Congress Review

Review of International Liver Congress 2021

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PICTURESQUE Geneva, Switzerland, encircling Lac Léman with the famous Jet d'Eau fountain and overlooked by the Alps, would have been a vibrant setting to host the 56th annual International Liver Congress (ILC). Accustomed to meetings of this nature, flaunting three officially spoken languages, and usually a bustling economic hotspot, the Swiss financial centre is home to the highest number of international organisations in the world, including headquarters for Europe's United Nations and the Red Cross. Home to the CERN laboratory for nuclear research, containing the world's largest atom smasher, the city is familiar with revolutionary science. This drew attention to Geneva in 2014 when the monumental creation of antimatter and discovery of the elusive Higgs boson particle took place. Hoping to share in the metropolis' scientific legacy, attendees of ILC 2021 felt the underlying ethos of 'beating liver disease together' entwined in all the discussions that took place.

Woven together by the European Association for the Study of Liver (EASL), creating only their second fully virtual gathering in hepatology, this innovative online experience successfully overcame the digital barriers enforced by the COVID-19 pandemic to deliver a plethora of informative sessions, headed by EASL Secretary General Philip Newsome. He summarised the event's reach at close of congress: "I hope you have enjoyed our almost 150 sessions with over 500 presentations," also paying tribute to the diverse contributions made by young investigators, nurses, patients, and allied healthcare professionals. The success of the congress was illuminated in that over the 4 days, the ILC welcomed nearly 6,500 delegates from >100 countries, hosting 400 international faculties and close to 900 abstract presenters.

Content at ILC 2021 spanned several therapy areas; within broader hepatology fields, topics of focus included viral hepatitis, liver tumours, cirrhosis,

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immune-mediated and cholestatic disease, and finally metabolism, alcohol, and toxicity. During his farewell, Newsome highlighted the notable roundtable discussions that took place over the course of the congress, examining non-alcoholic fatty liver disease and hepatitis B. Other highlights from the event included the clinical studies conducted as a part of the EASL consortium on vascular liver disease, amidst studies relating to management of hepatitis B and C and liver cancer prevention, and emerging data suggesting we are nearing successful treatment for rare liver diseases like α-1-antitrypsin deficiency.

Conversations remained optimistic despite virtual barriers to discussion, mentioning the impressive 630,000 EUR awarded by EASL as fellowships and grants, some extended to aid research during the COVID-19 pandemic and to support future research leaders in hepatology. Sharing in this assistance are Teresa Brevini and Jan Masek, foundation EASL fellowship awardees, who appeared in a memorable presentation to share their research journeys. Newsome commended this session: "Really inspiring to hear their commitment to liver research, and it gave me reassurance that hepatology is going to be in safe hands as we go forwards."

Thomas Berg was congratulated as the incoming Secretary General during the welcome address and will guide the next phase of this international initiative, where he promises to "build on the decades of ILC tradition and improve it with new knowledge," especially at ILC 2022, due to take place in London, UK, and aiming to safely 'savour science together again'. Shedding light upon the success of another digital ILC, Berg commented: "The world of science and healthcare has been incredibly adaptable through an intensely digital time; we have missed the pure energy and dynamism of meeting in person".

ILC 2021 sparked a great deal of media attention during its course; on Day 1 alone there were >5 million impressions using the twitter hashtag #ILC2021, which would reach 21 million by Day 3. "We have managed to successfully bring together the hepatology community once again," stated Berg at the closing event. The highest engagement with any streamed content was seen in a 'lifestyle and the liver' presentation covering non-alcoholic fatty liver disease, viewed live by >2,000 attendees; this has undoubtedly reached more viewers since joining the hundreds of hours of content available on-demand on the EASL attendance platform.

