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THE INTERNATIONAL LIVER CONGRESS™ 2019

CONGRESS REVIEW

EASL™
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HOT TOPICS

NAFLD in Young Adults

New study reports unexpectedly high rates of NAFLD in young adults

ILC Recognition Award

Deirdre Kelly CBE, Flair Jose Carrihlo and Vincenzo Mazzafarro acknowledged for major scientific contributions to liver research

ICE-HBV

Coalition launches global scientific strategy to cure hepatitis B

Liver Cancer

Real world studies demonstrate safety and efficacy of nivolumab in HCC treatment

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A MESSAGE FROM TOM HEMMING KARLSEN

On behalf of my colleagues at the European Association for the Study of the Liver (EASL), I would like to extend a huge thank you to everyone that attended and contributed to the International Liver Congress™ 2019 (ILC 2019) – the 54th annual meeting of EASL.

What we witnessed at the congress was the culmination of 54 years of work, collaboration and continued expansion by EASL. The meeting brought together over 8,500 clinicians, scientists and hepatologists from 117 countries, creating a unique opportunity to discuss the latest clinical innovation in hepatology. Attendees explored, examined and debated new research and scientific breakthroughs in many exciting fields, and were able to network and develop future collaborations with other delegates, presenters, faculty and industry.

The ILC 2019 attracted 2,500 abstract submissions, of which 70% were accepted by our expert panel of 150 reviewers for presentation within a state-of-the-art scientific programme, either orally or via posters. These abstracts were placed into six topic tracks, encompassing all the major areas within hepatology, to ensure the programme was tailored to the specific interests of each delegate. Thanks to the work of the Governing Board over the last few years we have seen an expansion of these six disciplines to deliver a comprehensive programme for all audiences.

The world of hepatology is changing and it is vital to recognise the multi-disciplinary nature of modern hepatology. As a specialty, we are forming new and important alliances with diabetes, obesity and oncology associations to enhance educational programming and clinical care. Public health research is also thriving and EASL is becoming increasingly active in driving policy agendas.

It would be impossible to build such a huge event without the ongoing support of our sponsors, many of whom we have been collaborating with for a long time and we would like to extend our sincere thanks for this continued partnership.

Finally, I would like to thank the EASL Office, for the invaluable work they are doing for our community and their contribution to making this congress such a success.

Warmest Regards,

Tom Hemming Karlsen

EASL Secretary General

SCIENTIFIC HIGHLIGHTS

GENERAL SESSIONS

Tom Hemming Karlsen, EASL Secretary General

UK study reports high rates of NAFLD in young adults

A large prospective study conducted among young adults in the UK has reported unexpectedly high rates of suspected NAFLD, with one in five participants showing signs of steatosis and one in 40 having fibrosis. The study conducted by a team from Bristol in the UK examined a cohort of >4000 young adults (mean age 24.0 ± 0.8 years) who had previously taken part in the Avon Longitudinal Study of Parents and Children (ALSPAC), which had reported a NAFLD prevalence at a mean age of 17.9 years of 2.5% (ultrasound criteria).

In the present study, 4021 young adults had fibroscans performed using the Echosens 502 Touch® system. Scans from those with known alcohol use disorder or excessive daily alcohol intake were excluded from the analysis.

Of the 3128 individuals whose fibrosis scores were eligible for analysis, 76/3128 (2.4%) had some degree of fibrosis and eight (0.3%) had scores equivalent to fibrosis stage 4 (F4). A total of 680 out of 3277 individuals (20.8%) were found to have steatosis, with just under half of these (n=331; 48.7%) classified as severe (S3). A positive association was observed between increases in liver enzymes (ALT, aspartate aminotransferase, and gamma-glutamyl transferase), increasing fibrosis scores ($p \leq 0.002$), and increasing controlled attenuated parameter (CAP) scores ($p<0.001$). Positive associations were found between F score and CAP score ($p<0.001$) and between increasing steatosis grade, cholesterol levels, triglycerides, and low-density lipoprotein ($p<0.001$). BMI rose significantly with both F and CAP scores ($p<0.001$ for both).

"To the best of our knowledge, this is the only study to assess NAFLD prevalence in young adults using elastography," said Dr Kushala Abeysekera from the University of Bristol in the UK. "One in five young adults had evidence of NAFLD, with half having steatosis, and one in 40 of our cohort had evidence of fibrosis.

"The results of our study suggest greater public health awareness of NAFLD is needed in young adults in the UK."

Kushala Abeysekera

HBV integrates into the human genome in HBeAg-negative disease

Integration of hepatitis B virus (HBV) DNA into the human genome is not restricted to the early phases of chronic HBV infection but also frequently occurs in individuals with hepatitis B e antigen (HBeAg)-negative disease, according to researchers from Italy and the UK. The researchers evaluated liver tissue from 40 HBeAg-negative, treatment-naïve individuals, who were monitored for at least 2 years prior to tissue sampling. DNA and RNA were extracted from the tissue and the intrahepatic total HBV DNA, cccDNA, and pgRNA were quantified. Whole exome sequencing was used to detect HBV integration events, with the threshold of parameters predicting HBV integration defined by the area under the receiver operating characteristic (AUROC).

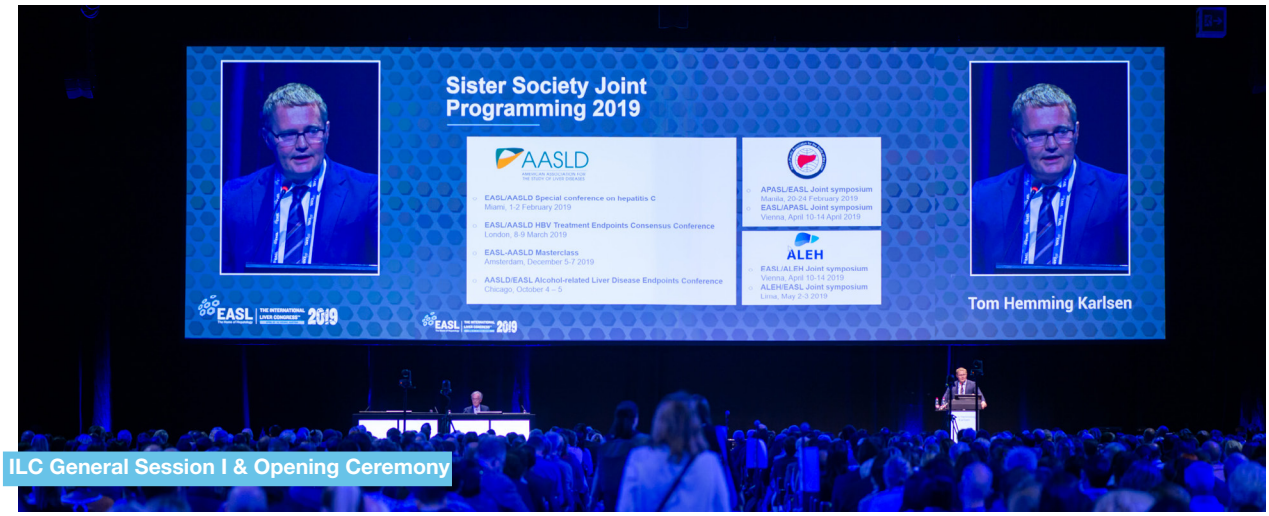
Study participants were classified according to their levels of viraemia: Group 1 had serum HBV DNA <2000 IU/mL (n=8), Group 2 had HBV DNA 2000–20,000 IU/mL (n=14), and Group 3 had HBV DNA >20,000 IU/mL (n=18). Hepatitis B virus integration was detected in all three groups, with an overall prevalence of 35.4% (14/40 participants). Overall, HBV integration in genomic regions relevant for gene expression was detected in 35.4% of patients: 25.0% in Group 1, 14.4% in Group 2, and 55.6% in Group 3. “Notably, HBV integration was evident in a significant proportion of patients in Groups 1 and 2, despite low viraemia and a limited intrahepatic reserve,” remarked Dr Romina Salpini from the University of Rome, Italy who presented the results from this award-winning study.

Most HBV integration events occurred in intronic regions flanking the exons – regions critical for RNA splicing and gene expression. In particular, HBV integration was detected in signal sequences whose modification or loss could hamper the splicing event, thus favouring the production of aberrant proteins. Among the 17 recognised integration events, 11 involved the region encoding HBx protein, three involved the HBs antigen/polymerase(pol)-encoding region, and three involved the HBV core-encoding region. In six patients, HBV integration localized in genes regulating cell proliferation, including NUP85, COL18A1, AGBL5 and ANKRD52, which are associated with an unfavourable prognosis in liver cancer. Integrated HBV was also found in genes regulating lipid and drug metabolism (CYP2UI, LMF-1) and those regulating the antiviral and inflammatory response (NRC3C1, IFITM-1). By AUROC, HBsAg >5000 IU/mL identified the occurrence of HBV integration with the best diagnostic accuracy (83.5%).

Romina Salpini

“HBV integration in genomic regions relevant for gene expression occurs across all groups of patients with HBeAg-negative disease, including a significant percentage of low viraemic patients who currently do not meet treatment criteria,” said Dr Romina Salpini from the University of Rome, Italy. “Localization of HBV integration events suggests this event can be involved not only in carcinogenesis, but also in mechanisms regulating antiviral immunity, inflammatory responses, and hepatocyte metabolism."

“This is a timely reminder that these patients may also be at risk of disease progression and the development of HCC and deserve adequate monitoring.”



