. Josefs-Hospital Wiesbaden, Gastroenterology, Wiesbaden, Germany; [4]Paul-Ehrlich-Institut, Virology, Langen (Hessen), Germany*
Email: kai-henrik.peiffer@kgu.de

Background and Aims: The HBV surface proteins (HBsAg) coat the viral particle and form in addition subviral particles (SVPs). Loss of HBsAg represents a functional cure and is an important treatment goal in HBV infected patients. We aimed to analyze the impact of the HBV genotypes A-E (GTA-GTE) and mutations in the preS-domain on HBsAg expression, composition, and morphology of SVPs in a large European cohort of HBeAg negative chronic HBV infected patients.

Method: Sera of HBeAg negative chronic HBV infected patients from the German multicenter Albatros study were used. Mutations in preS were determined by direct and deep sequencing. SVPs were characterized via HBsAg-specific western blotting, sucrose density gradient centrifugation and electron microscopy. For a more detailed analysis of the impact of pre S mutations on HBsAg expression a GTA 1.5-fold HBV genome with a 15 aminoacid deletion in the preS1 domain was analyzed in cell culture in comparison to a GTA 1.5-fold genome from a patient without mutations in the preS domain.

Results: We observed a genotype-specific ratio of the three surface proteins (SHBs/MHBs/LHBs), which reflects differences in the morphology and composition of released SVPs with a higher particle density in HBV GTB and GTD in comparison to GTA, GTC and GTE. A higher filaments/spheres ratio was observed in HBV GTB and GTD. While deletions/mutations in the preS1/preS2 domain detected in the released viral genomes do not affect the molecular weight of MHBs and LHBs in our patients, LHBs molecular weight is altered in our *in vitro* analysis using a HBV genome harboring a preS1-deletion. As secreted HBsAg and the released viral genomes cannot be derived from the same genetic source in these patients, HBsAg must be derived from the integrated DNA.

Conclusion: Differences in composition and morphology of SVPs may result in a genotype-specific immunogenicity and pathogenesis. As HBsAg can be sufficiently expressed from integrated DNA, this HBsAg source has to be considered for novel antiviral strategies in HBeAg negative chronic HBV infected patients.

SAT-373

Recapitulation of the complete HDV replication cycle in a novel hepatoma cell line allows for efficient antiviral compound evaluation

F. Lempp[1,2], F. Schlund[1], L. Rieble[1], L. Nussbaum[1], C. Eck[1], Y. Ni[1,2], S. Urban[1,2]. *[1]University Hospital Heidelberg, Molecular Virology, Heidelberg, Germany; [2]German Center for Infection Research (DZIF), Partner site Heidelberg, Heidelberg, Germany*
Email: florian.lempp@med.uni-heidelberg.de

Background and Aims: Chronic Hepatitis Delta Virus (HDV) infections represent the most severe form of viral hepatitis. As a satellite virus, HDV depends on the helper function of Hepatitis B Virus providing the envelope proteins for progeny virus secretion. After the identification of the cellular receptor NTCP, novel cell culture models for HDV have been established allowing entry and replication of the virus. However, virus assembly and progeny release is blocked due to the lack of the HBV surface proteins. Our aim was to generate a novel cell line that recapitulates the full HDV replication cycle including progeny secretion and to use this cell line for evaluation of antiviral compounds currently in clinical development and to test the infectivity of patient-derived serum HDV compared to cell-culture derived virus (HDVcc).

Method: HepG2 cells were stably transduced to overexpress NTCP and the three HBV surface proteins. An in-cell ELISA assay was established for fast and reliable quantification of HDV infection. Drug treatment during initial infection with the two investigational drugs Myrcludex B and Lonafarnib and the approved drug Interferon-alpha (IFNa) were performed and progeny virus was quantified by reinfection experiments.

Results: After infection with HDV, our novel cell line secreted infectious progeny virions for more than 20 days. Evaluation and activity testing of antiviral drugs showed that Myrcludex B (IC50: 1 nM) and IFNa (IC50: 20 IU/ml) dose-dependently inhibited initial infection, but in the case of IFNa, inhibition was only to about 20-30% of uncompeted infection. Lonafarnib inhibited progeny virus secretion (IC50: 35 nM) but lead to a substantial intracellular accumulation of Hepatitis Delta Antigen. Inoculation of the cell line with patient-derived virus versus HDVcc lead to similar infection extents, however, kinetics of progeny secretion was delayed and induction of innate immune responses was drastically reduced in patient-derived virus versus HDVcc.

Conclusion: We have established the first susceptible cell line that recapitulates the full replication cycle of HDV. Using these cells, we have validated the mechanism of action of investigational drugs and, for the first time, determined IC50 concentrations based on progeny virus secretion. The cell line presents an ideal tool for drug evaluation and small compound or siRNA/CRISPR-Cas screening.

SAT-374

Proteomic analysis of hepatitis B virus cccDNA-specific associated proteins identifies crucial regulators of viral transcription and RNA processing

B. Testoni[1,2], D. Avila[3], J. Walther[3], J.D. Zhang[3], A.J. Muelle-Breckenridge[3], F. Chapus[1,2], M. Locatelli[1,2], H. Meistermann[3], S. Maadadi[1], A. Diederichs[1], J. Fresquet[1], C. Bieniossek[3], J. Young[3], S. Luangsay[3], F. Zoulim[1,2,4]. [1]*CRCL, INSERM U1052, Lyon, France;* [2]*Université Lyon 1, Lyon, France;* [3]*Hoffmann-La Roche Ltd, Basel, Switzerland;* [4]*Hospices Civils de Lyon, Lyon, France*
Email: barbara.testoni@inserm.fr

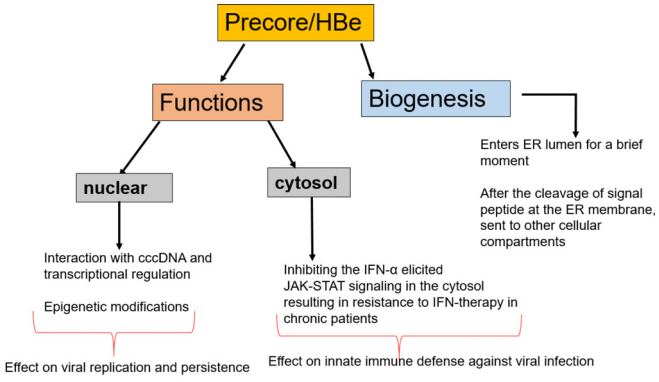
Background and Aims: Covalently-closed-circular (ccc)DNA is responsible for the persistence of hepatitis B virus (HBV) infection. The cccDNA pool stably resides in the nucleus of infected cells, unaffected by current available antiviral therapies, and serves as template for all viral transcripts. Histones, HBV core (HBc) protein and cccDNA are closely linked together to build a dynamic chromatin structure that is subject to the regulation by transcription factors and cofactors translating into different levels of biological activity. A comprehensive knowledge of the network of cccDNA-interacting partners controlling its activity during chronic infection is still lacking. To this aim, we developed a new approach to identify and characterize the global cccDNA-associated proteome combining cccDNA-specific ChIP to high-throughput Mass Spectrometry (MS) analysis, named chromatin proteomics (ChroP).
Method: The ChroP protocol was performed using 4 batches of HepG2-NTCP cells and 5 batches of primary human hepatocytes (PHHs) comparing mock *versus* HBV-infected cells at 9 days post-inoculation, when the cccDNA pool is stable and transcriptionally active. The HBV minichromosome and its associated proteins were specifically enriched by performing an Hirt DNA extraction followed by a sequential histone H3 + HBc ChIP to exclude all HBV replicative intermediates not associated to chromatin structure.
Results: Gene Set Enrichment Analysis highlighted fundamental differences in the cccDNA-associated protein network between PHH and HepG2-NTCP cells: while transcription and RNA dynamics were among the most enriched pathways in PHH, innate immune response, lipid metabolism and angiogenesis were the most over-represented pathways in HepG2-NTCP cells. By applying the majority voting system, the overall data reflect a core network of cccDNA partners involved in nuclear matrix localization, transcriptional regulation and RNA processing/export. Functional silencing of selected network members by RNA interference severely affected viral replication and indicated the FUS protein as one of the key players in coupling the regulation of viral RNA transcription and processing by connecting cccDNA with the spliceosome machinery and the Transcription Export (TREX) complex involved in RNA nuclear export.
Conclusion: We developed a new methodology able to identify host factors essential for cccDNA biological activity in HBV infectious models and to reveal new potential therapeutic targets.

SAT-375

Biogenesis and function of intracellular hepatitis B e antigen

B. Mitra[1], E.S. Kim[1], R. Mao[1,2], J. Wang[2], Y. Liu[1], J. Zhang[2], H. Guo[1]. [1]*Indiana University School of Medicine, Microbiology and Immunology, Indianapolis, United States;* [2]*Huashan Hospital, Fudan University, Department of Infectious Diseases, Shanghai, China*
Email: haitguo@umail.iu.edu

Background and Aims: Antagonism of host innate immune defenses against HBV infection by the viral proteins and existence of nuclear, covalently closed circular (ccc) HBV DNA are speculated to cause HBV persistence and development of chronic hepatitis. The circulating HBeAg (p17) is known to manipulate host immune responses to assist in the establishment of persistent viral infection. However, the function(s) of the intracellular form of HBeAg, previously reported as the precore protein intermediate (p22) without the N-terminal signal peptide, remains elusive. Here, we report that p22 is playing a role in maintaining HBV chronic infection by inhibiting IFN-α mediated antiviral response and interacts with ccc DNA. Further, we also confirm the presence of a novel ER sorting mechanism for distribution of p22 and secretory HBeAg.
Method: Liver biopsies from HBeAg(-) and HBeAg(+) patients treated for six months with interferon-alpha (IFNα) were used for the RNA-seq. To investigate the effect of p22 in regulating host IFN-α elicited JAK-STAT signalling, interferon-sensitive response element (ISRE) activity was measured by a luciferase reporter assay and quantitative RT-PCR was done to detect the expression level of interferon stimulated genes (ISGs) upon IFN-α stimulation in absence or presence of p22. Transient overexpression of HA-tagged p22 in HepG2 and 293T cells preceding subcellular and microsomal fractionations was used for the mechanistic study of p22-mediated JAK-STAT inhibition and for understanding the biogenesis of p22, respectively. Co-immunoprecipitation was employed to study p22's interaction with karyopherin-α1 (Kα1). Chromatin immunoprecipitation using stable cell lines with cccDNA-dependent HA-tagged p22 expression in a tet-off system were used to study the p22-cccDNA interaction.
Results: The p22 but not the secreted HBeAg(p17) significantly reduced ISRE activity and expression of ISGs upon IFNα stimulation. RNA-seq analysis of ISG induction profile from IFN-α treated patients showed that HBeAg(+) patients exhibited reduced and weak antiviral ISG upregulations compared to HBeAg (-) patients. Mechanistic study indicated that p22 blocks the nuclear translocation of pSTAT1/2 by competing with the latter to interact with Kα1. Secondly, we found a nuclear form of p22 that can bind to cccDNA. Thirdly, we have identified that a portion of p22, after the cleavage of its signal peptide and formation in endoplasmic reticulum, gets released back into the cytosol through an ERAD-independent mechanism.
Conclusion: Thus, our results indicate that there is a novel ER sorting mechanism for the distribution of the p22 and secretory p17, and p22 may contribute to HBV persistence and affect prevailing IFN-therapy by interfering with IFNα elicited JAK-STAT signalling and regulating cccDNA metabolism.



SAT-376

EFTUD2 restricts hepatitis B virus infection by regulating RIG-I expression

C. Zhu[1], F. Xiao[2], Q. Wang[3], T. Zhu[3], L. Kong[3], J. Li[3]. [1]*The First Affiliated Hospital of Nanjing Medical University, Department of Infectious Disease, Nanjing, China;* [2]*Stanford University School of Medicine, Department of Microbiology and Immunology;* [3]*The First Affiliated Hospital of Nanjing Medical University, Department of Infectious Disease*
Email: chuanlong@yahoo.com

Background and Aims: Recently, RIG-I has been identified dually functions as an innate sensor and direct antiviral factor for hepatitis B virus (Sato S, et al. Immunity, 2015). We have reported that EFTUD2 exercised antiviral ability via RIG-I pathway in HCV JFH1 culture

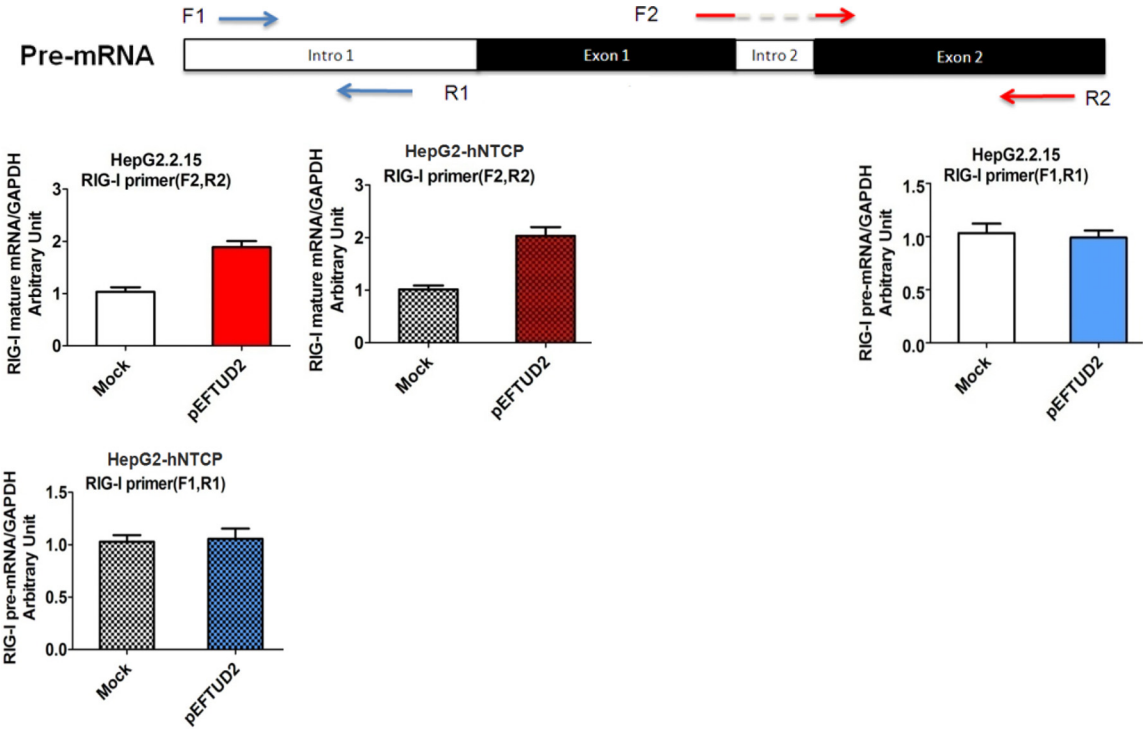


Figure 1: (abstract: SAT-376): EFTUD2 upregulates RIG-I mature mRNA expression.

system (Zhu C, et al. J Virol, 2015), but its role in HBV infection remains unknown. In this study, we evaluate whether EFTUD2 can restrict HBV infection through regulating RIG-I expression.

Method: We overexpressed EFTUD2 by plasmid transfection, then performed siRNA knockdown of RIG-I in HepG2.2.15 or HBV-infected HepG2-NTCP cells. Selected gene expression were monitored by quantitative PCR and Western-blot. Levels of viral antigen expression and HBV DNA were measured by enzyme-linked immunosorbent assay and quantitative PCR, respectively.

Results: EFTUD2 overexpression inhibited HBV replication from 6,511,626 ± 1,108,827 to 3,030,405 ± 403,128 IU/ml ($p = 0.0069$) in HepG2.2.15 cells, and meanwhile reduced HBsAg and HBeAg production by 58.9 ± 9.1% (13.49 ± 1.27 vs 5.54 ± 1.25; $p = 0.0015$) and 39.7 ± 2.0% (22.86 ± 1.83 vs 13.79 ± 1.34; $p = 0.0022$) in culture supernatants, respectively. We further confirmed EFTUD's anti-HBV ability in a novel HBV culture system, namely HepG2-NTCP infected with HBV. Moreover, EFTUD2 overexpression resulted in a increase in RIG-I mature mRNA level in both HepG2.2.15 and HBV-infected HepG2-NTCP, indicating RIG-I mediate EFTUD2's antiviral effect, which could be reversed by specific siRNA against RIG-I.

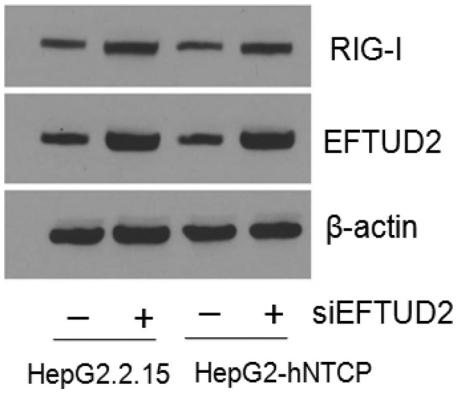


Figure 2: EFTUD2 upregulates RIG-I protein expression.

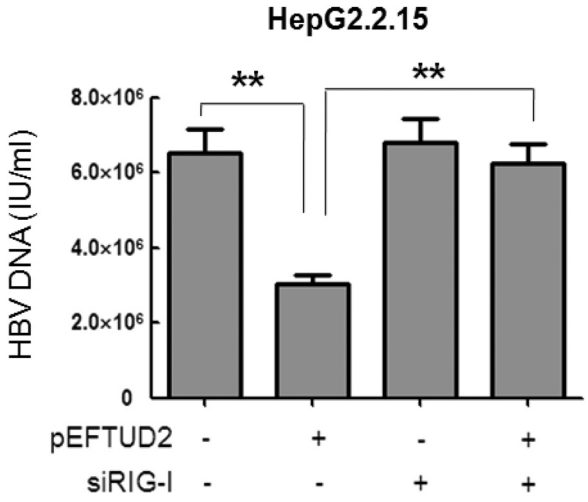


Figure 3: EFTUD2-induced antiviral effect is dependent of RIG-I pathway.

Conclusion: Our data demonstrate that EFTUD2 inhibits HBV infeciton through upregulating RIG-I expression, and may provide a potential antiviral target for anti-HBV therapy in the future.

SAT-377

Hepatitis E virus activates signal transducer and activator of transcription 3 to facilitate virus replication

W. Wang[1], Y. Wang[2], C. Qu[1], S. Wang[2], J. Zhao[2], M. Peppelenbosch[1], Q. Pan[1]. [1]*Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Beijing 302 hospital, Beijing, China*
Email: w.wang.2@erasmusmc.nl

Background and Aims: Hepatitis E virus (HEV) is the most common causes of acute viral hepatitis globally, but the mechanisms by which it corrupts hepatocyte cellular machinery to facilitate its replication remain only partially understood. STAT3 is a vital transcription factor centrally involved in cell signaling pathways to exert diverse cellular

responses. This study aims to reveal the interactive dynamics of STAT3 with hepatitis E virus (HEV) and the consequences for viral replication.
Method: The HEV infectious model (Huh7 cells containing the full-length HEV genome, Kernow-C1 p6) was used. Paraffin-embedded liver tissues from 21 HEV patients were also used.
Results: Here, we demonstrate that HEV potently activates STAT3 phosphorylation in the liver of hepatitis E patients and in cell cultures. This corresponded to a concomitant increase in STAT3-related transcriptional activity. Mechanistically, HEV-mediated STAT3 activation is independent of classical humoral IL-6 and interferon signaling but involves hijacking of Janus kinases (JAKs) and Src kinases via the active viral infection. Importantly, genetic or pharmacological inhibition of STAT3 activation constrained HEV replication. Conversely, over-expression of the activated form of STAT3 increased HEV replication.
Conclusion: Our results revealed a previously undescribed function of STAT3 as a pro-HEV host factor. HEV-induced STAT3 phosphorylation in turn create a favorable environment to facilitate HEV replication. Therefore, STAT3 serves as a promising target for the development of antivirals against HEV.

SAT-378

Pro-fibrogenic mediator osteopontin is intimately involved in chronic hepatitis B and promotes cccDNA production

S. Phillips[1,2], J. Coombes[1,2], S. Mistry[1,2], M. Simonova[3], T. Hadzhiolova[3], S. Pavlova[3], K. Katzarov[3], P. Kennedy[4], U. Gill[4], T. Pereira[5], F.E. Pereira[6], R. Williams[1,2], W. Syn[1,2], S. Chokshi[1,2].
[1]Institute of Hepatology, Foundation for Liver Research, London, United Kingdom; [2], King's College London, Faculty of Life Sciences and Medicine, London, United Kingdom; [3]Clinic of Gastroenterology and Hepatology, Military Medical Academy, Sofia, Bulgaria; [4]Hepatology, Centre for Immunobiology, Blizard Institute, Barts and The London School of Medicine and Dentistry, Queen Mary, University of London, London, United Kingdom; [5]Laboratório de Patologia Experimental, Centro de Pesquisas Gonçalo Moniz/Fiocruz, Salvador, BA, Brazil; [6]Núcleo de Doenças Infecciosas, Universidade Federal do Espírito Santo, ES, Vitória, Brazil
Email: s.phillips@researchinliver.org.uk

Background and Aims: We have previously shown that host proteins actively participate in HBV replication (Phillips et al, Gastroenterology 2015). This study aimed to dissect the role of host-protein and pro-fibrogenic mediator Osteopontin (OPN) in chronic HBV infection (CHB) during the clinical phases of CHB, HBV-driven liver injury and to also evaluate its role in driving covalently closed circular DNA (cccDNA) formation.
Method: OPN levels were measured by ELISA in sera/plasma (S/P) of healthy controls (HC) and 102 CHB patients during disease phases; HBeAg(+)CHB (CI;Immunotolerant), HBeAg(+)chronic hepatitis (CH; Immune active), HBeAg(-)CI (Inactive carrier) and HBeAg(-)CH. OPN was also quantitated in CHB patients with different fibrosis stages (n = 81) intrahepatically, in S/P and in paired CHB patients undergoing NUC treatment (n = 9). Finally, HepaRG cell-line infected with HBV was cultured over 72h in presence/absence of recombinant OPN (recOPN) and neutralizing OPN-specific aptamers. Cells and supernatants were harvested at 24, 48 and 72 hours. HBV replication and antigenemia were assessed by qPCR and cccDNA was quantified using digital droplet PCR.
Results: S/P OPN levels were elevated by 4-fold in CHB ($p = 0.002$) and increased with fibrosis stages ($p = 0.006$). In HBeAg(-)CI and CH, OPN levels were elevated in comparison to HC (4.3-fold; $p = 0.054$; 4.7-fold; $p = 0.005$). However, HBeAg(+)CI exhibited decreased OPN levels compared to all other groups; HC (5.2-fold; $p = 0.001$), HBeAg(+)CH (13.8-fold; $p = 0.06$), HBeAg(−)CI (22.6-fold; $p < 0.001$) and HBeAg(−)CH (24.7-fold; $p < 0.001$). Interestingly, CHB patients with no fibrosis but with elevated vireamia displayed increased level of S/P OPN compared to HC (4.5-fold; $p = 0.0003$). Furthermore, patients whose viral load became undetectable during antiviral treatment had a significant reduction in S/P OPN (1.5-fold; $p = 0.039$). In vitro, HepaRG treatment with recOPN significantly enhanced viral replication, antigen production and cccDNA levels (34-fold; $p = 0.02$) whereas neutralising OPN aptamers decreased all viral parameters and cccDNA levels ($p = 0.04$).
Conclusion: OPN levels directly correlate with viral replication rates, severity of HBV-driven fibrosis and exhibit differential expression during the different phases of CHB disease, thus identifying a marker for CHB driven liver disease. We also demonstrate that OPN is directly involved in HBV replication and can augment cccDNA levels. Finally, we show that neutralisation of OPN can reduce cccDNA and reveal a novel therapeutic strategy for CHB.

SAT-379

Whole genome viral sequencing reveals subgenotype specific dynamics of antiviral treatment response in HBeAg positive and treatment naive chronic hepatitis B patients

O. Podlaha[1], K. Agarwal[2], A. Thompson[3], G. Foster[4], D. Samuel[5], H. Yatsuhashi[6], A. Gaggar[1], K. Kitrinos[1], Z. Jiang[1], M. Tong[7], E. Gane[8], M. Brunetto[9]. *[1]Gilead Sciences, Inc., Foster City, California, USA; [2]Kings College Hospital NHS Trust, London, United Kingdom; [3]St. Vincent's Hospital Sydney, Sydney, Australia; [4]Barts Health NHS Trust, London, United Kingdom; [5]Hopital Paul Brousse, Villejuif, France; [6]National Hospital Organization Nagasaki Medical Center, Nagasaki, Japan; [7]Huntington Medical Research Institutes, Pasadena, California, USA; [8]Auckland Clinical Studies, Auckland, New Zealand; [9]UO Epatologia, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*
Email: ondrej.podlaha@gilead.com

Background and Aims: Full genome viral deep sequencing may provide valuable insights into which clinical outcomes are genetically driven. Our goal was to identify associations between the baseline population genetic structure of the hepatitis B virus (HBV) and antiviral treatment response.
Method: Whole genome HBV amplicons from 1098 HBeAg positive and negative chronic hepatitis B patients enrolled in two global phase 3 studies of tenofovir alafenamide versus tenofovir disoproxil fumarate (GS-US-320-0108 and GS-US-320-0110) were sequenced on Illumina MiSeq instrument. Single nucleotide variation was assessed across the entire ~3.2Kb HBV genome and multidimensional scaling approach was applied to patient-level HBV genome consensus to identify genetic clusters within each HBV genotype. Sub-genotype groups defined by genetic clusters were investigated for treatment response differences measured by HBV DNA and HBsAg decline from baseline while controlling for relevant confounding factors.
Results: Among all patients, we identified multiple genetic clusters of HBV within each viral genotype (GT A = 2, B = 3, C = 2, D = 2). Only genotype C clusters (Figure 1A), broadly corresponding to subgenotype C1 and C2, displayed significant differences in treatment response dynamics among HBeAg positive treatment naïve patients (C1 N = 197, C2 N = 83, Figure 1B). HBV C1 patients experienced ~0.5 $\log_{10}$IU/ml greater reduction in HBV DNA at week (wk) 4, 8, and 12 compared to HBV C2 patients ($p = 7.9e-05$, 1.1e-04, and $p = 2.7e-03$ respectively). Although HBV C1 patients had significantly higher median levels of baseline HBV DNA (7.9 $\log_{10}$IU/ml) than HBV C2 patients (7.3 $\log_{10}$IU/ml, $p = 2.8e-04$), the viral genetic structure remained a significant factor in treatment response dynamics (wk 4 $p = 1.0e-04$, wk 8 $p = 1.5e-05$, and wk 12 $p = 3.0e-03$). Geographically, two locations displayed clear HBV C1 and C2 distribution separation (HBV C1: Korea + Japan, HBV C2: Hong Kong) suggesting lower HBV migration rates between these regions. Analogous but non-significant trend differences were also observed in HBsAg decline between HBV C1 and C2 cohorts. Importantly, despite different treatment response dynamics, viral suppression at wk 24 and 48 was similar between HBV C1 and C2 patients.

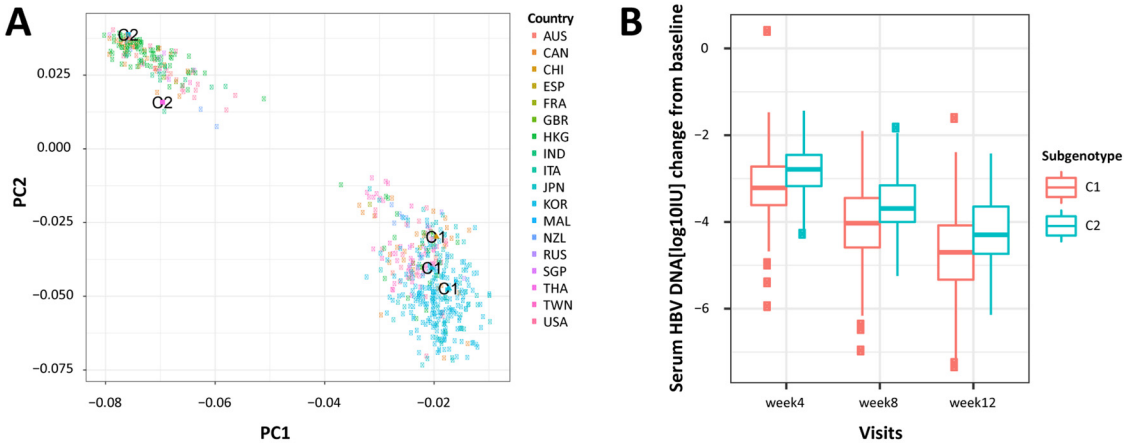


Figure 1

A. HBV genotype C population substructure. Multidimensional scaling approach was applied to patient-level HBV genome consensus to identify genetic clusters within HBV genotype C. HBV subgenotypes C1 and C2 were included for reference. **B.** Significant differences in decline of HBV DNA in serum between patients infected with C1 and C2 HBV at week 4, 8, and 12 during antiviral therapy (p=1.1e-05, p=2.6e-05, and p=7.7e-05 respectively).

Figure: (abstract: SAT-379)

Conclusion: Our data indicate that the population genetic structure within genotype C of HBV contributes to variation in treatment response dynamics. The geographic association with baseline HBV DNA warrants further investigation.

SAT-380

Control of glycokinase activity by the HCV protein NS5A increases lipogenesis

C. Jacquemin[1], B. Panthu[1], C. Ramière[1], X. Hanoulle[2], L. Perrin-Cocon[1], P. Andre[1], V. Lotteau[1], O. Diaz[1]. *[1]INSERM U1111 – CNRS UMR5308 Université Lyon 1, ENS de Lyon, Centre International de Recherche en Infectiologie (CIRI), LYON cedex 07, France; [2]CNRS UMR8576 Université de Lille1, Unité de Glycobiologie Structurale et Fonctionnelle, France*
Email: olivier.diaz@inserm.fr

Background and Aims: We have previously shown that HCV increases glycolytic rate, through a direct interaction between NS5A and hexokinase 2 in Huh7 cells. There are four hexokinase isoenzymes, HK1-3 and glucokinase (GCK), with different tissue, subcellular distributions, molecular and enzymatic properties. All HK catalyze the synthesis of glucose-6P from glucose, GCK has a lower affinity for its substrate and is not inhibited by Glc-6P, which makes its activity tightly regulated by Glc concentration but not by the demand for end pathway products. Huh7 expresses HK2 but in vivo hepatocytes express GCK isoenzyme. This differential expression of HK isoenzymes raises the question of the ability of NS5A to interact with GCK and increase glycolysis in normal hepatocytes. We therefore investigated whether NS5A could increase GCK activity and the glycolysis flux of hepatocarcinoma cells expressing this isoenzyme.
Method: Modulation of GCK catalytic parameters by NS5A and its domains in acellular assays was investigated with purified proteins. To determine whether the modulation catalytic activity of GCK was functional in cells, we invalidated Huh7 for HK2 by CRISPR/Cas9 and expressed GCK by lentiviral transduction. The generated cell line was used to analyze the impact of GCK modulation by NS5A on glycolysis and viral replication.
Results: NS5A interacts with GCK and acts as an allosteric activator through its domain 2. In GCK-Huh7 cells, expression of NS5A increased Glc consumption and intracellular lipid droplets. Interestingly, we observed that the expression of GCK in Huh7 cells was sufficient to increase intracellular neutral lipids and secretion of apoB-lipoproteins indicating that *de novo* lipogenesis was restored in this cell line. In addition, HCV-RNA association to lipoprotein fractions was enhanced in supernatant of HCV-infected GCK-Huh7.
Conclusion: NS5A increases glycolysis by its direct interaction with GCK thus supporting the supply of energy and metabolites necessary for viral replication. The resulting lipogenesis observed in cells expressing GCK could promote viral assembly and production of the low-density form of HCV in the form of lipo-viral-particles (LVP) which are the most infectious particles in vivo. Our model will allow to functionally analyze how HCV modulates glycolysis and lipogenesis leading to the production of LVP.

SAT-381

Evolution and persistence of resistance-associated substitutions of hepatitis c virus after daclatasvir plus asunaprevir treatment failures

Y. Jeong[1,2], B. Jin[1,2], H.W. Lee[3], H.J. Park[1], D.Y. Kim[1], K.-H. Han[1], S. Kim[1], S.H. Ahn[1]. *[1]Institute of Gastroenterology, Department of Internal Medicine, Yonsei University College of Medicine; [2]Brain Korea 21 Plus Project for Medical Science, Yonsei University; [3]Yonsei University College of Medicine, Department of Internal Medicine, Institute of Gastroenterology, Seoul, Korea, Rep. of South*
Email: ycjeong0919@yuhs.ac

Background and Aims: Daclatasvir plus asunaprevir (DCV + ASV) treatment is an all-oral direct-acting antiviral (DAA) therapy for the genotype 1b HCV-infected patients. Despite its high sustained virologic response (SVR) rate, the treatment failures are observed even in patients without baseline NS5A polymorphisms. In this study, we investigated how resistance-associated substitutions (RASs) of NS5A and NS3 evolved after treatment failures and assessed the effect of those substitutions on viral fitness.
Method: Sera from the patients who failed in DCV + ASV treatment were collected and viral RNA was isolated. The viral genome sequences of NS3 and NS5A were determined by direct sequencing after RT-PCR amplification. In order to assess the effect of RASs on viral fitness, they were introduced in the genotype1a or 1b HCV RNA either as single substitutions or as multiple substitutions and investigated by Luciferase reporter assay and focus-forming assay after transfection into the Huh7.5 cells. To make quasi-species *in vitro*,

wild-type (WT) and mutant RNAs were co-transfected into Huh7.5 cells in different ratios and investigated by reporter assay.
Results: We followed up the RASs identified in patients who failed in DCV + ASV treatment. Typical RASs of NS3 at D168 and those of NS5A at L31 and Y93 were commonly observed after DCV + ASV treatment failures. Interestingly, the RASs of NS3 reverted to the wild-type amino acid within one year after treatment failures. However, the RASs of NS5A were stable over one year after cessation of treatment. The effect of NS3 and NS5A RASs on viral RNA replication was assessed after mutagenic substitution in the genotype 1b HCV RNA. Among the single substitutions, the effect of D168V was more substantial than the others and the effect of the triple mutant combination (D168V + L31V + Y93H) was the most severe. When the Y93 mutagenic substitution was tested with infectious genotype 1a HCV RNA, the Y93 affected both viral RNA replication and virus production. To make quasi-species environment *in vitro*, WT and Y93N RNAs were co-transfected into the Huh7.5 cells and the RNA replication capacity measured report assay was plotted as percentage compared to that of the 100% transfection of luciferase HCV RNAs. The RNA replication capacity of Y93N increased from 50% to 69% and WT decreased from 50% to 28%.
Finally, the effect of *trans*-complementation of NS5A protein was assessed for Y93N substitution and the result suggests that such *trans*-complementation effect of NS5A protein may help maintain the RASs of NS5A for a long time even after cessation of the DAA treatment.
Conclusion: The RASs of NS5A and NS3 after DCV + ASV treatment failures were identified and analyzed regarding viral evolution and fitness change. The results from this study would help understand the emergence and persistence of RASs and provide retreatment guidelines for the patients who failed in DCV + ASV therapy

SAT-382

FXR agonist GW4064 represses HBV replication in adult but not in young C3H/HeN mice after HBV transduction with rAAV2/8-HBV

F. Fusil, C. Ménard, C. Ramière, A. Ollivier, K. Mouzzanar, V. Lotteau, F.L. Cosset, P. Andre. *INSERM U 1111 – CNRS UMR5308 Université Lyon 1, ENS de Lyon, Centre de Recherche International en Infectiologie, Lyon, France*
Email: patrice.andre@inserm.fr

Background and Aims: HBV life cycle is linked to the bile salts (BS) nuclear receptor FXR activity. HBV competes with BS for entry through NTCP and FXR response elements in HBV genome have been identified. HBV infection modulates BS pathway in vivo and in HepaRG and PHH cellular models. Reciprocally, treatments with FXR agonists repress HBV replication in these models. HBV transfection by hydrodynamic injection in C3H/HeN leads to rapid viral clearance in adult mice but to chronic HBV infection in young or gut microbiota free adult mice. We wondered if transduction with rAAV2/8-HBV vector lead also to chronic and acute infections in young and adult C3H/HeN mice and if treatment with the FXR agonist GW4064 influences the infection outcome.
Results: Transduction with 5×10^{10} GE rAAV2/8-HBV lead to chronic HBV replication with stable viral load (around 1×10^{8} copies/ml) and HBsAg titers from d7 to d91 p.i. in 6-week old C3H/HeN mice. In 12-week old mice, viral load was lower at d7 and d35 (−0.5 and −1.5 log10 copies/ml respectively) than in younger mice and went back to d7 level at d91. HBsAg titers evolved similarly. In 6-week old mice infected with 2×10^{10} GE rAAV2/8-HBV and treated for 4 week with GW4064 at 50 mg/kg by daily gavage or diluent, viral load remained stable and did not vary between the two groups. In 12-week old mice, GW4064 treatment inhibited the viral load and HBsAg rebounds observed in control mice (−1.1 Log10 copies/ml and −0.8 log10rfu/ml respectively). Surprisingly HBeAg titers did not vary during the 4-week treatment.
Conclusion: HBV infection outcome in C3H/HeN varied with age at time of infection. HBV replication was stable at a high level in young mice when in adult mice HBV replication was first repressed before rebounding after several weeks. This model of infection has limitations with numerous rAAV2/8-HBV extra-chromosomic concatemers and integrated genomes. The presence of these rAAV-HBV forms may explain the late rebound of HBV replication in adult mice that does not occur after hydrodynamic injection of HBV genome. Interestingly, treatment with FXR agonist represses HBV expression in adult only, suggesting that the difference of infection evolution with age is partially dependent on FXR activity. BS metabolism matures with gut microbiota maturation. These data further stress out the role of FXR in HBV life cycle and suggest that the frequent chronic infections in childhood are also in part due to the immaturity of BS metabolism.

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Cellular retinoic acid-binding proteins regulation of hepatitis C virus infection

B.R. Bang, T. Saito. *University of Southern California, Medicine, Los Angeles, United States*
Email: saitotak@usc.edu

Background and Aims: Retinoic Acid (RA) is known to potentiate both innate and adaptive immunity, and therefore has been termed "the anti-infective agent". Epidemiological and immunological studies reported its potent anti-microbial properties to a variety kind of viral pathogens such as, but not limited to, measles, HIV, and influenza virus.
The majority of dietary *retinoid (vitamin A)* is *stored* in hepatic stellate cells and hepatocytes. The biogenesis of RA, the final metabolite of vitamin A, takes place in the cytoplasm. Cellular retinoic acid-binding protein (CRABP) 1 and 2 are localized in the cytoplasm and binds to RA. Then, CRABPs translocate to the nucleus, resulting in the regulation of more than 500 genes through the activation of the nuclear receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR). CRABP1 and 2 shares high homology, and thus are predicted to have redundant functionality. To date, however, the role of CRABPs in the cell biology of hepatocytes as well as the potential influence on HCV lifecycle has never been investigated.
Consequently, this study is designed to define the biological functions of CRABPs with an ultimate goal to understand the mechanism by which HCV establishes an efficient viral lifecycle in the cells comprising a substantially high concentration of the antiviral organic compound, RA.
Method: Huh7 cells expressing CRABP1 or CRABP2 at the comparable degree to primary human hepatocytes were established as in vitro study tools. Then, Huh7-CRABP1 and 2 cells were used for molecular virological studies with biochemical and genetic approaches to assess the significance of CRABPs on HCV lifecycle.
Results: Our results found HCV replication was suppressed in the cells expressing CRABP2 while viral lifecycle was substantially upregulated in the cells expressing CRABP1. Our transcriptome analysis of Huh7-CRABP1 and 2 cells suggested that these CRABPs differentially regulate the cellular metabolism of lipids. Follow up microscopic analysis revealed that CRABP1 offers a platform for the formation of HCV replication complex via accumulation of lipid droplet (LD). In contrast, we found that antiviral effect of CRABP2 resulted from the inhibition of LD formation.
Conclusion: This study results revealed the unrecognized role of vitamin A in the regulation of lipid metabolism in hepatocytes. We discovered that CRABP1 and 2 differentially regulate HCV infection via modulation of LD abundance. These findings indicate that CRABPs can be an attractive therapeutic target for both HCV infection and fatty liver diseases.

SAT-384

GalXC technology enables potent and durable RNAi-mediated inhibition of hepatitis B virus in preclinical models

M. Koser, K. Craig, G. Chopda, W. Cyr, C. Lai, H. Dudek, W. Wang, B. Brown, M. Abrams. *Dicerna Pharmaceuticals, Cambridge, United States*
Email: mabrams@dicerna.com

Background and Aims: Chronic Hepatitis B Virus (HBV) infection is a significant cause of worldwide morbidity and mortality. RNA interference (RNAi) technology offers the potential to pharmacologically intervene at every stage of the viral life cycle. GalXC technology represents a novel structural class of subcutaneously- or intravenously-administered, hepatocyte-targeting RNAi therapeutics which can silence any expressed RNA with high specificity and long duration. In this poster, we will review the identification, optimization, and characterization of two GalXC compounds targeting the HBsAg and HBx protein open reading frames (ORFs).
Method: GalXC drug candidates were evaluated in wild type mice, nonhuman primates and in three preclinical HBV models: HDI-HBV (hydrodynamic injection), AAV-HBV (adeno-associated virus model) and PXB-HBV (PhoenixBio humanized liver mouse). Potency, duration, translational potential, tolerability, and pharmacokinetic properties were investigated.
Results: GalXC-HBV lead compounds, which cover >95% of HBV genomes across all genotypes, resulted in >90% reduction of HBV pregenomic RNA (pgRNA) and viral mRNAs in the liver. Maximum inhibition of HBsAg was of >3.5 logs, with suppression lasting >7 weeks after a single 3 mg/kg dose. Differences in magnitude of response from model to model were noted and will be discussed. We will also report pharmacodynamic differences observed between the two lead compounds, which target different open reading frames in the viral genome.
Conclusion: These data strongly support clinical development of GalXC RNAi therapeutics for chronic HBV infection, and highlight the need to evaluate preclinical-stage HBV therapeutics in multiple models.

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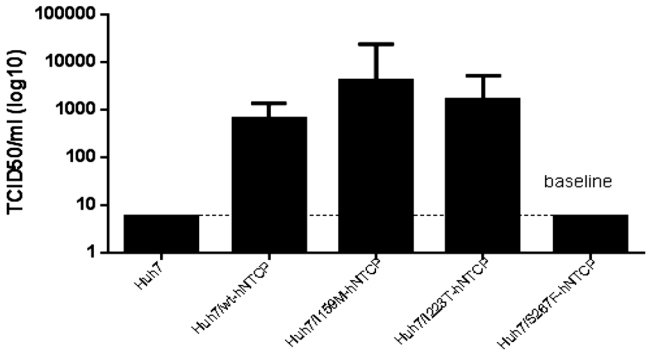
Sodium taurocholate cotransporting popypeptide variants modulate HDV entry according to their function as a bile acid transporter but do not influence the antiviral effect of Myrcludex-B

O. Anastasiou[1,2], S. Westhaus[2], M. Anspach[2], L. Timmer[2], S. Susser[3], C. Sarrazin[3], G. Gerken[1], V. Keitel[4], H. Wedemeyer[5], M. Lu[2], J. Stindt[4], S. Ciesek[2]. [1]*University Hospital Essen, Department of Gastroenterology and Hepatology, Essen, Germany;* [2]*University Hospital Essen, Institute of Virology;* [3]*University Hospital Frankfurt, Department of Gastroenterology and Hepatology;* [4]*University Hospital Düsseldorf, Department of Gastroenterology and Hepatology;* [5]*Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany*
Email: olympia.anastasiou@uni-due.de

Background and Aims: Several polymorphisms have been described in the sodium taurocholate cotransporting polypeptide (NTCP). Some of them have been associated with the course of hepatitis B virus (HBV) infection. Aim of the present study was to characterize to what extend HDV entry and bile acid transport capability differ in three coding NTCP variants (I159M, I223T, S267F) and to evaluate if these NTCP variants may alter sensitivity to antiviral treatment with Myrcludex-B.
Method: Huh7 cells stably expressing wildtype (wt) or mutant NTCP were infected with *in vitro* generated HDV particles in the presence or absence of Myrcludex-B. Infectivity was assessed with immunofluoresence staining for HDV antigen and standard 50% tissue infectious dose (TCID50) assay. Bile acid transport was assessed via a 3[H]-taurocholate transport assay.
Results: While Huh7 cells expressing NTCP S267F were resistant to HDV infection, cells expressing I159M or I223T were more susceptible to HDV. In line, NTCP I159M showed enhanced bile acid transport activity while bile acid transport activity was strongly reduced for NTCP S267F. All NTCP variants had no impact on the antiviral effect of Myrcludex-B. Other HDV virus cycle steps such as particle assembly, release or replication were not affected.



Conclusion: NTCP mutations can influence its function as a bile transporter and entry receptor for HDV. The S267F mutation leads to loss of function in both cases, while the I159M and I223T lead to greater infectivity by HDV viral particles, but have no effect on Myrcludex-B efficacy in blocking the entry of the virus.

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Hepatitis E virus lifecycle and identification of 3 forms of the ORF2 capsid protein

C. Montpellier[1], C. Wychowski[1], I.M. Sayed[2,3], J.-C. Meunier[4], J.-M. Saliou[1], M. Ankavay[1], A. Bull[4], A. Pillez[1], F. Abravanel[5], F. Helle[6], E. Brochot[6], H. Drobecq[1], R. Farhat[1], C.-M. Aliouat-Denis[1], J.G. Haddad[1], J. Izopet[5], P. Meuleman[2], A. Goffard[1], J. Dubuisson[1], L. Cocquerel[1]. [1]*Center for Infection and Immunity of Lille- Molecular and Cellular Virology, CNRS-UMR8204/Inserm-U1019, Lille, France;* [2]*Laboratory of Liver Infectious Diseases, Department of Clinical Chemistry, Microbiology and Immunology, Ghent University, Ghent, Belgium;* [3]*Assiut University, Microbiology and Immunology Department, Faculty of Medicine, Assiut, Egypt;* [4]*University F. Rabelais, Inserm-U966, Tours, France;* [5]*CHU Toulouse, Hôpital Purpan, Laboratoire de virologie, National Reference Center for Hepatitis E, Toulouse, France;* [6]*Centre Universitaire de Recherche en Santé, Centre Hospitalier Universitaire et Université de Picardie Jules Verne, EA4294, Laboratoire de Virologie, Amiens, France*
Email: laurence.cocquerel@ibl.cnrs.fr

Background and Aims: Hepatitis E virus (HEV) infection is a major cause of acute hepatitis worldwide. Approximately 2 billion people live in areas endemic for HEV and are at risk of infection. The HEV genome encodes 3 proteins, including the ORF2 capsid protein. Detailed analyses of the HEV lifecycle has been hampered by the lack of an efficient viral culture system.
Methods: We performed studies with gt3 HEV cell culture-produced particles (HEVcc) and patient blood and stool samples. Samples were fractionated on iodixanol gradients and cushions. Infectivity assays were performed in vitro and in human liver chimeric mice. Proteins were analyzed by biochemical and proteomic approaches. Infectious particles were analyzed by transmission electron microscopy. HEV antigen levels were measured with the Wantaï ELISA.
Results: We developed an efficient cell culture system and isolated HEV particles that were infectious in vitro and in vivo. Using transmission electron microscopy, we defined the ultrastructure of HEVcc and particles from patient sera and stool samples. We also identified the precise sequence of the infectious particle-associated ORF2 capsid protein. In cultured cells and in samples from patients, HEV produced 3 forms of the ORF2 capsid protein: infectious/

intracellular ORF2 (ORF2i), glycosylated ORF2 (ORF2g), and cleaved ORF2 (ORF2c). The ORF2i protein associated with infectious particles, whereas the ORF2g and ORF2c proteins were massively secreted glycoproteins not associated with infectious particles. ORF2g and ORF2c were the most abundant antigens detected in sera from patients.
Conclusions: We developed a cell culture system and characterized HEV particles; we identified 3 ORF2 capsid proteins (ORF2i, ORF2g, and ORFc). These findings will advance our understanding of the HEV lifecycle and improve diagnosis.

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Serum HBcrAg levels as a predictor of slow HBV DNA suppression following initiation of nucleoside therapy in HBV/HIV co-infected individuals

R. Byrne[1], S. Montague[1], M. Bruce[1], K. Childs[1], I. Carey[1], K. Agarwal[1], G. Dusheiko[2]. *[1]Kings College Hospital, Instittute of Liver Studies, London, United Kingdom; [2]Kings College Hospital, Institute of Liver Studies, London, United Kingdom*
Email: ruthbyrne@nhs.net

Background and Aims: Hepatitis B core-related antigen (HBcrAg) has emerged as a surrogate marker for intrahepatic cccDNA and has a potential use in the monitoring of chronic hepatitis (HBV) infection. There are little data on its utility in HBV/HIV coinfected patients. A proportion of HBV/HIV co-infected patients adhering to dual active antiviral therapy with suppressed HIV have persistent HBV replication and may warrant more intensive surveillance, monitoring and management of liver disease co-factors. The aim of this small pilot study is to evaluate HBcrAg levels in HBV/HIV infected patients to determine if it is has a role in risk stratification of this cohort.
Method: 30 patients with chronic HBV/HIV coinfection, on tenofovir (TDF)-based antiretroviral therapy (ART), were identified retrospectively. Patients were classified into two groups: those with fully suppressed HIV(<50 copies/ml) and HBV(<20 IU/ml) at week 48 of TDF-based ART (group A, n = 15) and those with persistent HBV replication despite an undetectable HIV viral load, reflecting adherence to therapy, at week 48 of TDF based ART (group B, n = 15). Serum HBcrAg was tested at baseline (initiation of TDF-based ART) and at week 48 of therapy. HBcrAg was measured by an automated CLEIA-method (Lumipulse G 1200 HBcrAg, Fujirebio).
Results: There was no significant difference between group A and B in sex, age, distribution of HBV genotypes, baseline CD4 count and HBV DNA level. In group A, 6/15(40%) patients were e-Antigen positive at baseline; 4(67%) of whom seroconverted e-Antigen by week 48. Higher levels of e-Antigen positivity were observed in group B (n = 10, 67%) and rates of e-Antigen seroconversion were lower than group A (n = 1, 10%). At baseline there was a significant difference in HBcrAg levels between the two groups (group A 4.88 ± 1.75 $\log_{10}$ kU/ml, and group B 6.84 ± 0.59$\log_{10}$ kU/ml, p < 0.001). At week 48 there was a significant difference in HBcrAg levels between the two groups (group A 3.71 ± 1.67 $\log_{10}$ kU/ml, and group B 6.21 ± 1.08 $\log_{10}$ kU/ml, p <0.001).
Conclusion: In this small, HBV/HIV cohort baseline HBcrAg levels were higher in those that failed to suppress HBV DNA despite good adherence to HBV active ART. There may be a role for HBcrAg as a predictor of slow HBV response and therefore a potential tool to risk stratify this group and identify those that need closer surveillance. Further work in larger cohorts is required to fully establish the clinical utility of HBcrAg in this group.

SAT-388

Statins suppress hepatitis B virus replication and reduce hepatoma cell viability by interfering with Rho-GTPases

M. van de Klundert[1], M. Ringelhan[1,2], U. Protzer[1]. *[1]Institute of Virology, Technical University of Munich/Helmholtz Zentrum München, Munich, Germany, Germany; [2]Technical University of Munich, Munich, Germany, Second Medical Department, University Hospital rechts der Isar*
Email: maarten.van-de-klundert@tum.de

Background and Aims: It has been observed that statins reduce the chance of developing hepatocellular carcinoma (HCC) in hepatitis B virus (HBV) infected individuals, and reduce HCC related mortality when applied during palliative care. Statins inhibit the HMG-CoA-reductase dependent cholesterol synthesis pathway, but also have immune modulatory functions and interfere with the activity of Rho-GTPases by preventing their prenylation. In this study, we aim to assess the effect of statins and Rho-GTPases on HBV replication and on HCC formation and viability.
Results: We previously identified terbinafine, an FDA-approved, orally available antifungal drug, to functionally affect the HBV accessory protein HBx. Beside its antifungal activity, terbinafine suppresses the activity of Rho-GTPases and was thus chosen for comparison to fluvastatin, a clinically approved statin. In primary human hepatocytes (PHH), HBx expression is critical for the initiation and maintenance of HBV RNA transcription. Terbinafine efficiently suppressed HBV replication in PHH, with an IC50 of 2–3 ug/ml (PHH). In hepatoma cell lines, terbinafine and fluvastatin efficiently suppressed the replication of wildtype HBV. The suppression of HBV replication by fluvastatin was relieved by pretreatment with geranylgeraniol, indicating that the antiviral effect of this statin relies on interfering with Rho-GTPase activity. Interestingly, we observed that fluvastatin and terbinafine were already toxic to hepatoma cells at concentrations that were not affecting PHH viability in cell culture. In HBV transgenic mice, terbinafine and fluvastatin concentrations that critically interfered with hepatoma cell line viability were well tolerated, and did not lead to an increase in ALT. We are currently investigating the effect of fluvastatin and terbinafine on early markers of HCC development in HBV transgenic mice.
Conclusion: Inhibition of Rho-GTPases reduces HBV antigen expression by suppressing HBV RNA transcription, and selectively reduces the viability of transformed hepatocytes. Our results suggest that statins prevent HCC development by suppressing Rho-GTPases.

SAT-389

Understanding the multiphasic viral kinetics of cute HBV infection observed in humanized uPA/SCID mice using an agent-based modeling approach

A. Hailegiorgis[1], Y. Ishida[2,3], M. Imamura[3], N. Hiraga[3], C. Tateno[2,3], S. Uprichard[4], K. Chayama[3], H. Dahari[1]. *[1]Loyola University Medical Center, Division of Hepatology, Medicine; [2]PhoenixBio Co., Ltd, Japan; [3]Hiroshima University, Japan; [4]Loyola University Medical Center, United States*
Email: harel.dahari@gmail.com

Background and Aims: The uPA/SCID humanized chimeric mouse model is a useful tool for studying the dynamics of HBV infection and treatment response. Interestingly, despite the absence of an adaptive immune response or cell death due to HBV, we found that HBV infection from initiation to steady state in these mice (n = 42) is highly dynamic with 7 distinct kinetic phases. Current models of HBV infection based on differential equations are not able to reproduce this highly dynamic picture. Thus to explain this multiphasic kinetics and gain insight into dynamics that produce this complex viral expansion pattern, we have developed a stochastic agent-based model (ABM).
Methods: In the model, each human hepatocytes is represented as an individual agent. With the inoculation of free virus into the blood, the model attempts to recapitulate the initial infection of human hepatocytes and subsequent production and spread of progeny virus in humanized chimeric mouse liver. When uninfected cells are exposed to HBV, they become infected and enter an eclipse phase in which they do not yet secret virus. They then proceed to a productive phase in which they are able to release virions which can go on to infect additional human hepatocytes. Initial model conditions (e.g., HBV inoculums and number of human hepatocytes) and several model parameters (e.g., viral clearance from blood) were calculated/defined based on experimental design and detailed kinetic analysis.

Results: The model reproduces well the complex serum HBV kinetic pattern of 7 distinct phases observed in chimeric mice inoculated with 10^8 HBV genome equivalents when the following parameters are assumed: (1) The eclipse phase lasts between 10–48 hours, (2) Once the infected cell passes the eclipse phase, its production rate is not constant, but rather increases over time initially starting with long production cycle of 1 virion per 20h but gradually reaching 1 virion per hour after 3 days. Thereafter (about ~3.25 days), the virion production increases dramatically to reach to a steady state production rate of 3 virions per hour. The model was validated by showing it could accurately simulate the viral kinetics observed with lower HBV inoculation doses (10^4–10^7 genome equivalents), in which similar (but delayed) patterns were observed.
Conclusions: Modeling suggests that the initial slow but increasing rate of virus production from each cell plays major role in generating the observed multiphasic HBV kinetic patterns in humanized mice. However, further experiments are necessary to confirm nature and causes of the emerging patterns.

SAT-390

Understanding HDV and HBV dynamics during acute co-infection in humanized uPA/SCID chimeric mice using an agent-based modeling appraoch

U. Kumar[1], T. Uchida[2], A. Hailegiorgis[1], N. Hiraga[2], K. Walsh[1], M. Imamura[2], C. Koh[3], T. Heller[3], J. Glenn[4], S. Uprichard[1], K. Chayama[2], H. Dahari[1]. *[1]Loyola University Medical Center, United States; [2]Hiroshima University, Japan; [3]Liver Diseases Branch, NIDDK, NIH, United States; [4]Stanford University School of Medicine, United States*
Email: harel.dahari@gmail.com

Background and Aims: Studying hepatitis D virus (HDV) and hepatitis B virus (HBV) dynamics during acute co-infection in humans is lacking due to the uncertainty of the exact time of infection and limited frequent kinetic data. The humanized uPA/SCID chimeric mouse model is a useful tool for studying the dynamics of HDV/HBV co-infection. We previously showed that while HBV infection from initiation to steady state in mice (n = 4) was highly dynamic (with 5 distinct kinetic phases eventually reaching a viral plateau at ~8.7 log cp/ml), HDV was below detection until week 2 post inoculation (pi), but once detected increased until week 5 pi followed by a plateau of ~9.8 log cp/ml. To explain these kinetic patterns we have developed a stochastic agent-based model.
Methods: In the model, each human hepatocytes is represented as an individual agent. With the inoculation of HDV and HBV into the blood, the model attempts to recapitulate the initial infections of human hepatocytes and subsequent production and spread of progeny viruses in humanized chimeric liver. When uninfected cells are exposed to HBV and/or HDV, they become infected and enter an eclipse phase in which they do not yet secret virus. HBV-infected cells then proceed to a productive phase in which they are able to release HBV virions which can go on to infect additional human hepatocytes. HDV-infected cells can proceed to a productive phase in which they are able to release HDV virions only if the cells are also infected with HBV. Initial model conditions (e.g., 10^6 HBV and 10^6 HDV genome equivalents and ~10^8 human hepatocytes) and several model parameters (e.g., viral clearance from blood) were calculated/defined based on experimental design and detailed kinetic analysis.
Results: The model reproduces well the 5 distinct HBV kinetics phases observed when the following parameters are assumed: (1) The eclipse phase lasts between 10–48 h, (2) Once the infected cell passes the eclipse phase, its production rate is not constant, but rather increases over time initially starting with a long production cycle of 1 virion/20 h but gradually reaching 1 virion/h after 3 days, followed by a dramatically increase to reach to a steady state production rate of 3 virions/h. To reproduce the observed HDV kinetic patterns the following parameters were assumed to be different relative to HBV: (i) ~20-fold higher HDV infection rate, (ii) shorter production cycle with HDV reaching its max production within ~2 days pi, and (iii) ~7-fold higher steady state production rate (~26 virions/h).
Conclusions: Modeling results provide insights into HDV and HBV dynamics during acute infection in humanized chimeric mice. Further experiments are necessary to confirm nature and causes of the emerging patterns.

SAT-391

Molecular diversity of HDV strains that spread in France: a study of 2224 clinical strains prospectively collected during fifteen years

A. Gerber[1], F.L. Gal[1], S. Dziri[1], C. Alloui[1], D. Roulot[2], Z.B. Abdesselam[2], S. Brichler[1], E. Gordien[1]. *[1]Hôpitaux universitaires de Paris Seine Saint Denis, laboratoire de microbiologie clinique, BOBIGNY, France; [2]hôpitaux Universitaires de Paris Seine Saint Denis, Unité d'Hépatologie, BOBIGNY, France*
Email: athenais.gerber-ext@aphp.fr

Background and Aims: We recently described that HDV genus is composed of 8 different genotypes characterised by a nucleotide sequence similarity of 85% and 80% according to the partial so called *R0* region or to the full-length genome respectively. Furthermore, genotypes can be segregated into 2 to 4 subgenotypes, characterised by an inter-subgenotype similarity >90% and >84% for HDV-1. We aimed in this study to provide the main results of a molecular characterization of strains that infected all new HDV-positive patients diagnosed in France between 2001 and 2016 and to highlight the main possible consequences of such a genetic diversity.
Method: A total of 2,224 serum/plasma samples were collected. Demographical data (age, gender, country of origin, date of infection, risk factors) were recorded. HDV genotyping was performed as previously described, using sequencing and phylogenetic analyses of *R0* amplicons.
Results: About 150–250 new HDV-infected-patients per year were diagnosed. They were originated from Africa (mainly Cameroon, Mali, Côte d'Ivoire, Central African Republic), 49.3%; Western (France) 16.7% and Eastern Europe (Romania, Georgia), 16.4%; Asia, (Mongolia), 8%; Turkey and The Middle East (3%). They were more often infected at birth in their country of origin. Since 2004, the rate of infected-Eastern European patients reached from less to 5% to near 20%, while the number of French patients regularly decreased since this date from 45% to less than 10%. We characterised 1771 HDV-1 (79.6%); 321 HDV-5 (15%); 62 HDV-7 (2.8%); 33 HDV-6 (1.5%); 33 HDV-8 (1.5%) and 2 HDV-2 and HDV-3 (each 0.08%). Subgenotypes 1a and 1b from Africa and 1d from Europe were found equivalently.
Conclusion: HDV genotypes -1 and -5 to -8 circulate in all regions of France. Infected-patients came mainly from countries of high endemic, mainly Sub-Saharan Africa and Eastern Europe. African strains account for 60%. This is a main point for the management of these patients as we previously showed that most "in-house" or commercial assays underestimated or failed to quantify HDV viral load of these strains. In addition, HDV-5, was found to be significantly associated to hepatocellular carcinoma compared to HDV-1 and to other African genotypes. In conclusion further studies are still needed to assess for a role of the HDV genetic diversity in the natural history of the infection and under treatment at the era of news developing drugs.

