EASL
The Home of Hepatology

THE INTERNATIONAL LIVER CONGRESS™
APRIL 10 - 14, VIENNA, AUSTRIA
2019

ILC 2019™ MEDIA KIT

THE INTERNATIONAL LIVER CONGRESS™
VIENNA, AUSTRIA | 10-14 APRIL, 2019

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ABOUT EASL

The European Association for the Study of the Liver (EASL) is a not-for-profit medical association dedicated to pursuing excellence in liver research, clinical practice of liver disorders, and in providing education to all those interested in hepatology.

Whilst the roots of the association were founded in Europe in 1966, EASL continues to engage globally with all stakeholders in the liver field wherever they are based. Our aim is to spread knowledge, expertise and best practice as well as the latest scientific breakthroughs in hepatology and the International Liver Congress™ is our annual platform for achieving this aim.

EASL's mission is to be the Home of Hepatology so that all who are involved with treating liver disease can realise their full potential to cure and prevent it.

The purpose of the association is to promote communication between European scientists, academics and stakeholders interested in the liver and its disorders. In particular, the association shall:

- Promote research concerning the liver
- Promote education of physicians, scientists as well as public awareness of liver diseases and their management
- Act as an advisor to European and national health authorities concerning liver diseases, the provision of clinical services and the need for research funding
- Foster European multicentre controlled trials
- Facilitate scientific exchange
- Facilitate participation of Young Investigators at its meetings

Welcome Message From The EASL Secretary General: Prof. Tom Hemming Karlsen

"On behalf of EASL, I welcome you to the International Liver CongressTM (ILC) 2019 and thank you for your support of Europe's leading organisation dedicated to advancing the scientific, medical and public understanding of the liver.

Since its foundation in 1966, EASL has evolved into a driving force by supporting the education of healthcare professionals, promoting research in the field of liver disease and fostering policy changes to support liver health. The role that our media partners play in helping us to achieve these goals cannot be under-estimated and, as an organisation, we are most grateful for your ongoing support in reporting on and communicating the latest science presented at our annual congress.

I hope that you will find this year's ILC scientific programme both informative and valuable and should you require any further information or support then please do not hesitate to contact our media team.

Thank you again for your support and I wish you a stimulating congress and a pleasant stay in Vienna."

ABOUT THE INTERNATIONAL LIVER CONGRESS™

This annual congress is the biggest event in the EASL calendar, attracting scientific and medical experts from around the world to learn about the latest in liver research. Attending specialists present, share, debate and conclude on the latest science and research in hepatology, working to enhance the treatment and management of liver disease in clinical practice.

The International Liver Congress™ 2019 takes place from 10-14 April 2019 at the Reed Messe Wien Congress and Exhibition Center, Vienna, Austria.

10-14 April, 2019

Vienna, Austria

International Delegates

The latest in liver research

CONTACT

The ILC 2019 Press Team look forward to welcoming you in the press room.

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PRESS CONFERENCE PROGRAMME

Date	Schedule	Theme	Chair	Abstract Title/Conference Details	Presenters
Wednesday 10.04.2019	11.00-13.00	A Global Scientific Strategy to Cure Hepatitis B	Peter Revill	The International Coalition to Eliminate HBV (ICE-HBV) will launch a Global Scientific Strategy to Cure Hepatitis B	Peter Revill Anna Lok Mark Bulterys Su Wang Markus Cornberg
Thursday 11.04.2019	9.30-10.30	Public health crisis of fatty liver disease	Professor Philip N. Newsome	THU-299 Increased risk of mortality with liver disease progression in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients: An analysis of French national hospital care	Jerome Boursier Zobair Younossi
				PS-062 The increasing importance of non-alcoholic fatty liver disease in human deficiency virus (HIV) positive patients	
				GS-06 Positive results from REGENERATE: A phase 3 international, randomized, placebo-controlled study evaluating obeticholic acid treatment for NASH	
Friday 12.04.2019	10.30-11.30	New therapeutic approaches	Professor Markus Cornberg	GS-13 Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of bulevirtide (Myrcludex B) in with PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection	Heiner Wedemeyer Lu Gao Jasmohan S Bajaj Joost PH Drenth Manisha Balwani
				PS-074 A first-in-class orally available HBV cccDNA destabilizer ccc_R08 achieved sustainable HBsAg and HBV DNA suppression in the HBV circle mouse model through elimination of cccDNA-like molecules in the mouse liver	
				PS-087 Fecal microbiota capsules are safe and effective in patients with recurrent hepatic encephalopathy: A randomized, blinded, placebo-controlled trial	
				PS-192 Lanreotide reduces liver growth in autosomal dominant polycystic kidney disease: Data from a 120-week randomized clinical trial	
				GS-14 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	
Saturday 13.04.2019	10.00-12.00	Viral Hepatitis Elimination	TBC	The EASL International Liver Foundation (EILF), in collaboration with the US Centers for Disease Prevention and Control will officially launch the first ever Centre of Excellence in Viral Hepatitis Elimination to showcase leading efforts to eliminate viral hepatitis and to fuel other countries to kick-start or expand and enhance their programmes. Minister Davit Sergeenko of the Ministry of Internally Displaced Persons from the Occupied Territories, Labour, Health and Social Affairs of Georgia will be present to accept the award on behalf of the Georgian HCV elimination programme	Massimo Colombo Jeffrey V. Lazarus David Sergeenko Francisco Averhoff
Saturday 13.04.2019	14.30-15.30	Best of late breaking abstracts	Professor Francesco Negro	LB-02 Elafibranor, a peroxisome proliferator-activated receptor alpha and delta agonist demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid treatment	Velimir Luketic
				LB-03 Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir treatment in patients with chronic hepatitis B	Terry CF Yip
				LB-06 Interim safety and efficacy results of the ABI-H0731 phase 2a program exploring the combination of ABI-H0731 with Nuc therapy in treatment-naive and treatment-suppressed chronic hepatitis B patients	Jacob Lalezari
				PS-178 Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir: the SMART-C study	Gregory Dore
				Multicenter, Double-blind, Placebo-controlled, Randomized Trial of Emricasan in Subjects with NASH Cirrhosis and Severe Portal Hypertension (PH)	Guadalupe Garcia-Tsao

EMBARGO: 00.01 Wednesday, 10 April, 2019

'Real-world' experience confirms effectiveness of sofosbuvir/velpatasvir/voxilaprevir in people with chronic hepatitis C (HCV) infection failing direct-acting antivirals (DAAs)

ILC 2019: Real-world' studies in Germany and the USA confirm high rates of sustained virological response with sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) in individuals with chronic HCV infection failing DAAs

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
'Real-world' studies conducted in Germany and the USA have confirmed the effectiveness and tolerability of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) when used to treat individuals with chronic hepatitis C (HCV) infection who had previously failed direct-acting antivirals (DAAs). The two studies presented today at The International Liver Congress™ 2019 in Vienna, Austria, reported sustained virological response rates (SVR) of 93–100%, confirming the effectiveness of this treatment in clinical practice.

DAAs have transformed HCV therapy and made virological cure possible in most patients.[1] Combination regimens of DAAs achieve SVR rates in excess of 90%, regardless of HCV genotype (GT), disease stage, or treatment history.[2] While DAAs rarely fail to achieve viral clearance, up to 10% of patients will experience virological relapse/failure,[3] with HCV RNA reappearing a few weeks after completing therapy. In the past, treatment options for these patients were limited.[4,5] The once-daily, all-oral combination tablet containing SOF/VEL/VOX, was approved in Europe in July 20176 for patients infected with any genotype who have previously failed therapy with DAAs.[1]

In the first study presented today, a German research group evaluated all consecutive patients enrolled into the German Hepatitis C Registry (DHC-R) who were retreated with SOF/VEL/VOX ± ribavirin (RBV) due to virological failure up to February 2019 (N=110; HCV GT1 [71%], GT3 [34%], and GT4 [5%]; median age 54 years; 86% male; 27% with cirrhosis). Prior DAA regimens included paritaprevir/ritonavir/ombitasvir ± dasabuvir ± RBV (PrO ± D ± RBV [n=30]), ledipasvir/sofosbuvir ± RBV (LDV/SOF ± RBV [n=35]), SOF/velpatasvir ± RBV (SOF/VEL ± RBV [n=18]), daclatasvir + SOF ± RBV (DCV + SOF ± RBV [n=13]), elbasvir/grazoprevir (EBR/GZR [n=8]), SOF + RBV (n=2), and simeprevir + SOF + RBV (n=1). Four patients had received SOF/VEL/VOX + RBV (HCV GT1b [n=2], GT3a [n=2]).

According to investigator Dr Johannes Vermehren from the Goethe University Hospital in Frankfurt, Germany, with SVR data available from 74 patients as of February 2019, sustained virologic response was 100%. SOF/VEL/VOX was well tolerated, with fatigue (14%) and headaches (10%) the most frequently reported adverse events (AEs). No severe AEs were attributed to SOF/VEL/VOX treatment.

In the USA, data from 196 patients treated with SOF/VEL/VOX between July 2017 and April 2018 were collected from a health management program provider (Trio Health) and analysed. Duration of treatment was 12 weeks for all but one patient, who received treatment for >12 weeks. Seven patients (4%) also received RBV off-label. Most patients were treatment experienced (173/196; 88%) while 21 patients (11%) were treatment naïve. Treatment status for two patients was unavailable. The most frequently-used prior therapies were: LDV/SOF ± RBV (n=92), SOF/VEL ± RBV (n=20), EBR/GZR ± RBV (n=19), other SOF-based regimens (n=17), and PrOD (n=11). The SVR rates at 12 weeks after therapy in the per-protocol and intent-to-treat groups were reported to be 98% (183/186) and 93% (183/196), respectively.

Of the 3 patients that did not achieve SVR12 in the per-protocol group, 2/3 were white males, cirrhotic (F4), and had prior regimens of SOF/VEL and LDV/SOF ± RBV while 1/3 was a black female with moderate fibrosis (F2); her prior regimen was not specified. One patient had a baseline viral load between 800K-6MM and the other 2 patients had baseline viral loads >6MM. The insurance types were: 1 (commercial), 1 (Medicare), and 1 (not specified); all 3 patients were GT1.

"We are now seeing real-world evidence that SOF/VEL/VOX is highly effective when used in clinical practice to treat patients who have failed previous DAA therapy," concluded Dr Bruce Bacon from Saint Louis University School of Medicine, St Louis, USA.

"This important real-world experience from Germany and the USA showed that almost all patients with chronic hepatitis C – Including DAA treatment failures – can finally be cured," said Professor Markus Cornberg from Hannover Medical School in Germany, a member of EASL's governing board.

Onsite location references

Session title: Viral hepatitis C: Therapy and resistance (Posters)
Time, date and location of session: 09:00–19:00, 11 April 2019, Poster area
Presenter: Johannes Vermehren, Germany
Abstract: Retreatment with sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C virus infection and prior DAA failure: An analysis from the German hepatitis C registry (DHC-R) (THU-188)
Session title: Viral hepatitis C: Therapy and resistance (Posters)
Time, date and location of session: 09:00–19:00, 11 April 2019, Poster area
Presenter: Bruce Bacon, USA
Abstract: Effectiveness of the salvage therapy sofosbuvir-velpatasvir-voxilaprevir (SOF-VEL-VOX) in chronic hepatitis C: Clinical practice experience from the TRIO Network (THU-116)

Author disclosures

Johannes Vermehren has received speaking fees from AbbVie, Gilead, Intercept, and Merck/MSD.

Bruce Bacon consults for, is on the speakers' bureau for, and received grants from Merck. He advises for, is on the speakers' bureau for, and received grants from AbbVie and Gilead. He advises for and is on the speakers' bureau for Janssen. He advises for and received grants from Bristol-Myers Squibb. He is on the speakers' bureau for Valeant.