Reflecting on the successes of EASL in adapting once more to an online format, the concluding remarks from the farewell handover looked ahead to continuing to provide opportunities for high engagement, inspiration, and creativity within hepatology research. Hopefully participants of ILC 2021 will expand on the content shared at this scientific epicentre to improve liver care worldwide, energised by a more successful, immersive online experience than ever before. ■

ILC 2021 REVIEWED →

Chronic Liver Disease, Alcohol Use Disorders, and the Burden of COVID-19 in France

UNTIL recently, there was uncertainty surrounding the risk of death following severe acute respiratory syndrome coronavirus 2 infection in people with chronic liver disease. For this reason, a recent national study in France explored the outcomes of all adult patients (aged ≥18 years) who were discharged in 2020 with a diagnosis code for COVID-19. The researchers calculated adjusted odds ratios to measure the association between chronic liver disease, alcohol use disorders, and 30-day in-hospital mortality. The results of this investigation were presented by Vincent Mallet, Managing Senior Physician and Professor, Hepatology Unit, Cochin University Hospital, Paris, France, at EASL's ILC 2021.

The study used the French National Hospital Discharge database to select individuals (N=187,283) aged ≥18 years who were discharged in 2020 with a diagnosis code for COVID-19. The mean age of the group was 66 years (standard deviation: ±22 years), and 25% were male.

In total, 8.7% (n=16,338) of patients diagnosed with chronic liver disease were admitted for COVID-19 in France in 2020. Of these, 24.1% (n=3,943) died, including 63.9% (n=2,518) after a liver-related complication. The adjusted mortality hazard ratios for chronic liver disease and alcohol use disorders were 1.23 (95% confidence interval: 1.10–1.38; p<0.001) and 1.12 (95% confidence interval: 1.07–1.17; p<0.001), respectively. Finally, Mallet revealed that chronic liver disease increased the odds of in-hospital COVID-19 mortality by approximately 80%.

In summary, chronic liver disease and alcohol use disorders were an independent risk factor of COVID-19 mortality. In addition, Mallet noted that therapeutic effort limitation might have contributed to COVID-19 death of individuals with a liver-related complication or with alcohol use disorders. ■

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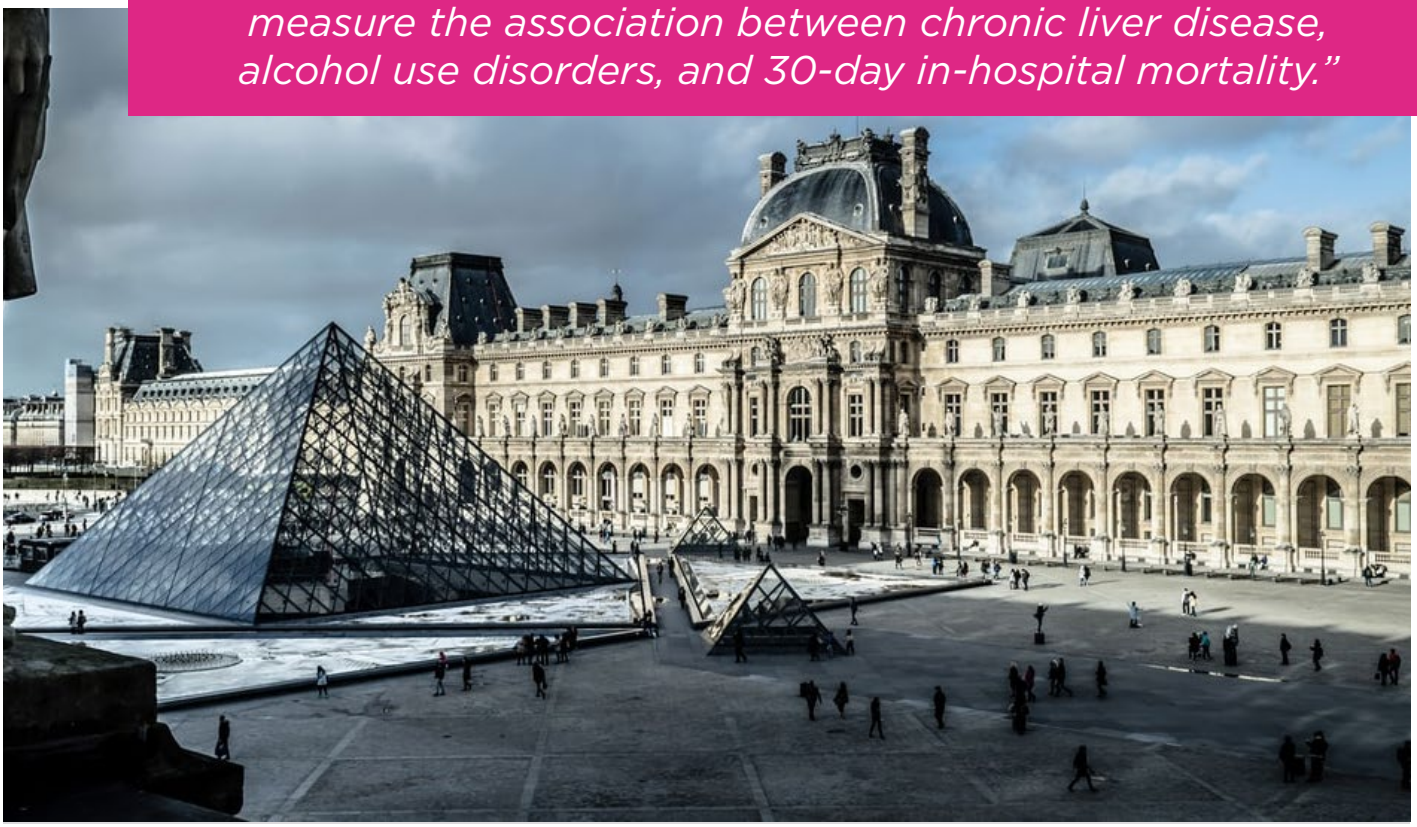