ILC General Session I & Opening Ceremony

Glecaprevir/Pibrentasvir effective and well tolerated in 'real-world' HCV study

A large 'real-world' study conducted in Germany has confirmed that glecaprevir/pibrentasvir (G/P) achieves high rates of sustained virological response (SVR) and is well tolerated in a diverse group of individuals with chronic hepatitis C virus (HCV) and a range of commonly-encountered comorbidities and complications. The study conducted using data from the German Hepatitis C Registry (DHC-R) evaluated the outcomes of a large population of adults with HCV genotypes 1–6 who were treated with G/P according to the local label. Since most individuals were treatment naïve and without cirrhosis (84%), G/P was administered for 8 weeks in the majority. A total of 1698 individuals were assessed: 439 (26%) were receiving opioid substitution therapy, 247 (15%) had psychiatric conditions, 106 (6%) had substantial alcohol abuse/dependence, 107 (6%) were coinfected with HIV, and 47 (3%) were active drug users.

According to Professor Markus Cornberg from Hannover Medical School in Germany, who presented the study results, in the ITT population, the overall SVR rate 12 weeks (SVR12) after the end of G/P treatment was 96.6% (964/998 patients), with similarly high response rates observed across all subgroups analysed. Excluding patients who discontinued G/P prematurely and did not achieve SVR12, those who were lost the follow-up, and those with HCV reinfection, the modified SVR12 rate was 99.5% (964/969 patients).

At the end of treatment, the mental and physical component scores of the 36-Item Short Form Health Survey (SF-36), significantly improved from baseline across the entire cohort. However, patients with comorbidities generally reported lower scores at baseline and showed greater improvements at the end of treatment compared with those without comorbidities. G/P was generally well tolerated, with three patients discontinuing due to adverse events. Six individuals had HCV reinfection post-treatment and five individuals had virological relapse.

"In this real-world analysis, on-label treatment with G/P was safe and highly effective, and improved patient-reported outcomes in patients with key comorbidies"

- Professor Markus Cornberg

Lubiprostone produces promising results in NAFLD proof of concept study

The laxative, lubiprostone, has produced promising results in a Phase 2, proof of concept study involving individuals with non-alcoholic fatty liver disease (NAFLD). The type 2 chloride channel activator, which is approved in some countries for the treatment of constipation, has been investigated in NAFLD based on the theory that the condition is associated with increased gut permeability ('leaky gut'), which could potentially be ameliorated with lubiprostone treatment.

In a Phase 2, randomized, double-blind, placebo-controlled study (The LUBIPRONE Study), 150 individuals with NAFLD with constipation (diagnosed based on Rome IV criteria), an alanine aminotransferase (ALT) level of >40 IU/L, a liver fat content as measured by MRI-PDFF of ≥5.2%, and a liver stiffness measured using MR elastography of <6.7 kPa, were randomized to receive oral lubiprostone 12 µg once-daily (n=47), lubiprostone 24 µg once-daily (n=51), or placebo (n=41) for 12 weeks (full analysis set: N=139). The primary endpoint of the study was the change in ALT levels from baseline at 12 weeks. Gut permeability was assessed using the lactulose-mannitol ratio (LMR), with a key secondary endpoint of LMR change from baseline at 12 weeks.

After 12 weeks of treatment, significantly greater reductions in mean ALT levels were observed in the lubiprostone groups (–13 ± 21 U/L with lubiprostone 12 µg and –14 ± 19 U/L with lubiprostone 24 µg) compared with the placebo group (+0.6 ± 25 U/L; p=0.004 and p=0.001, respectively).

Significantly greater reductions in LMR (–4 ± 12 x 103 and –5 ± 13 x 103 vs +5 ± 10 x 103; p=0.008 and p=0.001, respectively), liver fat deposition (MRI-PDFF) (–2.5 ± 3.0% and –2.3 ± 2.5% vs +0.25 ± 2.0; p=0.0001 for both comparisons) and liver stiffness (MRE) (–0.22 ± 0.4 kPa and –0.31 ± 0.6 kPa vs –0.07 ± 0.5 kPa; p=0.01 and p=0.0008, respectively) were observed. No statistically significant differences in efficacy were observed between the lubiprostone 12 µg and 24 µg groups, however, significantly higher rates of adverse events (particularly diarrhoea) were observed in the lubiprostone 24 µg group compared with the placebo group (p=0.0025).

"This is the first proof of concept, randomized, placebo-controlled trial to show the effect of lubiprostone in NAFLD patients"

- Dr Takaomi Kessoku

"Lubiprostone showed favourable efficacy and tolerability when administered at 12 µg doses to NAFLD patients, suggesting [that] manipulating gut permeability may be a promising novel target for the treatment of NAFLD," concluded Dr Takaomi Kessoku from Yokohama City University School of Medicine in Yokohama, Japan.


Zobair Younossi

Obeticholic acid improves liver fibrosis in patients with NASH

A daily dose of obeticholic acid (OCA) 25 mg significantly improves liver fibrosis and other key histological features of non-alcoholic steatohepatitis (NASH), according to an interim analysis of the Phase 3, REGENERATE study. The analysis, which was presented by Dr Zobair Younossi, Professor and Chairman of the Department of Medicine at Inova Fairfax Medical Campu in Falls Church, Virginia, USA, included 931 patients with biopsy-confirmed NASH, fibrosis stages F2 and F3, and a NAFLD activity score (NAS) ≥4 (intention to treat [ITT] population). Participants were randomized to receive OCA 10 mg/day (n=312), OCA 25 mg/day (n=308) or placebo (n=311) (ITT population), with a pre-planned interim analysis conducted after 18 months of treatment.

The primary endpoints of the study, which were determined by the U.S. Food and Drug Administration (FDA), were fibrosis improvement based on histology (≥1 stage) and no worsening of NASH and NASH resolution, with no worsening of fibrosis as assessed by liver biopsy. Study success was defined as the achievement of one of these two primary endpoints.

At 18 months, among the group of patients with fibrosis stages F2 or F3 who received OCA 25 mg/day (n=308) (ITT analysis), 23.1% had fibrosis improvement by ≥1 stage and no worsening of NASH compared with 11.9% of patients in the placebo group (p=0.0002), and 11.7% had NASH resolution and no worsening of fibrosis (vs 8.0% in the placebo group; p=0.13). Although the NASH resolution primary endpoint was not met, 35.1% of patients receiving OCA 25 mg showed improvements in hepatocellular ballooning (p=0.0011 vs placebo), and 44.2% of patients had improvements in lobular inflammation (p=0.0322 vs placebo) (ITT analysis). Dose-dependent reductions in liver enzymes were also observed.

OCA was generally well tolerated, with pruritus being the most commonly-reported adverse event, affecting 51% (336/658) of the OCA 25 mg/day treatment group, 28% (183/653) of the OCA 10 mg/day treatment group, and 19% (123/657) of the placebo group. More participants withdrew from the study as a result of pruritus in the OCA 25 mg/day group (9%) than in the OCA 10 mg/day (<1%) or placebo (<1%) groups. “There is an urgent need for effective treatment regimens for NASH,” said Dr Younossi.

"These first results from the REGENERATE study give us hope that a new targeted approach to NASH treatment may soon become available and potentially reverse some of the liver damage associated with this important liver disease”

- Dr Zobair Younossi

Manisha Balwani

Givosiran meets primary endpoint in Phase 3 acute hepatic porphyria study

The investigational RNA interference (RNAi) therapeutic, givosiran, which targets aminolevulinic acid synthase 1 (ALAS1), has met its primary endpoint in the Phase 3 ENVISION study involving individuals with the rare liver disease, acute hepatic porphyria (AHP). The double-blind, placebo-controlled trial, which randomized 94 individuals with AHP to receive subcutaneous (sc) givosiran 2.5 mg/kg (n=48) or placebo (n=46) once-monthly for 6 months of double-blind treatment (Sardh et al, 2019), reported a statistically significant reduction in the composite annualized rate of porphyria attacks requiring hospitalization, an urgent healthcare visit, or hemin administration (primary endpoint) among those who received givosiran (3.2 [95% CI 2.25, 4.59]) compared with those who received placebo (12.5 [95% CI 9.35, 16.76]) – a mean reduction on 74%. All components of the composite primary endpoint and all subgroup analyses for the primary endpoint favoured givosiran treatment.

Five of the nine secondary endpoints, including urinary aminolevulinic acid (ALA) levels at 3 months and 6 months in patients with acute intermittent porphyria (AIP), porphobilinogen (PBG) levels at 3 months in AIP patients, and annualized attack rate in patients with AHP (including AIP) were also statistically significantly in favour of givosiran (all $p<0.0001$). Givosiran produced rapid and sustained reductions in median ALA and PBG levels (by 92% and 89%, respectively) compared with baseline at 6 months.

At least one adverse event (AEs) was reported in 43/48 (89.6%) givosiran- and 37/46 (80.4%) placebo-treated patients, with at least one serious AE reported in 10/48 (20.8%) and 4/46 (8.7%) givosiran- and placebo-treated patients, respectively. Two patients receiving givosiran treatment experienced the serious adverse event of chronic kidney disease; other serious adverse events reported by one patient each were asthma, device-related infection, and gastroenteritis. The AEs reported in ≥5% of givosiran recipients and observed more frequently than with placebo were nausea, injection site reactions, headache, fatigue, and chronic kidney disease.

“The overall safety and tolerability profile [of givosiran] was encouraging in AHP, a serious illness,” concluded Dr Manisha Balwani from Mount Sinai Icahn School of Medicine in New York, USA, who presented the study results.

METABOLISM, ALCOHOL & TOXICITY

NASH patients with advanced liver disease are costly to treat

Patients with NASH and advanced liver disease carry a heavy burden of comorbidities and are expensive to manage, according to the results of a large Italian database study. The study involved identifying adults with NAFLD/NASH from the records of >9 million people in databases held by eight local health units in Italy. From these databases, 9729 people with NAFLD/NASH who were hospitalized during the study period (2011–2017) were identified: most (9470; 97.3%) did not have advanced liver diseases, however, 131 (1.3%) had CC, 303 (3.1%) had DCC, 11 (0.1%) had undergone a liver transplant (LT), and 79 (0.8%) had HCC. Across all cohorts, the comorbidity burden was high: 32.5%–49.4% had type 2 diabetes, 40.5%–90.9% had renal impairment, 79.5%–93.7% had cardiovascular disease, and 35.4%–46.6% had hypertension.