References

1. Vermehren J, et al. Challenges and perspectives of direct antivirals for the treatment of hepatitis C virus infection. J Hepatol. 2018;69(5):1178–87.
2. Naggie S, Muir AJ. Oral combination therapies for hepatitis C virus infection: successes, challenges, and unmet needs. Annu Rev Med. 2017;68:345–58
3. Benítez-Gutiérrez L, et al. Prevention and management of treatment failure to new oral hepatitis C drugs. Expert Opin Pharmacother. 2016;17(9):1215–23.
4. Bourlière M, et al. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV -infection. N Engl J Med. 2017;376(22):2134–46.
5. Chhatwal J, et al. Hepatitis C virus re-treatment in the era of direct-acting antivirals: projections in the USA. Aliment Pharmacol Ther. 2018;47(7):1023–31.
6. European Medicines Agency. European Public Assessment Report (EPAR) for the Public: Vosevi. Available from: https://www.ema.europa.eu/documents/overview/vosevi-epar-summary-public_en.pdf. Last accessed February 2019.

EMBARGO: 00.01 Thursday,11 April, 2019

High rates of liver disease progression and mortality observed in patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH)

ILC 2019: New studies in Germany and France support the need for early detection and effective interventions among NAFLD/NASH patients.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
Two independent national studies have reported high rates of liver disease progression and mortality among patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis (NAFLD/NASH). The studies reported today at The International Liver Congress™ 2019 in Vienna, Austria, found that within 10 years of diagnosis, up to 11% of patients with NAFLD/NASH had progressed to advanced liver diseases (defined as NAFLD/NASH patients with compensated cirrhosis [CC], decompensated cirrhosis [DCC], liver transplant [LT] or hepatocellular carcinoma [HCC]), and up to 27% of patients with NAFLD/NASH and CC had developed liver decompensation.

Fatty liver is a complex condition that affects up to one-quarter of adults worldwide.[1] The condition is considered to be the liver manifestation of metabolic syndrome[2] and encompasses a histological spectrum from the relatively benign non-alcoholic fatty liver to NASH, which typically has an aggressive course.[3] NAFLD/NASH can lead to cirrhosis or HCC,[4] and is set to become the predominant cause of liver disease in many parts of the world;[5] however, their natural history remains incompletely defined.[3]

In the first study, 215,655 NAFLD/NASH patients were identified retrospectively from a German insurance claims database (InGef; 2011–2016) with 100,644 new events of different liver severity stages identified during the follow-up: 79,245 events (78.7%) of non-progressive NAFLD/NASH, 411 events (0.4%) of CC, 20,614 events (20.5%) of DCC, 11 events (0.01%) of LT and 363 events (0.4%) of HCC. Amongst those with advanced liver diseases, mortality rate during 1 year of follow-up increased by up to 50% (range 8.8-51.2%), compared with non-progressive NAFLD/NASH patients (1.2%, $p<0.0001$). This trend continued over 5 years of follow-up, with only 2.8% of the non-progressive NAFLD/NASH patients dying, compared with 14.8% of CC patients, 25.6% of DCC patients, and 64.5% of HCC patients. After adjusting for patient demographics and comorbidities, the mortality risk increased significantly ($p<.0001$) with liver disease progression. As compared to non-progressors, the risk of mortality for NAFLD/NASH patients with CC, DCC, LT and HCC was 2.71, 4.21, 2.23 and 13.69 times higher respectively.

“Perhaps most worryingly, during the 5-year study period, 11% of the NAFLD/NASH patients progressed to advanced liver diseases and 17% of CC patients progressed to DCC, after accounting for any dying patients,” said Professor Ali Canbay from the University of Magdeburg Medical School in Magdeburg, Germany, who presented the study findings. “This demonstrates very clearly the need for early detection and effective treatment to prevent progression and potentially reduce mortality.”

In the second study, French investigators identified 125,052 NAFLD/NASH patients from the French National Database on hospital care (PMSI; 2009–2015), of whom 1,491 (1.2%) were diagnosed with CC, 7,846 (6.3%) with DCC, and 1,144 (0.9%) with HCC. As was seen in Germany, a small cohort of patients progressed rapidly, with 5.6% of NAFLD/NASH patients progressing to more severe liver disease during 7 years of follow-up, and 27.5% of NAFLD/NASH patients with CC progressing to DCC.

Mortality was high across all cohorts and increased with liver disease progression. After 1 year, 2.1% of NAFLD/NASH patients, 4.6% of CC patients, and 19.1% of DCC patients had died. The corresponding mortality rates after 7 years of follow-up were 7.9%, 16.3%, and 34.6% respectively.

“Before this study, we had very limited data on the disease progression and mortality of NAFLD/NASH patients in our country,” explained Professor Jerome Boursier from Angers University Hospital in Angers, France.

“We were surprised by the high overall mortality rate among these patients (7.9%) – almost twice that of the general population of a similar age – as well as the apparent rate of under-diagnosis of cirrhotic patients, the majority only being identified following a decompensation event.”

“This shows us we must direct greater effort into finding and treating NAFLD/NASH patients as early as possible, so we can stop or even reverse disease progression.”

Professor Philip Newsome (Vice-Secretary EASL) said, “These data demonstrate the significant morbidity and mortality found in patients with NAFLD and reinforces the need to identify those patients most at risk for appropriate treatment.”

Onsite location references

Session title: ‘NAFLD – Clinical burden natural history’
Time, date and location of session: 16:45–17:00, 11 April 2019, Strauss 1–2
Presenter: Ali Canbay, Germany
Abstract: Increasing risk of disease progression and mortality in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients with advanced liver disease: A German real-world analysis (PS-060)
Session title: ‘NAFLD: Clinical aspects except therapy’
Time, date and location of session: 09:00–19:00, 11 April 2019, Poster Area
Presenter: Jerome Boursier, France
Abstract: Increased risk of mortality with liver disease progression in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis patients: An analysis of French national hospital care (THU-299)

Author disclosures

Ali Canbay is an advisor for Gilead Sciences, Inc. Nandita Kachru and A. Burak Ozbay are employees of Gilead Sciences, Inc. during the conduct of this study. Data analyses were performed by Xcenda GmbH, a consultant of Gilead Sciences, Inc., of which Dominic Meise and Jennifer Haas are employees. This study was funded by Gilead Sciences, Inc. Jerome Boursier is a consultant for Abbvie, Allergan, Biorad, Diafir, Echosens, Genfit, Gilead Sciences, Inc., Intercept, Native, and Siemens. Jeremy Fraysse and Sanatan Shreay are employees of Gilead Sciences, Inc. Data analyses were performed by CEMKA-EVAL, a consultant for Gilead Sciences, Inc., of which Antoine Lafuma and Cecile Fabron are employees. This study was funded by Gilead Sciences, Inc.

References

1. Younossi ZM, et al. Global epidemiology of non-alcoholic fatty liver disease - Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
2. Wainwright P, Byrne CD. Bidirectional relationships and disconnects between NAFLD and features of the metabolic syndrome. Int J Mol Sci. 2016;17(3):367.
3. Bertot LC, Adams LA. The natural course of non-alcoholic fatty liver disease. Int J Mol Sci. 2016; 17(5): 774.
4. Manne V, et al. Pathophysiology of non-alcoholic fatty liver disease/Non-alcoholic steatohepatitis. Clin Liver Dis. 2018;22(1):23–37.
5. Loomba R, Sanyal AJ. The global NAFLD epidemic. Nat Rev Gastroenterol Hepatol. 2013;10(11):686–90.

EMBARGO: 00.01 Thursday,11 April, 2019

HIV-infected individuals at high risk of non-alcoholic fatty liver disease (NAFLD) and progressive liver disease

ILC 2019: Latest studies confirm increasing burden of NAFLD in people with HIV infection as viral hepatitis prevalence and associated mortality decline.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
The increasing burden and risk of non-alcoholic fatty liver disease (NAFLD) associated with HIV infection have today been highlighted in two studies presented at The International Liver Congress™ 2019 in Vienna, Austria. These studies found that, whilst prevalence and mortality rates associated with viral hepatitis in HIV-infected individuals have been declining, rates associated with NAFLD are increasing, leading to a risk of progressive liver disease.

People living with HIV infection appear to be at greater risk of developing NAFLD than the general population.[1] The prevalence of NAFLD worldwide has been estimated to be 25%,[2] while the prevalence in populations with HIV has been far higher in most reported studies.[1,3,4] NAFLD represents an important risk factor for the development and progression of liver disease,[5] and with the availability of effective hepatitis B and C antiviral medications, it is conceivable that NAFLD could become the most prominent liver disease affecting individuals with HIV in the future.[3]

The first study presented in Vienna aimed to assess the prevalence and mortality trends of NAFLD, viral hepatitis, and other liver diseases in HIV-infected individuals. The records of >47,000 HIV-infected Medicare recipients in the USA were searched, and >10,000 individuals with liver disease were identified: 5,628 with HCV-related disease, 1,374 with HBV-related disease, 645 with HCV/HBV-related disease, 2,629 with NAFLD, and 198 with other liver diseases.

During the 10 years between 2006 and 2016, the prevalence rates for viral hepatitis decreased from 27.75 to 24.17 per 100,000 population ($p=0.009$) whilst the rates for NAFLD more than doubled from 5.32 to 11.62 per 100,000 population ($p<0.001$). Mortality rates related to viral hepatitis also decreased from 3.78 to 2.58 per 100,000 population ($p=0.006$), whilst mortality related to NAFLD increased from 0.18 to 0.80 per 100,000 population ($p=0.041$).

'Our study shows that, as highly effective treatments for HBV and HCV infections lead to reduced associated mortality in HIV-infected populations, NAFLD is becoming an increasingly important cause of liver disease,' said Dr Zobair Younossi, Professor and Chairman of the Department of Medicine at Inova Fairfax Medical Campus in Falls Church, Virginia, USA, who presented the study results.

The second study, involving teams from Canada, the UK and Italy, used a diagnostic algorithm based on current EASL guidelines in HIV-negative populations[6] to identify individuals with NAFLD from two cohorts of adults with living with HIV without significant alcohol intake or viral hepatitis coinfection (the LIVEr disease in HIV [LIVEHIV] and Modena HIV Metabolic Clinic [MHMC] cohorts).

Of the 1,228 HIV-infected individuals reviewed (mean age 50 years; 73% males; time since diagnosis 16 years), 31.8% had NAFLD. Based on elevated alanine aminotransferase (ALT) levels and/or significant fibrosis, 25.2% of these patients were considered to be at risk of progressive liver disease compared with 18.4% of patients without NAFLD. Independent predictors of liver disease progression requiring specialist referral were found to be male sex, diabetes, and duration of HIV infection.

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Based on elevated alanine aminotransferase (ALT) levels and/or significant fibrosis, 25.2% of these patients were considered to be at risk of progressive liver disease compared with 18.4% of patients without NAFLD. Independent predictors of liver disease progression requiring specialist referral were found to be male sex, diabetes, and duration of HIV infection.

"Applying current NAFLD guidelines developed for HIV-negative populations, we have identified significant proportions of patients with HIV infection at risk of NAFLD and progressive liver disease," said Dr Sila Cocciolillo from the Royal Victoria Hospital, McGill University Health Centre, Montreal, Canada. "We think this supports the need for dedicated monitoring of these patients, with referral to hepatology services when required."

Professor Philip Newsome (Vice-Secretary, EASL) said, "These studies indicate the changing profile of liver disease in patients with HIV – whilst viral hepatitis is still the major cause of liver disease in such groups, NAFLD is becoming a much commoner problem. This reinforces the need to study of therapeutic agents in patients with NAFLD and HIV, an area which is seldom examined."