SAT-392

Molecular diversity of HBV and HDV amino-acid sequences involved in HDV virion morphogenesis according to HBV and HDV genotypes: study of 1590 clinical strains

A. Gerber[1], S. Dziri[1], S. Brichler[1], C. Alloui[1], D. Roulot[2], Z. Ben Abdesselam[3], F. Le Gal[4], E. Gordien[4]. *[1]Hôpitaux Universitaires de Paris Seine Saint Denis, Laboratoire de microbiologie clinique, Bobigny, France; [2]Hôpitaux Universitaires de Paris Seine Saint Denis, Unité d'Hépatologie, BOBIGNY, France; [3]Hôpitaux Universitaires de Paris Seine*

Saint Denis, Unité d'Hépatologie, BOBIGNY, France; [4]Hôpitaux Universitaires de Paris Seine Saint Denis, Laboratoire de microbiologie clinique, BOBIGNY, France
Email: athenais.gerber-ext@aphp.fr

Background and Aims: Hepatitis delta virus (HDV) is a satellite of the hepatitis B virus (HBV) that requires HBV envelope to form its own virions. HBV and HDV are characterized by a high genetic diversity in respectively 10 and 8 different genotypes and in several subgenotypes within genotypes. Molecular determinants involved in HDV virion morphogenesis, have been previously described within the third antigen loop (AGL-3) of the HBV surface envelope and at the C-terminus of the large delta protein (L-HDAg), involving respectively conserved Tryptophan residues (W) and a Proline-rich region. In this study, we aimed to analyze the molecular diversity of these sequences according to genotypes from a large cohort of clinical samples.
Method: A total of 1,590 plasma samples of HDV-infected patients were studied. HBV-HDV genotyping was performed using sequencing (Sanger method) and phylogenetic analyses of amplicons encompassing the regions of interest (AGL-3 and L-HDAg). Amino-acid sequences were determined, aligned, and compared according to the different HBV/HDV genotypes couples, to several human and animal (for HBV) reference sequences.
Results: Overall, 526 HBV/HDV couples were characterized, showing various genotype combinations with significant association between strains of a same geographic origin, while 21 (4%) unexpected associations could be found. We identified: 62 HBV/A, 9 HBV/B, 3 HBV/C, 221 HBV/D, 222 HBV/E, 9 HBV/G; and 416 HDV-1, 1 HDV-2, 71 HDV-5, 7 HDV-6, 21 HDV-7 and 8 HDV-8. Considering the sequence of the AGL-3, 3 of the four key positions involved in HDV particles morphogenesis previously described were conserved i.e., W196, Methionine (M) 197 and W201 in 99% of the sequences. Interestingly, these same positions were also strictly conserved in Bat, Ground Squirrel, Woodchuck and Wooly Monkey sequences, suggesting as for the Woodchuck, that these animals would support experimental HDV infection. On the HDV side, despite a high apparent polymorphism of the L-HDAg C terminus, several hydrophobic amino-acids, remarkably Proline residues known to be involved protein-protein interactions, are found all along this region.
Conclusion: HDV virion morphogenesis seems to be the result of an adaptation of the L-HDAg via a Proline-rich motif to allow Delta ribonucleoprotein binding to a conserved hydrophobic motif of the helper HBV-AGL-3 (WMXXXW), where X is a W or M. To date this has occurred, only in humans in different parts of the world.

SAT-393
Deep sequencing analysis highlights variations associated with HBeAg seroconversion in adolescents with chronic hepatitis B

C. Combet[1], N. Bhardwaj[2], O. Podlaha[2], A. Gaggar[3], B. Feierbach[2], K. Kitrinos[2], K. Murray[4], F. Zoulim[1]. *[1]Inserm 1052, Lyon, France; [2]Gilead Sciences, Foster City, United States; [3]Gilead Sciences, Inc, Foster City, California, United States; [4]University of Washington School of Medicine, and Seattle Children's Hospital, Seattle, United States*
Email: neeru.bhardwaj@gilead.com

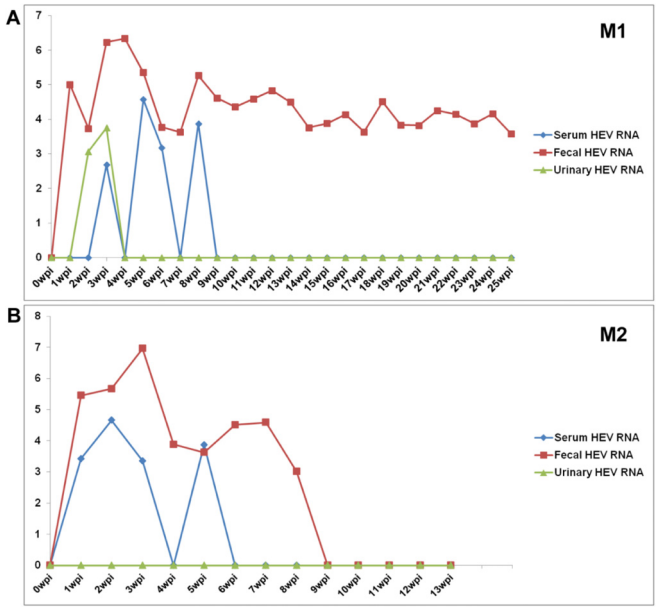
Background and Aims: HBeAg seroconversion (SC) is an important outcome for chronic hepatitis B (CHB) infected patients. The influence of viral dynamics on HBeAg SC is unclear. To address this gap, a longitudinal study of HBV full genome (FG) viral diversity was conducted in patients who experienced spontaneous HBeAg SC.
Method: GS-US-174-0115 was a double-blind, placebo (PBO)-controlled, phase 3, 192-week clinical trial that evaluated tenofovir disoproxil fumarate (TDF) in adolescents (12 to <18 years) with CHB. In PBO patients (n = 42), deep sequencing of HBV FG amplicons was performed using the Illumina MiSeq (150bp paired-end reads) at baseline (BL), Week 8 and Week 72. Additionally, for PBO patients with HBeAg SC prior to Week 72 (genotype (GT) A = 3; GTB = 1; GTD = 3), the time of HBeAg SC was also sequenced. The average nucleotide diversity of the HBV FG was calculated using Shannon entropy and variants were detected with a cutoff of 2%.
Results: In PBO patients who either were HBeAg+ without SC (n = 31) or HBeAg- at baseline (n = 4), there was not a significant change in diversity in the HBV FG over 72 weeks. Conversely, HBeAg+ PBO patients that achieved HBeAg SC (n = 7) experienced a drop in viral diversity at Week 72 (p = 0.04; Avg time post-SC = 26 weeks; Avg change from BL = −17%). The drop in viral diversity coincides with the reduction of serum HBV DNA (Avg change from BL = −4.10 $\log_{10}$ copies/mL). We analyzed the dynamics of 15 basal core promoter (BCP), pre-Core (pC), and Core (C) variants previously identified to be associated with HBeAg status [EASL 2017: ILC2017-RS-2810]. One to 4 of these variants enriched or reached a frequency of >98% in the viral population at Week 72 in all HBeAg SC patients. Two pC and C variants, A1846T and T2441C, were commonly present at high frequency from BL and did not appear related to SC in GTA or D. The most frequently sampled variants that enriched at or after SC were the BCP variants A1762T and G1764A (lower HBeAg production), and the pC variant G1896A (stop mutation), which was not seen in GTA patients. Interestingly, the single nucleotide deletion variants A1762del and G1764del also emerged in patients prior to SC, but were eliminated or reduced post-SC.
Conclusion: At the time of spontaneous HBeAg seroconversion in CHB adolescents, multiple BCP, pC and C mutations are present, indicating complex viral dynamics. Unique combinations of variants enrich in a patient's viral population post-SC, indicating selection for HBeAg defective viruses during natural history.

SAT-394
Prevalence, pathogenesis and cross-species transmission of a novel hepatitis E virus from bactrian camels

L. Wang, H. Zhuang, L. Wang. *Peking University Health Science Center, Microbiology and Infectious Disease Center, Beijing, China*
Email: lingwang@bjmu.edu.cn

Background and Aims: Hepatitis E virus (HEV) is a major cause of acute viral hepatitis worldwide. There are currently 7 major genotypes of HEV (HEV1-7). HEV mainly transmits via fecal-oral route and is considered a porcine zoonosis. However, novel HEV strains have been detected in various species of animals. The ever-expanding host range has posed a threat to humans. In 2016, a study reported the identification of a novel genotype of HEV (temporarily classified as HEV8) in Bactrian camels (*Camelus bactrianus*) in Xinjiang, China. Bactrian camels mainly live in northwestern China and southwestern Mongolia, and are important domestic livestock for transportation, tourism, meat and milk product. Therefore, people with close contact to Bactrian camels may be at risk of zoonotic infection. In this study, we investigated the prevalence, pathogenesis and the capacity of cross-species transmission of HEV8.
Method: During January 2017 and April 2017, we collected fresh fecal samples from Bactrian camels from four different provinces/regions in China, including Inner Mongolia (25 samples), Gansu (40 samples), Hebei (200 samples), Anhui (30 samples). Real-Time and nested reverse transcriptase PCR was performed. Two healthy female cynomolgus macaques were intravenously inoculated with 10^5 copies of HEV8-positive fecal suspension. Viraemia, fecal and urinary shedding of virus, liver functions and seroconversion to anti-HEV were monitored weekly. Liver biopsy was performed at one week pre-inoculation, 3 week-post-inoculation (wpi), 13 wpi and 25wpi. Immunofluorescence analysis was carried out for detection of HEV ORF2/3 proteins (Bioss, Woburn) in liver.
Results: HEV8 was detected in four fecal samples (1.4%, 4/295) collected from Bactrian camels in Anhui province (1/30, 3.3%), Gansu province (2/40, 5%) and Inner Mongolia (1/25, 4%). Two inoculated macaques (M1 and M2) subsequently developed robust infection with viraemia, uremia, fecal shedding and seroconversion (Figure). Liver functions of M1 and M2 remained normal during the study. M2 stopped virus shedding at 9 wpi (Figure A). Surprisingly, M1

developed chronic infection and HEV could be detected in both feces and liver at 25 wpi (Figure B). Liver histopathology showed inflammatory cells infiltration, focal necrosis and hydropic degeneration at 13 and 25 wpi.



Conclusion: We performed a comprehensive study unraveling previous unknown knowledge of epidemiology, pathogenesis and cross-species transmission of the novel HEV8 strain from Bactrian camels. Our results showed that HEV8 circulated in different regions of China. The successful infection of two macaques suggests a high risk of zoonotic infection to humans. Both acute and chronic-type infections were observed in the infected macaques indicating diverse patterns of pathogenesis which warrants further investigating.

SAT-395

Mitochondrial electron transport chain complex III: a promising antiviral target for hepatitis E virus

C. Qu, S. Zhang, W. Wang, M. Li, M. Peppelenbosch, Q. Pan. *Erasmus MC, Gastroenterology and Hepatology, Rotterdam, Netherlands*
Email: c.qu@erasmusmc.nl

Background and Aims: Hepatitis E virus (HEV) infection has emerged as a global health issue; whereas no approved medication is available. Although ribavirin is effective as off-label treatment for chronic hepatitis E, a substantial proportion of patients do not tolerate or develop resistance and eventually fail to clear the virus. Electron transport chain (ETC), a key component of the mitochondria, is the main site that produce Adenosine triphosphate (ATP) and Reactive oxygen species (ROS). This study aims to investigate the role of ETC in HEV infection.
Method: An HEV infectious model and an HEV sub-genomic model were used. Western-blot assay, luciferase activity and qRT-PCR were used to evaluate the effects on HEV. Flow cytometry was used to analyze ROS level.
Results: To investigate the potential role of ETC in HEV infection, we have profiled the effect of targeting different complexes of ETC by pharmacological inhibitors. We found that Antimycin A (AMA), a FDA-approved drug that inhibits complex III of ETC, effectively inhibited HEV viral RNA. This effect is equivalent to the anti-HEV potency of ribavirin. The anti-HEV effect of AMA was further confirmed by western-blot assay of the viral protein ORF2. We further demonstrated that the anti-HEV of AMA is independent of ATP production, ROS level and pyridine depletion. By using pharmacological inhibitors and genetic approaches, we shed light on an effective basal defense role of mitochondria permeability transition pore (MPTP) against HEV replication and showed that MPTP inhibitors attenuate the anti-HEV effect of AMA.
Conclusion: The complex III of ETC is essential in sustaining HEV infection representing a viable target by existing FDA-approved inhibitors.

SAT-396

HCV induced-miR-21 activation triggers lipid accumulation and promotes viral replication

S. Clément-Leboube[1], C. Sobolewski[2], G. Diana[3], Á. Rojas[3], N. Goossens[4], C. Stéphanie[3], N. Calo[2], F. Negro[5], M. Foti[6]. [1]*University hospital, Division of Clinical Pathology, Geneva, Switzerland;* [2]*Faculty of Medicine, University of Geneva, Cell Physiology and Metabolism, Geneva, Switzerland;* [3]*Faculty of Medicine, University of Geneva, Pathology and Immunology, Geneva, Switzerland;* [4]*University hospital, Division of Gastroenterology, Geneva, Switzerland;* [5]*University hospital, Divisions of Clinical Pathology and of Gastroenterology, Geneva, Switzerland;* [6]*Faculty of Medicine, University of Geneva, Cell Physiology and Metabolism, Geneva*
Email: sophie.clement@unige.ch

Background and Aims: Hepatitis C virus (HCV) infection is a major cause of chronic liver metabolic disorders that may lead to hepatocellular carcinoma. We previously reported the critical role of the phosphatase PTEN in both HCV-induced steatosis and HCV life cycle. PTEN was downregulated by the core protein of HCV genotype 3a (HCV-3a core) through a mechanism involving a 3′ untranslated region-dependent repression of mRNA translation. We further demonstrated that miR-21, a potent oncomiR targeting PTEN, is involved in hepatic steatosis associated with diet-induced obesity in mice. Here, we investigated the role of miR-21 in HCV-induced PTEN downregulation and its potential impact on both HCV-3a-induced steatosis and viral life cycle.
Method: miR-21 expression and activity were measured in Huh-7 cells overexpressing HCV-3a core or infected with culture-derived Jc1 HCV. PTEN expression, lipid droplet (LD) morphology and cholesterol ester (CE) levels were assessed in HCV-3a core transduced Huh-7 cells exposed to miR-21 inhibitors, and in mouse primary hepatocytes isolated from either Flox/flox control or miR21 knockout (KO) mice and expressing HCV-3a core protein. HCV replication, entry and viral particle production were investigated, using a subgenomic replicon, pseudoparticles and cell cultured-derived Jc1 HCV, respectively. A meta-analysis was performed to evaluate the expression of miR-21 in livers from chronic hepatitis C patients.
Results: While miR-21 expression level was not affected by HCV-3a core, its activity was significantly and transiently increased at days 2 and 3 post transduction. The anti-miR-21 partially prevented the HCV-3a core-induced PTEN downregulation and CE accumulation in LD in Huh-7 cells. Furthermore, the lack of miR-21 expression in primary mouse hepatocytes from miR-21 KO mice prevented the increase of LD size induced by the HCV-3a core. The anti-miR-21 also decreased both HCV replication and the production of infectious particles in Huh-7 cells, while no effect on HCV entry was noted as assessed using pseudoparticles. Finally, in the meta-analysis, HCV infection was significantly associated with increased liver miR21-5p (standardized mean difference 0.65 [95%CI 0.19–1.10, p = 0.005]) with limited heterogeneity (I^2 = 39%, p = 0.18).
Conclusion: Altogether, our data indicate that miR-21 activation by HCV is a key molecular step promoting both HCV 3a-induced steatosis and HCV life cycle.

SAT-397

Hepatitis E virus replication and interferonresponse in human placental-derived cells

P. Behrendt[1], L. Knegendorf[2], S. Drave[2], K. Resner[2], D. Todt[2], M. Friesland[2], M. Engelmann[2], R. Brown[2], Y. Debing[3], V.L.D. Thi[4], H. Wedemeyer[5], J. Neyts[3], M.P. Manns[5], T. Pietschmann[2], E. Steinmann[2]. [1]*Medical School Hannover, Department for Gastroenterology, Hepatology and Endocrinology, Hannover, Germany;* [2]*Twincore, Experimental Virology, Hannover, Germany;* [3]*REGA Institute for Medical Research, Department of Microbiology and Immunology, Leuven, Belgium;* [4]*The Rockefeller University, Laboratory of Virology and Infectious Disease, New York, United States;* [5]*Medical School Hannover, Gastroenterology, Hepatology and Endocrinology, Hannover, Germany*
Email: behrendt.patrick@mh-hannover.de

Background and Aims: The Hepatitis E virus (HEV) is one major cause of viral hepatitis and shows high epidemic potential in developing countries. Notably, HEV infection has a high incidence among pregnant women and might take a serious course. High maternal mortality rates of about 25% in association with fulminant hepatic failure have been observed in HEV-infected pregnant women. However, the underlying pathogenic mechanisms remain largely unexplained and the cases have only been reported for infections with genotype (gt) 1 HEV, while gt 3 infections remain often subclinical without severe impairment. In this study, we investigated whether HEV is capable of performing the full viral life cycle in placental-derived cells (JEG-3).
Method: In this study, subgenomic replicons (SGR) for both genotypes and a full-length HEV clone for gt 3 were utilized to investigate, whether HEV is capable of performing the whole viral life cycle in the human placental-derived cell line JEG-3. Viral replication and release was compared to the human hepatoma cell line HepG2. Additionally, viral response upon IFN-alpha-a1 as well as Ribavirin treatment was investigated.
Results: JEG-3 cells supported HEV RNA replication of both SGRs and the full-length gt 3 clone and showed high replication capacity. We could confirm virus assembly and release by the detection of intra- and extracellular viral capsid through an HEV antigen ELISA and of viral entry by infection with cell culture-acquired genotype 3 virions. Furthermore, we could show that both genotypes in placental cells have a similar sensitivity to Ribavirin compared to HEV in hepatoma cells. In contrast, we experienced HEV gt 1 SGR to respond significantly lower to the antiviral activity of Interferon IFN-alpha-a1 in JEG-3 cells compared to HEV gt 3 SGR. However, this effect cannot be seen in HepG2 cells. Simultaneous determination of interferon-stimulated gene expression levels demonstrated an efficient downregulation by both HEV genotypes, although the gt 1 SGR replicates less efficient in tissue culture in comparison to the gt 3 SGR.
Conclusion: In conclusion, we found that HEV is capable of performing the full viral life cycle in a placental cell line *in vitro* and identified a potential pathogenic mechanism in host interferon response contributing to severe outcomes of HEV infection during pregnancy. Further studies should address the identification of genotype-dependent differences and a follow up on the host interferon response in HEV infection. JEG-3 cells could serve as an *in vitro* model for future research in this field.

SAT-398

Are there different profiles in microRNA expression in HBV/HDV co-infected patients reflecting plasma HBsAg and HBcrAg concentrations?

I. Carey[1], B. Li[2], M. Bruce[1], S. Montague[1], A. Gaggar[2], K. Agarwal[1]. [1]*King's College Hospital, Institute of Liver Studies, London, United Kingdom;* [2]*Gilead Sciences, Inc. Research and Development Department, Foster City, United States*
Email: ivana.kraslova@kcl.ac.uk

Background: MicroRNA expression in plasma of HBV/HDV co-infected patients demonstrated 2 distinct patterns: one driven specifically by HDV replication (miR-98-5p and miR-663b down-regulation) and second linked with HBV replication (f.e. upregulation of miRNA122-5p). HBsAg is critical for HDV replication and the patients with "active" HBV/HDV co-infection (HDV RNA positive) have higher HBsAg concentrations than HDV "exposed" patients (anti-HDV antibodies positive, HDV RNA negative). Plasma HBsAg originates from cccDNA and integrated DNA. Hepatitis B core related antigen (HBcrAg) reflects more accurately cccDNA transcription activity than HBsAg. "Active" HBV/HDV co-infected patients have higher HBcrAg levels in plasma than HDV "exposed" patients. There are no data assessing the differences in microRNA expression patterns linked with HBsAg and HBcrAg.
Aims: To compare miRNA profiles between patients with high HBsAg (>10,000 IU/ml) vs. low HBsAg (<10,000 IU/ml) and between patients with detected HBcrAg (>2 $\log_{10}$U/ml) vs. not detected HBcrAg (<2) and assess their relationship with plasma HBsAg and HBcrAg levels.
Materials and Methods: MiRNA was extracted from serum of 50 HBV/HDV co-infected patients, all HBeAg negative: 25 HDV RNA positive and 25 HDV RNA negative. Plasma levels of HBsAg, HBV DNA and HBcrAg were measured by Abbott ARCHITECT®, TaqMan real-time PCR and on LuminexG assay. MiRCURY LNA™ Universal RT microRNA PCR was performed for 742 miRNAs and 165 miRNAs were detected in all patients. Based on HBsAg levels: 15 patients had HBsAg > 10,000 IU/ml and 35 patients had HBsAg < 10,000 IU/ml. For HBcrAg concentrations: 24 patients had HBcrAg > 2 $\log_{10}$ U/ml (detected) vs. 26 patients with not detected HBcrAg. The comparison of miRNA profiles according to HBsAg levels and HBcrAg detectability was performed using limma algorithm with P values adjusted for multiple testing correction and Spearman correlations.
Results: 41 microRNAs were expressed differently between patients with high vs. low HBsAg and 40 of them showed strong bivariate correlations with HBsAg levels. miRNA122-5p was upregulated in patients with high HBsAg and correlated with HBsAg levels ($r = 0.91$, $p < 0.001$). The expression of 31 microRNAs differ between patients with detected vs. not detected HBcrAg. While 27 mircoRNAs were expressed similarly in patients with high HBsAg and detected HBcrAg, there were some microRNA expressing exclusively only patients with high HBsAg (miRNA125a-5p linked with disease progression) or patients with detected HBcrAg (miRNA142-3p linked with inflammation).
Conclusions: Patients with high HBsAg levels have a distinctive microRNA profile, which are broadly similar to microRNA expression in patients with detected HBcrAg, but with differences for few microRNAs which reflect dissociations between individual HBV replication steps (HBsAg production or cccDNA transcriptional activity).

SAT-399

Dimerization: A structural feature for the protection of Hepatitis E virus capsid protein against trypsinization

W. Wei[1], J. Meng[2], N. Behloul[3], S. Baha[3]. [1]*School of Medicine, Southeast University, Department of Microbiology and Immunology, Nanjing, China;* [2] *School of Medicine, Southeast University, Nanjing, Department of Microbiology and Immunology;* [3] *School of Medicine, Southeast University, Department of Microbiology and Immunology*
Email: jihongmeng@hotmail.com

Background and Aims: Orally-transmitted viruses have evolved the ability to resist the extreme conditions of the host's gastrointestinal environment, especially the proteolysis of their structural proteins. However, the mechanisms allowing these viruses to survive these harsh conditions remain unclear. Here we use truncated HEV capsid proteins to gain insights into the proteolysis resistance of HEV capsid protein.
Method: We adopted computational and biochemical methods to investigate the resistance of different ORF2 proteins to trypsin proteolysis. Further, we expressed the mutated p179 proteins, naturally occurring as monomers and investigated the influence of

dimerization state on the proteolytic resistance of HEV capsid proteins. Then we applied computational methods to elucidate how the dimerization could protect the P2 domain from trypsinization. At last, we use western blot assay to investigate if trypsin action could affect the exposure of the neutralizing epitopes or not.

Results: In our research, we found the trypsin digestion sites to be highly conserved among the HEV strains. Furthermore, the constructs of the HEV capsid protein that contain an extended P2 domain were digested within the extensions leaving the P2 domain intact. The trypsinization seems to occur in three possible double cleavages at R451-R619, R460-R631 or R460-R631. The dimerization disrupts the trypsin action at three main sites in the P2 domain R542, K544 and K554. These sites are very exposed in the monomeric P2 domain constructs which makes the monomeric forms very susceptible to trypsin action. Western blot analysis showed that all the truncated proteins and the proteolysis products were strongly reactive against the HEV-neutralizing monoclonal antibody.

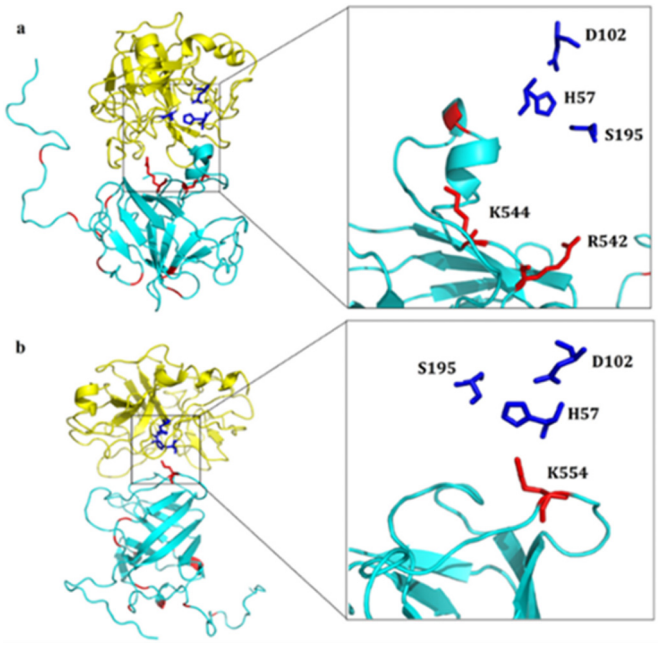


Figure: Illustration of the docking results of p179 monomer and trypsin (PDB ID: 418G). The trypsin and the monomeric p179 are shown in yellow and cyan cartoon representation, respectively. The trypsin catalytic triad is shown in blue sticks and the proteolytic sites in p179 (K554, K544 and R542) in red sticks.

Conclusion: Given the transmission route of HEV, the evolutionary forces may have selected sequence and structural features (P2 domain dimerization) that make the HEV capsid protein highly resistant to trypsin but more likely, for all the other gastrointestinal proteases. Another interesting application of our findings could be that the trypsinization did not affect the antigenicity of HEV ORF2 proteins and therefore they could be regarded as potential oral vaccine candidates.

SAT-400

The correlations between HBV markers in sera and HBVcccDNA for genotypes

M. Takeshi, K. Jong-Hon, Y. Yasushi, T. Kunihiko, M. Hiroyuki. *Teine-Keijinkai Hospital, Center for Gastroenterology, Sapporo, Japan*
Email: mtake0402@gmail.com

Background and Aims: Covalently closed circular (ccc) DNA in hepatitis B plays important roles in viral natural history. It is well known that HBV markers in sera are linked to quantified HBV ccc DNA in liver tissue. However, it remains unknown as to whether similar correlation exists between genotype(Gt) B and C. We investigated the association between HBV Gt B and Gt C, HBV markers in sera, and HBV ccc DNA in liver tissue.

Method: Intrahepatic HBV ccc DNA was quantified using specimen obtained by liver biopsy or from excised liver tissue, and serum HBV markers such as Hepatitis B core related antigen(HBcrAg), HBV DNA and Hepatitis B antigen(HBsAg) were also quantified in Hepatitis B e antigen (HBeAg)-negative patients. Correlation between the HBV ccc DNA and serum HBV marker was investigated for respective HBV genotypes.

Results: A total of 50 HBeAg-negative patients were enrolled in this study. Among them, 12 patients had Gt B and 38 had HBV Gt C. The median age was 61/50.5 (Gt B/C) year old. Seven cirrhotic cases were included in Gt C group. The median HBV ccc DNA levels was 4.1/3.3 log copies/μg (<1.7–5.3). The median levels of HBV markers in sera, namely HBV DNA, HBcrAg and HBsAg were 4.70/3.35 log copies/ml, 3.15/3.60 logU/ml and 3.15/3.25 logIU/ml, respectively. HBV ccc DNA was significantly lower in Gt C (p 0.0429), but no difference was observed in other HBV markers for genotypes. HBV ccc DNA was correlated with HBV DNA (r = 0.697; p = 0.0118) and HBcrAg (r = 0.5810; p = 0.0476), but not related with HBsAg (r = 0.3558, p = 0.2564) in Gt B. In Gt C, HBV ccc DNA was correlated with HBV DNA (r = 0.614; p = 0.0001, HBcrAg (r = 0.542; p = 0.0006 and HBsAgr = 0.476; p = 0.0033). The median ratio of HBV DNA to HBV ccc DNA was 0.7033/0.9121 (GtB/GtC), the median ratio of HBcrAg was 0.875/1.3250, and the median ratio of HBsAg was 1.250/1.250. The median ratio of HBcrAg to HBV ccc DNA was significantly lower in GtB (p = 0.0058) than in GtC and the median ratio of HBsAg tended to be lower (p = 0.0812) in GtB.

Conclusion: The HBV markers were correlated with HBV ccc DNA in Gt C. However, the correlation was not observed for all of the markers for Gt B, with HBsAg showing no correlation with HBV ccc DNA level. In addition, it was suggested that the secretion ability of HBsAg and HBcrAg may be different depending on the Gt.

SAT-401

Estrogen receptor R1 and CAD are host factors for HDV replication and antiviral targets

E. Verrier[1], A. Weiss[2], C. Bach[1], L. Heydmann[1], L. Mailly[1], T. Garcia[3], P. Pale[3], C. Schuster[1], C. Sureau[4], M. Zeisel[1], L. Brino[2], T. Baumert[1,5]. *[1]Inserm, Institut de recherche sur les maladies virales et hépatiques UMRS 1110, Université de Strasbourg, Strasbourg, France; [2]IGBMC, Plateforme de Criblage Haut-débit, Illkirch, France; [3]Institut de Chimie, Université de Strasbourg, CNRS UMR 7177 Laboratoire de Synthèse, Réactivité Organiques et Catalyse, Strasbourg, France; [4]INTS, Laboratoire de Virologie Moléculaire, Paris, France; [5]Nouvel Hôpital Civil, Institut Hospitalo-universitaire, Pôle Hépato-digestif, Strasbourg, France*
Email: e.verrier@unistra.fr

Background and Aims: Hepatitis D virus (HDV) is a small, circular DNA virus co-infecting hepatocytes with HBV and requiring HBV envelope proteins to produce infectious particles. Chronic hepatitis B/D results in more severe liver disease and an increased risk of liver cancer compared to HBV mono-infection and is considered as the most severe form of viral hepatitis. To date, licensed HDV-specific therapies are absent and novel antiviral strategies are expected to improve patients' outcome and cancer risk.

Method: Taking advantage of the HDV-susceptible NTCP-overexpressing Huh-106 cell line, we combined a dual high-throughput screening approach to identify new host factors as antiviral targets for HDV infection. First, we applied a high-throughput loss-of-function screen using a siRNA library targeting more than 7000 druggable genes to identify hepatocyte factors required for HDV infection. Next, we performed a small molecule screen to identify anti-HDV compounds using the Prestwick library comprising 1200 FDA-approved drugs.

Results: The loss-of-function screen identified 202 host factor candidates for HDV infection. Validation studies identified *ESR1*

(estrogen receptor E1) and *CAD* (trifunctional protein carbamoyl-phosphate synthetase 2, aspartate transcarbamylase, and dihydroorotase) as a host factor pathway playing a key role in host cell pyrimidine biosynthesis. Interestingly, Fulvestrant, an antagonist of the estrogen receptor 1 (ESR1) was identified in the small molecule screen as an efficient inhibitor of HDV infection. On the other hand, the treatment of Huh-106 cells with ESR1 agonists or modulators, such as Norgestimate or Toremifene induced an increase in HDV infection, confirming the relevance of ESR1 for HDV replication. Kinetic assays revealed that ESR1 mediates the early steps of HDV replication. Moreover, the antiviral effect of the Fulvestrant was associated with a decrease in *CAD* expression, which is known to be induced by the SP1/ESR1 complex. Robust antiviral activity of the CAD inhibitor PALA in both Huh-106 and primary human hepatocytes confirmed the role of CAD as antiviral target.

Conclusion: Using a combined small molecule and loss-of-function screening approach we identified ESR1 and CAD as host factors for HDV replication and novel targets for antiviral therapy. Our approach the door to new therapeutic strategies targeting host-dependency factors for HDV cure.

SAT-402

Defining hos DNA repair factors in the formation of the hepatitis B virus covalentrly close circular DNA persistence reservoir

K. Doernbrack[1], E. Verrier[2], L. Heydmann[2], F. Wrensch[2], A. Maglott-Roth[3], L. Brino[3], M. Nassal[1], T. Baumert[2,4]. [1]*University Hospital Freiburg, Dept of Internal Medicine II/Molecular Biology, Freiburg, Germany;* [2]*Inserm, Institut de recherche sur les maladies virales et hépatiques UMRS 1110, Université de Strasbourg, Strasbourg, France;* [3]*IGBMC, Plateforme de Criblage Haut-débit, Illkirch, France;* [4]*Nouvel Hôpital Civil, Institut Hospitalo-universitaire, Pôle Hépato-digestif, Strasbourg, France*
Email: e.verrier@unistra.fr

Background and Aims: Current treatments can control but rarely cure chronic hepatitis B virus (HBV) infection. During HBV replication, the viral relaxed circular (rc) DNA is converted into an episomal covalently closed circular (ccc) DNA, serving as a template for the transcription of viral RNAs and playing a key role in virus persistence. The structure of HBV rcDNA, including a gap, a flap and protein plus RNA adducts implies a crucial role for cellular DNA repair machinery in cccDNA formation. To identify the respective repair factors involved in that process, we set up a novel high-throughput (HS) screening assay for the quantification of cccDNA activity.

Method: Exploiting the highly efficient cccDNA formation by duck HBV (DHBV) even in human cells, we generated TetOFF HepG2 lines harboring a DHBV genome and producing an HA-tagged HBe antigen (HA-HBeAg) exclusively from a functional cccDNA but not from the integrated virus DNA. As the HA-tag is present on the precore region, the HA signals are specific for HBeAg – and not HBcAg (Figure 1). Therefore, the quantification of HA-HBeAg using an HA-specific ELISA allows to quantify cccDNA formation and activity. Using a loss-of-function screening strategy and a targeted shRNA library, we plan to identify the DNA repair factors required for cccDNA formation.

Results: A control DHBV TetOFF line, named HA2/3 cell line, showed increasing, Southern blot-detectable cccDNA after 7 days of induction. Concomitant HA-HBeAg secretion was demonstrated by Western blot and HA-specific ELISA in the supernatant of HA2/3 cells. Assay sensitivity was substantially increased by using chemiluminescent substrate. Secreted HBeAg levels are increasing from day 7 to day 20 before reaching a plateau. Interestingly, the siRNA-mediated silencing of the expression of *POLK*, coding for the DNA Polymerase Kappa which is known to be involved in cccDNA formation triggered a decrease in HBeAg secretion. HA2/3 Cells have been adapted to robust growth in 96-well format, and efficient delivery of shRNA in these cells was demonstrated by a strong decrease in *POLK*-, *TDP2*-, and *SIRT1*- (putative positive controls for the screen) expressions after lentiviral transduction of respective shRNA sequences.

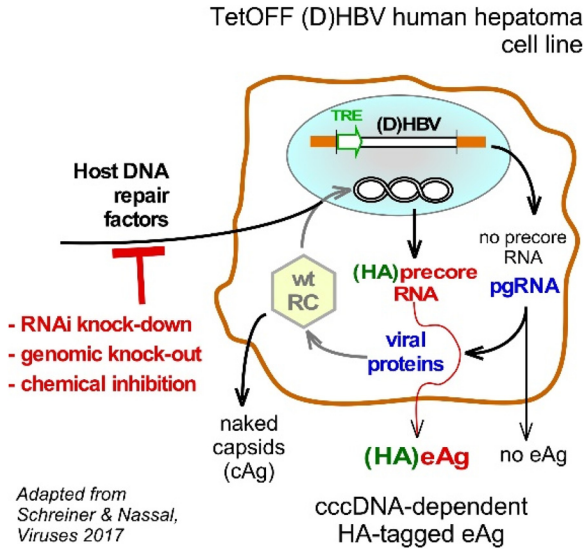


Figure 1: TetOFF inducible cell line allowing the production of DHBV cccDNA-dependent HA-tagged HBeAg.

Conclusion: The new HA2/3 cell line allows sensitive and time-resolved monitoring of cccDNA formation – and its inhibition – by a non-invasive quantifiable and principally HS-suited assay. The shRNA screen using a DNA repair library will allow to identify new host factors required for cccDNA formation. Moreover, this assay is also suitable for small molecule screens. Taken together, our model will allow to identify new host targets and small molecules specifically targeting cccDNA formation and will pave the way to novel antiviral strategies targeting cccDNA for viral cure.

Viral Hepatitis A, B, C, D, E: Immunology

SAT-405

MicroRNA-155 regulates pro- and anti-inflammatory cytokine expression in human monocytes/macrophages during chronic hepatitis C virus infeciton

Y. Zhang, P. Zhang, C. Fan, X. Zheng, Z. Yao, Z. Jia. *Tangdu Hospital, Department of Infectious Diseases, Xi'an, China*
Email: zyfmmu@hotmail.com

Background and Aims: Hepatitis C virus (HCV) dysregulates innate and adaptive immune responses, leading to chronic viral infection in most humans. Monocytes/macrophages (M/M_{Φ}) play a crucial role in linking innate and adaptive immunity to control viral infection. We have previously shown that a transcription factor – T-box expressed in T cells (T-bet) is up-regulated in M/M_{Φ} to dampen M/M_{Φ} functions via enhancing T-cell immunoglobulin and mucin domainprotein-3 (Tim-3) expression in chronic HCV infection; however, the molecular mechanisms that control its expression in M/M_{Φ} remain largely unknown. MicroRNAs (miR) have been implicated as key regulators controlling diverse biological processes through posttranscriptional repression. In this study, we investigated the effect of miRNA-155onM/M_{Φ} function through regulating T-bet signaling in the setting of chronic HCV infection.

Method: Forty chronic HCV infected patients and 40 healthy subjects (HS) were recruited. $CD14^{+}$ monocytes were purified, followed by RT-PCR analysis of miR155 levels. MiR155 levels were also detected in monocytic THP-1 cells stimulated with LPS, HCV core or HCV NS5,

and THP-1 cells co-cultured with HCV$^+$ or HCV$^-$ Huh7.5 cells. Furthermore, CD14$^+$ monocytes isolated from chronically HCV-infected individuals and HS were transfected with miR155 mimics, miR155 inhibitors or negative control. TNF-α and JNK1, 2, 3 were detected by ELISA and RT-PCR. T-bet, IL-12 and Il-10 were tested by flow cytometry. SOCS1 were detected by WB and RT-PCR.

Results: We demonstrated that miR-155 was up-regulated in CD14$^+$ M/M$_\Phi$ in HCV-infected patients compared to healthy subjects. Upon LPS, HCV core or NS5 stimulation, miR-155 was up-regulated in monocytic THP-1 cells. Up-regulation of miR-155 was also observed in THP-1 cells incubated with HCV$^+$ Huh7.5 cells. Moreover, up-regulation of miR-155 in CD14$^+$M/M$_\Phi$ from HCV-infected patients induced TNF-α production and JNK signaling activation, leading to T-bet up-regulation, thereby, promoting inflammatory responses. Also, miR-155 up-regulation in CD14$^+$ M/M$_\Phi$ of HCV-infected patients resulted in increased IL-12 and decreased IL-10 productions via inhibiting the suppressor of cytokine signaling 1 (SOCS1) signaling.

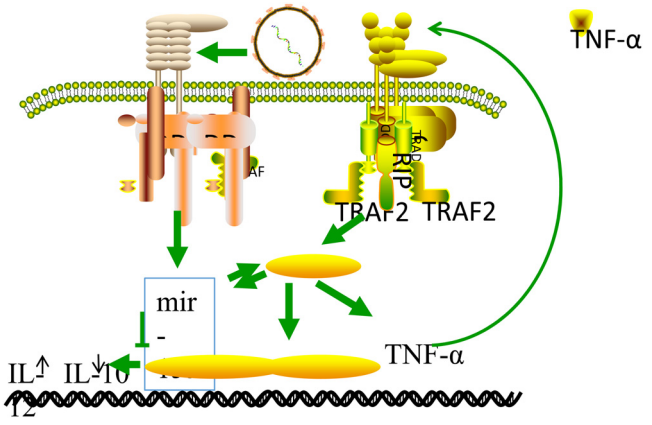


Figure: A model for miR155 regulation of monocyte functions in the setting of chronic HCV infection.

Conclusion: These results indicate that miR-155 up-regulation in M/M$_\Phi$ during HCV infection enhances the activation of TNF-α and JNK pathways to promote the expression of transcription factor T-bet and triggers pro-as well as anti-inflammatory mediators, such as IL-12, TNF-α, and IL-10, via the SOCS1 signaling. Our data reveal new information for elucidating the mechanisms of chronic HCV infection.

SAT-406

Depletion of RIPK1 in hepatocytes exacerbates PolyI:C and Murine Hepatitis Virus induced liver damage

M. Farooq, C. Piquet-Pellorce, S. Dion, M.S. Eugenio, A. Filliol, C. Raguenes-Nicol, M.-T. Dimanche-Boitrel, J.L. Seyec, M. Samson.
IRSET – U.1085 Inserm, Rennes, France
Email: michel.samson@univ-rennes1.fr

Background and Aims: The protein kinase RIPK1 plays a crucial role on the crossroad of stress-induced signaling pathways that affects cell's decision to live or die. Thus, RIPK1 is involved in the signal transduction pathway activated during the recognition of viral pathogen-associated molecular patterns (PAMPs) by the Toll-like receptor 3 (TLR3). The present study aimed to define the role of RIPK1 in hepatocytes when this pathway is stimulated with Poly I:C, a synthetic analog of double-stranded RNA or when a fulminant hepatitis is induced by Murine Hepatitis Virus type 3 (MHV3) infection.

Method: Mice deficient for RIPK1 specifically in liver parenchymal cells (RIPK1$^{LPC\text{-}KO}$) and their wild-type littermates (RIPK1$^{fl/fl}$) have been challenged by Poly I:C. Etanercept, a TNF alpha receptor decoy, or clodronate encapsulated liposomes were injected prior administration of Poly I:C to explore the respective role of TNF alpha and macrophages in induced hepatitis. Primary cultures of mouse hepatocytes isolated from RIPK1$^{LPC\text{-}KO}$ or RIPK1$^{fl/fl}$ mice were also established to investigate the direct impact of Poly I:C on normal or deficient liver parenchymal cells. Besides, fulminant hepatitis induced by MHV3 were compared in RIPK1$^{LPC\text{-}KO}$ and RIPK1$^{fl/fl}$ mice. Different clinico-pathological investigations (ALT, liver histology, qPCR…) were conducted to analyze challenged animals.

Results: Administration of Poly I:C led to increased serum ALT in RIPK1$^{LPC\text{-}KO}$ mice, reflecting liver damage through elevated apoptosis as illustrated by cleaved-caspase 3 labeling. Prior neutralization of TNF alpha protected hepatocytes from apoptosis in Poly I:C challenged RIPK1$^{LPC\text{-}KO}$ mice. Besides, depletion of macrophages also resulted in complete protection. In *in vitro* primary mouse hepatocytes, Poly I:C never induced direct cell death whatever the murine genotype, while it always stimulated an anti-viral response as characterized by the induction of PKR, Mx1 and OAS gene expression even in absence of RIPK1. Additionally, it has been discovered that RIPK1$^{LPC\text{-}KO}$ mice were more sensitive to MHV3 induced fulminant hepatitis.

Conclusion: Our data sustain the protective role played by RIPK1 in hepatocytes during viral induced fulminant hepatitis which is carried out through TNF alpha secreted from macrophages.

SAT-407

A novel chimpanzee adenoviral vectored HBV vaccine, encoding multiple HBV antigens with a shark invariant chain adjuvant, for use in HBV immunotherapy

S.K. Chinnakannan[1], T. Cargill[1], T. Donnison[1], A. Ansari[1], M. Maini[2], T. Evans[3], E. Barnes[1]. [1]*Peter Medawar Building, Nuffield Department of Medicine, Oxford, United Kingdom;* [2]*University College of London, Division of Infection and Immunity UCL, London, United Kingdom;* [3]*Vaccitech, Oxford, United Kingdom*
Email: senthil.chinnakannan@ndm.ox.ac.uk

Background and Aims: Chronic hepatitis B virus (HBV) infects 257 million people globally. Current therapies suppress HBV but rebound occurs on cessation of therapy; novel therapeutic strategies are urgently required. To develop a potent therapeutic HBV vaccine that will induce T-cells to all major HBV antigens and generate anti-HBs antibodies, using Chimpanzee adenoviral vectors and shark class-II invariant (sIi) chain as a genetic adjuvant.

Method: We designed two HBV immunogens SIi-HBV-CP$_{mut}$S and HBV-CP$_{mut}$S; encoding precore (PreC), core, non-functional polymerase (P$_{mut}$), PreS1, PreS2 and surface antigens (Figure 1a). The large envelope protein of HBV (composed of PreS1, PreS2 and surface proteins) was generated separately using furin 2A (F2A) peptide cleavage protein. A 26 amino-acid sequence, derived from shark invariant chain (sIi), was inserted at the 5′ end of the SIi-HBV-CPmutS immunogen. The immunogens were encoded in chimpanzee-adenoviral vector (ChAdOx2) and tested in naïve mice given i.m. HBV-specific T-cell responses were assessed using IFN-ϒ ELISpot and intracellular cytokine (ICCS) assays.

Results: Vaccination generated very high magnitude HBV specific T-cell responses to all HBV antigens (Figure 1b). The mean magnitude of total HBV-specific T-cell responses in inbred BALB/c and outbred CD1 mice were 3858 and 3821 spot forming units [SFU]/10^6 splenocytes (shown on the left side of Figure 1) and 4514 and 2979 SFU/10^6 intrahepatic lymphocytes (shown on the right side of Figure 1b) respectively. ICCS showed that HBV specific CD8+ T cells were polyfunctional producing both IFN-ϒ and TNF-α.

The inclusion of shark invariant chain (data shown in blue coloured bars in Figure 1b) significantly enhances the T-cell magnitude for both splenocytes (3821 mean total SFU/10^6 with sIi vs. 386 mean total SFU/10^6 without sIi, $p < 0.0001$) and intrahepatic lymphocytes (2979 mean total SFU/10^6 with sIi vs. 461 mean total SFU/10^6 without SIi, $p = 0.0002$). Importantly, T cells to the non-HBV SIi peptides were not generated.

Conclusion: We have generated a highly potent HBV vaccine that induces T-cells against all major HBV proteins, using chimpanzee

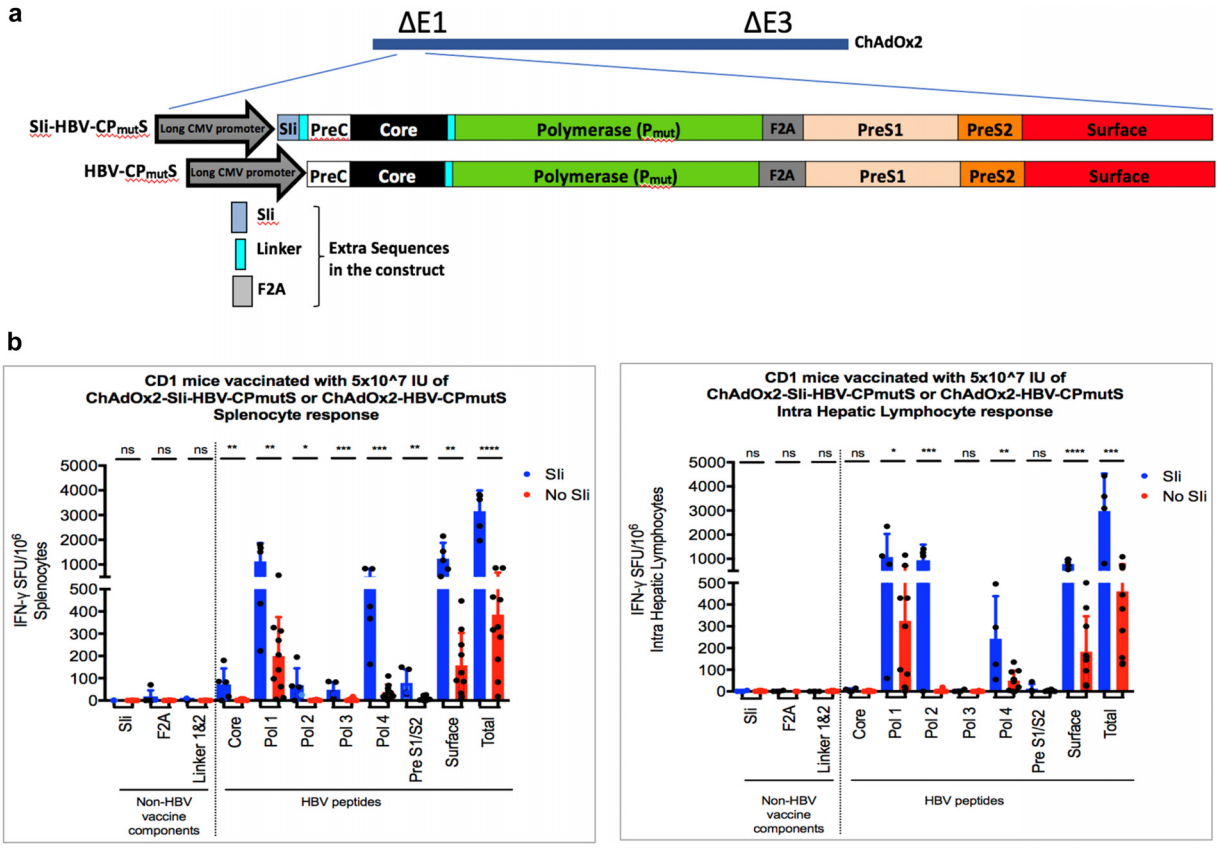


Figure 1: (abstract: SAT-407): ChAdOx2-HBV vaccines. (b) Comparison of the immunogenicity of ChAdOx2-HBV vaccines with and without Shark Invariant Chain (SIi)

adenoviral vector and class-II invariant chain technologies. These pre-clinical studies pave the way for new studies of HBV immunotherapy in humans with chronic HBV infection.

SAT-408

Modeling HBV infections and immune responses in humanized mouse models

M. Dusseaux[1], G. Masse-Ranson[1], S. Darche[1], J. Ahodantin[2], Y. Li[1], E. Beaumont[3], P. Moreau[4], C. Neuveut[4], P. Soussan[5], P. Roingeard[3], D. Kremsdorf[5], J.D. Santo[1], H. Strick-Marchand[1]. *[1]Institut Pasteur, Immunology, Paris, France; [2]CIMI-Paris, Paris, France; [3]Université François-Rabelais Tours, Inserm U966, Tours, France; [4]Institut Pasteur, Virology, Paris, France; [5]CIMI Paris, Inserm U1135, Paris, France*
Email: hstrick@pasteur.fr

Background and Aims: While Hepatitis B virus (HBV) infects and replicates in hepatocytes, its evasion and modulation of the immune response is key to the physiopathology observed in patients. The cross-talk between the immune system and infected hepatocytes results in either viral control with functional cure or viral persistence with chronic infections.
Method: HBV's limited species tropism has restricted the development of relevant in vivo systems, thus we have established a mouse model harboring both a humanized immune system (HIS) and human hepatocytes (HUHEP) in BALB/c Rag2$^{-/-}$IL2Rc$^{-/-}$SIRP^{NOD} Alb-uPA^{tg} hosts. HIS-HUHEP mice are robustly and stably engrafted with human myeloid and lymphoid cells homing to lymphoid organs as well as high levels of human liver chimerism. To model the diversity of pathological outcomes in patients with different viral loads, HIS-HUHEP mice were infected with a low or high dose of HBV, and the human immune response was evaluated.
Results: HBV-infected HIS-HUHEP mice developed chronic HBV with a full viral life cycle (HBV DNA, HBsAg and HBeAg in the plasma, cccDNA in the liver) and maintained partially controlled viremia for several months. Immune responses in HBV-infected HIS-HUHEP mice were characterized by increased NK and T cell recruitment and activation in the liver and spleen, as well as antigen specific antibodies (anti-HBsAg and anti-HBcAg) in the plasma. Elevated levels of pro-inflammatory, as well as immunosuppressive, cytokines and chemokines were observed in the plasma and liver, which was enriched in PD-L1+ cells. Mice inoculated with lower viral loads had more moderate immune responses, whereas higher viral loads resulted in PD-1+ exhausted memory T cells. Antiviral treatment of HBV-infected HIS-HUHEP mice resulted in restoration of naïve immune phenotypes.
Conclusion: Humanized mouse models offer a platform to assess the complex interactions between the virus, host cell, and immune response in viral hepatitis. Immunopathologies induced by co-infections (HIV/HBV, HDV/HBV, HCV/HBV) have yet to be explored in immunocompetent models and could give insights into the accelerated disease phenotypes and allow testing of novel therapeutic strategies.

SAT-409

Highly immunogenic virally vectored T cell vaccine against HCV are able to induce specific CD4+ T cell helper responses

I. Esposito[1], F. Hartnell[1], L. Swadling[1], C. Phetsouphanh[1], A. Brown[1], C.D. Lara[1], A. Folgori[2], S. Capone[2], E. Barnes[1], P. Klenerman[1].
[1]University of Oxford, Peter Medawar Department, Oxford, United Kingdom; [2]Reithera srl, Roma, Italy
Email: ilaria.esposito@ndm.ox.ac.uk

Background and Aims: Induction of functional CD4+ T cell helper responses are the hallmark of a protective response against HCV associated with spontaneous clearance of virus. Recent vaccination studies have shown priming and boosting of high levels of T cell

responses against HCV in healthy volunteers, although much less data is available about the specificity, memory phenotype and functional quality of help induced. For this reason, we want to analyse the characteristics of CD4+ T cell helper populations undergoing HCV vaccination with novel recombinant adenoviral prime/poxvirus boost regimens (clinical trials EudraCT number 2007-004259-12 and 2009-018260-10). In addition, we want to compare these responses to a population of 10 HLA-matched individuals with spontaneous resolution of HCV, as well as 21 undergoing DAA-mediated cure following HCV genotype 1 chronic infection (recruited in a separate study).

Method: We analysed CD4+ T cell helper populations using MHC Class II tetramers encoding for NS region of HCV virus in healthy vaccinated individuals, spontaneous resolvers and patients following DAA therapy. Peptide-specific T cell responses were tracked over time using flow cytometry and frequency, proliferative capacity, surface phenotype, functional responses as well as the expression of exhaustion markers measured.

Results: The vaccination regimen induced tetramer positive CD4+ T cells at all measured time points, especially 1–4 weeks after boosting (mean 0.06%). Similar frequencies were obtained for those tracked following spontaneous resolution of disease (mean 0.04%). In addition, the phenotype, including CD127and CD28 expression and functional capacity of peptide specific CD4+ T cell responses characterized after vaccination (mean ± SD = 79.6% ± 11.4% at boosting) are comparable to spontaneous resolver individuals (mean ± SD = 69.3% ± 17.4%). The vaccination is able to induce a high percentage of specific CD4 + effector and central T cells memory at each time points analogous to spontaneous resolvers as well as low expression of exhaustion markers.

In contrast, helper responses in chronic infection were infrequently detected and poorly functional, and did not recover following HCV cure.

Conclusion: The nature of CD4+ T cell help examined in detail using MHC Class II tetramers resembled "protective memory" that is seen following spontaneous clearance of HCV.DAA cure does not allow for resurrection of exhausted CD4+ T cell memory in chronic infection. Further studies to assess the response to vaccination in those cured by DAA therapy will address whether effective help can be induced longer term.

SAT-410

Induction of liver sinusoidal endothelial cells immune activation by HBeAg during HBV infection

Q. Yu, J. Luo, S. Yang, Q. Wang, Y. Liu, L. Wang, D. Yang, J. Liu. *Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Infectious Diseases, Wuhan, China*
Email: jialiu77@hotmail.com

Background and Aims: Liver sinusoidal endothelial cells (LSECs) play a crucial role in maintaining the homeostasis of the hepatic microenvironment through induction of Ag-specific T cell tolerance. It has been shown that some viruses infection or TLRs stimulation can induce the maturation of LSECs, which reverts their suppressive properties to induce T cell immunity. However, little is known about whether and how the function of LSECs in regulating T cell immunity is regulated during HBV infection. Here, we investigated the function and mechanism of LSECs regulating CD8+ T cell immunity during HBV infection.

Method: Mice were hydrodynamic injected (HI) with plasmid pAAV/HBV1.2 or pSM2, and their LSECs were freshly isolated at different time points post injection and co-cultured with polyclonal TCR-activated T cells. LSECs freshly isolated from naïve mice were stimulated by recombinant HBV antigen protein and co-cultured with polyclonal TCR-activated T cells. Human LSECs were isolated and stimulated by recombinant HBeAg, and were co-cultured with Dynabeads activated T cells. The phenotype and function of LSECs were characterized by flow cytometry, quantitative PCR, and functional assays.

Results: Compared to LSECs of naive mice or HI control mice, LSECs separated from HBV HI mice at 14 days post injection (dpi) reverted their suppressive properties to enhance T cell immunity. Further analysis demonstrated that both in vitro and in vivo HBeAg stimulation could induce the maturation of naive LSECs and enable them to promote the IFN-γ production of TCR-activated CD8+ T cells. LSECs separated from HBeAg-deficiency HBV HI mice were less capable of promoting T cell immunity compared to those separated from wild type HBV HI mice. In contrast, replenishing HBeAg expression in HBeAg-deficiency HBV HI mice resulted in better LSEC activation and led to accelerated HBV clearance. Both LSECs separated from HBV HI mice and HBeAg stimulated LSECs showed increased TNF-α production. TNF-α blockade partially abolished the ability of HBeAg-stimulated LSECs to promote effector T cell response. In contrast, adding TNF-α to the cocultures of unstimulated LSECs and activated T cells abrogated the suppression of T cell IFN-γ production by LSECs. Importantly, in vitro HBeAg stimulation could also induce the maturation of human LSECs and enable them to promote the IFN-γ production of TCR-activated CD8+ T cells.

Conclusion: Our data suggest that HBV replication can revert LSECs suppressive properties to promote T cell immunity, which is partially mediated by HBeAg induced TNF-α production of LSECs.

SAT-411

Regulation of antiviral CD8 T cell response by MMP mediated soluble CD100 releasing in HBV infection

S. Yang, L. Wang, Q. Yu, Q. Wang, Y. Liu, J. Luo, D. Yang, J. Liu. *Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Department of Infectious Disease, Wuhan, China*
Email: jialiu77@hotmail.com

Background and Aims: CD100 is the first semaphorin described to have immune functions and serves important roles in T cell responses. Proteolytic cleavage of CD100 from the cell surface by matrix metalloproteinases (MMPs) gives rise to a soluble fragment of CD100 (sCD100), which is also thought to have immunoregulatory properties. Here, we characterized the expression and possible role of CD100/sCD100 in regulating antiviral response during HBV infection in patients and HBV-replicating mouse model. However, there is a paucity of information about how CD100 modulates the T cell response during HBV infection.

Results: We found that surface CD100 expression on T cells of chronic Hepatitis B (CHB) patients was significantly increased compared to that of healthy controls (HC). Meanwhile, CHB patients showed significantly lower concentrations of serum sCD100 than HC. Correspondingly, decreased surface CD100 expression on T cells in PBMCs and elevated serum sCD100 levels were observed in the mice which eliminated HBV from their livers but not in the HBV-tolerant mice. In vivo sCD100 treatment led to enhanced CTL response and accelerated viral clearance in the HBV-tolerant mice. Interestingly, activation of liver sinusoidal endothelial cells by sCD100 treatment was observed. In vitro sCD100 treatment also resulted in enhanced HBV-specific CD8 T cell response in PBMCs of some CHB patients. In contrast, blockade of the interaction of CD100 and its ligand CD72 by CD72 blocking antibody treatment resulted in decreased HBV-specific CD8 T cell response and HBV persistence in mice. We also investigated the possible mechanism involved in membrane CD100 shedding during HBV infection. Our results demonstrated that MMP2 and MMP9 are responsible for the cleavage of CD100 from the surface of T cells. In CHB patients, significantly lower serum MMP2 concentration was observed than that of HC. Compared to HBV-tolerant mice, mice which eliminated the virus showed elevated MMP2 expression in the liver during the acute phase of infection. In vivo inhibition of MMP2 and MMP9 activity resulted in decreased HBV specific CTL response and delay HBV clearance in mice.

Conclusion: In conclusion, our results indicated CD100/sCD100-CD72 interaction is important for the induction of antiviral T cell response and viral clearance during HBV infection. We hypothesize that insufficient liver MMP2 production during HBV infection results in impaired membrane CD100 cleavage, which leads to lack of activation stimulation for intrahepatic antiviral T response and thus the persistence of HBV infection. This study provides a new mechanism to elucidate HBV persistence in patients and a new target for developing strategies to overcome T cell tolerance in chronic HBV infection.

SAT-412

Transcriptomic profiling of intrahepatic B cells suggests a B-cell impairment in the immune active phase of chronic hepatitis B

S.V. Hees[1,2,3], J. Hou[3], A. Grooshuismink[3], K. Kreefft[3], S. Bourgeois[1,4], A. Boonstra[3], T. Vanwolleghem[1,2,3]. *[1]Antwerp University Hospital, Department of Gastroenterology and Hepatology, Antwerp, Belgium; [2]Antwerp University, Laboratory of Experimental Medicine and Paediatrics, Antwerp, Belgium; [3]Erasmus Medical Center, Department of Gastroenterology and Hepatology, Rotterdam, Netherlands; [4]ZNA Stuivenberg, Department of Gastroenterology and Hepatology, Antwerp*
Email: stijn.vanhees@uantwerpen.be

Background and Aims: Using a systems biology approach, we recently demonstrated a significant activity of B-cell related genes in whole blood and liver biopsies during sequential clinical phases of a chronic Hepatitis B Virus (HBV) infection. We here investigated for the first time the transcriptome of paired sorted B cells from liver and blood across the different HBV clinical phases.

Method: CD19+ B cells were purified by cell sorting (FACS Aria) from PBMC of healthy controls (HC; n = 13) and untreated HBV patients in the 4 different HBV clinical phases: Immune Tolerant (IT; n = 3), Immune Active (IA; n = 14), Inactive Carrier (IC; n = 9) and HBeAg negative phase (ENEG; n = 16). In addition, paired CD19+ B cells were sorted from core needle liver biopsies of 6 IA, 5 IC and 3 ENEG patients. RNA-sequencing and data analysis was performed using Unique Molecular Identifiers. Two different bio-informatical analysis approaches were applied: 1. Analysis of Differentially Expressed Genes (DEG) with q < 0.2 and fold-change > 1.5; 2. Gene pattern analysis on a literature based selected set of B-cell related genes (n = 92). FACS analysis was performed to assess CD10, CD21, CD27, CD38 and IgD expression on peripheral CD19+ B cells.