NAFLD/NASH patients with advanced liver disease were hospitalized, on average, 4.2–4.4 times per year compared with 2.9 times for those without advanced liver disease ($p<0.05$), and their hospital stays were significantly longer (58.9–63.8 days/year vs 35.3 days/year; p-values 0.09–<0.0001). The mean annual number of outpatient visits and pharmacy prescription fills were also significantly higher among the group of patients with NAFLD/NASH and advanced liver disease compared with those without advanced liver disease ($p<0.05$ for both comparisons). The mean total annual healthcare costs increased with disease severity and were ≥86% higher among the NAFLD/NASH patients with advanced liver disease compared with those without advanced liver disease, primarily as a result of higher inpatients costs.

According to Dr Jie Ting from Gilead Sciences, Inc. in the USA, who presented the study results, the total mean annual healthcare costs associated with hospitalized NAFLD/NASH patients were at least 86% higher in those with advanced liver disease compared with those without, primarily as a result of higher inpatients costs: €10,745 for NAFLD/NASH patients without advanced liver disease, €19,681 for those with CC, €19,808 for those with DCC, €65,137 for those with LT, and €26,220 for those with HCC (2017 total mean annual costs; $p<0.001$ for all comparisons). A similar trend was observed after adjusting these costs for patient characteristics and comorbidities such as type 2 diabetes and cardiovascular disease, suggesting that liver-related complications accounted for at least 50% of total healthcare costs among patients with advanced liver disease: €10,603 for those without advanced liver disease, €20,352 for those with CC, €20,059 for those with DCC, €69,838 for those with LT, and €26,014 for those with HCC.

Dr Ting believes the higher prevalence of DCC diagnosis compared with CC observed in the study suggests missed opportunities to screen and diagnose patients at an earlier stage. “All of this really points to the fact that we need to identify patients earlier on and, with the availability of effective treatments, we could potentially lower the risk of progression and perhaps avoid the costs associated with progression.”

Rate of NAFLD more than doubles in HIV-infected individuals over 10 years

Between 2006 and 2016, the rate of NAFLD has more than doubled among HIV-infected individuals, according to the results of a large retrospective US Medicare study. The study presented by Dr Zobair Younossi, Professor and Chairman of the Department of Medicine at Inova Fairfax Medical Campus in Falls Church, Virginia, USA, evaluated data from >28 million Medicare recipients, and identified 47,062 HIV-positive individuals, with 10,474 of these having liver disease (5628 [53.7%] with HCV-related disease, 1374 [13.1%] with HBV-related disease, 645 [6.2%] with HCV/HBV-related disease, 2629 [25.1%] with NAFLD, and 198 [1.9%] with other liver diseases). During the 10 years between 2006 and 2016, the prevalence of viral hepatitis among HIV-positive individuals decreased from 27.8 to 24.1 per 100,000 population ($p=0.009$) while rates for NAFLD more than doubled from 5.3 to 11.6 per 100,000 population ($p<0.001$). Mortality rates related to viral hepatitis also decreased from 3.8 to 2.6 per 100,000 population ($p=0.006$), while mortality related to NAFLD increased from 0.2 to 0.8 per 100,000 population ($p=0.041$).

“Over the last decade, the prevalence of HIV has decreased in the Medicare population,” said Dr Younossi. “Despite this overall decrease, the number of Medicare recipients with HIV and liver disease has been increasing and this is almost entirely driven by an increase in NAFLD.

"Given the increasing clinical and ecnomic impact of NAFLD in HIV patients, clinicians must be more vigilant in identifying and managing NAFLD in this patient population"

- Dr Zobair Younossi

Screening diabetic patients for NAFLD may not be cost effective

The efficacy and cost of new treatments for NAFLD will be key to determining whether screening for NAFLD/NASH in diabetic patients is cost-effective. This was the conclusion from an Israeli study conducted using a Markov model designed to assess the impact of screening for liver fibrosis using transient elastography in 50-year-old individuals with diabetes. The model was developed based on the natural history of NAFLD and the assumption that any hypothetical new treatment would be relevant only for patients with NAFLD and significant fibrosis (F2–F3), with individuals found to have cirrhosis being managed according to current guidelines. The annual cost of the hypothetical new treatment was set in the range of $20,000 to $100,000; the treatment was assumed to reduce the annual progression rate by 15% and increase the annual regression rate by 15%.

According to Dr Yaakov Maor from the Institute of Gastroenterology and Hepatology in Rehovot, Israel, if a new NAFLD treatment was to cost $40,000 per year, the average cost of a screening strategy would be $213,347, with a no-screening strategy costing $94,791 (a difference of $118,556). The average quality-adjusted life-year (QALY) of the screening strategy would be 15.86 compared with 15.25 for the no-screening strategy (a difference of 0.61), and the incremental cost-effectiveness ratio (ICER) would be $195,481 per QALY. In contrast, if the annual cost of a new treatment was to be $100,000, the ICER would increase to $509,301 per QALY.

“What this shows us is that, for a NAFLD screening strategy in patients with diabetes to be cost effective, the cost of any new treatments must be relatively low: approximately ~$40,000 per year,” said Dr Maor. ‘It will be important to reassess this when more effective medications become available.”

Gut microbiome could help detect NAFLD-related cirrhosis

Researchers from the USA have uncovered a unique microbiome-derived signature that may help to detect NAFLD-related cirrhosis. The team from the University of California in La Jolla, USA, used 16S rRNA amplicon sequencing to characterize the gut microbiome compositions of 203 individuals from two well-characterized twin and familial cirrhosis cohorts from the university’s NAFLD Research Center, including 98 probands encompassing the spectrum of NAFLD and their first-degree relatives. All individuals were assessed using MRI-PDFF for quantifying hepatic steatosis and MRE for quantifying liver fibrosis.

A significant familial correlation of the gut microbiome composition was found within biologically-related pairs compared to random unrelated pairs at the level of the phyla ($p=0.023$) and 16S sequences of bacterial strains ($p<0.0001$). Related individuals with shared-housing were found to have a lower phylogenetic dissimilarity than those who did not share housing ($p=0.045$), suggesting that shared housing may drive the familial correlation of the gut microbiome. The research team identified 27 bacterial features that were significant for the detection of NAFLD-related cirrhosis, with 16 of them significantly increased in NAFLD-related cirrhosis and 11 of them significantly decreased. When the 27 bacterial features were combined with age, sex, and body mass index, a high diagnostic accuracy for the detection of NAFLD-related cirrhosis was observed in both the training and validation cohorts (receiver operating characteristic curve [AUROC]: 0.92 and 0.87, respectively).

“This study reports a strong familial correlation of gut-microbiome driven by shared-housing, and provides evidence for a novel faecal microbiome-derived signature to detect NAFLD-cirrhosis,” concluded Dr Caussy.

High rates of disease progression and mortality in NAFLD/NASH patients

A study conducted in Germany has identified high rates of liver disease progression and mortality among individuals with non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH). The study retrospectively evaluated 215,655 NAFLD/NASH patients from a German insurance claims database between 2011 and 2016 and identified 100,644 incident events of liver disease that were followed up over a period of 5 years. A total of 79,245 events (78.7%) of non-progressing NAFLD/NASH, 411 events (0.4%) of compensated cirrhosis (CC), 20,614 events (20.5%) of decompensated cirrhosis (DCC), 363 events (0.4%) of hepatocellular carcinoma (HCC), and 11 events (0.01%) of liver transplantation (LT) were evaluated. During the first year of follow-up, the mortality rate amongst NAFLD/NASH patients with advanced liver disease increased by almost 50% (range 8.8%–51.2%) compared with those with non-progressing NAFLD/NASH (1.2%). After 5 years of follow-up, mortality rates were 2.8% in the non-progressing NAFLD/NASH group, 14.8% in the group with CC, 25.6% of the group with DCC, and 64.5% of the group with HCC.

“Nearly 98% of NAFLD/NASH patients had already had a decompensation event at the time of first cirrhosis diagnosis,” noted Professor Ali Canbay from the University of Magdeburg Medical School in Magdeburg, Germany. “Early identification and safe and effective treatment options are needed to halt or reverse fibrosis to prevent disease progression and the associated long-term costs.”

Consuming red meat and cholesterol increases the risk of cirrhosis in NAFLD

A study investigating dietary risk factors in NAFLD has suggested that eating unprocessed red meat and cholesterol may increase the risk of developing cirrhosis among individuals with NAFLD. In contrast, eating fruit and fibre may protect against cirrhosis development. The nested case-control study, which used data from the prospective Multiethnic Cohort (MEC) of >215,000 men and women from Hawaii and California, identified all cases of NAFLD between 1999 and 2015 using Medicare claims, and matched these individuals against controls without liver disease based on age, sex, ethnicity and length of Medicare enrollment. Diet was assessed at baseline using a comprehensive and validated quantitative food frequency questionnaire (QFFQ).

A total of 2974 cases of NAFLD were identified (518 with cirrhosis and 2456 without cirrhosis) and these were matched with 29,474 controls. Dietary factors significantly associated with NAFLD were processed and unprocessed red meat (p=0.016 and p=0.011 for trend), unprocessed poultry (p=0.005), and cholesterol (p=0.005). Unprocessed red meat (p=0.003) and cholesterol (p=0.002) were significantly associated with NAFLD with cirrhosis. In contrast, fruit and fibre intake were protective factors in NAFLD. The associations were generally similar across the wide spectrum of racial and ethnic groups represented in the study cohort, supporting the external validity of the observed associations.

“As you know, diet is modifiable, so this is something to consider when you are treating patients within clinical trials and clinical practice,” concluded Dr Mazen Noureddin from the Cedars Sinai Medical Center in Los Angeles, USA, who presented the study findings.