Onsite location references

Session title: 'NAFLD - Clinical burden natural history'
Time, date and location of session: 17:15–17:30, 11 April 2019, Strauss 1–2
Presenter: Zobair Younossi, USA
Abstract: The increasing importance of non-alcoholic fatty liver disease in human deficiency virus (HIV) positive patients (PS-062)
Session title: 'NAFLD: Diagnostics and non-invasive assessment'
Time, date and location of session: 09:00–17:00, 13 April 2019, Poster Area
Presenter: Sila Cocciolillo, Canada
Abstract: Application of guidelines for fatty liver in two prospective cohorts of human immunodeficiency virus positive patients (SAT-286)

Author disclosures

Zobair Yonoussi has received consulting fees from Gilead, Intercept, Bristol-Myers Squibb, Novo
Nordisk, Shinogi and Novartis.
Sila Cocciolillo has no relevant disclosures

References

1. Maurice JB, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. AIDS. 2017;31(11):1621–32.
2. Younossi ZM, et al. Global epidemiology of nonalcoholic fatty liver disease – Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
3. Rockstroh JK. Non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) in HIV. Curr HIV/AIDS Rep. 2017;14(2):47–53.
4. Verna EC. Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in patients with HIV. Lancet Gastroenterol Hepatol. 2017;2(3):211–23.
5. Kaspar MB, Sterling RK. Mechanisms of liver disease in patients infected with HIV. BMJ Open Gastroenterol. 2017;4(1):e000166.
6. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.

EMBARGO: 00.01 Thursday,11 April, 2019

Autoimmune diseases of the liver may be partly triggered by exposure to an environmental factor

ILC 2019: UK disease clustering study suggests that environmental exposure may play a key role in the development of some autoimmune liver diseases.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
Investigators from a large population-based study conducted in northern England have suggested that exposure to a persistent, low-level environmental trigger may have played a role in the development of autoimmune diseases of the liver within that population. The study, which was discussed today at The International Liver Congress™ 2019 in Vienna, Austria, found a significant clustering of cases of primary biliary cholangitis (PBC), autoimmune hepatitis (AIH), and primary sclerosing cholangitis (PSC) in well-defined regions of north-east England and North Cumbria, suggesting an environmental agent (or agents) may have been involved.

The autoimmune liver diseases, PBC, AIH, and PSC, are relatively rare diseases that are associated with significant morbidity and mortality.[1,2] These conditions affect people of all ages and are chronic, life-long conditions.[2] The underlying cause of these autoimmune liver diseases is not fully defined, although an interaction between a genetic predisposition to autoimmunity and environmental factors has been proposed.[2]

Disease clustering, whereby an abnormally large number of cases have been found in a well-defined geographical region, has been reported previously for PBC in two areas of Northern England[3,4] and New York.[5] However, according to the investigators in today's study, equivalent studies have not been performed in AIH or PSC.

The study reported today was conducted by a team of researchers from Newcastle in Northern England, supported by the National Institute for Health Research Newcastle Biomedical Research Centre. The team identified a large cohort of individuals from North-East England and North Cumbria who had PBC (n=2,150), AIH (n=963), or PSC (n=472). Spatial point analyses were used to investigate disease clustering using postal addresses, and, for those with a known year of diagnosis, spatio-temporal analyses were undertaken.

Areas with a higher than expected number of patients with each of these three conditions were found at approximately 1–2 km, with extra clusters for AIH and PSC at approximately 10 km and 7.5km in PBC. There was no sign of more patients being diagnosed within a particular timeframe that suggests an infection is less likely to be associated with development of these diseases.

"This study suggests that exposure to a persistent, low-level environmental agent may have played a role in the pathogenesis of all three autoimmune liver diseases studied, not just PBC," 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 varying distances of peak clustering raises the possibility that different environmental factors contribute to PBC, AIH, and PSC.

"In previous PBC clustering studies, water reservoirs, industrial or coal mining factors, or waste disposal site toxins have been implicated,"[6] noted Dr Dyson. "Further work is ongoing to try to identify factors that may potentially be associated with the clustering observed in our study.

"This study is very important, since autoimmune diseases of the liver are infrequent but have an increasing incidence overall," said Professor Marco Marzioni from the Università Politecnica delle Marche, Ancona, Italy, and an EASL Governing Board Member.

"However, their triggers are as yet unknown. Environmental factors have been considered, but no solid data have emerged so far. The study presented today has sufficient scientific rigour to reinforce the idea that environmental exposure may play a major role in triggering autoimmune diseases of the liver."

Onsite location reference

Session title: 'Autoimmune and cholestasis I'
Time, date and location of session: 17:15–17:30, 11 April 2019, Hall C2
Presenter: Jessica Dyson, UK
Abstracts: Disease clustering in autoimmune liver diseases points towards environmental factors being important in their aetiology (PS-014)

Author disclosures

Jessica Dyson is supported by the National Institute for Health Research Newcastle Biomedical Research Centre.

References

1. Dyson JK, et al. Unmet clinical need in autoimmune liver diseases. J Hepatol. 2015;62(1):208–18.
2. Arndtz K, Hirschfield GM. The pathogenesis of autoimmune liver diseases. Dig Dis. 2016;34(4):327–33.
3. Triger DR. Primary biliary cirrhosis: an epidemiological study. Br Med J. 1980;281(6243):772–5.
4. Prince MI, et al. The geographical distribution of primary biliary cirrhosis in a well-defined cohort. Hepatology. 2001;34(6):1083–8.
5. Ala A, et al. Increased prevalence of primary biliary cirrhosis near Superfund toxic waste sites. Hepatology. 2006;43(3):525–31.
6. Smyk D, et al. PBC triggers in water reservoirs, coal mining areas and waste disposal sites: from Newcastle to New York. Dis Markers. 2010;29(6):337–44.

EMBARGO: 00.01 Thursday,11 April, 2019

Homelessness may be a barrier to success for hepatitis C 'Treatment as Prevention' programmes

ILC 2019: 'Treatment as Prevention' programme for hepatitis C in Iceland reports high levels of cure, but homelessness is found to be a barrier to success.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
A national 'Treatment as Prevention' programme for hepatitis C has today reported high levels of cure but found that homelessness more than doubles the chance of failing treatment with direct-acting antiviral (DAA) drugs. First results from the Treatment as Prevention for Hepatitis C (TraP HepC) initiative in Iceland, which were reported today at The International Liver Congress™ 2019 in Vienna, Austria, indicate that a cure from HCV infection can be achieved with one course of treatment in almost 90% of programme participants, although cure rates may be lower among injection drug users.

Injection drug use is the most important risk factor for hepatitis C virus (HCV) transmission in many countries, and the prevalence of HCV infection is highest among people who inject drugs (PWID) than among any other risk group.[1,2] Multiple studies have provided evidence that people with HCV who inject drugs can be treated successfully with antiviral drugs, yet access to treatment across Europe still appears to be limited.[3]

In an effort to improve this situation and achieve World Health Organization HCV elimination targets, many countries in Europe have implemented harm reduction and/or hepatitis C elimination programmes, which build on the concept of treatment to prevent onward transmission of HCV.3,4 The TraP HepC programme in Iceland was launched in January 2016 and since the launch of the programme, all HCV-positive individuals have been offered direct-acting antiviral (DAA) agents, with priority groups including PWID and those with advanced liver disease.[4]

"During the first 2 years of the programme, 631 individuals – which amounts to 80% of the estimated HCV-infected population in Iceland – were initiated on DAA treatment," explained Dr Magnús Gottfredsson from the National University Hospital in Reykjavik, Iceland, who presented the first results from the programme. "Recent injection drug use was reported by 210 of these individuals, with more than half injecting in the 30 days prior to treatment."

"Forty individuals in our cohort (6.3%) were homeless."

According to Dr Gottfredsson, in the ITT analysis the overall cure rate after the first treatment attempt was 89.2%. Cure was achieved in a significantly smaller proportion of the cohort reporting injection drug use within the past 6 months (82.9%) compared with the cohort without recent injection drug use (92.4%; $p<0.0001$). Individuals with recent injection drug use were more likely to discontinue treatment (15.2% vs. 4.5%; $p<0.0001$), however, even when the analysis was restricted to those who completed treatment, the chance of cure was lower among those with recent injection drug use (89.9% vs. 95.3%; $p=0.025$).

Homelessness was associated with a greater chance of persistent viraemia at ≥12 weeks, with a relative risk (RR) of 2.42 (95% CI 1.34, 4.37; $p=0.007$), while living in a halfway house was associated with a lower risk (RR 0.37; 95% CI 0.12, 1.16; $p=0.068$).

"Overall, in its first 2 years, the Trap HCV programme has achieved high rates of treatment success among some diffcult-to-reach and -treat HCV-infected populations," said Dr Gottfredsson. "We were concerned, however, to find that homelessness is a risk factor for treatment failure, which we suspect is due to treatment discontinuation. Interventions must be targeted towards this group of individuals to limit the spread of HCV infection."

This is an important study, since it demonstrated the feasibility of treating this group of patients, although with a lower rate of success' said Professor Helena Cortez-Pinto from the Hospital Universitário de Santa Maria, Lisbon, Portugal, and an EASL Governing Board member.

Onsite location reference

Session title: 'Cascade of care towards elimination of viral hepatitis'
Time, date and location of session: 17:45–18:00, 11 April 2019, Strauss 3
Presenter: Magnús Gottfredsson, Iceland
Abstract: Is homelessness the biggest hurdle to treatment success in the management of HCV in the era of direct acting antivirals? Results from the TraP HepC nationwide treatment initiative in Iceland
(PS-072)

Author disclosures

Magnús Gottfredsson has received speaking fees from Gilead. Gilead provided DAAs at no cost to the TraP Hepatitis C Program in an epidemiological study setting.

References

1. Alter MJ. HCV routes of transmission: what goes around comes around. Semin Liver Dis. 2011;31(4):340–6.
2. Martin NK, et al. The hepatitis C virus epidemics in key populations (including people who inject drugs, prisoners and MSM): the use of direct-acting antivirals as treatment for prevention. Curr Opin HIV AIDS. 2015;10(5):374–80.
3. Wiessing L, et al. Hepatitis C virus infection epidemiology among people who inject drugs in Europe: a systematic review of data for scaling up treatment and prevention. PLoS One. 2014;9(7):e103345.
4. Olafsson S, et al. Treatment as Prevention for Hepatitis C (TraP Hep C) - a nationwide elimination programme in Iceland using direct-acting antiviral agents. J Intern Med. 2018;283(5):500–7.

EMBARGO: 00.01 Thursday,11 April, 2019

Obeticholic acid improves liver fibrosis and other histological features of nonalcoholic steatohepatitis

ILC 2019: Interim analysis of the Phase 3 REGENERATE study suggests that obeticholic acid holds promise as a future treatment for NASH

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
A prespecified interim analysis of the ongoing Phase 3 REGENERATE study has confirmed that obeticholic acid (OCA) is effective in the treatment of nonalcoholic steatohepatitis (NASH) with liver fibrosis. The 18-month analysis, which was reported today at The International Liver Congress™ 2019 in Vienna, Austria, demonstrated that the 25 mg dose of OCA studied improved fibrosis in almost one-quarter of recipients, with significant improvements also reported in other histological markers of NASH.