Results: FACS analysis of peripheral B-cell subsets did not show significant differences between different HBV phases. Analysis of DEG in peripheral B cells revealed only 5 common DEG across all HBV clinical phases vs. healthy controls. However, each individual HBV clinical phase showed a significant number of DEG (IA: n = 912; ENEG: n = 874; IC: n = 785 and IT: n = 562) when compared to the HC B cell transcriptome, with most overlapping DEG (n = 348) in the IA and ENEG phase. This is highly suggestive for different roles of B cells during the distinct HBV clinical phases. Gene pattern analysis demonstrated lower expression of 4 genes, including PDL1 and IL2RA in peripheral B cells across all HBV clinical phases vs. healthy controls. Applying the gene set pattern analysis on intrahepatic B cells showed an upregulation of genes encoding B cell inhibitory proteins in the IA phase relative to the IC and ENEG phase. In addition, intrahepatic CXCR3 transcription was higher in both IA and ENEG phases. These patterns were absent in blood (Figure 1), suggesting a liver-specific HBV-associated B-cell impairment, but active recruitment during the IA phase. Detailed assessment and functional analysis of specific genes is ongoing in both liver and peripheral B cells.

Conclusion: This is the first assessment of gene expression profiles of B cells by RNASeq in blood and liver of chronic HBV patients. Bio-informatical analysis demonstrated a high number of DEG not only when comparing paired liver and blood B cells, but also -more importantly- when comparing the distinct phases of disease differing in levels of viral replication and liver damage.

SAT-413

Dysfunctional surface antigen-specific memory B cells accumulate in chronic hepatitis B infection

A. Burton[1], L.J. Pallett[2], L. Mccoy[1], K. Suveizdyte[1], O.E. Amin[1], F. Froghi[3], B.R. Davidson[3], U.S. Gill[4], P.A. Blair[5], C. Mauri[5], N. Pelletier[6], M. Maini[1]. *[1]UCL, Division of Infection and Immunity, London, United Kingdom; [2]Division of Infection & Immunity, London, United Kingdom; [3]UCL, Institute of Liver and Digestive Health, London, United Kingdom; [4]Barts and the London, Centre for Immunobiology, London, United Kingdom; [5]UCL, Division of Medicine, London, United Kingdom; [6]Roche Innovation Center, Roche Pharma and Early Research Development, Basel, Switzerland*
Email: alice.burton.14@ucl.ac.uk

Background and Aims: One important and under-researched component of the natural control of hepatitis B (HBV) infection is the development of antibodies against HBV surface antigen (HBsAg; anti-HBs), which are a hallmark of functional cure. The production of insufficient antibodies to neutralise the large quantities of circulating HBsAg suggests there may be defects in the global and/or HBsAg-specific memory B cell compartments.

Method: Using a novel bait reagent and 16-color flow cytometry, we have comprehensively analysed the phenotype and function of global

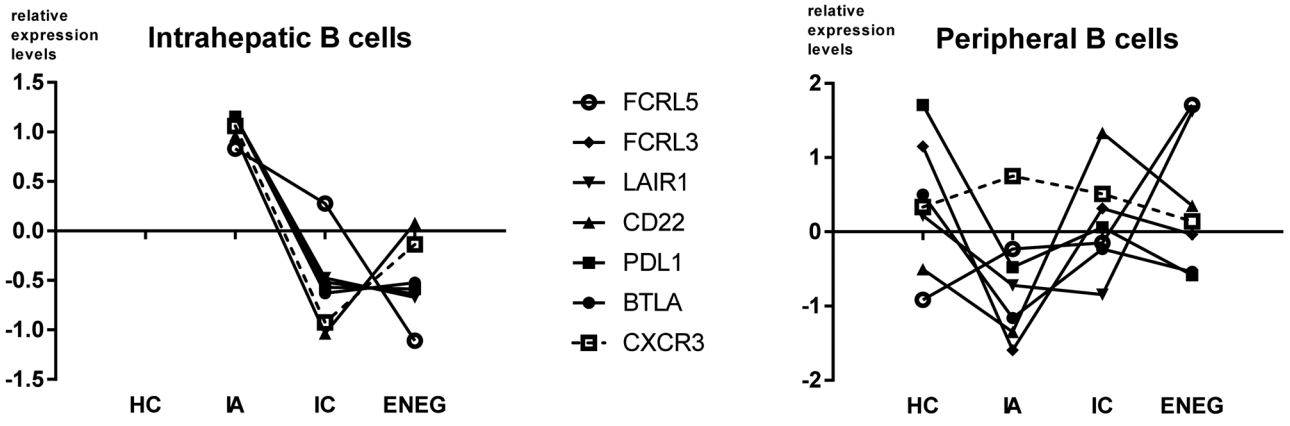


Figure 1: Relative expression levels of genes encoding B cell inhibitory proteins (continuous lines) and CXCR3 (dotted line) in intrahepatic vs peripheral B cells across the different HBV clinical phases.

Figure: (abstract: SAT-412)

and HBsAg-specific B cell subsets in a heterogeneous cohort of patients with chronic HBV infection (CHB) and HBV-vaccinated healthy controls.
Results: We show that HBsAg-specific B cells are detectable in CHB, despite the lack of circulating anti-HBs antibodies in these patients. However, in patients with CHB, HBsAg-specific memory B cells with an atypical, dysfunctional phenotype (defined as $CD27^{-}CD21^{lo/-}$) are expanded compared to vaccinated healthy controls. This population expresses high levels of inhibitory receptors, and accordingly exhibits impaired cytokine production, B cell receptor signaling and differentiation into plasma cells compared to classical memory B cells. Preliminary data suggest that immune complexes, known to circulate in patients with chronic HBV infection, may further suppress B cell receptor signaling through binding to inhibitory Fc-receptors preferentially expressed on atypical memory B cells. Atypical memory B cells with a dysfunctional phenotype are further enriched within the HBV-infected liver, where they constitute a higher proportion of the mature B cell pool than in healthy controls.
Conclusion: Overall, these data suggest that chronic antigen exposure in CHB can drive dysfunction of HBsAg-specific B cells, that may contribute to the failure of immune control.

SAT-414
Hepatitis B virus entry in primary human hepatocytes initiates toll-like receptor 2-dependent immune signaling

Z. Zhenhua[1], M. Trippler[1], C. Real[1], M. Werner[1], T. Kemper[2], H. Baba[3], J.-W. Treckmann[4], A. Paul[4], G. Gerken[1], J. Schlaak[5], M. Lu[2], R. Broering[1]. *[1]University Duisburg-Essen - Medical Faculty, Dept. of Gastroenterology and Hepatology, Essen; [2]University Duisburg-Essen - Medical Faculty, Institute for Virology, Essen, Germany; [3]University Duisburg-Essen - Medical Faculty, Dept. of Pathology and Neuropathology, Essen; [4]University Duisburg-Essen - Medical Faculty, Dept. of General-, Visceral- and Transplantation Surgery, Essen, Germany; [5]Evangelisches Klinikum Niederrhein gGmbH, Duisburg, Germany*
Email: ruth.broering@uni-due.de

Background and Aims: It has become clear that not only the adaptive but also the innate immune system is involved in the pathogenesis of Hepatitis B virus (HBV) infection. Here, we analyzed the immune activation pattern in primary human hepatocytes (PHH) infected with HBV in vitro.
Method: PHH were isolated after perfusion and digestion of liver tissue obtained after tumor resections or transplantations. PHH were treated with cell culture-derived HBV particles (HepG2.117) or negative control particles and cultured for 1–10 days. Infection was monitored by the release of HBsAg and HBeAg, transcription of viral genes and immunocytochemistry staining. Changes in gene expression were analyzed by microarray, quantitative RT-PCR and western blot analysis. TLR ligands, entry inhibitor and neutralizing antibodies were used to characterize the initial immune response in PHH exposed to HBV.
Results: PHH could be efficiently infected with cell culture-derived HBV particles, indicated by the secretion of viral antigens and expression of viral mRNAs. The exposure of PHH to HBV particles induced a gene expression profile, more comparable to that induced by TLR2 ligand Pam3Cys, than those induced by viral sensors TLR3 or TLR7-9, leading to the induction of inflammatory and chemoattractant cytokines. Treatment with HBV as well as Pam3Cys activated ERK1, JNK and p38 mitogen-activated protein kinases as well as NFκB. Furthermore, HBV-induced gene expression could be neutralized by TLR2-specific antibodies. Blockade of HBV-mediated TLR2 activation enhances viral replication but did not affect HBsAg or HBeAg secretion. Furthermore, pretreatment with HBV entry inhibitor (Mycludex-related peptide) suppressed infectivity as well as the TLR2-mediated immune response to HBV. Interestingly, PHH isolated from HBV-infected patients revealed a higher responsiveness to TLR2 stimulation compared to uninfected resection or transplantation controls, indicated by elevated induction of cytokine gene expression.
Conclusion: The present data suggest that TLR2 is involved in recognition of HBV during the infection process and activate innate immune responses in the early phase of infection. Consistently, recent data suggest that TLR2 might be involved in antiviral responses during hepadnaviral infection and play an important role in the pathogenesis of chronic HBV infection.

SAT-415
Probing new HBV therapies using fine needle aspirates to sample compartmentalised liver-resident immunity and hepatocytes

U.S. Gill[1], L.J. Pallett[2], A. Burton[2], K. Stegmann[2], P. Kennedy[1], M. Maini[2]. *[1]Blizard Institute, Barts and The London SMD, QMUL, Centre for Immunobiology, London, United Kingdom; [2]UCL, Division of Infection & Immunity, London, United Kingdom*
Email: upkargill@hotmail.com

Background and Aims: In order to optimally refine the multiple new therapeutic strategies in the pipeline for Hepatitis B virus (HBV) cure, evaluation of virological and immunological changes at the site of infection is required. This has been underscored by our recent demonstration that specialised subsets of tissue-resident CD8 T *(Pallett et al., JEM 2017)* and NK cells (*Stegmann et al., Sci Rep 2016*), adapted to provide frontline defence, are compartmentalised within the liver and consequently cannot be sampled in the blood. We therefore investigated if fine needle aspirates (FNA), well-suited for repeated sampling, could be used to study the local immune landscape in parallel with HBV-infected hepatocytes.
Method: Patients with HBV (n = 19) and those without viral infection (n = 8) undergoing percutaneous liver biopsy for diagnostic purposes were included. Matched samples for blood, liver biopsy and FNA from the same patients were analysed in parallel. 16-colour multiparameter flow cytometry was used to characterise a range of immune cells including circulating, liver-infiltrating (T, B, NK & MAIT cells) and liver-resident populations (T and NK cells) as well as hepatocytes.
Results: Comparable populations of CD4 T, CD8 T, B, NK and MAIT cells were identified by FNA to those seen in material from liver biopsy. Populations of tissue-resident memory CD8 T cells ($CD69^{+}CD103^{+}$) with a comparable PD-$1^{hi}CD39^{hi}$ phenotype, were identified by both FNA and liver biopsy, and not seen in the blood. Importantly, HBV-specific T cells (analysed by HLA-A2/HBV-dextramer or intracellular cytokine staining following overnight overlapping peptide stimulation) could be identified by FNA at similar frequencies to those from biopsies and significantly enriched compared to blood. The large subset of liver-resident NK cells ($CXCR6^{+}$ T-$bet^{lo}EOMES^{hi}$), seen on biopsy were also identified by FNA and not seen in the blood. Moreover, by FNA we could simultaneously identify populations of live hepatocytes, which expressed SRB-1, PDL1 and HBsAg, whereas these were not viable after the processing required for liver biopsies.
Conclusion: We demonstrate for the first time that FNA identifies a range of immune cells including local specialised sentinel HBV-specific T cells and NK cells, together with HBV-infected hepatocytes. The broad sampling achieved by this rapid, painless and safe technique makes it an attractive method for longitudinal sampling of the liver, important in optimising new therapies for HBV.

SAT-416
HBV-specific T cell responses in low replicating inactive carrier patients are independent of Hepatitis B surface antigen load

U.S. Gill[1], N. Hansi[1], N.L. Bert[2], K. Kunasegaran[2], G.E. Dolman[1], D. Tan[3], W. Tong[4], M. Maini[5], A. Bertoletti[2], P. Kennedy[1]. *[1]Blizard Institute, Barts and The London SMD, QMUL, Centre for Immunobiology, London, United Kingdom; [2]Duke-NUS Medical School, Emerging Infectious Diseases, Singapore, Singapore; [3]Singapore Institute for Clinical Sciences, Agency for Science, Technology & Research (A*STAR), Infection & Immunity Program, Singapore, Singapore; [4]Royal London Hospital, Barts Health*

NHS Trust, Department of Virology, London, United Kingdom; [5]UCL, Division of Infection & Immunity, London, United Kingdom
Email: upkargill@hotmail.com

Background and Aims: HBeAg negative chronic infection *(EASL CPG 2017);* formerly referred to as the inactive carrier (IC) phase of disease; is considered to represent an end to immune mediated liver damage. These patients, however remain at risk of disease progression, thus specialist follow-up is mandated. Characterised by normal ALT & low HBV DNA, recent data highlight the utility of quantitative HBsAg (qHBsAg), where patients with qHBsAg <1,000 IU/ml are potentially at lower risk of disease progression and HCC *(Tseng et al, Hepatology, 2013).* Moreover, the impact of HBsAg level on the immune profile in IC patients remains poorly understood. We investigated whether qHBsAg modulated global and HBV-specific T cell responses in IC patients.
Method: 150 (male = 72, median age 34 years, range 12–70) consecutive treatment naïve HBeAg negative IC patients (ALT < 40, HBV DNA < 2,000 IUml) were longitudinally followed and analysed. In a subset, at the extreme levels of qHBsAg (<1,500 & >15,000) immune responses were measured. Sorted fractions of CD4 & CD8 T cells were evaluated using NanoString, for mRNA transcription of 600 immune genes. HBV-specific T cells were analysed using IFNγ ELISpot and correlated with qHBsAg levels.
Results: A significant negative correlation between qHBsAg and age was observed ($r^2 = 0.09$, $p = 0.0002$). Patients with qHBsAg < 1,500 IU/ml (median = 42 years) were significantly older than those with qHBsAg > 15,000 IU/ml (median = 31 years; $p = <0.0001$). There was no difference in the frequency of HBV-specific T cells in patients with qHBsAg <1,500 IU/ml vs. those with >15,000 IU/ml ($p = 0.7$). Patients with low qHBsAg levels upregulated 16 genes on CD4 and 15 genes on CD8 T cells in comparison to those with high qHBsAg. Significantly upregulated genes on CD4 T cells (KLRG1, HLA-DQ1, PYCARD) and CD8 T cells (KLRG1, MYD88, BST2) associated with senescence, IFNγ and NFκB signaling were seen in IC patients with low qHBsAg.
Conclusion: The addition of qHBsAg may enhance risk stratification and optimise management of IC patients. All patients demonstrated a low frequency of HBV-specific T cells; importantly those with lower qHBsAg did not demonstrate improved antigen-specific immunity, thus challenging the perceived immunosuppressive effect of HBsAg. Patients with lower levels of HBsAg expressed genes associated with inhibitory signaling and transcriptional regulation of DNA potentially due to increased hepatocyte turnover leading to reduced cccDNA and HBsAg production.

SAT-417

Outcome of anti-viral immunity in the liver is shaped by the level of antigen expressed in infected hepatocytes

K. Manske[1], N. Kallin[1], B. Bingsch[2], K. Steiger[3], R. Thimme[2], P.A. Knolle[1], D. Wohlleber[1]. *[1]Rechts der Isar Hospital, Technical University of Munich, Institute of Molecular Immunology and Experimental Oncology, Munich, Germany; [2]University Medical Center Freiburg, Klinik für Innere Medizin II, Freiburg, Germany; [3]Rechts der Isar Hospital, Technical University of Munich, Institute of Pathology, Munich, Germany*
Email: katrin.manske@tum.de

Background and Aims: 5–10% people infected with Hepatitis B virus (HBV) develop chronic hepatitis accounting for 240 million chronic hepatitis B patients worldwide. Still, the decisive factors ruling between elimination or persistence of viral infection of the liver are not entirely understood. We aimed to establish a novel model system to study immune escape and surveillance of acute self-limited and chronic liver infection in mice. Here, we dissect the factors determining the outcome of viral infection with the help of novel recombinant adenoviruses reflecting the hepatropism and hepatocyte-restricted antigen expression of hepatitis viruses.
Method: We generated identical replication-deficient recombinant adenoviruses expressing eGFP and CBG99-luciferase as marker proteins and the antigen ovalbumin driven either by the strong ubiquitous CMV-promoter (Ad-CMV-GOL) or by the weaker hepatocyte-specific Transthyretin (TTR)-promoter (Ad-TTR-GOL). After infection of mice, dynamics of anti-viral immunity was characterized by *in-vivo*-bioluminescence imaging, serum ALT levels, immunohistochemistry and realtime PCR. Antigen-specific CD8 T cells were analyzed by flow-cytometry.
Results: We generated a liver infection model for acute self-limited and chronic hepatitis in mice, where ovalbumin serves as soluble antigen. Ad-TTR-GOL infection developed into persistent infection, whereas Ad-CMV-GOL infection was cleared. We identified that CD8 T cell immunity against virus-infected hepatocytes is controlled at various levels determining self-limited or persistent disease outcome. First, hepatocyte-restricted antigen-expression led to delayed dynamics of the induction of antigen-specific CD8 T cells and curtailed CD8 T cell expansion – 10.000-fold after Ad-CMV-GOL compared to 150-fold after Ad-TTR-GOL infection. Second, antigen-specific CD8 T cells primed against antigens selectively expressed by hepatocytes co-expressed high levels of inhibitory molecules like PD-1, Tim-3, LAG-3, CTLA-4 and CD160. Third, virus-infected hepatocytes expressing sub-critical levels of antigen escaped from MHC I-restricted killing by effector CD8 T cells.
Conclusion: Our study identifies deficits in CD8 T cell immunity and escape of infected hepatocytes from CD8 T cell killing promoting viral persistence and highlights the importance to address both, restoration of CD8 T cell dysfunction and overcoming local hurdles of effector T cell function in the liver to eliminate virus-infected hepatocytes.

SAT-418

The RNA genome of hepatitis E virus robustly triggers antiviral interferon response

W. Wang[1], Y. Wang[2], C. Qu[1], S. Wang[2], M. Peppelenbosch[1], J. Zhao[2], Q. Pan[1]. *[1]Erasmus University Medical Center, Rotterdam; [2]Beijing 302 hospital, Beijing*
Email: w.wang.2@erasmusmc.nl

Background and Aims: The outcomes of hepatitis E virus (HEV) infection are diverse, ranging from asymptomatic carrier, self-limiting acute infection, fulminant hepatitis to persistent infection. This is closely associated with the immunological status of the host. This study aims to understand the innate cellular immunity as the first-line defense mechanisms in response to HEV infection.
Method: Two dimensional hepatic and extra-hepatic cell lines (Huh7.5, HepaRG, HEK293 and U87 cells) as well as three dimensional primary mouse and human liver organoids were used.
Results: Phosphorylation of STAT1, a hallmark of the activation of antiviral interferon (IFN) response, was observed in the liver tissues of majority of HEV infected patients, but not in the liver of uninfected individuals. In cultured cell lines and primary liver organoids, we found that HEV RNA genome potently induced IFN production and antiviral response. This mechanism is conserved among different HEV strains, including genotype 1, 3 and 7 as tested. Interestingly, the single-stranded HEV RNA (ssRNA) is sufficient to trigger the antiviral response, without requirement of viral RNA synthesis and the generation of RNA replicative form or replicative intermediate. Surprisingly, the m^7G cap and poly A tail are not required, although both are the key features of HEV genome. Mechanistically, this antiviral response occurs in a RIG-I-, MDA5-, MAVS- and β-catenin-independent, but IRF3 and IRF7-dependent manner. Furthermore, the integrity of the JAK-STAT pathway is essentially required.
Conclusion: HEV infection elicits an active IFN-related antiviral response in vitro and in patients. It is triggered by the viral RNA and mediated by IRF3/7 and the JAK-STAT cascade. These findings have revealed new insights on HEV-host interactions and provided the basis for understanding the pathogenesis and outcome of HEV infection.

SAT-419

The impact of HBsAg on general and HBV-specific immunity

N.L. Bert[1], M. Hong[2], D. Tan[3], K. Kunasegaran[2], Y. Cheng[4], E. Brecht[3], U.S. Gill[5], C. Frey[6], E. Newell[4], P. Kennedy[5], A. Bertoletti[2,3,4]. *[1]Duke-NUS Medical School, Emerging Infectious Diseases, Sinagpore, Singapore; [2]Duke-NUS Medical School, Emerging Infectious Diseases, Singapore; [3]Singapore Institute for Clinical Sciences, A*STAR, Singapore; [4]Singapore Immunology Network (SIgN), A*STAR, Singapore; [5]Barts and The London School of Medicine and Dentistry, QMUL, London, United Kingdom; [6]Gilead Sciences, Department of Immunology/Inflammation, Foster City, United States*
Email: nina@duke-nus.edu.sg

Background and Aims: The large amounts of subviral particles containing HBsAg that are secreted by hepatocytes infected with Hepatitis B virus (HBV) or with HBV-DNA integration have been suggested to play immunomodulatory roles. This hypothesis has never been convincingly demonstrated. Our aim was to test whether HBsAg can impact on the function of total or antigen specific immune cells.

Method: To address this question we respectively used CyTOF, a novel mass cytometry technology able to simultaneously analyze the expression of 42 markers involved in activation, differentiation, exhaustion and anti-viral effector function of T and NK cells, and classical in vitro ELISPOT assay utilizing libraries of HBV peptides (312) covering the whole proteome of HBV genotypes A, B and C. We studied 145 patients with chronic HBV (CHB) infection characterized by a wide range of serum HBsAg concentrations (0.5–35,600 IU/ml).

Results: We found that patients with different quantities of circulating HBsAg showed similar frequencies of CD4 and CD8 T cells of memory, naïve and effector phenotype. Besides, the frequency of NK cell subsets appeared similar in patients with high and low levels of HBsAg. Production of different cytokines and cytotoxicity-associated molecules was not altered in relation to HBsAg levels, and there was no correlation with expression of several immunoregulatory receptors, including PD-1, CTLA-4 and TIM-3. On the other hand, the determination of the HBV antigen specificity of T cell responses detected in CHB patients (39 HBeAg+, 45 anti-HBe+) showed a progressive reduction of HBsAg-specific T cells that correlated with duration of infection. The majority of detectable HBV-specific T cells target HBsAg (56% of total HBV-T cells) in young HBeAg+ CHB patients (<15 years). HBsAg-specific T cells were still detectable at high frequency in HBeAg+ CHB patients younger than 25 years (46% of HBV-T cells), but progressively declined in patients between 25 and 35 years (22% of HBV-T cells), and were hardly found in adult CHB anti-HBe+ patients (5% of HBV-T cells).

Conclusion: Taken together, our systematic profiling of the impact of HBsAg on the immunity of CHB patients did not detect general immunological parameters of tolerance or suppression that correlate with HBsAg values. However, HBsAg has clearly a progressive and profound effect on the persistence of HBsAg-specific T cells that are progressively eroded in relation to the length of infection.

SAT-420

Normalization of NK cell phenotype is delayed after successful interferon-free therapy in cirrhotic patients with chronic HCV infection

E. Perpiñan[1,2], S.P. del Pulgar[1,2], M.C. Londoño[1,2], Z. Mariño[1,2], S. Lens[1,2], C. Bartres[1,2], A. Pla[1,2], P. González[1,2], M. García-López[1,2], E. Pose[1], X. Forns[1,2], M. Maini[3], G. Koutsoudakis[1,2]. *[1]Liver Unit, Hospital Clinic, University of Barcelona, IDIBAPS, Barcelona, Spain; [2]CIBEREHD, Barcelona, Spain; [3]Division of Infection and Immunity, University College London, London, United Kingdom*
Email: perpinan@clinic.cat

Background and Aims: Natural killer (NK) cells play an important role in control of viral infections, especially in the liver where they are enriched among lymphocytes. Chronic hepatitis C virus (HCV) infection alters NK cell phenotype, which can be normalized rapidly during interferon-free therapy (Serti, E. *et al*, Gastroenterology. 2015). Here, we focused on potential changes of NK cell phenotype induced by viral eradication in patients with liver cirrhosis.

Method: NK cells of 22 HCV-infected cirrhotic patients were analyzed by flow cytometry at baseline (BL), at week 4 during therapy (W4) and at weeks 12 and 48 after the end of therapy (FU12 and FU48). Samples obtained from 12 non-HCV cirrhotic patients and 12 healthy individuals, matched by age and sex, served as two distinct control sets.

Results: At BL, frequencies of $CD56^{dim}$ and $CD56^{bright}$ cells were decreased or increased, respectively, compared to healthy controls ($p < 0.05$). Moreover, frequencies and expression levels of activating NKp30, NKp46, HLA-DR and inhibitory KIR2DL2/L3, NKG2A, CD85j receptors on total NK cells were also significantly increased ($p < 0.05$). At W4 and FU12, despite viral eradication, frequencies of $CD56^{dim}$ and $CD56^{bright}$ cells and their receptor profile remained similar to BL.

However, at FU48, $CD56^{dim}$ and $CD56^{bright}$ cell frequencies were normalized. Moreover, there was a clear decline in the frequency of NKp30+ $CD56^{bright}$ cells and in the frequencies of NKp46+, HLA-DR+, KIR2DL2/L3+, NKG2A+ total NK cells, reaching similar levels to those in healthy controls. A similar restoration pattern was observed for the expression levels of NKp46, KIR2DL2/L3 and NKG2A, but not CD85j, on total NK cells.

Concerning NK cell function, the frequency of the degranulation marker CD107a within the $CD56^{dim}$ cells was higher than that in both control sets, either at BL or during follow-up ($p < 0.005$). Still, the incremental degranulation of the $CD56^{dim}$ population upon *in vitro* stimulation was significantly lower ($p < 0.01$).

Conclusion: NK cell phenotype normalization does not occur immediately after viral eradication in cirrhotic HCV-infected patients. At FU48, NK cell receptor expression was restored while NK cell degranulation remained significantly altered. These data suggest that HCV infection has a more sustained imprint on NK cells in patients with cirrhosis, with implications for immune restoration.

SAT-421

Transcriptome profiling of hepatitis B virus-infected human hepatocyte derived from chimeric mice with humanized liver

S. Nakamoto, T. Kanda, S. Wu, K. Takahashi, M. Nakamura, S. Yasui, S. Ogasawara, E. Suzuki, Y. Ooka, T. Saito, A. Tawada, T. Chiba, M. Arai, K. Kobayashi, S. Kiyono, H. Maruyama, N. Kato, H. Shirasawa. *Nihon University School of Medicine, Japan*
Email: nakamotoer@yahoo.co.jp

Background and Aims: The role of innate immune system on the course of hepatitis B virus (HBV) infection is less well understood. Clinically, relatively long incubation period is observed during acute HBV infection. Furthermore, immune response is minimal during immune tolerant phase of chronic infection. To understand the contribution of immune response in HBV-infected hepatocyte, transcriptome analysis was performed using in vitro model of HBV infection.

Method: Human hepatocytes derived from chimeric mice with humanized liver (PXB cell) were cultured on the cell culture plate and infected with 5 or 25 genome equivalents of HBV per cell (HBV-L or HBV-H, respectively). RNA was collected 6 hours, 1 day, 5 days and 23 days after infection (6H, D1, D5, D23, respectively). RNA sequence was carried out on an Illumina Hiseq 1500 sequencer. Reads are mapped to human and HBV reference, and expression was calculated as RPKM (Reads Per Kilobase of exon model per Million mapped reads).

Results: HBV RNA level of 6H and D1 was around the lower detection limit and only small parts of its entire genome was covered by reads. On day 5, HBV transcription was significantly increased and higher in

HBV-H cells compared to HBV-L cells (670 RPKM vs. 150 RPKM). At this point, nearly the whole HBV genome was covered by mapped reads. On day 23, continuous HBV replication was confirmed by HBV DNA and HBsAg level in the culture medium as well as HBV RNA in the cells (75 RPKM in the HBV-L cells). Gene expression of non-infected cells was compared between different time points. The correlation coefficient was 0.87 between 6H and D1 and 0.78 between 6H and D5. The correlation was much stronger between the same time points: 0.998 (D5 control vs. D5 HBV-L), and 0.989 (D5 control vs. D5 HBV-H). The expression of interferons including interferon alpha, beta and lambda was neither detected nor induced by HBV infection at these time points. The analysis of differentially expressed genes suggested that antiviral genes including RIG-I and ISG15 is less affected by HBV infection (0.9-fold and 1.2-fold). Among the cytosolic DNA sensor pathways, STING was not detected at any time points. The expression of IFI16 and cGAS was low (<1 RPKM) and was not induced significantly by HBV infection (<2 fold). Furthermore, antiviral genes were not significantly enriched in HBV-infected cells by gene set enrichment analysis.
Conclusion: These data indicate that without other cells such as immune cells, hepatocyte is little affected by HBV infection at least in the conditions studied, consistent with the previous findings showing the stealth nature of HBV and the defect of DNA sensor pathway in hepatocyte.

SAT-422

PTEN-mediated beta-catenin/PD-L1 signaling in hepatocytes modulates hepatitis B virus immune evasion from T cell responses

Y. Sun[1], M. Qu[1], M. Yu[1], L. Tang[1], G. Li[1], W. Zheng[1], C. Li[2]. *[1]School of Basic Medical Sciences, Wuhan University, Wuhan, China; [2]School of Basic Medical Sciences, Wuhan University, Department of Physiology, Wuhan, China*
Email: lichangyong@whu.edu.cn

Background and Aims: Hepatitis B virus (HBV) has developed active tactics to evade host immune surveillance or interfere with immune signaling pathways and induce immunosuppression, which favor their replication. However, the underlying molecular mechanisms are still poorly defined. Programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) signaling plays a critical role in regulating T cell homeostasis. This study was designed to investigate the functional roles and molecular mechanisms by which phosphatase and tensin homolog deleted on chromosome 10 (PTEN)-mediated β-catenin/PD-L1 signaling in parenchymal liver cells (hepatocytes) influenced T cell immune responses *in vitro* and *in vivo*.
Method: A mouse model of acute HBV infection was produced by hydrodynamic injection with a pUC18 vector containing 1.3-fold over length HBV genome (pHBV1.3) via the tail vein in a volume of saline equivalent to 8% of the body weight. The total volume was delivered within 6–8 seconds. Coculture experiments with hepatocytes and Jurkat T cells were established.
Results: β-catenin and PD-L1 expression in the liver positively correlated with HBV load in mice. Moreover, HBV infection inhibited PTEN, but upregulated β-catenin and PD-L1 expression in hepatocytes, which in turn augmented PD-1 expression, decreased interleukin-2 (IL-2) secretion, and induced apoptosis in Jurkat T cells. However, disruption of β-catenin inhibited PD-L1 expression in hepatocytes, which was accompanied by decreased PD-1 expression, and increased IL-2 production in T cells. Furthermore, PTEN overexpression inhibited β-catenin/PD-L1 expression in hepatocytes in response to HBV infection, which in turn promoted T cell immune response, and enhanced their ability to clear HBV.
Conclusion: By identifying the molecular pathways by which PTEN-mediated β-catenin/PD-L1 signaling in hepatocytes regulates T cell response, our findings provide the rationale for novel therapeutic target to treat chronic HBV infection.

SAT-423

Nuclear DNA sensor protein IFI16 recognizes hepatitis B virus covalently closed circular DNA and regluates the antiviral innate immunity

Y.-Q. Lu, H. Ma, X.-B. Pan, L. Wei. *Peking University People's Hospital, Hepatology Institute, beijing, China*
Email: pxbdxq@hotmail.com

Background and Aims: The nuclear DNA-sensor protein IFI16 has been demonstrated as an essential role in triggering antiviral immunity during several virus infections. Whether IFI16 recognizes hepatitis B virus (HBV) covalently closed circular DNA (cccDNA) in the nucleus of hepatocytes and whether an antagonist strategy is developed, remain unknown.
Method: Expression and distribution of IFI16 in liver-derived cell lines were analyzed by using of western blotting and immunocellulerchemistry. The interaction between IFI16 and HBV DNA was analyzed using of chromatin immunoprecipitation. The effect of IFI16 and its fragments on HBV replication was tested in the cells cultures. IFI16 levels in peripheral blood mononuclear cell (PBMCs) of CHB patients were analyzed by using qPCR and western blotting.
Results: An interferon inducible and exclusively nuclear location of IFI16 was detected in HepG2 cells. Binding of IFI16 with nuclear cccDNA was detected in the stable HBV-replicating HepAD38 cells. IFI16 mostly translocated to cytoplasm and was degraded in the HepAD38 cell, and a blunted interferon inducible response was observed. The translocation and degradation of IFI16 in HepAD38 cells were inhibited by interferon treatment, cellular differentiation induction and inhibition of cccDNA formation. Cytoplasm fragment IFI16 significantly impaired the function of DNA sensors including IFI16, cGAS and DAI. IFI16 mRNA increased in PBMCs in the CHB patients with IFN therapy. The changes of IFI16 positively correlated with the HBeAg seroconversion and decline of serum HBV DNA levels. However, the long degraded fragment of IFI16 in PBMC correlated with high load of serum HBV DNA.
Conclusion: The innate immune DNA sensor IFI16 is differentiation inducible in hepatocytes. IFI16 recognizes nuclear HBV cccDNA but is degraded in cytoplasm. The degraded fragments negatively regulates the DNA sensors-related interferon signal pathway. Our results reveal a key mechanism of chronicity of HBV infection.

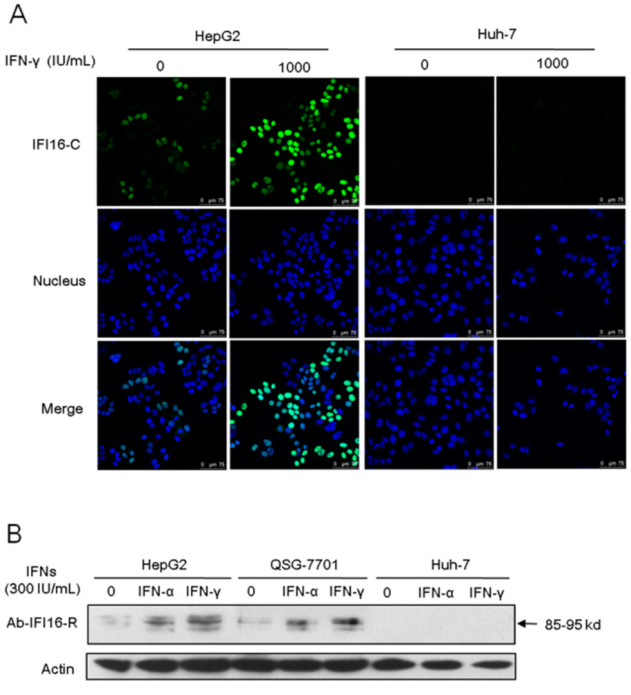


Figure 1: Interferon inducible expression of IFI16 in HepG2 cells.

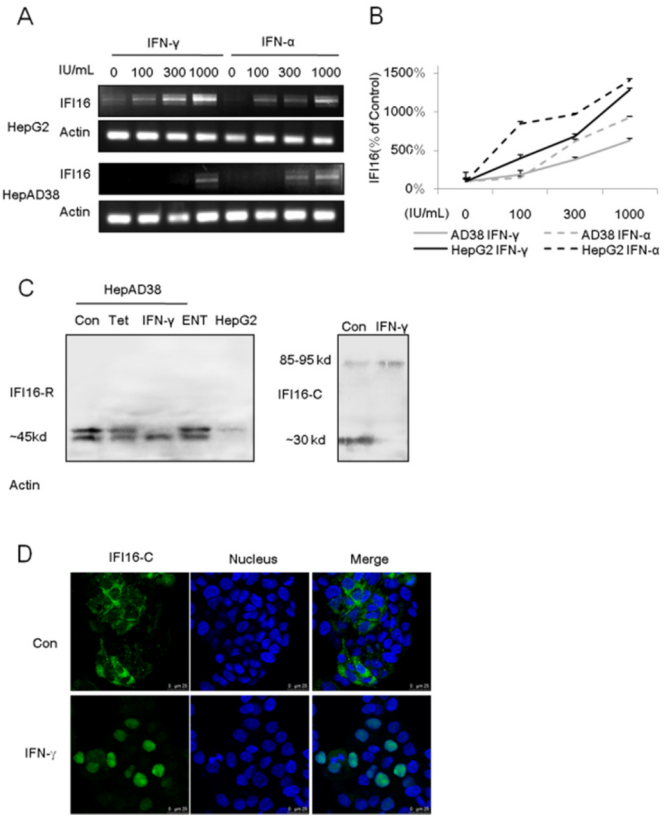


Figure 2: A blunted interferon inducible response of IFI16 in HepAD38 cells (A and B); Degradation and cytoplasmic translocation of IFI16 in HepAD38 cells were inhibited by interferon treatment (C and D).

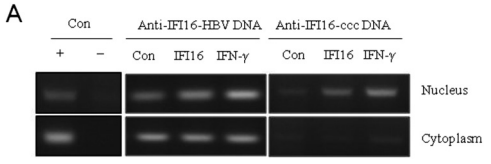


Figure 3: The binding of IFI16 and HBV DNA was detected by CHIP assay.

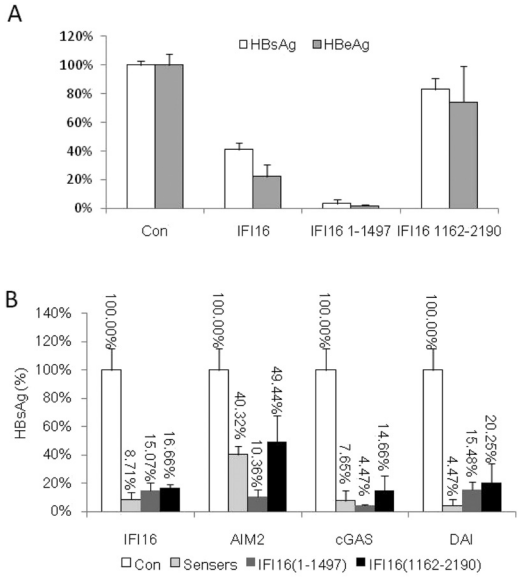


Figure 4: Cytoplasmic fragment of IFI16 inhibited functions of IFI16, cGAS and DAI to inhibit HBV replication.

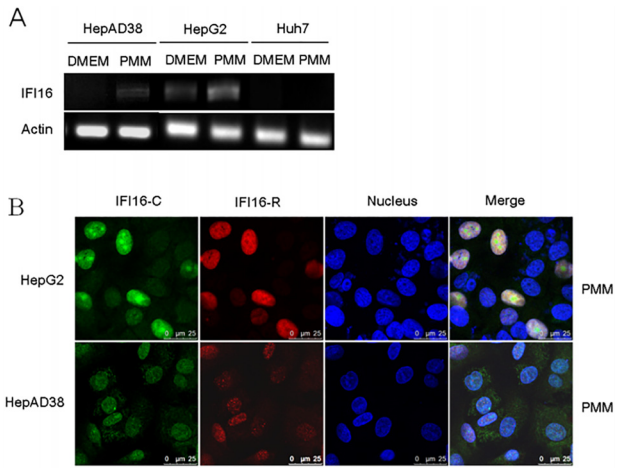


Figure 5: Cellular differentiation induced by PMM culture enhanced the IFI16 expression in HepG2 and HepAD38 cells, and leaded the relocation of cytoplasmic IFI16 into nucleus of HepAD38 cells.

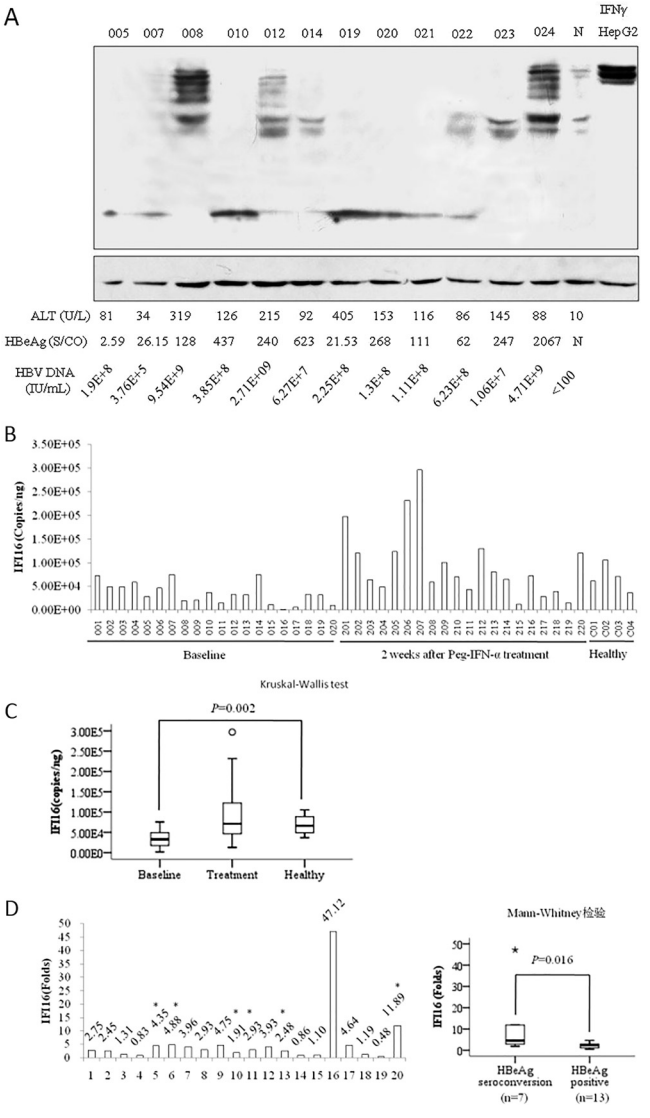


Figure 6: The degradation of IFI16 in PBMC of CHB patients. (A) The changes of IFI16 in PBMC of CHB patients treated with interferon-alpha. (B and C). Change folds of IFI16 in PBMC correlated with the HBeAg seroconversion of in CHB patients treated with IFN-a.

SAT-424

Upregulated innate immune responses in a hepatitis C virus exposed uninfected cohort

I. Shawa, K. Bennett, D. Sheridan, D. Felmlee, D. Hegazy, A. Ahmed, C. Wood, S. Jackson, G. Fejer, M. Cramp. *Plymouth University, Peninsula Schools of Medicine and Dentistry, Plymouth, United Kingdom*
Email: kbennett6@nhs.net

Background and Aims: We have previously defined a proportion of people who inject drugs (PWIDs) who despite a long history of sharing needles and other paraphernalia remain HCV uninfected. This exposed but uninfected (EU) cohort test negative for both HCV antibodies and RNA and exhibit a phenotype of resistance to HCV infection. We have previously reported low level T cell and humoral responses to HCV, but it remains unclear if these can prevent infection and recent evidence points to an important role for innate immune responses in control of HCV infection. The aim was to characterise antiviral innate cytokine responses in EU compared to healthy controls.
Method: 38 EUs and 11 controls were studied. Interferon alpha (IFN-a) production following overnight stimulation of peripheral blood mononuclear cells (PBMCs) with low infective doses of Influenza A virus H3N2 strain was assessed using enzyme-linked immunosorbent assay (ELISA). Influenza A virus was used at an approximate multiplicity of infection (MOI) of 0.14 (29.04×10^6 PFU), and 0.005 (9.68×10^6 PFU), categorized as low dose and very low dose respectively. MOI is the average number of virus particles infecting each cell. Unstimulated PBMCs and medium only were used as negative controls.
Results: EU cases produced significantly greater amounts of IFN-a in response to influenza following both low and very low dose exposure than healthy volunteers with the greatest difference following very low dose exposure.

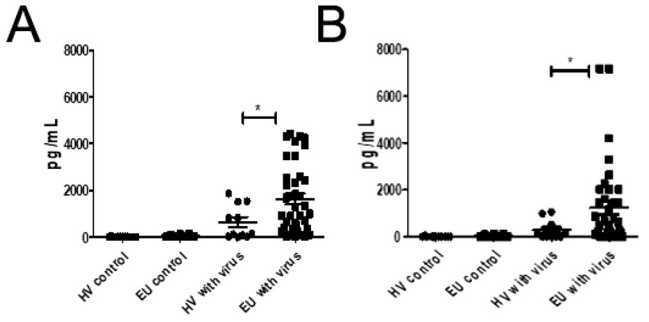


Figure: IFN-a secretion in response to (A) low dose influenza A virus (29.04×10^3 PFU) and (B) very low dose influenza A virus (9.68×10^3 PFU): EU cases show significantly greater IFN-α production in response to both low and very low dose Influenza A virus than healthy volunteers. The Wilcoxon signed rank test was used to determine the differences between the two cohorts ($p < 0.002$ and $p < 0.001$ respectively). HV = healthy volunteer. EU = exposed uninfected.

Conclusion: The increased IFN-a production in response to low dose influenza virus indicates an enhanced induction of early anti-viral innate cytokine responses in EU subjects. We suggest that following exposure to low doses of HCV an enhanced innate immune response may contribute to the resistance to clinical HCV disease seen in our EU cohort.

SAT-425

MicroRNA-181C potentially relieved fulminant viral heaptitis by targeting TNF-a in mice

D. Xi, M. Wang, Z. Zhang, J. Chen, F. Wang, Q. Ning. *Tongji Hospital of Tongji Medical College, Huazhong University of Science and Technology, Department and Institute of Infectious Disease*
Email: qning@vip.sina.com

Background and Aims: Hepatocyte apoptosis induced by tumor necrosis factor (TNF)-α/TNFR1 is an important pathway for the incidence of fulminant viral hepatitis. Accumulating evidence suggests that some microRNAs (miRNAs) are involved in severe exacerbation of hepatitis B. The relationship between circulating miRNAs and HBV associated acute-on-chronic liver failure (HBV-ACLF) needs to be further investigated. The purpose of our study was to identify the aberrant expression of miRNAs in HBV-ACLF and to investigate its potential role during the progression of HBV-ACLF.
Method: miRNA expression profile by miRNA microarray analysis was performed on pooled Peripheral Blood Mononuclear Cell (PBMC) obtained from patients with chronic hepatitis B (CHB) or HBV-ACLF, respectively. Selected unnormal expressed miRNAs were verified in more clinical samples by quantitative real-time PCR (qRT-PCR). A luciferase reporter assay was conducted to confirm whether TNF-α is a direct target of miR-181c. mmu-miR-181c agomir was delivered by tail vein injection into murine hepatitis virus (MHV)-3-infected BALB/cJ mice to evaluate its interference effect in fulminant viral hepatitis mouse model.
Results: The results from microarray analysis showed that 7 kinds of miRNAs were down-regulated and 9 kinds of miRNAs up-regulated in the PBMC of HBV-ACLF patients compared with that of patients with CHB. Among the deregulated miRNAs, the expression of hsa-miRNA-181c significantly decreased in HBV-ACLF, while serum TNF-α significantly increased. Furthermore, TNF-α was verified as a target of miR-181c by luciferase reporter assay. miR-181c significantly improved fulminant viral hepatitis mice survival rate from 0 to 30%, ameliorated inflammatory infiltration, hepatocyte necrosis and apoptosis, and prolonged survival time.

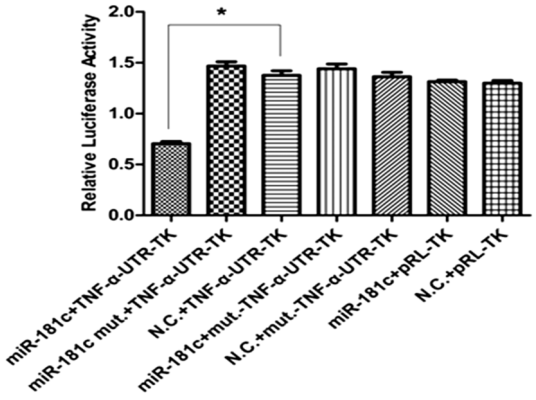


Figure: Luc-3′UTR reporter expression assay showed TNF-α was one target of miR-181c. Mut.-TNF-α-UTR: mutated TNF-α 3′-UTR, TK: pRL-TK vector.

Conclusion: Our data suggested that miR-181c might have therapeutic potential for the treatment of fulminant hepatitis.

SAT-426

HLA-A2 restricted CD8+ T cell immune hierarchy towards full length hepatitis E virus for T cell-based therapy in chronic HEV

C. Soon[1], M.S. Chen[2], M.P. Manns[3], H. Wedemeyer[4], M. Cornberg[1]. *[1]Hannover Medical School; [2]Karolinska Institutet; [3]Dept. of Gastroenterology, Hepatology and Endocrinology, Hannover Medical School, Hannover, Germany; [4]Department of Gastroenterology and Hepatology, University Clinic Essen, Essen, Germany*
Email: Soon.Chai@mh-hannover.de

Background and Aims: Hepatitis E virus (HEV) infection is often asymptomatic and resolves spontaneously in immunocompetent people. But in vulnerable individuals, especially immunosuppressed patients of solid organ transplantation, HEV infection could lead to chronic hepatitis. Currently, there is only one treatment option available for chronic HEV (ribavirin), which is not ideal as cases of resistance have been reported. We aim to identify immune hierarchy

of CD8+ T cells epitopes towards full length HEV, and characterize the immune functionality, as the basis to develop T cell-based therapy for chronic HEV patients.
Method: CD8+ T cells from acute HEV patients (n = 13) and HEV seronegative healthy persons (n = 8), all HLA-A2 positive, were expanded *in vitro* for 3 weeks using 15-mer HEV genotype 3 overlapping peptides, spanning all open reading frame-encoded proteins. T cell response was examined by intracellular cytokine staining and the frequency of HEV-specific CD8+ T cells was determined by staining of dextramers (bearing epitopes that are predicted *in silico*). 15-mer peptides that trigger robust cytokine production are narrowed down to 9-mer. HEV-specific CD8+ T cells were sorted using dextramer for T cell receptor (TCR) repertoire sequencing, the results were used in mRNA synthesis for TCR redirection assay. Donor lymphocytes redirected with TCR are co-cultured with T2 cells loaded with target peptide or with HEV-transfected HLA-A2 HepG2 cells.
Results: HEV-specific CD8+ T cell responses are found across ORF1 and ORF2, the non-structural and capsid part of the HEV genome, respectively. Notable responses are detected more in patients than in HEV-naïve healthy individuals. Of all the identified possible epitopes, only one was seen in both patient and healthy cohorts. This high hierarchy epitope, located in the RNA-dependent RNA polymerase (RdRP) region in ORF1, is then selected for further investigation. T cells with TCR of this epitope were sequenced; the results were used to generate gene constructs for TCR redirection assay. Post TCR redirection, not only the donor lymphocytes could bind to the same dextramer, the lymphocytes also recognize the cognate peptide presented by T2 cells, with significant MIP-1β, IFNγ and TNFα production within 7 hours of co-culturing. Cytokines production was also observed when TCR redirected lymphocytes were co-cultured with HEV-transfected HepG2 cells.
Conclusion: Our study identified potential HEV-specific CD8+ T cell epitope, which is vital to TCR design that possesses strong multi-functionality and specificity for T cell therapy.

SAT-427
Development and characterization of unique hepatitis C virus neutralizing antibodies associated with infection outcome

S.E. Baran[1], S. Eliyahu[1], A. Davidovich[1], M. Brown[2], M. Gal-Tanamy[1], A. Nimer[3]. *[1]Bar Ilan, Faculty of Medicine, Zafed, Israel; [2]Liver Institute, Rabin Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel; [3]Western Galilee Hospital, Internal Medicine Department, Naharia, Israel*
Email: mgtanamy@gmail.com

Background and Aims: In most cases, HCV causes chronic infections, however 20–40% of infected individuals experience spontaneous recovery, suggested to be mediated by HCV-specific natural immunity. Therefore, using HCV as a model for comparing immune responses between spontaneous clearers (SC) and chronically infected individuals (CI), may empower identification of unique mechanisms dictating viral infection outcomes and designing vaccines and immunotherapeutics. We hypothesized that SC patients develop a unique set of HCV-specific antibodies with distinct properties, as compared to CI patients. We aimed to study the nature of successful immune response against HCV and develop effective HCV-neutralizing antibodies correlating with infection outcome.
Method: Sera and B cells from a panel of CI and SC patients and healthy controls were isolated. Sera were screened for HCV neutralization and binding and B cells for constructing two antibodies libraries, one from CI samples and second from SC samples, using phage display technology. Specific HCV-binding and neutralizing antibodies were isolated from these libraries and characterized.
Results: We have observed high level of HCV-specific antibodies in the sera of CI patients compared to low levels of antibodies in the sera of SC's. Nonetheless, high levels of HCV neutralization were observed with SC's sera, pointing for the presence of highly neutralizing antibodies in SC. Following five rounds of panning, we have isolated a panel of 10 unique antibodies; 3 from CI library and 7 from SC library. Antibodies isolated from SC library demonstrate moderate binding to genotype 1a HCV envelope protein E2 by ELISA, but higher HCV-neutralization efficiency, compared to those isolated from CI library. However, the Abs from CI demonstrated broader range of neutralization when tested with all HCV 7 genotypes compared to Abs from SC. Interestingly, three Ab isolated from SC showed high sequence similarity to Ab sequences present in HCV-specific B cells and were also enriched in total B-cell repertoires sequenced from cohorts of CI and SC by next generation sequencing.
Conclusion: This study suggests that SC patients exhibit unique, specific and efficient B cells response comparing to CI. The isolation of unique antibodies may open new avenues to effective immunoglobulin-based therapies that could prove helpful in preventing or treating HCV-related liver disease and would benefit vaccine development effort.

SAT-428
EP2 associated with the inflammatory storm in HBV related acute-on-chronic liver failure

Y. Wang, C. Chen, M. Zheng, J. Wo, F. Chen, Z. Chen, H. Zhu. *State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, the First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310003, China, Hangzhou, China*
Email: zhuhh72@zju.edu.cn

Background and Aims: Systemic inflammation is the major pathogenesis of HBV related acute-on-chronic liver failure (HBV-ACLF). EP2 (Prostaglandin E Receptor 2) and EP4 (Prostaglandin E Receptor 4) receptor are inhibitory receptors that regulate the balance of immunity. However, their sustained hypoexpression promotes excessive immune response. We investigated their role in the immune dysregulation in patients with ACLF.
Method: Blood samples were collected from 50 patients with HBV-ACLF, 50 patients with chronic hepatitis B (CHB), 20 patients with decompensated cirrhosis, and 48 healthy controls (HC). We measured the plasma cytokine levels with luminex and assessed whole blood or peripheral blood mononuclear cells (PBMC) for expression of EP2, EP4, Toll-like re-ceptors and HLA-DR on subsets of innate and adaptive immune effector cells. Immune responses to lipo-polysaccharide (LPS) or Escherichia coli (Ecoli) were measured by flow cytometry, to quantify cytokine production, bacterial phagocytosis and reactive oxygen species (ROS) production in the presence or absence of small molecular chemicals blocking against EP2.
Results: Antibacterial innate and adaptive immune responses were greatly enhanced in patients with HBV-ACLF, compared with controls. Patients with HBV-ACLF have higher levels of plasma cytokines than healthy controls. More PBMC from patients with HBV-ACLF produced IFN-γ in response to LPS, compared with controls. In addition, patients with HBV-ACLF had enhanced levels of neutrophil and monocytic ROS production in response to Ecoli stimulation, compared with controls (MFI of ROS produced in monocyte HC:ACLF = 4905:13336, $p = 0.003$; MFI of ROS produced in neutrophil HC:ACLF = 7366:29162, $p = 0.014$). EP2 expression on CD8+ T cells from patients with ACLF and decompensated cirrhosis, but not with CHB was lower than those from healthy controls (HC: ACLF = 44.5%:6.5%, $p < 0.01$). EP2 expression on CD8+ T cells was associated with the occurrence of multiple organ failure and level of plasma inflammatory cytokines. Small molecular chemicals against EP2 increased both cytokine producing PBMC and neutrophil and monocyte ROS production.
Conclusion: Down regulation of EP2 expression is associated with the occurrence of multiple organ failure and the high expression of inflammatory factors in patients with ACLF, which is related to the dysregulation of immune cell functions.

SAT-429

Cytokine-dependent activation of MAIT cells by the TLR8 agonist GS-9688 but not the TLR7 agonist GS-9620

S. Daffis, M. Morar, D. Pattabiraman, C. Voitenleitner, S. Fletcher, H. Javanbakht. *Gilead Sciences, Biology, Foster City, United States*
Email: Hassan.javanbakht@gilead.com

Background and Aims: GS-9688 is a selective small molecule agonist of toll-like receptor 8 (TLR8) in clinical development for the treatment of chronic hepatitis B (CHB). GS-9620 is an oral small molecule TLR7 agonist which has recently completed phase 2 studies in CHB patients. Oral GS-9688 and GS-9620 induce an immune response by pre-systemic activation of gut-associated and intrahepatic immune cells. Mucosal associated invariant T (MAIT) cells are innate-like T cells enriched in the gut and liver that likely play a role in host antiviral defense. Here we characterized in vitro activation of MAIT cells in human peripheral blood mononuclear cells (PBMCs) from healthy donors (HD) and CHB patients by GS-9688 and GS-9620.
Method: PBMCs obtained from HDs and age-matched CHB patients (n = 8) were treated for 18 hours with GS-9688 (156nM) or GS-9620 (10nM) and cytokines were analyzed by Luminex® assay. Intracellular levels of IFN-γ and TNF-α (antiviral cytokines), and granzyme B (a marker of cytotoxic function) in MAIT cells ($CD3^+TCR\gamma\delta^-CD161^+ V\alpha7.2^+$) were evaluated by flow cytometry.
Results: Consistent with previous studies, GS-9688 strongly induced IL-12p70 and IL-18, but had minimal effect on IFN-α (a TLR7-induced cytokine) in HD PBMCs. GS-9688 also strongly induced intracellular IFN-γ (38-fold increase), granzyme B (17-fold increase) and TNF-α (4-fold increase) levels in MAIT cells. Cytokine neutralization studies demonstrated that GS-9688 indirectly activates MAIT cells, predominantly via production of IL-12p70 and IL-18. The frequency of MAIT cells and activation by GS-9688 were comparable in PBMCs from HDs and CHB patients. GS-9620 induced dose-dependent IFN-α, but little to no IL-12p70 and IL-18 in PBMCs. Consistent with this cytokine profile, GS-9620 only weakly induced intracellular IFN-γ, granzyme B and TNF-α levels in MAIT cells.
Conclusion: In line with previous studies with prototypic TLR agonists, GS-9688 –but not GS-9620– strongly induced cytolytic and non-cytolytic functions of human MAIT cells in vitro. These data confirm that these innate-like T cells are indirectly activated by TLR8 but not TLR7 agonists, suggesting there are important immunological differences in the intrahepatic response induced by GS-9688 and GS-9620.

SAT-430

Characterization of theHEV-specific CD8+ T-cell response in acute and chronic hepatitis E virus infection

J. Kemming[1,2], M. Panning[3], M. Luetgehetmann[4], S. Pischke[4], J.S.Z. Wiesch[4], R. Thimme[2], C. Neumann-Haefelin[2]. *[1]Albert-Ludwigs University Freiburg, Faculty of Biology, Freiburg, Germany; [2]University Hospital Freiburg, Department for Internal Medicine II, Freiburg, Germany; [3]University Hospital Freiburg, Institute of Virology, Freiburg, Germany; [4]UKE Hamburg, 1. Medical Clinic, Hamburg, Germany*
Email: janine.kemming@uniklinik-freiburg.de

Background and Aims: Hepatitis E Virus (HEV) infection is one of the leading causes of viral hepatitis worldwide. Immune competent individuals clear infection spontaneously, whereas in immune suppressed patients chronic infection can occur, ultimately leading to liver cirrhosis and Hepatocellular Carcinoma (HCC).
In order to clear infection an effective virus-specific CD8+ T-cell response is compulsory for other viral hepatitis viruses. For HEV infection this CD8+ T-cell response to date has not been studied in detail. In this study we focused on the HEV-specific CD8+ T-cell response in acute and chronically HEV infected patients.
Method: We comprehensively studied the HEV-specific CD8+ T-cell responses of 22 HEV-infected patients with antigen-specific expansion, functional testing and pMHCI-tetramer stainings. Of the 22 patients, 13 patients were acutely infected, 4 had a chronic HEV infection and 5 patients resolved HEV infection.
Results: We identified the first 13 HEV-specific CD8+ T-cell epitopes to date which are restricted by the HLA alleles A*01:01, A*02:01, A*03:01, B*27:05 and B*3501. We were able to detect HEV-specific CD8+ T-cell responses in all resolvers and in the acutely infected patients, that contracted with time. The magnitude of the CD8+ T-cell response varied according to the HLA allele by which it was restricted. The 4 HLA-B27 restricted epitopes mounted the highest CD8+ T-cell responses. In HLA*B27+ patients up to 40% of bulk CD8+ T-cells stained *ex vivo* were specific for single HEV-specific epitopes. None of the chronic HEV Patients was HLA-B*27:05 positive. The HEV-specific CD8+ T-cell response in the chronic patients was diminished in comparison to the acute disease course, but was partially restored after ribavirin therapy.
Conclusion: Here we show a putative role for host factors like HLA alleles in HEV infection and that a strong and specific CD8+ T-cell response is associated with viral clearance whereas a weak CD8+ T-cell response is associated with viral persistence.