NAFLD Research Think Tank

European NAFLD Consortia report impressive research progress

Representatives from four major European NAFLD consortia reported impressive progress at this year’s NAFLD Research Think Tank held at The International Liver Congress™ 2019 in Vienna, Austria. Professor Quentin Anstee from the Institute of Cellular Medicine at Newcastle University in the UK and Laurent Castera from the University of Paris-VII France updated the meeting on the status of four major ongoing programmes.

“Fatty liver is a huge challenge in terms of understanding disease pathophysiology and developing better non-invasive diagnostics and therapeutics,” said Professor Anstee. “With European Union funding, there have been a number of consortia established that have really helped to move the needle forwards.”

Progress reported to date:

- Elucidating Pathways of Steatohepatitis (EPoS) is now within 6–9 months of project completion (37 discovery-line publications and >100 congress presentations already generated)
- LITMUS: An international effort to validate NAFLD/NASH biomarkers now has 47 partners involved in 14 European countries
- European NAFLD Registry is now using a ‘hub and spoke’ model to increase recruitment (6708 histologically-characterized NAFLD patients already enrolled at April 2019)
- The LiverScreen Project, whose aim is to validate the accuracy and clinical value of transient elastography for detecting liver fibrosis in the general population, now has research teams in eight European countries and 2905 patients enrolled

LIVER TUMOURS

Nivolumab and pembrolizumab effective in the 'real-world' treatment of advanced HCC

Investigators from Austria and Germany have reported that both nivolumab and pembrolizumab offer an acceptable safety profile and can produce meaningful benefits in clinical practice, even when used in patients with advanced HCC and those who have been extensively pretreated. A multicentre study retrospectively evaluated 65 individuals who received nivolumab (n=34) or pembrolizumab (n=31) between 2015 and 2018 at six centres in Austria and Germany. Of these, 32 (49%) were Child-Pugh A, 28 (43%) were Child-Pugh B, and five (8%) were Child-Pugh C. Immunotherapy was used as a first-, second-, third-, or fourth-line treatment in nine (14%), 27 (42%), 26 (40%), and three (5%) individuals, respectively. 46 individuals had at least one follow-up imaging report and were evaluable for radiological response.

No complete response was observed in this cohort. However, the overall response rate (CR + PR) and disease control rate (CR + PR + SD) in all patients was 12% and 49%, respectively. Thirty-five individuals (54%) had radiological disease progression and 36 (55%) died during follow-up. The median time to progression was 5.5 months (95% CI 3.5–7.4); the median progression-free survival was 4.6 months (95% CI 3.0, 6.2), and the median overall survival was 11.0 months (95% CI 8.2, 13.8). The most common adverse events were infections (n=7), rash (n=6), pruritus (n=3), fatigue (n=3), diarrhoea (n=3), and hepatitis (n=3), but most of them were low grade. Outcomes and safety results were similar between those with Child-Pugh A and B, however, median overall survival was significantly shorter in Child-Pugh B patients (16.7 vs 8.6 months; p=0.065).

"PD-1 targeted immunotherapy was safe, even in Child-Pugh B patients," said Dr Matthias Pinter from the Medical University of Vienna, Austria. "Efficacy in terms of overall survival and radiological response was comparable to those reported in Phase 2 trials."

Safety of nivolumab in the 'real world' similar to that in HCC clinical trials

A 'real world' study conducted in Spain has confirmed that the safety profile of nivolumab when used in clinical practice for the treatment of hepatocellular carcinoma (HCC) is similar to that observed in a Phase 1/2 clinical trial (Checkmate 040). The retrospective observational study presented by Dr Leonardo Gomes da Fonseca from the Hospital Clinic of Barcelona in Spain evaluated data from 42 individuals who received nivolumab outside clinical trials (primarily via compassionate use programmes): seven (16.7%) had received nivolumab first line, 20 (47.6%) had received the treatment second line (after sorafenib), and 15 (37.7%) had received the third line (primarily after sorafenib and regorafenib). Most patients (71.4%) in the cohort had hepatitis B or C infection, and more than half (54.8%) had received previous locoregional therapies. The most commonly-used nivolumab regimen was 240 mg every 2 weeks (in 66.7% of patients).

Nineteen Grade 1 or 2 and seven Grade 3 or 4 adverse events (AEs) were reported in 17 patients. Corticosteroids were required for the management of AEs in five individuals (11.9%). A total of 11 (26.2%) patients developed a potential immune-related event (four with Grade 3 or 4 events and seven with Grade 1 or 2 events).

In the first-line cohort (n=7), with a median follow-up of 6.9 months (interquartile range [IQR] 1.3–11.2 months), two patients (28.7%) had died. In the second-line cohort (n=20), with a median follow-up of 13.5 months (IQR 8.5–26.2 months) since the start of sorafenib treatment, 10 patients (50.0%) had died. In the third-line cohort (n=15), with a median follow-up of 21.7 months since the start of sorafenib treatment, five patients (33.3%) had died.

"Due to the short-term follow-up and the number of events, it was only possible to estimate the overall survival in the second-line cohort," explained Dr Gomes da Fonseca. The overall survival (OS) since the start of first-line treatment was 28.8 months (95% CI 9.4, not estimable). In terms of radiological evaluation, growth of pre-existing lesions was the predominant pattern, observed in 18 patients (42.8%). New extrahepatic lesions were reported in 17 patients (40.5%), and new intrahepatic lesions were reported in 3 patients (7.1%). No progression was observed in four patients (9.5%).

"The safety profile [of nivolumab] in this real-life cohort is similar to that reported in clinical trials (El-Koueiry et al., 2017) said Dr Gomes da Fonseca. "Most of the serious adverse events were immune-related, reflecting the need for a high level of suspicion. "Prospective and controlled results are awaited to define the impact of nivolumab on overall survival and how to better assess response."

Gut microbiota affects clinical response to nivolumab in locally-advanced HCC

The therapeutic potential of modulating the gut microbiome prior to immunotherapy has once again been highlighted by the results of a small pilot study assessing the association between the microbiome and clinical response to nivolumab in locally-advanced HCC. The study conducted in Taiwan evaluated the results from 20 individuals with advanced HCC who received nivolumab treatment and who completed faecal examination for gut microbiome analysis as well as having radiographic assessments of their tumour response every 6–8 weeks. Fifteen of these patients had faecal samples collected prior to the initiation of nivolumab treatment.

On evaluation using RECIST v1.1 criteria, two patients (10%) had a complete response (CR), six (30%) had a partial response (PR), four (20%) had stable disease, and 8 (40%) had progressive disease (PD) on nivolumab treatment. In an analysis of gut microbiota diversity, the investigators reported no significant differences between the nivolumab-recipients with controlled disease (n=12) and those with disease progression (n=8). However, the composition of the gut microbiota was notably different between those with controlled and progressive disease, with a statistically significant enrichment of faecal samples with Betaproteobacteria, Burkholderiales, Alcaligenaceae, Roseburia, and Sutterella observed among the treatment responders.

“The composition of the gut microbiota was different between these two groups and maybe it will serve as a new biomarker for immunotherapy in locally-advanced HCC,” said Dr Pei-Chang Lee from the Taipei Veterans General Hospital in Taipei, Taiwan. “This finding may highlight the therapeutic potential of modulating the microbiome before immunotherapy to enhance the treatment response to immune checkpoint inhibitors for HCC.”

Lenvatinib ‘an important option’ in the treatment of unresectable HCC

The oral multikinase inhibitor, lenvatinib (LEN), which was developed as a first-line treatment for unresectable HCC, has produced encouraging results in a ‘real-world’ study involving almost 80 individuals undergoing treatment for unresectable HCC in clinical practice in Japan. Of these individuals, 33 were tyrosine kinase inhibitor (TKI)-naïve and 44 were TKI-experienced; 11 had previously received treatment with regorafenib (REG).

The cohort included patients with ECOG performance status 2, Child-Pugh class B disease, and portal vein invasion – all criteria that would have excluded them from the Phase 3 REFLECT trial. Therapeutic response to LEN was evaluated retrospectively 4 weeks after starting LEN using contrast-enhanced CT or MRI findings based on modified RECIST (mRECIST) (n=52).

At 4 weeks (n=52), one patient showed a complete response (CR), 19 had a partial response (PR), 22 had stable disease (SD), and 10 had progressive disease (PD), with an overall response rate (ORR) of 38.5% and a disease control rate (DCR) of 80.8%.

“These results are similar to those reported in the REFLECT trial,” said Dr Atsushi Hiraoka from the Ehime Prefectural Central Hospital in Matsuyama, Japan, who presented the study results.

The 1-, 2- and 3-month progression free survival (PFS) rates in TKI-naïve individuals were 90.1%, 82.1%, and 80.1%, respectively. Overall survival (OS) rates at the same timepoints were 98.6%, 96.9%, and 93.4%, respectively.

Hand-foot skin reaction was the most frequently-reported adverse event in this study, affecting 31 individuals (40.3%). Other frequently-reported adverse events included general fatigue (33.8%), and appetite loss (28.6%).

"Our results showed early therapeutic response in patients with unresectable HCC who received LEN, thus a survival benefit can be expected. LEN may be an important option for not only first- but also second- and third-line therapy, thus helping to meet the current unmet need in regard to TKI treatment failures for unresectable HCC patients."

- Dr Atsushi Hiraoka

CHOLESTASIS & AUTOIMMUNE

UK study links environmental agent exposure with autoimmune liver diseases

A study conducted in the north of England has found evidence that exposure to an unknown environmental agent or agents may have played a role in the pathogenesis of the autoimmune liver diseases, PBC, autoimmune hepatitis (AIH), and PSC.