Nonalcoholic steatohepatitis is a severe form of nonalcoholic fatty liver disease (NAFLD) and is characterized by the presence of steatosis, hepatocellular ballooning, and lobular inflammation.[1] The condition is associated with rapid progression of fibrosis, which can eventually lead to the development of cirrhosis and hepatocellular carcinoma.[1,2] The global prevalence of NASH has been estimated to range from 1.50% to 6.45%, with almost 60% of individuals with NAFLD who undergo biopsy found to have NASH.[3] There are currently no medications approved in Europe or the USA specifically for the treatment of NASH.[2,4]

Obeticholic acid is a potent activator of the farnesoid X nuclear receptor that was shown to improve liver histology and fibrosis in a Phase 2 clinical trial (FLINT) published in 2015.[5] The Phase 3 trial reported today is the first study in NASH to be designed in conjunction with regulatory authorities, with the aim of achieving approval for OCA in NASH with fibrosis.[6]

In the analysis reported today, 931 individuals with biopsy-confirmed NASH and significant or severe fibrosis (stages F2 or F3) were randomized to receive OCA 10 mg/day (n=312), OCA 25 mg/day (n=308), or placebo (n=311). The primary endpoints of the study were either fibrosis improvement (≥1 stage) with no worsening of NASH or NASH resolution with no worsening of liver fibrosis on liver biopsy. The most pronounced benefits were observed in the OCA 25 mg treatment group. Once daily OCA 25 mg met the primary endpoint of fibrosis improvement (≥1 stage) with no worsening of NASH in 23.1% of patients (p=0.0002 vs placebo). 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 lobular inflammation (p=0.0322 vs placebo). Dose-dependent reductions in liver enzymes were also observed.

Pruritus, the most commonly-reported adverse event (AE), affected 51% of the OCA 25 mg/day treatment group, 28% of the OCA 10 mg/day treatment group, and 19% of the placebo group. More participants withdrew from the study due to 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, a common liver disease which can lead to cirrhosis, liver failure and need for transplant,” said Dr Zobair Younossi, Professor and Chairman of the Department of Medicine at Inova Fairfax Medical Campus in Falls Church, Virginia, USA, who presented the study results. “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.”

Professor Philip Newsome, Vice-Secretary of EASL, said. “These data are very exciting as they demonstrate for the first time in a phase 3 trial that medical therapy, in this case obeticholic

acid, is able to improve liver fibrosis compared to placebo – a key treatment goal in NASH."

Onsite location reference

Session title: 'General session 1'
Time, date and location of session: 15:15–15:30, 11 April 2019, Main plenary
Presenter: Zobair Younossi, USA
Abstract: Positive results from REGENERATE: a Phase 3 international, randomized, placebo-controlled study evaluating obeticholic acid treatment for NASH (GS-06)

Author disclosures

Zobair Younossi has received consulting fees from Gilead, Intercept, Bristol-Myers Squibb, Novo Nordisk, Shionogi and Novartis.

References

1. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
2. Lucas C, et al. A systematic review of the present and future of non-alcoholic fatty liver disease. Clin Exp Hepatol. 2018;4(3):165–74.
3. Younossi ZM, et al. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.
4. Connolly JJ, et al. Future pharmacotherapy for non-alcoholic steatohepatitis (NASH): review of Phase 2 and 3 trials. J Clin Transl Hepatol. 2018;6(3):264–75.
5. Neuschwander-Tetri BA, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2015;385(9972):956–65.
6. Ratzui V, et al. REGENERATE: a Phase 3, double-blind, randomized, placebo-controlled multicenter study of obeticholic acid therapy for nonalcoholic steatohepatitis. J Hepatol. 2016;64(2):S214–5.

EMBARGO: 00.01 Thursday,11 April, 2019

High cost of advanced non-alcoholic fatty liver disease/ non-alcoholic steatohepatitis (NAFLD/NASH) revealed but screening high-risk patients may not be cost effective (NASH)

ILC 2019: Italian study reveals high cost of advanced liver disease in NAFLD/NASH patients and missed opportunities to diagnose earlier, yet screening high-risk individuals for NAFLD may not be cost effective if treatments are too expensive

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

11 April 2019, Vienna, Austria:
The high cost of treating advanced liver disease in patients with non-alcoholic fatty liver disease/ nonalcoholic steatohepatitis (NAFLD/NASH) has been revealed in a study presented today at The International Liver Congress™ 2019 in Vienna, Austria. The results highlight potential missed opportunities for early diagnosis and treatment, and the need to improve this to avoid the high economic burden associated with disease progression. However, a second study suggested that screening for NAFLD in a high-risk population (patients with diabetes) would not be cost-effective if treatment options are too expensive.

NAFLD is the most prevalent form of chronic liver disease in the world, paralleling the epidemic of obesity and type 2 diabetes mellitus.[1,2] The natural history of NAFLD in some individuals is to progress from NAFLD to NASH, cirrhosis, hepatocellular carcinoma (HCC), and end-stage liver disease, and the presence of type 2 diabetes is thought to play a key role in its progression.[2] The costs associated with the care of patients with NAFLD have recently been found to be very high,[3,4] however, there is a lack of real-world data on the true economic burden of the condition.[3]

The first study aimed to characterize the health resource utilization and costs associated with patients with NAFLD/NASH and advanced liver disease (defined as NAFLD/NASH patients with compensated cirrhosis [CC], decompensated cirrhosis [DCC], liver transplant [LT], or HCC). Investigators studied the records of almost 10,000 NAFLD/NASH patients in Italy who were hospitalized during the study period (2011–2017) and identified 131 individuals (1.3%) with CC, 303 (3.1%) with DCC, 11 (0.1%) with LT, and 79 (0.8%) with HCC. NAFLD/ NASH patients with advanced liver disease were hospitalized, on average, 4.2–4.4 times per year compared with 2.9 times for patients without advanced liver disease ($p \leq 0.05$). The total mean annual healthcare costs associated with hospitalized NAFLD/NASH patients were at least 86% higher in those with advanced liver disease versus those without, primarily as a result of higher inpatients costs: €10,576 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 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: €2,418 for those without advanced liver disease, versus €9,318 for those with CC, €9,717 for those with DCC, €55,677 for those with LT, and €16,185 for those with HCC ($p<0.01$ for CC, DCC, and HCC; $p=0.08$ for LT).

'The annual costs associated with NAFLD/ NASH patients with advanced liver disease are extremely high and increase as liver disease progresses, highlighting the need for effective interventions to prevent progression,' said Dr Salvatore Petta from the University of Palermo in Italy. 'Additionally, in our study, there was a lower prevalence of CC compared with DCC, suggesting a missed opportunity to diagnose the disease at an earlier stage.'

So could screening for NAFLD in high-risk

populations be cost effective?

Not according to a group of Israeli researchers, who presented their findings in Vienna today. In the Israeli study, a computer model was constructed to assess the impact of screening for liver fibrosis using elastography in individuals with diabetes, with a hypothetical new treatment capable of reducing the annual rate of progression by 15% and increasing the rate of regression by 15% being given to patients found to have NASH and significant liver fibrosis (F2–F3). In the model, individuals with cirrhosis would be managed according to current guidelines. The annual cost of the hypothetical new treatment was set in the range of $20,000 to $100,000.

'We were motivated to do this analysis in-line with guideline recommendations to screen patients with diabetes for NAFLD[5] and in-light of recent findings that several novel interventions have been shown to improve fibrosis in NAFLD/NASH,[6]' explained Dr Yaakov Maor from the Institute of Gastroenterology and Hepatology in Rehovot, Israel.

According to these researchers, if a new 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.'

Onsite location reference

Session title: 'NAFLD - Clinical burden natural history'
Time, date and location of session: 17:00–17:15, 11 April 2019, Strauss 1–2
Presenter: Jie Ting, USA
Abstract: Non-alcoholic fatty liver disease/Non-alcoholic steatohepatitis patients with advanced liver disease had high burden of comorbidities, healthcare resource utilization and costs: Results from Italian administrative databases (PS-061)
Session title: 'NAFLD - Clinical burden natural history'
Time, date and location of session: 17:30–17:45, 11 April 2019, Strauss 1–2
Presenter: Yaakov Maor, Israel
Abstract: Screening diabetic patients for non-alcoholic fatty liver disease: Is it cost-effective (PS-063)

Author disclosures

Salvatore Petta is an advisor to Gilead Sciences Inc. Jie Ting is an employee of Gilead Sciences Inc, during the conduct of this study. The study he presented was funded by Gilead Sciences Inc.
Yaakov Maor has no relevant disclosures.

References

1. Marcellin P, Kutala BK. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. Liver Int. 2018;38 Suppl 1:2–6.
2. Bertot LC, Adams LA. The natural course of non-alcoholic fatty liver disease. Int J Mol Sci. 2016; 17(5): 774.
3. Allen AM et al. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large U.S. claims database. Hepatology. 2018;68(6):2230–38.
4. Sayiner M, et al. Variables associated with inpatient and outpatient resource utilization among Medicare beneficiaries with nonalcoholic fatty liver disease with or without cirrhosis. J Clin Gastroenterol. 2017;51(3):254–60.
5. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–402.
6. Sumida Y, Yoneda M. Current and future pharmacological therapies for NAFLD/NASH. J Gastroenterol. 2018;53(3):362–76.

EMBARGO: 00.01 Friday, 12 April, 2019

Non-alcoholic fatty liver disease found in large numbers of teenagers and young adults: is a public health crisis looming?

ILC 2019: UK population-based study finds large numbers of young adults have nonalcoholic fatty liver disease (NAFLD) and many of these already have fibrosis.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

12 April 2019, Vienna, Austria:

A large population-based study in the UK has revealed new evidence that large numbers of young adults have features suggestive of nonalcoholic fatty liver disease (NAFLD), and that one in 40 of these have already developed fibrosis. The study, based at the University of Bristol and presented today at The International Liver Congress™ 2019 in Vienna, Austria, suggests that greater awareness of NAFLD is needed among young adults if a public health crisis is to be avoided.

NAFLD is described as the accumulation of lipids in the liver (steatosis) that is not related to alcohol consumption.[1] The condition is considered the hepatic manifestation of metabolic syndrome and has a clear association with obesity, diabetes and hyperlipidaemia.[2] NAFLD is the most common form of chronic liver disease among both adults and children, with an estimated global prevalence of 20–30%,[2,3] although this varies with age.[4] Prevalence is continuing to rise,[5] which has major public health and economic implications, including increased cardiovascular disease-related morbidity,[6] greater burden on transplant services,[7] and a rising hepatocellular carcinoma (HCC) prevalence.[8]

For the study presented today, investigators from the University of Bristol in the UK evaluated 4021 young adults from the Children of the 90s prospective birth cohort (also known as the Avon Longitudinal Study of Parents and Children, or ALSPAC), which had previously been assessed for NAFLD as teenagers using ultrasound criteria. The prevalence of NAFLD in the original cohort of teenagers was 2.5%. Revisiting the same cohort as young adults (mean age of 24 years), the investigators used transient elastography to assess steatosis and fibrosis. All individuals with known excessive alcohol intake were excluded from the analyses.

Of the 3128 individuals whose scans were eligible for analysis, 76/3128 (2.4%) had some degree of fibrosis and eight (0.3%) had fibrosis evaluations equivalent to stage 4 (F4) fibrosis. A total of 680 out of 3277 individuals (20.8%) were found to have steatosis (indicative of NAFLD), with just under half of these (n=331; 10.1% of the entire cohort) staged as severe (S3). A positive association was observed between increases in liver enzymes (alanine aminotransferase, aspartate aminotransferase, and gamma-glutamyl transferase), increasing fibrosis (F) scores (all $p \leq 0.002$), and increasing controlled attenuated parameter (CAP) scores ($p<0.001$), indicative of liver damage. Positive associations were seen between F score and CAP score ($p<0.001$) and between increasing steatosis grade, cholesterol levels, triglycerides, and low-density lipoprotein ($p<0.001$). Finally, BMI rose significantly with both F and CAP scores ($p<0.001$ for both).