SAT-431

A pan-genotype HCV T cell vaccine, in a simian adenovirus vector, to target T cell epitopes conserved across multiple HCV genotypes

T. Donnison[1], A. von Delft[1], S.K. Chinnakannan[1], J. Lourenco[2], C. Hutchings[1], A. Brown[1], P. Klenerman[1], E. Barnes[1]. *[1]University of Oxford, Nuffield Department of Medicine, Oxford, United Kingdom; [2]University of Oxford, Department of Zoology, Oxford, United Kingdom*
Email: ellie.barnes@ndm.ox.ac.uk

Background and Aims: The development of a prophylactic hepatitis C virus (HCV) vaccine has been hindered by viral genomic variability. A phase-I human clinical trial demonstrated that a viral vector T-cell vaccine encoding a subtype-1b HCV immunogen (non-structural proteins 3 to 5) induces HCV-specific T-cell responses targeting dominant epitopes that are highly variable and have reduced cross-recognition of variants at the population level. Therefore, we generated simian adenovirus vaccines encoding an immunogen with genetic sequence that is conserved between HCV genotypes with genetic adjuvant, truncated class-II shark invariant chain, sIi(tr) aa47-72.
Method: Combined conserved segments formed novel immunogens for HCV genotypes 1 and 3, and 1–6. Putative artificial epitopes in junction regions were abrogated. *In silico* analysis enabled exclusion of potential cross-reactive human self-peptides and identified HCV T-cell epitopes. Simian adenoviral vaccine vectors encoding the HCV immunogen (ChAdOx1-gt1-6) were constructed with and without sIi (tr). Immunogenicity was evaluated in inbred and outbred mice at 10^{7-8} IU single intramuscular dose, using both genotype-specific and conserved sequence peptide pools in *ex vivo* IFN-γ ELISpot assays and intracellular staining. A genotype-1b HCV immunogen, encoding non-structural proteins 3–5 in the ChAdOx1 vector, was used as a control.
Results: ChAdOx1 conserved segment HCV vaccines primed high-magnitude, broad, cross-reactive T-cell responses in inbred and outbred mice. The mean magnitude of Gt1-6L-induced total T-cell responses was 795 and 859 IFN-γ spot forming units (SFU)/10^6 splenocytes for genotype-1a and -3a peptide pool stimuli, respectively, in outbred mice. Immunogens containing shark invariant chain (sIi; aa47-72) induced T cells with enhanced immunogenicity to genotype-specific peptide pool stimuli. $CD8^+$ and $CD4^+$ cytokine-producing T cells were specific for HCV sequences that have high percentage sequence identity across all HCV genotypes. *In silico* analysis showed that conserved immunogens contain multiple epitopes described in natural HCV infection.
Conclusion: Novel pan-genotypic HCV simian adenoviral vectored vaccines, with genetic adjuvant sIi(tr), encoding conserved segments from all major HCV genotypes, contain multiple T-cell epitopes described in human infection, and are immunogenic in mice. These

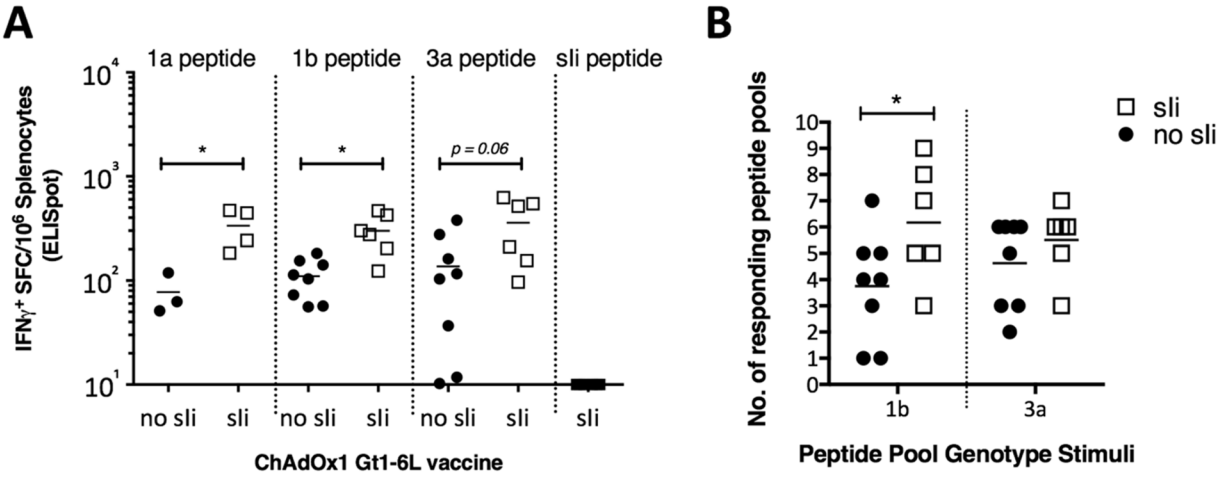


Figure: (abstract: SAT-431): *Ex vivo* IFN-γ ELISpot data displaying the total magnitude (A) and breadth (B) of the HCV genotype-specific T cell response in CD-1 outbred mice three weeks after a single 10^7 infectious unit (IU) intramuscular prime vaccination.

studies pave the way for the assessment of pan-genotypic HCV T-cell vaccines in humans.

SAT-432

Performance of recomWell HEV and Wantai HEV in acute Hepatitis E and German blood donors

S. Schulz, F. Struck. *Mikrogen GmbH, Neuried, Germany*
Email: schulz@mikrogen.de

Background and Aims: Hepatitis E virus (HEV) is now known to be endemic in Europe and often described as the most frequent viral cause for acute hepatitis. HEV ELISA test systems are used routinely as screening assays in serological diagnostics and for epidemiological studies. In this evaluation the performance of the improved versions of *recom*Well HEV IgG, IgM was compared to Wantai HEV IgG, IgM. Both brands represent the two most commonly used commercial HEV ELISA assays in Europe.

Method: Diagnostic sensitivity of *recom*Well HEV IgM (new) and Wantai IgM was evaluated using 89 well-defined samples from patients with confirmed acute HEV infection. PCR-positive patient samples of various HEV genotypes and subsequent follow-up samples from one PCR-positive blood donor have been analyzed. Diagnostic specificity of *recom*Well HEV IgM (new) and Wantai IgM was determined with a panel consisting of 359 samples (200 blood donors, 159 patient samples, clinical suspicion of non-E-hepatitis confirmed as HIV, HCV, HAV, Parvo B19, EBV, or CMV pos.). 200 sera from healthy German blood donors have been analyzed with *recom*Well HEV IgG (new & previous version) and Wantai IgG in order to determine seroprevalences.

Results: *Recom*Well HEV IgM shows excellent diagnostic sensitivity, achieving 98.9%. Only one serum from a total of 89 was not found positive, whereas Wantai HEV IgM missed 6 sera, reaching a sensitivity of 93.3%. Furthermore, *recom*Well HEV IgM is reactive in all PCR-positive patient samples with various genotypes (1a, 3a and 4b, d, f), whereas Wantai IgM is missing one sample. Analysis of paired samples demonstrates that *recom*Well HEV IgM detects IgM specific antibodies for several months starting at the end of the viremic phase. Interestingly, Wantai HEV IgM is not able to detect specific antibodies in any sample of this PCR-positive individual. Both test systems, *recom*Well HEV IgM and Wantai HEV IgM, show a convincing diagnostic specificity of 98.6%. Analysis of 200 German blood donors results in similar HEV seroprevalences for *recom*Well IgG (33%) and Wantai IgG (32%). The clear improvement in sensitivity is demonstrated by the comparison of the new (33%) and previous version (18.5%) of *recom*Well HEV IgG.

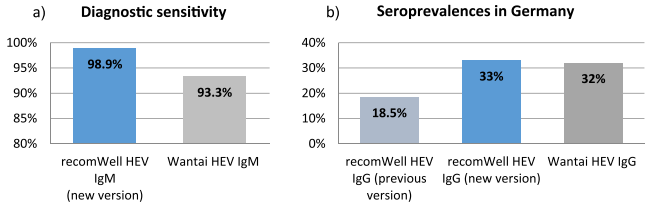


Figure: (a) Diagnostic sensitivity, 89 well-defined patient samples with confirmed acute HEV infection (b) Seroprevalences in Germany (200 healthy blood donors).

Conclusion: Yielding a diagnostic sensitivity of 98.9% *recom*Well HEV IgM performs better compared to Wantai HEV IgM with 93.3%. Furthermore, *recom*Well HEV IgM picks up all PCR-positive samples, including various genotypes, whereas Wantai IgM misses 2 samples. Diagnostic sensitivity for IgG antibodies is similar to Wantai HEV IgG, as reflected by the determination of comparable seroprevalences for German blood donors. In summary, *recom*Well HEV assays are highly suitable for the detection of acute Hepatitis E as well as seroprevalence studies.

SAT-433

Ex vivo characterization of co-inhibitory molecules on MHC class II tetramer positive HCV-specific CD4+ T cells in HCV infection

C. Ackermann[1], S. Kummer[1], M. Smits[2], V. Matzat[1], F. Piecha[1], J. Eberhard[1], T. Böttler[2], J.S.Z. Wiesch[1]. [1]*University Medical Center Hamburg-Eppendorf, I. Department of Internal Medicine, Hamburg, Germany;* [2]*University Hospital Freiburg, Department of Medicine II, Freiburg im Breisgau, Germany*
Email: c.ackermann@uke.de

Background and Aims: In acute HCV infection $CD4^+$ T cells lose their functionality and the infection becomes chronic in a majority of patients. Up-regulation of inhibitory receptors may be a critical step in the development of T cell dysfunction in chronic infection. The comprehensive analysis of this loss of function, including the exact expression profiles and (co-)blockade of these coinhibitory and coactivatory molecules will help to understand the development of chronification versus protection in HCV infection and other viral infections.

Method: MHC class II tetramer-associated magnetic bead enrichment technique and multicolor cytometry were perfomed with PBMCs from patients with acute (n = 10), chronic (n = 8) and resolved (n = 6) HCV infection to assess the expression of different inhibitory and stimulatory markers on total and specific $CD4^+$ T cells. The cells

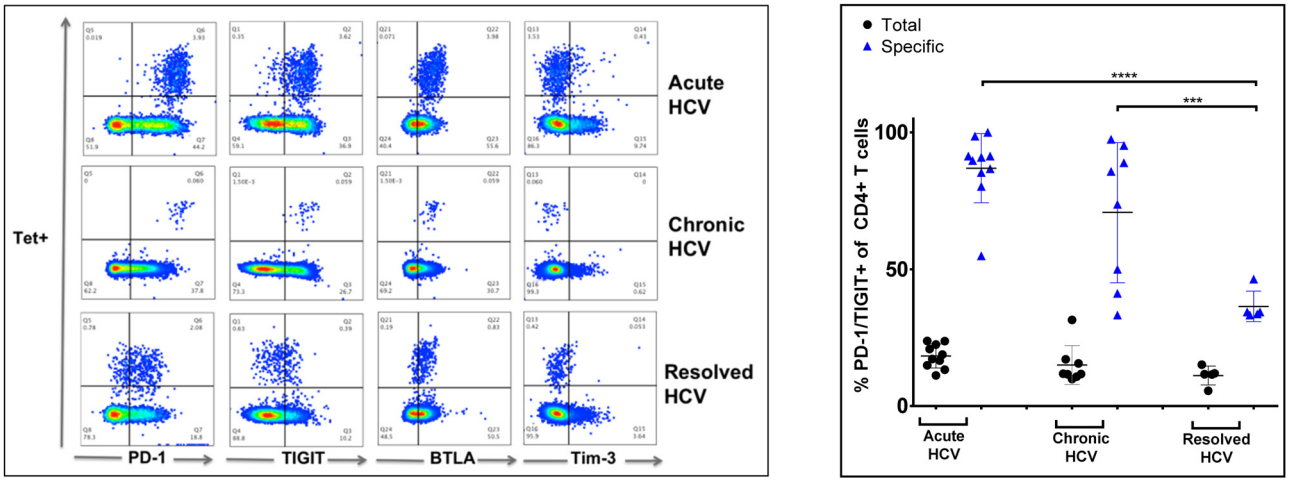


Figure: (abstract: SAT-433)

were stained with fluorescently conjugated monoclonal antibodies against CD3, CD4, CD45RO, CCR7, PD-1, TIGIT, BTLA, Tim-3, Ceacam1, LIGHT, OX40, CD226 and LIVE/DEAD™ Fixable Near-IR. Stained and fixed cells were analyzed by flow cytometry using BD LSRFortessa™.
Results: We were able to detect HCV-specific $CD4^+$ T cells from patients with acute (n = 10), chronic (n = 8) and resolved (n = 6) HCV infection using HLA-DRB1*01:01, DRB1*04:01 and DRB1*15:01-restricted tetramers. In agreement with previous studies, we observed significantly higher ($p = 0.0054$) frequencies of HCV-specific $CD4^+$ T cells during acute compared with chronic infection. Almost all HCV-specific $CD4^+$ T cells show an effector memory (EM) phenotype (CD45RO + CCR7-) independ of the infection state. Nevertheless, we found in slight decrease ($p = 0.0287$) in the EM phenotype of specific $CD4^+$ T cells from patients with chronic compared to acute HCV infected patients. We analyzed the expression pattern of different inhibitory and stimulatory receptors from patients with acute, chronic and resolved HCV infection and found an increased inhibitory receptor expression level on specific $CD4^+$ T cells from patients with acute and chronic HCV infection compared to patients which spontaneously eliminate the virus. Especially, the PD-1 and TIGIT co-expression was significantly higher ($p < 0.0001$) on specific $CD4^+$ T cells from acute and chronic infected patients.
Conclusion: Increased inhibitory receptor expression play a crucial role in the development of T cell dysfunction. We found an increased expression of the inhibitory markers TIGIT and PD-1 on HCV-specific $CD4^+$ T cells. To block molecules such as TIGIT and PD-1 separately or in combination will depend on deeper knowledge of expression patterns and underlying molecular mechanisms. However, these findings reveal TIGIT together with PD-1 as a novel marker of dysfunctional HCV-specific $CD4^+$ T cells and suggest TIGIT along with other checkpoint receptors may be novel curative targets to reverse T cell exhaustion.

SAT-434
Association of PD1 and TIM3 polymorphisms with HBV susceptibility

C. Huang[1], C. Xia[1,2], H. Zhu[1], J. Wo[1], F. Chen[1], M. Zheng[1], Z. Chen[1]. [1]*The State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital of School of Medicine, Zhejiang University, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, Hangzhou, China, Hang Zhou, China;* [2]*Department of Infectious Diseases, Hangzhou First People's Hospital, Nanjing Medical University, Hangzhou, China.*
Email: chenzhi@zju.edu.cn

Background and Aims: Programmed cell death 1 (PD1) and T-cell immunoglobulin and mucin domain-containing molecule 3 (TIM3) play important roles in regulating immune reaction of hepatitis B virus (HBV) infection. Whether the genetic variants of PD1 and TIM3 can influence the susceptibility and progression of HBV infection or not has not been confirmed. In this article, we tried to investigate the relation of PD1 and TIM3 polymorphisms with HBV infection.
Method: Four PD1 single-nucleotide polymorphisms (SNPs) (rs10204525, rs2227982, rs41386349, rs36084323) and three TIM3 SNPs (rs1036199, rs10515746, rs11742259) were genotyped by TaqMan probe in 898 HBV-infected patients and 364 healthy controls of South China. The 898 patients include 222 asymptomatic carriers (AsC), 276 chronic hepatitis B (CHB), 105 acute on chronic liver failure (ACLF) and 295 liver cirrhosis (LC). The association of the SNP sites with HBV infection was then analyzed using statistical methods.
Results: SNP rs10204525 and rs2227982 of PD1 are significantly associated with HBV infection. Per rs10204525, its odds ratio (OR) is 0.823, 95% confidence interval (CI) is 0.679–0.997 and p = 0.046; per rs2227982, its OR is 1.231, 95%CI is 1.036–1.463 and p = 0.018. On the contrary, SNP rs1036199 and rs10515746 of TIM3 have lower frequency in HBV patients. Per rs1036199, its OR is 0.430, 95%CI is 0.206–0.894 and p = 0.020; per rs10515746, its OR is 0.430, 95%CI is 0.206–0.894 and p = 0.020. Further haplotype-based association analysis indicates that haplotype block AT, formed by SNPs rs10204525 and rs2227982 is significantly associated with HBV infection (OR = 1.230, 95%CI = 1.035–1.463, p = 0.019).
Conclusion: Rs10204525 and rs2227982 of PD1, and rs1036199 and rs10515746 of TIM3 associate with HBV infection.

SAT-435
Preclinical mechanistic and efficacy evaluation of a novel small molecule TLR7 agonist RO7020531 for the treatment of chronic hepatitis B

L. Dai[1], X. Yu[1], Y. Yu[1], L. Gu[1], J. Zhao[1], L. Zhu[1], G. Ottaviani[2], H. Yun[1], M. Ait-Goughoulte[2], M. Ilnicka[2], J. Xie[1], L. Wang[2], A. Feng[1], J. Young[2], L. Gao[1]. [1]*Roche Innovation Center Shanghai;* [2]*Roche Innovation Center Basel*
Email: lu.gao@roche.com

Background and Aims: Chronic hepatitis B (CHB) is a major global healthcare problem. Functional impairment of immune responses is a key feature of chronic HBV infection. An immune enhancer is needed to restore HBV-specific B- and T cell responses. An orally available small molecule RO7020531 is currently being tested in Phase I with the potential to modulate immune responses against HBV infection. Here we report the key features of this compound and its anti-HBV effect in preclinical studies.

Method: In vitro assessments of the potency, specificity, and cytotoxicity were performed using appropriate cell lines overexpressing TLR3, 7, 8, and 9 and human PBMC. In vivo efficacy was studied in a mouse model with a recombinant adeno associated virus carrying hepatitis B virus genome (AAV HBV) in either C57BL/6 mice or SCID mice. The levels of HBV DNA, HBsAg, and HBeAg in mouse serum were measured by quantitative polymerase chain reaction (qPCR), HBsAg chemiluminescent immunoassay (CLIA), HBeAg CLIA kits, and mouse IgG ELISA development kit, respectively.
Results: RO7020531 is a double prodrug of RO7011785, a TLR7-selective agonist. Ex vivo stimulation of human PBMCs by RO7011785 led to the induction of IFNα and various cytokines and chemokines, such as TNFα, IL-6 and IP-10. Depletion of plasmacytoid dendritic cells (pDC) and monocytes in PBMC greatly reduced the production of IFNα and IL-6, respectively, induced by RO7011785. In a mouse model, RO7020531 stimulated type I interferon response mainly in the spleen and lymph nodes, but not in the gastrointestinal (GI) tract. Moreover, anti-HBV effects of RO7020531 were observed in a dose-dependent manner in the AAV-HBV mouse model, where the TLR7 agonist significantly reduced the levels of HBV DNA and HBsAg. The innate immune response triggered by RO7020531, such as the upregulation of cytokines and interferon-stimulated genes (ISG), were recapitulated in the AAV-HBV model. Notably, the ability of RO7020531 to suppress viremia and to reduce HBsAg was dependent upon adaptive immune responses, since these antiviral effects were largely abrogated in the AAV-HBV model using SCID mice where T and B cells were absent. Indeed, we confirmed that RO7020531 promoted the emergence of anti-HBs antibody in the serum and increased HBsAg-specific T and B cells in the spleen.
Conclusion: The small molecule RO7020531 represents a promising anti-HBV agent with the potential to trigger innate and HBV-specific adaptive immune responses to reduce HBV DNA and HBsAg. These unique features warrant further evaluation of the anti-HBV efficacy of this molecule in a clinical setting.

SAT-436

A systematic comparison reveals dynamic differences in early adaptive immune responses of acute-resolving versus chronic HBV replication

Q. Wang, Y. Liu, D. Yang, J. Liu. *Department of infectious diseases, Wuhan, China*
Email: jialiu77@hotmail.com

Background and Aims: Chronic hepatitis B virus (HBV) infection has been characterized by lack of effective adaptive immune responses which are vital for the viral clearance. However, very little is known about the dynamics of adaptive immune responses during the early phase of chronic HBV infection especially in the spleen and the liver.
Method: We kinetically characterized the feature differences of adaptive immunity, including the frequencies, phenotypes and function of antigen presenting cells and T cells in the spleen, the PBMCs and the liver, of chronic versus acute-resolving HBV replication by using hydrodynamic injection (HI) mouse model.
Results: We found that, both mice with acute-resolving HBV replication (AR mice) and mice with chronic HBV replication (CH mice) showed early splenomegaly accompanied by T cell expansion in spleen but not in liver after HI. Interestingly, CH mice showed early and continuous increase of HBV specific CD8+ T cells in spleen in a comparable extent to that in the AR mice. However, the splenic T cells of CH mice showed no activation phenotype compared with those in AR mice. Besides, increases of activated effector CD8+ T cells in PBMCs and liver at later time points were only observed in AR mice but not CH mice. CH mice also showed insufficient dendritic cells (DCs) expansion in spleen and increased DCs PD-L1 expression in liver compared to AR mice. Adoptive transferring total splenocytes or splenic CD8+ T cells of AR mice to CH mice revealed that their ability in breaking HBV tolerance varies at different stages of HBV clearance. Moreover, inducing functional activation of endogenous HBV specific CD8+ T cells of CH mice was achieved through adoptive transfer of splenocytes from AR mice.
Conclusion: Our results suggest that early T cell priming and expansion firstly happen in periphery after HBV antigen exposure in both acute-resolving and chronic replication. The paucity of T cell activation, and following migration and liver infiltration is a key feature of the adaptive immune responses during the early phase of chronic HBV replication, which is probably caused by the dysfunction of DCs. Fully viral clearance and activation of endogenous CD8+ T cells are achievable during this phase through adoptive transfer of splenocytes from AR mice.

Alcoholic liver disease

SAT-441

Alcoholic liver disease replaces HCV infection as the leading indication for liver transplantation in the United States

G. Cholankeril[1], A. Goel[1], P. Puri[2], A. Ahmed[1]. *[1]Stanford University School of Medicine, Division of Gastroenterology and Hepatology, Stanford, United States; [2]Virginia Commonwealth University, Division of Gastroenterology, Hepatology and Nutrition, Richmond, United States*
Email: georgetc@stanford.edu

Background and Aims: The arrival of second-generation direct-acting antiviral agents has reduced the burden of chronic hepatitis C virus (HCV) on the liver transplant (LT) allocation system in the United States (US). However, recent trends have also demonstrated a rise in alcohol use and alcohol-related mortality in the US. Therefore, our aim was to evaluate current trends among the leading indications for liver transplantation in the US.
Method: Using the United Network for Organ Sharing (UNOS) registry, we evaluated annual waitlist additions and LT trends in patients for the three leading indications of chronic liver disease (CLD), (1) HCV, (2) alcoholic liver disease (ALD), and (3) non-alcoholic steatohepatitis (NASH) for LT in the US from January 1, 2012 to October 31, 2017. Etiology of CLD was determined through diagnoses codes and HCV serology and categorized in mutually exclusive cohorts. Patients listed as Status 1A, received prior LT or had concomitant hepatocellular carcinoma were excluded. Clinical demographics and characteristics among waitlist additions were compared using Chi-square test for categorical variables and Kruskal-Wallis for quantitative variables.
Results: During the study period, the annual number of waitlist additions and liver transplant surgeries due to CLD was 2.1% and 7.6%, respectively. From 2012 to 2015, HCV remained the leading etiology among CLD waitlist additions (28%) and LT recipients (24%). Since 2016, ALD was the leading indication for waitlist additions in the US (ALD 28%, HCV 25%, NASH 19%, $p < 0.001$). ALD (31%) and NASH (21%) has accounted for over half of CLD waitlist additions in 2017.
From 2016 onwards, both ALD and NASH have surpassed HCV as the first and second leading indications for LT for CLD, respectively (Figure). There was a notable reduction in the annual percentage of LT recipients with HCV, declining to 17% in 2017. Compared to HCV and NASH waitlist additions from 2015 to 2016, ALD waitlist additions were significantly younger in age (ALD 54, IQR [47–51]; HCV 59, [IQR 55–63]; NASH 60 IQR [54–65]; $p < 0.001$) but had a higher severity of hepatic decompensation including median Model for End-Stage Liver Disease score at listing (ALD 21, IQR [15–30]; HCV 14, IQR [10–21]; NASH 17 IQR [13–24]; $p < 0.001$).

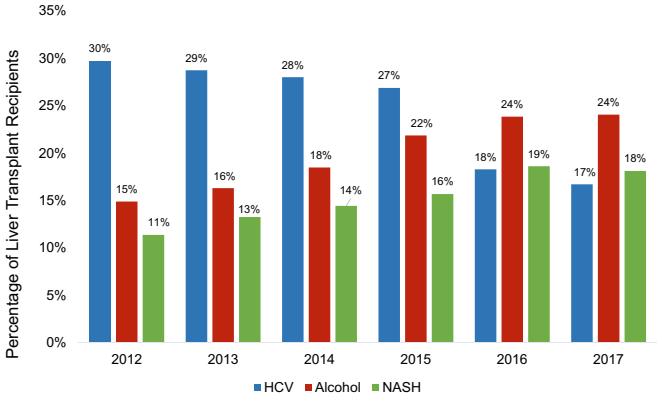


Figure: Annual Trends in the three Leading Indications for Liver Transplantation in the United States.

Conclusion: ALD has now become the leading indication for liver transplantation in the US. However, patients with ALD are presenting for LT with a higher severity of illness than other patients with CLD. Drastic measures are needed to aggressively address these ominous trends in the rising rates of ALD-related liver transplantation.

SAT-442

Individualized prediction of the risk of liver-related death in patients with alcoholic cirrhosis

M. Astrid[1], J. Henrion[2], K. Jean-François[3], S. Florent[4], T. Eric[5], C. Moreno[5], D. Pierre[5,6]. *[1]CHU UCL Namur, Department of Gastroenterology and Hepatology, Yvoir, Belgium; [2]Jolimont Hôpital, Department of Gastroenterology and Hepatology, La Louvière, Belgium; [3]Université de Lausanne, Laboratory for Investigative Neurophysiology (The LINE), Department of Radiology and Department of Clinical Neurosciences, Lausanne, Switzerland; [4]École polytechnique fédérale de Lausanne, Lausanne, Switzerland; [5]Hôpital Erasme, Université Libre de Bruxelles, Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Brussels; [6]Clinique Saint-Luc Bouge, Department of Gastroenterology and Hepatology, Namur, Belgium*
Email: pierre.deltenre01@gmail.com

Background and Aim: In patients with cirrhosis, prognostic models providing a precise estimate of the risk of death are essential for patient care. The aim of this work was to develop a model allowing an individualized prediction of the risk of liver-related death among patients with alcoholic cirrhosis, that takes into account the impact of abstinence.

Method: Data related to death and causes of death were collected among patients with alcoholic cirrhosis consecutively seen in a single center during a 21-year period. Abstinence was defined as discontinuation of any alcohol intake within the first 12 months following inclusion. Multivariate Fine and Gray proportional hazards models were used to identify factors associated with liver-related death. We calculated Akaike information criterion values by adding variables using a forward step by step approach to build the best competing risk regression (CRR) model that predicts liver-related death. To validate the prediction of the model, a cross validation procedure was applied using a training set of 80% and a testing set of 20% of the data randomly chosen. The Brier score was used to estimate the quality of the prediction of the different models tested, the model with the lowest Brier score providing the best prediction.

Results: 489 patients (68% of male, median age 55 years [95% CI: 54–56], 45% Child-Pugh stages B or C, median MELD score 9.0 [95% CI: 8.5–9.7]) were included. During follow-up (median, 57 months), 247 patients died, 12 from hepatocellular carcinoma, 156 from liver failure and 76 from non-liver related causes. Three variables were independently associated with liver-related mortality: age (HR: 1.02, 95% CI: 1.01–1.04, $p = 0.01$), Child-Pugh score (HR: 1.20, 95% CI: 1.11–1.29, $p < 0.001$) and abstinence (HR: 0.42, 95% CI: 0.28–0.63, $p < 0.001$). A CRR model using these 3 variables as covariates was built, providing a continuum risk of death at 5 years in abstainers (Figure 1) and consumers (Figure 2). For any combination of age and Child-Pugh score, patients who did not abstain from alcohol had a greater risk of dying at 5 years than patients who abstained from alcohol. According to the Brier score, the prediction of liver-related death at 5 years was better using the CRR model than with the random model in 100% of the cases, with the Kaplan Meier model in 93%, and with the Cox model in 92%. The prediction of liver-related death was not better when the MELD score was used in the CRR model instead of the Child-Pugh score.

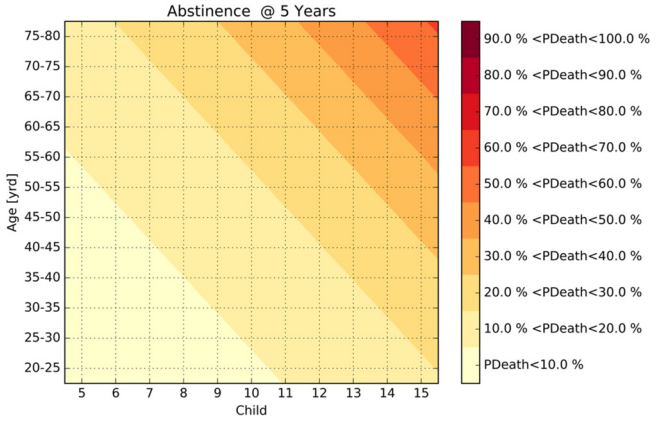


Figure 1

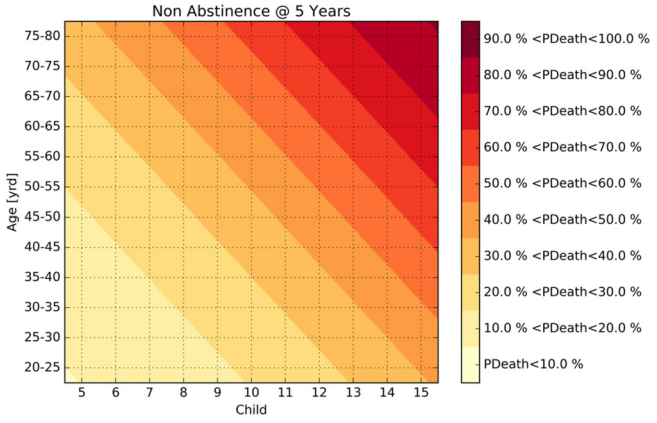


Figure 2

Conclusion: The CRR model combining age, Child-Pugh score and abstinence accurately predicts the risk of liver-related death on an individual basis among patients with alcoholic cirrhosis. Huge differences in 5-years prediction of death were observed in patients who abstained and who did not abstain from alcohol. This model may serve as a tool for prognosis assessment in a daily practice and may help to motivate patients to stop drinking.

SAT-443

Liver transplantation for alcoholic hepatitis: a systematic review with meta-analysis

M. Astrid[1], D. Margaux[2], T. Eric[3], C. Moreno[3], D. Pierre[3,4]. *[1]CHU UCL Namur, Department of Gastroenterology and Hepatology, Yvoir, Belgium; [2]CHUV Centre hospitalier universitaire vaudois, Division of Gastroenterology and Hepatology; [3]Hôpital Erasme, Université Libre de Bruxelles, Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology; [4]Clinique Saint-Luc Bouge, Department of Gastroenterology and Hepatology, Namur, Belgium*
Email: pierre.deltenre01@gmail.com

Background and Aims: The rate of alcohol relapse among patients who underwent liver transplantation for alcoholic hepatitis (AH) is not precisely known. The aim was to synthesize the available evidence on liver transplantation for AH to assess alcohol relapse and 6-month survival.
Method: Meta-analysis of trials evaluating liver transplantation for AH, either clinically severe or diagnosed on the explant.
Results: Eleven studies were included. The pooled estimate rate for alcohol relapse was 0.22 (95% CI = 0.12–0.36) in overall analysis with high heterogeneity between studies (I^2 = 76%), 0.20 (95% CI = 0.07–0.43) in the subgroup analysis including patients with clinically severe AH (I^2 = 84%), 0.14 (95% CI = 0.08–0.23) among patients with clinically severe AH in sensitivity analysis excluding the discrepant studies that did not use stringent selection criteria for liver transplantation (I^2 = 0%), and 0.15 (95% CI = 0.07–0.27) for recurrent harmful alcohol consumption among patients with clinically severe AH (I^2 = 3%). The risk of alcohol relapse was not different between AH transplanted patients and patients with alcoholic cirrhosis who underwent elective liver transplantation in sensitivity analysis excluding the discrepant studies (OR = 1.68, 95%CI = 0.79–3.58, p = 0.2, I^2 = 16%). The pooled estimate rate for 6-month survival was 0.85 (95% CI = 0.77–0.91, I^2 = 49%), and 0.80 among patients transplanted for clinically severe AH (95% CI = 0.69–0.88, I^2 = 30%). AH transplanted patients had as good 6-month survival as patients who underwent elective liver transplantation (OR = 2.00, 95% CI = 0.95–4.23, p = 0.07, I^2 = 0%).
Conclusion: Using stringent selection criteria, 14% of patients with clinically severe AH have alcohol relapse after liver transplantation. The percentage of alcohol relapse of AH transplanted patients is similar than that of patients who underwent elective liver transplantation.

SAT-444

Heparin like effect increases risk of mortality and bleeding tendency in patients with severe alcoholic hepatitis during systemic Inflammatory Response (SIRS) and sepsis

M. Premkumar[1], P. Saxena[2], R. Mirza[2], P. Jain[3], P. Bhatia[4], G. Kumar[3], S. Sukriti[5], C. Bihari[2], A. Choudhury[6], S.K. Sarin[7]. [1]*Institute of Liver and Biliary Sciences, Hepatology, New Delhi, India;* [2]*Institute of Liver and Biliary Sciences, Hematology, New Delhi, India;* [3]*Institute of Liver and Biliary Sciences, Research, New Delhi, India;* [4]*Institute of Liver and Biliary Sciences, Clinical Nutrition, New Delhi, India;* [5]*Institue of Liver and biliary Sciences, Molecular and cellular medicine, India;* [6]*Institute of Liver & Biliary Sciences, Hepatology, New Delhi, India;* [7]*Institute of Liver and Biliary Sciences, Department of Hepatology, Vasant kunj, India*
Email: drmadhumitap@gmail.com

Background and Aims: Rebalanced coagulation in liver disease is set to a lower level, and despite an increased prothrombin time (PT),

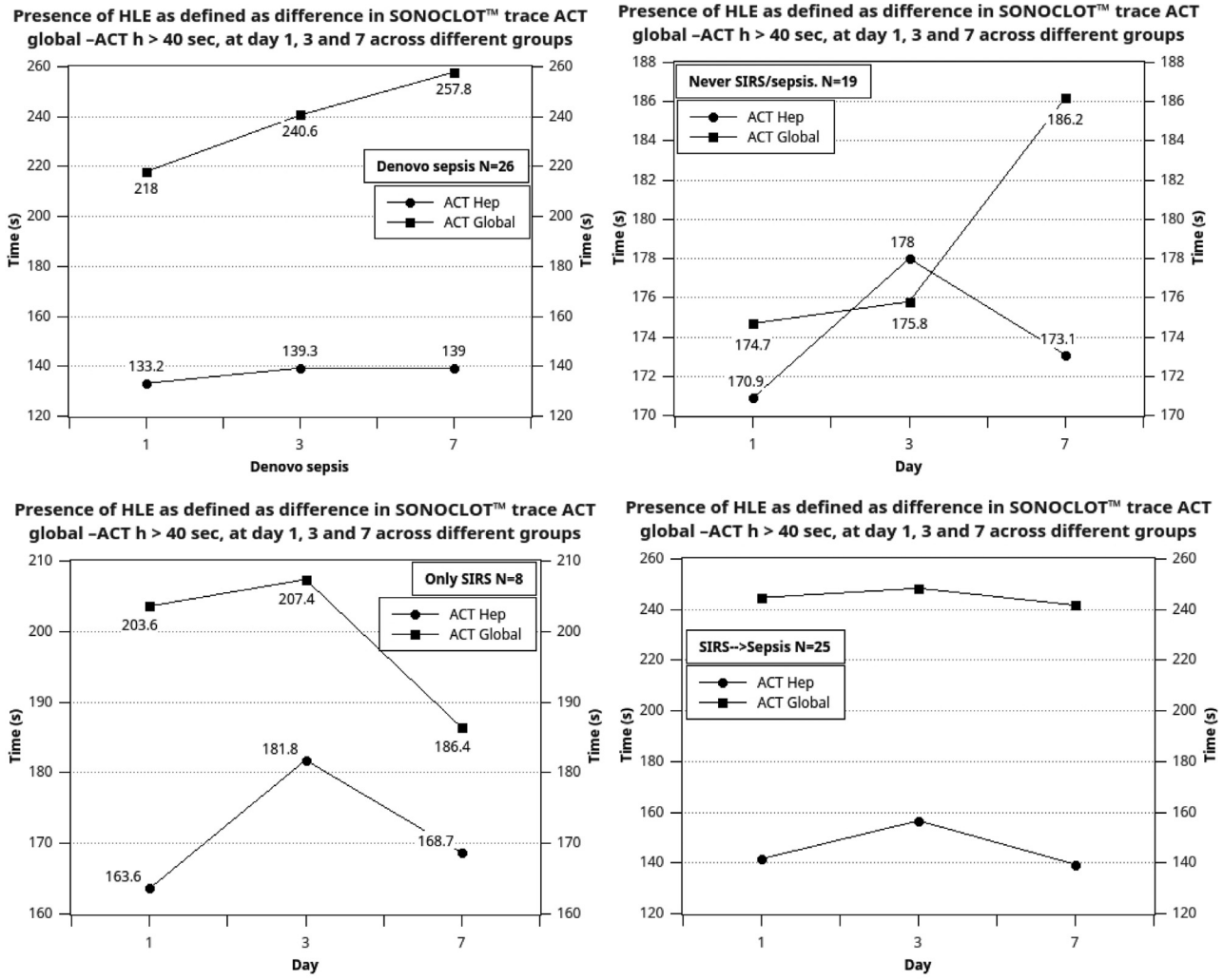


Figure 1: (abstract: SAT-444)

bleeding may only be caused when superadded factors like infection supervenes. The later could be due to generation of endogenous heparinoids or a heparin like effect (HLE) due to sepsis. The coagulation dysfunction in alcoholic hepatitis is not well studied.
Methods: Consecutive patients with severe alcoholic hepatitis (SAH), defined as Discriminant function (DF) >32;[DF = 4.6 × (patient's PT (seconds) – control's PT) + serum bilirubin level (in mg/dl)], who had no sepsis at presentation, were assessed at day 0, 3, and 7 for development of SIRS/sepsis, changes in coagulation parameters, disease progression and bleeding events. A global coagulation assay called SONOCLOT™ (global and heparinized) to measure the HLE, and specific assays i.e. factor VIII, vonWillebrand factor (vWF), protein C (PrC) and antithrombin III (AT), tissue plasminogen activator, tissue factor and plasminogen activator inhibitor were measured at the mentioned time points. These were compared with conventional parameters like platelet count, activated partial thromboplastin time and international normalized ratio (INR).
Results: Out of 145 screened patients with SAH, 78 (44.3 ± 11.7 years; 97% male) with no evidence of sepsis were recruited. At day 0, HLE was present in 20 (71.4%) and severe HLE was noted in 7 (25%) patients with SIRS. Presence of HLE at day 0 was noted in 20 (83.3%) subjects with sepsis at day 3 ($p = 0.003$), and in 32 (82.1%) subjects with sepsis at day 7 ($p = 0.001$). Predictors of mortality at day 0 were Factor 8[OR 4; 95%CI 1.0–1.45; ($p = 0.03$)], and at day 3, low PrC [OR 0.9; 95%CI 0.89–0.98 ($p = 0.007$)], low AT [OR 0.8; 95%CI 0.8–0.94 ($p = 0.008$)] and high INR [OR6.3; 95%CI 1.4–27.9 ($p = 0.015$)]. Bleeding events were seen in 55% [skin-39%, gastrointestinal-18.4%, and multiple sites-39%]. (Figure 1) The effects of sepsis on day28 mortality (OR 7.8;95%CI6.73 to 8.36; P = 0.002) and bleed events [OR 9.01; 95% CI6.74 to 9.39; ($p = 0.004$)] were significant. A deranged SONOCLOT™ was a predictor of bleeding (OR 3.5; $p = 0.05$) and mortality (OR = 2.9; 95% CI2.1–6.9, $p = 0.056$). The presence of HLE, at day 0 showed high mortality risk [OR 4.5; 95%CI 2.8 to 5.6; $p = 0.02$)].
Conclusion: Endogenous heparinoids contribute to coagulation abnormalities in patients with SAH. Presence of HLE in SAH is associated with an increased risk of sepsis, tendency to bleed and mortality.

SAT-445

Prevalence of alcoholic steatosis in the general adult Portuguese population

J.A.M.C.P. Leitao[1], S. Carvalhana[2], J. Cochicho[1], A.P. Silva[3], F. Velasco[4], I.S. Medeiros[5], A.C. Alves[6], M. Bourbon[6], B. Oliveiros[7], V. Rodrigues[8], A. Carvalho[1,9], H. Cortez-Pinto[2,10]. *[1]Centro Hospitalar e Universitário de Coimbra EPE, HUC, CHUC, Internal Medicine A, Coimbra, Portugal; [2]Hospital de Santa Maria, Department of Gastroenterology, Lisboa, Portugal; [3]Centro Hospitalar de Vila Nova de Gaia e Espinho, EPE, Department of Gastroenterology, Vila Nova de Gaia, Portugal; [4]Hospital de Faro, Centro Hospitalar do Algarve, EPE, Department of Gastroenterology, Faro; [5]Hospital Espírito Santo E.P.E, Évora, Department of Gastroenterology, Évora; [6]Instituto Nacional de Saúde Dr. Ricardo Jorge, Biosystems and Integrative Science Institute (BioISI), Lisboa, Portugal; [7]Faculdade de Medicina, Universidade de Coimbra, Laboratório de Bioestatística e Informática Médica, Coimbra, Portugal; [8]Faculdade de Medicina, Universidade de Coimbra, Instituto de Higiene e Medicina Social, Coimbra, Portugal; [9]Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal; [10]Faculdade de Medicina, Universidade de Lisboa, Laboratório de Nutrição, Lisboa*
Email: jorge.a.leitao@gmail.com

Background and Aims: Fatty liver is very frequent in the general population. Although many studies evaluated the prevalence of non-alcoholic fatty liver disease there is scarce information regarding alcoholic fatty liver. We aimed to estimate the prevalence of alcoholic hepatic steatosis, and to what extent it depended on obesity and its interaction.
Method: A cross-sectional study, with a random sample of the adult Portuguese population (18–79 years). All participants were evaluated with anthropometric measures, blood tests, ultrasound (US) to evaluate hepatic steatosis (Hamaguchi's US for steatosis defined by a presence of a score ≥2), and a semi-quantitative food frequency questionnaire (FFQ), representative of the usual intake over the previous year, including alcohol consumption. Three groups were defined regarding alcohol consumption: 1) harmful alcohol consumption (HAC) (males > 30 g/day; females > 20 g/day), n = 308; 2) moderate (MAC) (any alcohol consumption below these limits, n = 267); 3)null alcohol consumption (NC), n = 259. Alcoholic steatosis (AS) was considered if patients had steatosis and harmful alcoholic consumption.
Results: 834 participants were enrolled, 440 male, age 49.8 ± 17.2 years. Prevalence of AS was 18.1% (95% CI: 15.1–21.1%), 29% in male, 5.8% in women. General prevalence of steatosis was 37.9% (CI 95%: 32.9–39.5%), 45.7% in males, 25.6% in females, increasing with age: 16.8% in 18–34 years, 40.8% in 35–64 and 47.0% in > 65 years. Prevalence of hepatic steatosis, in the HAC was 49% (95% CI: 43.6–54.8%), MAC: 32.5% (95% CI: 26.9–38.2%), and NC: 24.7% (95%CI: 19.3–29.9%). Probability of having steatosis, according to different patterns of alcohol consumption and BMI are described in Table, demonstrating the strong increased risk due to interaction of obesity with alcohol consumption. However the risk associated with obesity is stronger than with harmful alcohol consumption.

Table: Odds Ratio (95% Confidence Interval) for the individual effect and interaction with alcohol consumption and BMI

BMI	Drinking status		
	Null	Moderate	Harmfull
		1.49 (CI: 1.02–2.18)	2.89 (CI: 2.02–4.15)
Normal weight	1	1.93 (CI: 0.79–4.68)	1.55 (CI: 0.60–4.00)
Overweight	2.90 (CI: 1.24–8.79)	2.48 (CI: 1.69–3.84)	4.04 (CI: 2.71–6.02)
4.74 (CI: 3.13–7.19)			
Obese	16.50 (CI: 7.01–38.83)	4.25 (CI: 2.35–7.78)	17.97 (CI: 9.63–33.54)
14.77 (CI: 9.25–23.56)			

All p values were <0.05 except Normal * Moderate p = 0.357.

Conclusion: Prevalence of alcoholic steatosis in the general population is lower than that of NAFLD, and obesity seems a strong risk factor than harmful alcohol consumption. However the concomitance of the two factors, obesity and alcohol consumption showed a supra-additive interaction between the two. Nonetheless in obese individuals, moderate alcohol consumption associated with reduced prevalence of steatosis.

SAT-446

Making sense of liver function tests: Is the Intelligent Liver Function Test (iLFT) cost-effective?

K. Boyd[1], J. Dillon[2], S. Inglis[2], M. Rezaeihemami[1]. *[1]University of Glasgow, Health Economics and Health Technology Assessment, IHW, Glasgow, United Kingdom; [2]University of Dundee, School of Medicine, Dundee, United Kingdom*
Email: kathleen.boyd@glasgow.ac.uk

Background and Aims: Liver function tests are widely used by GPs in primary care to identify liver disease. Abnormal results are common though, and are followed by (i) a lengthy process of retesting and referral which is costly to both patients and health services, or (ii) are left uninvestigated – potentially overlooking curable liver disease which would otherwise be fatal. iLFT is a semi-automated liver test cascading system with a structured diagnostic algorithm to maximise the efficiency of requesting LFTs and improve diagnosis. This study undertook a cost-effectiveness analysis of the iLFT decision tool compared to routine practice in Scotland, UK.
Method: An economic evaluation alongside the trial, and lifetime model undertaken from the perspective of NHS of Scotland. A step wedge design trial was carried out which compared effectiveness of diagnosis before and after the introduction of the iLFT system. Within

trial outcomes are reported as incremental cost per correct diagnosis at six months follow up, while a Markov model was used to extrapolate out to a lifetime analysis with discounted costs and quality adjusted life years gained in each arm, to account for early detection of Alcoholic Liver Disease (ALD) and Non-alcoholic Liver Fatty liver Disease (NAFLD). Probabilistic sensitivity analysis was undertaken with a 1000 iteration monte carlo simulation.

Results: The within trial analysis found costs to be £185 (CI 95% £166, £202) and £328 (CI 95% £231, £425) in routine practice and iLFT arms respectively. Probability of correct diagnosis (true positive and true negative) was 0.41 (CI 95% 0.37, 0.45) in routine and 0.92 (95% CI 0.85, 0.99) in iLFT, resulting in an ICER of £284 (CI 95% £128, £440). The lifetime model found iLFT to dominate routine practice with an incremental cost saving of £3216 (CI 95% -£7643, -£897) and an incremental QALY gain of 0.021 (CI 95% 0.009, 0.04).

Conclusion: iLFT increases Liver diagnosis, while improves quality of care and is cost effective with a low ICER of £284 per correct diagnosis and over a patient lifetime is a dominant strategy saving the NHS an average £3,216 per patient. Given these results iLFT should be recommended and widely implemented across the NHS.

SAT-447

Combination of the Lille model with baseline scores is useful to predict mortality in severe alcoholic hepatitis: a confirmation study in a large database of patients

A. Louvet[1], J. Labreuche[2], M. Thursz[3], D.J. Kim[4], S. Atkinson[3], S. Sidhu[5], J. O'grady[6], E. Akriviadis[7], E. Sinakos[7], R. Carithers[8], M.-J. Ramond[9], W.C. Maddrey[10], T. Morgan[11], A. Duhamel[2], P. Mathurin[1]. *[1]Hôpital Huriez, Service des maladies de l'appareil digestif, Lille, France; [2]CHU de Lille, Unité de biostatistiques, Lille, France; [3]Imperial College, Hepatology, London, United Kingdom; [4]Hallym University, Internal medicine, Chuncheon, Korea, Rep. of South; [5]Danayand Medical College, Gastroenterology, Ludhiana, India; [6]King's College Hospital, Institute of Liver studies, London, United Kingdom; [7]Aristotle University, Internal medicine, Thessaloniki, Greece; [8]University of Washington, Medicine, Seattle, United States; [9]Hôpital Beaujon, Service d'hépatologie, Clichy, France; [10]Southwestern medical center, Medicine, Dallas, United States; [11]Veterans Affairs, Longbeach Heathcare System, Long Beach, United States*

Email: alexandre.louvet@chru-lille.fr

Background and Aims: Prediction of outcome in severe alcoholic hepatitis is important to adapt patient management. For such purpose, we previously showed that the combination of baseline score (i.e. MELD and Maddrey scores) to a dynamic model, the Lille model, is useful. Our aim was to validate in a huge independent database from a meta-analysis of individual data from 11 RCTs testing corticosteroids or pentoxifylline vs. placebo.

Method: We defined 4 risk groups of mortality at 2 and 6 months using the 16th, 50th and 84th centiles of the prognostic index (MELD + Lille or Maddrey + Lille) and report observed and predicted probabilities of overall mortality and in the different treatment groups.

Results: On overall patients, median age was 48 years (IQR 41–55.6), 67% were males, bilirubin was 16.6 mg/dl (10–24.8), prothrombin time was 19.9 s (17–23.5), INR was 1.8 (1.6–2.1). Among the available data, the Maddrey + Lille score was calculated in 1559 patients treated with corticosteroids (n = 865), pentoxifylline (n = 298) and placebo (n = 396). MELD + Lille was available in a total of 1249 patients treated with corticosteroids (n = 746), pentoxifylline (n = 252) and placebo (n = 251). Calibration and discrimination were good for all groups, regarding of the allocated treatment. To illustrate the predictive capacity of the combined scores, we show in the table the observed and predicted survivals at 2 and 6 months for the Lille + MELD score, according to the risk group. Observed and predicted survivals were close in overall and in the three treatment groups (corticosteroids, pentoxifylline, placebo). C-statistics was at 0.72 in the total cohort and ranged between 0.7 and 0.73 in the three treatment groups, close to the previously published study (0.75). We observed that 44.9% (335/746), 60.7% (153/252) and 57% (143/251) of patients were classified at high or very high risk of mortality in the groups corticosteroids, pentoxifylline and placebo respectively. Similar results were observed using the Maddrey + Lille combined score with a good calibration and a good discrimination. C-statistics was at 0.72 in overall and ranged from 0.69 to 0.73 in the three treatment groups.

Conclusion: The combined models (MELD + Lille or Maddrey + Lille) should be used to predict outcome and adapt therapeutic strategy in severe alcoholic hepatitis. Patients with a MELD + Lille greater than 2.53 have a high risk of mortality at 2 and 6 months. Among them, those with a score greater than 3.88 have a predicted risk of mortality of around 80% that make them potential candidates for early liver transplantation.

Table 1: (abstract: SAT-447):

Table

	Overall			Corticosteroids alone			Pentoxifylline alone			Placebo alone		
	Death/N	Observed	Predicted	Death/N	Observed	Predicted	Death/N	Observed	Predicted	Death/N	Observed	Predicted
2-month mortality												
Risk group												
Very low (1.29-1.76)	7/212	0.034	0.062	5/140	0.036	0.062	1/34	0.030	0.065	1/38	0.026	0.061
Low (1.77-2.53)	60/406	0.153	0.105	45/271	0.169	0.106	5/65	0.080	0.103	10/70	0.148	0.105
High (2.54-3.88)	125/425	0.306	0.286	75/230	0.334	0.281	23/99	0.250	0.300	27/96	0.286	0.284
Very high (3.89-5.44)	124/206	0.629	0.639	70/105	0.671	0.649	29/54	0.580	0.645	25/47	0.541	0.609
6-month mortality												
Risk group												
Very low (1.29-1.76)	19/212	0.097	0.100	14/140	0.105	0.099	4/34	0.138	0.104	1/38	0.026	0.097
Low (1.77-2.53)	92/406	0.243	0.166	65/271	0.249	0.167	10/65	0.183	0.163	17/70	0.266	0.166
High (2.54-3.88)	177/425	0.450	0.418	106/230	0.481	0.412	34/99	0.405	0.436	37/96	0.415	0.416
Very high (3.89-5.44)	138/206	0.712	0.798	75/105	0.720	0.807	33/54	0.683	0.803	30/47	0.714	0.772
***C-statistics** (95%CI)*	0.72 (0.69 to 0.75)			0.73 (0.69 to 0.76)			0.73 (0.67 to 0.79)			0.70 (0.64 to 0.76)		

SAT-448

Higher early post-liver transplant mortality in recipients with severe alcoholic hepatitis versus alcoholic cirrhosis

B. Lee[1], G. Im[2], J. Dodge[1], M. Voigt[3], J. Rice[4], M.R. Lucey[4], D. Foley[5], L. Platt[6], A. Gurakar[6], N. Mehta[1], G. Therapondos[7], H. Han[8], D. Victor[9], O. Fix[10], L. Dinges[10], D. Dronamraju[11], C. Hsu[12], M. Rinella[13], H. Maddur[13], S. Eswaran[14], J. Hause[14], R.M. Ghobrial[15], Z. Li[6], N. Terrault[1]. [1]*University of California at San Francisco (UCSF), Gastroenterology, San Francisco, United States;* [2]*Icahn School of Medicine at Mount Sinai, Gastroenterology;* [3]*University of Iowa Carver College of Medicine, Gastroenterology;* [4]*University of Wisconsin School of Medicine and Public Health, Gastroenterology;* [5]*University of Wisconsin School of Medicine and Public Health, Surgery;* [6]*Johns Hopkins University School of Medicine, Gastroenterology;* [7]*Ochsner Medical Center, Gastroenterology;* [8]*Keck School of Medicine of USC, Gastroenterology;* [9]*Houston Methodist Hospital, Gastroenterology;* [10]*Swedish Medical Center, Gastroenterology;* [11]*University of Maryland School of Medicine, Gastroenterology;* [12]*Perelman School of Medicine at the University of Pennsylvania, Gastroenterology;* [13]*Northwestern University Feinberg School of Medicine, Gastroenterology;* [14]*Rush Medical College, Gastroenterology;* [15]*Houston Methodist Hospital, Surgery*
Email: brian.lee6@ucsf.edu

Background and Aims: Increasingly, liver transplantation (LT) is being offered to patients with alcoholic hepatitis (AH) despite a paucity of data regarding post-LT outcomes compared to alcoholic cirrhosis (ALC). The American Consortium of Early Liver Transplantation for Alcoholic Hepatitis (ACCELERATE-AH) is a multi-center cohort from 8 UNOS regions studying early LT for severe AH and here, we compare early and late post-LT mortality in AH vs. ALC in ACCELERATE-AH sites.

Method: All persons transplanted for alcohol-related liver disease since the first LT for AH at each of 12 ACCELERATE-AH centers were included. AH was defined as clinically-diagnosed severe AH, no prior diagnosis of liver disease or episodes of AH, and LT before 6 months of abstinence. ALC was defined as a UNOS listing diagnosis of alcoholic cirrhosis and not already within the AH group. Patients with HCV, hepatocellular carcinoma, HIV, other liver diseases, prior LT, and live-donor recipients were excluded. Site-specific and UN OS registry data were utilized. Graft failure and death were the primary outcomes. To evaluate the likelihood of death and associated factors, Cox proportional hazard ratios were calculated, adjusting for age and center level clustering.

Results: A total of 822 LT recipients from 2006 to 2016 were included: 123 with AH and 699 with ALC. Median follow-up was 2.0 years in both groups. Only 28% of AH patients had the correct listing diagnosis of AH in UNOS. AH patients vs. ALC were younger (42 vs. 54, $p < 0.001$), with college education (50% vs. 41%, $p = 0.005$), and higher MELD (38 vs. 30, $p < 0.001$). Donor characteristics were similar between groups. Cumulative unadjusted 1- and 3- year graft (94% and 83% vs. 90% and 83%, $p = 0.85$) and patient survival (94% and 85% vs. 94% and 86%, $p = 0.47$) were similar for AH vs. ALC. In multivariable analysis, AH as indication for LT (HR 1.42, $p = 0.02$), mechanical ventilation at LT (HR 2.00, $p = 0.02$) and DRI (HR 1.96, $p = 0.002$) were associated with increased risk of death after adjusting for age and center clustering. When stratified by age <50 versus ≥50, AH vs. ALC in those aged ≥50 was associated with increased risk of death ≤90 days post-LT (HR 4.07, $p = 0.003$).

Conclusion: Misclassification of AH in UNOS is frequent, highlighting the challenge in using UNOS alone to study LT outcomes in AH. After adjustment for covariates influencing survival, AH as indication for LT was associated with a 40% higher risk of post-LT death compared to ALC as indication, with the risk most pronounced in patients aged ≥50 and within 90 days post-LT. As mortality within the first 90 days is unlikely related to alcohol use post-LT, additional studies are essential to elucidate the factors contributing to early post-LT mortality in patients with AH.

SAT-449

Bayesian sparse regression modelling more accurately predicts mortality risk than commonly used prognostic scoring systems in patients with severe alcoholic hepatitis

S. Atkinson[1], M. Allison[2], E. Forrest[3], J. Wason[4], M. Thursz[5], P. Newcombe[4]. [1]*Liver Unit, United Kingdom, London, United Kingdom;* [2]*Cambridge University Hospitals NHS Foundation Trust, Department of Medicine, Cambridge, United Kingdom;* [3]*NHS GGC, Hepatology, Glasgow, United Kingdom;* [4]*MRC Biostatistics Unit, Biomedical Campus, Cambridge, United Kingdom;* [5]*Imperial College, Department of Hepatology, London, United Kingdom*
Email: stephen.r.atkinson@gmail.com

Background and Aims: Severe alcoholic hepatitis (sAH) is associated with significant mortality and heterogeneity in outcomes. Understanding mortality risk is important in guiding clinical decision-making. Several scoring systems, derived by logistic regression, have been applied to the condition; even those using biochemical changes over 7 days have modest discrimination and calibration for mortality. The aim of this study was to use Bayesian Variable Selection (BVS) to derive a superior predictive model of mortality in sAH.

Method: Patients with sAH (clinical diagnosis, DF > 32) were recruited to the Steroids or Pentoxifylline for severe Alcoholic Hepatitis (STOPAH) trial. The endpoint was 90-day mortality. Model fitting was performed in patients not treated with prednisolone (n = 534); initially under 10-fold cross-validation. The prednisolone treated population (n = 534) was used for validation. A BVS algorithm "R2BGLiMS" was used to derive prognostic models from 29 candidate biomarkers. Area under the curve (AUC) analysis and net reclassification index (NRI) were used to compare discrimination and calibration with MELD, GAHS and Lille. Low and high mortality risk were defined as <10% and >80% predicted mortality. Modelling was performed first using baseline clinical data and then incorporating data available at day 7.

Results: At 90 days 141 and 143 patients had died in the non-prednisolone and prednisolone treated arms, respectively. The BVS model using baseline data had an AUC of 0.79 when cross-validated in the untreated patients. This was little changed when limited to 6 biomarkers (BVS-6, AUC 0.76) and compared favourably to the MELD and GAHS scores (AUCs 0.71 and 0.70, respectively). BVS-6 offered superior stratification by mortality risk compared to GAHS and MELD (NRI 0.29 [95% CI 0.20–0.38] and NRI 0.26 [95% CI 0.17–0.34], respectively, both $p < 0.0001$). A BVS model using only six day 7 variables offered improved predictive performance (AUC 0.78), and was superior to the Lille score in terms of discrimination (AUC 0.70) and mortality risk stratification (NRI 0.44, 95% 0.32–0.56, $p < 0.0001$, Table 1). The baseline BVS-6 model remained superior to MELD and GAHS in the prednisolone treated cohort (AUCs: 0.74 vs. 0.69 and 0.71, respectively). The day 7 model was also superior to Lille (AUC 0.79 vs. 0.72) and offered much improved mortality risk stratification (NRI: 0.38, 95% CI 0.24–0.51, $p < 0.0001$).

Conclusion: Bayesian Variable Selection to model clinical outcomes in patients with severe alcoholic hepatitis allowed derivation of prognostic models with improved prognostic capacity compared to currently used. Findings were validated in an independent, prednisolone-treated cohort of patients. Such models could significantly enhance clinical decision-making by more accurately informing risk.

Table 1: Reclassification table for Lille score *vs.* BVS model using day 7 data

		Bayesian variable selection Day 7 model		
	Mortality risk	0-10%	10-80%	80-100%
Lille	*Patients who survived (n=264)*			
	0-10%	21	7	0
	10-80%	65	168	3
	80-100%	0	0	0
	Patients who died (n=99)			
	0-10%	0	5	0
	10-80%	5	79	10
	80-100%	0	0	1

SAT-450

Insufficient diagnostic accuracy of general practitioners and routine liver function tests lead to high risk of under-referrals of patients with alcohol induced advanced liver fibrosis

T.L. Hansen[1,2,3], K. Lindvig[1,2,3], S. Detlefsen[2,4], B.S. Madsen[1], J. Hansen[2,5], M. Kjærgaard[1,2,3], M. Thiele[6], A. Krag[1,2]. *[1]Odense University Hospital, Department of Gastroenterology and Hepatology, Odense, Denmark; [2]University of Southern Denmark, Institute of Clinical Research, Odense M, Denmark; [3]Odense University Hospital, Odense Patient data Explorative Network (OPEN), Odense, Denmark; [4]Odense University Hospital, Department of Pathology, Odense, Denmark; [5]Odense University Hospital, Department of Infectious Diseases, Odense, Denmark; [6]Odense University Hospital, University of Southern Denmark, Department of Gastroenterology and Hepatology, Odense C, Denmark*
Email: thor.lars.hansen@rsyd.dk

Background and Aims: Alcohol is the leading cause of liver-related death worldwide. The majority of alcoholic cirrhosis patients are diagnosed when they firstly decompensate, but have been in contact with primary healthcare years before decompensation. General practitioners (GPs) rely on standard liver blood tests to assess which patients to refer to secondary care. We therefore aimed to evaluate the diagnostic accuracy and inter-observer variance of experienced GPs and routine liver blood tests for diagnosing advanced alcoholic liver fibrosis, defined as histologic Kleiner fibrosis stage ≥F3.

Method: We presented two GPs with a questionnaire that contained clinical and laboratory data on 235 alcoholic patients, all whom had concomitant reference liver biopsy and biochemistry. GPs were blinded to the histology and to each other's answers. We asked the GPs to guess if the patient had ≥F3. We also assessed the diagnostic accuracy of ALT, AST, GGT, ALP, INR, platelet count and bilirubin using upper limit of normal(ULN) as cut-off. Finally, we calculated GPs inter-observer variance and compared the diagnostic accuracy of GPs and individual routine liver blood tests with fibrosis indices APRI, FIB4 and Forns.