Advanced Hepatic Fibrosis Correlating with Weaker COVID Vaccine Response

FEATURING double-vaccinated patients with hepatic fibrosis, researchers have assessed the factors affecting coronavirus vaccine immune response. Rifaat Safadi, who headed the study, presented at ILC 2021, was able to conclude based on their findings that older age and advanced fibrosis with decreased steatosis were risk factors for a lower response to the Pfizer-BioNTech vaccine.

A lot of attention has been drawn to this topical study, as the ongoing COVID-19 pandemic warrants constant study in this field; this is particularly relevant in studies that bring forward evidence for at-risk populations like the present investigation. The research analysed 88 patients living with hepatic fibrosis, all having received both doses of the vaccine, and aimed to assess their immune response. This was achieved using histologic non-alcoholic fatty liver disease activity score (NAS) grading and clinical research network (CRN) fibrosis scoring, both of which presented significant changes.

The mean NAS score was 2.9±1.2 (p=0.045) in the excellent responders, compared with good responders; mainly because of significant steatosis changes of 1.6±0.9 against 1.2±0.7 (p=0.02). Alongside this, hepatocyte ballooning and lobular inflammation were found to be similar; advanced fibrosis scoring was noted in 23% versus 48% (p=0.05, respectively) of each group. Findings revealed that advanced fibrosis correlated with a weaker vaccine response, confirmed by significant changes in blood tests.

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Despite bringing forward relevant and insightful findings, these results would be carried further into the spotlight if the sample size were to be expanded and include a larger and more diverse population. Safadi describes the implications of their research, adding that a third dose vaccine booster in populations with risk factors should be evaluated in future trials of this nature. ■