“This is the largest study to date to analyse fibrosis and steatosis in young adults with suspected NAFLD using transient elastography,’” said Dr Kushala Abeysekera, from the University of Bristol in the UK, who presented the results of the study. “We were concerned to find that, at only 24 years of age, one in five had steatosis and one in 40 had evidence of fibrosis, based on elastography results, in a group of largely asymptomatic, predominantly Caucasian young people.”

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

Prof 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.”

Onsite location reference

Session title: ‘General session II’
Time, date and location of session: 08:45–09:00, 12 April 2019, Main Plenary
Presenter: Kushala Abeysekera, UK
Abstract: The prevalence of non-alcoholic fatty liver disease in young adults: An impending public health crisis? (GS-08)

Author disclosures

Funding from the UK Medical Research Council (Grant ref: R103083-101), David Telling Charitable Trust, and the University of Bristol provide core support for ALSPAC.

References

1. Okur G and Karacaer Z. The prevalence of non-alcoholic fatty liver disease in healthy young persons. North Clin Istanb. 2016;3(2):111–7.
2. Andronescu CI, et al. Nonalcoholic fatty liver disease: epidemiology, pathogenesis and therapeutic implications. J Med Life. 2018;11(1):20–3.
3. Abd El-Kader SM and El-Den Ashmawy EM. Non-alcoholic fatty liver disease: The diagnosis and management. World J Hepatol. 2015;7(6):846–58.
4. Sherif ZA, et al. Global Epidemiology of Nonalcoholic Fatty Liver Disease and Perspectives on US Minority Populations. Dig Dis Sci. 2016;61(5):1214–25.
5. Younossi Z, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018;15(1):11–20.
6. Francque SM, et al. Non-alcoholic fatty liver disease and cardiovascular risk: Pathophysiological mechanisms and implications. J Hepatol. 2016;65(2):425–43.
7. Pais R, et al. NAFLD and liver transplantation: Current burden and expected challenges. J Hepatol. 2016;65(6):1245–57.
8. Said A and Ghufran A. Epidemic of non-alcoholic fatty liver disease and hepatocellular carcinoma. World J Clin Oncol. 2017;8(6):429–36.

EMBARGO: 00.01 Friday, 12 April, 2019

MSDC-0602K shows potential for improving markers of liver disease in individuals with non-alcoholic steatohepatitis (NASH)

ILC 2019: Second-generationthiazolidinedione, MSDC-0602K may significantly improve liver enzymes, fibrosis, and glycaemic markers with minimal adverse events, according to a Phase 2b study.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

12 April 2019, Vienna, Austria:
An interim analysis from the ongoing, 12-month, Phase 2b EMMINENCE trial of the novel second-generation thiazolidinedione, MSDC-0602K, has reported significant improvements in liver enzymes and markers of fibrosis after 6 months of treatment in individuals with biopsy-confirmed non-alcoholic steatohepatitis (NASH). The results, which were presented today at The International Liver Congress™ 2019 in Vienna, Austria, represent a promising new approach to management of a disease where there are currently no approved treatment options.

It is estimated that ~25% of the world population has nonalcoholic fatty liver disease (NAFLD), which is frequently associated with metabolic disorders including type-2 diabetes.[1] ~59% of individuals with NAFLD are estimated to progress to NASH, which in turn can lead to cirrhosis, liver failure, and hepatocellular carcinoma.[1] The prevalence of NAFLD/NASH is increasing worldwide, with one recent model in the USA predicting an increase in NASH cases from 16.5 million to 27.0 million between 2015 and 2030.[2] To address this growing health burden, thiazolidinediones are one of several drug classes being investigated for their potential to mitigate disease and reduce liver damage.[3]

Thiazolidinediones are understood to achieve insulin sensitivity by targeting the peroxisome proliferator-activated receptor-gamma (PPARγ) transcription factor but their use has been limited by PPARγ-related side effects.[4] More recently, thiazolidinedione binding sites have been identified on the mitochondrial pyruvate carrier (MPC),[5] inhibition of which has been shown in animal models to protect against liver damage.[6] MSDC-0602K is a second-generation thiazolidinediones that has been formulated to limit PPARγ binding while maintaining efficacy through MPC inhibition.[7,8]

In the EMMINENCE trial, 402 participants with a NAFLD Activity Score of ≥4 including ballooning and inflammation ≥1 and F1–3 fibrosis were randomized 1:1:1:1 to receive MSDC-0602K 62.5 mg, 125 mg, or 250 mg, or placebo, daily. Over 50% of participants also had type-2 diabetes, and >60% had baseline fibrosis ≥F2. The interim analysis presented today was conducted in the first 328 participants to complete 6 months of therapy.

According to Principal Investigator, Dr Stephen Harrison from the University of Oxford, UK, MSDC-0602K 125 mg demonstrated improvements in most disease markers at 6 months, with statistically significant placebo-corrected reductions in alanine aminotransferase (ALT; 27.0%; $p<0.001$) and aspartate aminotransferase (21.3%; $p=0.012$). Improvements in ALT were also seen in the MSDC-0602K 250 mg group (20.1%; $p=0.004$). The MSDC-0602K 125 mg dose also demonstrated statistically significant reductions in bilirubin, alkaline phosphatase, and gamma-glutamyl transferase, as well as improvements in several fibrosis markers including APRI Score and Fibro Test (both $p<0.05$). In participants with type-2 diabetes, all doses of MSDC-0602K were associated with significant improvements in HbA1c, a marker of glycaemic control. The adverse event profile of MSDC-0602K was similar to that of placebo, with a modest dose-dependent, placebo-corrected weight increase of ≤2%, which was statistically significant in the MSDC-0602K 125 mg and 250 mg groups.

Importantly, unlike pioglitazone, no difference from placebo for any dose was seen in the frequency of peripheral edema by physical exam.

"This is the largest Phase 2b study in NASH to include paired biopsies, and even in this interim analysis, MSDC-0602K has demonstrated significant effects on multiple markers of liver disease," said Dr Harrison.

"MSDC-0602K validates the strategy to develop novel thiazolidinediones to target the MPC, and may have the potential to ameliorate NASH and fibrosis and, in patients with type 2 diabetes, to improve glycaemic control."

Prof Philip Newsome (Vice-Secretary, EASL) said, "This study is very exciting, with early data suggesting that MSDC-0602K shows promise in reducing markers of liver injury and fibrosis, in the absence of any significant adverse events. We look forward to seeing the results of liver biopsy analysis."

Onsite location reference

Session title: 'NAFLD - Clinical Therapy'
Time, date and location of session: 17:30–17:45, 12 April 2019, Main plenary
Presenter: Stephen Harrison, UK
Abstract: Six month interim results of MSDC-0602K in a large phase 2b NASH study demonstrate significant improvement in liver enzymes and glycemic control (NCT02784444) (PS-111)

Author disclosures

Dr Harrison has received consulting fees from Cirius Therapeutics

References

1. Younossi ZM, et al. Global epidemiology of non-alcoholic fatty liver disease - Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1): 73–84.
2. Estes C, et al. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;67(1):123–33.
3. McCommis, KS. Treating hepatic steatosis and fibrosis by modulating mitochondrial pyruvate metabolism. Cell Mol Gastroenterol Hepatol. 2018;7(2):275–84.
4. Colca JR, Kletzien RF. What has prevented the expansion of insulin sensitisers? Expert Opin Investig Drugs. 2006;15(3): 205–10.
5. Colca JR, et al. Identification of a mitochondrial target of thiazolidinedione insulin sensitizers (mTOT)--relationship to newly identified mitochondrial pyruvate carrier proteins. PloS One. 2013;8(5):e61551.
6. Rauckhorst AJ, et al. The mitochondrial pyruvate carrier mediates high fat diet-induced increases in hepatic TCA cycle capacity. Mol Metab. 2017;6(11):1468–79.
7. Divakaruni AS, et al. Thiazolidinediones are acute, specific inhibitors of the mitochondrial pyruvate carrier. Proc Natl Acad Sci USA. 2013;110(14):5422–7.
8. McCommis, KS. Targeting the mitochondrial pyruvate carrier attenuates fibrosis in a mouse model of nonalcoholic steatohepatitis. Hepatology. 2017;65(5):1543–56.

EMBARGO: 00.01 Friday, 12 April, 2019

Calmangafodipir may reduce liver injury after paracetamol overdose: final results from the POP trial

ILC 2019: Phase 1 study demonstrates that superoxide dismutase mimetic, calmangafodipir, is well tolerated and may reduce liver injury after paracetamol overdose.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

12 April 2019, Vienna, Austria:
Final results from a Phase 1 study suggest that the novel superoxide dismutase mimetic, calmangafodipir, is well tolerated and may reduce liver injury after paracetamol overdose. The study, which was presented today at The International Liver Congress™ 2019 in Vienna, Austria, found that administration of calmangafodipir in combination with N-acetylcysteine (NAC) within 24 hours of overdose was associated with lower levels of biomarkers of hepatoxicity compared with N-acetylcysteine alone.

Paracetamol overdose is the most common cause of acute liver failure in the Western world, accounting for almost 50% of all cases in the USA[1] and around 60% in the UK.[2] NAC is the mainstay of treatment for paracetamol overdose, effectively preventing hepatotoxicity when used within 8 hours of paracetamol ingestion.[3] However, the treatment has major shortcomings, with a complex and arduous 21-hour intravenous (IV) treatment regimen and a high risk of potentially severe adverse events, including anaphylactoid reactions.[3]

Calmangafodipir (PP100-01) is a superoxidase dismutase mimetic that has been shown to prevent paracetamol toxicity in mice.[4,5] The agent has recently been explored in a Phase 1 tolerability and safety study,[3] the results of which were presented today in Austria.

This randomized, open-label study involved 24 individuals who were recruited from the Emergency Department of a large teaching hospital in the UK within 24 hours of a single or staggered paracetamol overdose. All were considered candidates for NAC treatment at study enrolment. Participants were randomly assigned to one of three dosing cohorts, with each cohort randomized to receive NAC + calmangafodipir (n=6), or NAC alone (n=2). Calmangafodipir was administered IV between the first two NAC bags at doses of 2, 5, or 10 µmol/kg. The primary endpoint of the study was the safety and tolerability of the combination treatment. Secondary endpoints included alanine aminotransferase (ALT) activity and the biomarkers of hepatotoxicity, full-length keratin-18 (FLK18) and microRNA-122 (miR-122), measured at baseline, 10 hours and 20 hours after starting NAC treatment.

According to the investigators, the median time from overdose to starting NAC was 10.3, 6.5, 7.3 and 6.7 hours for the NAC alone, NAC + calmangafodipir 2, 5 and 10 µmol/kg groups, respectively. All participants experienced at least one adverse event (AE); however, no AEs or serious AEs were attributed to calmangafodipir. No increases in ALT were observed in any of the treatment groups during the study. Individuals who received the combination treatment had smaller increases in FLK18 than individuals who received NAC alone. Between baseline and 20 hours, median FLK18 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. The median (range) FLK18 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.

"Calmangafodipir was well tolerated when coadministered with NAC in this study," said Dr James Dear from the University of Edinburgh in the UK, who presented the latest study results.

"Although the results are preliminary and need confirmation in a larger study, the evidence suggests the treatment may reduce liver injury after paracetamol overdose."

Prof Philip Newsome (Vice-Secretary, EASL) said, "These data demonstrate the potential value of novel agents in addition to N-AcetylCysteine in the management of paracetamol overdose. We look forward to testing in larger studies and in particular the value of calmangafodipir in patients presenting late after a paracetamol overdose."