Results: The prevalence of advanced fibrosis was 25%. The two GPs disagreed substantially in their prediction of advanced fibrosis, with a Kappa of 0.46. GP#1 guessed that 34% of patients had ≥F3, while GP#2 guessed that 15% of patients had ≥F3. The GPs (#1 and #2) incorrectly classified 36/58 (62%) and 27/58 (47%) of patients with ≥F3 fibrosis, while 22 (38%) and 31 (53%) guesses were false-negative (Table). Their false-positive rates were 45/177 (25%) and 8/177(5%). Routine liver blood tests were of insufficient help in the diagnosis of ≥F3, since values above ULN had poor sensitivity. The best single test was INR with an AUROC of .80. Indirect fibrosis tests combining routine markers performed better than the INR, but not in a statistically significant manner (P = 0.544 for comparison between Forns index and INR).

Table:

Variable	ULN	Overall AUROC	Sensitivity (%)	Specificity (%)
GP#1	–	–	62	75
GP#2	–	–	47	96
ALP	105 U/L	0.77	69	75
ALT	70/45 U/L	0.54	9	85
AST	45/35 U/L	0.72	60	73
Bilirubin	25 µmol/L	0.75	29	96
GGT	115/75 U/L	0.71	64	64
INR	1.3	0.80	43	96
Platelet count	350/400 10^9-/L	0.76	5	94
FIB-4	3.25	0.83	56	90
APRI score	1.0	0.78	37	89
Forns Index	6.8	0.83	68	87

Conclusion: General practitioners fail to diagnose up to half of alcohol overusing patients with biopsy-verified severe fibrosis or cirrhosis, resulting in a high risk of under-referrals of diseased patients to secondary care. This may be because GPs rely on the upper limit of normal for routine blood tests, which has poor sensitivity. There is consequently a need for better screening tools improving the diagnosis of advanced fibrosis in primary care.

SAT-451

Delineating complement activation molecular patterns in patients with alcoholic hepatitis

R. Mccullough[1], M. Sheehan[1], K. Poulsen[1], R. Chen[2], S. Roychowdhury[1], T. Mcintrye[2], L. Nagy[1]. *[1]Cleveland Clinic, Pathobiology, Cleveland, United States; [2]Cleveland Clinic, Department of Cellular and Molecular Medicine, Cleveland, United States*
Email: len2@po.cwru.edu

Background and Aims: Chronic alcohol abuse underlies the pathogenesis of alcoholic liver disease (ALD). Alcoholic hepatitis (AH), a severe form of ALD, can occur at any point along the ALD spectrum and is characterized by inflammation and hepatocellular injury. Impairment of renal function occurs in ALD; acute kidney injury is associated with higher mortality in AH. Complement, a critical component of the innate immune system, is an important patho-physiological contributor to ethanol-induced liver injury. In addition to mediating microbial defense, complement contributes to the resolution of inflammation by promoting clearance of damaged tissue via recognition molecules, opsonins and receptors. Complement is activated via three independent pathways, the classical, lectin, and alternative; the balance of these pathways generates complement activation molecular patterns (CAMPs). Our recent work in murine models of ALD indicates that classically- versus alternatively-activated complement may have differential impact on progression of ALD, whereby the classical pathway contributes to non-resolving inflammation and the alternative pathway promotes resolution/wound healing via the clearance of damaged tissue/cells. Evidence for complement activation has been reported in AH; however, CAMPs in AH patients are unknown. Delineating CAMPs will further our understanding of the patho-physiological mechanisms of AH and potentially identify individuals particularly susceptible for specific complications associated with increased mortality in AH.

Method: Complement activation was measured in serum and urine from patients enrolled in the Defeat Alcoholic Hepatitis (DASH) consortium and healthy controls (HC). AH explants and HC livers were obtained from the Clinical Resources for AH Investigations at Johns Hopkins University. Sectioned liver biopsies from AH patients were obtained from the Cleveland Clinic coPATH repository.

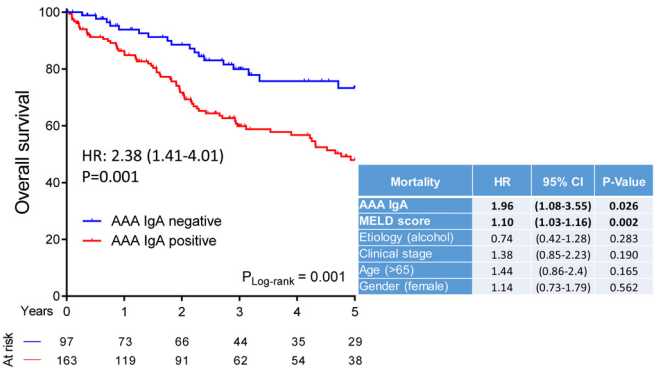
Results: Complement activation was higher in AH patients compared to HC; C3 and C5 activation products accumulated in liver and serum, respectively. Evidence for alternative activation was observed via the accumulation of Factor B fragments (*f*Ba) in liver and serum. C4d accumulation in liver, indicating activation via the classical pathway, was increased in AH patients and positively associated with the degree of fibrosis. Complement activation products C5a and *f*Ba, and KIM-1, a marker of kidney injury, were increased in AH urine. Consistent with a protective function of the alternative pathway, urinary *f*Ba negatively correlated with KIM-1.
Conclusion: Taken together, these data indicate that both classical and alternative pathway activation occurs in AH. These data suggest that CAMPs may be useful to develop as biomarkers to predict clinical outcomes and that targeting specific CAMPs are a potential therapeutic intervention in AH.

SAT-452

Presence of IgA isotype F-actin is frequent in patients with cirrhosis and consitutes the risk of progressive disease course

B. Balogh[1], T. Tornai[1], N. Sipeki[1], Z. Vitális[1], I. Tornai[1], P. Antal-Szalmás[2], T. Dinya[3], G.L. Norman[4], T. Bruns[5], M. Papp[6]. *[1]University of Debrecen, Faculty of Medicine, Institute of Internal Medicine, Department of Gastroenterology, Debrecen, Hungary; [2]University of Debrecen, Faculty of Medicine, Department of Laboratory Medicine; [3]University of Debrecen, Faculty of Medicine, Department of Surgery; [4]Inova Diagnostics Inc.; [5]University Hospital Jena, Department of Internal Medicine IV; [6]University of Debrecen, Faculty of Medicine, Insitute of Internal Medicine, Department of Gastroenterology*
Email: baloghboglarka23@gmail.com

Background and Aims: Gut barrier failure and the consequential pathological bacterial translocation (BT) are characteristic features of cirrhosis and play an important role in the progression of liver disease. Our aim was to investigate, whether hallmarks of gut barrier failure are associated with accelerated progression of liver disease in cirrhosis and the development of specific complications and liver-related death.
Method: Sera from 260 outpatients with cirrhosis (male: 129, age: 56 ± 11 yrs, alcohol: 167 [64.2%]) and from 155 healthy subjects were assayed for the presence of antibodies against filamentous actin [AAA IgA and IgG] and gliadin [AGA IgA and IgG]) and for intestinal fatty acid-binding protein (I-FABP) by ELISA. Association of gut failure markers with disease specific characteristics was assessed at baseline and the course of liver disease was evaluated in a 5-year follow-up observational study for decompensating events (ascites, variceal bleeding, hepatic encephalopathy and/or bacterial infection) and liver-related death. BT was assessed based on the presence of anti-microbial antibodies (anti-OMP Plus IgA and/or endotoxin core antibody IgA [EndoCab]).
Results: Elevated concentrations of IgA-AAA (62.7 vs. 4.4%) and IgA-AGA (27.7 vs. 2.6%) were more often observed in cirrhosis as compared to healthy controls ($p < 0.001$ for both). In addition, I-FABP was increased in cirrhosis as compared to controls (741 vs. 244 pg/mL, $p < 0.001$) and correlated with serum levels of IgA-AAA and IgA-AGA. IgA-AAA positivity was associated with alcoholic etiology, liver oriented scores and decompensated clinical stage (all $p < 0.001$). Serological markers of BT were more often found in patients with elevated IgA AAA compared to those without (72.3 vs. 13.5% for IgA-EndoCab and 85.2 vs. 20.5% for IgA anti-OMP, $p < 0.001$ for both). In patients with compensated disease stage ($n = 131$) the risk of decompensation was higher in patients with elevated IgA-AAA (HR [95%CI]: 1.85 [1.06–3.24]), as was the risk of liver-related mortality (HR: 2.66 [1.27–5.56]). Such associations were not observed for IgG-AAA and IgA/IgG-AGAs. In the overall cohort, IgA-AAA remained an independent predictor of liver-related death (HRadj: 1.96 [1.08–3.55]) when adjusting for important clinical variables (MELD score, etiology, clinical stage).



Mortality	HR	95% CI	P-Value
AAA IgA	1.96	(1.08-3.55)	0.026
MELD score	1.10	(1.03-1.16)	0.002
Etiology (alcohol)	0.74	(0.42-1.28)	0.283
Clinical stage	1.38	(0.85-2.23)	0.190
Age (>65)	1.44	(0.86-2.4)	0.165
Gender (female)	1.14	(0.73-1.79)	0.562

Conclusion: Presence of IgA antibodies against filamentous-actin indicate patients with an unfavourable outcome in cirrhosis, which may be related to intestinal damage beyond being related to bacterial translocation. IgA-AAA might be consider as a novel serologic marker of the disease progression.

SAT-453

The TIM3-Gal9 immune checkpoint axis is inter-linked with severity of Alcoholic Liver Disease

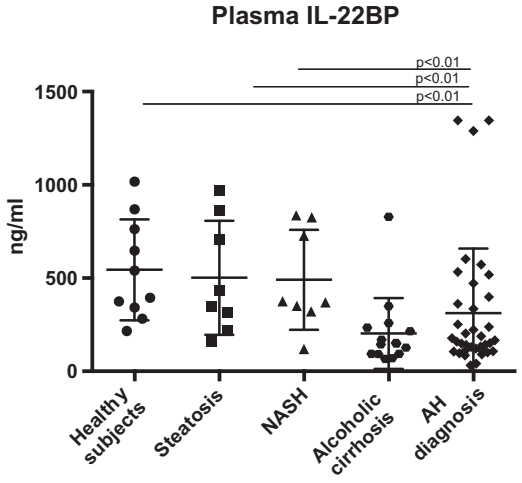
A. Riva[1,2], H. Adams[1,2], V. Patel[1,2], S. Azarian[1,2], G. Wright[3], S. Tarff[3], K. Katzarov[4], M. Simonova[4], T. Hadzhiolova[4], S. Pavlova[4], R. Williams[1,2], A. Evans[5], S. Chokshi[1,2]. *[1]Institute of Hepatology London, Foundation for Liver Research, London, United Kingdom; [2]Division of Transplantation, Immunology and Mucosal Biology, Faculty of Life Sciences and Medicine, King's College London, London, United Kingdom; [3]Department of Gastroenterology, Basildon University Hospital, Basildon, United Kingdom; [4]Department of Gastroenterology, Military Medical Academy, Sofia, Bulgaria; [5]Department of Gastroenterology, Royal Berkshire Hospital, United Kingdom*
Email: a.riva@researchinliver.org.uk

Background and Aims: Susceptibility to overwhelming bacterial infection represents a significant cause of mortality in alcoholic liver disease (ALD). T-cell immunoglobulin and mucin domain (TIM)3 is a well characterised immune checkpoint receptor that modulates the equilibrium between protective anti-pathogen immunity and host-induced immunopathology. We have previously shown (Markwick et al, Gastroenterology, 2015) that hyper-expression of TIM3 on adaptive T-cells suppresses antibacterial immunity in ALD and *in vitro* blockade can rescue impaired innate and adaptive immunity. However, the role of soluble (s)TIM3, its ligand Galectin(sGal)9 and other checkpoint receptors in antibacterial immunity and in ALD is unknown and is the aim of this study.
Method: We measured levels of soluble checkpoint receptors in plasma samples from patients with alcohol-related cirrhosis (ARC, Child-Pugh A/B/C, $n = 6/8/8$), severe alcoholic hepatitis (SAH, Maddrey's DF > 32, $n = 13$), alcohol-related acute-on-chronic liver failure (ACLF, $n = 6$, longitudinal) and healthy controls ($n = 13$) and correlated these findings with demographic and clinical characteristics. Receiver operating characteristic area under the curve analysis (AUROC) was used to investigate the discriminatory power of sTIM3 as a disease biomarker.
Results: Plasma sTIM3 was significantly different in patients and controls ($p < 0.0001$), with greater amounts in ARC ($p = 0.0004$), SAH ($p < 0.0001$) and ACLF ($p = 0.0065$) patients. sGal9 was also significantly higher in SAH vs. controls ($p = 0.0116$). Stratification of ARC patients according to Child-Pugh score (CP) indicated greater levels of sTIM3 in CP-C compared to CP-A or CP-B patients. Levels of sTIM3 in CP-C, SAH and ACLF patients were higher than controls ($p = 0.0004$, $p = 0.0003$, $p = 0.0156$ respectively). AUROC analysis for sTIM3 produced a value of 0.936 (95%CI 0.868–1.000, $p < 0.001$) and at a cut-off of 2427.053 pg/mL the discriminatory sensitivity and

specificity between ALD patients and controls were 90.2% and 88.5% respectively.
Conclusion: Our results show that the TIM3-Gal9 axis plays an important role in the pathogenesis of ALD and that sTIM3 represents a novel biomarker of disease severity.

SAT-454
Interleukin-22 binding protein in alcoholic hepatitis
S. Støy, T.L. Laursen, E. Glavind, B. Deleuran, H. Vilstrup, T.D. Sandahl. *Aarhus University Hospital, Hepatology and Gastroenterology, Aarhus, Denmark*
Email: sidsel.stoy@clin.au.dk

Background and Aims: In alcoholic hepatitis, interleukin (IL)-22 production in circulating immune cells is high and associated with improvement in the disease probably through aiding the anti-microbial defence and liver regeneration. Soluble IL-22 binding protein (BP) controls IL-22 bioactivity. A pathological IL-22BP up-regulation may thus block IL-22 anti-microbial and regenerative functions as seen in inflammatory bowl disease. However, IL-22BP knockout mice are more susceptible to acute liver injury and have delayed regeneration. This may point to more complex effects of IL-22BP on IL-22 functions. We investigated the plasma levels of IL-22BP in patients with alcoholic hepatitis, its association with disease outcome and how IL-22BP affects IL-22.
Method: We followed 39 patients hospitalized alcoholic hepatitis for 90 days after diagnosis. Controls were 15 patients with stable alcoholic cirrhosis, 15 healthy subjects, 8 patients with simple steatosis and 8 patients with non-alcoholic steatohepatitis. By ELISA, we measured plasma levels of IL-22BP, IL-22 and the IL-22 induced anti-microbial peptide lipocalin-2. Effects of IL-22BP on IL-22 gene induction in HepG2 cells were measured by qPCR.
Results: Plasma IL-22BP was reduced by 50% in patients with alcoholic hepatitis compared with the levels in all control groups but alcoholic cirrhosis patients (figure 1). Consistently, plasma IL-22 and lipocalin-2 were elevated in alcoholic hepatitis patients ($p < 0.05$). At diagnosis, plasma IL-22BP was negatively associated with Model of Endstage Liver disease ($r=-0.40$, $p = 0.02$). The patients who died before day 90 had lower IL-22BP plasma levels at diagnosis ($p = 0.16$) and this was significant at day 7 (mean(SD) dead: 115(42) ng/ml alive: 292 (221) ng/ml, $p < 0.05$). *In vitro,* IL-22BP dose-dependently inhibited the induction of lipocalin-2 in HepG2 cells by IL-22. Interestingly, IL-22BP also reverted the reduction of IL-22R expression in HepG2 cells induced by IL-22.



Conclusion: In alcoholic hepatitis low plasma IL-22BP is associated with increased mortality. This may be explained by diminished IL-22 signalling at low IL-22BP levels, as IL-22BP seems important for sustaining adequate IL-22R expression.

SAT-455
The bile acid biome and its relationship to the development and severity of alcoholic hepatitis
P. Puri[1], F. Mirshahi[2], S. Liangpunsakul[3], D. Crabb[3], V. Shah[4], G. Gores[4], P. Kamath[4], H. Malhi[4], M. Sikaroodi[5], S. Raedeva[6], P. Gillevet[5], N. Chalasani[3], A. Sanyal[2]. [1]*Virginia Commonwealth University, Division of Gastroenterology, Hepatology and Nutrition, Richmond, United States;* [2]*Virginia Commonwealth University, Gastroenterology and Hepatology;* [3]*Indiana University, Internal Medicine, Gastroenterology, Hepatology and Nutrition;* [4]*Mayo Clinic, Gastroenterology and Hepatology;* [5]*George Mason University, Microbiome Analysis Center;* [6]*The National Institute on Alcohol Abuse and Alcoholism, Bethesda*
Email: drppuri@yahoo.com

Background and Aims: The impact of alcohol consumption and development of alcoholic hepatitis (AH) on the intestinal microbiome, its associated changes in bile acid profile, and the relationship of such changes to the severity of AH are not known. Aims: (1) To characterize fecal BAs in AH subjects with moderate (MAH) and severe (SAH) disease compared to heavy drinking controls (HDC), and (2) To relate changes in fecal BAs with microbial ecology and disease severity.
Method: Three groups of subjects were studied: (1) controls without obvious liver disease who drank heavily (HDC), (2) MAH, and (3) SAH. AH was defined by NIAAA consensus criteria. Bile acids were measured by LC-MS and microbiota were assessed by 16S rRNA pyrosequencing. Pairwise, multiple group comparisons with correction of false discovery (q-value), and regression analyses were performed.
Results: 50 subjects (58% males, mean age 46 ± 12 years) were studied (HDC = 20, MAH = 8, SAH = 22). *Firmicutes Clostridia* was diminished and *Firmicutes Bacilli* was markedly increased in SAH vs. HDC (both $p = 0.0001$). *Firmicutes Clostridia* inversely correlated with total bilirubin ($r2 = 0.22$, $p = 0.0004$), alkaline phosphatase ($r2 = 0.13$, $p = 0.009$), MELD score ($r2 = 0.33$, $p < 0.0001$) and DF ($r2 = 0.22$, $p = 0.02$). While glycine conjugates of chenodeoxycholate and cholate as well as taurochenodeoxycholate were significantly increased in SAH vs. HDC (p-and q-values <0.05 for all), secondary BAs [deoxycholate (DCA), glyco/tauro-DCA, lithocholate (LCA), glyco-LCA, and urso-DCA) were noticeably decreased in SAH vs. HDC (p- and q-values <0.05 to <0.0001 for all). Notably, DCA and LCA directly correlated with *Firmicutes Clostridia* abundance ($r2 = 0.33$, $p < 0.0001$ for both). In univariate analysis, DCA and LCA were inversely correlated with increasing total bilirubin ($r2 = 0.21$ and 0.28, $p = 0.008$ and <0.0001, respectively) and alkaline phosphatase ($r2 = 0.12$ and 0.17, $p = 0.01$ and 0.002, respectively). Least square fit regression modeling showed that interaction of total bilirubin and alkaline phosphatase correlated with DCA ($r2 = 0.36$, $p = 0.003$) and LCA ($r2 = 0.45$, $p = 0.0007$).
Conclusion: (1) Cholestasis perturbs microbial ecology in SAH with depletion in protective commensal Clostridia. (2) Diminished Clostridia in cholestasis likely impairs deconjugation and dehydroxylation given increased fecal primary conjugated BAs and decreased deoxy- and lithocholate. These data support a role for the bile acid biome in the development and severity of alcoholic hepatitis.

SAT-456
Collagen proportionate área is an independent predictor of long term outcome in patients with alcoholic liver disease
M.G. Misas[1], A. Koutsoumarakis[1], Y. Huang[2], M. Thiele[3], A. Hall[4], C. Covelli[1], E. Buzzetti[1], L.I. Prat[1], D. Roccarina[1], S. Detlefsen[5], T.V. Luong[1], G. Jeffrey[2], M. Pinzani[1], E. Tsochatzis[1]. [1]*UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, United Kingdom;* [2]*School of Medicine and Pharmacology Australia, University of Western Australia, Nedlands, Western Australia, Australia;* [3]*Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark;* [4]*Sheila Sherlock Liver Centre, Royal Free London NHS Foundation Trust and UCL Institute for Liver and Digestive Health.*

University College of London, London, United Kingdom; [5]Department of Pathology, Odense University Hospital, Odense, Denmark
Email: martaguemi@gmail.com

Background and Aims: Quantitative fibrosis assessment with collagen proportionate area (CPA) measurement predicts clinical outcomes in patients with hepatitis C virus (HCV) infection and non-alcoholic fatty liver disease (NAFLD). We tested the ability of CPA to quantify fibrosis and predict clinical outcome in patients with alcoholic liver disease (ALD)
Method: We retrospectively included a cohort of patients, from two centers, with biopsy-proven ALD and long-term follow-up, irrespective of fibrosis stage and a contemporary cohort of patients with similar clinical features and available non-invasive fibrosis assessment with Fibroscan (FS) and shear wave Elastography (SWE). All patients with concomitant primary cause of liver disease were excluded. Clinical details and laboratory parameters were collected at biopsy time. Follow-up data were collected at the time of the last clinical follow-up or death. Hepatic decompensation and liver-related mortality were considered as the combined primary outcome. For CPA analysis, we captured images of liver biopsy sections stained with picro-Sirius red and used digital image analysis to measure collagen deposition areas at whole biopsy macro and x4 power magnification. CPA was calculated as a proportion of the collagen area of the whole parenchyma and expressed as a percentage
Results: We included 352 patients, 242 with long-term follow up and 110 in the contemporary cohort. 86 patients (34.8%) had at least one episode of hepatic decompensation and/or died during a median follow-up of 70.9 (IQR 244) months. CPA significantly correlated with fibrosis stage across the whole spectrum of fibrosis. High magnification CPA (CPA-high) was significantly higher than low magnification CPA (CPA-low) in stage F0-F2 but was similar in patients with significant fibrosis (≥F3). A CPA-low higher than 7.1 and a CPA-high above 9.3 had a sensitivity and specificity of 93.8%, 90.4% and 90.6%, 88%, respectively, to predict significant fibrosis (AUROC of 0.96 CPA-low and 0.95 CPA-high). Both CPA-low and CPA-high significantly correlated with liver stiffness as measured by FS and SWE ($r = 0.84$ and 0.85 for CPA-low, $r = 0.81$ and 0.80 for CPA-high). Presence of advanced fibrosis (OR 2.28, $p = 0.04$), abstinence (OR 0.4, $p = 0.001$) and CPA (CPA-low or CPA-high, OR 1.032, $p = 0.05$; OR = 1.033, $p = 0.03$ respectively) were independent predictors of hepatic decompensation and/or liver-related mortality in multivariable Cox-regression analysis
Conclusion: CPA is an independent predictor of clinical outcomes in patients with ALD and should be routinely measured in biopsy specimens

SAT-457

Hepatoprotective biomarkers, amphiregulin and soluble Fas, increase during ELAD treatment in alcoholic hepatitis subjects

P. Bedard[1], J. Lapetoda[1], L. Landeen[1], A. Al-Khafaji[2], A. Parikh[3], A. Duarte-Rojo[4], B. Borg[5], G. Mccaughan[6], L. Stein[7], L. Teperman[8], M. Allison[9], N. Shah[10], R. Subramanian[11], R. Malik[12], R. Brown[13], R. Macnicholas[14], S. Habib[15], S. Asrani[16], T. Adhami[17]. *[1]Vital Therapies, Inc., Research Cell Biology, San Diego, United States; [2]University of Pittsburgh Medical Center, United States; [3]Rutgers University, Medical School, United States; [4]University of Arkansas for Medical Sciences, United States; [5]University of Mississippi Medical Center, Jackson, United States; [6]Royal Prince Alfred Hospital, Australia; [7]Piedmont Atlanta Hospital, United States; [8]New York University, United States; [9]Cambridge University Hospital Addenbrookes, United Kingdom; [10]Rush University Medical Center, United States; [11]Emory University, United States; [12]Beth Israel Deaconess Medical Center, United States; [13]Columbia University Medical Center, United States; [14]Sir Charles Gairdner Hospital, Australia; [15]University of Arizona Medical Center, United States; [16]Baylor University Medical Center, United States; [17]Cleveland Clinic Foundation, United States*
Email: pbedard@vitaltherapies.com

Background and Aims: Hallmarks of alcoholic hepatitis (AH) are increased hepatocellular death, decreased liver function, and additional pro-inflammatory responses if necrotic cells are not removed. We previously reported that TL C3A cells release hepatocyte mitogens (amphiregulin [AR], TGF-α, and PDGF-BB) and can inhibit Fas-induced apoptosis in primary human hepatocyte cultures. This study links the hepatoprotective effects of AR and sFas assessed by in vitro studies with biomarker analysis of severe AH subjects' plasma from the VTI-208 Phase 3 trial conducted by Vital Therapies, Inc.
Method: VTI-208 subjects' plasma (11 Control, 14 ELAD) meeting VTL-308 Phase 3 trial criteria (<50 years, <2.5 INR, <1.3 mg/dL creatinine, <16 mg/dL bilirubin, <30 MELD score) were immunoassayed for AR and sFas at screen and study days 3, 5, 7, 14, and 28 and longitudinally analyzed by ANOVA ($p < 0.05$ significance). Additional comparisons were made of bilirubin (Bili) levels during the 5-day treatment period.
Results: Control and ELAD subjects in this pre-defined subset were not significantly different for demographics, number of organ failures, or concentrations of AR and sFas at screen. MELD scores were not clinically different at screen. AR and sFas levels in ELAD subjects were significantly increased vs screen levels during study D3, D5, and D7 ($p = 0.0003$, D3; $p = 0.043$, D5; $p = 0.027$, D7), and D3 ($p = 0.0012$), respectively (i.e. during ELAD treatment), suggestive of receiving a dose of these factors from the VTL C3A cells. Bili levels were significantly decreased in ELAD treated subjects at D3, D5, and D7 compared to both screen and control subjects.
Conclusion: Subjects on ELAD experienced increases in AR and sFas during treatment, with corresponding early changes in Bili levels, which others have previously shown to be prognostic of survival. These data suggest hepatoprotection occurs during ELAD treatment, perhaps by inhibiting apoptosis through epidermal growth factor receptor activation, competition for Fas ligand, or reducing oxidative stress, as was previously demonstrated using in vitro primary human hepatocyte models. These clinical biomarker data suggest that the observed improvement in 91-d survival in these pre-defined ELAD subjects is likely due to a multi-therapeutic approach via cell-based treatment.

SAT-458

The use of proton pump inhibitors among patients with alcoholic cirrhosis is not related with increased risk of death

U. Bang, F. Bendtsen. *University Hospital of Hvidovre, Gastrounit*
Email: ucb@dadlnet.dk

Background and Aims: There are speculations that the use of proton pump inhibitors (PPI) may be related with increased risk of death in patients with cirrhosis. The aim was to study the association between use of PPI and mortality in patients with alcoholic cirrhosis in a retrospective nationwide cohort.
Method: Patients with alcoholic cirrhosis (ICD-10 code K70.3) from 1994 to 2014 were identified. We used data from the Danish Prescription Database and patients with at least two claims of PPI were categorized as users of PPI. We used covariates and propensity score to match users of PPI with non-users on a 1:1 ratio. We used claims of opioids to determine a healthy adherer profile and address for healthy adherer bias. The cohort entry of the non-users was adjusted to account for immortal time bias. We report the mortality rate in deaths per 1,000 person-years and assessed differences in mortality using Cox regression.
Results: We identified a total of 24,752 patients with alcoholic cirrhosis of whom we excluded 1,763 due to cancer, 584 due to chronic viral hepatitis, 277 due to non-alcoholic fatty liver disease and 3,025 due to a follow-up time shorter than 30 days. Of the remaining 19,687, a total of 6,114 had a history of opioid claims and were eligible for propensity score matching. The final propensity score matched cohort consisted of 2,592 patients. The mean age was 56 (SD 10) years at cohortentry, and we found 35% being females, 14% still working, 66% retired, 82% used diuretics during follow-up, and

16% used non-specific beta-blockers. We found a slightly lower prevalence of admission due to alcohol for the non-users compared with the users of PPI (49% vs. 57%, p = 0.0002). We found that 69% of the PPI users and 70% of the non-users died during follow-up with mortality rates of 132 (95%CI 123–141) and 130 (95%CI 122–139), respectively. No difference in mortality rate between PPI users and non-users was found (HR 1.0; 95%CI 0.9–1.1, p = 0.9) (Figure).

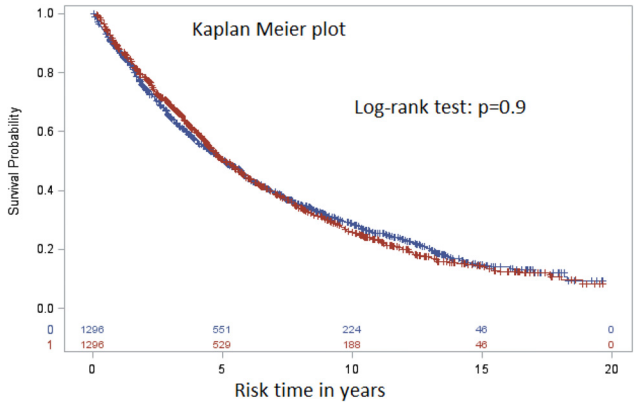


Figure: Kaplan-Meier plot of mortality of patients with alcoholic cirrhosis stratified into user and non-users of proton-pump inhibitor.

Conclusion: This is the first nationwide study of the use of PPI and mortality and we did not find any association between the use of PPI and changes in mortality. We conclude that the use of PPI is safe however we cannot exclude harmful effects in subgroups, which need to be explored further.

SAT-459

miRNA regulation of macrophage M1/M2 polarization of Kupffer cells and PBMCs in alcoholic liver disease

A. Kim, P. Saikia, M. Mcmullen, R. Mccullough, L. Nagy. *Cleveland Clinic, Pathobiology*
Email: kima7@ccf.org

Background and Aims: Alcoholic hepatitis (AH) is an inflammatory condition that leads to increased short-term morbidity among people with alcoholic liver disease (ALD). In response to chronic ethanol, Kupffer cells, the resident macrophage of livers, become sensitized to bacterial lipopolysaccharides (LPS) and express more pro-inflammatory cytokines. Additionally, chronic LPS stimulation leads to increased pro-inflammatory/M1 polarization of macrophages. We recently discovered that 35kD hyaluronic acid (HA35) decreased sensitivity to LPS in Kupffer cells from chronic ethanol-fed rats. Here we use miRNA sequencing to understand the regulation of M1 polarization in AH and a potential role for HA35 in promoting anti-inflammatory M2 polarization. Additionally, we tested PBMCs from AH patients to explore HA35 as a potential therapeutic for inflammation caused by ALD.
Method: Kupffer cells were isolated from male rats fed a chronic Lieber-Decarli diet or pair-fed control diet. Cells were plated then exposed to +/–HA35 for 5 hours or 24 hours and then +/–LPS for 1 hour. We then isolated small RNAs, generated libraries, and sequenced using an Illumina HiSeq. We used Bowtie to align reads and EdgeR to calculate differential expression. PBMCs were also isolated from AH patients with a MELD score >20 and healthy controls then treated similarly with HA35 and LPS.
Results: Differential expression analyses revealed 105 misregulated miRNAs in Kupffer cells from the chronic ethanol-fed rats compared to pair-fed (FDR < 0.2). 39/105 miRNAs clustered in 9 distinct regions of the genome. Each cluster contained at least 3 differentially expressed miRNAs, where 8/9 clusters had decreased expression in chronic ethanol. Three downregulated clusters contained miRNAs with known roles in M2 polarization, including miR125a, let-7c, miR221, and miR222. Treatment with HA35 for 5 hours lead to increased Arg-1 and decreased iNOS expression, indicating a potential anti-inflammatory effect. This result was supported by decreased expression of CD86 (M1 marker) and increased expression of CD206 (M2 marker) after 24 hours of HA35 treatment. PBMCs from AH patients, compared to healthy controls, were protected from LPS stimulation after pre-treatment with HA35. Preliminary results indicated increased expression of M2 polarization markers after long term HA35 treatment, including CD206 and CD23.
Conclusion: We hypothesize that increased M1 polarization of Kupffer cells after chronic ethanol is caused by global repression of miRNAs associated with M2 polarization. Kupffer cells isolated from chronic ethanol-fed rats displayed lower expression of a number of M2 associated miRNAs, but HA35 decreased the pro-inflammatory effect of LPS and increased M2 polarization. HA35 also reduced the effect of LPS in PBMCs from AH patients. Together, these data support HA35 as a potent anti-inflammatory therapy in ALD.

SAT-460

The correlation of obesity with morbidity and mortality in alcoholic hepatitis

Y. Yasiralazzawi, Y. Al-Abboodi, D. Devuni, G. Szabo. *Umass medical center, Gastroenterology, Worcester*
Email: yasiralazzawi@gmail.com

Background and Aims: The incidence of alcoholic hepatitis (AH) in the USA has increased and it is associated with significant morbidities and mortality, that increase paralleled with an increase in the obesity numbers. The correlation of the obesity and the outcomes in patients with AH have not been well studied. Our aim is to study the morbidities (acute kidney injury (AKI), hepatic encephalopathy (HE), spontaneous bacterial peritonitis (SBP) and pneumonia) and the mortality in the obese and non-obese patients with AH.
Method: We used in the National Inpatient Sample (NIS) dataset with the primary diagnosis of AH and we divided the cohort into two groups obese vs non-obese. ICD-9 codes for SBP, AKI, HE, pneumonia and death were used. Obesity defined in the data as body mass index of ≥30.
Multivariate logistic regression statistical test (SPSS softwere) is used to compare the odd ratio of mortality and inpatient morbidity between the two groups.
Results: The NIS 2009 included 18834 patients with AH and we divided the patients into two groups based on their BMI, 952(5%) were obese (BMI ≥ 30) vs 17882 (95%) were non-obese (BMI < 30). Male represented 70% of the cohort while Caucasian race represented 71% of the cohort.
The obese group was found to have more infections when compared to the non-obese group. Pneumonia was found in 6.7% of the obese group and in 5.3% of the non-obese group while SBP was found in 1.5% of the obese group and in 1.3% of the non-obese group. AKI and HE were also reported more frequent in the obese group as AKI was found in 19.5% of the obese group and in 13.5% of the non-obese group while HE found in 14.2% of the obese group and in 10.7% of the non-obese group.
Upon comparison between the two groups, the risk of the infections was not different between the two groups but the risk of AKI was higher in the obese group with an OR of 1.5 (P < 0.0001). The risk of HE in obese group was 1.3 times higher than the non-obese group (P = 0.001) and the mortality rate was significantly higher in the obese group when compared with the non-obese group with OR of 1.5 (P = 0.006).
Conclusion: Obesity is associated with increased morbidity and mortality rate in AH patients when compared to non-obese patients. Obesity is a risk factor for AKI and hepatic encephalopathy in patients with AH.

Table 1:

Age	48+/−18
Race:	Percentage
White	71.8%
African-American	12.3%
Hispanic	11.2%
Asian	1%
Native American	1%
Others	2.5%
Sex:	
Male	70%
Female	30%
Alcoholic hepatitis:	18834
Obese	952(5%)
Non-obese	17882 (95%)

Table 2:

Complications of alcoholic hepatitis	Obese group	Non obese group	Odd ratio	CI 95%	P-Value
Pneumonia	64 (6.7%)	942 (5.3%)	1.2	0.9–1.6	0.52
Hepatic encephalopathy	135 (14.2%)	1919 (10.7%)	1.3	1.1–1.6	0.001
Acute kidney injury	186 (19.5%)	2406 (13.5%)	1.5	1.3–1.8	0.000
Spontaneous bacterial peritonitis (SBP)	14 (1.5%)	241 (1.3%)	1.09	0.6–1.8	0.74
Mortality	54 (0.2%)	692 (3.6%)	1.5	1.1–1.9	0.006

SAT-461

Serum metabolic profiling for the identification of patients with severe alcoholic hepatitis

A. Horhat[1], P. Fischer[2], H. Corina[3], R. Ioana[4], C. Camelia[5], M. Tantau[6], C. Socaciu[7], B. Procopet[6], S. Horia[8]. *[1]Regional Institute of Gastroenterology and Hepatology "Octavian Fodor", Cluj-Napoca, Romania, Hepatology Department, Cluj-Napoca, Romania; [2]University of Medicine and Pharmacy "Iuliu Hatieganu", University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania; [3]Center for Applied Biotechnology BIODIATECH, Cluj-Napoca, Romania; [4]University of Medicine and Pharmacy "Iuliu Hatieganu", Pathology Department, Cluj-Napoca, Romania; [5]University of Medicine and Pharmacy "Iuliu Hatieganu", Research Center for Functional Genomics and Translational Medicine; [6]University of Medicine and Pharmacy "Iuliu Hatieganu", Gastroenterology and Hepatology, Cluj-Napoca, Romania; [7]Center for Applied Biotechnology BIODIATECH, Applied Biotechnology in Diagnostic and Molecular Therapy; [8]Regional Institute of Gastroenterology and Hepatology "Octavian Fodor", Hepatology Department, Cluj-Napoca, Romania*
Email: adelinahorhat@yahoo.com

Background and Aims: Severe alcoholic hepatitis (SAH) bares high mortality and morbidity rates, as well as high healthcare costs. Although serum biomarkers are available, its diagnostic relies on liver biopsy. Furthermore, the differential diagnosis between SAH and decompensated cirrhosis (DC) is impossible taking into account clinical and biological changes. In both conditions development of infections is common, leading to further impairment of hepatic function, complications, and increased mortality.
The aim of the study was to assess the metabolic phenotype of patients with severe alcoholic hepatitis and to identify potential biomarkers to differentiate SAH from DC.
Method: Seventy patients with biopsy proven SAH (Maddrey Discriminant Function ≥32) and 112 DC patients. Untargeted semiquantitative LC-MS based metabolomic analysis was performed using Thermo Scientific UHPLC UltiMate 3000 system and a Bruker Daltonics MaXis Impact MS detection equipment. After the chromatograms' analysis 3000–4000 molecular masses were identified. The matrix was further analyzed through univariate and multivariate statistical analysis using MetaboAnalyst3.0.
Results: Twelve potential biomarkers were identified. Of the five metabolites with increased levels in SAH, 2-Hydroxyglutarate (HG) (1.6063 fold change, $p = 1.6*10^{-23}$) and 12-Oxo-20-trihydroxy-leukotriene B4 (3OH-LTB4) (2.0671 fold change, $p = 5.23*10^{-12}$) were the most upregulated. Of the seven metabolites with decreased thresholds in SAH, 1,3,7-Trimethyluric acid (TMUA) (1.2289 fold change, $p = 2.9*10^{-7}$) was the most significant one. All three metabolites showed a very good accuracy for differentiation between SAH and DC (AUCs of 0.96 [95%CI: 0.926–0.991], 0.86 [95%CI: 0.796–0.913] and 0.84 [95% CI: 0.765–0.916], respectively).
In the subgroup of patients without infection (42 with SAH and 74 DC), decanoylcarnitine (10-OC) was significantly higher in SAH patients (0.96 fold change, $p = 2.57*10^{-4,}$ AUC= 0.73 [95%CI: 0.616–0.828]) compared with DC.
Conclusion: Alcoholic hepatitis appears to have a different metabolic profile compared with decompensated cirrhosis, in general and in the absence of infection. The identified metabolites (HG, 3OH-LTB4, TMUA and 10-OC) are involved in beta and omega oxidation of lipids, showing the importance of these pathways in the pathogenesis of SAH.

SAT-462

Persistence of decompensation despite long-term abstinence in alcoholic cirrhosis is associated with poor outcomes and lower survival

A. Clemente[1], D. Rincón[1,2,3], C. Martínez[1], C. Villaseca[1], E. Cervilla[1], M. Romero[1], A.M Matilla[1,2], R. García[1,2], G. Clemente[1,2], R. Bañares[1,2,3]. *[1]Hospital General Universitario Gregorio Marañón, Liver Unit, Madrid, Spain; [2]CIBERehd, Madrid, Spain; [3]Universidad Complutense, Madrid, Spain*
Email: ana.clemente@salud.madrid.org

Background and Aims: Alcohol withdrawal is a main prognostic factor in alcoholic cirrhosis. However, it has not been explored whether the effect of abstinence (>6 months) is homogeneous along the whole spectrum of the disease. Aim: to analyse if abstinent patients who remain decompensated have a worse evolution compared to viral or non-abstinent alcoholic ones.
Method: 190 decompensated patients consecutively admitted to our Liver Unit were included (viral n = 106; abstinent n = 54; non-abstinent n = 30). Patients with suspected or confirmed alcoholic hepatitis were excluded. Baseline and epidemiologic features were compared by ANOVA. Kaplan Meier curves were used to compare survival among the groups.
Results: Median age, 59 years (36–87). Male: 74%. MELD score was significantly higher in abstinent alcoholics (16 Vs 12 in active alcoholic and 11 in viral, p = 0.002). Abstinent patients had higher leukocyte count at admission than non-abstinent and viral (8.9×10^3 Vs 8.2×10^3 Vs 6.5×10^3, p = 0.004). CRP was also higher in abstinent patients (3.2 Vs. 2.2 in both non-abstinent and viral patients, p = 0.1). Previous ascites or encephalopathy was more frequent in abstinent patients (76% Vs 60% Vs 60%;p = n.s, and 45% Vs 23% Vs 26%;p = n.s). Bacterial infection and reason for admission were similar among all groups. ACLF at admission was more frequent in abstinent patients (35% Vs 11% in non-abstinent and 8% in viral, p = 0.004). 1-year survival was higher in active alcoholic than in abstinent ones with a trend towards statistical significance (Figure 1, Log-Rank 0.19, Breslow 0.091). No statistically significant differences were found in the proportion of patients who received liver transplantation during follow-up (5.3% non-abstinent Vs 24% abstinent Vs 19% viral, p = n.s). We made a case-control sub-study including 30 patients per group, matched by MELD and age. 1-year survival was similar among all groups (Log-Rank 0.770). MELD (HR 1.04, p = 0.036), age (HR 1.03, p = 0.001) and CRP (HR 1.07, p = 0.04) were found as independently predictive variables of survival.

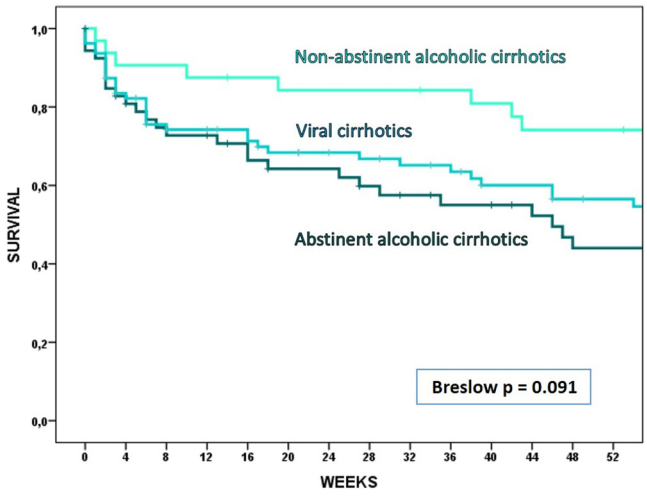


Figure 1:

Conclusion: Alcoholic cirrhotic patients who remain decompensated despite long-term alcohol withdrawal seem to have a worse prognosis as compared to non-abstinent alcoholic or viral cirrhotics due to a more advance disease in spite of etiological treatment. Therefore, this subgroup of patients could benefit from more intensive management as well as prioritization strategies on liver transplant list.

SAT-463

Corticosteroid treatment is associated with a resolution of altered CD4+ T cell phenotype in patients with severe alcoholic hepatitis

A. Dhanda[1,2], E. Yates[1], M. Cramp[1,2]. [1]*Plymouth University, Hepatology Research Group, Plymouth, United Kingdom;* [2]*Plymouth Hospitals NHS Trust, South West Liver Unit, Plymouth, United Kingdom*
Email: ashwin.dhanda@nhs.net

Background and Aims: Severe alcoholic hepatitis (SAH) is an acute inflammatory condition leading to liver failure and death in 30% of patients within 90 days. Corticosteroids have a proven short-term survival benefit but non-responders have the highest mortality. *In vitro* lymphocyte steroid sensitivity predicts 90-day outcome and $CD4^+$ T cell subsets are most resistant. We therefore hypothesised that $CD4^+$ T cells would have altered phenotype and response to corticosteroid treatment in non-responders. We examined $CD4^+$ T cell cytokine expression in patients with SAH before and after corticosteroid treatment.

Method: Consecutive patients with SAH, defined as recent onset jaundice with bilirubin >80 µmol/l in heavy alcohol drinkers (>60 g or 80 g ethanol/day in females and males respectively) with DF >32, were recruited. All patients were treated with prednisolone for 28 days after exclusion or adequate treatment of infection. 90-day outcome was recorded. Blood was taken at baseline and on day 7 of corticosteroid treatment and $CD4^+$ T cells were isolated by negative selection. T cells were cultured for 4 days with anti-CD3/CD28 T cell receptor stimulation before intracellular cytokine expression was quantified by flow cytometry.

Results: 30 patients were recruited (13 male; mean age 52, baseline DF 69). 90-day mortality was 20%. Baseline IL-10 was higher in non-survivors than survivors (2.4% v 1.5% of $CD4^+$ T cells; $p = 0.02$) but IL-17 and interferon gamma (IFNg) expression was similar. There was reversal of IL-10/IL-17 ratio in non-survivors compared to survivors (1.2 v 0.6; $p = 0.04$). On day 7 of corticosteroid treatment, all but 1 patient had an enhanced response to T cell receptor activation with greater IL-17 expression compared to baseline (1.6% v 12.6%; $p = 0.01$). However, cytokine expression (IL-17, IFNg or IL-10) at day 7 was not associated with 90-day survival. IL-10/IL-17 ratio was significantly lower than at baseline (0.9 v 0.1; $p = 0.01$) but was not associated with outcome.

Conclusion: These data suggest that $CD4^+$ T cells from patients who die from SAH have an altered phenotype favouring suppression of inflammation. Corticosteroid treatment enhances $CD4^+$ T cell cytokine expression and reverses the IL-10/IL-17 ratio but does not reveal any association with outcome. Therefore, initial immune dysfunction may predict outcome in SAH but steroid non-response in these patients is not completely explained by changes in T cell phenotype.

SAT-464

Morphometrical quantification of fibrosis correlates with clinical cirrhosis stage and predicts long-term survival in patients with alcoholic liver disease

K. Lackner[1], L. Binder[2], F. Rainer[2], R.E. Stauber[2]. [1]*Medical University of Graz, Institute of Pathology, Graz, Austria;* [2]*Medical University of Graz, Department of Internal Medicine, Graz, Austria*
Email: rudolf.stauber@medunigraz.at

Background and Aims: Histological subclassification of cirrhosis may allow definition of fibrosis stages with different clinical severity and prognosis. However, the value of histological staging is limited by intra- and interobserver variability. We therefore aimed to determine the relationship between morphometrically quantified fibrosis measured as collagen proportionate area (CPA) and clinical cirrhosis stages and long-term survival in patients with alcoholic cirrhosis.

Method: Liver biopsies of 149 consecutive patients with alcoholic liver disease (ALD), without other cause of liver disease were studied. CPA was quantified using TissueStudio® software (Definiens™). In addition, fibrosis was staged semiquantitively using the clinical research network (CRN) and Laennec systems. Clinical cirrhosis stages at the the time of liver biopsy were determined according to D`Amico. Complete follow up and outcome data were available from all patients.

Results: Mean CPA values progressively increased with Laennec fibrosis stage and correlated with clinical D`Amico stage ($p < 0.001$). Based on ROC analysis a CPA cut-off of 35% was found optimal for discrimination of prognosis. Patients with CRN stage ≥3 and CPA >35% had significantly worse 5-year survival than patients with CPA <35% ($p = 0.035$) whereas Laennec stage was not associated with survival ($p = 0.294$).

Conclusion: These findings suggest that morphometrical subclassification yields two cirrhosis stages with distinct clinical outcomes. CPA measurements may favorably substitute for semiquantitative histological fibrosis staging in ALD avoiding intra- and interobserver biases which limit the utility of conventional histological fibrosis staging.

SAT-465

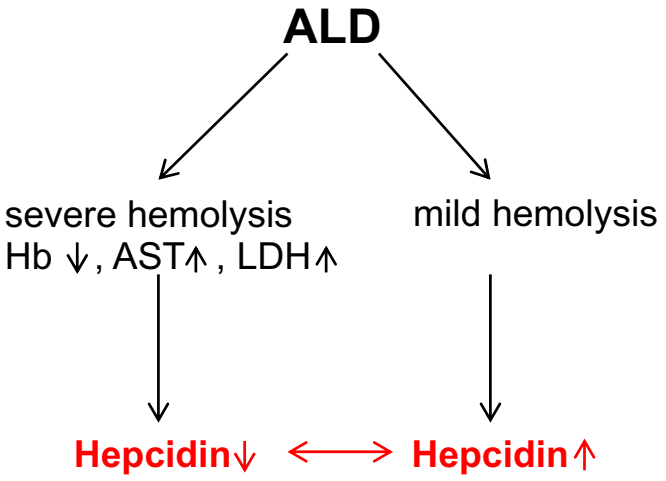
Masked hemolysis as novel factor contributing to hepatic iron overload in ALD

V. Rausch[1], I. Silva[1], T. Peccerella[2], S. Mueller[1]. [1]*Center for Alcohol Research and Salem Medical Center, University of Heidelberg, Heidelberg, Germany;* [2]*Salem Medical Center and Center for Alcohol Research and Liver Disease, University of Heidelberg, Heidelberg, Germany*
Email: vanessa.rausch@uni-heidelberg.de

Background and Aims: Patients with alcoholic liver disease (ALD) develop in ca. 50% prognostically unfavourable hepatic iron overload (HIO) and anemia, however, the underlying molecular mechanisms and the role of the systemic iron masterswitch hepcidin are poorly understood. Herein, we identify hemolysis as novel factor in disrupting hepcidin regulation and eventually causing HIO.

Method: Iron-related parameters, hepcidin (mRNA and serum levels), molecular and laboratory markers were studied in a large cohort of Caucasian heavy drinkers (n = 831, age range 22–87 years, mean alcohol consumption 192 g/day). Severe and mild hemolysis was further studied *in vivo* in age-matched C57BL/6 mice using two different phenylhydrazine (PHZ) treatment regimens. Histology, iron stain, mRNA and protein expression were studied both in liver and

spleen. An erythophagocytosis model (oxidized red blood cells co-cultivated with differentiated human THP-1 macrophages) was finally used to recapitulate *in vivo* findings and to analyse the underlying mechanisms *in vitro*.
Results: Indirect evidence for hemolysis (anemia, high ferritin, high LDH, high MCV) as cause for HIO was found in 16.4% of a large population of heavy drinkers. Notably, further indicators of hemolysis (haptoglobin, vitamin B12, folic acid) were not significantly changed most likely due to impaired liver synthesis in Alcoholics. Despite higher ferritin levels as compared to controls, hepcidin was not adequately upregulated in the hemolysis group suggesting a suppressive effect of hemolysis. We next recapitulated suppression of hepcidin in a murine model of severe PHZ-induced hemolysis. PHZ induced severe anemia, elevated transaminases, transferrin saturation and LDH within 24 hours. In the same time period, hemoxygenase 1 was highly induced while hepcidin was significantly lowered by 50%. Histology confirmed an increased number of phagocytosed erythrocytes in the spleen and iron-loaded Kupffer cells in the liver. In contrast, the mild hemolysis model strongly upregulated hepcidin mRNA. We finally study *in vitro* the process of erythrophagocytosis in human primary macrophages exposed to oxidized red blood cells. In confirmation of the *in vivo* findings, hepcidin showed also a concentration-dependent biphasic response. At physiological low levels of oxidized erythrocytes as found as normal age-mediated turnover, hepcidin was induced while it was strongly suppressed at higher pathological levels of oxidized erythrocytes.



Conclusion: Our data suggest that suppression of hepcidin by masked hemolysis seems to be an important mechanism leading to hepatic iron overload in patients with ALD.

SAT-466
Use of rifaximin in alcoholic hepatitis: Pilot study
C. Jimenez[1], M. Ventura[2], M. Sala[3], N. Cañete[4], M. Poca[5], M. Simón-Talero[1], J. Altamirano[1], R. Bataller[2], V.M.V. Blasco[1]. *[1]Hospital Vall d'Hebron, Liver Unit, Barcelona, Spain; [2]University of Pittsburgh Medical Center., Division of Gastroenterology, Hepatology, and Nutrition; [3]Hospital Germans Trias i Pujol, Gastroenterology Unit, Barcelona; [4]Hospital del Mar, Hepatology, Barcelona; [5]Hospital de la Santa Creu i Sant Pau, Gastroenterology Deparment, Barcelona*
Email: cesarjim14@hotmail.com

Background: Rifaximin (RFX), a non-absorbable oral antibiotic can reduce bacterial overgrowth and bacterial translocation in patients with liver disease.
Aims: To know if addition of RFX to the treatment of patients with alcoholic hepatitis (AH) is safety, can reduce bacterial infections, other complications and mortality at 90 days.
Method: In this multicenter pilot study, 24 consecutive severe AH patients (discriminant function of Maddrey >32) were recruited. They received 1200 mg/day of RFX in addition to standard steroid treatment. Finally, 19 patients were included (5 patients were withdrawn because of infection at admission). Results were compared with a prospective collected historical cohort (HC) of patients with AH paired by MELD (INTEAM cohort). The main variable to evaluate was the presence of bacterial infections at 90 days. Secondary variables to evaluate were safety of RFX, complications (renal failure, hepatic encephalopathy, gastrointestinal bleeding, liver failure) and death at 90 days. Clinical and biochemical variables, decrease of bilirubin (-Δ bili) and decrease of MELD (-Δ MELD) were evaluated at 7 and 90 days, respectively.
Results: In the rifaximin group (RG), 15 patients were male. The basal MELD was 22 ± 4 and basal bilirubin 13.7 ± 8.8 mg/dL; 15 patients had F3-F4 in liver biopsy. In the HC, basal MELD was 23 ± 6 and basal bilirubin 14.6 ± 8.7 (p = ns). Eight infections were observed in 4 patients of the RG while 7 infections were observed in 6 patients of the HC (p = ns). During the 90 days of follow up, there were 3 non-infectious complications in 3 patients of RG compared to 10 complications presented by 8 patients in the HC (p = ns). The overall 90-day mortality was 16% (3 patients) in RG and 47% (9 patients) in HC (p = 0.081). One patient died due to infection in the RG *vs* 5 patients in the HC. At day 7, a decrease in bilirubin was observed in 17 out of 19 patients in RG vs 8 out of 19 in HC (p = 0,006); the (−Δ Bili) was 8.71 mg/dl vs −4.32 mg/dl in the HC (p = 0.043). At day 90, the (−Δ MELD) was 6.7 in RG *vs* 4.7 in the HC (p = ns). No one adverse effect was attributable to RFX.
Conclusion: In this pilot study, we didn't observe a significant decrease of infections with the addition of rifaximin. RFX was a safe and well tolerated in patients with AH. A trend towards lower overall mortality and a significant decrease in bilirubin levels was observed in RG patients. These findings could support a certain beneficial effect of RFX.

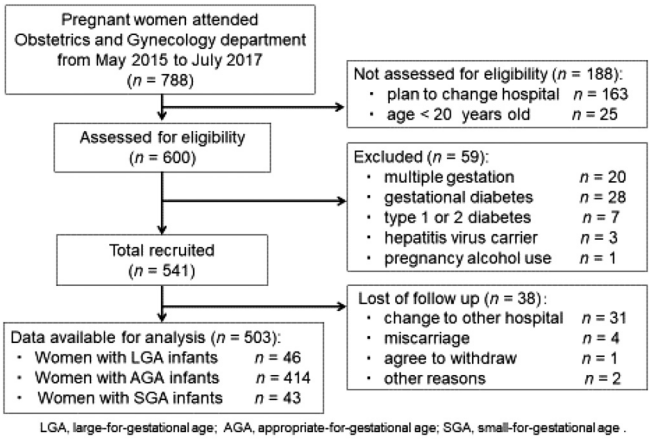
NAFLD: Clinical aspects except therapy

SAT-471
Maternal dietary patterns and the risk of large-for-gestational age births
S. Minato[1,2], N. Sakane[2], I. Hayashi[1,2], M. Suzuki[2], Y. Nose[1,2], S. Nirengi[2], N. Nagai[1]. *[1]University of Hyogo, Graduate School of Human and Environmental Science; [2]National Hospital Organization, Kyoto Medical Center, Division of Preventive Medicine, Clinical Research Institute*
Email: ne16i004@stshse.u-hyogo.ac.jp

Background and Aims: Large-for-gestational age (LGA) births is associated with an increased risk of pediatric obesity and non-alcoholic fatty liver disease (NAFLD). NAFLD is frequently first identified by elevated serum alanine aminotransferase (ALT). Elevated ALT levels in pregnant women are associated with an increased risk of LGA births. However, there is limited evidence on the association between the maternal dietary patterns and LGA. We aimed to identify the maternal dietary patterns among Japanese pregnant women that associated with an increased risk of LGA births.
Method: This case-control study enrolled pregnant women with LGA or appropriate-for-gestational age (AGA) infants attending our hospital from 26-5-2015 to 25-10-2017. LGA was defined as birthweight >90th percentile for gestational age. Exclusion criteria were as follows: multiple gestations, diabetes mellitus (DM), gestational DM, hepatitis virus, and alcohol use in pregnancy. We collected information on maternal diet using a food frequency questionnaire at three time points: first, second, and third trimester.

Maternal ALT levels were measured in the third trimester. In addition, to investigate whether genetic background acts as a related factor of LGA births, PNPLA3 polymorphism (rs738409) and microsomal triglyceride transfer protein (MTP) polymorphism (rs1800591) were determined using ABI PRISM 377 DNA sequencer. Maternal baseline characteristics were compared between the LGA and AGA groups with statistical analysis of Student's t-test and chi-square test or Fisher exact test. A two-tailed $P < 0.05$ was considered statistically significant.

Results: Of 541 recruited pregnant women, we identified 46 women with LGA infants and 414 women with AGA infants. The dropout rate was 7.0%. The maternal body weight gain during pregnancy, log-transformed ALT levels and total energy intake at third trimester were significantly higher in the LGA group than in the AGA group. The intake of low-fat dairy products per 1,000 kcal of energy intake in the LGA group was significantly lower than that in the AGA group. In addition, rates of keeping in mind eating vegetable and fish in the LGA group were significantly lower than in the AGA group. There were no differences in glucose levels, maternal age, pre-pregnancy body mass index, genotype and allele frequency of PNPLA3 and MTP, and intake of normal- and high-fat dairy products between the two groups.



LGA, large-for-gestational age; AGA, appropriate-for-gestational age; SGA, small-for-gestational age .

Figure . Pregnant women recruitment and follow-up flow diagram.

Conclusion: These findings suggest that some maternal dietary patterns are associated with an increased risk of LGA births. Further studies will be required to clarify these issues in the future.

SAT-472

Impact of short term weight loss (very low calorie diet vs bariatric surgery) on hepatic insulin resistance and plasma lipidomic profile

C. Barbieri[1], F. Carli[1], M. Gaggini[1], A. Iaconelli[2], A. Veneziani[2], F. Rubino[3], G. Mingrone[2], A. Gastaldelli[1]. *[1]Institute of Clinical Physiology, CNR, Pisa, Italy, Cardiometabolic Risk Unit; [2]Catholic Univeristy, Department of Internal Medicine, Rome, Italy; [3]King's College, Division of Diabetes and nutritional Sciences, Bariatric and Metabolic Surgery, London,*
Email: amalia@ifc.cnr.it

Background and Aims: Bariatric surgery (BS) is associated with a fast weight loss not only in adipose tissue but also in the liver and it is considered as a possible treatment for obese patients with NAFLD. RYGB in particular is associated with a fast metabolic improvement. We have shown that insulin resistance (IR) especially in the liver (Liver-IR) is reduced already 1-week after surgery. A recent report in diabetic rats reported that 3 days of very low caloric intake (VLCI) are sufficient to change liver lipidomic profile. Thus, we tested if improvement in Liver-IR after 1-week of either VLCI or BS was associated with a better lipid metabolism in the liver reflected by the improvement in plasma lipidomic profile.

Method: The cohort comprised 20 morbid obese non-diabetic patients (BMI = 44.2 ± 0.7 kg/m^2). Subjects were admitted twice to the hospital to measure hepatic, adipose tissue and muscle IR by stable isotope tracer infusion during fasting and during a hyper-insulinemic euglycemic clamp (HE-Cl). The first time patients were studied at baseline and 1-week after VLCI (600 kcal/day). Approximately 3-months later patients were admitted again for bariatric surgery, gastric banding LAGB (n = 10) or bypass RYGB (n = 10), and IR was evaluated one week after surgery. In all subjects we measured endogenous glucose production (EGP), lipolysis (RaGlycerol), peripheral (M/I), hepatic (Liver-IR = (EGP•Ins)) and adipose (Adipo-IR = (RaGlycerol•Ins)) insulin resistance and lipidomic profile (triacylglicerol (TAG), diacylglycerol DAG, lysophosphatidylcholine (LysoPC), phosphocholine (PC) end ceramide (Cer) by LC-MS QTOF).

Results: After 1-week of VLCI, patients lost 2.1 kg without significant changes in Hep-IR, Adipo-IR, M/I or DI. RYGB and LAGB led to greater weight loss, (5.5 and 5.2 kg) and significant improvement in Liver-IR, EGP and lipolysis. Only RYGB improved also Adipo-IR and M/I.
After 1-week of either VLCI or BS circulating triglyceride concentrations were unchanged (from 150 mmg/dl to 149 to 129 mg/dl, p = ns). Despite an improvement in Liver- and Adipo-IR after VLCI or BS, the plasma lipidomic profile was unaltered (in average DAG 1.35%, Cer 0.54%, LysoPC 33.85%, PC 44.22% and TAG 20.03%; after VLCI = DAG 1.39%, Cer 0.54%, LysoPC 32.27%, PC 44.97%, and TAG 20.84%; after BS = DAG 1.95%, Cer 0.51%, LysoPC 34.30%, PC 43.07% and TAG 20.18%). The changes in inflammatory markers were mild and similar in RYGB and LAGB.

