EASL 2023

Review of the European Association for Study of the Liver (EASL) Congress 2023

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STRIVING to become the 'home of hepatology', the annual European Association for Study of the Liver (EASL) Congress took place in Vienna, Austria, between the 21st–24th June 2023. This meeting facilitated the exchange of scientific knowledge, promoted research of the liver, and provided education to participants as EASL continues to tackle liver disease.

Austria's capital and most populous city is one ingrained with a rich history in music, where residents Mozart and Beethoven made their name. During this event, Vienna hosted an orchestra of 6,000 delegates from 108 countries interested in advancing care for the liver.

Thomas Berg, EASL Secretary General, acted as conductor for the opening ceremony by welcoming all of the delegates, and updating attendees on where EASL is in its 4-year strategy; this aims to keep the organisation focused throughout changes in leadership, uniting hepatology, and increasing its member base.

Berg introduced Maggie Bassendine, University of Newcastle, UK, who was recognised as EASL Congress Honorary President for this event. Bassendine reflected on the growth of EASL, from its founding in 1966 when it was made up of just 70 hepatologists, to today. Bassendine acknowledged some of the major scientific events on this journey, including the discovery of hepatitis C and the human genome project, and described the EASL as a "trailblazer" for gender equality with its balance in presenters.

Aleksander Krag, EASL Vice-Secretary General, spoke during this ceremony about EASL's interaction with global societies, such as World Health Organization (WHO) Europe, and their collaborations to advance liver health. Krag spotlighted events like World Liver Day in April 2023, where organisations came together. Later in the Congress, Krag succeeded Berg as Secretary General, with Debbie Shawcross, King's College London, UK, stepping in as Vice-Secretary.

Gathering clinicians, researchers, nurses, and other healthcare professionals with an interest in liver disease, EASL 2023 offered the chance to engage with several types of interactive sessions. These came in the form of symposia, abstract presentations, ePosters, workshops, and even the chance to have your liver scanned via ultrasound. "We are very proud of having something for everybody," was the way Saskia van Mil, EASL Scientific Committee, described the diversity and spread of the scientific programme on offer. EASL also made a real effort

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as an association to interact with the people and the city of Vienna, providing school clinics and education to the locals. This is an avenue they hope to continue in future congresses, starting with the 2024 meeting which will be held in Milan, Italy, next summer.

> **"We are very proud of having something for everybody."**

Eric Trépo, EASL Young Investigator Task Force Governing Board Representative, was on hand to deliver the Emerging Leader Awards, dedicated annually to vibrant fellows under the age of 40, with outstanding contributions to liver research. These were awarded to David Pinato, Imperial College London, UK; and Lung Yi Mak, University of Hong Kong, Hong Kong. The Nurses and AHPs Rising Star Award was delivered by Patrizia Künzler-Heule, Chair of EASL Nurses and AHPs Task Force, to Marta Carol Perdiguer, University of Barcelona, Spain. EASL Recognition Awards were also given to Julia Wendon, King's College London, UK; George Papatheodoridis, University of Athens, Greece; and Antonio Bertoletti, Duke-NUS Medical School, Singapore, for their major scientific contributions to the field.

Quoting Abraham Lincoln, Thomas Berg looked ahead as they thanked their support group for their guidance during their time leading the association. Berg encouraged participation and growth for EASL and the wider field of hepatology, stating: "The best way to predict the future is to create it."

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This edition of *EMJ Hepatology* contains the scientific highlights from EASL 2023, summarising the press releases shared and abstracts from presenters at congress, and covering branches of hepatology from hepatocellular carcinoma to cirrhosis.

Liver Disease: A Potential Use for Faecal Microbiota Transplant

THE ANNOUNCEMENT of a pioneering clinical trial to assess whether faecal microbiota transplant (FMT) could be used to not only treat advanced liver disease, but also combat antimicrobial resistance, was made at EASL 2023.

Researchers from King's College London, UK, plan to build on their FMT research initially conducted in the National Institute for Health and Care Research (NIHR)-funded PROFIT trial. This was a European safety and feasibility trial conducted in 32 patients with liver disease, which showed that endoscopically-delivered FMT was safe and well-tolerated. The team also found that endoscopically-administered FMT modified patient gut microbiota, and enhanced intestinal barrier function, antimicrobial mucosal immunity, and metabolism of ammonia. These results are of interest, given the susceptibility of patients with liver cirrhosis to infections, and concerns with antimicrobial resistance.