Infusion Chemotherapy with Sintilimab May Help Cure Liver Cancer

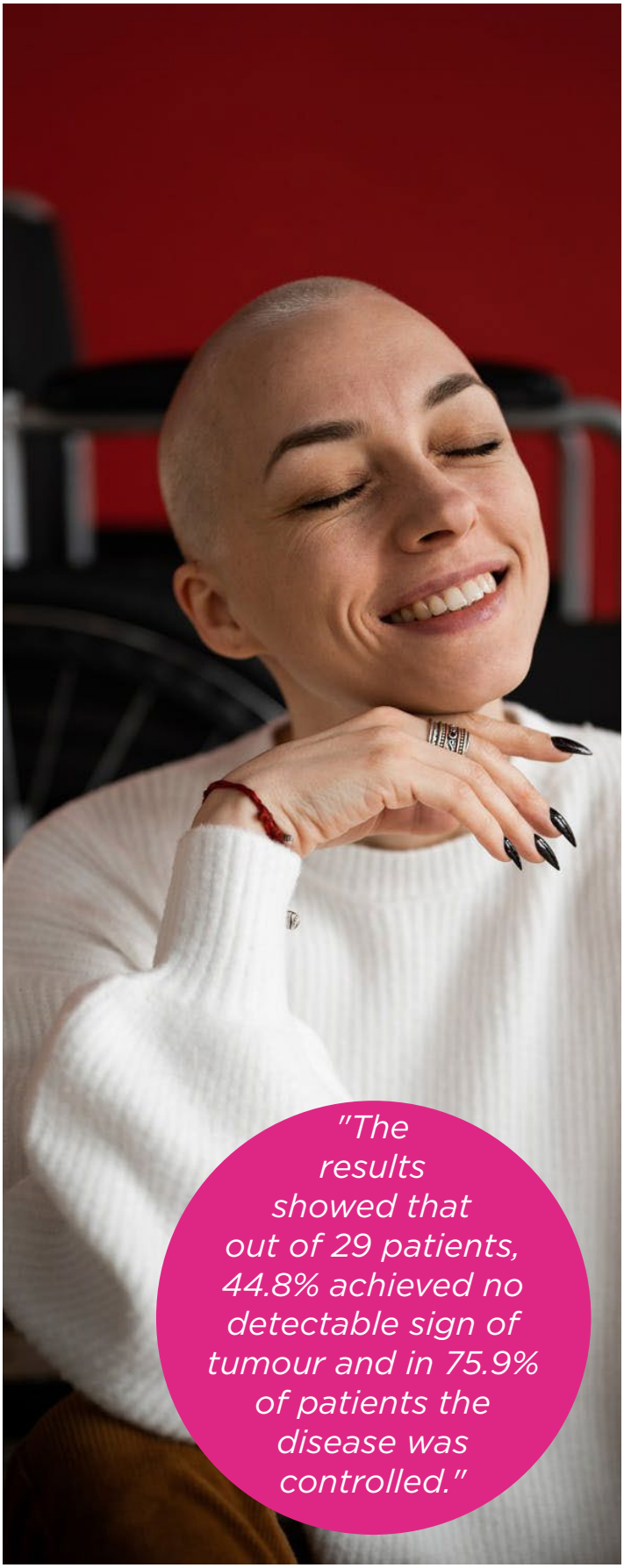
HEPATOCELLULAR carcinoma (HCC) is the most prevalent primary liver cancer in adults. Current treatment includes chemotherapy, surgery, and liver transplantation. When treating cancer, many successful therapies use a combination of drugs as this can help target different parts of the MAP-kinase pathway involved in the development of the cancer.

Li Xu from the Sun Yat-sen University Cancer Centre, Guangzhou, China, tested the safety and efficacy of this approach for resectable HCC by combining hepatic arterial infusion chemotherapy of modified FOLFOX (folinic acid, fluorouracil, and oxaliplatin; FOLFOX-HAIC) with sintilimab, a monoclonal antibody that inhibits programmed cell death, and shared the findings at ILC 2021. The scientists recruited 30 patients who had recently been diagnosed with HCC. The patients were mostly male and aged 34–70 years, with locally advanced disease.

The tumours of studied patients were regularly evaluated every 6–8 weeks, for a median treatment cycle of two years. Patients who had reduction in tumour size and were eligible to undergo surgery were referred for hepatectomy and continued to take sintilimab only.

The results showed that out of 29 patients, 44.8% achieved no detectable sign of tumour and in 75.9% of patients the disease was controlled. Overall, 14 patients studied remain tumour-free now. There were few serious adverse events (AE) in this study; most AEs were of the lowest grade (Grade 1), which included rash, itch, and fever. However, one patient experienced a reversible Grade 4 AE: immune-related liver dysfunction.

Overall, the combination of FOLFOX-HAIC with sintilimab demonstrated beneficial results with a good safety profile and high conversion rate. The researchers suggest that this combined approach to treating HCC could possibly cure this life-threatening liver cancer in the future. ■



Improved Prognosis with New Liver Dialysis Device

ENTERING the liver dialysis device market is the novel DIALIVE machine, addressing demand for effective treatment to combat acute-on-chronic liver failure (ACLF). Current disease-modifying practice options are limited to steroids; however, this holds an inherent risk of new infection, and large proportions of patients are non-responders and may require dialysis for kidney failure, pressors for raising low blood pressure, and support aimed at individual organs. Antibiotics are also used to treat infection, and liver transplant is an option, but is unavailable for many patients.