Conclusion: The hepatic effects of BS on the liver IR of non diabetic morbid obese subjects are visible already 1-week after surgery and independent of caloric intake; in general the effects were more pronounced after RYGB than LAGB, but 1-week was not sufficient to observe a significant change in plasma lipidomic profile.

SAT-473

Substantial healthcare utilization (HCU) and costs among non-alcoholic steatohepatitis (NASH) patients with comorbid diabetes mellitus (DM): Real-world analysis of 2007–2015 US Medicare data

S.C. Gordon[1], S. Li[2], Y. Peng[2], X. Wang[2], R. Wong[3]. *[1]Henry Ford Hospital, Detroit, United States; [2]Chronic Disease Research Group, Minneapolis; [3]Highland Hospital, Oakland, United States*
Email: sgordon3@hfhs.org

Background and Aims: DM is a known risk factor for NASH. Data on HCU and costs in NASH patients with compensated cirrhosis (CC) by DM status is lacking. This study aimed to evaluate the impact of concurrent DM on HCU and costs among NASH patients with CC.

Method: The study population was extracted from 2007–2015 US Medicare 20% sample data and included NASH/Non-Alcoholic Fatty Liver Disease (NAFLD) patients (identified via ICD codes) with CC aged ≥18 years. First CC diagnosis date marked the index date. Patients with viral hepatitis, HIV, alcoholism or alcoholic liver disease, toxic liver disease, Wilson's disease, autoimmune hepatitis, biliary cirrhosis, gaucher + LAL-D, sclerosing cholangitis, hemochromatosis were excluded. Comorbidities were defined during the 6 months pre-index period (pre). HCU and costs were analyzed during the 6 months pre- and post-index period (post), and adjusted to per patient (PP) annual values in 2015 USD.

Results: The cohort included 3,775 NASH/NAFLD CC patients with mean age 67.0 (± 10.9) years and 63.3% females. More than 98% had at least one comorbidities including DM (74.8%), hyperlipidemia (91.6%), and hypertension (93.9%). Annual mean visits (inpatient, outpatient or physician) for CC cohort were 33.9 (pre) vs. 40.7 (post) ($p < 0.001$). Total costs for CC cohort was $19,385 (pre) vs. $33,504 (post) ($p < 0.001$). Comorbidity burden was high in both CC DM patients and CC non-DM patients – hypertension 97.1% (DM) and

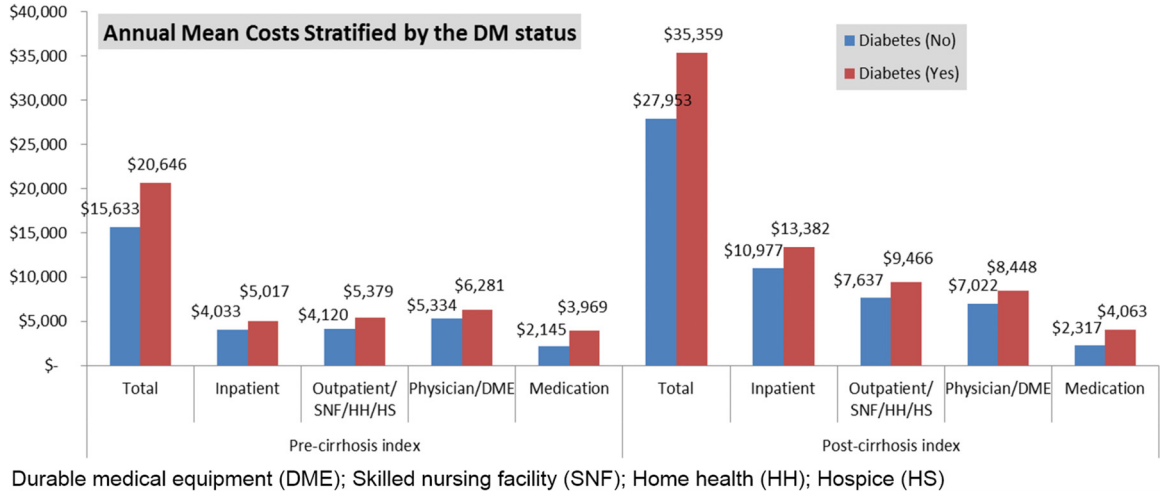


Figure: (abstract: SAT-473)

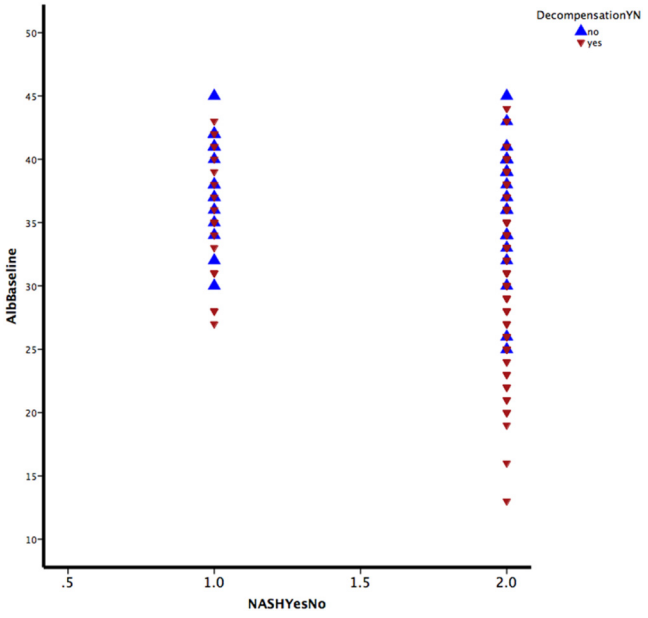
84.7% (non-DM); hyperlipidemia 95.3% (DM) and 80.7% (non-DM). For CC DM patients, mean inpatient visits were 0.52 (pre) vs. 0.99 (post) ($p < 0.001$), and for CC non-DM patients, mean inpatient visits were 0.37 (pre) vs. 0.76 (post) ($p < 0.001$). The total costs for CC DM patients were $20,646 (pre) vs. $35,359 (post) ($p < 0.001$), and for CC non-DM patients were $15,633 (pre) vs. $27,953 (post) ($p < 0.001$).
Conclusion: Medicare patients with NASH/NAFLD and CC reported a high comorbidity burden – 75% of them were diagnosed with DM. Diagnosis of CC increased HCU and costs by 20% and 72.8%, respectively. When stratified by DM status, impact of CC diagnosis on HCU and costs among NASH/NAFLD patients was even more substantial – inpatient visits increased by 89.7% (CC DM) and 102.5% (CC non-DM); costs increased by 71.3% (CC DM) and 78.8% (CC non-DM). Early identification and effective treatment of NASH/NAFLD CC patients is needed to reduce the risk of disease progression and higher associated HCU and costs.

SAT-475

Prediction of decompensation events in NASH cirrhosis patients

R. Forlano[1], D. Kockerling[1], R. Nathwani[1], J. Clancy[1], H. Marcinkowski[1], M. Yee[1], M. Thursz[1], H. Antoniades[1], A. Dhar[1], P. Manousou[1].
[1]*Department of Hepatology, Imperial College London*
Email: robertaforl@gmail.com

Background and Aims: Non-Alcoholic Steatohepatitis (NASH) induced cirrhosis is predicted to be the leading indication for liver transplantation worldwide. Estimating the prognosis of these patients remains challenging, considering the wide heterogeneity of this group. Few studies have compared the predictive value of conventional scoring systems according to different causes.
We aim to examine the performance of biochemical parameters and prognostic scoring systems in predicting the first episode of decompensation in NASH cirrhosis compared to other etiologies.
Method: 204 consecutive patients with cirrhosis referred to a tertiary care centre were prospectively enrolled in the study. Cirrhosis was diagnosed either clinically or histologically. Patients were followed-up for decompensation events and examination and biochemical data collected at baseline and at 6, 12, 18 months. Statistical analysis was performed using chi-square test and Cox regression analysis (SPSS).
Results: 204 patients were enrolled: 63% patients were male, median age 57.4 years. Etiologies were: 20% NASH, 52% alcohol, 20% viral hepatitis and 8% PBC/PSC.
In the whole group, 110 (54%) patients experienced at least one event of decompensation during the follow-up: 17/41 pts (41%) in NASH group, 93/163 (57%) in non-NASH group. Overall, the NASH group showed higher level of baseline albumin (36 ± 5 vs 32 ± 6, $p = 0.002$) (Figure 1) and body weight (94 vs 79, $p = 0.02$) compared to the non-NASH. There was no difference in terms of baseline Child-Pugh score (7 vs 7, $p = 0.1$), MELD (11.2 vs 11.9, $p = 0.4$) and UKELD (50.1 vs 51, $p = 0.23$).



Within the NASH group, baseline creatinine (78 vs 63, $p = 0.001$), PLT count (130 vs 143, $p = 0.001$), albumin (35 vs 39, $p = 0.002$) and UKELD (50.6 vs 46.8, $p = 0.001$) were significantly higher in the subgroup with decompensation compared to the subgroup without. There was no statistically significant difference in Child-Pugh score, MELD, cholesterol and HbA1c levels.
Within the non-NASH group, baseline Child-Pugh score (8 vs 5, $p = 0.002$), MELD (11.3 vs 8.6, $p = 0001$) and UKELD (51.7 vs 48,2, $p = 0.002$) were significantly higher in the subgroup with decompensation compared to the subgroup without. There was no difference in baseline albumin, HbA1c, cholesterol, PLT and creatinine.
Finally, Cox regression analysis for the prediction of cirrhosis decompensation revealed that UKELD was the strongest predictor in the NASH group (HR 1.172, $p = 0.017$, 95%CI 1.029–1.334), while Child Pugh Score in non-NASH group (HR 1.165, $p = 0.004$ 95%CI 1.049–1.293).

Conclusion: UKELD is the strongest predictor of decompensation in NASH related cirrhosis compared to Child Pugh score in the non-NASH aetiologies. Higher albumin and hypothetically body composition may explain a poorer predictive value of Child-Pugh score in the NASH population.

SAT-476

A mobile application for the management and follow-up of patients with Non-Alcoholic Fatty Liver Disease

R. Forlano[1], B.H. Mullish[1], N. Katertsidis[2], N. Giannakeas[3], A. Tzallas[3], M. Tsipouras[4], M. Yee[1], S. Taylor-Robinson[1], M. Thursz[1], P. Manousou[1]. *[1]Department of Hepatology, Imperial College London; [2]Department of Computer Engineering, University of Ioannina, Greece; [3]Department of Computer Engineering, Technological Educational Institute, Epirus; [4], Department of Informatics and Telecommunication Engineering, Greece*
Email: robertaforl@gmail.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) represents an increasing cause of chronic liver disease worldwide, with an estimated global prevalence of ~25%. Its prevalence has grown proportionally with obesity, sedentary lifestyle, unhealthy diet and metabolic syndrome. First line treatment is a combination of dietary modifications and increased physical activity. To address the challenge of empowering patients and clinicians to better manage lifestyle, we have designed a novel mobile application entitled F for Fitness.

Method: We have developed an intelligent and integrated solution for patients with Non-Alcoholic Fatty Liver Disease, consisting of: A smart mobile application for coaching and monitoring patients during their daily activities and a cloud-based web application for the management of patients and the storage/analysis of data. The central web application features intelligent issue tracking and a Powerful web analytics providing real-time track of users and their behavior. It is based on Apache Cordova, HTML5, JavaScript and supporting Android, iOS, Windows Phone.

Results: We specified, prototyped and developed a system consisting of an Android app accessible to the patients and a central platform accessible to the clinicians. The app consists of five main screens: Exercise, Food and Water Intake, Alcohol Consumption and Weight/BMI. Exercise is expressed in steps, meters and calories per day. Each meals recorded choosing between different visual options, ranging from raw ingredients to processed food. Similarly, the patients are asked to enter the quantity and the type of alcohol consumed daily. In order to give an educational feedback, nutritional facts are displayed after each choice and a pie chart shows the amount of calories consumed vs burned at the end of the day. Water intake is also required for the correct interpretation of variations in weight and BMI. Finally, each section tracks the history from the beginning of the use of the app. Built-in sensors and third party devices could fit in easily to manage health and environmental records such as heart rate, blood pressure, glucose levels.

Through the central platform, clinicians can access to the records and analyze patients' diet, food intake/exercise balance and alcohol habits. Moreover, each record is pre-filled with clinical data, such as latest Liver Function tests, Liver Stiffness Measurement and Histology report. Push notifications could be send to the patient by the operator, when necessary.

Conclusion: F for Fitness is a novel application prototype in Non-Alcoholic Fatty Liver Disease. This application acts as an educational tool for the patients and as a real-time follow up of lifestyle for the clinicians, allowing for a personalized management in this group. F for Fitness might be used in clinical practice and in future studies to monitor the effectiveness of behavioural programs.

SAT-477

Lipofuscin is detected in early stages of the disease in liver biopsies of patients with Non-Alcoholic Fatty Liver Disease

R. Morrison[1], R. Forlano[2], N. Giannakeas[3], A. Tzallas[3], M. Tsipouras[4], J. Lloyd[1], M. Yee[2], M. Thursz[2], P. Manousou[2], R.D. Goldin[1]. *[1]Department of Cellular Pathology, Imperial College, London; [2]Department of Hepatology, Imperial College London; [3]Department of Computer Engineering, Technological Educational Institute, Epirus; [4]Department of Informatics and Telecommunication Engineering, Greece*
Email: rebecca.morrison@imperial.nhs.uk

Background and Aims: Lipofuscin is a cytoplasmic pigment formed as part of the process of autophagy. Even though lipofuscin modifications have been reported in hepatocytes in a number of conditions, such as aging and carcinogenesis, its role in chronic liver disease is unclear. It is well known that autophagy plays a crucial role in the pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD). It has been shown in experimental models that suppression of autophagy aggravates hepatic steatosis and NASH, while an increase improves fibrosis.

We aimed to detect lipofuscin accumulation using autofluorescence in liver biopsies of patients with NAFLD. We further correlated lipofuscin with clinical data.

Method: 78 consecutive patients with biopsy-confirmed NAFLD were retrospectively evaluated. Lipofuscin was reported as either absent or present in zone 3 after examination of Haematoxylin & Eosin stained slides under light microscopy. Biopsies were independently scored by two histopathologists and digitalised. Each image was then analysed by automated softwares to obtain Fat Percentage (Fat%) and Collagen Proportionate Area (CPA). Clinical and biochemical data were collected for all the patients included. Statistical analysis was performed using Chi-square test and logistic regression analysis.

Results: Under light microscopy, 25 liver biopsies were positive and 53 negative for lipofuscin. The group with lipofuscin showed higher HDL levels (2.1 vs 1.2 mmol/l, $p = 0.034$), lower LDL (2.1 vs 3.4 mmol/, $p = 0.04$) and lower ferritin levels (133 vs 277 ng/l, $p = 0.002$). Moreover, in this group, median fibrosis stage and median CPA were respectively 1.1 (±1.3) and 4.8% (± 5.5)compared to 2.5 (± 1.17, $p = 0.003$) and 8.7% (±2.7, $p = 0.002$) in the group without lipofuscin. Similarly, the number of "possible" and "definite" cases of NASH (7vs 22, $p = 0.001$) and the number of acute cardiovascular events (1 vs 4, $p = 0.02$) were significantly lower in the group with lipofuscin compared to the group without. There was no difference regarding steatosis grade and Fat%, lobular inflammation or ballooning score.

Logistic regression analysis showed that the presence of advanced fibrosis stage (F3-F4) was an independent factor for lipofuscin negativity (OR = 1.64, $p = 0.015$).

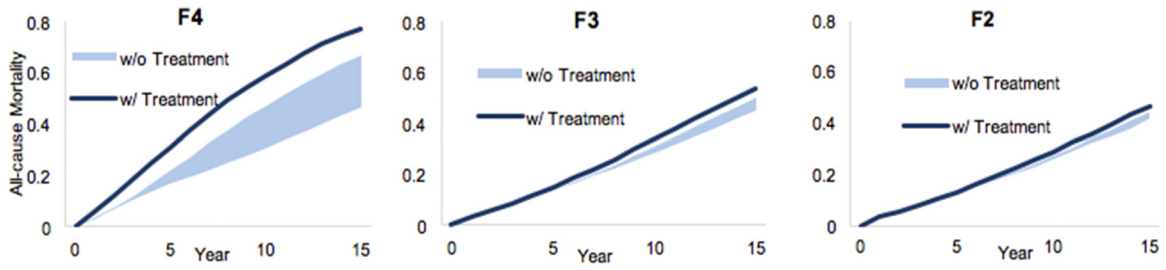
Conclusion: This is the first study involving the detection of lipofuscin accumulation in liver biopsies of patients with NAFLD. Lipofuscin is detected in early disease stage. Hypothetically, it may reflect the presence of an underlying autophagy mechanism which is still preserved in the early stages of the disease.

SAT-478

Stage-specific benefits of treatment associated fibrosis regression in patients with NASH: a Markov modeling approach

J. Chhatwal[1], S. Samur[1], E. Bethea[1], C. Hur[2], A. Samir[2], K. Corey[2], R. Loomba[3]. *[1]Harvard Medical School, Massachusetts General Hospital, Institute for Technology Assessment, Boston, United States; [2]Harvard Medical School, Massachusetts General Hospital, Boston, United States; [3]University of California at San Diego, Division of Gastroenterology, San Diego, United States*
Email: jagchhatwal@mgh.harvard.edu

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western industrialized countries, and 10–20% of NAFLD patients have



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nonalcoholic steatohepatitis (NASH). Several pharmacological treatments for NASH are in early stages of development and have used fibrosis regression as a primary outcome. Our aim was to project the long-term clinical benefit of fibrosis regression that could result from new potential treatments.

Method: We developed a Markov-based mathematical model that simulated the lifetime course of NASH patients as they progressed through the stages of the natural history: including NASH fibrosis states (F0–F4), decompensated cirrhosis (DC), and hepatocellular carcinoma (HCC). The baseline patient characteristics in the model were derived from NASH Clinical Research Network data. The model accounted for both liver-related and non-liver-related mortality. Disease progression rates and mortalities were derived from published studies. Model-predicted overall survival was independently validated with 15-year data from three published observational studies. Patients with NASH fibrosis stages F2–F4 were assumed to be eligible for treatment. We simulated long-term outcomes of regression of fibrosis by one stage in 40% of patients, as observed in early-stage clinical trials.

Results: Our model predicted that fibrosis regression as the result of pharmacological treatment in 40% of F4 patients could reduce all-cause mortality from 77.0% to 46.3–66.6% (Figure), cumulative incidence of DC from 37.8% to 5.6–25.9%, and cumulative incidence of HCC from 19.7% to 0.5–13.4%. Fibrosis regression in 40% of F3 patients would reduce all-cause mortality from 53.3% to 44.7–50.2%, cumulative incidence of DC from 11.9% to 2.6–8.7% and cumulative incidence of HCC from 6.1% to 1.3–4.4%. Fibrosis regression in 40% of F2 patients would reduce all-cause mortality from 46.8% to 41.5–44.6%, cumulative incidence of DC from 6.1% to 0.29–4.1% and cumulative incidence of HCC from 3.1% to 0.1–2.0%.

Conclusion: Based on available data from investigational NASH therapies, regression of fibrosis could substantially improve overall survival and long-term outcomes in NASH patients—the magnitude of the benefits will be higher in patients having stage F4 followed by stage F3 and F2. Potential new therapies could reduce the rising burden and mortality resulting from NASH, especially if patients are diagnosed and treated in earlier stages.

SAT-479

NAFLD/NASH patients with compensated cirrhosis (CC) had a high prevalence of comorbidities, substantial liver disease progression, and increased annual number of hospitalizations and associated costs in France: a PMSI database analysis

J. Boursier[1], C. Fabron[2], A. Lafuma[2], I. Bureau[2]. [1]*Angers Hospital University, France;* [2]*CEMKA, Bourg La Reine, France*
Email: jeboursier@chu-angers.fr

Background and Aims: Non-Alcoholic Fatty Liver Disease (NAFLD)/Nonalcoholic Steatohepatitis (NASH) can progress to fibrosis, a leading cause of CC and end stage liver disease (ESLD) (decompensated cirrhosis, hepatocellular carcinoma or liver transplant). Limited real-world data exists on disease progression and costs for NAFLD/NASH patients. This study evaluated liver disease progression and hospitalization costs in French NASH/NAFLD CC patients.

Method: Patients ≥18 years of age with NAFLD/NASH (ICD-10: K76.0, K75.8) were identified from the French National Database on hospital care (PMSI) between 2009 and 2015. Patients with other causes of liver disease were excluded. All hospitalizations, whatever the cause, with CC diagnosis were extracted. The index dates were first dates of CC diagnosis in the study period.

Results: This study identified 131,898 NAFLD/NASH patients with a hospitalization. During the study period, 11.2% (n = 14,822) experienced CC, ESLD, and/or death. For the 1.2% (n = 1,546) patients diagnosed with CC in the study period, mean age was 62.4 ± 12.9 years and 54.3% were female. For patients who progressed to CC during the study period, the mean time to progression from NAFLD/NASH to CC was 22.4 months. During the study period, 16.2% (n = 251) of CC patients progressed to ESLD (mean time 20.0 months) and 8.3% of CC patients (n = 128) died (mean time 22.8 months). Comorbidities were: hypertension (67%), hyperlipidemia (40%), obesity (57%), T2DM (68%). The prevalence of comorbidities was significantly higher in T2DM than no T2DM patients. The number of annual hospitalizations per patient and length of stay significantly increased following CC diagnosis (0.5 ± 1.0 to 2.2 ± 2.6 and 1.5 ± 4.2 to 4.4 ± 6.8 days, respectively, both $p < 0.0001$). Mean cost per hospitalization stay and annual hospitalization costs significantly increased following CC diagnosis and these costs were higher for T2DM patients than no T2DM. Specifically, cost per stay increased from €879 ± 1,921 to €2905 ± 3,268 and annual hospitalization costs increased from €2025 ± 6,792 to €7171 ± 21,718 (both $p < 0.0001$).

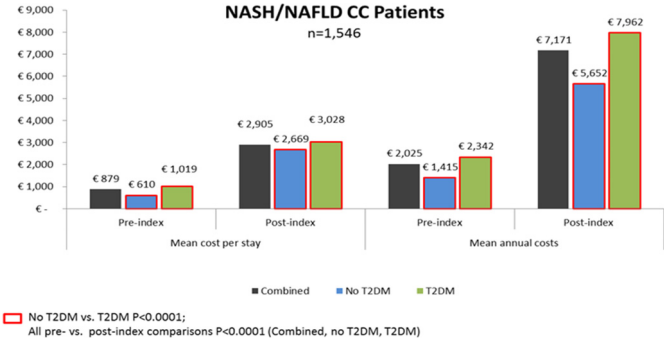


Figure: Mean cost per hospital stay and mean annual hospitalization costs for NASH/NAFLD CC patients pre- and post-index and stratified by T2DM and no T2DM patients

Conclusion: NAFLD/NASH CC patients experienced over 15% progression to ESLD and over 8% died over the 7 year study period. These patients had an over 300% increase in annual number of hospitalizations and over 250% increase in annual hospitalization costs following CC diagnosis. Improved treatment options are needed to decrease disease progression in NAFLD/NASH patients.

SAT-480

Histological severity is related to cardiovascular events in lean but not in overweight and obese subjects with NAFLD

A. Feldman[1], S. Eder[1], S. Ruhaltinger[1], M. Strasser[1], G. Strebinger[2], U. Huber-Schönauer[2], D. Niederseer[2], L. Stechemesser[3], B. Paulweber[3], C. Datz[2], E. Aigner[3]. [1]*Paracelsus Medical University, First Department of Medicine, Salzburg, Austria;* [2]*Hospital Oberndorf, Department of Internal Medicine, Oberndorf, Austria;* [3]*Paracelsus Medical University, First Department of Medicine*
Email: alexandra.feldman@outlook.com

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) typically affects overweight and obese subjects. Fatty liver is a known risk factor for cardiovascular diseases. We aimed to investigate the baseline characteristics of lean NAFLD subjects who subsequently developed cardiovascular events.
Method: In total, 464 patients had received the clinical and histological diagnosis of NAFLD at our two centres between 1997 and 2014 of whom 353 (76.1%) were available for follow-up after 8.8 (1–19) years. They were allocated to one of 3 groups according to BMI at the time of the liver biopsy: lean (BMI ≤ 25 kg/m, n = 48), overweight (BMI 25–30 kg/m², n = 195) and obese (BMI ≥ 30 kg/m², n = 110). A specific analysis with regard to cardiovascular events was performed.
Results: In 135 (38.2%) subjects a cardiovascular event had occurred, in 19 (39.6%) lean, 67 (34.3%) overweight and 49 (44.5%) obese subjects. In lean subjects with cardiovascular events, a higher degree of perisinusoidal fibrosis ($p < 0.001$; $p = 0.011$) and steatosis ($p = 0.016$; $p = 0.001$) were reported compared to obese and overweight subjects with cardiovascular events. Further, lean subjects with cardiovascular events had a higher degree of ballooning ($p = 0.001$) and periportal fibrosis ($p = 0.01$) in comparison to overweight subjects with events. Moreover, lean subjects with cardiovascular events had a higher rate of perisinusoidal fibrosis ($p = 0.042$) compared to those lean subjects without cardiovascular events. Framingham Risk Score at baseline was higher in each BMI group comparing subjects with to those without an event ($p < 0.01$ for all groups) and was similar comparing all subjects with events among all BMI categories.
Conclusion: Cardiovascular events in lean subjects were related to more pronounced histological changes such as ballooning and fibrosis, while no such link was observed in overweight and obese subjects. Likewise, fibrosis was also linked to cardiovascular disease among lean subjects. These findings suggest that histological severity may be particularly linked to cardiovascular events in lean NAFLD subjects in addition to risk estimates derived from traditional risk scores.

SAT-481

Characterization of patients with Both Alcoholic and Nonalcoholic Fatty Liver Disease (BAFLD) in a large United States cohort

N. Alkhouri[1], A. Singh[2], A. Vigni[3], M. Noureddin[4], R. Lopez[2], K. Watt[5], E. Lawitz[1,6], F. Poordad[1,6], K.V. Kowdley[7]. [1]*Texas Liver Institute, San Antonio, United States;* [2]*Cleveland Clinic;* [3]*Texas Liver Institute;* [4]*Cedars Sinai Medical Center;* [5]*Mayo Clinic;* [6]*University of Texas (UT) Health San Antonio;* [7]*Swedish Medical Center*
Email: alkhouri@txliver.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome (MetS) and is characterized by the presence of liver steatosis in the absence of significant alcohol consumption. However, MetS and significant alcohol intake coexist in certain individuals which may lead to the development of both alcoholic and nonalcoholic fatty liver disease, an entity we propose to call BAFLD. The aim of the current study was to assess the clinical characteristics of patients with BAFLD in comparison to those with NAFLD in a large cohort of subjects in the United States.
Method: Adult subjects who participated in the National Health and Nutrition Examination Survey (NHANES) between 2003–2014 were included. Diagnosis of NAFLD was made based on elevated alanine aminotransferase (ALT) (>30 U/l in males and >19 in females) and being overweight (body mass index [BMI] ≥25 kg/m²) in the absence of other causes of chronic liver disease. Patients with BAFLD met the criteria for NAFLD but also had either MetS or type 2 diabetes and consumed excessive amounts of alcohol defined as ≥ 3 drinks/day for men and ≥ 2 drinks/day for women. Univariable analysis was performed to assess differences between NAFLD and BAFLD and multivariable analysis was performed to compare disease severity based on a validated fibrosis score (FIB4 index) after adjusting for MetS components.
Results: The prevalence of NAFLD was at 25.9% (95% CI; 25.1, 26.8) and that of BAFLD was 0.84% (0.67, 1.02) which corresponds to an estimated 1.24 million Americans affected by BAFLD. Compared to NAFLD, patients with BAFLD were more likely to be male (75.8% ± 3.9 vs. 46.9% ± 0.87), smokers (45.3% vs 17.6%), have higher ALT (53.1 vs 38.2 U/l), AST (43.3 vs 31.2), triglycerides (268 vs 186 mg/dl) and lower platelets (243 vs 261 k/ul); $p < 0.01$ for all. More importantly, after adjusting for MetS components, BAFLD patients were significantly more likely to have advanced fibrosis [adjusted OR (95% CI) based on FIB4 index > 2.67 was 3.2 (1.4, 7.0), $p = 0.004$].
Conclusion: A significant percentage of the American general population is afflicted by BAFLD. Patients with BAFLD tend to have more advanced disease based on biomarkers of liver injury and fibrosis scores. Therefore, special attention should be paid to this population to identify the burden of liver disease and intervene in a timely fashion.

SAT-482

Increased gut permeability is associated with oxidative stress in patients with NAFLD

F. Baratta[1,2], M.D. Ben[1], D. Pastori[1,2], G. Labbadia[1], M. Novo[1], R. Carnevale[1], F. Violi[1], F. Angelico[2]. [1]*Sapienza University of Rome, Internal Medicine and Medical Specialties, Rome, Italy;* [2]*Sapienza University of Rome, Anatomical, Histological, Forensic Medicine and Orthopedic Science, Rome*
Email: francesco.baratta@uniroma1.it

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) represents the most common liver disease worldwide. Based on multiple hits hypothesis, oxidative stress plays a pivotal role in NAFLD onset and progression from simple steatosis to steatohepatitis (NASH). However, factors inducing oxidative stress in NAFLD are still unknown. Clinical e experimental data demonstrated that intestinal bacterial overgrowth and augmented gut permeability were associated with NAFLD. Aim of the study was to investigate the relationship between oxidative stress and LPS in patients with NAFLD.
Method: We enrolled 44 were patients affected by non-alcoholic steatohepatitis (NASH); 50 subjects with simple steatosis (NAFL) and 50 subjects without hepatic steatosis balanced for age, gender and BMI were used as controls. Serum bacterial lipopolysaccharide (LPS) and serum zonulin, a marker of gut permeability, were measured with ELISA technique. Serum NOX2-derived peptide (sNOX2dp), a marker of NADPH oxidase activation, was detected in serum by enzyme-linked immuno- sorbent assay method.
Results: Patients had no difference in diabetes and arterial hypertension prevalence and in statin and aspirin use. NASH patients, as compared to NAFL and controls, had increased median sNOX2dp ($p < 0.001$) and increased median LPS ($p < 0.001$). At bivariate analysis sNOX2dp was correlated with LPS ($rs = 0.608$, $p < 0.001$), γGT ($rs = 0.576$, $p = 0.000$), AST ($rs = 0.560$, $p = 0.000$) and ALT ($rs = 0.620$, $p = 0.000$). LPS was correlated with zonulin ($rs = 0.375$; $p < 0.001$). At linear regression analysis, after correction for age, sex, BMI and diabetes and aspirin use, LPS above median (Beta = 0.059; $p < 0.05$) and liver diagnosis (Beta = 0.913; $p < 0.001$) were independently associated with sNOXdp.

	NASH (n = 44)	NAFL (n = 50)	Controls (n = 50)	P
Age (ys)	49.6 ± 11,8	51.3 ± 10.0	52.7 ± 14.1	0.449
Women (%)	48.0	56.0	46.7	0.609
Diabetes (%)z	33.3	20.0	14.0	0.069
Arterial Hypertension (%)	37.8	50.0	56.0	0.198
Statins (%)	26.7	32.0	42.0	0.273
Anti-platelet drugs (%)	8,9	10.2	14.0	0.700
Smokers (%)	33.3	30.0	34.0	0.901
Body Mass Index (kg/m^2)	28.9 ± 4.1	29.5 ± 3.6	28.5 ± 4.0	0.327
Obesity (BMI ≥ 30 kg/m^2)	36.0	48.0	33.3	0.289
γGT (UI/l)	45.0 (33.5/100.0)	19.0 (14.2/28.5)	16.0 (11.0/21.0)	0.000
AST (UI/l)	38.0 (29.5/51.5)	18.0 (15.0/21.2)	17.0 (15.0/21.0)	0.000
ALT (UI/l)	61.0 (44.0/96.5)	20.0 (16.0/24.2)	15.0 (13.7/19.0)	0.000
Glycaemia (mg/dl)	103.2 ± 33.7	97.6 ± 20.1	95.3 ± 23.3	0.329
sNOXdp	36.0 (33.0–38.0)	25.0 (23.0–27.0)	9.0 (8.7–11.0)	0.000
LPS	109.2 (45.4–138.6)	77.0 (39.8–107.7)	49.5 (36.2–60.0)	0.000
Zonulin	3.8 (2.0–5.50.000)	2.9 (2.1–4.6)	2.7 (1.9–3.9)	0.092

Conclusion: In conclusion, patients with NAFLD have higher sNOXdp indicating more oxidative stress in this setting. LPS increase may result from impaired gut permeability and induce oxidative stress.

SAT-483

Increasing trend for Hepatocellular Carcinoma (HCC) linked to Nonalcoholic Fatty Liver Disease (NAFLD) in the United States

E. Miller[1], L. Dakhoul[2], H.A. Sbeih[1], E. Mao[1], A. Delemos[3], P. Roche[3], A. Scanga[4], E.V. Gomez[2], S. Gawrieh[2], N. Chalasani[2], J. Wattacheril[5].
[1]MD Anderson Cancer Center; [2]Indiana University School of Medicine; [3]Carolinas Healthcare System; [4]Vanderbilt University Medical Center; [5]Columbia University College of Physicians and Surgeons
Email: emiller1@mdanderson.org

Background and Aims: NAFLD is a leading cause of cirrhosis in the United States (US). In addition to the risk of HCC in cirrhotic patients with NAFLD, there are recent reports of HCC in NAFLD patients without cirrhosis. We aim to identify the proportion of HCC in NAFLD patients with and without cirrhosis and describe their tumour characteristics over a 15-year period at 5 US academic liver centres.
Method: Centre-specific cancer registries were used to identify patients with well-characterized HCC from January 2000 to June 2014. Patient and tumour-related characteristics, liver disease aetiologies, cirrhosis presence/absence, treatment of HCC and survival data were extracted. We defined NAFLD as chronic liver disease with ≥ 3 risk factors (elevated body mass index (BMI), diabetes, hypertension, hyperlipidaemia, coronary artery disease or peripheral vascular disease) in the absence of another aetiology. NAFLD and non-NAFLD patients were compared according to the presence or absence of cirrhosis.
Results: We identified 2,454 HCC patients over the study period. 472 patients (19.2%) had NAFLD; 161 of these (34.1%) had no evidence of cirrhosis. Compared to all others, NAFLD patients were older, more frequently white (83.7% vs. 70.9%), had higher BMI, and had more comorbidities. Among cirrhotic patients, NAFLD-linked HCCs were larger (5.3 cm vs. 4.8 cm; p = 0.019) and more likely to be resected than transplanted, compared to HCC without NAFLD. For non-cirrhotic patients, comparison of NAFLD and non-NAFLD patients revealed no significant differences in tumor size or stage, although non-NAFLD HCC patients were more likely to be transplanted. NAFLD was not associated with higher mortality rates (HR 0.93; p = 0.24). See Table for NAFLD trends in HCC over time.
Conclusions: We observed an increasing trend in the proportion of NAFLD-HCC in the United States. A third of HCCs linked to NAFLD appear to occur in individuals without cirrhosis, but interestingly these patients also exhibited a downward trend among all causes of HCC over time. HCCs linked to NAFLD are larger in size and are less likely to be transplanted.

Table: Trends in HCC linked to NAFLD with or without cirrhosis

	HCC seen			
	2000–2004 (N = 464)	2005–2009 (N = 752)	2010–2014 (N = 1238)	P for trend*
Proportion linked to NAFLD (%)	16	20	20	0.045
with cirrhosis (%)	58	62	71	0.024
without cirrhosis (%)	42	38	28	<0.01

*All P values calculated by Cochran-Armitage trend test for ordered groups.

SAT-484

Non-alcoholic fatty liver disease in non-obese young adults

Y. Maor[1], S. Daher[2], E. Israeli[3], S.D. Malnick[4], E. Melzer[1], L. Katz[5].
[1]Kaplan Medical Center, Institute of Gastroenterology and Hepatology; [2]Hadassah Medical Center, Department og Gastroenterology and Hepatology; [3]Hadassah Medical Center, Department of Gastroenterology and Hepatology; [4]Kaplan Medical Center, Department of Medicine C; [5]Sheba Medical Center, Tel-Hashomer, Department of Gastroenterology
Email: halish@netvision.net.il

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is usually associated with obesity, the metabolic syndrome and insulin resistance. However, relatively little attention has been given to NAFLD in non-obese individuals. Data regarding the outcome of non-obese NAFLD is limited and contradictory. In a cohort of almost 2,000 young adults with NAFLD we previously showed a higher prevalence of metabolic co-morbidity including, diabetes mellitus than in age-matched controls. Our aim was to characterize a sub-group of non-obese young adults with NAFLD from this cohort.
Method: For the study, we included soldiers born after 1975 and who have been recruited after 2000. Cases of NAFLD were diagnosed in those soldiers with a compatible ICD-9 code and from ultrasound reports. Patients with known chronic liver diseases or hepatitis B and C infection were excluded. Individuals with BMI < 27 kg/m^2 at diagnosis of NAFLD were considered non-obese. Epidemiologic, anthropometric, clinical and laboratory data was collected from these groups.
Results: The study group included 1,421 subjects (86.9% male, mean age 22.6 years; range 18–41 years), of whom 204 (14.4%) were non-obese (BMI < 27 kg/m^2). Among young adults with NAFLD there were more women from a higher socioeconomic background. There were more subjects born in Ethiopia among non-obese NAFLD and more subjects born in Western countries among obese. At recruitment, non-obese young adults with NAFLD had a significantly lower BMI (22.6 ± 3.8 *vs.* 29.8 ± 5.4; p < 0.0001), and better military medical profile (less co-morbidity) than obese (0.61, 95% CI = 0.43–0.86; p = 0.003). Non-obese NAFLD had significantly higher HDL, lower LDL serum levels and a lower rate of elevates serum aminotransferases (ALT ≥ 45 IU/l) than obese NAFLD patients (p ≤ 0.02). Compared with obese, non-obese NAFLD in the young was associated with a significantly lower prevalence of: hypertension, dyslipidemia, and impaired fasting glucose (p ≤ 0.025), and borderline lower prevalence of diabetes mellitus (1.5% *vs.* 4.4%; p = 0.051).
Conclusion: Non-obese young adults with NAFLD are affected to a lesser extent with metabolic abnormalities, and probably with diabetes mellitus as well. This factor may put this sub-group at a lower risk of future cardio-metabolic morbidity. Therefore, these individuals may be considered to have a relatively benign disorder.

SAT-485

Risk factors for development of severe liver disease in more than 400 000 patients with type 2 diabetes: A population-based cohort study

K. Björkström[1], S. Franzén[2], B. Eliasson[3], M. Miftaraj[2], S. Gudbjornsdottir[4], Y. Trolle-Lagerros[5], A.-M. Svensson[6], H. Hagström[7]. *[1]Karolinska Institutet, Department of Medicine, Huddinge, Stockholm, Sweden; [2]Swedish National Diabetes Register, Gothenburg, Sweden; [3]University of Gothenburg, Gothenburg, Sweden; [4]National Diabetes Register, Gothenburg, Gothenburg, Sweden; [5]Karolinska Institutet, Department of Medicine, Huddinge, Sweden; [6]Gothenburg University, Gothenburg, Gothenburg, Sweden; [7]Karolinska Institutet, Stockholm, Sweden*
Email: karl.bjorkstrom@ki.se

Background and Aims: Patients with type 2 diabetes mellitus (T2DM) are at an increased risk of liver-related morbidity and mortality. Few studies have examined the association between T2DM and liver disease using population-based cohorts with available data on risk factors and confounders. The aim of this study was to compare the incidence of severe liver disease in patients with T2DM to that of non-diabetic matched controls, and to identify risk factors for development of clinically relevant liver disease.
Method: We used the Swedish National Diabetes Register, covering around 90% of all Swedish patients with T2DM. Each patient with T2DM was matched for age, sex, county and educational level to five controls free of T2DM. We used Swedish population-based registers to identify cases with incident severe liver disease during follow-up, defined as ICD-codes for cirrhosis, decompensated liver disease or liver failure, hepatocellular carcinoma and/or liver-related mortality. A multivariate Cox regression model was applied to estimate hazard ratios and to identify risk factors for development of severe liver disease.
Results: A total of 428 220 patients with T2DM and 2 141 100 non-diabetic controls were included, with a median follow-up of 7.7 years. Having T2DM was associated with an increased risk of developing severe liver disease compared to controls (adjusted HR 2.32, 95% CI 2.25–2.39, $p < 0.001$). Within the group of patients with T2DM, risk factors associated with development of severe liver disease were age, HbA1c, body mass index, glomerular filtration rate, microalbuminuria, blood pressure medication and smoking. Treatment with lipid-lowering drugs and male sex were associated with a reduced risk of development of severe liver disease (Table 1).

Table 1: Risk factors for development of severe liver disease

Variable	Adjusted hazard ratios (95% CI)	
Age (years)	1.04 (1.03–1.04)	<0.001
HbA1c (mmol/mol)	1.01 (1.00–1.01)	0.04
Body mass index (kg/m^2)	1.03 (1.02–1.04)	<0.001
GFR (ml/min/1.73 m^2)	1.01 (1.00–1.01)	<0.001
Microalbuminuria (yes/no)	1.22 (1.06–1.41)	0.01
Blood pressure medication (yes/no)	1.31 (1.14–1.50)	<0.001
Smoking (yes/no)	1.78 (1.55–2.05)	<0.001
Lipid-lowering drugs (yes/no)	0.59 (0.53–0.67)	<0.001
Male sex (yes/no)	0.72 (0.64–0.81)	<0.0001

Conclusion: Patients with T2DM are at a high risk for development of severe liver disease. Knowledge of risk factors can be used to identify patients at an increased risk for manifest cirrhosis or future severe liver disease.

SAT-486

Multidisciplinary intervention on lifestyle improves the management of patients with nonalcoholic fatty liver disease

S. Policarpo[1], M. Machado[2], D. Barreira[2], H. Cortez-Pinto[2]. *[1]Hospital Santa Maria, Serviço de Dietética e Nutrição, Lisbon, Portugal; [2]Hospital Santa Maria, Serviço de Gastrenterologia, Lisbon, Portugal*
Email: saraopolicarpo@gmail.com

Background and Aims: Lifestyle changes are difficult to implement. We aimed to assess the efficacy of a multidisciplinary team (MdT – gastroenterologist, dietitian and psychologist) in a combined intervention in patients with nonalcoholic fatty liver disease (NAFLD).
Method: Patients with NAFLD were invited to be managed in a MdT. Lifestyle modification (physical activity and Mediterranean diet) was applied. Anthropometric and clinical data [including liver biochemistry, transient hepatic elastography, NAFLD Fibrosis Score (NFS) and Fibrosis 4 score (FIB4)] were collected. Patients maintaining follow-up for at least 3 month were compared with those who declined MdT. Pregnant women, patients submitted to bariatric surgery and loss of follow up were excluded.
Results: 67 patients were included, 67.2% males, age 56 ± 12 years, mean time of diagnosis 8.3 ± 7.2 years. At baseline, BMI was 31.3 ± 5.6 kg/m^2, with 89.7% of patients being overweight and 56.7% obese; 50% of patients were F2-F3 and 22.2% F3-F4 as assessed by elastography; FIB4 was >2.67 in 12.5% of patients and NFS >0.675 in 30.5%, suggesting advanced fibrosis. After 3 months, 90.9% of patients lost weight and liver enzymes decreased in the majority of patients (AST in 73.6% and ALT in 71.7%), NFS decreased in 67.5% and FIB4 in 61.2%. From the 67 patients, 23.9% declined MdT (no-MdT group). After 3 months, weight decreased in 96% on MdT vs. 75% on the no-MdT ($p = 0.027$) and patients on MdT presented higher weight loss (3.8 kg vs. 2 kg no-MdT group). AST decreased in 78% of patients on MdT *vs.* 58.3% on no-MdT ($p = 0.018$), ALT decreased in 78% of patients on MdT *vs.* 50% on no-MdT ($p = 0.035$); FIB4 decreased in 50% of patients on no-MdT vs. 64.9% on MdT ($p > 0.005$) and NFS improved in 80% of patients on no-MdT vs. 67.5% on MdT ($p > 0.005$). Analyzing the 25 patients who were previously followed in Hepatology Unit, only 20% had lost weight before MdT, with a global positive variation in weight (0.8 ± 1.01%) as compared to negative variation after 3 months (4.9 ± 0.5%, $p < 0.001$). Similarly, previous to MdT, AST only decreased in 45% (globally increased 72 ± 35% *vs.* 19 ± 10 decrease after 3 months, $p = 0.048$) and ALT decreased in 38% (globally increased 86 ± 38% *vs.* 27 ± 11 decrease after 3 months, $p = 0.023$).
Conclusion: The aggregate data strongly suggests that a multidisciplinary team can improve the management of patients with NAFLD, increasing the efficacy of lifestyle interventions.

SAT-487

Long-term associations between non-high density Lipoprotein Cholesterol and Apolipoprotein B in young adulthood and subclinical atherosclerosis in persons with nonalcoholic fatty liver disease in middle age: the CARDIA study

L. Vanwagner[1,2], J. Wilkins[2,3], H. Ning[2], N. Allen[2], J. Siddique[2], C. Lewis[4], N. Terrault[5], J.J. Carr[6], M. Rinella[7], D. Lloyd-Jones[2,8]. *[1]Northwestern University Feinberg School of Medicine, Medicine-GI & Hepatology; [2]Northwestern University Feinberg School of Medicine, Preventive Medicine; [3]Northwestern University Feinberg School of Medicine, Division of Cardiology; [4]University of Alabama Birmingham, Preventive Medicine; [5]University of California San Francisco, Division of GI & Hepatology; [6]Vanderbilt University, Radiology; [7]Northwestern University Feinberg School of Medicine, GI & Hepatology; [8]Northwestern University Feinberg School of Medicine, Cardiology*
Email: lvw@northwestern.edu

Background and Aims: Coronary heart disease (CHD) is a leading cause of death in nonalcoholic fatty liver disease (NAFLD). Non-high density lipoprotein-C (NHDL-C) represents cholesterol *concentration* within atherogenic lipoproteins, while apolipoprotein B (apoB) represents particle *number* because each particle contains 1 molecule of apoB. High apoB may be the strongest clinical predictor of CHD risk in the general population; whether this is true in NAFLD is unknown. We sought to quantify associations between apoB, NHDL-C and the discordance between apoB and NHDL-C levels in young adulthood, with prevalent NAFLD, and coronary artery calcium (CAC) in adults with NAFLD in midlife.

Method: CARDIA recruited young adults ages 18 to 30 years in 1985–86. Participants with complete baseline data and year 25 (Y25) computed tomography (CT)-measured NAFLD and CAC score were included. NAFLD was defined as liver attenuation ≤ 40 Hounsfield Units after exclusions for other liver fat causes. CAC was defined as Agatston score >0. Baseline NHDL-C or apoB values were divided into tertiles and 4 mutually exclusive concordant/discordant groups, stratified based on being above or below median NHDL-C or apoB levels.

Results: Analysis included 2,508 participants (baseline age 27 years; 58% women; 53% white). Y25 NAFLD prevalence was 10%. Compared with the lowest tertile, higher odds of NAFLD were seen in the middle and high tertiles of apoB and NHDL-C in separate adjusted models. High NHDL-C and low apoB, but not high apoB and low NHDL-C, was associated with NAFLD. Among NAFLD participants (n = 261), NHDL-C/apoB discordance was not associated with CAC. Highest odds of CAC were observed in NAFLD participants with high NHDL-C (**TABLE**).

Table: NHDL-C, ApoB and Concordance/Discordance between NHDL-C and ApoB Categories in Relation to NAFLD or CAC > 0 Among Persons with NAFLD

		NAFLD Prevalence n = 2,508		CAC > 0 among NAFLD n = 261
	N	AOR (95% CI)*	N	AOR (95% CI)*
NHDL-C tertiles[¶]				
Low	835	REF	52	REF
Middle	837	**1.5 (1.0, 2.3)**	79	1.9 (0.68, 5.5)
High	836	**2.5 (1.7, 3.6)**	129	**3.6 (1.4, 9.5)**
ApoB tertiles[†]				
Low	834	REF	56	REF
Middle	832	**1.7 (1.1, 2.5)**	90	1.1 (0.40, 2.8)
High	842	**2.0 (1.4, 2.9)**	115	**3.0 (1.2, 7.2)**
Concordance/Discordance in NHDL-C/ApoB				
Low/low	1036	REF	68	REF
Low/high	217	1.5 (0.79, 2.7)	31	1.1 (0.25, 4.6)
High/low	194	**3.5 (2.1, 5.8)**	144	1.2 (0.38, 3.8)
High/High	1060	**2.1 (1.5, 2.9)**	18	**3.5 (1.5, 8.3)**

*Adjusted for center, sex, race, baseline (age, education, smoking, alcohol, BMI, physical activity, systolic blood pressure/medication).
[¶]Median NHDL-C 121.7; Tertiles: low 27–107; middle 107–135; high 135–326 mg/dl.
[†]Median ApoB 89.0; Tertiles: low 26–79; middle 80–100; high 101–192 g/dl.

Conclusion: High NHDL-C is a strong early risk marker for both NAFLD and atherosclerosis among adults with NAFLD in midlife. Based on our findings, the additional benefit of measuring apoB levels for CHD risk stratification in adults with NAFLD is not apparent.

SAT-488

Association of nonalcoholic fatty liver disease with changes in left ventricular structure and function: The coronary artery risk development in young adults (CARDIA) study

L. Vanwagner[1,2], H. Ning[2], J. Wilcox[3], C. Lewis[4], J. Lima[5], J.J. Carr[6], M. Rinella[7], S. Shah[8], D. Lloyd-Jones[8,9]. *[1]Northwestern University Feinberg School of Medicine, Division of Gastroenterology and Hepatology, Chicago, United States; [2]Northwestern University Feinberg School of Medicine, Preventive Medicine, Chicago, United States; [3]Northwestern University Feinberg School of Medicine, Division of Cardiology, Chicago, United States; [4]University of Alabama Birmingham, Preventive Medicine, United States; [5]Johns Hopkins University, Cardiology; [6]Vanderbilt University, Radiology; [7]Northwestern University Feinberg School of Medicine, Division of Gastroenterology & Hepatology; [8]Northwestern University Feinberg School of Medicine, Cardiology; [9]Northwestern University Feinberg School of Medicine, Preventive Medicine*
Email: lvw@northwestern.edu

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is associated with high cardiovascular morbidity/mortality, including heart failure (HF). Abnormalities in left ventricular (LV) structure/function are associated with HF risk. Thus, understanding the relationship between NAFLD and change in LV structure/function over time may provide insight into the link between NAFLD and HF. In a large prospective population-based sample of U.S. adults, we examined the relationship between NAFLD and markers of LV structure/function.

Method: Participants from the CARDIA study year 25 (Y25) exam (age 43–55, 58% women, 48% black) with CT measured liver fat and comprehensive echocardiography were included (n = 1,876). Echocardiography was repeated at Y30 follow up (age 47–62). NAFLD was defined as liver attenuation ≤ 40 Hounsfield units after exclusions. LV geometry was classified into normal and abnormal by integrating relative wall thickness (RWT) and LV mass index. LV diastolic function was defined using Doppler and tissue Doppler imaging markers.

Results: NAFLD prevalence was 10%. At Y30 NAFLD participants had higher LV mass, RWT, prevalent LV hypertrophy and abnormal LV geometry versus non-NAFLD ($p < 0.01$). Those with NAFLD had impaired LV relaxation (E/A ratio), higher LV filling pressures (E/e" ratio) and lower ejection fraction (58.9% vs. 60.0%, $p < 0.01$). In multivariable analyses NAFLD was independently associated with markers of abnormal LV structure/function (Table). Adjustment for BMI attenuated associations.

Table: Association of NAFLD with Prevalent and Incident Markers of Left Ventricular Structure and Function

Parameters	Base[a]		Multivariable[b]		Multivariable + **BMI**	
	Estimate	P-value	Estimate	P-value	Estimate	P-value
Y30 LV systolic function						
Ejection Fraction	−0.88 (0.41)	0.03	−0.61 (0.44)	0.16	−0.53 (0.44)	0.23
Y30 LV diastolic function						
E/A ratio	−0.11 (0.02)	<0.0001	−0.06 (0.03)	0.02	−0.04 (0.03)	0.10
E/e' ratio	0.76 (0.17)	<0.0001	0.31 (0.18)	0.04	0.22 (0.18)	0.22
Y30 LV geometry						
LVH	2.8 (2.0–4.0)	<0.0001	1.6 (1.01–2.5)	0.04	1.3 (0.8–2.0)	0.30
Abnormal LV geometry	2.4 (1.7–3.4)	<0.0001	1.5 (1.0–2.2)	0.05	1.3 (0.8–1.9)	0.29
Y25 to Y30 change in LV geometry						
LVH	3.1 (1.9–5.2)	<0.0001	2.1 (1.2–3.8)	0.01	1.6 (0.9–2.9)	0.15
Abnormal LV geometry	2.9 (1.7–4.8)	<0.0001	2.0 (1.2–3.5)	0.01	1.6 (0.9–2.8)	0.09

*Odds ratio (95% confidence interval) or β (standard error) from logistic or linear regression.
[a]Base: Y25 age, race, sex, center, education, income, alcohol use, smoking status, physical activity.
[b]Multivariable: Base + Y25 systolic blood pressure, total and HDL cholesterol, diabetes, GFR, medication for hypertension or lipids, and Y25 LV hypertrophy (LVH models) or LV mass/RWT (geometry models).

Conclusion: NAFLD is associated with subclinical changes in LV structure/function, which are precursors to HF. Obesity mediates this association and thus, may be a potential therapeutic target for prevention of HF in NAFLD.

SAT-489

Investigating the relationship between rare genetic variants and advanced fibrosis in pediatric nonalcoholic fatty liver disease

J. Wattacheril[1], S. Kleinstein[1,2], P.R. Shea[1,2], J. Lavine[1], M. Subramanian[3], R. Myers[3], J. Lefkowitch[1], C. Behling[4], S. Xanthakos[5], D. Goldstein[2,3]. *[1]Columbia University College of Physicians and Surgeons, Medicine; [2]Institute of Genomic Medicine; [3]Gilead Sciences, Inc; [4]Pacific Rim Pathology; [5]Cincinnati Children's Hospital*
Email: jjw2151@cumc.columbia.edu

Background and Aims: Nonalcoholic Fatty Liver Disease (NAFLD) is a common human disease that is estimated to affect 20–40% of the Western population. Common genetic variation in the patatin like

phospholipase domain containing 3 (*PNPLA3*) and transmembrane 6 superfamily member 2 (*TM6SF2*) genes have been associated with an increased risk of developing NAFLD, the severity of nonalcoholic steatohepatitis (NASH), and fibrosis in adults. We aimed to explore the role of rare genetic variants in an extreme phenotype of NAFLD: pediatric patients with advanced fibrosis.

Method: Whole exome sequencing data was generated for 230 pediatric patients diagnosed with NAFLD by histology recruited from the Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN). Case-control single variant and gene-based collapsing analyses were used to test for rare variants that were enriched or depleted within the pediatric NAFLD cohort across seven clinically relevant phenotypes: fibrosis (116 bridging/cirrhotic stage 3/4 vs. 114 stage 0), steatosis (160 high vs. 70 low), NASH (132 aggregate vs. 96 no NASH), lobular inflammation (101 high vs. 129 low), hepatocyte ballooning (86 present vs. 144 absent), portal inflammation (203 present vs. 26 absent), and NAFLD activity score (NAS; 96 scored >4 vs. 134 scored ≤4). All results were adjusted for multiple testing using a Bonferroni correction.

Results: No genome-wide significant associations were found between rare variation and advanced fibrosis, steatosis, NASH, lobular inflammation, hepatocyte ballooning, portal inflammation or NAS. A biologically interesting, but non-genome-wide significant enrichment was observed in *MACF1* (microtubule-actin crosslinking factor 1) in NASH vs non-NASH subjects (gene-based p = 0.08) as well as subjects with advanced fibrosis vs those with no fibrosis (gene-based p = 0.06). Other non-significant genes of interest included *HERC1*, *ASCC3*, *CUX1*, and *CACNA2D4*, enriched in subjects without fibrosis. No enrichment of rare variants in *PNPLA3* or *TM6SF2* was observed across phenotypes.

Conclusion: In a cohort of children with histologically proven NAFLD, no genome-wide significant associations were found between rare variation and seven unique histologic features. Of particular interest is the lack of enrichment in established genes of interest in adults: *PNPLA3* and *TM6SF2*. Larger cohorts of children with NAFLD and advanced fibrosis are needed to conclusively determine whether rare genetic variation is an important factor in pediatric NAFLD and if pediatric and adult NAFLD represent different disease phenotypes.

SAT-490

Hepatic steatosis in an adult population: stronger correlation with the presence of obesity and insulin resistence than with the dietary pattern. Results from a cross-sectional study

J.A.M.C.P. Leitao[1], J. Cochicho[1], S. Carvalhana[2], F. Velasco[3], A.P. Silva[4], I.S. Medeiros[5], A.C. Alves[6], M. Bourbon[6], B. Oliveiros[7], V. Rodrigues[8], A. Carvalho[1,9], H. Cortez-Pinto[10]. [1]*Centro Hospitalar e Universitário de Coimbra EPE, HUC, CHUC, Internal Medicine A, Coimbra, Portugal;* [2]*Hospital de Santa Maria, Department of Gastroenterology, Lisboa, Portugal;* [3]*Hospital de Faro, Centro Hospitalar do Algarve, EPE, Department of Gastroenterology, Faro, Portugal;* [4]*Centro Hospitalar de Vila Nova de Gaia e Espinho, EPE, Department of Gastroenterology, Vila Nova de Gaia, Portugal;* [5]*Hospital Espírito Santo E.P.E, Évora, Department of Gastroenterology, Évora, Portugal;* [6]*Instituto Nacional de Saúde Dr. Ricardo Jorge, Biosystems and Integrative Science Institute (BioISI), Lisboa, Portugal;* [7]*Laboratório de Bioestatística e Informática Médica, Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal;* [8]*Faculdade de Medicina, Universidade de Coimbra, Instituto de Higiene e Medicina Social, Coimbra, Portugal;* [9]*Faculdade de Medicina, Universidade de Coimbra, Coimbra, Portugal;* [10]*Faculdade de Medicina, Universidade de Lisboa, Laboratório de Nutrição, Lisboa, Portugal*
Email: jorge.a.leitao@gmail.com

Background and Aims: Hepatic steatosis is very frequent in the general population, mostly associated with obesity and insulin resistance. Typical dietary patterns have been difficult to identify with controversial information. We aimed to estimate in a representative sample of the Portuguese adult population, what was the contribution of the dietary pattern in what concerns macronutrients and food groups for the presence of steatosis as well as the other traditional risk factors for steatosis.

Method: Population based study with a random sample of adult people (18–79 years), from National Health System registers not stratified by sex or regions. Participants, underwent past medical history, anthropometric measures, semi-quantitative food frequency questionnaire (FFQ) representative of the usual intake over the previous year, physical activity index (IPAQ), blood tests and ultrasound to diagnose hepatic steatosis (HS) according to Hamaguchi's ultrasonographic score (defined by a score ≥ 2). Statistical analysis was performed using SPSS 23.0.

Results: 834 participants were enrolled: 440 male (52.8%) mean age 49.8 + 17.2 years. Steatosis (S) was present in 37.9% when adjusted to national adult population. Dietary pattern showed that S had a more elevated caloric intake, (2731.97 vs 2589.09 Kcal; p = 0.032), although with no differences regarding the percentage calories from carbohydrates 44.1 ± 8.0 vs 46.7% ± 8.0, ns, lipids: 33.9 ± 3.1% vs 34.7 ± 6.9%;ns) or proteins (17.4 ± 3% vs 17.6 ± 3.1, ns). There was a significantly higher consumption of red meat in S, with no differences in amount of soft drinks, fruits, vegetables or legumes. In univariate analysis, main associations with S were: male sex, age, increased waist circumference, BMI >30 kg/m^2, alcohol abuse (males >30 g/day; females >20 g/day), insulin resistance (IR) (HOMA test >2.5), elevated triglycerides (HTG), and low HDL cholesterol. In multivariate analysis, age 35–64 years (p = 0.0015), BMI 25–30 and >30 kg/m^2 (p = 0.001), alcohol abuse (p = 0.002), serum glucose >100 mg/dl (p = 0.006), IR (<0.001), HTG (p = 0.001), and low HDL (p = 0.024), significantly associated with steatosis.

Conclusion: In the general population, the presence of steatosis strongly correlates with excessive alcohol consumption, obesity, aspects of the metabolic syndrome and insulin resistance, with no particular dietary pattern identified except increased caloric intake as well as red meat consumption.

SAT-491

Mixed hepatic iron deposition but not serum ferritin is associated with the presence of nonalcoholic steatohepatitis (NASH)

E. Buzzetti[1,2], S. Petta[3], R. Manuguerra[4], D. Cabibi[5], T.V. Luong[6], E. Corradini[2], M. Pinzani[1], A. Craxi[3], A. Pietrangelo[2], E. Tsochatzis[1]. [1]*UCL Institute for Liver and Digestive Health, Royal Free Hospital and UCL, London, United Kingdom;* [2]*University Hospital Policlinico of Modena and University of Modena and Reggio Emilia, Division of Internal Medicine 2 and Center for Hemochromatosis, Modena, Italy;* [3]*University of Palermo, Section of Gastroenterology and Hepatology, Di. Bi.M.I.S., Palermo, Italy;* [4]*Royal Free Hospital, Department of Cellular Pathology, London, United Kingdom;* [5]*University of Palermo, Department of Sciences for the Promotion of Health and Mother and Child Care, Anatomic Pathology, Palermo, Italy;* [6]*Royal Free Hospital, Department of Cellular Pathology, London, United Kingdom*
Email: buzzetti.elena@gmail.com

Background and Aims: High serum ferritin (SF) is a common finding in NAFLD but whether this reflects hepatic inflammation or true iron-overload has not been clarified.