Patients with cirrhosis are at high-risk for antimicrobial resistant infections due to a disproportionate exposure to antibiotics, with one-quarter of patients receiving long-term antibiotic treatment. For many patients with cirrhosis, liver transplant is the only definitive treatment option available; however, transplant cannot be performed in the setting of an antimicrobial-resistant infection. Therefore, infections in this patient cohort can be severe and fatal. This spotlights the need to identify strategies to overcome the risk of such infections, and reduce antibiotic use in this cohort to help improve patient outcomes and incidence of antimicrobial resistance.

The announced PROMISE trial, funded by a NIHR and Medical Research Council (MRC) partnership, is the next stage in this research. It aims to recruit 300 patients diagnosed with liver cirrhosis from 16 sites across the UK, to evaluate whether oral FMT capsules containing freeze-dried stool from healthy volunteers reduce the likelihood of getting an infection. Enrolled participants will be randomised to receive either oral FMT capsules or placebo every 3 months for 2 years.

Debbie Shawcross, King's College London, and chief investigator for the PROMISE trial, discussed how results from the PROFIT trial are encouraging, and that the PROMISE trial may offer new hope for patients with cirrhosis.

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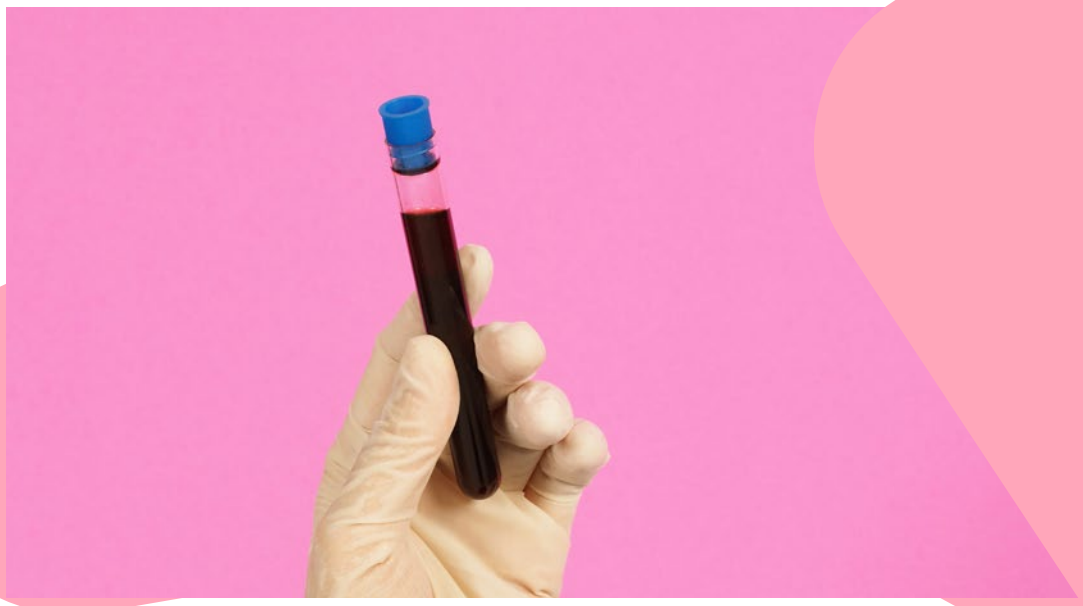

Long-Term Efficacy of Tenofovir Alafenamide in Patients with Chronic Hepatitis B

RESEARCH presented at the EASL 2023 explored the long-term efficacy of tenofovir alafenamide (TAF) in patients with hepatitis B e antigen (HBeAg)-positive and -negative chronic hepatitis B (HBV). In data from two similarly designed double-blind, randomised, Phase III studies on patients with HBeAg-positive and -negative chronic HBV, TAF demonstrated non-inferior efficacy compared to tenofovir disoproxil fumarate (TDF). The final 8-year results from the trial were shared at EASL 2023.