The study conducted by a team from Newcastle Upon Tyne in the UK identified a large cohort of individuals diagnosed with PBC (n=2150), AIH (n=963) and PSC (n=472) living in the North-East of England and North Cumbria, and used spatial point analysis to investigate the presence and patterns of disease clustering according to postal addresses. For individuals with a known year of diagnosis, spatio-temporal analyses were also undertaken.

Significant spatial clustering was reported at approximately 1–2 km for all three conditions. In PBC, the clustering appeared again at 7.5 km and this was sustained to the limits of the 20 km spatial range. In AIH, clustering peaked at approximately 1 km, with further clustering between 7.5 km and 12.5 km. In PSC, clustering peaked at approximately 1 km, 2 km, and between 7.5 km and 12.5 km. No significant temporal clustering was found in any of the conditions investigated, although a trend towards temporal clustering was observed for PSC.

“This study raises some important questions,” said Dr Jessica Dyson, Associate Clinical Lecturer at Newcastle University and Consultant Hepatologist at Newcastle upon Tyne Hospitals NHS Foundation Trust in the UK.

"The demonstration of spatial clustering may suggest that environmental exposure plays a role in disease pathogenesis."

- Dr Jessica Dyson

She also proposed that areas with higher prevalence could reflect the distribution of environmental risk factors and that the presence of spatial but not temporal clustering suggests a persistent, low-level environmental trigger. She said the distances between clusters suggested that different environmental factors may be important in the different autoimmune conditions.

Methylation-controlled J-protein a potential drug target in cholestatic liver disease

Inhibition of methylation-controlled J-protein (MCJ) in hepatocytes could reduce bile acid toxicity and represent a novel therapeutic target in cholestatic liver disease, according to the results of several preclinical studies conducted in Spain and the USA. The studies were undertaken based on the hypothesis that MCJ represses the function of the mitochondrial respiratory chain, so its deficiency could mitigate the oxidative stress caused by cholestasis, thereby decreasing cell death, inflammation and fibrosis.

To study the effects of mitochondrial respiratory chain inhibition by MCJ on bile acid-induced liver toxicity, researchers used liver samples from patients with the chronic cholestatic liver diseases, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), and wild-type (WT) and MCJ knockout (MCJ-KO) mice that had been subjected to complete bile duct ligation (BDL) to mimic cholestatic liver injury.

Hepatic MCJ levels were found to be upregulated in the liver disease patients and in the mice under bile duct ligation. MCJ deficiency protected liver tissue from inflammatory infiltration and JNK activation, with loss of MCJ protecting hepatocytes from mitochondrial membrane depolarization, ROS overproduction, JNK activation and ATP depletion resulting from bile acid toxicity.

In vivo inhibition of MCJ expression by MCJ-specific small interfering RNA (siRNA) was found to reduce liver injury caused by bile acids in the BDL mouse model.

“The specific mechanisms involved in mitochondrial dysfunction caused by cholestasis are still controversial,” said Dr Paula Iruzubieta from Marqués de Valdecilla University Hospital in Santander, Spain.

"Our results indentfy MCJ as a key regulator of cholestatic liver disease and a potential therapeutic target to mitigate cholestasis-induced liver injury."

- Dr Paula Iruzubieta

Obeticholic acid may prevent and reverse cholestasis-induced cognitive decline

Obeticholic acid (OCA) could prevent and reverse cholestasis-induced cognitive decline by preserving the integrity of the blood–brain barrier (BBB) and neuronal health. Researchers from Newcastle Upon Tyne in the UK have used the bile duct ligation (BDL) mouse model to investigate both the mechanisms responsible for cholestasis-induced memory impairment ("brain fog") and the therapeutic potential of both OCA and ursodeoxycholic acid (UDCA). "Cognitive deficits are a real problem for patients with PBC," explained PhD study, Lucy Gee, from the Institute of Cellular Medicine at Newcastle University in Newcastle upon Tyne in the UK. "The domains of deficit are mainly based around memory and concentration, and particularly visuo-spatial memory."

Bile duct ligation or sham surgery were performed in mice, with a subgroup of animals receiving either OCA or UDCA prophylactically or as treatment. Activity and cognitive function were evaluated 8–9 days after surgery using standardized behavioural and cognitive tests. The group reported that prophylaxis and treatment with OCA improved cognitive function in the BDL mice compared with no treatment. No significant benefit was observed with UDCA.

Astrocyte coverage of the BBB was found to be significantly reduced and neural senescence was increased in the hippocampus in the BDL mice – OCA treatment restored astrocyte coverage of the BBB and reversed cholestasis-induced P21+ cellular senescence and telomere DNA damage in this model. Finally, the group reported that the farnesoid X receptor (the receptor for OCA) was expressed on endothelial cells of the BBB, suggesting that OCA could directly regulate the BBB.

"These data suggest that, with earlier implementation, OCA may be effective in treating cognitive symptoms of PBC," said Ms Gee. "A clinical trial is warranted."

Fungal gut dysbiosis reported for the first time in patients with PSC

Patients with PSC have been found to have altered fungal gut microbiota associated with an impaired fungi–bacteria correlation network. In the first study of its kind to evaluate fungal gut microbiota, the bacterial and fungal composition of the faecal microbiota were analysed in a cohort of patients with PSC and concomitant inflammatory bowel disease (IBD) (n=27), patients with PSC only (n=22), patients with IBD only (n=33), and healthy controls (n=30). A decreased biodiversity, an altered composition, and a disrupted correlation network between bacteria and fungi were observed in the patients with PSC that was independent of IBD status. Notably, an increased proportion of Exophiala genus and Sordariomycetes class, and a decreased proportion of Saccharomycetales order, Saccharomycetes class, Saccharomycetaceae family, and Saccharomyces cerevisiae species were observed. "The increased abundance of Exophiala was particularly striking in the subgroup of PSC patients," said Dr Sara Lemoinne from Sorbonne University and the Saint-Antoine Hospital in Paris, France.

"We have confirmed that PSC is associated with bacterial dysbiosis," she said. "For the first time, we have also shown that PSC is also associated with fungal gut dysbiosis."

VIRAL HEPATITIS

Novel agents targeting cccDNA clearance in chronic hepatitis B infection bring hope of future cure

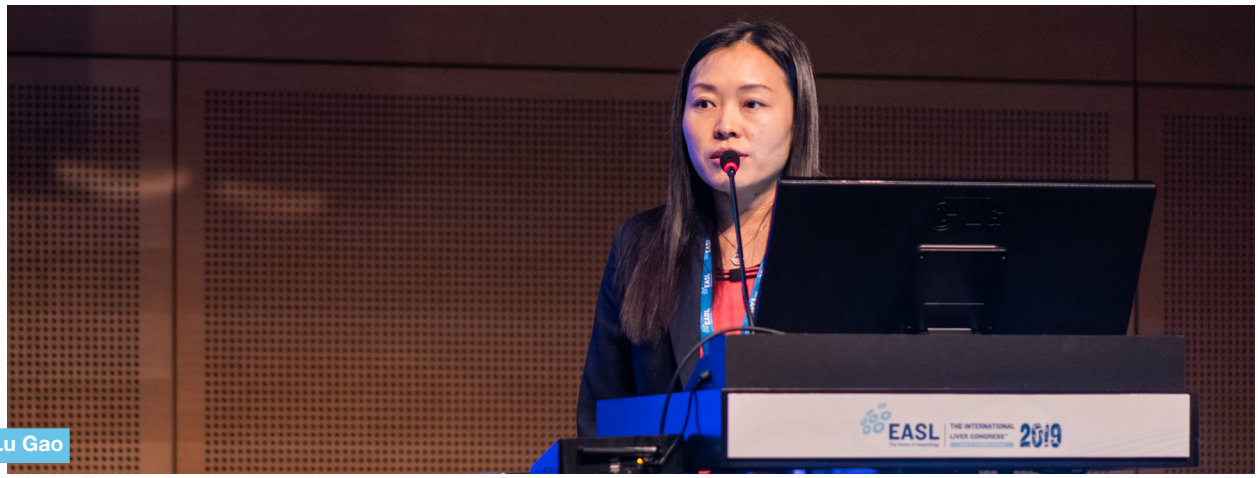
Persistence of covalently closed circular DNA (cccDNA) in the nuclei of infected hepatocytes remains a major barrier to achieving cure with current therapies used in the treatment of chronic hepatitis B (HBV) infection, and many research teams are focussed on finding novel agents that target cccDNA clearance. Two series of studies presented at this year's meeting reported promising results and generated a buzz amongst delegates.

ccc_R08: a novel oral small molecule

In the first study series, teams from Roche Innovation Centres based in Basel and Shanghai investigated the potential of the novel oral small molecule, ccc_R08, to reduce cccDNA levels in infected human hepatocytes and in the HBVcircle mouse model. Initially, primary human hepatocytes (PHHs) were infected with HBV, with ccc_R08 treatment initiated 2 days later. According to the investigators, potent and dose-dependent inhibition of HBV DNA, hepatitis B surface antigen (HBsAg), and hepatitis B e antigen (HBeAg) was observed, with pre-existing levels of cccDNA significantly reduced by the agent. No significant cytotoxicity was reported with ccc_R08 in PHHs or in multiple proliferating cell lines up to 100 µM. In addition, no significant effects on mitochondrial DNA were observed, suggesting a specific effect on cccDNA.

The in vivo efficacy of ccc_R08 was evaluated using the HBVcircle mouse model, with ccc_R08 dosed orally twice-daily for 2 weeks. The serum levels of HBV DNA, pgRNA, HBsAg, and HBeAg were all significantly reduced and sustained during the off-treatment follow-up period. At the end of follow-up, levels of cccDNA molecules in the livers of ccc_R08-treated mice were reduced to below the lower limit of quantification. In contrast, entecavir, which was used as a control in this study, did not impact the cccDNA levels in this model.

"These data encourage exploration of this type of molecule in the clinic to evaluate its potential for curing chronic hepatitis B infection", concluded Dr Lu Gao from the Roche Innovation Centre Shanghai in China.