In this study we assessed the presence and pattern of hepatic iron deposition, its correlation with SF and liver disease severity in patients with NAFLD.

Method: Patients with biopsy-proven NAFLD were retrospectively selected at two European centers. Clinical and biochemical details at the time of liver biopsy were collected. Liver biopsy samples were reviewed by a single pathologist in each center; presence of iron was assessed in hepatocytes (HC) and reticuloendothelial cells (RES) and graded. NASH was defined as the combination of any degree of steatosis, hepatocyte ballooning and lobular inflammation.

Results: Of the 472 patients with NAFLD, NASH was found in 248 (52%) patients, 88 of which had advanced fibrosis (≥F3).

Stainable hepatic iron was found in 120 (25%) patients and the pattern of deposition was HC in 38%, RES in 20%, mixed in 42% of cases. Subjects with stainable hepatic iron were more likely to be male and have high SF.

A mixed pattern of iron deposition was significantly associated with the presence of NASH when compared to absence or other patterns of

iron deposition. SF was not significantly different in patients with NASH or ≥ F3 fibrosis compared to those with no NASH or fibrosis <3. BMI, diabetes, ALT and a mixed hepatic iron deposition) were independently associated to NASH (Table).

	HR (95% CI)	p	HR (95% CI)	p
Age	1.01 (1.01–1.02)	0.01		NS
BMI	1.04 (1.01–1.08)	0.02	1.04 (1.01–1.08)	0.02
Hypertension	1.40 (0.95–2.07)	0.09		
Diabetes	3.02 (2.02–4.52)	<0.0001	2.66 (1.67–4.24)	< 0.0001
ALT	1.007 (1.003–1.01)	<0.0001	1.01 (1.01–1.02)	< 0.0001
Ferritin	1.001 (1–1.001)	0.09		
Hepatic iron				
No	–		–	
HC	0.79 (0.43–1.47)	0.46	0.65 (0.32–1.32)	0.24
RES	0.79 (0.35–1.83)	0.56	0.64 (0.24–1.72)	0.38
Mixed	2.29 (1.21–4.32)	0.01	2.41 (1.15–5.05)	0.02

Age (HR 1.04, 95%CI 1.01–1.06, p = 0.008), diabetes (HR 2.57, 95%CI 1.34–4.91, p = 0.004), platelets (HR 0.98, 95%CI 0.98–0.99, p < 0.0001) and BMI (HR 1.06, 95%CI 1.001–1.11, p = 0.044) were the only independent predictors of advanced fibrosis.

Conclusion: In NAFLD patients, presence of iron in both hepatocytes and RES is associated with NASH. The underlying mechanisms need to be investigated in future studies; such finding could provide the basics for the selection of patients at higher risk of disease progression by using modern MRI-based iron detection techniques.

SAT-492

NAFLD has a negligible role for survival in old subjects

L. Terenzi, F. Bergolari, V. Tallarico, D. Magalotti, M. Zoli, G. Bianchi.
University of Bologna, Medical and Surgical Sciences, Bologna, Italy
Email: marco.zoli@unibo.it

Background and Aims: NAFLD is the liver manifestation of metabolic syndrome, a risk factor for mortality and cardiovascular morbidity, but we ignore the role of steatosis "per se" in survival.
Method: Within the Pianoro Project (people > 65 years), anamnestic, clinical and laboratory data related to diabetes, hypertension, obesity, BMI, waist circumference, dyslipidemia were collected in 1144 subjects (551 M, 593 F, median age 72 years). We tried to evaluate the outcome of these subjects.
Results: We had information, with a follow-up of 12 years, for 672 subjects, 352M/320F; 294 were still alive. Among them, 286 have steatosis (176 degree 1, 96 degree 2, 14 grade 3), 355 a pathological waist circumference, 307 overweight, 103 mild obese, 7 moderate/severe obese, 208 with hypertriglyceridemia, 243 with low HDL cholesterol, 90 diabetic, 465 hypertese.
The dead subjects were older (75vs.70 years), there was no statistically significant difference in the BMI class, even though the BMI class, related with the steatosis class, decreased in relation to the age group (for each of the comparisons p < 0.001).
Patients still alive had higher BMI classes, albeit not significant (p = 0.068), and more relevant steatosis (p = 0.037). The variables associated with higher mortality were hypertension (p = 0.026), hypertriglyceridemia (p = 0.027) and low HDL cholesterol (=0.028). A logistic regression found that these variables, except BMI class and steatosis, and age were associated to an increased mortality.
In 516 subjects we know the exact survival and compute the time-dependent role of our variables. Kaplan-Meier analysis found that diabetes (p = 0.015), hypertension (p = 0.001), low HDL-cholesterol (p = 0.026), hypertriglyceridemia (p = 0.034) and advanced age class (>74 years, p < 0.001) were associated with increased mortality, while grade of steatosis (p = 0.017) and BMI class (p = 0.027) are protective. Cox's analysis revealed that aging (p < 0.001, Odds Ratio 1,11), hypertriglyceridemia (p = 0.002; OR 1.64) and diabetes (p = 0.078, OR 1,38) produced a worse outcome. Anamnestic/clinical records of hypertension and low HDL appear to be associated to a low mortality but the exact role of current pharmacological therapy should be considered (p = 0.014, OR 0.71; p = 0.03, OR 0.70, respectively). Steatosis and BMI class had no role.
Conclusion: The data obtained in our study, about elderly subjects, suggest a negligible role of hepatic steatosis and BMI class "per se" in prediction of survival, which need further considerations.

SAT-493

Do patients with abnormal liver tests and nonalcoholic fatty liver disease get statins even when indicated?

R. Rosenblatt[1], A. Buckholz[2], Z. Sherman[2], G. Ghosh[2], C. Lucero[1], A. Jesudian[1], B. Fortune[1], R. Schwartz[1], S. Kumar[1]. [1]*New York Presbyterian Hospital, Weill Cornell Medicine, Gastroenterology and hepatology, New York, United States;* [2]*New York Presbyterian Hospital, Weill Cornell Medicine, Medicine*
Email: RussellRosenblatt@gmail.com

Background and Aims: Hyperlipidemia and other components of metabolic syndrome are often concomitant diseases in patients with nonalcoholic fatty liver disease (NAFLD). Additionally, the most common cause of morbidity and mortality in patients with NAFLD is cardiovascular disease (not liver disease) and statin use is often warranted. However, NAFLD patients commonly have abnormal liver tests and providers can be hesitant to start statins, despite evidence that patients with a baseline elevation in liver enzymes are not at increased risk of hepatotoxicity. The aim of this study is to evaluate statin use in patients with hyperlipidemia using a nationally representative database.
Method: The National Health and Nutrition Examination Survey (NHANES), a nationally-representative survey, from 2005 to 2014 was used. Using a validated algorithm, adult patients with diabetes were included. Patients were excluded if they had viral hepatitis, excessive alcohol consumption, were pregnant, or had transaminase elevation >500 IU/l. Statin use was assessed by NHANES interviewers and hyperlipidemia was defined as an LDL >130 or patient history. Abnormal liver tests were defined as ALT >40 IU/l. Multivariate logistic regression was performed controlling for age and gender to assess for the effect of abnormal ALT on patients with hyperlipidemia, metabolic syndrome, and diabetes.
Results: 136,833,627 weighted participants were included in the sample; 74.6% had hyperlipidemia, 93.5% of which were taking a statin. Patients diagnosed with hyperlipidemia who had abnormal ALT were less likely to take a statin (86.3% vs. 89.1%, p = 0.001). Multivariate analysis noted that, when controlling for age and gender, abnormal ALT significantly decreased the odds of patients taking statins if they had diabetes (OR 0.75, 95% CI 0.57–0.99, p = 0.04), but not metabolic syndrome or hyperlipidemia.

Table 1: Odds of statin use

Variable	OR (95% CI)	P-value
Diabetes	0.75 (0.57–0.99)	0.04
Metabolic syndrome	0.94 (0.75–1.17)	0.60
Hyperlipidemia	1.01 (0.82–1.25)	0.92

*Controlling for age and gender

Conclusion: This study demonstrates that statins are underutilized in patients, who despite having appropriate indications for their use, have abnormal liver tests. When controlling for age and gender, statins are underused in patients with diabetes especially. Further education is needed to encourage providers to use statins to improve cardiovascular outcomes in patients with NAFLD.

SAT-494

The effect of microvascular complications of diabetes on advanced fibrosis in nonalcoholic fatty liver disease

R. Rosenblatt[1], A. Buckholz[2], G. Ghosh[2], A. Jesudian[1], C. Lucero[1], B. Fortune[1], R. Schwartz[1], S. Kumar[1]. [1]*New York Presbyterian Hospital, Weill Cornell Medicine, Gastroenterology and Hepatology;* [2]*New York Presbyterian Hospital, Medicine*
Email: RussellRosenblatt@gmail.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) is a rapidly rising cause of liver disease and transplantation. Diabetes (DM) increases risk of advanced fibrosis, which affects overall and liver-related outcomes. While DM is a risk factor, the effect of glucose control has a less clear impact on advanced fibrosis. As hemoglobin A1c only captures glucose control for 3 months, microvascular changes from DM can be a more accurate long-term marker of glucose control. The aim of this study is to identify the impact of microvascular changes from DM on advanced fibrosis.

Method: The National Health and Nutrition Examination Survey (NHANES), a nationally-representative survey, from 2005 to 2014 was used. Using a validated algorithm, adult patients with DM were included. Patients were excluded if they had viral hepatitis, excessive alcohol consumption, pregnancy, or transaminase elevation >500I U/L. Advanced fibrosis was defined by ALT >40 and an elevated NAFLD fibrosis score, FIB-4 score, or AST to platelet ratio index. Microvascular changes included microalbuminuria, defined as a spot urine albumin:urine creatinine ratio >30 mg/g, and self-reported retinopathy. Multivariate logistic regression evaluated advanced fibrosis and included factors that independently increase the risk of advanced fibrosis.

Results: 13,942,859 weighted participants were included; 24.1% of patients had microvascular changes, of which 16.8% had microalbuminuria. These patients were older, had a higher mean hemoglobin A1c and longer DM duration. On multivariate logistic regression controlling for age, gender, race, and other DM characteristics, microvascular changes were not significantly associated with advanced fibrosis. However, with the same model, microalbuminuria significantly increased the risk of advanced fibrosis (OR 1.95, p = 0.03).

Table 1: Risk of advanced fibrosis

Variable	OR (95% CI)	P-value
Microvascular changes	1.33 (0.74–2.38)	0.34
Microalbuminuria	1.95 (1.06–3.57)	0.03
Retinoapthy	0.48 (0.20–1.16)	0.10

*Controlling for age, gender, race, obesity, DM duration, insulin dependence, and hemoglobin A1c

Conclusion: Using a nationally-representative survey, microvascular changes in sum were not associated with advanced fibrosis. However, microalbuminuria, objectively measured, in comparison to retinopathy, nearly doubled the risk of advanced fibrosis even when controlling for hemoglobin A1c. Further studies are required to better assess the effect of glucose control on advanced fibrosis.

SAT-495

Associations between sarcopenia and nonalcoholic fatty liver disease and advanced fibrosis in the United States

K. Wijarnpreecha[1], M. Scribani[2], D. Kim[3]. [1]*Bassett Medical Center, Internal Medicine, Cooperstown, United States;* [2]*Bassett Research Institute, Bassett Medical Center, Cooperstown, United States;* [3]*Division of Gastroenterology and Hepatology, Stanford University, Palo Alto, United States*
Email: dr.karn.wi@gmail.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) may be associated with sarcopenia, which share risk factors including chronic inflammation, insulin resistance, vitamin D deficiency. This study aimed to determine whether sarcopenia is independently associated with NAFLD and advanced fibrosis in a nationally representative sample of US adults.

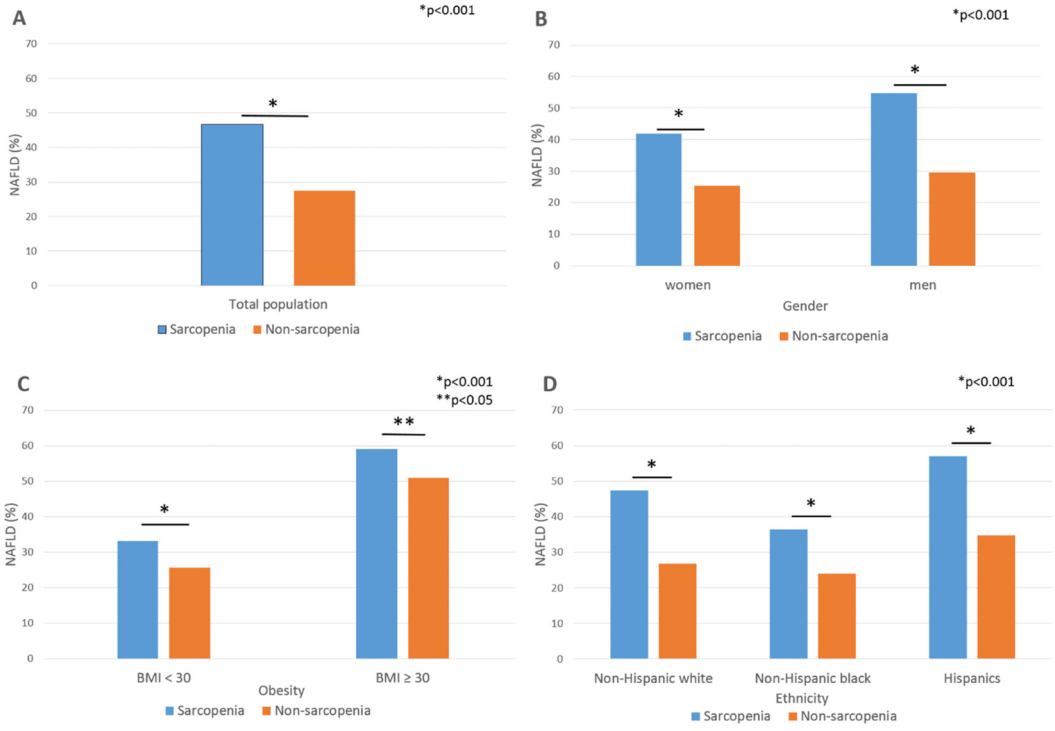


Figure 1: (abstract: SAT-495) Prevalence of NAFLD according to sarcopenia status. (A) Total population, We stratified by (B) gender, (C) obesity status, and (D) ethnicity.

Method: Cross-sectional data from 11,325 participants in the third National Health and Nutrition Examination Survey were analyzed. NAFLD was diagnosed by ultrasonographic hepatic steatosis without evidence of other liver diseases. The presence of advanced fibrosis was determined by the NAFLD fibrosis score. Sarcopenia was defined as skeletal muscle index that was measured by bioelectrical impedance analysis.
Results: NAFLD was more common in subjects with sarcopenia than in those without (46.7% vs. 27.5%), which was consistent in analyses stratified by gender, obesity status, and ethnicity. A univariate analysis showed that sarcopenia was associated with NAFLD (odds ratio [OR], 2.31; 95% confidence interval [CI], 2.01–2.64), which remained significant after adjustment for age, gender, ethnicity, metabolic risk factors, and vitamin D deficiency (OR 1.24; 95% CI 1.03–1.48). This finding persisted even after adjustment for C-reactive protein as a marker of chronic inflammation. Furthermore, NAFLD-associated advanced fibrosis was more common in subjects with sarcopenia than in those without (7.8% vs. 1.6%), which was also consistent in analyses stratified by gender, obesity status, and ethnicity. Sarcopenia was associated with NAFLD-associated advanced fibrosis independent of metabolic risk factors, vitamin D deficiency, and chronic inflammation (OR, 1.79; 95% CI, 1.18–2.72). An additional sensitivity analysis was conducted including insulin resistance in the model with similar results.
Conclusion: In this nationally representative sample of American adults, sarcopenia was independently associated with increased risk of NAFLD and NAFLD-associated advanced fibrosis independent of well-defined risk factors. Interventions to strengthen muscle mass may present an opportunity to reduce the burden of NAFLD and advanced fibrosis.

SAT-496

The platelet count is declining in American adults in parallel with an increase in risk factors for nonalcoholic fatty liver disease

A. Singh[1], A. Vigni[2], A. Tabbaa[3], E. Lawitz[2], F. Poordad[2], A. Scott[2], T. Okubote[2], M. Scott[2], M. Mansouri[2], R. Lopez[4], M. Noureddin[5], N. Alkhouri[2]. *[1]Cleveland Clinic - Main Campus, Gastroenterology and Hepatology, Cleveland, United States; [2]Texas Liver Institute, San Antonio, United States; [3]UC San Francisco, San Francisco, United States; [4]Cleveland Clinic - Main Campus, Cleveland, United States; [5]Cedars Sinai Hospital, Digestive Disease Center, Los Angeles*
Email: singha4@ccf.org

Background and Aims: Platelet count has been shown to be the single most useful laboratory investigation for identifying subclinical cirrhosis of varying etiologies. Evidence suggest that the prevalence of chronic liver disease is on the rise in the US. We aimed to investigate trends in platelet count in the American population and assess its correlation with risk factors for chronic liver disease.
Method: Adult (18 years or older) who participated in the National Health and Nutrition Examination Survey (NHANES) from 1999 to 2014 were identified and divided into 4 time periods (1999–2002, 2003–2006, 2007–2010, 2011–2014). To assess trends in platelet count across the cycles, a linear regression analysis was also performed. Since we combined different NHANES cycles, combined weights were calculated following the instructions provided in the NHANES analytic guidelines.
Results: A total of 19,734 patients were included in the final analysis. There was no difference in gender and age distribution. The platelet count decreased progressively over the years (267 k/uL ± 1.4, 271.9 ± 1.5, 252.3 ± 1.4 and 236.7 ± 1.3, in the 4 time periods respectively; $p < 0.001$). No differences were noted between the time periods in terms of the average number of alcoholic drinks per day or prevalence of chronic viral hepatitis. On the other hand, significant increases were noted in the prevalence of all the major risk factors for nonalcoholic fatty liver disease (NAFLD) including central obesity (45.7% in 1999–2002 to 52.2% in 2011–2014), diabetes (7.5% to 9.6%), glycohemoglobin % (5.3 to 5.5), hypertriglyceridemia (31.6% to 36.2%), and metabolic syndrome (22.9% to 25.3%), $p < 0.001$ for all. Interestingly, Mexican-Americans, an ethnic group with known increased risk for NAFLD, had a steeper decline in platelet count compared to Caucasians.
Conclusion: Over the past 2 decades, the average platelet count in the US general population has decreased by more than 40 k/ul. There was no increase in alcohol consumption or viral hepatitis during the same time period but significant increases of risk factors for NAFLD were present.

SAT-497

Real world evidence showing high rates of cardiovascular events in NAFLD patients regardless of liver disease

A. Sanyal[1], K. Cusi[2], R.J. Firpi[3], N. Gitlin[4], C. Levy[5], L. Malahias[6], R. Reddy[7], C. Schoen[6], L.M. Weiss[8], A. Lok[9]. *[1]Virginia Commonwealth University, Division of Gastroenterology and Hepatology, and Nutrition, Richmond, United States; [2]University of Florida, Division of Endocrinology, Diabetes, and Metabolism, Gainesville, United States; [3]University of Florida, 1600 SW Archer Road, Gainesville, United States; [4]Atlanta Gastroenterology Associates; 550 Peachtree Street NE, Suite 1720, Atlanta, United States; [5]University of Miami Miller School of Medicine; [6]TARGET PharmaSolutions, Inc., Chapel Hill, United States; [7]University of Pennsylvania, Hospital of the University of Pennsylvania, Division of Gastroenterology and Hepatology, Philadelphia, United States; [8]Gastro Florida, Clearwater, United States; [9]University of Michigan, Division of Gastroenterology and Hepatology, Ann Arbor, United States*
Email: lmalahias@targetpharmasolutions.com

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) affects approximately 30% of the adult population in North America. NAFLD is associated with increased cardiovascular (CV) events and mortality. Most of the existing data are derived from tertiary care centers. There is a need for "real-world" data to confirm the prevalence of CV disease in those with NAFLD. We sought to define the profile of CV risk factors in those with nonalcoholic fatty liver (NAFL), nonalcoholic steatohepatitis (NASH), and NAFLD cirrhosis in a real-world cohort of participants with NAFLD.
Methods: TARGET-NASH is a prospective study of the entire spectrum of NAFLD in the community and enrolls participants from a variety of clinical settings using commonly used, pragmatic case definitions. Across group comparisons were made by ANOVA. CV events were defined as myocardial infarction, stroke, angina, or cardiac interventions. CV disease history was defined as any cardiac disorder. A multivariable regression analysis was performed to identify factors associated with CV events.
Results: A total of 1494 participants (NAFL = 359, NASH = 574, NAFLD cirrhosis = 561) were studied. The median age was similar across groups (55–62 years) but the proportion of participants >50 years of age was highest in those with cirrhosis. Participants with NAFLD cirrhosis had a higher prevalence of type 2 diabetes (66.8 vs 37.3 vs 21.7%), hypertension (64.5 vs 50.0 vs 47.6%), dyslipidemia (39.6 vs 37.9 vs 22.6%), sleep apnea (28.3 vs 19.3 vs 6.7%), and ever smoked status, yes (54.7 vs 40.8 vs 46.8%), than those with NASH or NAFL, respectively ($p < 0.0001$ for all comparisons except ever smoked $p = 0.0003$). A significantly higher proportion of participants with NAFLD cirrhosis had ≥1 CV event (15.7 vs 7.1 vs 6.4%, $p < 0.0001$) and CV disease history (26.4 vs 17.2 vs 13.9%, $p < 0.0001$). Multivariate regression identified age, race, gender, dyslipidemia, smoking, and sleep apnea as independent predictors of experiencing ≥1 CV events. NAFLD cirrhosis was also identified as an independent predictor relative to NASH and NAFL.
Conclusion: A high proportion of participants with NAFLD have risk factors for CV disease and a high proportion regardless of disease severity experienced ≥1 CV event. Attention to CV diseases along with liver diseases is important in all patients with NAFLD.

SAT-498

The relationship between NAFLD and breast cancer: High prevalence and poor prognosis

Y.-S. Lee[1], C.U. Lee[1], S.J. Suh[2], Y.K. Jung[1], J.H. Kim[1], Y.S. Seo[3], H.J. Yim[4], J.E. Yeon[1], K.S. Byun[4]. *[1]Korea University College of Medicine, Department of Internal Medicine, Seoul, Korea, Rep. of South; [2]Korea University Ansan Hospital, Department of Internal Medicine, Ansan-si, Gyeonggi-do, Korea, Rep. of South; [3]KUMC Anam hospital, Internal Medicine, Korea, Rep. of South; [4]Korea University College of Medicine, Department of Internal Medicine, Gyeonggi-do, Korea*
Email: jeyyeon@hotmail.com

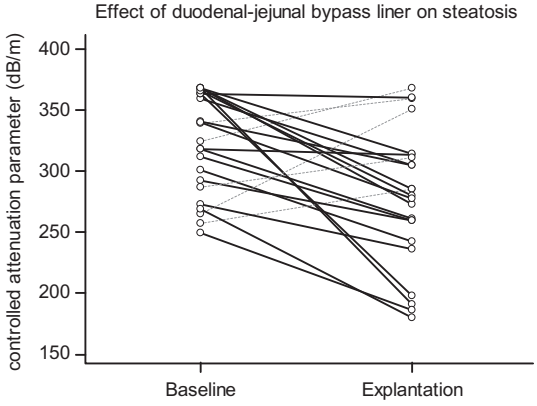
Background and Aims: Breast cancer is most common cancer in women worldwide, and it is a main cause of death in women. The incidence of breast cancer is correlated with metabolic component including diabetes, hypertension, and obesity. Likewise breast cancer, metabolic components are important risk factors for development of nonalcoholic fatty liver disease (NAFLD). In this study, we analyzed the prevalence of NAFLD in patients with breast cancer and the effect of NAFLD on the prognosis of breast cancer.
Method: Total 492 patients with breast cancer who received operation were enrolled from January 2010 to June 2014. Patients who had other chronic liver disease including chronic viral hepatitis B/C, autoimmune hepatitis, and primary biliary cholangitis and significant alcohol abuse (more than 140 g/week in women and 210 g/week in men) were excluded. Hepatic steatosis was evaluated by non-enhanced computed tomography (CT) scan. We measured values of regions of interest (ROI) for 5 times in liver and spleen, respectively. We diagnosed NAFLD when the average ROI of liver is higher than it of spleen 15 or more. 135 healthy controls who took non-enhanced CT scan were also analyzed.
Results: Mean age and BMI were 51.6 ± 11.0 years and 24.7 ± 9.9 kg/m^2, respectively. The prevalence of DM and hypertension were 9.5% and 24.6%, respectively. The prevalence of NAFLD in patients with breast cancer was 43.5% (214/492) and it was significantly higher comparing with healthy control (29.6%, 40/135) ($p = 0.004$). Overall survival did not showed significant difference between NAFLD group and non-NAFLD group ($p = 0.958$ by log-rank test). However, recurrence rate was significantly higher in patients with NAFLD (10.7%, 23/214) comparing with those without NAFLD (5.4%, 15/278) ($p = 0.027$). The disease free survival was significantly higher in in patients with NAFLD comparing with those without NAFLD ($p = 0.033$ by log-rank test). 15.9% of patients (34/214) experienced ALT elevation above 3 times of upper normal range, whereas only 10.4% of patients (29/278) showed elevation of ALT above 3 times of upper normal range ($p = 0.049$).
Conclusion: The prevalence of NAFLD in patients with breast cancer is significantly high compared to healthy control group. Moreover, breast cancer patients with NALFD showed poor prognosis in aspect of recurrence. Therefore, diagnostic evaluation of NAFLD would be important in patients with breast cancer.

SAT-499

Impact of duodenal-jejunal bypass liner on non-alcoholic fatty liver disease

T. Karlas[1], J. Feisthammel[1], T. Schütz[2], M. Blüher[3], R. Lichtinghagen[1], V. Keim[1], A. Hoffmeister[1], J. Wiegand[1]. *[1]Universitätsklinikum Leipzig, Klinik für Gastroenterologie und Rheumatologie; [2]Universitätsklinikum Leipzig, IFB Adipositas Erkrankungen; [3]Universitätsklinikum Leipzig, Klinik für Endokrinologie und Nephrologie*
Email: johannes.wiegand@medizin.uni-leipzig.de

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) is strongly linked to obesity and type 2 diabetes mellitus (T2DM). Bariatric surgery induces weight loss, improves T2DM and NAFLD in morbidly obese patients. The endoscopically implanted duodenal-jejunal bypass liner (DJBL) is a less-invasive alternative to bariatric surgery, however data on the influence of NAFLD are limited so far. Thus, we characterized NAFLD after DJBL insertion.
Method: In patients undergoing DJBL treatment for T2DM and/or obesity NAFLD was prospectively characterized by liver stiffness measurement (transient elastography (TE) using M- and XL-probe as appropriate) including controlled attenuation parameter (CAP), and by the enhanced liver function (ELF) score. Alanine-aminotransferase (ALT), gamma-glutamyltransferase (GGT) and ferritin were used as parameters of hepatic inflammatory activity.
Results: DJBL was inserted in 31 patients and explanted in two cases after <2 weeks due to abdominal discomfort. Thus, 29 patients (59% female, median age 57 years) underwent DJBL treatment for a median period of 12 months (range 6.2–16.7). All of these achieved a significant weight loss (median loss 10%; BMI baseline 39.5 ± 8.6 vs. 35.2 ± 8.2 kg/m² at end of treatment, $p < 0.001$) and 52% an improvement of T2DM (HbA1c 7.3 ± 1.3 vs. 7.0 ± 12%, $p = 0.154$).
Serial TE/CAP and ELF values between baseline and end of DJBL treatment were available in 23 and 26 patients, respectively.
CAP improved from 332 (249–368) to 283 (180–368) dB/m ($p = 0.003$, Figure), ALT, GGT, and ferritin from 0.63 (0.31–4.41) to 0.43 (0.18–3.46) µkat/l ($p < 0.001$), 0.66 (0.22–7.74) to 0.37 (0.11–5.46) µkat/l ($p < 0.001$), and 147 (18–487) to 61 (9–402) ng/ml ($p < 0.001$), respectively. The number of patients with ALT, GGT and ferritin values upper the normal limit decreased from 11 to 3, 10 to 3, and 8 to 1.



Hepatic fibrosis assessed by TE (6.3 (3.6–23.4) vs. 4.9 (3–11.6) kPa) and ELF (9.00 (7.96–11.29) vs. 9.02 (7.93–10.77)) did not improve significantly. The number of patients with TE >7.9 kPa or ELF >9.8 was 4 vs. 4 and 4 vs.2.
Conclusion: DJBL is an effective option for endoscopic treatment of obesity and improves hepatic steatosis and inflammatory activity within a short period of time.

SAT-500

Nonalcoholic fatty liver disease in the first trimester and subsequent development of gestational diabetes: A prospective cohort study

W. Kim. *Boramae Medical Center, Internal Medicine, Seoul, Korea, Rep. of South*
Email: wonshiri@yahoo.com

Background and Aims: Recent evidences suggest that nonalcoholic fatty liver disease (NAFLD) is associated with impaired glucose tolerance and may be a manifestation of metabolic syndrome. We explored whether NAFLD can also be an independent risk factor for gestational diabetes in pregnant women.
Method: In this prospective cohort study, singleton pregnant women were assessed for NAFLD at 10–14 weeks by two different approaches: (1) the appearance of the liver on ultrasound and (2) the Fatty Liver-Index (FLI). Stored maternal blood samples at the time of liver ultrasound were assayed for adiponectin and selenoprotein. Patients were screened for gestational diabetes using the two-step approach (50 g oral glucose screening test followed by 100 g glucose tolerance test) at 24–28 weeks.

Results: (1) Among 608 women enrolled in the study, the prevalence of NAFLD was 18.4% based on liver ultrasound, and 5.9% (36/608) of women developed gestational diabetes; (2) Patients with gestational diabetes had higher rate of fatty liver in ultrasound, and had also higher fatty liver index; (3) The risk of subsequent gestational diabetes was significantly increased in cases with NFALD, and appeared to be related to the severity of the disease. This relationship between NAFLD and gestational diabetes remained significant after adjustment for clinical variables and HOMA-IR; (4) The prediction model constructed with clinical factors and fatty liver index predicted better the risk of gestational diabetes than that with clinical factors alone; (5) The maternal serum adiponectin and selenoprotein were closely correlated with both NAFLD and the risk for gestational diabetes.
Conclusion: The sonographic and/or biochemical evidence of NAFLD in early pregnancy is an independent risk factor for gestational diabetes. Both adiponectin and selenoprotein may be the biomarker linking NAFLD and gestational diabetes.

SAT-501

Plasma cells in non-alcoholic steatohepatitis correlates with disease activity

M. Lamba[1], C. Stedman[1,2], J. Ngu[1]. [1]*Christchurch Hospital, Department of Gastroenterology, Christchurch, New Zealand;* [2]*University of Otago, Christchurch, New Zealand*
Email: Mehullamba@gmail.com

Background and Aims: Plasma cells are often seen in liver specimens of patients with non-alcoholic steatohepatitis (NASH), however their significance is not known. We aimed to compare the clinical phenotypes of NASH based on the presence or absence of plasma cell: plasma-cell positive NASH (Ppos-NASH) and plasma-cell negative NASH (Pneg-NASH).
Method: All patients diagnosed with NASH between 01/01/2006 and 31/12/2016 were included. The diagnosis of NASH was confirmed if steatosis was present in over 5% of hepatocytes and non-alcoholic fatty liver disease activity score (NAS) was 3 or more. Patients with significant alcohol consumption (>14 units/week for females, >21 units/week for males), autoimmune liver disease, viral hepatitis, metabolic and hereditary liver diseases were excluded. Diagnosis of Ppos-NASH was based on detection of any number of plasma cells on liver biopsy. Liver decompensation was defined as development of any of the following: ascites, hepatic encephalopathy, hepato-renal syndrome or hospital admission with variceal bleeding.
Results: Sixty consecutive patients with diagnosis of NASH were included. The mean age at presentation was 49 years and 53.3% patients were male. Plasma cells were present in liver histology of 26.7% patients. Majority of patients with Ppos-NASH were female (68.7%) compared to Pneg-NASH (42.5%) ($p < 0.05$). Ppos-NASH patients had higher degree of steatohepatitis at the time of first biopsy compared to Pneg-NASH patients (mean NAS score 5.06 compared to 4.05, $p < 0.05$). Presence of plasma cells was not correlated to age at presentation or presence of advanced fibrosis. Levels of anti-neutrophil antibody, albumin, alanine aminotransferase and aspartate aminotransferase were not significantly different in Ppos-NASH compared to Pneg-NASH. During a median follow-up of 6 years, the risk of liver-decompensation in Ppos-NASH was 19.64% (95%CI 4.77–62.44), which was not significantly different from Pneg-NASH – 7.3% (95%CI 2.51–22.45). Similarly, overall survival at 6 years was not significantly different between Ppos-NASH and Pneg-NASH patients at 84.61% (95%CI 51.22–95.91) and 74.9% (95%CI 56.55–86.36) respectively.
Conclusion: We demonstrate that presence of plasma cells in NASH is associated with higher grade of inflammation, but not with presence of advanced fibrosis. It is not known whether plasma cells actively contribute to liver inflammation or are an epiphenomenon.

SAT-502

Cardiovascular risk factors and fibrosisseverity in NAFLD: is there a link?

D. Roccarina[1], M. Guerrero[1], L.I. Prat[1], E. Buzzetti[1], A. Goyale[1], F. Arico[2], F. Arico'[1], M. Rosselli[1], M. Pinzani[1], E. Tsochatzis[1]. [1]*UCL Institute for Liver and Digestive Health, Sheila Sherlock Liver Unit, Royal Free Hospital, London, United Kingdom,* [2]*University Hospital and School of Medicine, Department of Internal Medicine, Messina, Italy*
Email: davideroccarina@gmail.com

Background and Aims: It is well documented that patients with NAFLD have an increased cardiovascular risk due to the presence of metabolic comorbidities. However, it is not clear whether cardiovascular risk is associated with an increased risk of liver disease in patients with NAFLD. Carotid artery intima media thickness (CCA IMT) can be used as a predictor of increased cardiovascular risk. Therefore, we evaluated if IMT correlates with fibrosis severity in such patients.
Method: Consecutive patients with NAFLD were included. Transient elastography (TE) with FibroScan (Echosens) was performed in all patients and significant fibrosis was defined as a liver stiffness (LS) value ≥ 7.2 kPa. Abdominal fat thicknesses (subcutaneous minimum and maximum (SCmin, SCmax), pre-peritoneal (PP), peri-renal (PR), visceral (VF) and abdominal fat index (AFI, PP/SCmin), epicardial fat thickness (EF), spleen size (SS) and CCAs IMT were measured using Affiniti 70G ultrasound (Philips). A right CCA IMT >75 percentile was considered as significant predictor of cardiovascular disease according to published data.
Results: We enrolled 319 consecutive patients with NAFLD, 56.3% male, mean age 54 ± 13y, BMI 31.7 ± 5.8 kg/m2, waist circumference (WC) 107 ± 15 cm, 44% with diabetes, 55.7% hypertension, 81% hyperlipidaemia.
In the univariate analysis, a LS value ≥ 7.2 kPa was associated with diabetes, hypertension, right CCA IMT >75 percentile, age, BMI, WC, VF, SS, cholesterol, platelets, AFI, EF, GGT and ALT. In the multivariate analysis predictors of significant liver fibrosis were diabetes (OR 3.652, 95%CI 1.814–7.354, p = <0.0001), AFI (OR 0.549, 95% CI 0.342–0.881, p = 0.013), SS (OR 1.305, 95% CI 1.080–1.577, p = 0.006) and ALT (OR 1.012, 95% CI 1.004–1.020, p = 0.003). Conversely, predictors of a right CCA IMT > 75 percentile were increasing age (OR 1.096, 95%CI 1.060–1.134, p < 0.0001) and waist circumference (OR 1.034, 95%CI 1.010–1.057, p = 0.005). In the subset of 112 patients with available liver biopsy, the presence of NASH or significant fibrosis was not associated with an increased CCA IMT or epicardial fat.
Conclusion: Significant liver fibrosis is independent of increased cardiovascular risk in patients with NAFLD and is mainly associated with presence of diabetes, increasing ALT and decreasing AFI. Therefore, the progression of liver fibrosis is at least in part due to factors which are independent of the general features conditioning cardiovascular risk in patients with metabolic syndrome. Targeted interventions for components of the metabolic syndrome should be offered to all NAFLD patients irrespective of the severity of the underlying liver disease.

SAT-503

Prevalence, severity and patterns of clinicalpractice in outpatient visits for suspected NAFLD – the German CONSTANS STUDY

J. Schattenberg[1], U. Schönnenbeck[2], W. Marcus[1], P.R. Galle[1], D. Schuppan[3], Q. Anstee[4], R. Pais[5], V. Ratziu[5]. [1]*University Medical Center Mainz, Department of Medicine, Mainz, Germany;* [2]*University Medcial Center Mainz, Department of Medicine, Mainz;* [3]*Institute of Translational Immunology, Research Center for Immune Therapy (FZI), University Medical Centre Mainz, Mainz, Germany;* [4]*Institute of Cellular Medicine, Newcastle-upon-Tyne, United Kingdom;* [5]*Hôpital La Pitié Salpêtrière, Hepatology, Paris, France*
Email: joern.schattenberg@unimedizin-mainz.de

Background and Aims: Non-alcoholic fatty liver disease (NAFLD) has become one of the most prevalent chronic liver diseases in

Western countries but no real-world data on the burden of NAFLD on health-care resources are available from European countries. The proportion of patients with NAFLD seen in outpatient visits and the utilization of medical resources for the management of these patients are unknown. This study aimed to assess the prevalence of NAFLD among outpatients in a specialized liver clinic at a tertiary care center.

Method: All outpatient visits at the liver clinic of the University Medical Center Mainz over a total of 20 weeks in 2 independent intervals in 2016 and 2017 were included. Data of patients with suspected NAFLD from the 2016 cohort was available for a 6 month follow-up study and the utilized resources, final diagnosis and disease severity was analyzed in this group. The cohort is part of the pan-European EPoS CONSTANS study.

Results: A total of 1973 patients (mean age 51.9 ± 15.3 y, 51% females) were seen in the outpatient clinic. Among the 2016 cohort 15.6% were newly addressed for suspected NAFLD, 40.5% for chronic viral hepatitis, 8.7% for alcoholic liver disease, 2.2% for suspected gastrointestinal cancer, and 28.7% for miscellaneous reasons. In the work-up of these patients, a follow-up visit was scheduled in 78%, 89% of patients underwent additional blood tests, 72% imaging by ultrasound and 20% Fibroscan. A liver biopsy was ordered in 7% and 2.4% of patients were hospitalized. Patients with suspected NAFLD presented with steatosis on imaging studies (2.3%), altered liver function tests (5.9%), known NAFLD (7.8%), increased ferritin level (0.1%) or cirrhosis of unknown origin (3.9%). In the 6 months following the initial 2016 consultation, NAFLD was confirmed in 50% of cases. In this group 23% were diagnosed with NASH on liver biopsy, 10% NAFL on liver biopsy and 9% had NAFLD cirrhosis. 14% of patients did not undergo biopsy but remained with suspected NAFLD. In 24% of patients a final diagnosis was not established in the 6 month follow-up period. The resources utilized to reach these diagnosis was ultrasound in 86%, 31% Fibroscan, 5% MRI, 8% CT, and 37% liver biopsy. In the group of patients that underwent liver biopsy during follow-up, NASH was found in 37% and advanced fibrosis/cirrhosis in 41%. Cost analyses for medical resource utilization will be presented.

Conclusion: In this prospective study, based on real-world data, 15.6% of patients at a Hepatology outpatient clinic were referred with a presumptive diagnosis of NAFLD, which was the second most common cause of consultation. Of these, half had confirmed NAFLD including 46% (3.1% of the entire cohort in 2016) with advanced fibrosis/cirrhosis. Both the prevalence of this condition and medical resource utilization and related costs are indicative of the substantial burden of disease NAFLD places on hepatological practice.

SAT-504

Analyze of ballooning biomarker in patients with non-alcoholic steatohepatitis: A multicenter study

Y. Honda[1], T. Kessoku[1], W. Tomeno[1], K. Imajo[1], M. Yoneda[1], S. Saito[1], T. Nakahara[2], S. Ooeda[3], H. Takahashi[3], H. Hyogo[4], Y. Eguchi[5], A. Nakajima[1]. *[1]Yokohama City University School of Medicine; [2]Hiroshima University; [3]Saga Medical School; [4]JA Hiroshima General Hospital; [5]Saga Medical School*
Email: rainbowman0803@gmail.com

Background and Aims: The progression of non-alcoholic fatty liver disease (NAFLD) has been considered to be complex involving multiple genetic factors interacting with the environment and lifestyle, however, the fundamental pathophysiology of NASH is still unknown. Recently, paired liver biopsy studies revealed that the annual fibrosis progression rate was found to be 0.07 stages for nonalcoholic fatty liver (NAFL) and 0.14 stages for patients with NASH. This means that it is important to noninvasively diagnose the presence or absence of ballooning, which is characteristic pathological findings diagnosis for NAFL or NASH. This study aimed to understand pathophysiology of NAFLD and to identify novel blood markers sensitive to ballooning.

Method: A total of 135 patients with NAFLD (NAFL = 88, NASH = 47) between 2014 and 2016 were enrolled from four Hepatology centers in Japan. NASH was diagnosed by steatosis, lobular inflammation, and hepatocyte ballooning. For the histological feature scoring system, we used the NAFLD activity score. Fibrosis were scored independently using the NASH Clinical Research Network scoring system. RNA-seq data analysis from liver biopsy samples was obtained from Ion Proton system, and pathway enrichment analysis was performed based on the known pathways from Ingenuity Pathways analysis. Metabolomics profiling analysis were carried out in plasma samples. Ethical approval for this study was given by the respective Institutional Review Board and subject written informed consent was obtained for all subjects.

Results: Potential pathways highly correlated with fibrosis stage and ballooning score, e.g. Coagulation System and Axonal Guidance Signaling were identified in NGS profiling in the NAFLD-related subjects. Plasma type IV collagen 7S was highly correlated with ballooning score (correlation coefficient = 0.47), and potential secreted collagens may be a diagnostic marker for ballooning. The metabolomics study indicated plasma metabolites including ether-linked lyso-phospholipids were possible biomarkers of NASH and established a new non-invasive score model, which included lisophosphatidylcholine (LPC) (e-16:0), phosphatidylcholine (PC) (aa-32:0) and xanthine to estimate ballooning score of NASH.

Conclusion: The potential pathways and the potential blood biomarkers need to be evaluated further and may result in target identification in drug discovery and non-invasive diagnosis in NASH.

SAT-505

Health-related quality of life correlates with histological severity in non-alcoholic fatty liver disease

Y. Huber[1], C. Labenz[1], T. Siebler[1], B. Straub[2], M.-A. Wörns[1], P. Galle[1], K. Hallsworth[3], M. Boyle[3], Q. Anstee[3], J. Schattenberg[1]. *[1]I. Department of Medicine, University Medical Center of the Johannes Gutenberg University, Mainz, Germany; [2]University Medical Center of the Johannes Gutenberg University Mainz, Institute of Pathology; [3]Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, United Kingdom; Liver Unit, Newcastle Upon Tyne Hospitals NHS Trust, Freeman Hospital, Newcastle upon Tyne, United Kingdom*
Email: yvonne.huber@unimedizin-mainz.de

Background and Aims: Chronic liver disease potentially exerts a negative effect on a patient's health-related quality of life (HRQL). Aim of the current study was to explore the impact of disease severity defined by liver histology in patients with non-alcoholic fatty liver disease (NAFLD) on patient reported outcomes (PROs).

Method: As part of recruitment into the prospective EPoS NAFLD Registry, the Chronic Liver Disease Questionnaire (CLDQ), a liver disease specific instrument to assess HRQL, was measured in NAFLD patients within 6 months of routine diagnostic liver biopsy at centers in UK (Newcastle) and Germany (Mainz). A low score represents a lower quality of life.

Results: A total of 247 patients (54.3% male) were included in this study. The mean age was 52.1 (± 12.7) years. Mean CLDQ-overall score was 4.9 (± 1.3) and ranged from the lowest 4.2 (category: worry) to highest 5.4 (category: activity). Women exhibited a significantly lower CLDQ overall score than men (mean (SD) 4.6 (± 1.3) vs. 5.2 (± 1.2), $p < 0.01$). Reflecting lower HRQL, there was a negative correlation between overall CLDQ score and both BMI and presence of type 2 diabetes mellitus ($p < 0.05$). Laboratory parameters, especially liver function tests had no influence on HRQL. In contrast, histological features of NAFLD on liver biopsy had a significant impact on HRQL. Patients with a lower Steatosis-Activity-Fibrosis-score (SAF) showed higher HRQL (SAF0 vs. SAF3: 5.2 (± 1.5) vs. 4.4 (± 1.4), $p < 0.05$). Advanced fibrosis and cirrhosis (F3/F4) was observed in 103 patients

(41.7%) and these patients reported a significantly lower HRQL compared to patients with early or intermediate fibrosis (F0-2) (F3-4 vs. F0-2.: 4.8 (± 1.2) vs 5.1 (± 1.3), p < 0.05).
Conclusion: There is a substantial symptom burden in patients with NAFLD. Histological disease severity negatively impacts the reported HRQL, with an effect evident even in the absence of cirrhosis. Hepatic inflammation and fibrosis had the most profound effect on patient-related outcomes (PROs).

SAT-506

Influence of non-alcoholic fatty liver disease on cardiovascular risk in patients with stable coronary heart disease

I. Vakalyuk. *Ivano-Frankivsk national Medical University, Internal Medicine Department, Ivano-Frankivsk, Ukraine*
Email: ivakal5@gmail.com

Background and Aim: To evaluate the contribution of non-alcoholic fatty liver disease (NAFLD) in predicting risk of major cardiovascular events by cumulative proportion surviving depending on the SYNTAX score (SS) I in patients with stable coronary heart disease (CHD).
Method: 147 patients (aged: 54.2 ± 5.7 years) with stable CHD who have had an acute coronary syndrome with an indication of percutaneous coronary interventions more than 3 months ago were examined. Patients were categorized into 3 groups according to the SS I value, calculated during acute coronary event: Group I – SS I value was less than 22 (n = 61); Group II – SS I value was from 23 to 32 (n = 57); Group III – SS I value was more than 32 (n = 28). In each group, patients without NAFLD (subgroup A), with nonalcoholic steatosis (subgroup B) and with nonalcoholic steatohepatitis (NASH) (subgroup C) were identified. General clinical examination, ECG, EchoCG, liver elastography, liver ultrasound, evaluation of the liver functional state were performed to all patients. Each coronary lesion based on angiogram at the time of acute coronary event was scored to SS I, which was calculated with the SS I online calculator. Survival analysis based on Kaplan–Meier curves was evaluated by a two-year cumulative proportion surviving (%), the difference between groups was determined by Cox's F and Gehan's Wilcoxon tests.
Results. It was established that stable CHD course by SS I values depends on the presence and severity of NAFLD. In particular, in Group I NAFLD was observed in 14 (23.0%) patients: nonalcoholic steatosis was in 12 (19.7%) patients; NASH – in 2 (3.3%) patients. Moreover, 47 (77.0%) patients of Group I had no signs of NAFLD (p < 0.05). In Group II 20 (35.1%) patients were with nonalcoholic steatosis; 12 (21.1%) patients – with NASH; 25 (43.9%) patients – without NAFLD (p < 0.05). The most severe course of stable CHD was observed in patients of Group III: 7 (25.0%) patients were without NAFLD; 9 (32.1%) patients – with nonalcoholic steatosis; 12 (42.9%) patients – with NASH (p < 0.05). A two-year cumulative proportion surviving was the highest in patients without NAFLD: it was 89.6% at Group IA; 72.8% – at Group IIA; 63.7% – at Group IIIA (p < 0.05) respectively. In patients with nonalcoholic steatosis a two-year cumulative proportion surviving was significantly lower: 74.1% – at Group IB; 62.2% – at Group IIB; 55.6% – at Group IIIB (p<0.05) respectively. The lowest a two-year cumulative proportion surviving in patients with NASH was observed: 62.3% – at Group IC; 53.7% – at Group IIC; 43.9% – at group IIIC (p < 0.05) respectively.
Conclusion: The course of stable CHD depends on the NAFLD presence and severity and is the most prognostically unfavorable in patients with NASH. The severe course of NAFLD forms a high risk of major cardiovascular events by SS I values and causes a significant decrease of a two-year cumulative proportion surviving in patients with stable CHD combined with NAFLD.

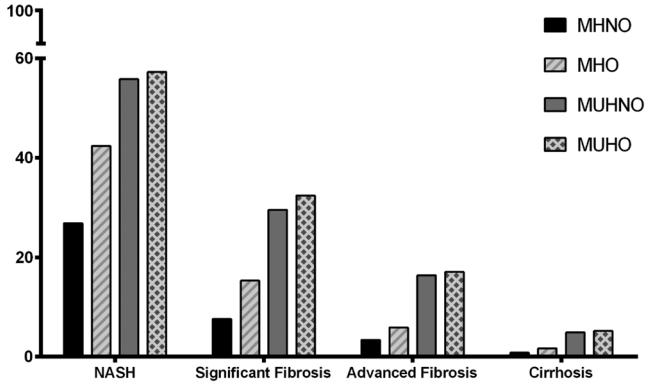
SAT-507

Metabolically unhealthy status impacts on the risk of significant liver injury in biopsy-proven NAFLD patients beyond obesity

J. Ampuero[1], R. Aller[2], R. Gallego-Durán[3], J. Banales[4], J. Crespo[5], N. Mora-Cuadrado[2], C. Garcia-Monzon[6], M.J. Pareja[7], E. Vilar-Gomez[8], R. Jiménez-Agüero[4], J. Caballería[9], M.T.A. Loste[5], D. Escudero-García[10], J. Gómez-Camarero[11], J.L.C. Panero[12], D.A. De Luis Román[2], Á. Gónzalez-Rodriguez[6], M. Latorre[13], A. Albillos[14], V. Aguilar-Urbano[15], J. Salmerón[16], J.L. Olcoz-Goñi[17], P. Aspichueta[18], Á. Santos-Laso[4], O.L. Iacono[19], P. Iruzubieta[5], I. Graupera[9], M. García-Torres[10], E. Badia-Aranda[11], J.A. Guerra[12], R. Francés[20], H. Pastor[3], E.D. Pozo-Maroto[6], M. Diago[13], R. Martin-Mateos[14], S. Benlloch[21], C. Fernández-Rodríguez[22], F.J.G.-S. Rey[23], P. Estevez[24], R.J. Andrade[25], J. Turnés[26], M.R. Gomez[3]. *[1]Institute of Biomedicie of Seville (IBIS), Sevilla, Spain; [2]Hospital Clínico Universitario de Valladolid. Centro de Investigación de Endocrinología y Nutrición. Universidad de Valladolid, Spain; [3]Hospital Universitario Virgen del Rocio, Sevilla. Instituto de Biomedicina de Sevilla. CiberEHD. Spain; [4]Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute – Donostia University Hospital – University of the Basque Country (UPV/EHU), Ikerbasque, CIBERehd, San Sebastián, Spain; [5]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [6]Liver Research Unit Hospital Universitario Santa Cristina Instituto de Investigación Sanitaria Princesa Madrid, Spain; [7]Hospital Universitario Juan Ramón Jiménez, Huelva, Spain, Spain; [8]Instituto Nacional de Gastroenterología, La Habana, Cuba, Cuba; [9]Liver Unit. Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBPAS). Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD). Barcelona, Spain; [10]Hospital Clínico de Valencia, Spain; [11]Hospital Universitario de Burgos, Spain; [12]Hospital Universitario Puerta de Hierro, Madrid, Spain; [13]Hospital General Universitario de Valencia, Spain; [14]Hospital Universitario Ramón y Cajal, Madrid, Spain; [15]Agencia Sanitaria Costa del Sol, Marbella, Spain, Spain; [16]Hospital Universitario San Cecilio, Granada, Spain, Spain; [17]Hospital Universitario de León, Spain, Spain; [18]Biocruces Research Institute, Barakaldo. Department of Physiology, Faculty of Medicine and Nursing, University of Basque Country UPV/EHU, Leioa, Department of Physiology, Faculty of Medicine and Nursing; [19]Hospital Univeristario Tajo, Aranjuez, Spain, Spain; [20]CIBERehd-Hospital General Universitario de Alicante. Universidad Miguel Hernández., Spain, Spain; [21]Hospital Universitari i Politecnic La Fe, Valencia. CIBERehd, Spain, Spain; [22]Hospital Universitario Fundación de Alcorcón, Universidad Rey Juan Carlos, Spain, Spain; [23]Hospital Universitario La Paz, CIBERehd, Madrid, Spain; [24]Complejo Hospitalario Universitario de Vigo, Spain, Spain; [25]Unidad de Gestión Clínica de Enfermedades Digestivas, Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain, Spain; [26]Complejo Hospitalario de Pontevedra, Spain, Spain*
Email: javi.ampuero@gmail.com

Background and Aims: Metabolically healthy obesity (MHO) coud explain the reduced risk compared with metabolically unhealthy obesity (MUHO), while some non-obese people are at risk of NAFLD-related outcomes (metabolically unhealthy non-obesity, MUHNO) in opposite to non-obese subjects with a few metabolic risk (metabolically healthy non-obesity, MHNO). We aimed to define the impact of the metabolically healthy status on the outcomes of obese and non-obese patients showing biopsy-proven NAFLD.
Method: We designed a multi-center cross-sectional study, including 1,058 biopsy-proven NAFLD patients from the HEPAmet Spanish registry. Metabolically healthy status was strictly defined by the lack of metabolic risk factors (T2DM, low HDL, hypertriglyceridemia, arterial hypertension). NASH and significant fibrosis (F2-4) were identified by SAF and Kleiner scores. CKD-EPI equation was used to assess the kidney function. The atherogenic index of plasma was calculated by triglycerides/HDL-c.
Results: NASH and significant fibrosis were present in 52.2% (552/1058) and 12.9% (137/1058). MHO (OR 1.88 (95%CI 1.00–3.66);p =

0.050), MUHNO (OR 3.70 (95%CI 2.11–6.46);p < 0.0001) and MUHO (OR 3.47 (95%CI 2.05–5.87);p < 0.0001) were independently related to NASH together with HOMA, ALT levels, and platelets. Significant fibrosis was more frequently observed in MUHNO (OR 3.89 (95%CI 1.57–9.61);p = 0.003) and MUHO (OR 3.92 (95%CI 1.63–9.44);p = 0.002)), together with platelets, albumin, ALT, HOMA, and age, in comparison with obese and non-obese patients with healthy status. MUHNO showed higher liver damage than obese people with healthy condition (NASH 55.8% (126/226) vs. 42.4% (50/118); p < 0.05; significant fibrosis 31.7% (260/821) vs. 11.4% (27/237); p < 0.0001), despite they showed significant differences in weight (BMI 42 ± 9 vs. 27 ± 2)(Fig). Glomerular filtration rate was lower in the presence of unhealthy (91.7 ± 18) than healthy metabolism (95.6 ± 17) (p = 0.007). Pathological atherogenic index was higher in patients with adverse metabolism conditions (p = 0.0001).



Conclusion: Metabolic unhealthy status showed a greater prevalence of NASH, significant fibrosis, kidney dysfunction and atherogenic profile. Interestingly, there were no differences between obese and non-obese patients with unhealthy status. In addition, we observed that metabolically healthy obesity was not a full healthy condition (risk for NASH). Thus, we should focus our messages especially on obese and unhealthy non-obese NAFLD patients.

SAT-508

Clinical Outcomes in biopsy-proven NAFLD patients from the HEPAmet Spanish Registry

J. Ampuero[1], R. Aller[2], R. Gallego-Durán[1], J. Banales[3], J. Crespo[4], N. Mora-Cuadrado[2], C. Garcia-Monzon[5], M.J. Pareja[6], E. Vilar-Gomez[7], R. Jiménez-Agüero[3], J. Caballería[8], M.T.A. Loste[4], D. Escudero-García[9], J. Gómez-Camarero[10], J.L.C. Panero[11], D.A. De Luis Román[2], Á. Gónzalez-Rodriguez[5], M. Latorre[12], A. Albillos[13], V. Aguilar-Urbano[14], J. Salmerón[15], J.L. Olcoz-Goñi[16], P. Aspichueta[17], Á. Santos-Laso[3], O.L. Iacono[18], P. Iruzubieta[4], I. Graupera[8], M. García-Torres[9], E. Badia-Aranda[10], J.A. Guerra[11], R. Francés[19], H. Pastor[1], E.D. Pozo-Maroto[5], M. Diago[12], R. Martin-Mateos[13], S. Benlloch[20], C. Fernández-Rodríguez[21], F.J.G.-S. Rey[22], P. Estevez[23], R.J. Andrade[24], J. Turnés[25], M.R. Gomez[1]. *[1]Hospital Universitario Virgen del Rocio, Sevilla. Instituto de Biomedicina de Sevilla. CiberEHD, Spain; [2]Hospital Clínico Universitario de Valladolid. Centro de Investigación de Endocrinología y Nutrición. Universidad de Valladolid, Spain; [3]Department of Liver and Gastrointestinal Diseases, Biodonostia Health Research Institute – Donostia University Hospital, University of the Basque Country (UPV/EHU), Ikerbasque, CIBERehd, San Sebastián, Spain; [4]Hospital Universitario Marqués de Valdecilla, Santander, Spain; [5]Hospital Universitario Santa Cristina Instituto de Investigación Sanitaria Princesa Madrid, Spain; [6]Hospital Universitario Juan Ramón Jiménez, Huelva, Spain; [7]Instituto Nacional de Gastroenterología, La Habana, Cuba; [8]Hospital Clínic. Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBPAS), Centro de Investigación en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Barcelona, Spain; [9]Hospital Clínico de Valencia, Spain; [10]Hospital Universitario de Burgos, Spain; [11]Hospital Universitario Puerta de Hierro, Madrid, Spain; [12]Hospital General Universitario de Valencia, Spain; [13]Hospital Universitario Ramón y Cajal, Madrid, Spain; [14]Agencia Sanitaria Costa del Sol, Marbella, Spain; [15]Hospital Universitario San Cecilio, Granada, Spain; [16]Hospital Universitario de León, Spain; [17]Biocruces Research Institute, Barakaldo, Department of Physiology, Faculty of Medicine and Nursing, University of Basque Country UPV/EHU, Leioa, Spain; [18]Hospital Univeristario Tajo, Aranjuez, Spain; [19]CIBERehd-Hospital General Universitario de Alicante. Universidad Miguel Hernández, Spain; [20]Hospital Universitari i Politecnic La Fe, Valencia. CIBERehd, Spain; [21]Hospital Universitario Fundación de Alcorcón, Universidad Rey Juan Carlos, Spain; [22]Hospital Universitario La Paz, CIBERehd, Madrid, Spain; [23]Complejo Hospitalario Universitario de Vigo, Spain; [24]Instituto de Investigación Biomédica de Málaga-IBIMA, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, CIBERehd, Málaga, Spain; [25]Complejo Hospitalario de Pontevedra, Spain*
Email: javi.ampuero@gmail.com

Background and Aims: To examine clinical outcomes in biopsy-proven NAFLD patients by histological features (fibrosis score).
Method: This prospective multicentre study included 568 Spanish patients with biopsy-proven NAFLD from the Spanish Registry HepaMET from 2015–2017. NASH and fibrosis were defined according to Steatosis, Activity, and Fibrosis (SAF) score. Patients' mortality, fibrosis progression, and comorbidities were examined. Mean follow-up time was 2.6 +* 2.7 years.
Results: Half of the study patients were males. Mean age was 50 +* 11 years old and average BMI was 35.7 +* 9 kg/m^2, 46.7% (265/568) had NASH. Fibrosis stage distribution was: F0 36.6%, F1 26.8%, F2 18.3%, F3 11.1% and F4 7.2%. Prevalence of NAFLD-related risk factors was: obesity 56.7% (322/496), hypertension 46.3% (260/562), hypertriglyceridemia 38.8% (215/554), dyslipemia 32.4% (159/490), and T2DM 31.7% (178/562). During the follow-up period, clinical outcomes were: (a) death 1.2% (7/568), (b) fibrosis progression 12% (39/325), (c) decompensated cirrhosis 12.2% (5/41), (d) cardiovascular events 3.9% (16/417), (e) chronic kidney disease 3.8% (14/368), (f) development of T2DM 5% (19/384), low HDL 22.2% (50/225), hypertriglyceridemia 8.3% (28/339), hypertension 7.3% (22/302), and (g) neoplastic processes 3.2% (18/568). Impact of baseline histology on clinical outcomes was shown in the Table.
Conclusion: Histological features of advanced fibrosis were related to raised mortality. Moreover, baseline fibrosis was strongly related to fibrosis progression, neoplasms, renal insufficiency, and development of new onset of T2DM. NASH was associated with increased risk of developing dyslipidemia during follow-up.

SAT-509

Hepatitis C Virus eradication by direct antiviral agents improves carotid atherosclerosis in patients with advanced fibrosis/ compensated cirrhosis

S. Petta[1], L.E. Adinolfi[2], A.L. Fracanzani[3], V. Calvaruso[1], F. Rini[1], C. Camma[1], V.D. Marco[1], M. Giordano[2], A. Marrone[2], R. Nevola[2], A. Pinto[4], L. Rinaldi[2], D. Torres[4], A. Tuttolomondo[4], L. Valenti[5], S. Fargion[5], A. Craxi[1]. *[1]Sezione di Gastroenterologia e Epatologia, Di.Bi.M.I.S, Università di Palermo, Italia, Sezione di Gastroenterologia e Epatologia, Di.Bi.M.I.S, Università di Palermo, Italia, Palermo, Italy; [2]Department of Medical, Surgical, Neurological, Geriatric, and Metabolic Sciences, University of Campania "Luigi Vanvitelli", 80100 Naples, Italy., Napoli, Italy; [3]Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Italy; [4]Sezione di Medicina Interna con Stroke Care, Dipartimento Biomedico di Medicina Interna e Specialistica (Di.Bi.M.I.S), Università di Palermo, Italia; [5]Department of Pathophysiology and Transplantation, Ca' Granda*

Table 1: (abstract: SAT-508).