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A study presented at ILC 2021 investigated 32 patients with ACLF with alcoholic cirrhosis, randomised to either receive standard care initiatives (outlined above) or DIALIVE treatment. DIALIVE treatment acts by replacing dysfunctional albumin as well as removing pathogens and damage-associated molecular patterns. Endpoints included safety, device performance, and the clinical and pathophysiologic effects, measured in patients requiring intensive care admission with acute flare-ups of chronic liver disease.

Banwari Agarwal, lead investigator, admitted their small sample size limits the strength of conclusions drawn from the described investigation. However, the study found that patients treated with DIALIVE were significantly more likely to recover from flare-ups and recover to pre-illness levels of liver and wider organ function. The device also exhibited good safety scores, significantly increased the proportion of patients resolving ACLF, and reduced time to resolution.

The study highlighted DIALIVE's simplicity of practice, emphasising ease of assembly, alongside good safety and efficacy scores. Future study is warranted to analyse the method's ability to correct impaired liver function, specifically its safety and usefulness against pathobiological mechanisms of declining albumin and systemic inflammatory response, on a large scale. ■

Food Insecurity, Poverty, and Mortality in NAFLD and Advanced Fibrosis

DISCOVERY of a significant interaction between food insecurity and poverty–income ratio among those with advanced fibrosis has been made in a USA study, shared at ILC 2021. Led by Ani Kardashian, University of Southern California, Los Angeles, California, USA, the researchers followed a large population for a median of 7.2 years, reporting that food insecurity was associated with greater mortality in adults with advanced fibrosis.

The investigation was of longitudinal design, including 34,134 participants and spanning nearly a decade in most cases. A sub-group of 4,816 had non-alcoholic fatty liver disease (NAFLD): 58% were male, with median age 51 years, and 14% below the poverty line. Meanwhile, 1,654 had advanced fibrosis: 55% male, with mean age 69 years, and 15% below the poverty line. Food insecurity was present in 28% and 21% of these groups, respectively. In the NAFLD participants, the all-cause age-adjusted mortality was 12 per 1,000 person-years, and 32 per 1,000 person-years for the advanced fibrosis cohort.

Food insecurity was independently associated with higher all-cause mortality in both sub-groups, (NAFLD: hazard ratio: 1.46, 95% confidence interval: 1.08–1.97; advanced fibrosis: hazard ratio: 1.37, 95% confidence interval: 1.01–1.86), observed in multivariate models adjusted for age, ethnicity, poverty–income ratio, education level, insurance status, HbA1c, BMI, and smoking. Kardashian and colleagues noted a significant interaction between food insecurity and poverty–income ratio in the population with advanced fibrosis and poverty (p=0.015). Based on this, Kardashian stated that, independent of other known causes, food insecurity was associated with greater all-cause mortality in adults with both advanced fibrosis and NAFLD, particularly when affected by poverty, but not among those without poverty.

Future studies to promote a better understanding of the relationship are needed. The sample size and duration are strengths of this study, putting forward strong evidence that intervention is necessary to address the food insecurity among adults with liver disease; in particular, prioritising at-risk categories to target improvement in their health outcomes. ■

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Promising Gene Silencing Technique Aimed at Reducing Steatohepatitis

TARGETING the metabolism of hormones, fatty acids, and bile acids, HSD17B13 is a member of the hydroxysteroid dehydrogenase family; if manipulated correctly with ARO-HSD gene therapy, there is opportunity to provide strong protection against alcoholic and non-alcoholic steatohepatitis (NASH). Led by Rohit Loomba, University of California, San Diego, California, USA, this investigation shared at ILC 2021 the results of the first ongoing human clinical study tackling HSD17B13 expression in hepatocytes.