Lu Gao

IL-21 delivered by adeno-associated virus injection

In the second study, a team from Fudan University in Shanghai, China, used several newly-developed mouse models of HBV persistence to investigate the antiviral effects of IL-21 delivered via adeno-associated virus (AAV) injection (AAV-IL-12). In the first investigation, a single injection of AAV-IL-21 administered to genotype B persistent strain (BPS) mice efficiently induced clearance of both serum HBV markers and BPS DNA and rcccDNA from the mouse liver, with long-lasting protective memory reported. In a second set of investigations, IL-21-induced HBV clearance was found to be associated with activation and liver infiltration of CD8+ T cells, with CD8 antibody injections reported to negatively impact AAV-IL-21 effectiveness. Adoptive transfer of CD8+ T cells from AAV-IL-21-cured BPS persistence mice induced HBV clearance in acceptor BPS persistence mice. Finally, transfer of splenocytes stimulated with IL-21 and HBsAg induced HBV clearance in treatment-naïve BPS persistence mice.

"Our results demonstrate IL-21 as a sound basis for novel therapeutics against chronic HBV infection, with potential in removing cccDNA-harbouring hepatocytes via activated CD8+ T cell responses and establishing subsequent long-term protection," concluded Dr Zhongliang Shen from Fudan University in Shanghai, China.

Treatment as Prevention programme for hepatitis C reports high levels of success

A Treatment as Prevention Programme for hepatitis C virus (HCV) infection in Iceland (TraP HepC programme) has reported high rates of cure, but highlighted injection drug use and homelessness as potential barriers to overall programme success. The TraP HepC programme provided direct-acting antivirals (DAAs) without restriction to all HCV-infected individuals, with priority given to those with recent injection drug use (IDU), prisoners, and patients with advanced liver disease. Before October 2016, participants were offered sofosbuvir/ledipasvir with or without ribavirin (SOF/LDV ± RBV); after that date, sofosbuvir/velpatasvir (SOF/VEL) ± RBV were used.

According to Dr Magnús Gottfredsson from the National University Hospital in Reykjavik, Iceland, who presented the first results from the programme, 631 HCV-positive individuals were initiated on DAAs during the first 2 years, representing 80% of the estimated total HCV-infected population.

The overall cure rate at ≥12 weeks (SVR12+) after the first treatment attempt was 89.2% (intention-to-treat analysis). Among those individuals reporting recent injection drug use, 82.9% achieved SVR12+ compared to 92.4% of those who did not (p=0.0006). Individuals with recent IDU were more likely to discontinue treatment (15.2% vs 4.5%, p<0.0001) and, even when the analysis was restricted to those who completed treatment (n=580), the chance of cure on the first attempt was lower (89.9% vs 95.3%, p=0.025).

Homelessness among those recently injecting drugs was associated with a significantly greater chance of persistent viraemia at ≥12 weeks (relative risk [RR] 2.42 (95% CI 1.34-4.37), p=0.008). In contrast, living in a halfway house was associated with a lower risk (RR 0.37 (95%CI 0.12-1.16), p=0.068). More than 90% of those who remained viraemic after the first treatment attempt have now been retreated.

“Despite population challenges, our elimination efforts in Iceland are going well, even among active drug users,” explained Dr Gottfredsson. “Although rates of cure were lower among patients with a recent history of IDU, the vast majority of these patients are nevertheless cured on the first treatment attempt with DAAs.

"Homelessness is associated with a lower chance of treatment success, probably due to a higher chance of treatment discontinuation. We need to intensify our efforts with this group to increase our reduction of HCV."

- Dr Magnús Gottfredsson

EBR/GZR effective in patients with HCV infection receiving opioid agonist therapy

A ‘real-world’ observational study involving individuals with chronic HCV genotype 1 (GT1) infection receiving opioid substitution therapy has reported high rates of sustained virological response (SVR) with elbasvir/grazoprevir (EBR/GZR) treatment.

The retrospective database study was conducted using information from HCV GT-1-infected individuals receiving opioid agonist/antagonist therapy (OAT) in the US Veteran Affairs (VA) population.

“Historically, patients on opioid substitution therapy were not offered HCV therapy because of concerns related to patients’ compliance and potential drug–drug interactions,” explained Dr Amy Puenpatom from Merck Sharp & Dohme, a subsidiary of Merck and Co., Inc. in Kenilworth, NJ, USA, who presented the study findings on behalf of the investigators.

The study identified 611 individuals who had completed at least 12 weeks of EBR/GZR treatment and who had either a diagnosis of opioid use disorder or been prescribed medication for opioid dependence: 549 (89.9%) of the cohort were treatment naïve prior to receiving EBR/GZR, and 416 (68.1%) had a mean baseline viral load ≥800,000 UI/mL.

A total of 471 individuals (77.1%) had a history of alcohol abuse and 548 (89.7%) had a history of drug abuse. Seventy-one percent of the population were receiving concomitant psychiatric medications (n=434).

The majority of individuals (526/611; 86%) had received EBR/GZR without ribavirin for 12 weeks; the remaining 85 people (14%) had received other EBR/GZR-based regimens.

SVR was achieved by 586/611 patients (95.9% [95% CI 94.0%, 97.3%). SVR was achieved in similarly high proportions of patients (96.1%–100%) with a history of alcohol or drug abuse, among those with HCV/HIV coinfection, and among those receiving concomitant psychiatric medications.

“EBR/GZR was an effective treatment option for a challenging population of patients with HCV GT1 infection receiving OAT,” concluded Dr Puenpatom.

CIRRHOSIS & COMPLICATIONS

Could calmangafodipir help reduce liver injury after paracetamol overdose?

The manganese-based superoxide dismutase mimetic, calmangafodipir (PP100-01), may help to reduce liver injury after paracetamol overdose when administered in combination with N-acetylcysteine (NAC). A Phase 1, randomized, open-label, increasing-dose study conducted by a team from the Royal Infirmary of Edinburgh and the University of Edinburgh in the UK, recruited 24 individuals from the Emergency Department within 24 hours of a single or staggered paracetamol overdose. All participants were considered candidates for NAC treatment at study enrolment. Participants were randomly assigned to one of three sequential dosing cohorts, with each cohort randomized to receive NAC + calmangafodipir (n=6) or NAC alone (n=2). Calmangafodipir was administered as a bolus intravenously (IV) between the first two NAC bags at doses of 2, 5, or 10 µmol/kg per cohort. Adverse events were assessed and blood sampling undertaken at 2, 10, and 20 hours after starting the first NAC administration. The primary endpoint of the study was the safety and tolerability of the combination treatment. Secondary endpoints included alanine aminotransferase (ALT) levels and the biomarkers of hepatotoxicity, full-length keratin-18 (keratin-18) and microRNA-122 (miR-122), measured at baseline, 10 hours and 20 hours after starting NAC treatment.

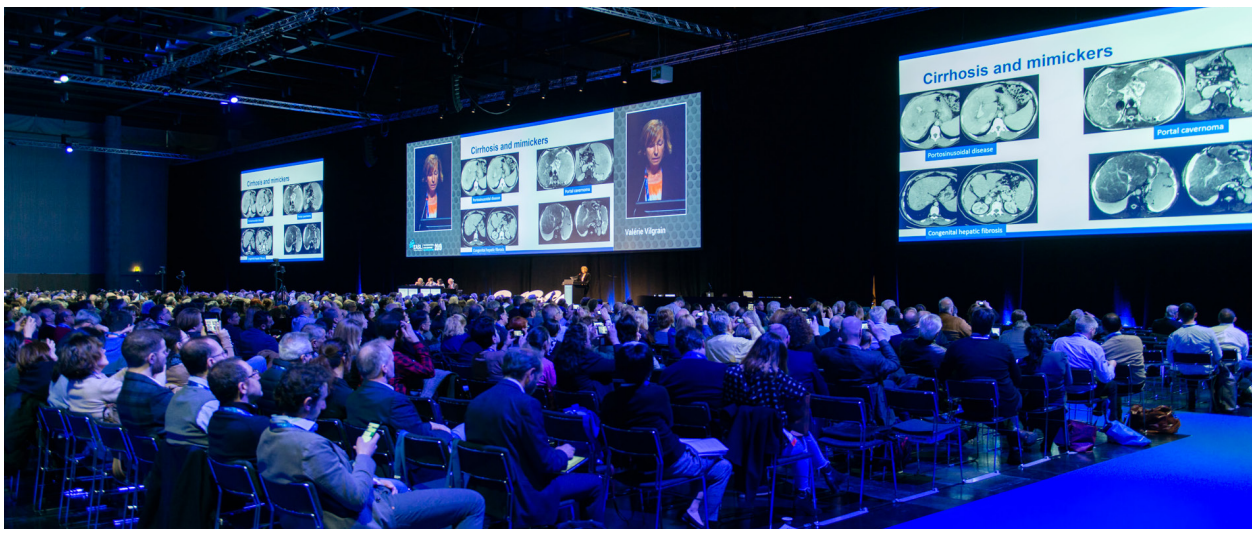
According to Dr James Dear from the University of Edinburgh in the UK, who presented the study results, the mean time from overdose to starting NAC ranged from 8.6 to 12.1 hours per group. The mean total amount of paracetamol ingested ranged from 185 to 397 mg/kg per group.

All participants experienced at least one adverse event (AE), however, no AEs or SAEs were definitely attributed to calmangafodipir. Pre-defined increases in ALT were more common in the NAC monotherapy group than in the combination therapy groups. “An ALT greater than 100 is clinically-important in the UK because that is the indication to carry on NAC,” said Dr Dear. Two patients in the NAC monotherapy group had an ALT >100 U/L at 20 hours while no patients in the combination treatment groups met this endpoint.