Onsite location reference

Session title: 'Acute and acute-on-chronic liver failure - Translational aspects'
Time, date and location of session: 16:30–16:45, 12 April 2019, Lehar 4
Presenter: James Dear, UK
Abstracts: PP100-01 (calmangafodipir) for overdose of paracetamol (The POP trial): Principal results (PS-099)

Author disclosures

James Dear is a member of the Expert Advisory Group for the Innovative Medicines Initiative-funded EU TransBioLine Consortium. This study was funded by PledPharma AB

References

1. Bernal W, et al. Acute liver failure: A curable disease by 2024? J Hepatol. 2015;62(1 Suppl):S112–20.
2. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525–34.
3. POP Trial Investigators, Dear J. Randomised open label exploratory, safety and tolerability study with calmangafodipir in patients treated with the 12-h regimen of N-acetylcysteine for paracetamol overdose-the PP100-01 for Overdose of Paracetamol (POP) trial: study protocol for a randomised controlled trial. Trials. 2019;20(1):27.
4. Karlsson JO, et al. Calmangafodipir [Ca4Mn(DPDP)5], mangafodipir (MnDPDP) and MnPLED with special reference to their SOD mimetic and therapeutic properties. Drug Discov Today. 2015;20(4):411–21

EMBARGO: 00.01 Friday, 12 April, 2019

First-in-class small molecule eliminates cccDNA in the hepatitis B virus (HBV)-infected liver

ILC 2019: Orally-administered small molecule, ccc_R08, eliminates covalently closed circular DNA (cccDNA) in the liver of an HBV cccDNA mouse model: a step towards a sterilizing cure?

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

12 April 2019, Vienna, Austria:
A novel, orally-administered small molecule, ccc_R08, reduces serum markers of hepatitis B virus (HBV) infection and eliminates covalently closed circular DNA (cccDNA) from the liver, according to the results of a study presented today. Roche Researchers based in Shanghai, China, presented their findings at The International Liver Congress™ 2019 in Vienna, Austria, suggesting further exploration of this type of molecule was warranted to evaluate its potential as a cure for chronic HBV infection.

HBV infection is a major public health concern, with more than 1 million people dying each year as a result of this infection.[1] Modern antiviral treatments have significantly reduced the morbidity and mortality associated with chronic HBV infection, however, the rate of functional cure defined as HBsAg loss remains less than 10% and it is unclear if a sterilizing cure can be achieved.[2]

HBV is a partially double-stranded DNA virus.[3] After entry of the virus into human hepatocytes, a cccDNA is formed and maintained in the nuclei of infected cells, where it persists in a stable form and serves as a template for the transcription of all viral genes.[3] The persistence of cccDNA in the nuclei of infected hepatocytes is a major barrier to achieving sterilizing cure with existing therapies in chronic HBV infection, and new agents are needed to achieve cccDNA elimination from the liver.[4]

The discovery of an orally-available small molecule with the potential to eliminate cccDNA in the livers of HBV-infected individuals is welcome news. As Dr Lu Gao from the Roche Innovation Centre in Shanghai, China explained, the novel cccDNA destabilizer, ccc_R08, was first evaluated in human hepatocytes that had been infected with HBV. When first administered at two days after infection, ccc_R08 was able to significantly reduce levels of cccDNA without any significant effects on the mitochondrial DNA or significant signs of cellular toxicity.

In a follow-on experiment, ccc_R08 was administered orally twice daily for 2 weeks to mice who had been transduced with circular DNA to replicate HBV using a cccDNA-dependent mechanism similar to that observed in humans.[5] According to Dr Gao, serum levels of HBV DNA, pregenome RNA (pgRNA), hepatitis B surface antigen (HBsAg), and hepatitis B e antigen (HBeAg) were all significantly reduced during ccc_R08 treatment, with these reduced levels sustained in the post-treatment follow-up. By the end of follow-up, levels of HBV cccDNA-like molecule in the liver were below the lower limit of quantification in the treated animals. In contrast, in a control group of animals that received entecavir, no impact on cccDNA was observed.

“We were encouraged to see that this agent had the potential to reduce pre-existing cccDNA from the liver in this animal model of HBV replication, even to undetectable levels,” Dr Gao told the meeting.

“We think this type of molecule is well worth exploring further to evaluate its potential to cure chronic HBV infection in humans.”

Onsite location reference

Session title: 'Hepatitis B - drug development'
Time, date and location of session: 16:15–16:30, 12 April 2019, Hall C2
Presenter: Lu Gao, China
Abstract: A first-in-class orally available HBV cccDNA destabilizer ccc_R08 achieved sustainable HBsAg and HBV DNA suppression in the HBV circle mouse model through elimination of cccDNA-like molecules in the mouse liver (PS-074)

Author disclosures

Lu Gao is an employee of Roche R&D Center (China) Ltd.

References

1. Seto WK, et al. Chronic hepatitis B virus infection. Lancet. 2018;392(10161):2313–24.
2. Kwon H, Lok AS. Hepatitis B therapy. Nat Rev Gastroenterol Hepatol. 2011;8(5):275–84.
3. Levrero M, et al. Control of cccDNA function in hepatitis B virus infection. J Hepatol. 2009;51(3):581–92.
4. Yang HC, Kao JH. Persistence of hepatitis B virus covalently closed circular DNA in hepatocytes: molecular mechanisms and clinical significance. Emerg Microbes Infect. 2014;3(9):e64.
5. Yan Z, et al. HBVcircle: A novel tool to investigate hepatitis B virus covalently closed circular DNA. J Hepatol. 2017;66(6):1149–57.

EMBARGO: 00.01 Friday, 12 April, 2019

Faecal microbiota capsules effective and well tolerated in individuals with recurrent hepatic encephalopathy

ILC 2019: Oral faecal microbiota capsules reduce hospitalizations, improve duodenal microbial diversity, and enhance cognitive function when added to standard-of-care in individuals with cirrhosis and recurrent hepatic encephalopathy

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

12 April 2019, Vienna, Austria:
Faecal microbiota transplantation (FMT) performed using oral capsules is effective and well tolerated in individuals with cirrhosis and recurrent hepatic encephalopathy, according to the results of a study presented today at The International Liver Congress™ 2019 in Vienna, Austria. The study, which enrolled individuals already receiving standard-of-care treatment, found that oral FMT reduced hospitalizations, improved duodenal microbial diversity, and enhanced cognitive function.

Hepatic encephalopathy (HE) is a neurological syndrome that is a hallmark of liver failure[1] and affects up to 40% of individuals with liver cirrhosis.[2] Recurrent HE, which is defined as two or more episodes of HE over a period of 6 months,[2] leads to frequent hospitalizations[1] and to an increased risk of irreversible brain injury.[3] Standard-of-care for both episodic treatment and the prevention of recurrence is lactulose, with or without the antibiotic rifaximin.[2] These treatments and other antibiotics used during the management of cirrhosis can lead to changes in the gut microbial landscape (dysbiosis), triggering further episodes of HE and leading to a microbiota profile that has been linked to cognitive impairment and systemic inflammation.[3]

FMT using an enema formulation has been shown to reduce hospitalizations, improve cognition, and reduce dysbiosis in individuals with recurrent HE.[3] The study presented today evaluated the safety, tolerability, and health impact of a new capsule formulation for delivering FMT in a group of 20 individuals with cirrhosis and recurrent HE already receiving lactulose/rifaximin treatment.

This was a randomized, participant-blinded, placebo-controlled study. Individuals were randomized 1:1 to receive 15 FMT capsules (prepared from a single donor with enrichment with beneficial Lachnospiraceae and Ruminococcaceae bacteria) or placebo. Efficacy assessments included endoscopies with duodenal/sigmoid biopsies, stool analysis, and cognitive function assessments performed using the EncephalApp and psychometric hepatic encephalopathy score (PHES). Assessments were performed pretreatment and 2–4 weeks posttreatment, with a 5-month follow-up.

Six individuals in the placebo group required hospitalization/died compared with one in the FMT group (p=0.05). The number of hospitalizations was higher in the placebo (n=9) than in the FMT group (n=1; median 1.5 vs 0; p=0.02). At baseline, the microbial diversity in the stool, sigmoid and duodenal mucosa was similar between groups. Post-FMT, there was a significant increase in duodenal mucosal microbial diversity and relative abundance of Ruminococcaceae and Bifidobacteriaceae bacteria, with a decrease in Streptococcaceae and Veillonellaceae in FMT recipients. No changes in stool/sigmoid diversity was seen post-FMT but significant reductions in Veillonellaceae were observed post-FMT in the sigmoid mucosa and stool. Cognitive function, as assessed using EncephalApp scores, improved significantly in the FMT group vs the placebo group (p=0.02).

'Faecal microbiota transplant using a single stool donor enriched with bacterial species we know are deficient in this population is a promising approach to the potential treatment of patients with cirrhosis and recurrent HE,' said Dr Jasmohan Bajaj from Virginia Commonwealth University and the McGuire VA Medical Center in Richmond, USA. 'Larger studies are now needed to confirm these findings.'

‘Oral faecal microbiota capsules are an interesting innovation to modulate the gut microbiota in cirrhosis and could represent a novel treatment strategy to reduce the burden of recurrent hepatic encephalopathy’ said Annalisa Berzigotti, Associate Professor of Medicine at the University Clinic for Visceral Surgery and Medicine, University of Berne, Switzerland, and a member of the EASL governing board.

Onsite location reference

Session title: ‘Cirrhosis – Clinical aspects’
Time, date and location of session: 17:30–17:45, 12 April 2019, Hall C3
Presenter: Jasmohan Bajaj, USA
Abstract: Fecal microbiota capsules are safe and effective in patients with recurrent hepatic encephalopathy: A randomized, blinded, placebo-controlled trial (PS-087)

Author disclosures

This study was partly supported by NIH NCATS R21TR002024 and VA Merit Review CX001076 to Jasmohan Bajaj

References

1. Swaminathan M, et al. Hepatic encephalopathy: current challenges and future prospects. Hepat Med. 2018;10:1–11.
2. Vilstrup H, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice Guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology. 2014;60(2):715–35.
3. Bajaj JS, et al. Fecal microbiota transplant from a rational stool donor improves hepatic encephalopathy: A randomized clinical trial. Hepatology. 2017;66(6):1727–38.

EMBARGO: 00.01 Friday, 12 April, 2019

Glecaprevir/pibrentasvir (G/P) is effective and well tolerated in large 'real-world' studies in individuals with hepatitis C virus (HCV) infection

ILC 2019: German and US studies confirm the efficacy and safety of G/P in a broad range of individuals with HCV infection and other comorbidities, showing improvements in mental and physical well-being.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

12 April 2019, Vienna, Austria:
Two large 'real-world' studies conducted in Germany and the USA have confirmed the high rates of sustained virological response (SVR) observed in controlled clinical studies of glecaprevir/pibrentasvir (G/P) involving individuals with hepatitis C virus (HCV) infection. Across the two studies, which were presented today at The International Liver Congress™ 2019 in Vienna, Austria, a range of treatment-naïve and treatment-experienced individuals received G/P therapy, including those who are usually underrepresented in clinical trials such as patients receiving opioid substitution therapy, those with alcohol and/or active drug abuse, and those with psychiatric conditions and/or HIV coinfection.

Chronic infection with HCV remains a leading cause of morbidity and mortality, with an estimated 71 million individuals infected worldwide.[1,2] The availability of direct-acting antivirals (DAAs) has transformed the outlook for people with HCV infection, with recent drug development efforts focusing on simplifying treatment.[3] Glecaprevir/pibrentasvir (G/P) is a fixed-dose pan-genotypic DAA combination tablet that was approved in Europe in July 2017 for the treatment of adults with HCV infection.[3,4] In Phase 2 and 3 studies, G/P treatment led to an SVR in >95% of recipients, with no safety issues emerging.3 Real-world experience with the treatment is gradually expanding, and several post-authorization studies have recently been reported.[3,5,6]

The first study presented today involved an analysis of data from 1,698 adults with HCV genotype (GT) 1–6 infection who received G/P treatment and were included in the German Hepatitis C-Registry (DHC-R). Most individuals (84%) were treatment-naïve and free of cirrhosis, and therefore were treated for 8 weeks. In total, 439 individuals (26%) were receiving opioid substitution therapy (OST), 247 (15%) had a psychiatric disease, 106 (6%) had substantial alcohol abuse, and 47 (3%) were active drug abusers.