Conducted in healthy volunteers and patients with NASH or suspected NASH (both male and female, aged 19–52), ARO-HSD was administered by subcutaneous injection in a single-dose escalation design; doses of 25, 50, 100, and 200 mg were provided and followed to Day 113. Liver biopsy was conducted at baseline and Day 71, measuring change in hepatic HSD17B13 mRNA expression and protein level; safety assessment was also made in all subjects using laboratory measures of liver function. ARO-HSD was well-tolerated in all participants, without any treatment-related adverse events, drug discontinuations, or associated laboratory abnormalities. Five patients with suspected NASH were administered 100 mg ARO-HSD; they demonstrated reduction in hepatic HSD17B13 mRNA at Day 71 by an average of 84%, and decreased alanine aminotransferase by 46% at Day 85; two of the sub-group showed protein increases of 92% and 97%, respectively.

Lack of significant change to weight or lipid parameters, combined with the study results, helped the researchers to conclude that ARO-HSD is the first investigative RNA interference therapeutic to demonstrate robust inhibition of HSD17B13 mRNA. Advances in this sector, following studies with larger and longer design, will develop the insightful but limited results put forward by this pilot, conducted upon a small population. ■

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Resmetirom for the Treatment of Patients with Non-alcoholic Steatohepatitis

ON DAY 3 of this year's EASL ILC, 23rd–26th June 2021, Stephen Harrison, Visiting Professor of Hepatology, University of Oxford, UK, presented results from a 52-week, double-blind, placebo-controlled registration trial designed to evaluate the efficacy and safety of resmetirom in >2,000 patients with non-alcoholic steatohepatitis (NASH).

In total, 169 patients were enrolled in the open-label arm: all completed 16 weeks and 64 had completed 52 weeks. The average age was 55.7 years (standard deviation [SD]: ±11.5 years) and 69% of the cohort were female, with a mean BMI of approximately 36. Forty-three percent of the patients had been diagnosed with diabetes, 62% with hypertension, and 70% with dyslipidaemia. In addition, the mean Atherosclerotic Cardiovascular Disease (ASCVD) score was 11.5%. The Fibroscan (7.7 kPa; SD: ±3.6 kPa) and mean MRI-based proton density fat fraction (18%; SD: ±7%) were both consistent with NASH and fibrosis stage F2.

Treatment with resmetirom (100 mg daily) was associated with a statistically significant ($p<0.0001$) 53% reduction in MRI-measured proton density fat fraction, as well as a 62% reduction in sex hormone binding globulin, after 52 weeks of treatment. Harrison also reported a 23% reduction in low-density lipoprotein cholesterol, a 22% reduction in apolipoprotein-B, and a 39% reduction in lipoprotein(a). As above, all reductions were statistically significant compared with baseline measurements. The levels of alanine aminotransferase, aspartate aminotransferase, and γ-glutamyl transferase were found to be significantly reduced (by 22, 12, and 25 IU, respectively; $p<0.0001$). Likewise, significant reductions in several inflammatory and fibrosis markers (e.g., high-sensitivity C-reactive protein, reverse T3, and M30) were observed. Finally, Harrison noted that no safety flags were identified.

Overall, these results support the use of non-invasive tests to monitor the response of individual patients with NASH to resmetirom treatment. ■

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Increase in Alcohol Use Disorder During COVID-19 Pandemic

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COVID-19 has shocked, isolated, and changed us all in some way or another. The global pandemic took the world by surprise and had people completely change their way of living. This has greatly impacted the mental health of individuals, especially those with underlying mental illnesses or behavioural problems. As a result, some people have turned to various forms of comfort such as alcohol. Hospitals have seen a sharp increase, by two-fold, in patients admitted with alcohol-related liver disease. A study by Subhani and colleagues from Nottingham University, UK, aimed to identify the main characteristics in patients with alcohol use disorder (AUD) and compare the changes in AUD admissions before and during COVID-19.

The study involved two large cohorts of patients from Nottingham University Hospital. The first cohort (n=27,356) included patients admitted pre-COVID-19 between 1st April and 31st October 2019. The second cohort (n=20,598) had patients who had been admitted during COVID-19 between 1st April and 31st October 2020. All patients from this study were given an alcohol assessment (AUDIT-C) to identify patients with AUD and those at high risk. Questions included how often a person drank alcohol, how many units of alcohol they consumed each week, and whether an injury has ever resulted after drinking. The higher the score, the more likely the patient is at risk of alcohol dependency. In this study, high-risk scores included: 5-7, 8-10, and 11-12. The latter score represented individuals that were completely dependent on alcohol. Factors such as age, sex, and ethnicity were considered when scores were derived. Finally, the researchers used multinominal logistic regression analysis to determine if primary and secondary outcomes influenced AUD.