Individuals who received the combination treatment had significantly smaller increases in keratin-18 than individuals who received NAC alone. Between baseline and 20 hours, median keratin-18 levels increased 1.41-fold in the calmangafodipir 2 µmol/kg + NAC group, 1.02-fold in the calmangafodipir 5 µmol/kg + NAC group, and 1.17-fold in the calmangafodipir 10 µmol/kg + NAC group, compared with a 1.71-fold increase in the NAC monotherapy group (Figure). The median (range) keratin-18 levels at 20 hours were 306 U/L (118–2606 U/L) with NAC monotherapy, 212 U/L (98–572 U/L) with calmangafodipir 2 µmol/kg + NAC, 163 U/L (100–287 U/L) with calmangafodipir 5 µmol/kg + NAC, and 155 U/L (103–508 U/L) with calmangafodipir 10 µmol/kg + NAC. A similar pattern of increases was observed with miR-122.

“This is the first time a new therapeutic agent has been taken into humans with paracetamol overdose,” said Dr Dear. “Calmangafodipir was safe and tolerated in this trial and there may be evidence that it reduces paracetamol toxicity.

“This trial supports a further, robust efficacy study to determine for sure that calmangafodipir has evidence of efficacy.”



Faecal microbiota capsules may improve outcomes in patients with cirrhosis and hepatic encephalopathy

Faecal microbiota transplantation (FMT) performed using a capsule formulation improves duodenal mucosal diversity, dysbiosis, and barrier function, reduces hospitalizations, and enhances cognitive performance in patients with cirrhosis and recurrent hepatic encephalopathy (HE), according to the results of a randomized, participant-blinded, placebo-controlled study. The study was undertaken to determine the safety, tolerability, and impact of a single administration of faecal microbiota capsules prepared from a single donor with a high relative abundance of beneficial Lachnospiraceae and Ruminococcaceae compared with placebo in 20 outpatients with cirrhosis and recurrent HE (≥2 episodes) already receiving standard-of-care (lactulose/rifaximin). At baseline, stool collection, cognitive testing (EncephalApp Stroop and psychometric hepatic encephalopathy score [PHES]), and endoscopies with duodenal and sigmoid biopsies were performed. Cognitive testing, stool collection, and adverse event analysis was repeated at 30 days for every participant; endoscopies and biopsies were only repeated in the FMT-assigned individuals. All patients were followed for 5 months.

No differences in safety parameters were observed between the FMT and placebo treatment groups. The placebo group experienced a significantly higher total number of serious adverse events (SAE) (11 vs 1 SAEs; p=0.02) and more patients experienced an SAE in the placebo group (6 vs 1 patients; p=0.03) compared with the FMT group. The FMT group had numerically fewer HE episodes and HE episodes requiring hospitalization or an emergency room visit (1 vs 7 episodes for each outcome) and infections (2 vs 3 infections) than the placebo group, but the between-group differences were not statistically significant. Favourable changes in mucosal and stool microbial composition and enhancement of the small intestinal barrier were reported in the FMT group vs the placebo group. Significant improvements in the EncephalApp OnTime but not in the PHES scores were also observed in the FMT group.

“Further studies focused on larger sample sizes comparing upper to lower gastrointestinal modes of delivery and repeated administrations are needed in patients with recurrent HE,” concluded Dr Jasmohan Bajaj from Virginia Commonwealth University and the McGuire VA Medical Center in Richmond, USA.

POST GRADUATE COURSE

ANNALISA BERZIGOTTI - PGC COURSE ORGANISER

"The goal of this year’s PGC was to provide an updated overview on the management of end-stage liver disease. Drawing from the spirit of EASL education, our aim was to be both dynamic and interactive to ensure our audience took home key knowledge and insight. To facilitate this, we had questions relating to a specific complex clinical case, followed by experts answering through short presentations. These were followed by extensive discussions of each case by the experts, during which the audience posed questions both directly and through the ILC app.

The case consisted in cirrhosis due to NASH, an emerging etiology, with each session focusing on emerging and controversial management problems. We started by considering whether non-invasive or invasive methods should be used for achieving a definite diagnosis, then we dealt with how to manage portal hypertension.

We also addressed the significant problem of how to deal with major comorbidities, such as diabetes, sarcopenia and chronic kidney injury, while also focusing on the management of major complications of liver disease, including portal vein thrombosis, acute-on-chronic liver failure, infections, acute kidney injury and hepatic encephalopathy. Further discussion took place over the role of liver transplantation in end-stage liver disease.

As part of our efforts to drive an interdisciplinary approach in this setting, we invited experts from other sectors of medicine that are complementary to hepatology. Radiologists, pathologists and transplant surgeons all provided evidence-based insights for questions that extended the boundaries of hepatology, enabling the delivery of comprehensive perspectives and answers for attendees."

ILC **IN NUMBERS**

117
COUNTRIES REPRESENTED

8,560
PARTICIPANTS

4,024
ONLINE PARTICIPANTS*
*Through the live stream

TOP 10 PARTICIPATING COUNTRIES

United States	1,338
United Kingdom	778
Germany	624
Italy	449
France	415
Spain	392
China	371
Switzerland	237
Austria	231
Netherlands	189

5,956
APP DOWNLOADS

2,447
ABSTRACTS SUBMITTED

246
ORAL PRESENTATIONS

1,474
POSTER PRESENTATIONS

79
EXHIBITORS

555
EXHIBITOR BADGES

124
MEDIA REPRESENTATIVES

ILC **RECOGNITION AWARD**

DEIRDRE KELLY CBE

"I have been a member of EASL since I was a trainee at the Royal Free Hospital and never imagined that my work would be recognised in this way, so I am especially pleased to be awarded the ILC Recognition Award.

I am delighted that EASL has recognised the important advances being made in understanding the pathogenesis of paediatric liver disease. On a personal level, I am thrilled it reflects the wonderful work that the team in Birmingham have done over the years to care for so many children and families.

My career has been so varied and I have been quite fortunate along the way. Whilst completing my post-graduate training, I was lucky enough to be appointed as a Research Fellow in Hepatology and Gastroenterology to study folate metabolism and learn about liver disease at the same time. Hepatology was a new speciality then and there was much to learn and to achieve, so I became hooked.

I then had the wonderful opportunity to work with Professor Dame Sheila Sherlock at the Royal Free Hospital in London as a Wellcome Trust Clinical Research Fellow, where I was asked to look after children with liver disease, who were then cared for by adult hepatologists. It became clear to me that we knew very little about what caused liver disease in children and how best to diagnose and treat them. I found it both fascinating and challenging, and therefore retrained in paediatric medicine to specialise in Paediatric Liver Disease and care for children.

However, the most important aspect of my career was setting up and developing the Liver Unit at Birmingham Children's Hospital in 1989. I have been privileged to establish a motivated and dedicated team of surgeons, physicians and allied health professionals, and change the lives of many children with liver disease who would have otherwise died in infancy.

It is a really exciting time to be a hepatologist. We now have the opportunity to work together across borders and international networks, helping us consolidate our knowledge and treatment of both paediatric and adult liver disease. In addition, the medical management of liver disease has been transformed due to the development of new drugs, particularly anti-viral therapy, which has changed the outcome for many children and adults by significantly improving the quality of their lives and avoiding liver transplantation.

We are also part of the continuing revolution in genomics and proteomics which has opened up new disease mechanisms and targets for therapy, potentially curing diseases that were not even described when I was a medical student. In fact, for many of us it's too much of an exciting time to retire so I hope that I can continue to play an active part in this revolution and further my contributions to this dynamic field of medicine.

We now have the opportunity to work together across borders and international networks, helping us consolidate our knowledge and treatment of both paediatric and adult liver disease."

ILC **RECOGNITION AWARD**

FLAIR JOSE CARRILHO

"To my knowledge, I am the first Latin-American hepatologist to receive this award. With this decision, EASL has recognised the existence of a generation of Latin-American hepatologists who, with tremendous enthusiasm, imagination and effort, aided the progression of hepatology and improved the care of patients with liver diseases in a region of the world that has faced several periods of political and social turmoil, with great impacts on education and healthcare.

I would like to call attention to my contributions in the training of human resources in Brazil, in the study of the molecular epidemiology of the hepatitis B virus in Brazil and Latin America, and in the implantation of the screening and early detection of hepatocellular carcinoma in cirrhotic patients in São Paulo. More recently, I was nominated to coordinate a network of 59 hospitals in Latin America for the ACLARA study, which assesses the role of ethnicity on the clinical course of Acute-on-Chronic Liver Failure. This has been a highlight of my career.

In 2004, I was nominated Full Professor and Director of the Department of Gastroenterology at the University of São Paulo School of Medicine, and Head of Division of Clinical Gastroenterology and Hepatology of the Hospital das Clínicas. This new status enabled me to re-design the Department of Gastroenterology, applying the model employed by the early European Liver Units. The Department of Gastroenterology is now an integrated organisation with modern clinical research facilities where the members of staff work together in a coordinated fashion. In the future, the enormous increase in technological development will require hepatologists to have more clinical sense, comprehensive knowledge of general medicine and to be fully devoted to their patients.

One of my major legacies for the next generation of hepatologists will be the general improvement in knowledge concerning the management of cirrhosis and hepatocellular carcinoma in Brazil. Brazil is a country with great disparities in socioeconomic status and I am therefore interested in future projects concerning the linkages of care for patients at risk of cirrhosis and HCC, as well as point of care strategies for HCC screening, particularly in underprivileged areas of Brazil and Latin America.

I give my heartfelt thanks to my mentors, colleagues and family who have welcomed me on this journey."

VINCENZO MAZZAFERRO

YOUNG INVESTIGATOR AWARDEES

VIRGINIA HERNÁNDEZ-GEA

"My interest in research was initially sparked through my clinical training and, following this, within the laboratory where I attained a solid background in molecular biology. This was a priceless experience which has taught me how persistent you must be and how important it is to be team player in the competitive field of biomedical research.