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The studies measured efficacy through the missing equals excluded approach of the full analysis set, and included serial assessments for viral suppression (HBV DNA <9 IU/mL), alanine transaminase normalisation by 2018 American Association for the Study of Liver Diseases (AASLD) criteria, serologic responses, and fibrosis change by serum FibroTest (BioPredictive, Paris, France). The researchers additionally carried out resistance analyses, including deep sequencing of HBV pol/reverse transcriptase, both at baseline and annually for individuals with virologic breakthrough/blip; persistent viraemia, or treatment discontinuation with viraemia; as well as phenotyping qualifying samples.

The researchers found that of the 1,298 randomised and treated patients, 1,157 (89%; 775 TAF; 382 TDF) entered the open label (OL) phase, including 180 and 202 TDF-treated patients who began OL TAF at Week 96 (TDF-OL TAF 6-year) or Week 144 (TDF-OL TAF 5-year), based on timing of a protocol amendment. Overall, 974 (95%) of the participants completed the OL study treatment. The most common reasons for discontinuation were the withdrawal of consent, loss of follow-up, or investigator discretion. Similar rates of virologic suppression and alanine transaminase normalisation were achieved and maintained in all treatment groups. Additionally, sequencing and phenotype analyses over 6 years showed no resistance to TAF.

In conclusion, 8-year treatment with TAF, or up to 6 years after switch from TDF, virologic suppression rates remained high across all treatment groups, with 33% achieving HBeAg/hepatitis B e antibody seroconversion.

Vibration-Controlled Transient Elastography Scoring in At-Risk Patients with NASH

THE TARGET population for Phase IIb and III clinical trials in non-alcoholic steatohepatitis (NASH) is patients with NASH with fibrosis (F) 2–3. Due to high rates of screening failure during biopsies, which lead to slower enrolment and drug development, non-invasive tests have undergone development to reduce screening failure rates. Research aiming to assess composite scores related to vibration-controlled transient elastography through comparison to traditional methods was presented by Mazen Noureddin, Houston Methodist Hospital, Texas, USA, at EASL 2023.

The researchers used screening data from six ongoing biopsy-proved therapeutic NASH trials, which included over 5,000 patients. In the study, liver data was read centrally, and the diagnostic accuracy of FibroScan-AST score (FAST) and liver stiffness measurements (LSM) were assessed using vibration-controlled transient elastography. The cut-offs of 0.5 (FAST) and 8.2 kPa (LSM) were used to identify patients with F3. Similarly, the diagnostic accuracy of Agile 3+ (Echosens, Verona, Italy) and LSM were also assessed, with cut-offs of 0.6 (Agile 3+) and 9.7 kPa (LSM). Patients with F4 were excluded from the study.

A total of 1,048 patients with an average age of 54.7 years were included, of whom 61% were female. The data showed a fibrosis prevalence of 92 (9%) for F0, 231 (22%) for F1, 290 (28%) for F2, and 435 (42%) for F3 across participants. FAST showed better specificity (51.7 versus 8.4), negative predictive value (58.2 versus 48.6), positive predictive value (71.7 versus 62.2), positive likelihood ratio (1.59 versus 1.03), negative likelihood ratio (0.45 versus 0.66), and the correct classification (0.67 versus 0.61) compared with LSM in patients with NASH F2–3. Agile3+ showed better specificity (62.0 versus 35.7), positive predictive value (51.6 versus 43.5), positive likelihood ratio (1.78 versus 1.29), negative likelihood ratio (0.52 versus 0.48) and the correct classification (0.64 versus 0.53) compared with traditional LSM in patients with NASH F3.

Overall, the study concluded that FAST and Agile3+ performed more effective screening tests than traditional methods of liver stiffness in patients with NASH F2–F3 and NASH F3. The researchers recommend using these scoring systems as screening criteria in Phase IIb/III NASH clinical trials.

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Bulevirtide Safe in Treatment of Chronic Hepatitis D

BULEVIRTIDE (BLV) is safe and well-tolerated as monotherapy in the treatment of chronic hepatitis D, according to data presented at EASL 2023. BLV, a first-in-class entry inhibitor for chronic hepatitis D, was first conditionally approved for use in the European Union (EU) in July 2020.