The results showed that 18% of patients in both cohorts had AUD. Interestingly, more patients were alcohol-dependent in the COVID-19 cohort. Patients in the COVID-19 cohort also had a 16-fold increased risk of mental and behavioural disorders. Patients who were in all three alcohol risk groups were significantly younger than low-risk groups ($p<0.05$). Further to this, there was a higher occurrence of AUD in males and individuals of white ethnicity. Patients with COVID-19 with accompanying AUD had a significantly longer hospital stay and died at a younger age ($p<0.05$).

Subhani concluded that during the COVID-19 pandemic there were more patients with alcohol dependency compared to the pre-COVID-19 cohort. Some of these patients displayed mental health issues and behavioural problems. The results suggest that more individuals were drinking excessively during the pandemic and the effects of this were exacerbated in patients with COVID-19 as they died at a younger age. There is no doubt that COVID-19 has had a serious impact on alcohol-related disorders. Next steps such as providing targeted alcohol support services and closely monitoring patients with AUD might help decrease alcohol-related hospitalisations in the future. ■

Engineered Icosabutate Significantly Reduces Markers of NASH and Fibrosis

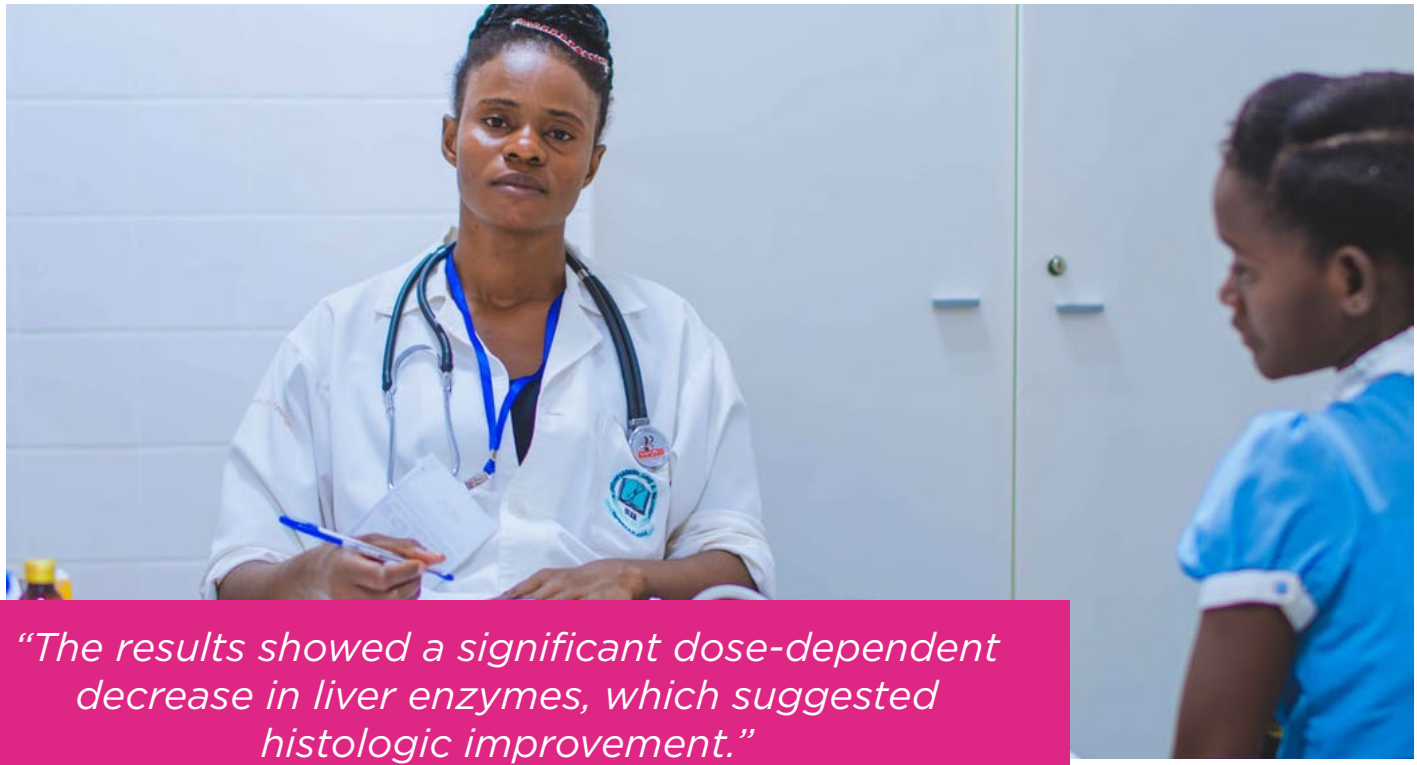
MANY individuals who have fat accumulating in the liver never even realise it. In the initial stages, a fatty liver is not necessarily worrisome. However, if the condition progresses to non-alcoholic liver disease and later non-alcoholic steatohepatitis (NASH), this can lead to serious health complications and, if left untreated, cirrhosis of the liver. Unfortunately, there is no cure for NASH, only non-specific medication and lifestyle changes to help manage symptoms.