As a specialist in liver hemodynamics, my research focuses on the physiopathy of vascular alterations leading to portal hypertension. During my post-doctoral fellowship, we discovered autophagy as a new regulatory pathway involved in hepatic stellate cells activation and fibrosis regulation, and when I started my own research team, I decided to continue investigating the role of autophagy in liver vascular homeostasis.

In the last few years, I have achieved competitive funding to build my own laboratory group, which continues to study the molecular regulation of liver fibrosis. Our further research into the role of autophagy in liver vascular homeostasis has indicated that autophagy regulates liver sinusoidal endothelial cells (LSEC) phenotype and protects LSEC from oxidative stress during the early phases of liver injury. Additionally, endothelial autophagy dysregulation activates HSC and aggravates fibrosis during mild acute liver injury. This has led to our conclusion that autophagy enhancement in LSEC may be a successful therapeutic strategy to slow down liver disease progression. I have also coordinated a multicentre clinical study to validate the beneficial role of pre-emptive TIPS in patients with acute variceal bleeding and the high risk of treatment failure and rebleeding.

I believe this award is a recognition of my work as a physician scientist. Becoming an independent translational researcher during a time of budget-cuts can be tough, frustrating and full of insecurities. To me, this award is a recognition of the effort, dedication and passion that will help me to continue pursuing my goal of consolidating my career as a physician scientist.

In the future, I hope to enjoy my work with the motivation, enthusiasm and passion of my first day. I envision continuing on in the search of a better understanding of liver diseases in a collaborative environment where I can bring out the best in myself."

MARTIN GUILLIAMS

"As a child, I was always fascinated by science and decided to study bio-engineering at the University of Brussels. My early professional research experience, which involved an industrial training period at a pharmaceutical company, enabled me to realise that I wanted to follow a pathway to an academic research position.

After completing my PhD and performing post-docs in Belgium and France, I obtained a Tenure Track Professorship position in the Faculty of Science of the Ghent University to start my own research group on liver Kupffer Cells, which I had developed a huge passion for. Three years later, in 2018, I then obtained my Tenured Professor position and I now lead a great team of motivated and unique scientists studying Kupffer cell biology.

Within the Kupffer cells field, I soon realised that there was a lack of tools to study these specifically in vivo and therefore devised a long-term strategy to generate these crucially needed tools. After working with world-class experts, including Bernard Malissen, Marc Dalod and Alain Beschin, we have now given our mouse-models to many labs working on hepatic infections, liver cancer, liver metabolism and liver transplantation and this should yield fantastic findings on the role of Kupffer cells in vivo.

We have been fortunate in obtaining an ERC Consolidator grant and are also joining forces with other liver experts around the globe to generate the Liver Human Cell Atlas. We have a great consortium which I am honoured to be part of. Our team will focus on providing different myeloid cells subsets in the mouse and human liver.

Becoming an ILC Young Investigator Awardee is my first European award and it means a great deal to me. It is also a great recognition for the work of the whole team who, each day, push the limits of technology to make sure we can work at the forefront of liver research. I am very humbled and grateful that I can work with such a great team of people that are so dedicated and talented, and I look forward to solving scientific puzzles in the future."

Honorary President
DOMINIQUE-CHARLES VALLA

"At ILC, THE meeting to attend in 2019, cholestatic and metabolic liver diseases have merged in a number of aspects, including assessment, pathophysiology and therapy. Recently proposed or completely novel, pharmacological approaches have flourished. Non-invasive testing becomes better defined alongside a clearer view of public health issues and resource utilization.

Increased attention has been paid to the causes of cirrhosis in understanding complications of cirrhosis and portal hypertension. Early endoscopy and TIPS for bleeding, and propranolol in advanced liver disease have remained under scrutiny. As a concept, acute-on-chronic liver failure comes of age. Novel indices improve prognosis and treatment stratification in severe alcoholic hepatitis.

Exciting treatment approaches are developing for hepatitis B and hepatitis D. Immunology drives advances in hepatitis B and hepatitis C vaccination. Various strategies are being evaluated for eradicating hepatitis C.

Hepatocellular carcinoma has seen a settlement of the controversy on DAAs for hepatitis C, and an improved perspective on systemic therapies.

Discussions of hot topics with experts continuously enlivened Hepatology Arena, a fully successful new initiative which has supplemented the now classical Meet-the-expert and Think-Tank sessions, and the Symposia. For the first time, policy statements in the major fields of liver disease have been voiced."

MEDIA HIGHLIGHTS

Coalition launches global scientific strategy to cure hepatitis B

The ICE-HBV Global Scientific Strategy was launched on the opening day of the ILC to lay the groundwork for the momentum behind HBV cure research and the long-term implementation of HBV cure preparedness worldwide. The strategy sets out a series of research priority areas to tackle HBV, covering elimination, immunity and implementation priorities.

"Curing hepatitis B is not a pipe dream and should not be thought of as such," said Dr Su Wang, Hepatitis B Foundation Board Member and President-Elect of the World Hepatitis Alliance. "The ICE-HBV Strategy is important in how it details a multi-pronged plan to attack and eliminate deadly HBV with virological and immunological approaches. But it is also landmark because it not only includes renowned scientists and clinicians, it values the contribution of the HBV patient community. People living with HBV have the central stake in a cure and should be included as a partner on this road to cure."

Read more via The Lancet Gastroenterology and Hepatology

Public health crisis of fatty liver disease

Thursday's Press Conference focused on the rising epidemic of fatty liver disease, covering the increasing significance of NAFLD in HIV positive patients and the need for early detection and effective interventions among NASH/NAFLD patients.

A large study that found unexpectedly high rates of suspected NAFLD in young adults achieved widespread media attention for the congress. Warning that the high levels of NAFLD among young people, caused by being overweight, the research signalled a potential public health crisis and placed people at an increased risk of liver cancer, diabetes and heart attacks.

Professor Philip Newsome (Vice-Secretary, EASL) said, "These data highlight the impact of the obesogenic environment and, in particular, its role in the development of NAFLD in a much younger sector of the population. This requires swift changes in public policy if we are to defuse the ticking time-bomb of obesity and NAFLD."

Read more via The Guardian

124
JOURNALISTS IN ATTENDANCE

3.1 BILLION
OPPORTUNITIES TO SEE FROM MEDIA COVERAGE

COVERAGE ACHIEVED ACROSS
21 COUNTRIES

New therapeutic approaches

New therapeutic approaches in liver disease was the theme of Friday's Press Conference, which included faecal microbiota capsules for patients with hepatic encephalopathy.

Experts also provided onsite journalists with the exclusive opportunity to receive first-hand information on ENVISION, a phase 3 study to evaluate efficacy and safety of givosiran, an investigational RNAi therapeutic targeting aminolevulinic acid synthase 1 in acute hepatic porphyria patients.

Read more via BBC News

The best of late-breakers at ILC

The final Press Conference covered a selection of the most exciting late-breaking abstracts submitted to the congress. Dr Jacob Lalezari presented interim data from two Phase 2a studies of ABI-H0731, suggesting promising tolerability and enhanced antiviral efficacy in combination with standard-of-care in chronic hepatitis B infection. "This interim analysis of two studies supports that ABI-H0731 in combination with Nucs appears to provide rapid, enhanced anti-HBV activity," explained Dr Lalezari.

Watch live recordings of all ILC 2019 Press Conferences

NURSES & ALLIED HEALTH PROFESSIONALS FORUM

Dr Paul Richardson from the Royal Liverpool University NHS, opened the session by introducing an enlightening case study regarding acute alcoholic hepatitis. Stating that Liverpool had "some of the worst alcohol metrics" in the UK, Dr Richardson affirmed the correlation between alcohol-related liver disease and deprivation, emphasising the marginalised status of patients in poorer areas. Richardson presented the case of 26-year-old woman from a deprived background suffering from cirrhosis, which is seen in 60-70% of patients who present alcoholic hepatitis. The case centred around a stimulating discussion that questioned whether this particular patient was eligible for liver transplantation.

The session then transitioned into an informative presentation given by dietician Mette Borre from the Aarhus University Hospital, regarding the essential role of nutrition in aiding the management of acute alcoholic hepatitis. Borre strongly recommended that "in cirrhosis and severe/acute alcoholic hepatitis, nutritional support should be provided to accelerate resolution of HE and improve survival in patients with low calorie intake." Although no universally effective nutritional tools for patients have been validated, Borre highlighted the importance of nutritional screening and a step-wise approach to diet that can be utilised by healthcare professionals. Relating to Dr Richardson's introduction, Borre concluded that nurses can play an instrumental role in motivating patients from all areas of society.

Paul Richardson

Mette Borre

The following session, presented by Dianne Backhouse from the Hull University Teaching Hospitals, focussed on measuring the impact of a new liver specialist nursing service on patient care. The streamlined service was introduced to improve patient care and deliver services more effectively. The clinics consist of dedicated cirrhosis surveillance clinics, a cirrhosis database and a nurse ward discharge clinic. Backhouse revealed the positive outcomes of the service, including reduced waiting times from 71 days to 14 days, no missed cancers and excellent patient feedback. The innovative scheme was characterised by Backhouse as "a unique service with a personal touch" and one that was intended to give other institutions inspiration to set up similar services for patients across Europe.

The following presentation, delivered by Dr Kate Hallsworth from the University of Newcastle, focussed on the role of physiotherapists when treating NASH. Hallsworth stated that in the absence of approved drug therapy, "lifestyle interventions really do remain the cornerstone of NAFLD management." Amongst an array of lifestyle changes, weight loss remains one of the most effective tools in reducing liver fat, inflammation and fibrosis. Hallsworth further propagated the benefits of a "holistic" approach to NAFLD, with weight loss and physical exercise often improving a patient's mental health, which is an unachievable function of the emerging NASH drugs entering the market.

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