MYR301, a Phase III randomised study, showed that BLV 2 mg or 10 mg subcutaneously was safe and well-tolerated, and superior to no-active hepatitis D virus (HDV) treatment based on combined viral and biochemical response, with similar efficacy for both doses at Week 48. Results at Week 96 were presented at the Congress.

Researchers randomised and stratified 150 patients with CDH into three arms based on the presence or absence of compensated cirrhosis. Arm A included no active anti-HDV treatment for 48 weeks, followed by 10 mg/day BLV for 96 weeks (n=51); arm B immediate treatment with 2 mg/day BLV for 144 weeks (n=49); and arm C immediate treatment with 10 mg/day BLV for 144 weeks. Follow-up continued up to 96 weeks after end of treatment (Week 240). Endpoints included combined response, defined as a HDV RNA decrease of ≥2 $\log_{10}$ IU/mL from baseline and ALT normalisation or undetectable HDV RNA; viral response, defined by HDV RNA decrease by ≥2$\log_{10}$ IU/mL from baseline or undetectable HDV RNA; change in liver stiffness by transient elastography and $\log_{10}$ change in HDV RNA; and alanine transaminase normalisation.

At baseline, 47% of participants had compensated cirrhosis, mean HDV RNA was 5.05 $\log_{10}$ IU/mL, mean ALT 110.9 U/L, mean liver stiffness 15 kPa, and 61% were on concomitant nucleos(t)ide analogues therapy. Of the 150 participants, 95% completed all 96 weeks of treatment. Results showed that efficacy responses had improved compared to Week 58. Arms B and C had similar combined responses and biochemical responses at Week 96.

> **"Results showed that efficacy responses had improved compared to Week 58."**

There were no serious adverse events, deaths, or drug discontinuations; however, researchers noted an increase in bile acids without an association to pruritus or other symptoms, as well as a higher proportion of injection site reactions in those who received 10 mg/day.

The team concluded that BLV is safe and well-tolerated through Week 96 in this population, and that biochemical and virological responses were higher with long-term therapy.

Potential to Safely Treat Patients with Liver Fibrosis

RESMETIROM appears to be safe and well-tolerated by patients with liver fibrosis and non-alcoholic steatohepatitis (NASH), according to the preliminary results of the MAESTRO-NASH trial, presented at EASL 2023. This Phase III registrational double blind, placebo-controlled trial is ongoing, and studies the effect of once daily 80 or 100 mg resmetirom compared with placebo in patients with liver fibrosis and NASH.

A total of 966 patients with liver fibrosis and NASH enrolled in the study from approximately 200 sites around the world. Two central pathologists used glass slides as a primary analysis to read liver biopsies; the results were then combined using a statistical algorithm to generate a single treatment effect. If the two readers disagreed, digitalised images were sent to a supportive consensus group. Unfortunately, 11 patients were excluded after Week 60 due to COVID-19 at the site.

The endpoints of the 52-week study were ≥1 stage reduction in fibrosis, with no worsening of Non-Alcoholic Fatty Liver Disease (NAFLD) Activity Score (NAS), or resolution of NASH, with no worsening of fibrosis. NASH resolution meant scores of 0 for ballooning and 0 for inflammation, as well as at least a 2-point reduction in NAS. Another key endpoint was a reduction of low-density lipoprotein cholesterol.

All endpoints were met with both doses, with similar results being obtained by the central pathologists. Other liver biopsy endpoints, including fibrosis reduction and NASH resolution, were met. A reduction was also seen in alanine transaminase, aspartate transaminase, and γ-glutamyltransferase levels. Both doses had similar numbers of serious adverse events, and saw an increase of diarrhoea and nausea at the start of therapy.

While ongoing, the preliminary results of this study support resmetirom as a potential treatment for patients with liver fibrosis and NASH. It has been well-tolerated in both treatment groups. ●

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Sensitivity to Combination Therapy Predicted by Deep Learning

RESEARCHERS have discovered that deep learning can predict the sensitivity of patients to atezolizumab-bevacizumab, the standard first-line treatment for hepatocellular carcinoma (HCC). Despite being the standard of care for this disease, objective responses to treatment with atezolizumab-bevacizumab are observed in just a minority of patients.