	Death	CVD events	Kidney disease	Neoplastic processes	DM	Low HDL	Hypertriglyceridemia	AH
F0	0,5%	2,7%	2%	3,4%	5,3%	17,6%	7,2%	4,5%
F1	0%	5,2%	3,6%	0,7%	3,9%	25,9%	10,2%	8,3%
F2	1,9%	7,8%	3,8%	1,9%	3,1%	28,6%	6,1%	11,4%
F3	4,8%	3,8%	6%	4,8%	16,1%	30,4%	2,8%	4,5%
F4	2,4%	0%	10,3%	12,2%	28,6%	16,7%	20%	17,6%
P	0.041	0.271	0.366	0.030	0.072	0.530	0.155	0.122
LogRank	9.950	5.161	4.309	10.743	8.592	3.170	6.664	7.286
	Death	CVD events	Kidney disease	Neoplastic processes	DM	Low HDL	Hypertriglyceridemia	AH
F0-2	0,6%	4,2%	2,8%	2,2%	4,4%	21,6%	8%	6,9%
F3-4	3,8%	2,4%	7,6%	7,7%	20%	25,7%	9.8%	10,3%
P	0.040	0.485	0.334	0.030	0.007	0.883	0.911	0.542
LogRank	4.200	0.488	0.993	4.728	7.218	0.022	0.012	0.372
	Death	CVD events	Kidney disease	Neoplastic processes	DM	Low HDL	Hypertriglyceridemia	AH
No NASH	0,8%	2,7%	2,7%	3%	6,1%	17,1%	9,6%	0%
NASH	1,5%	5,2%	4,4%	2,7%	6%	32,1%	5,8%	2,3%
P	0.149	0.431	0.343	0.885	0.985	0.141	0.465	0.756
LogRank	2.086	0.619	0.898	0.021	0.001	2.172	0.533	0.097

IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Milan, Italy
Email: petsa@inwind.it

Background and Aims: Recent clinical studies suggested an association between HCV infection and the wide spectrum of cardiovascular damage. Some studies in high selected patients eligible to IFN-based therapies suggested a positive effect of IFN treatment and/or HCV eradication on cardiovascular outcomes. All in all, we aimed to assess whether HCV eradication by direct antiviral agents (DAA)-based therapies improves carotid atherosclerosis in HCV-infected patients with advanced fibrosis/compensated cirrhosis.
Method: 182 consecutive HCV-infected patients with advanced fibrosis/compensated cirrhosis were evaluated by virological, anthropometric and metabolic measurements. Advanced fibrosis was diagnosed by histology (Scheuer score) and/or by liver stiffness measurement (LSM) by FibroScan (≥10 to ≤12 KPa); compensated cirrhosis was diagnosed by histology and/or by LSM (>12 KPa), and/or by evidence of oesophageal varices. All patients underwent DAA-based antiviral therapy according to AISF/EASL guidelines. Intima-media thickness (IMT) and carotid plaques, defined as focal thickening of ≥1.5 mm at the level of common carotid, were evaluated using ultrasonography at baseline and 9–12 months after the end of antiviral therapy.
Results: Fifthy-six percent of the population were males, mean age was 63.1 ± 10.4 years and 65.9% had compensated cirrhosis. One patient in five had diabetes, 14.3% were obese, 41.8% arterial hypertension and 35.2% were smokers. Mean IMT was 0.94 ± 0.29 mm, 42.9% had IMT ≥ 10 mm, and 42.9% had carotid plaques. All patients achieved a sustained virological response (SVR). Baseline factors independently associated with IMT as linear variable, with IMT ≥ 10 mm and with carotid plaques was older age ($p < 0.05$ for all variables in all models). IMT significantly reduced from baseline to 9–12 months after SVR (0.94 ± 0.29 mm vs. 0.81 ± 0.27, $p < 0.001$). Consistently, a significant reduction in the prevalence of patients with IMT ≥ 10 mm from baseline to follow-up was observed (42.8% vs. 17%, $p < 0.001$), while no changes were reported for carotid plaques (42.8% vs. 47.8%, $p = 0.34$). At linear regression analyses no factors were associated with IMT changes from baseline to follow-up ($p > 0.10$ for all). Consistently, a significant reduction in the IMT and in the prevalence of patients with IMT ≥ 10 mm from baseline to follow-up was observed in patients older/younger than 65 years, obese/nonobese, smokers/no smokers, with/without diabetes and with/without arterial hypertension ($p < 0.05$ for all).
Conclusion: HCV eradication by DAA improves carotid atherosclerosis in patients with advanced fibrosis/compensated cirrhosis with/without metabolic risk factors. Data about the impact of HCV eradication in patients with mild liver disease must be explored.

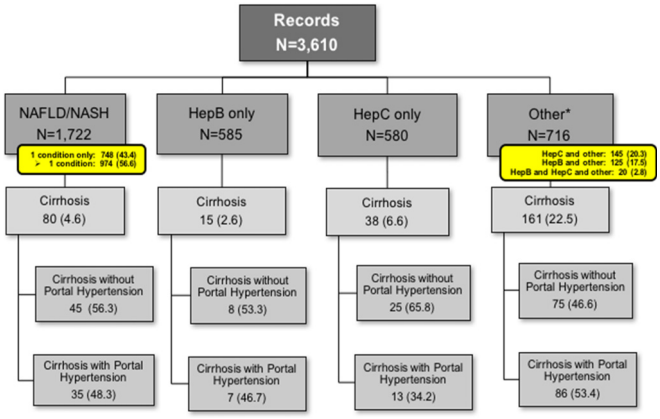
SAT-510

A Comprehensive Assessment of Serial Transient elastography in various Liver disease Etiologies at the Toronto Liver Centre (CASTLE-TLC)

M. Elkashab[1], H. Dallali[1], S. Kausar[1], M. Farshadi[1], M. Khurram[1], O. Muraru[1], M. Khan[2], J. Palmart[3], S. Loo[3], M. Magnes[1], K. Boctor[1].
[1]Toronto Liver Centre, Hepatology; [2]Gilead Sciences Canada; [3]Advisory Physicians Research Services Inc.
Email: boctork@gmail.com

Background and Aims: Liver disease is a major cause of morbidity and mortality globally, with non-alcoholic fatty liver disease (NAFLD) becoming a major cause for concern, followed by viral hepatitis (HBV & HCV) and alcoholic liver disease (ALD). To understand the burden of liver disease in Ontario, a comprehensive retrospective analysis is currently underway to characterize all liver disease patients at the Toronto Liver Centre (TLC).
Method: 3610 medical charts at the Toronto Liver Centre from Feb. 1995 to Sep. 2017 were reviewed and assessed for: patient demographics, liver disease etiology, liver fibrosis staged by Transient Elastography (TE), liver biopsy, imaging, & blood work, were collected & entered into a standardized form. Patient grouping was organized by primary liver etiology: NAFLD/NASH, HBV, HCV & Other (autoimmune hepatitis, alcoholic liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, etc.). Data on cirrhotic patients (based on TE vs. biopsy vs. ultrasound) was also assessed to determine: sensitivity, specificity, positive predictive value (PPV) & negative predictive value (NPV) for the presence or absence of cirrhosis.
Results: Of the 3610 records analyzed, 2378 had TE results with 85.7% having a Metavir score of F2 & below; only 9% of patients had a Metavir score > F3. Similar results were obtained with biopsy samples: 40/403 (9.9%) patients with biopsy results had a Metavir score > F3. For the entire cohort, only 8.14% of patients had cirrhosis, & only 3.91% of patients had cirrhosis with portal hypertension, 1722 patients had NAFLD/NASH, 585 HBV only, & 580 HCV only; the remainder had viral hepatitis plus another liver condition except NAFLD: 145 had HBV plus other liver disease (20.3%), 125 had HCV plus other liver disease (17.5%), & 20 had HBV/HCV coinfection & other liver disease (2.8%). Cirrhosis was present in 6.6% of patients

with HCV, 4.6% in NAFLD/NASH, 2.6% in HBV, and 22.5% in other diseases. Amongst the cirrhotic group as diagnosed by ultrasound distribution was: HCV (2.4%), HBV (1.0%), & NAFLD/NASH (1.1%). The rate of cirrhosis in patients that were reported to be F4 or greater by TE was: (72.7%) NAFLD/NASH, (62.5%) HBV, & (56.0%) HCV. The sensitivity, specificity PPV and NPV of F4 in TE to predict cirrhosis in patients with NAFLD/NASH is 72.73%, 98.08%, 62.50% & 98.79% respectively. For HBV patients the values were 62.50%, 98.26%, 41.67% & 99.25% respectively. For HCV patients the values were 56.00%, 93.54%, 45.16% & 95.72%.



*Made possible with financial support from Gilead Sciences Canada.

Conclusion: In this initial analysis of data from an ongoing retrospective analysis, the vast majority of patients had levels of liver fibrosis of F2 and below, and fewer than 10% had histology or TE results consistent with cirrhosis. There was a high degree of agreement between the various methods used to assess fibrosis and cirrhosis (TE, biopsy and ultrasound).

SAT-511

Predisposition to diabetes is related to insulin resistance in NAFLD patients and to decreased insulin secretion in HCV patients

G. Svegliati-Baroni[1,2], I. Pierantonelli[1], R. Younes[3], C. Rosso[4], C. Rychlicki[1], E. Bugianesi[4], A. Gastaldelli[5]. *[1]Polytechnic University of Marche, Department of Gastroenterology and Hepatology, Ancona, Italy; [2]Polytechnic University of Marche, Obesity Center, Ancona, Italy; [3]University of Torino, Division of Gastroenterology, Dept of Medical Sciences, Italy; [4]University of Torino, Division of Gastroenterology, Department of Medical Sciences, Italy; [5]Cardiometabolic Risk Unit, Institute of Clinical Physiology, CNR, Italy*
Email: pierantonelli_irene@libero.it

Background and Aims: Epidemiological studies have shown that both non-alcoholic fatty liver disease (NAFLD) and HCV are risk factors for the development of type 2 diabetes (T2DM). As the subjects become insulin resistant (IR), their glucose tolerance is maintained until amounts of plasma insulin are sufficient to overcome increased IR in the liver and in the muscle. When the pancreas fails its compensatory action, clinically over diabetes ensues. We undertook this study in order to evaluate the relative role of increased IR versus decreased pancreatic ß-cell function in chronic liver disease due to NAFLD or HCV.
Method: We analyzed the glucose and insulin profiles (at 0,30,60,90,120 min) during a 75 grams OGTT in 190 non diabetic patients (NAFLD n = 109, BMI = 27.4 kg/m^2; HCV n = 14 for genotype 3 and n = 67 for non-3, BMI= 25.3 and 23.8 kg/m^2 respectively) with liver biopsy and 12 controls (CT, BMI = 24.5 kg/m^2). We assessed peripheral insulin sensitivity (OGIS index) and insulin secretion during OGTT (ratio of incremental area under the curve of insulin to glucose, ΔAUC-I/ΔAUC-G), and ß-cell function as the insulin secretion/insulin resistance or disposition index (DI = OGIS·ΔAUC-I/ΔAUC-G). A low DI was used to indicate a predisposition to develop T2DM. Fibrosis was scored according to Metavir for HCV and Kleiner score for NAFLD.
Results: In this cohort of non-diabetic subjects with either NAFLD or HCV we found that NAFLD were more IR (lower OGIS, 8.9 vs 11.4 and 11.2 ml/min kg, NAFLD vs HCV and CT, $p < 0.0001$), while insulin secretion (ΔAUC-I/ΔAUC-G) was decreased in HCV but not in NAFLD compared to CT (0.9 vs 1.9 and 1.7, HCV vs NAFLD and CT, $p < 0.005$). Accordingly, the DI (a measure of ß-cell function) was significantly decreased in HCV but not in NAFLD (9.5 vs 15.8 vs 19.1 in HCV vs NAFLD vs CT, $p < 0.0001$). DI decreased proportionally to the impairment in glucose tolerance in both NAFLD and HCV ($r = -0.48$, $p < 0.0001$) but was unaffected by the degree of fibrosis.
Conclusion: In subjects with NAFLD the predisposition to T2DM is related more to increased muscle IR than reduced pancreatic insulin secretion while in HCV it is mainly due to an impairment in post-load insulin secretion.

SAT-512

The triglycerides and glucose (TyG) index: a new marker associated with Non Alcoholic Steatohepatitis (NASH) and fibrosis in obese patients?

S. Faure[1], R. Benjamin[2], J. Ramos[3], S. Medhi[4], N. David[4], L. Anne[5], F. Galtier[6], G.-P. Pageaux[7]. *[1]CHU Saint Eloi, Liver Unit, France; [2]CHU Saint Eloi, Anatomopathology, Montpellier, France; [3]CHU Saint Eloi, Anatomopathology; [4]CHU Saint Eloi, Bariatric Surgery, France; [5]CHU Montpellier, Montpellier, France; [6]Hospital Saint Eloi, CIC, Montpellier, France; [7]Hospital Saint Eloi, Liver Unit, Montpellier, France*
Email: stephharrys@yahoo.fr

Background and Aims: Non Alcoholic SteatoHepatitis (NASH) concerns 51% of obese patients and 22.5% of diabetics in the world. Patients with NASH in one third of cases develop fibrosis, which leads to cirrhosis and hepatocellular carcinoma. The main objective of this study is to determine a marker for screening patients requiring further liver investigations.
Method: This study concerns patients with morbid obesity, aged from 18 to 65 years, undergoing a bariatric surgery program. A blood test and a liver biopsy were performed at the beginning of bariatric surgery. Liver biopsies were standardly interpreted with evaluation of steatohepatitis and fibrosis by the NAS score. TyG index was calculated as follows: [Ln(fasting triglycerides)(mg/dl)*fasting glucose (mg/dl)/2]. Data were registred in a base ENNOV-CLINICAL and analysed by SAS. Risk factors for NASH were identified by Student or Wilcoxon for quantitative values, and by chi-deux ou test exact de Fisherfor qualitative values.
Results: 147 patients were included in the study (102 women and 45 men, mean age 42 +/- 12 years, mean BMI (body mass index) 42 +/−5 kg/m^2. Thirty patients were diabetic, but among the 117 non diabetics, 47 were insulinoresistants (HOMA >=3). Liver biopsies identified steatosis in 66% of the patients, 17 NASH (11%), 35 fibrosis (24%) with significant fibrosis in 11 patients (4 stage 2,4 stage 3 and 3 4). The risk factors predictive of NASH and/or fibrosis were: TyG index ($p < 0.0001$ and $p < 0.01$ respectively), GGT ($p < 0.001$ and $p < 0.01$), diabetes ($p < 0.001$), ALAT ($p < 0.01$), HOMA-IR ($p < 0.01$ and $p < 0.05$), sexe ($p < 0.01$), age ($p = 0.06$ and $p < 0.01$). Regarding advanced fibrosis F3 or F4, the same risk factors were significantly associated age ($p < 0.01$), ALAT ($p < 0.01$), GGT ($p < 0.01$, diabetes ($p < 0.05$) and TyG index ($p < 0.05$) excepted sexe and HOMA-IR.
Conclusion: TyG index seems to be an interesting marker to predict NASH or fibrosis in obese patients. Its advantage resides in routine blood tests as simple as glucose and triglycerides. Further studies are necessary to confirm these findings.

SAT-513

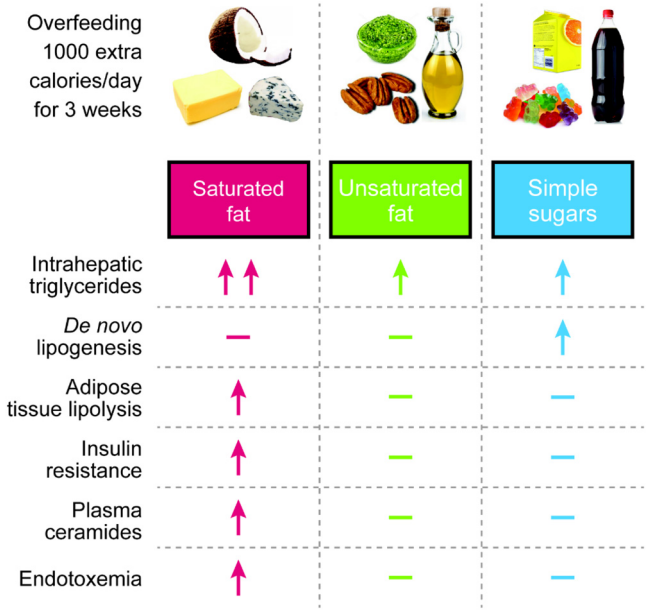
Saturated fat is more metabolically harmful for the human liver than polyunsaturated fat or simple sugars

P. Luukkonen[1], S. Sadevirta[1], Y. Zhou[2], A. Ali[3], L. Ahonen[3], S. Lallukka[4], M. Gaggini[5], C. Jian[6], A. Hakkarainen[1], N. Lundbom[1], H. Gylling[1], A. Salonen[6], M. Orešič[3], T. Hyötyläinen[3], A. Gastaldelli[5], M. Orho-Melander[7], A. Rissanen[1], L. Hodson[8], H. Yki-Järvinen[1].
[1]University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [2]Minerva Foundation Institute for Medical Research, Helsinki, Finland, University of Cardiff, Cardiff, United Kingdom; [3]Steno Diabetes Center, Gentofte, Denmark; [4]University of Helsinki, Biomedicum 2U, DP02b, Helsinki, Finland; [5]National Research Council, Cardiometabolic Risk Lab, Pisa, Italy; [6]University of Helsinki, Helsinki, Finland; [7]Lund University, Malmö, Sweden; [8]University of Oxford, Oxford, United Kingdom
Email: panu.luukkonen@fimnet.fi

Background and Aims: Weight gain predisposes to increased intrahepatic triglycerides (IHTG) and insulin resistance (IR), but these do not occur in all obese subjects. Adipose tissue lipolysis and hepatic *de novo* lipogenesis (DNL) are the main pathways contributing to IHTG, while ceramides are key mediators of IR. Ceramide synthesis is induced by saturated fatty acids and endotoxin, a component of gut microbiota. We hypothesized that dietary macronutrient composition influences the pathways and magnitude of weight gain-induced changes in IHTG and IR.

Method: We overfed 38 overweight subjects (age 48 ± 2 years, BMI 31 ± 1 kg/m^2, liver fat 4.7 ± 0.9%) 1000 extra calories/day of either saturated or polyunsaturated fat or simple sugars for 3 weeks. We measured IHTG (^{1}H magnetic resonance spectroscopy), pathways contributing to IHTG (lipolysis and hepatic DNL using [$^2H_5$]glycerol and ^2H_2O in the basal state and during euglycemic hyperinsulinemia), IR, plasma ceramides (UPLC-MS) and endotoxemia (fecal microbiota and circulating markers) at 0 and 3 weeks.

Results: Overfeeding of saturated fat increased IHTG more (55%, $p < 0.001$) than that of polyunsaturated fat (16%, $p < 0.02$) or simple sugars (32%, $p < 0.01$) despite similar increases in body weight (1.4 ± 0.3, 0.9 ± 0.3 and 1.4 ± 0.5 kg, respectively). Simple sugars increased hepatic DNL ($p < 0.05$) whilst saturated fat increased lipolysis ($p < 0.05$). Saturated fat but not other diets induced IR ($p < 0.05$), increased multiple circulating ceramide species ($p < 0.01$) and induced endotoxemia ($p < 0.05$).



Conclusion: These data demonstrate that macronutrient composition of calories overconsumed matters. Saturated fat exerts greater metabolic harm on the liver than polyunsaturated fat or simple sugars, which may be mediated by saturated fatty acid- and endotoxin-induced synthesis of ceramides.

SAT-514

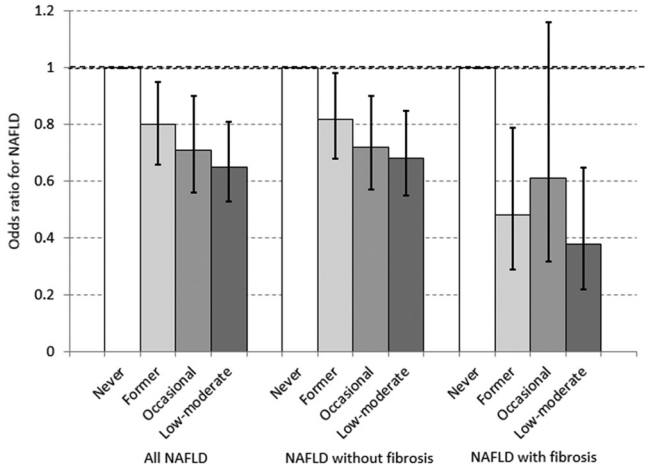
Low-moderate alcohol use is associated with a lower prevalence of non-alcoholic fatty liver disease in Hispanics/Latinos living in the US: Results from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL)

A. Unalp-Arida[1], C. Ruhl[2], E. Kallwitz[3], M. Daviglus[4], D. Sotres-Alvarez[5], D. Vidot[6], D. Lee[6], G. Talavera[7], L. Aviles-Santa[8].
[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, United States; [2]Social & Scientific Systems, Inc., Silver Spring, MD, United States; [3]Loyola University Chicago, Chicago, IL, United States; [4]University of Illinois at Chicago, Chicago, United States; [5]University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [6]University of Miami, Miami, FL, United States; [7]San Diego State University, San Diego, CA, United States; [8]National Heart, Lung, and Blood Institute, Bethesda, MD, United States
Email: cruhl@s-3.com

Background and Aims: Alcohol use is a known risk factor for liver injury; however, the dose-response effect on the liver has not been well studied among persons of Hispanic/Latino background. We examined the relationship between alcohol intake and non-alcoholic fatty liver disease (NAFLD) in a population-based cohort of Hispanics/Latinos living in the US.

Method: We included 14,786 viral hepatitis seronegative HCHS/SOL participants aged 18–74 years in 2008–2011 with transferrin saturation ≤ 50% and alcohol use in drinks/week ≤14 for women or ≤21 for men at baseline examination. NAFLD and liver fibrosis were defined as a high NAFLD liver fat score (≥1.257) (Kotronen, Gastroenterology, 2009;137:865) and high NAFLD fibrosis score (>0.676) (Angulo, Hepatology, 2007;45:846), respectively, using published cut-offs. Self-reported alcohol use (drinks/week) was categorized as never, former, occasional (<1), or low-moderate (1–14 for women or 1–21 for men). Complex survey logistic regression was used to estimate odds ratios (OR) for NAFLD by alcohol use adjusting for age, sex, Hispanic/Latino heritage group, attained education, BMI, and physical activity.

Results: The prevalence of never, former, occasional, and low-moderate alcohol use was 20%, 31%, 16%, and 33%, respectively. The prevalence of NAFLD and NAFLD with fibrosis was 17.2% and 1.6%, respectively. The prevalence of NAFLD was lower among occasional (15.7%) and low-moderate (14.7%) compared with never (19.9%) and former (18.8%) drinkers ($p < 0.001$). Compared to never drinkers, the age-adjusted odds of NAFLD was lower among occasional (OR, 0.81; 95% confidence interval (CI), 0.66–0.99) and low-moderate (OR, 0.79; 95% CI, 0.66–0.94) alcohol users. After multivariate adjustment, the odds were further decreased for occasional and low-moderate alcohol users, as well as former drinkers (Figure). NAFLD with fibrosis was more strongly associated with low-moderate and former drinking than was NAFLD without fibrosis (Figure). When consumption of wine, beer, and liquor was examined individually, ORs for all NAFLD among low-moderate compared with never drinkers ranged from 0.53 to 0.61 ($p \leq 0.001$ for each). The lower odds of NAFLD among former, occasional, and low-moderate alcohol users was no longer observed when further adjusting by homeostasis model assessment of insulin resistance deciles ($p \geq 0.34$ for each).



Conclusion: Among Hispanic/Latino adults in the HCHS/SOL, former and low-moderate alcohol use was associated with a lower prevalence of NAFLD and liver fibrosis; occasional drinking was associated with a lower prevalence of NAFLD. These cross-sectional associations may be mediated through effects of varying degrees of insulin resistance. Examination of the longitudinal relationship between alcohol use and liver health among HCHS/SOL participants is underway from 2014–2017.

SAT-515

Even modest alcohol use is associated with greater steatosis on magnetic resonance imaging in patients with NAFLD – a pilot study

V. Ajmera[1], M. Le[1], C. Caussy[1], P. Nguyen[1], C. Hernandez[1], R. Bettencourt[1], C. Behling[2], M. Valasek[1], C. Faulkner[1], E. Rizo[1], L. Richards[1], C. Sirlin[1], R. Loomba[3]. *[1]University of California, San Diego; [2]Sharp Medical Center; [3]University of California at San Diego, Division of Gastroenterology, Department of Medicine, San Diego, United States*
Email: v1ajmera@ucsd.edu

Background and Aims: The effect of modest alcohol use on NAFLD is unclear, however, a paired biopsy study suggested modest alcohol use was associated with less improvement in histologic steatosis. Therefore, we aimed to evaluate the cross-sectional and longitudinal associations between modest alcohol use and hepatic steatosis using a prospective cohort of adults with biopsy proven NAFLD and magnetic resonance imaging (MRI) proton density fat fraction (PDFF) as a quantitative measure of liver fat content.
Method: Participants with NAFLD, age ≥ 21 years, with paired MRI and alcohol history were included. Men and women who reported >2 and >1 drinks/day as well as participants in treatment arms of trials were excluded. The associations between alcohol use (baseline drinking status and change in drinking status) and steatosis (baseline PDFF and change in PDFF) were evaluated before and after adjustment for potential covariates.
Results: Of 57 participants (43% Hispanic, 65% female, mean age 50 years) meeting entry criteria, 65% drank monthly or less and 35% drank more than monthly. At baseline, more-than-monthly drinkers had higher mean PDFF (18.3% vs 14.6%, p = 0.08), were more often white (p = 0.05) and male (p = 0.08), but had no significant difference in prevalence of diabetes, hypertension, or aminotransferase levels. In a linear regression model adjusted for race and sex, participants who drank more than monthly had 4.4% higher mean PDFF (95% CI: −0.12 to 8.82%, p = 0.056) at baseline compared to those who drank monthly or less. At follow up MRI (mean ± SD of 380 ± 370 days later), there was no significant difference in PDFF change between participants who at baseline drank more than monthly vs. monthly or less, −2.77% vs −1.64% respectively, p = 0.52. Seven participants reported decreased drinking, 35 no change, and 9 increased drinking, with mean PDFF changes of −3.42%, −2.45% and −1.40% respectively, p = 0.51. In a logistic regression model adjusted for race and sex, no change or an increase in drinking at follow up had lower odds of PDFF reduction (OR: 0.41, 95% CI: 0.14–1.23, p = 0.114) than decreased drinking.
Conclusion: In this pilot study using an accurate, quantitative measure of hepatic steatosis, more than monthly alcohol use at baseline was associated with greater hepatic steatosis on adjusted analysis. Participants who lowered their drinking frequency had greater odds of steatosis reduction.

SAT-516

Role of nutritional intake on clinical presentation of lean and overweight NAFLD

R. Lombardi[1], G. Pisano[1], S. Spreafico[1], F. Iuculano[1], E. Fatta[1], S. Pelusi[1], L. Valenti[1], S. Fargion[1], A.L. Fracanzani[2]. *[1]Ca'Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Department of Pathophysiology and Transplantation, Milan, Italy; [2]Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Department of Pathophysiology and Transplantation, Ca' Granda IRCCS Foundation, Policlinico Hospital, University of Milan, Italy, Italy*
Email: anna.fracanzani@unimi.it

Background and Aims: Dietary macronutrient composition is associated with the presence of NAFLD, and epidemiologic studies show an inverse correlation between Mediterranean diet and cardiovascular events. To evaluate the role of dietary components on clinical presentation of NAFLD.
Method: We enrolled 159 consecutive newly diagnosed, untreated NAFLD, (M/F 89/36 mean age 50 ± 12). A semi-quantitative food-frequency questionnaire (dietary record including 118 food items and covering seven days) administered at enrollment used to calculate intake of energy and nutrients. A complete evaluation of anthropometric clinical and biochemical data was collected at presentation. Assessment and quantification of steatosis and subclinical atherosclerosis (mean carotid IMT and presence of carotid plaques) was obtained by B-mode ultrasound (US), cardiac definition of diastolic dysfunction (E/A), left ventricular mass, and visceral adiposity (epicardial adipose thickness (EAT)), by echocardiography.
Results: The mean BMI and waist circumference were 28.8 ± 5.2 and 103 ± 11 cm, prevalence of hypertension 52%, dyslipidemia 56%, obesity 35%, diabetes 11%, metabolic syndrome 44%. Eighteen % had "lean" NAFLD (BMI < 25). Mean IMT was 0.74 ± 0.2, with carotid atherosclerosis (IMT >1.0 mm) in 14%, and carotid plaques in 29%, E/A < 1 in 40%, mean EAT 5.8 ± 4 mm. Eight patients (5%) had cardiovascular events. Macro-nutrient intake adjusted for percentage of calories was: proteins 23, ± 4, fat 33,1 ± 5, carbohydrates 38.5 ± 8, fiber 2.7 ± 1. No difference of nutrient dietary composition and total amount of calories between lean and overweight/obese patients was observed. Among nutrients, fructose was significantly higher in patients with plaques (p = 0.03), vitamin E lower in patients with diastolic dysfunction (p = 0.03). At multivariate analysis adjusted for age, gender and BMI, fat resulted significantly associated with dyslipidemia (OR 1.2, 95%CI 1–1.4, p = 0.04), protein with hypertension (OR 1.23, 95%CI 1.02–1.5, p = 0.03), fat and carbohydrate with severe US steatosis (OR 1.3, 95%CI 1.1–1.5, p = 0.002 and OR 1.2, 95% CI 1.03–1.4, p = 0.01, respectively). No independent association was found between nutrients and carotid atherosclerosis, plaques and E/A.
Conclusion: Nutritional intake does not differ between lean and overweight NAFLD suggesting a genetic predisposition to NAFLD in lean subjects. It remains to be defined the role of individual micro- and macro-nutrients on cardiovascular damage in NAFLD.

SAT-517

Non-alcoholic fatty liver disease is omega-6 fatty acids diet dipendent in a group of obese children

A. Dalbeni[1], A. Mantovani[1], A. Tagetti[1], S. Bonafini[1], V. Paon[1], R. Gaudino[2], M. Montagnana[3], E. Danese[3], A. Donato[1], P. Minuz[1], C. Maffeis[2], F. Antoniazzi[2], F. Capra[4], C. Fava[1]. *[1]Division of General Medicine and Hypertension, Department of Medicine, Verona, Italy; [2]Pediatric Diabetes and Metabolic Disorders Unit, Regional Center for Pediatric Diabetes, Verona, Italy; [3]Department of Life and Reproduction Sciences, Verona, Italy; [4]University and Azienda Ospedaliera Universitaria Integrata of Verona, University of Verona, Italy*
Email: andrea.dalbeni@aovr.veneto.it

Background and Aims: Obesity leads to the clustering of metabolic syndrome (MetS) and cardiovascular (CV) risk factors, also in children. Non-alcoholic fatty liver disease often accompanies the MetS and it's described like a new independent CV risk factor. Quality of dietary fat, beyond the quantity, could influence the MetS, CV risk profile and also the development of NAFLD. The aim of this cross-sectional observational study was to investigate the associations of individual CV risk factors and NAFLD, characterizing the MetS, with erythrocyte fatty acid (marker of average intake), in a group of 70 obese children.
Method: Enrollment of obese children aged 5–18 years old (BMI > 90th percentile). Calculation of Fatty Liver Index (FLI) and Ultrasound (US) abdomen echography for the detection of NAFLD. Anthropometric measurement by calibrated instruments, ambulatory blood pressure (BP) measurement by validated instruments. Laboratory measurement of lipid, glucose and hepatic function indices. Erythrocyte membrane FA measurement by gas chromatography.
Results: Mean content of Omega-3 FA was low (omega-3 Index = 4.7 ± 0,8%). Non Omega-3 but Omega-6 FA, in particular arachidonic acid, were inversely associated with several futures of the MetS, in particular with the presence of steatosis: total amount of omega-6 FA was inversely correlated with waist circumference (rS = –0.393), waist/hip ratio (rS = –0.260); triglycerides (rS = –0.294), fasting insulin (rS = – 0.341), FLI (rS = –0.435), ALT (rS = –0.297) and GGT (rS = –0.256). They were directly correlated with HDL (rS = 0.327). Arachidonic acid showed inverse correlations with WC (rS = –0.352), waist/hip ratio (rS = –0.311), triglycerides (rS = –0.366), fasting insulin (rS = –0.337), FLI (rS = –0.472) and ALT (rS = – 0.331). Conversely, GLA showed a direct correlation with fasting insulin (rS = 0.347) and HOMA-IR (rS = 0.365). Total content of saturated FA was directly correlated to waist circumference (rS = 0.237), triglycerides (rS = 0.298), nighttime-DBP (rS = 0.251), FLI (rS = 0.479), ALT (rS = 0.291) and GGT (rS = 0.400). Palmitic acid directly correlated with waist circumference (rS = 0.354), waist/hip ratio (rS = 0.247), triglycerides (rS = 0.373), insulin (rS = 0.287) and HOMA-IR (rS = 0.335), FLI (rS = 0.515), ALT (rS = 0.239), GGT (rS = 0.339).
Conclusion: Our data suggest that omega-6 FA, especially AA, could be protective toward CV risk factors including NAFLD featuring the MetS and also to indexes of hepatic steatosis in obese children, whereas SFA seems to exert opposite effects. The level of omega-3 FA in our sample of obese children, is extremely low so that its putative beneficial effect could have not been detectable. Our findings agree with the current dietary recommendation to reduce the intake of SFA and support a possible beneficial effect of polyunsaturated FA intake, especially omega-6 FA.

SAT-518

Sarcopenia is associated with advanced liver fibrosis in patients with non-alcoholic fatty liver disease

J.G. Park[1], M.K. Kang[1], J.H. Baek[1], S.Y. Park[2], H.J. Lee[1], K. Hur[3], W.Y. Tak[3], Y.O. Kweon[4], S.Y. Jang[5], Y.R. Lee[4], H.W. Lee[6]. *[1]College of Medicine, Yeungnam University, Internal Medicine, Daegu, Korea, Rep. of South; [2]Kyungpook National University Hospital, Department of Internal Medicine, Daegu, Korea, Rep. of South; [3]School of Medicine, Kyungpook National University, Biochemistry and Cell Biology, Daegu, Korea, Rep. of South; [4]School of Medicine, Kyungpook National University, Internal Medicine, Daegu, Korea, Rep. of South; [5]Kyungpook National University School of Medicine, Internal Medicine, Daegu, Korea, Rep. of South; [6]Dongsan Medical Center, School of Medicine, Keimyung University, Internal Medicine, Daegu, Korea, Rep. of South*
Email: gsnrs@naver.com

Background and Aims: Sarcopenia has been known to increase risk of non-alcoholic fatty liver diseases (NAFLD) in previous study. However, there are limited studies in relationship between sarcopenia and fibrosis in large papulation. This study is to investigate association between sarcopenia and liver fibrosis in patients with NAFLD.
Method: A total of 53704 subjects were enrolled the study to be analyzed in single healthcare center. Fatty liver, and sarcopenia was diagnosed by ultrasound, and bioimpedance analysis, respectively. The cut-off values for sarcopenia were 7.0 kg/m2 for men and 5.7 kg/m2 for women. The stage of liver fibrosis is assessed by non-invasive scoring model including NAFLD fibrosis score (NFS), Fibrosis-4 (FIB-4) index, BARD score, and Forns index, which was determined as the upper value of each low cut-off.
Results: Of 10711 patients with NAFLD, 1389 (13.0%) were diagnosed with sarcopenia. The scarcopenic patients were older (47.7 vs. 49.1 years, p = 0.001), had lower levels of body mass index (24.4 vs. 20.4 kg/m2, p = 0.000) and waist circumference (82.1 vs. 72.6 cm, p = 0.000) compared to non-sarcopenic patients. In multivariate analysis, sarcopenia is associated with older age (odd ratio [OR]: 1.02, p = 0.001), women (OR: 2.25; p = 0.001), non-obese group (OR: 19.01, p = 0.001), and non-metabolic syndrome group (OR: 1.91, p = 0.001) in patients with NAFLD. The presence of sarcopenia was independent risk factor for liver fibrosis assessed by FIB-4 index, BARD score, and Forns index in multivariate analysis. (OR: 1.39, p = 0.000; OR: 1.64, p = 0.000; and OR: 1.23, p = 0.001, respectively) except NFS.
Conclusion: Sarcopenia is independent risk factor for liver fibrosis in patients with NAFLD.

SAT-519

Change of microbiota in patients with improved fatty liver and obesity

S.B. Ahn[1], D.W. Jun[2], E. Kim[2], H. Oh[2], J.Y. Jeong[3], J.H. Sohn[3], E.C.J. Jang[4]. *[1]Eulji university college of medicine, Internal Medicine; [2] Hanyang University School of Medicine, Internal Medicine; [3]Hanyang University, College of Medicine, Guri Hospital, Internal Medicine; [4]Soonchunhyang University College of Medicine, Department of Occupational and Enviroment Medicine*
Email: noshin@hanyang.ac.kr

Background and Aims: Changes in intestinal microbiota are known to play an important role in the development and progress of NAFLD. The purpose of this study was to investigate the changes in the composition of microbiota in patients with improved fatty liver after administration of probiotics.
Method: This study randomly divided 68 obese NAFLD patients into the probiotics and the placebo group for twelve weeks. The probiotics mixture consists of six kinds of probiotics (*Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus paracasei, Pediococcus pentosaceus, Bifidobacterium lactis,* and *Bifidobacterium breve*). Intrahepatic fat measured by MRI based technique. Feces samples were collected at the baseline and on a final visit to go through intestinal flora examination to analyze the types and number of microorganism in feces. DNA of bacteria were separately extracted to go through a real-time quantitative PCR.
Results: Significant increase of five strains except *Lactobacillus paracasei* was found in the probiotics group by qPCR in the stool sample. On the other hand, there was no difference of six strains in the control group. Bacteroidetes/Firmicutes ratio significantly increased in the probiotics group (0.46–27.2, p = 0.045). Deep sequencing of the fecal microbiome using next generation

sequencing of 16sRNA revealed that the amount of *Ruminococcaceae-2, Lachnospiraceae-2, Coprococcus, Lachnospiraceae-1, Ruminococcus*, and *Dorea* were increased in patients who were improved fatty liver. *Ruminococcaceae-2, Ruminococcaceae-1, Clostridiales-2, Lachnospiraceae-2* and *Coprococcus* were increased in patients with successful weight loss group.
Conclusion: Specific microbiota are associated with improvement of fatty liver and weight loss. These probiotics may be novel metabolic targets of fatty liver and obesity.

SAT-520
Role of L-carnitine in pathogenesis of the atherogenic dyslipidemia in ischemic heart disease with concominent nonalcoholic steatohepatitis
I. Skrypnyk[1], G. Maslova[1], O. Shcherbak[1]. [1]*Ukrainian Medical Stomatological Academy, Internal Medicine, Poltava, Ukraine*
Email: inskrypnyk@gmail.com

Background and Aims: Cardiovascular diseases are the most frequent reasons of deathless among the population of different worldwide countries, the important place between which is ischemic heart disease (IHD). One of the most perspective alternatives of secondary prevention and treatment of cardiovascular diseases is L-carnitine (LC), which is needed to be observed with a presence of nonalcoholic steatohepatitis (NASH).
Aim: to observe the concentration of L-carnitine in serum of pts with IHD considering of the presence of NASH.
Method: Study involved 68 IHD pts with the presence of Frederickson's atherogenic dyslipidemia types IIa and IIb. IHD's duration was 2–20 years. In the structure of IHD we have noticed: stable angina grade II – in 68 (100%) pts, diffusive cardiosclerosis in 68 (100%) pts among them postinfarction cardiosclerosis – in 27(39.7%) pts. Patients' age was 37–69 years. Ratio women/men was 17(25%)/51 (75%). Control group consists of 20 almost healthy (AH). Depending on NASH presence patients were divided into 2 groups: I(n = 32) – IHD and concomitant NASH; II(n = 36) – IHD without NASH. The parameters of the blood lipid spectrum were studied: cholesterol, triglycerides (TG), high-density lipoproteins (HDL) and low-density lipoproteins (LDL).
The L-carnitine level in the blood serum was determined by immunoenzyme method using special Human L-carnitine ELISA Kit (USA), referent range is 1, 2–50 pg/ml.
Results: In pts of group I the cholesterol level was higher in 1.4, LDL – in 2, TG – in 1.8 times, but the level of HDL was lower in 1.4 times versus AH people. In pts of group II the cholesterol level was increased in 1.3, LDL– in 1.9, TG– in 1.6 times ($p < 0.05$), but the level of HDL was decreased in 1.3 times ($p < 0.05$) versus AH. Also, in pts of group I with the presence of NASH increasing of LC in blood serum in 1.6 times compared with AH was noticed (3.71 ± 1.99 versus 2.35 ± 0.72 pg/ml; $p > 0.05$).
In pts of the group II without NASH was veraciously noticed increasing of blood's serum LC in 2.4 time compared with AH (5.62 ± 1.16 vs 2.35 ± 0.72 pg/ml; $p < 0.05$). In the same time was noticed the weak correlative connection between concentration of LC and TG in the blood serum ($r = +0.6$).
Conclusion: In IHD pts with lipid metabolism disorders an increase of LC concentration in the blood serum was observed in response to a high serum lipid level, namely TG. Mostly the higher concentration in the blood serum LC in pts with IHD without the presence of NASH can be explained by the violation of expressing of carnitine's receptor transporters in muscular tissue, which was observed in results of apart researches. Presence of forward correlative connection between concentration of LC and TG's concentration in the blood serum is arguing practicability of prescribing drugs with LC in complex therapy of diseases which are associated with violation of lipid metabolism.

SAT-521
Assessment of baseline Hepatitis B Virus (HBV) immunity and HBV vaccine responses in prospectively vaccinated adults with Non Alcoholic Fatty Liver Disease (NAFLD)
C. Coffin[1], C. Jenne[1], M.G. Swain[1], S. Jayakumar[1], C. Cooper[2], E. Kelly[3], S. Fung[4], A. Ramji[5], E. Tam[6], M. Ma[7]. [1]*University of Calgary, Cumming School of Medicine, Calgary, Canada;* [2]*University of Ottawa, The Ottawa Hospital and Regional Hepatitis Program, Canada;* [3]*University of Ottawa Health Services, Ottawa, Canada;* [4]*University Health Network, Toronto, Canada;* [5]*The University of British Columbia, Vancouver, Canada;* [6]*Lair Centre, Vancouver, Canada;* [7]*University of Alberta Hospital, Edmonton, Canada*
Email: cscoffin@ucalgary.ca

Background and Aims: The recombinant hepatitis B virus (HBV) vaccine consisting of major viral antigenic (surface) epitopes induces long-lived protective immunity in healthy adults. It is recommended that all persons with end-stage liver disease (including those due to Non-Alcoholic Fatty Liver, NAFLD) be vaccinated against the HBV. We aim to determine HBV vaccine responses in patients with NAFLD.
Method: In this ongoing multisite study, adults with NAFLD referred to hepatology were tested for serological markers of HBV infection (i.e., HBV surface antigen [HBsAg]) or immunity (i.e., antibody to HBsAg [anti-HBs]; antibody to core [anti-HBc]), and offered the HBV vaccine if non-immune (i.e., EngerixB®) or combined HAV/HBV vaccine (i.e., Twinrix®). Anti-HBs titres indicating protective immunity (i.e., >10 IU/l) were assessed at ~1–2 months after completion of 3-dose vaccine series. All prospectively recruited study subjects underwent standard clinical assessment, including anthropomorphic (Body mass index, BMI), liver stiffness measurement (LSM) by FibroScan®, and metabolic risk factors. We used appropriate statistical methods with two tailed tests in our analyses.
Results: In 431 NAFLD patients referred, 47% (202/431) were HBV immune or prior exposure. In 91/202 previously vaccinated, available retrospective BMI data correlated to mean anti-HBs titres (i.e., 92 U/l [BMI 18–25, lean NAFLD], 165 [BMI 25–30], 140 [BMI 30–35] and 102 [BMI >35]). Additionally, 20 naïve subjects were prospectively vaccinated (12 F, median age 52.5 y, median LSM 4.9 kPa, 5 type 2 diabetes mellitus [T2 DM]), and were classified at baseline in obesity class medium-high risk (n = 5, median BMI 39) vs. low-risk (n = 15, median BMI 31). In the 17 subjects that completed the study to date, the median anti-HBs titres was 18.2 mIU/l in the medium-high risk obesity group (n = 4, median LSM 6.1 kPa, 1 T2 DM) versus 1000 mIU/l in the low-risk obesity class (n = 13, median LSM 4.7 kPa, 1 T2 DM) ($p = 0.0078$).
Conclusion: The currently approved HBV vaccine induces protective immunity in low-medium risk obesity class non-cirrhotic NAFLD patients. However, lower anti-HBs titres was observed in those with either normal BMI (lean NAFLD) as well as higher obesity class patients. Given the global obesity epidemic, the impact of NAFLD and co-morbid metabolic syndrome on vaccine efficacy has important public health implications.

SAT-522
Clinical characteristics and epidemiology of patients with non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in a large community-based healthcare delivery system in the U.S.
H. Patton[1], A. Nyberg[1], K. Chiang[2], S.-J. Yang[3], S. Caparosa[4], J. Stern[4], L. Nyberg[1]. [1]*Southern California Permanente Medical Group, Hepatology Research, San Diego, United States;* [2]*Kaiser Permanente Southern California, Pharmacy Analytical Services, Downey;* [3]*Southern California Permanenete Medical Group, Department of Research and Evaluation, Pasadena, United States;* [4]*Southern California Permanente Medical Group, Department of Research and Evaluation, Pasadena*
Email: Heather.M.Patton@kp.org

Background and Aims: Little is known about nonalcoholic fatty liver disease (NAFLD) and Nonalcoholic Steatohepatitis (NASH) diagnosis in real world practice settings nor the spectrum of

Table: (abstract: SAT-522)

Demographic/ Comorbidity	KPSC population	NAFLD/NASH	NAFLD/ NASH CC	NAFLD/NASH CC + Portal Hypertension	NAFLD/ NASH DC
N	3,011,580	49,504	901	752	3495
Age, mean (SD)	46.4 (17.72)	54.3 (14.71)	66.0 (12.67)	66.6 (11.97)	64.7 (14.66)
Gender, N(%) Male	1,438,331 (47.8%)	22,115 (44.7%)	349 (38.7%)	325 (43.2%)	1484 (42.5%)
BMI kg/m^2, N(%)					
<25	704,700 (23.4%)	4336 (8.7%)	108 (12%)	108 (14.4%)	494 (14.1%)
25–30	852,707 (28.3%)	12,817 (25.9%)	221 (24.5%)	173 (23%)	726 (20.8%)
>30	909,497 (30.2%)	27,257 (55.1%)	463 (51.4%)	369 (49.1%)	1248 (35.7%)
Diabetes, N(%)	369,961 (12.3%)	17,594 (35.5%)	467 (51.8%)	443 (58.9%)	1375 (39.3%)
Dyslipidemia, N(%)	735,424 (24.4%)	23,338 (47.1%)	591 (65.6%)	491 (65.3%)	1728 (49.4%)
HTN, N(%)	1,182,245 (39.3%)	35,372 (71.5%)	708 (78.6%)	533 (70.9%)	2780 (79.5%)
CVD, N(%)	635,525 (21.1%)	21,073 (42.6%)	553 (61.4%)	458 (60.9%)	1613 (46.2%)

disease severity that is recognized. Kaiser Permanente Southern California (KPSC) is a large community-based integrated healthcare system. We sought to identify and characterize KPSC members with NAFLD/NASH.

Method: Patients were included if ≥18 yrs with ICD-10 code for NAFLD, NASH, or cryptogenic cirrhosis from 10/1/2015–12/31/2016, absent other liver disease or alcohol abuse, and met membership criteria. Medical exclusions, comorbidities, and cirrhosis were identified 1/1/2006–12/31/2016 using ICD 9/10 codes and/or other pertinent variables. Biopsy reports between 1/1/2006–12/31/2016 were accessed via procedure codes and reviewed in blinded fashion.

Results: Of 3011580 eligible KPSC members, an ICD10 code for NAFLD/NASH was identified in 49504 (1.6%), 5148 (10.4%) of whom had cirrhosis (Table). Cirrhosis cases were characterized as compensated (CC) (17.5%), compensated with portal hypertension (14.6%), and decompensated cirrhosis (DC) (67.9%). Non-invasive scoring systems were positive among cirrhosis cases as follows: APRI 20.7%, BARD 84.9%, FIB-4 41.4%, NAFLD Fibrosis Score 79.5%. Biopsy reports (n = 194) demonstrated simple steatosis in 10.8%, possible NASH in 49.5%, definite NASH in 8.2%, NASH Cirrhosis in 26.3%, and other diagnosis in 5.2%. 38.6% of biopsies had stage 3–4 fibrosis.

Conclusion: Rates of ICD-10 codes for NAFLD/NASH in a large, community-based healthcare system were 1.6% from 10/1/2015–12/31/2016, 10.4% of whom had cirrhosis at the time of identification. Comorbidity burden was high in this population. The majority of those identified as cirrhotic had advanced disease with 70% having experienced a decompensation event. Liver biopsy reports predominantly contained features of NASH and 36% had advanced fibrosis.

SAT-523

Sex hormone binding globulin levels are increased in HIV-infected men and are independently associated with lower odds of nonalcoholic fatty liver disease regardless of HIV serostatus

J. Price[1], R. Wang[2], E. Seaberg[2], T. Brown[3], M. Budoff[4], L. Kingsley[5], F.P. Jr[6], M. Witt[4], W. Post[3], J. Lake[7], C. Thio[3]. [1]*University of California, San Francisco, Medicine;* [2]*Johns Hopkins Bloomberg School of Public Health, Epidemiology;* [3]*Johns Hopkins University School of Medicine, Medicine;* [4]*Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Medicine;* [5]*University of Pittsburgh Graduate School of Public Health, Departments of Infectious Diseases and Microbiology and Epidemiology;* [6]*Northwestern University Feinberg School of Medicine, Medicine;* [7]*University of Texas Health Science Center at Houston, Medicine*
Email: Jennifer.Price@ucsf.edu

Background and Aims: Sex hormone binding globulin (SHBG) is a liver-derived protein that may have an important role in energy metabolism. In pre-clinical models, overexpression of SHBG is protective against nonalcoholic fatty liver disease (NAFLD) via decreased lipogenesis. SHBG levels are increased in HIV+ individuals. We hypothesized that higher SHBG may be protective against NAFLD in persons with HIV. Thus, we aimed to determine: (1) the association of SHBG with NAFLD among men in the Multicenter AIDS Cohort Study (MACS), and (2) whether adjustment for SHBG alters the association of HIV with lower NAFLD odds in the MACS.

Method: Non-contrast CT was used to assess NAFLD (liver/spleen Hounsfield unit ratio < 1) in 615 MACS participants who drank <3 alcoholic drinks/day and were hepatitis C or B virus-uninfected. Among 334 men with morning serum samples (228 HIV+, 106 HIV-), SHBG levels were measured using radioimmunoassay. Multivariable logistic regression models assessed associations between SHBG concentrations and NAFLD prevalence and evaluated the association between HIV and NAFLD with/without adjustment for SHBG.

Results: HIV+ men had higher SHBG levels than HIV- men. Median SHBG levels were highest in the HIV+ men without NAFLD (59.9 nmol/l), followed by the HIV- men without NAFLD (46.2 nmol/l) and were similar in the HIV+ and HIV- men with NAFLD (38.0 and 38.8 nmol/l, respectively). After adjusting for age, race, MACS site, HIV serostatus, visceral adipose tissue (VAT) area, logHOMA-IR, and *PNPLA3* genotype, higher SHBG was associated with lower NAFLD odds [odds ratio(OR) 0.47 per doubling, 95% confidence interval(CI) 0.28–0.79]. This finding was similar regardless of HIV serostatus. HIV infection was associated with lower NAFLD odds after adjusting for age, race, MACS site, VAT, HOMA-IR, and *PNPLA3,* but this was not statistically significant (OR 0.55, 95%CI 0.26–1.14). Additional adjustment for SHBG attenuated the association of HIV with lower NAFLD (OR 0.72, 95%CI 0.34–1.54).

Conclusion: SHBG levels were higher among HIV+ than HIV- men and were independently associated with lower odds of NAFLD regardless of HIV serostatus. After adjusting for SHBG, HIV serostatus was not significantly associated with NAFLD prevalence, suggesting that SHBG could partially explain previously reported associations between HIV infection and lower NAFLD prevalence in this cohort. Prospective studies of SHBG and NAFLD in HIV+ persons are warranted.

SAT-524

The conundrum of cryptogenic liver disease with advanced fibrosis: Poor clinical outcomes without treatment options

Z. Younossi[1], M. Stepanova[2], S. Harrison[3], A. Sanyal[4], V. Ratziu[5], B. Mccolgan[6], R. Myers[6], N. Afdhal[7], M. Abdelmalek[8], Z. Goodman[9]. [1]*Inova Fairfax Hospital, Department of Medicine, Falls Church, United States;* [2]*Center for Outcomes Research in Liver Disease;* [3]*Pinnacle Clinical Research;* [4]*Virginia Commonwealth University School of Medicine;* [5]*Hopital Pitie-Salpetriere, Medicine;* [6]*Gilead Sciences, Associate Director of Clinical Research;* [7]*Beth Israel Deaconess Medical Center and Harvard Medical School;* [8]*Duke Clinical Research Institute;* [9]*Betty and Guy Beatty Center for Integrated Research, Inova Health System*
Email: zobair.younossi@inova.org

Background and Aims: Currently, enrollment in clinical trials for non-alcoholic steatohepatitis (NASH) requires meeting strict pathologic criteria. Given that, although there are numerous treatment protocols for patients with histologic NASH, there are few protocol options for subjects with cryptogenic liver disease (CD) or

cryptogenic cirrhosis (CC). **Aim:** To compare disease progression outcomes in patients with advanced fibrosis with NASH and CD.
Method: Subjects with advanced fibrosis (NASH CRN stage 3–4) were screened for two phase 2b clinical trials of simtuzumab. All other causes of chronic liver disease were excluded. Based on histologic assessment by the central pathologist, 423 subjects with advanced fibrosis were classified as having advanced fibrosis and NASH (n = 302, stage 3 or 4 fibrosis with steatosis, hepatocyte ballooning, and lobular inflammation) or CD (n = 121, stage 3 or 4 fibrosis with no steatosis regardless of other histologic features). Clinico-laboratory data were available. Clinical disease progression was defined as histologic progression of fibrosis, decompensation, qualification for liver transplant (MELD ≥ 15), or death.
Results: Subjects (age 54 ± 8 years, 35% male, 56% baseline cirrhosis) were followed-up for 25 ± 9 months (max 42 months) during which time 22.0% had disease progression. Compared to subjects with NASH with advanced fibrosis, those with CD with advanced fibrosis had higher baseline ELF, FIB-4, APRI, NAFLD Fibrosis Score, and Fibrotest, as well as higher levels of hyaluronic acid and hepatic expression of alpha-smooth muscle actin (p < 0.05). In these patients, mean time to disease progression was shorter in CD than in NASH (11.6 ± 7.6 vs. 15.6 ± 6.1 months, p = 0.03) while the overall rate of events was similar between groups. Survival analysis showed that CD and NASH with advanced fibrosis have similarly poor outcomes (p = 0.19) (Figure). By limiting the analysis to subjects with baseline cirrhosis (F4 only), there was trend in lower event free survival in cryptogenic cirrhosis than NASH cirrhosis (p = 0.07) (Figure).

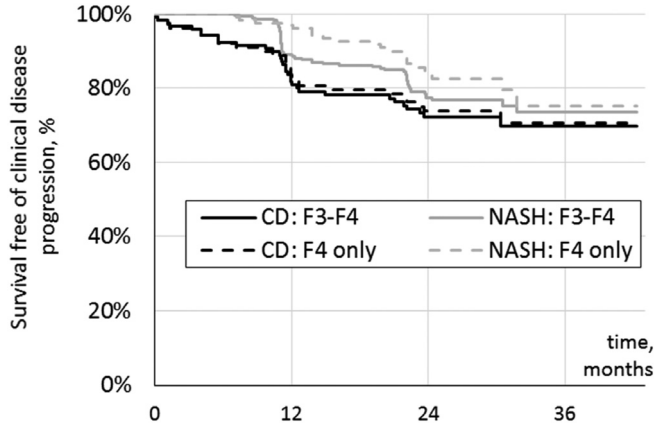


Figure: Clinical disease progression in CD and NASH.

Conclusion: NASH and CD with advanced fibrosis are both associated with similar rates of clinical disease progression. Given that subjects with advanced fibrosis and CD do not qualify for clinical trials of NASH, there is a need to develop new protocols for these patients with poor prognosis and without treatment options.

SAT-525

The worldwide prevalence of Non-alcoholic Steatohepatitis (NASH) in patients with Type 2 Diabetes Mellitus (DM)

P. Golabi[1], J. Paik[1], L. Deavila[1], N. Fukui[2], M. Srishord[1], Z. Younossi[3].
[1]Inova Health System, Betty and Guy Beatty Center for Integrated Research, Falls Church, United States; [2]Inova Fairfax Hospital, Center for Liver Disease, Department of Medicine, Falls Church, United States; [3]Inova Fairfax Hospital, Department of Medicine, Falls Church, United States
Email: zobair.younossi@inova.org

Background and Aims: NASH is regarded as the more progressive form of non-alcoholic fatty liver disease (NAFLD). DM is not only a known risk factor higher prevalence of NASH, but also seem to accelerate its progression. Our aim was to assess the global prevalence of NASH in patients with DM.

Method: PubMed, Ovid-Medline, EMBASE and Web of Science were searched from January 1989 to May 2017, for the terms involving NASH and type 2 DM. Morbidly obese and pediatric groups were excluded. Regions were classified according to the World Health Organization (WHO). All studies were reviewed by three independent investigators. Pooled NASH prevalence was calculated using random-effects models. Heterogeneity was investigated by subgroup analysis and meta-regression. The NASH prevalence estimates were stratified by region, diagnostic method, and mean BMI.
Results: After applying the inclusion and exclusion criteria to 1,589 studies (2003–2014), the final sample size was 27,020 patients with DM. The overall prevalence of NASH among patients with DM was 65.26% (95% CI, 51.73–76.71, n = 8) based histologic criteria for NASH. The highest NASH prevalence was reported from Western Pacific region (78%), followed by Southeast Asia (76%) and America (59%). Presence of advanced fibrosis (stage 3 and 4 by histology) was reported in 15 articles and the pooled overall percentage of advanced fibrosis was 15.05% (95% CI: 8.17–26.08, n = 15). A meta-regression model showed significant heterogeneity (I^2 = 96.62%) with WHO region (p = <0.01), diagnostic method (p = 0.403) and follow up time (p = 0.033) jointly accounted for 68% of the heterogeneity.
Conclusion: This meta-analysis reveals that the prevalence of NASH is very high among patients with DM. As the prevalence of DM and NASH are on the rise, an increase in the prevalence of advanced liver disease is inevitable.

SAT-526

Moderate alcohol consumption protects against fatty liver in males

T. Akahane[1], T. Namisaki[1], M. Kitade[1], K. Kaji[1], H. Takaya[1], N. Shimozato[1], S. Sato[1], H. Yoshiji[2]. *[1]Nara Medical University, Third Department of Internal Medicine, Kashihara, Nara, Japan; [2]Nara Medical University, Third Department of Internal Medicine, Kashihara, Japan*
Email: stakemi@naramed-u.ac.jp

Background and Aims: It has been recently reported that light-to-moderate alcohol consumption is associated with reduced prevalence of fatty liver in males, and moderate alcohol use is associated with improved insulin sensitivity and decreased cardiovascular mortality in the general population. We therefore aimed to elucidate the relationship between drinking patterns and fatty liver.
Method: This study assessed 2,429 Japanese males (mean age: 54.2 ± 9 years) who underwent medical examination at the Nara Health Promotion Center in 2012. Each subject's history of alcohol consumption was determined via a questionnaire. Subjects were classified according to alcohol consumption: non-drinker (ND), 0 g/day; light drinker (LD), <30 g/day; moderate drinker (MD), 30–60 g/day; and heavy drinkers (HD), >60 g/day. Fatty liver was diagnosed based on abdominal ultrasonography (hepatorenal echo contrast and liver brightness). Percentages of participants with fatty liver, obesity, elevated alanine aminotransferase (ALT) levels, and insulin resistance were compared among the four groups. Independent predictors of insulin resistance were determined by logistic regression analysis.
Results: The prevalence of fatty liver was the lowest in the MD group and highest in the ND group (p < 0.001). The prevalence of obesity (body mass index ≥ 25 kg/m^2) was not significantly different among the four groups (p = 0.133). The prevalence of elevated ALT levels (≥30 IU/l) was the lowest in the MD group (p < 0.05). The prevalence of insulin resistance (the homeostasis model assessment-insulin resistance ≥2.5) was the lowest in the MD group and highest in the ND group (p = 0.001). Chronic alcohol consumption was independently and inversely associated with insulin resistance after adjusting for obesity, hypertension, fasting hyperglycemia, and age. The odds ratios (95% confidence interval) were as follows: ND, 1; LD, 0.67 (0.50–0.90); MD, 0.48 (0.33–0.69): HD, 0.48 (0.30–0.76).
Conclusion: Moderate alcohol consumption is protective against fatty liver to improve insulin resistance.

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Vivien Woditsch
Dirk Wohlleber
Katharina Wolf
Danny Wong
Yu Jun Wong
Hyun Young Woo
Laura Wrzosek
Chao Wu
Wan-Jung Wu
Ming Xiong
Jing-Hang Xu
Minami Yagi
Shunhei Yamashina
Lei Yan
Hwai-I Yang
Jiayin Yang
Sokchea Yann
Yutaka Yasui
Chau-Ting Yeh
Apurva Yeluru
Sang young Yi
Hyung Joon Yim
Masayuki Yokoyama
Su Jong Yu
Mariam Zaghloul
Nekisa Zakeri
Alberto Zanetto
Qing-Lei Zeng
Xiangying Zhang
Haoming Zhou
Xinmin Zhou
Isabel Zvibel