An ongoing clinical trial, ICONA, shared at ILC 2021, studied the efficacy and safety profile of a novel oral drug engineered in a lab: a fatty acid called icosabutate. Icosabutate works by targeting the g-coupled protein receptor on the cell surface. The downstream effects of icosabutate result in decreased gene expression of fibrosis and pro-inflammatory genes.

The placebo-controlled trial included a total of 90 patients with confirmed NASH. Patients received either icosabutate 300 mg, icosabutate 600 mg, or a placebo in a randomised 1:1:1 ratio. The biomarkers relevant for NASH, fibrosis, and other closely related conditions were measured. The scientists conducted several plasma blood tests such as PRO-C3. PRO-C3 is a useful indicator of disease progression and the likelihood of fibrogenesis. Other tests conducted included enhanced liver fibrosis (ELF™) and high-sensitivity C-reactive protein to measure improvements in inflammation and fibrosis.

The results showed a significant dose-dependent decrease in liver enzymes, which suggested histologic improvement. The higher dose of icosabutate resulted in a significant decrease in PRO-C3 scores, therefore a lower chance of developing fibrogenesis. The ELF score and hsCRP were also significantly reduced; high-sensitivity C-reactive protein was decreased by 52%.

The tests show that there was an improvement in glycaemic control and key atherogenic lipoproteins, and no serious adverse events or safety concerns. The efficacy of icosabutate has shown some encouraging results, with low scores of PRO-C3 indicating improvement of fibrogenesis and possibly NASH. There were no serious adverse events or safety concerns. ■



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COVID-19 Restrictions Impacting Patients with Cirrhosis and Alcoholic Hepatitis

A COMPREHENSIVE Canadian study of hospital admissions has brought to light interesting information to do with the observed demographics and monthly admission rates over the course of the COVID-19 pandemic. This population study, shared at ILC 2021, identified 2,916 non-alcoholic cirrhosis hospitalisations: 2,318 for alcoholic cirrhosis and 1,408 with alcoholic hepatitis (AH), between 2018 and 2020.

Providing insight into the burden placed upon Canadian health infrastructure, and culminating in April 2020, researchers led by Abdel-Aziz Shaheen of Calgary University, Canada, noted significant increases in average monthly hospital admissions over the study period. Patients with AH admitted after implementation of COVID-19 restrictions had a younger median age of 43 years, compared with a prior median age of 47 years, but no significant difference was found in admission outcomes of the AH cohort. Monthly admissions were stable for both non-alcoholic and alcoholic cirrhosis; however, a 9% increase in AH admissions was observed per month between March and September. Average rate of AH hospitalisation compared to overall hospitalisation doubled from 11.6/10,000 to 22.1/10,000 in the same period.

These findings provoke further questioning to uncover why the average age of hospitalisation fell with the onset of social-distancing restrictions and AH admissions rose independently in the other two categories. These alarming statistics will prove useful to support other studies, but the data are restricted to the localised Albertan population of Canada. Expansion on the selection criteria to include a wider and more diverse population, and similar follow-up investigation conducted in the latter course of the pandemic to current-day, could improve the usefulness of these study insights. ■

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