Predictive biomarker development is crucial in improving outcomes for patients diagnosed with HCC. Previously, progress has been made in developing the *ABRS* gene signature to improve standard of care; however, it is very challenging to implement molecular profiling techniques into clinical practice, due to the expertise required in bioinformatics and molecular biology.

Lead study author Julien Calderado, Laboratoire d'Informatique Paris Descartes (LIPADE), Université Paris Cité, France, and colleagues aimed to develop a regression-based deep learning model, which had the ability to estimate *ABRS* expression value using histological digital slides of HCC disease. They then wanted to determine if this particular model could predict progression-free survival (PFS) in patients with HCC who have received treatment.

Their model, ABRS-P, was trained to use the Cancer Genome Atlas (TCGA), which was created to accelerate clinical understanding of the molecular basis of cancer. Specific image features were extracted from slides, and were incorporated, along with their *ABRS* gene signature expression as a label, into the model. This model was externally validated using two independent sets of data: a resection series from Henri Mondor University Hospital, University of Paris, France (n=225), and a biopsy series from Henri Mondor University Hospital and Avicenne University Hospital, Paris, France (n=157). This dataset had a significant difference compared to 3'RNA sequencing used in gene profiling technology.

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Researchers then tested a series of 122 biopsy samples taken from patients with HCC who were treated with atezolizumab-bevacizumab, against a control group treated with other systemic therapies (n=44). Spatial transcriptomics were performed on HCC samples. The mean Pearson correlation coefficient of ABRS-P was 0.62 (0.46–0.72). Patients with ABRS-P tumours showed prolonged PFS (p=0.0014) once atezolizumab-bevacizumab treatment was initiated. Researchers observed no impact on ABRS-P prediction on PFS in the patient cohort treated with other therapies.

To conclude, this study has shown that artificial intelligence, when applied to digital slides of HCC, can predict PFS in patients treated with atezolizumab-bevacizumab. It is hoped that fast and inexpensive biomarkers of sensitivity to specific therapies can be developed, which can be easily implemented in clinical settings, for a variety of diseases. ●

Effects of Naltrexone on Achieving Abstinence and Reducing Alcohol Craving in Patients with Cirrhosis

PRESENTED at EASL 2023, Manasa Alla, Institute of Liver and Biliary Sciences, New Delhi, India, emphasised the importance of establishing safety and efficacy profile of naltrexone in patients with alcohol-related liver disease.

Alla and colleagues performed a single-centre, double-blind, placebo-controlled, randomised trial between April 2020–July 2022 in patients (n=147) with compensated cirrhosis with alcohol use disorder (AUD). As per inclusion and exclusion criteria of the study, 100 patients with compensated cirrhosis fulfilling the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for AUD were enrolled and randomised between naltrexone or placebo, given for 12 weeks. The primary outcome was the proportion of patients achieving and maintaining alcohol abstinence at 12 weeks, while the secondary outcomes included the proportion of patients maintaining abstinence at 6 months and 12 months; adverse effects; lapses; and relapses at 3, 6, and 12 months. Both groups were offered behavioural therapy and counselling.

Both groups had comparable baseline demographics, clinical characteristics, alcohol use disorders identification test (AUDIT), and obsessive-compulsive drinking scale (OCDS) scores. At 12 weeks, a significantly higher proportion of patients achieved abstinence with naltrexone compared to the placebo group (64% versus 22%; p<0.001). Likewise, the maintenance of abstinence after 6-months of follow-up was higher with naltrexone (22% versus 8%; p=0.09).

At 12 weeks, the naltrexone group had a significantly lower number of relapses (28% versus 54%; p=0.01), while the placebo group had higher rates of relapses (28% versus 12%; p=0.07). Naltrexone demonstrated significantly lower mean craving scores at 12 weeks, as indicated by the OCDS-O score (6.63±1.16 versus 9.29±1.78; p<0.01) and the OCDS-C score (6.3±1.23 versus 9.02±1.86; p<0.01). Both groups demonstrated comparable adverse events, and no patients required discontinuation of the drug.

The authors concluded that naltrexone can be safely administered for AUD in patients with compensated cirrhosis, and it demonstrated efficacy in achieving abstinence, as well as reducing craving scores at the 3-month mark.

"At 12 weeks, a significantly higher proportion of patients achieved abstinence with naltrexone compared to the placebo group."