"These are all important comorbidities encountered in clinical practice that often have led to treatment being deferred in the past," explained Professor Markus Cornberg from Hannover Medical School in Germany, who presented the study findings.

In the intent-to-treat (ITT) population, the SVR rate at 12 weeks (SVR12) after the end of G/P treatment was 97% (964/998). Mental and physical component scores of the 36-Item Short Form Health Survey (SF-36) improved in key study subgroups, particularly in individuals with 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 a virological relapse.

"We found G/P treatment to be safe and highly effective, and to lead to significant improvements in reported physical and mental well-being, across this large, primarily treatment-naive cohort of HCV-infected individuals with typical comorbidies," said Professor Cornberg.

Similarly, positive results were also reported by a team of researchers in the USA, who analysed the data from 1,131 individuals who started G/P treatment between August 2017 and April 2018 and were included in the Trio Health disease management program.

Data were also analysed from 777 individuals who initiated treatment with sofosbuvir/velpatasvir (SOF/VEL) during the same period. In the ITT populations, the SVR12 rates were 93% (1,049/1,131) with G/P and 90% (701/777) with SOF/VEL; rates were higher (98% for both treatment regimens) in the per-protocol populations. Seventeen individuals (2%) completed G/P treatment and did not achieve SVR12. Factors found to be associated with virological failure with G/P were treatment experience (OR 0.14 [0.05–0.36]; p≤0.001), cirrhosis (OR 0.29 [0.11–0.80]; p=0.017), and viral load >6 MM in GT3 HCV (OR 0.14 [0.03–0.60]; p=0.008). Fifteen individuals (2%) completed SOF/VEL treatment and did not achieve SVR12. Patients that were treated with SOF/VEL plus RBV had a higher risk for virological failure (OR 0.16 [0.04–0.60]; p=0.007).

Onsite location reference

Session title: 'General session II'
Time, date and location of session: 08:30–08:45, 12 April 2019, Main Plenary
Presenter: Markus Cornberg, Germany
Abstract: Real-world safety, effectiveness, and patient-reported outcomes in patients with chronic hepatitis C virus infection treated with glecaprevir/pibrentasvir: Data from the German Hepatitis C-Registry (GS-07)
Session title: 'Viral hepatitis C: Therapy and resistance'
Time, date and location of session: 09:00–19:00, 11 April 2019, Poster Area
Presenter: Michael Curry, USA
Abstract: Clinical Practice experience with pan genotypic therapies glecaprevir-pibrentasvir and sofosbuvir-velpatasvir in the TRIO Network (THU-127)

Author disclosures

Markus Cornberg has participated in advisory committees/review panels for AbbVie, Biogen, BMS, Gilead, Janssen-Cilag, Merck Sharp & Dohme (MSD), Roche, and Spring Bank, and has carried out speaking/teaching engagements for AbbVie, BMS, Falk, Gilead, Janssen-Cilag, MSD, and Roche. He is on the data safety management board for Janssen-Cilag, and has received research support/grants from Roche.

References

1. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461–511.
2. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161–176.
3. D'Ambrosio R, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. J Hepatol. 2018 Nov 23. pii: S0168-8278(18)32543-1. doi: 10.1016/j.jhep.2018.11.011. [Epub ahead of print]
4. Lamb YN. Glecaprevir/pibrentasvir: first global approval. Drugs. 2017;77(16):1797–1804.
5. Berg T, et al. First real-world data on safety and effectiveness of glecaprevir/pibrentasvir for the treatment of patients with chronic hepatitis C virus infection: Data from the German Hepatitis C-Registry. J Hepatol. 2018;68;S37–S64. Abstract GS-007.
6. Reimer J, et al. Real-World data on safety and effectiveness of glecaprevir/pibrentasvir for the treatment of patients with chronic hepatitis C virus infection on opioid substitution therapy: latest results from the German Hepatitis C-Registry. Open Forum Infect Dis. 2018; 5(Suppl 1): S575.

EMBARGO: 00.01 Saturday, 13 April, 2019

Nivolumab and pembrolizumab display anti-tumour activity and adequate tolerance in 'real-world' studies in carcinoma

ILC 2019: 'Real-world' studies report the activity and safety profiles of nivolumab and pembrolizumab to be in line with those observed in hepatocellular carcinoma phase II clinical trials.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
'Real-world' studies conducted in Spain, Austria and Germany have reported activity and safety data for nivolumab and pembrolizumab in the treatment of hepatocellular carcinoma (HCC) that, according to the investigators, are in line with those observed in the phase II clinical trials. The studies reported today at The International Liver Congress™ 2019 in Vienna, Austria, found that these two immunotherapies were active and well tolerated even in heavily pretreated individuals and those with Child–Pugh class B (moderate) liver disease.

Hepatocellular carcinoma (HCC) is the most common primary liver cancer, with more than half a million people worldwide diagnosed with the condition each year.[1] Treatment options for early-stage HCC include ablative procedures, surgical resection, and liver transplantation and other options such as locoregional treatments and systemic therapies improve the overall survival of patients with intermediated or advanced HCC.[2] Immunotherapy with the checkpoint inhibitors, nivolumab and pembrolizumab, could represent a relatively new approach to the treatment of HCC.[3–6] Nivolumab and Pembrolizumab have a conditional approval in the USA for the second-line treatment of individuals with HCC who have previously received a tyrosine kinase inhibitor.[5] The details of the Phase 3 study of pembrolizumab in the second-line treatment of advanced HCC will be presened soon, but it was recently announced that the primary endpoints were not met.[7]

Results from 'real-world' studies with immune checkpoint inhibitors in the treatment of HCC have only recently begun to emerge, [8,9] and more data are needed.[2] In the first 'real-world' study presented today, the records of 42 individuals with HCC who received nivolumab outside clinical trials in Spain. In this cohort, almost all patients received nivolumb as second-line (n=20, 47.6%) or third-line (n=15, 35.7%).

Of the 20 individuals treated with nivolumab as a second-line therapy (60% Child-Pugh A; 40% Child-Pugh B), five had discontinued their first-line treatment (sorafenib) due to adverse events without radiological progression. In this cohort, the median follow-up since the start of first-line treatment was 13.5 months (interquartile range [IQR] 6.9–27.1) and overall survival (OS) was 28.8 months (95% CI 9.4–non-estimable), respectively. All except one of the 14 individuals treated with nivolumab in the third-line setting (85.7% Child-Pugh A) received nivolumab due to radiological progression. In this cohort, the median follow-up since the start of first-line treatment was 21.[3] months (IQR 15.6–24.4) and the OS was not calculated due to an insufficient follow-up and number of events

Fifteen (46.8%) individuals reported 25 AEs, of which five were Grade 3–4 and only one was Grade 5 (rejection after liver transplantation). Corticosteroids were required for the management of AEs in five individuals (15.6%).

"This study suggests that the safety profile of nivolumab when used in clinical practice is in line with that reported in clinical trials despite including patients outside of clinical trials," said Dr Leonardo Gomes da Fonseca from the BCLC group at the Hospital Clinic of Barcelona, Spain.

"The survival data must be interpreted bearing in mind that some patients had not progressed prior to receiving nivolumab and the overall patterns of progression were heterogeneous."

The second 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 first-, second-, third-, or fourth-line treatment in nine (14%), 27 (42%), 26 (40%), and three (5%) individuals, respectively.

Fifty-four individuals had at least one follow-up imaging report and were evaluable for radiological response.

The overall response and disease control rates reported in this study were 12% and 49%, respectively. Thirty-five (54%) individuals 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); median
progression-free survival was 4.6 months (95% CI 3.0, 6.2), and median OS 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). The
outcomes and safety results were comparable between Child-Pugh A and B patients; however, median overall survival was shorter in Child-Pugh B patients (16.7 vs 8.6 months; p=0.065).

“Immunotherapy with nivolumab or pembrolizumab was well tolerated in patients with advanced HCC, including those with Child-Pugh stage B disease and those who had been heavily pretreated,” said
Dr Matthias Pinter from the Medical University of Vienna, Austria. “Efficacy was comparable to that reported in Phase 2 studies.”

Onsite location reference

Session title: ‘Liver cancer – Systemic treatment and immunotherapy’
Time, date and location of session: 08:15–08:30, 13 April 2019, Hall C2
Presenter: Leonardo Gomes da Fonseca, Spain
Abstract: A multicentric study on real-life impact of nivolumab in patients with hepatocellular carcinoma (PS-137)

Session title: ‘Liver cancer – Systemic treatment and immunotherapy’
Time, date and location of session: 08:30–08:45, 13 April 2019, Hall C2
Presenter: Matthias Pinter, Austria
Abstract: PD-1 targeted immunotherapy in advanced hepatocellular carcinoma: Efficacy and safety data from an international multicenter real-world cohort (PS-138)

Author disclosures

Leonardo Gomes da Fonseca has received travel grant, lecture and consulting fees from Bayer and travel grants from Ipsen.Matthias Pinter served as consultant for Bayer, BMS, Eisai, Ipsen, and Lilly, and received travel support from Bayer, and speaking fees from Bayer, BMS, and MSD. He is also an investigator for Bayer, BMS, and Lilly.¬

References

1. IARC. Population fact sheets. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Accessed: March 2019
2. Forner A, et al. Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–14.
3. Iñarrairaegui M, et al. Clin Cancer Res. 2018;24(7):1518–24.
4. El-Khoueiry AB, et al Lancet. 2017;389(10088):2492–502.
5. Finkelmeier F, et al. Nivolumab for the
6. treatment of hepatocellular carcinoma. Expert Rev Anticancer Ther. 2018;18(12):1169–75.
7. Mody K, Abou-Alfa GK. Systemic therapy for advanced hepatocellular carcinoma in an evolving landscape. Curr Treat Options Oncol. 2019;20(2):3.
8. Merck Newsroom. Merck Provides Update on KEYNOTE-240, a Phase 3 Study of KEYTRUDA® (pembrolizumab) in Previously Treated Patients with Advanced Hepatocellular Carcinoma [Press release]. 2019. Available at: HERE
9. Finkelmeier F, et al. Feasibility and safety of nivolumab in advanced hepatocellular carcinoma: real-life experience from three German centers. J Cancer Res Clin Oncol. 2019;145(1):253–9.
10. Yoon SE, et al. Real-world data on nivolumab treatment in Asian patients with advanced hepatocellular carcinoma. Ann Oncol. 2018;29(Suppl 8):viii205–70.

EMBARGO: 00.01 Saturday, 13 April, 2019

Integration of hepatitis B virus into the human genome is a common occurrence in HBeAg-negative chronic infection

ILC 2019: Latest study suggests that 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 chronic infection, a group of patients who are not considered treatment candidates.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
A collaboration between scientists in Italy and the UK has yielded new evidence that integration of hepatitis B virus (HBV) DNA into the human genome is not restricted to the early phases of chronic HBV infection, but also occurs in individuals with hepatitis B e antigen (HBeAg)-negative infection, including those with low levels of HBV DNA who may not currently meet treatment criteria and are also defined as inactive carriers. This, say the investigators, could have important implications for the management of chronic HBV infection in the future.

Chronic HBV infection is a global threat to public health, and is associated with substantial liver-related morbidity and mortality.[1] HBV infects and replicates in hepatocytes, where the viral DNA becomes integrated into the host cell genome, with onward transmission to progeny cells.[1] The natural history of chronic HBV infection is divided into five phases: HBeAg-positive chronic infection, HBeAg-positive chronic hepatitis B, HBeAg-negative chronic HBV infection, HBeAg-negative chronic hepatitis B, and HBsAg-negative phase.[2] Integration of HBV DNA has been shown to occur early in the course of HBV infection,[3] producing a range of molecular changes that are thought to drive the development of hepatocellular carcinoma.[4] Until now, however, little has been known about integration events in later phases of infection or in those considered to have quiescent disease.

To investigate this further, researchers from Italy and the UK studied samples of liver tissue from 40 HBeAg-negative individuals, whom they grouped according to their levels of viraemia: Group 1 had HBV DNA <2,000 IU/ml (n=8), Group 2 had HBV DNA 2,000–20,000 IU/ml (n=14), and Group 3 had HBV DNA >20,000 IU/ml (n=18). Integration events were analysed using next-generation sequencing technology.

According to Dr Romina Salpini from the University of Rome, Italy, who presented the study results today at The International Liver Congress™ 2019 in Vienna, Austria, integration events were detected in all three groups, with an overall prevalence of 35.4%: 25% in Group 1, 14.3% in Group 2, and 55.6% in Group 3. Among the 17 recognised integration events, 11 involved the region encoding HBx protein, which regulates the transcription and regulation of HBV,5 three involved the HBs antigen/polymerase(pol)-encoding region, and three involved the HBV core-encoding region.

“We found that eleven out of 17 HBV integration events occurred preferentially within introns critical for RNA splicing and mRNA production,” said Dr Salpini. “In six individuals, HBV integration localised in human genes regulating cell proliferation, and we know some of these genes are involved in hepatocarcinogenesis. We also found integration in genes that regulate lipid metabolism”, she noted.

What this study has demonstrated is that HBV integration occurs across all types of patients with HBeAg-negative disease, including those with a low level of HBV DNA (<2,000 IU/ml). The localization of the HBV integration also suggests that these events are not restricted to carcinogenesis and may also be involved in mechanisms regulating hepatocyte metabolism and antiviral immunity.

"Our findings underline the complexity of chronic hepatitis B and the evidence of HBV integration in low viraemic patients, who do not meet treatment criteria, is a timely reminder that these patients are also at risk of disease progression and the development of HCC," added Dr Salpini. "We believe these findings will have implications for the HBV cure program".

Onsite location reference

Session title: 'General session 3'
Time, date and location of session: 11:30–11:45, 13 April 2019, Main plenary
Presenter: Romina Salpini, Italy
Abstract: The integration of hepatitis B virus into human genome is a common event in the setting of HBeAg negative disease: Implications for the treatment and management of CHB (GS-17)

Author disclosures

Romina Salpini has no relevant disclosures.

References

1. Seto WK, et al. Chronic hepatitis B virus infection. Lancet. 2018;392(10161):2313–24.
2. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–98.
3. Mason WS, et al. HBV DNA integration and clonal hepatocyte expansion in chronic hepatitis B patients considered immune tolerant. Gastroenterology. 2016;151(5):986-998.e4.
4. Budzinska MA, et al. Sequence analysis of integrated hepatitis B virus DNA during HBeAg-seroconversion. Emerg Microbes Infect. 2018;7(1):142.
5. Gong DY, et al. Role and functional domain of hepatitis B virus X protein in regulating HBV transcription and replication in vitro and in vivo. Viruses. 2013;5:1261–1271.

EMBARGO: 00.01 Saturday, 13 April, 2019

Bulevirtide shows promise in the treatment of chronic hepatitis B/D (HBV/HDV) coinfection

ILC 2019: First-in-class entry inhibitor bulevirtide (Myrcludex B) effective and well tolerated in combination with PEG-IFN- in Phase 2b study involving individuals with chronic hepatitis B/D virus coinfection, producing high rates of viral suppression both on and off treatment with good tolerability.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
A first-in-class treatment for chronic hepatitis B/D virus (HBV/HDV) coinfection has shown early promise, as the final results of a Phase 2b trial confirms high rates of viral suppression both on and off treatment, and good tolerability. When used in combination with peg-interferon-α 2a (PEG-IFN-α), above 50% of study participants who received bulevirtide (Myrcludex B) had undetectable HDV RNA after 48 weeks of treatment, which was sustained off-treatment in the majority of individuals. Undetectable levels of hepatitis B surface antigen (HBsAg) in some participants receiving the combination treatment also suggests a future role for bulevirtide in regimens targeted towards HBV cure.

HDV infection was first reported in humans in 1977, and is now thought to affect 15–20 million people in all age groups worldwide.1 HDV infection can be an acute or chronic disease, but only occurs in people coinfected with HBV.1 Chronic HDV infection is the most severe form of viral hepatitis infection and is often associated with the rapid development of cirrhosis and an increased risk of hepatocellular carcinoma.[1] Treatment options are currently very limited.[2]

Bulevirtide is a first-in-class agent that inhibits the entry of HDV into hepatocytes by blocking its binding to the sodium taurocholate cotransporting polypeptide (NTCP), thereby depriving HDV of key functions provided by HBV.[2,3] In the Phase 2b trial presented today at The International Liver Congress™ 2019 in Vienna, Austria, 60 patients with chronic HBV/HDV coinfection were randomized 1:1:1:1 into four treatment groups: PEG-IFN-α 180 µg once weekly (qw) by subcutaneous (sc) injection (n=15), bulevirtide 2 mg once daily (qd) by sc injection + sc PEG-IFN-α qw (n=15), sc bulevirtide 5 mg qd + sc PEG-IFN-α qw (n=15) or sc bulevirtide 2 mg qd (n=15) – with all treatments administered for 48 weeks. The primary endpoint of the trial was undetectable serum HDV RNA at 72 weeks (i.e. 24 weeks after treatment completion).

As Professor Heiner Wedemeyer from the Essen University Hospital in Germany explained, over 48 weeks, PEG-IFN-α monotherapy resulted in a median HDV RNA log reduction of –1.30 and a normalization of alanine aminotransferase (ALT) levels in 4/15 patients (27%). The combination of bulevirtide and PEG-IFN-α resulted in a median HDV RNA log reduction of between –4.81 and –5.59 and a normalization of ALT levels in 11/30 patients (37%). Monotherapy with bulevirtide resulted in a median HDV RNA log reduction of –2.84 and a normalization of ALT levels in 10/15 patients (67%). HDV RNA was undetectable in 2/15 (13%) of patients who received PEG-IFN-α, 2/15 patients (13%) who received bulevirtide monotherapy, and 15/30 patients (50%) who received combination treatment.

At week 72, PEG-IFN-α monotherapy was associated with a median HDV RNA log reduction of –0.26 and a normalization of ALT levels in 1/15 patients (7%). The combination of bulevirtide and PEG-IFN-α was associated with a median HDV RNA log reduction of between –1.48 and –4.04 and a normalization of ALT levels in 12/30 patients (40%), while monotherapy with bulevirtide was associated with a median HDV RNA log reduction of –1.08 and a normalization of ALT levels in 3/15 patients (20%). HDV RNA was undetectable in 12/30 patients (40%), who received combination treatment. Remarkably, 4/15 patients (27%) treated with 2mg bulevirtide + PEG-IFN-α had undetectable HBsAg levels and 3/4 patients experienced HBsAg seroconversion.

Bulevirtide was well tolerated, with 155 drug-related adverse events (AEs) reported (mainly asymptomatic increase in total bile salts) by week 72. Most AEs (n=122) were mild in intensity and all resolved without sequelae. No serious bulevirtide-related AEs were reported.

“The results of this trial suggest that bulevirtide is a promising treatment for chronic HDV infection, and that the combination of bulevirtide and PEG-IFN-α has the potential to cure HBV/HDV coinfection in some patients,” said Prof. Wedemeyer.

Onsite location reference

Session title: General Session III and award ceremony II
Time, date and location of session: 10:00 – 12:00, 13/04/2019, Main Plenary
Presenter: Heiner Wedemeyer, Germany
Abstract: Final results of a multicenter, open-label phase 2 clinical trial (MYR203) to assess safety and efficacy of bulevirtide (Myrcludex B) in with PEG-interferon Alpha 2a in patients with chronic HBV/HDV co-infection (GS-13)

Author disclosures

Heiner Wedemeyer has received honoraria for consulting or speaking and/or research grants (last 5 years) from Abbott, AbbVie, BMS, Boehringer Ingelheim, Eiger, Gilead, JJ/Janssen-Cilag, Merck/Schering-Plough, Myr GmbH, Novartis, Roche,
Roche Diagnostics, and Siemens

References

1. Koh C, et al. Pathogenesis of and new therapies for hepatitis D. Gastroenterology. 2019;156(2):461–76.e1.
2. Rizzetto M. Targeting hepatitis D. Semin Liver Dis. 2018;38(1):66–72.
3. Bogomolov P, et al. Treatment of chronic hepatitis D with the entry inhibitor myrcludex B: First results of a phase Ib/IIa study. J Hepatol. 2016;65(3):490–8.

EMBARGO: 00.01 Saturday, 13 April, 2019

SMART-C study suggests simplified monitoring of direct-acting antiviral treatment in hepatitis C is possible

ILC 2019: Randomized controlled study reports favourable virological outcomes with simplified monitoring of glecaprevir/pibrentasvir treatment in chronic hepatitis C infection.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
A randomized controlled study (SMART-C) designed to determine whether treatment monitoring can be simplified in individuals with chronic hepatitis C infection receiving glecaprevir/pibrentasvir (GLE/PIB)1 has reported favourable efficacy and safety outcomes. The study reported today at The International Liver Congress™ 2019 in Vienna, Austria found similar virological and safety outcomes between individuals monitored using a standard protocol and those seen only at 12 weeks after the end of treatment. This, say the investigators, could enhance HCV treatment scale-up, helping to achieve global elimination targets.

Current standard on-treatment monitoring in clinical trials involves clinic-based visits every 4 weeks.[1] However, in the modern era of direct-acting antivirals (DAAs), where treatments are easy to use, well tolerated, effective, and of a short duration, such intensive monitoring may no longer be necessary.[1] The DAA, glecaprevir/pibrentasvir is a suitable candidate for simplified monitoring as it has pangenotypic activity with good efficacy and tolerability, and is dosed once daily for a short duration of treatment (8 or 12 weeks for most).[1,2]

The hypothesis being tested in the study reported today was that a simplified on-treatment monitoring strategy would be non-inferior to the standard on-treatment strategy.[1] To test the hypothesis, treatment-naïve adults with chronic HCV infection without cirrhosis were randomized to receive treatment with GLE/PIB (300/120 mg) once-daily for 8 weeks and to be monitored using either a standard or simplified strategy. In the standard strategy group, participants attended study centre visits at baseline, weeks 4 and 8, and post-treatment week 12. With the simplified strategy, participants attended only at baseline and post-treatment week 12, with study nurse telephone contact made at weeks 4 and 8. Individuals thought to need extra adherence support, including those with recent injection drug use, were not eligible to participate. The primary endpoint was SVR at 12 weeks post-treatment (SVR12), with a non-inferiority margin for difference of 6%.

A total of 380 individuals were randomized (2:1) and treated with GLE/PIB in the simplified monitoring (n=253) and standard monitoring (n=127) arms. Overall, 60% of participants were male, 48% were genotype (GT) 1, 32% were GT3, 7% were HIV positive, and 10% were on opiate agonist therapy. In an intention-to-treat analysis, SVR12 was 92% (95% confidence interval [CI] 89%, 95%) in the simplified arm and 95% (95% CI 92%, 99%) in the standard arm. The difference between the arms was –3.2% (95% CI -8.2%, 1.8%), which was not statistically significant (p=0.25), but non-inferiority was not quite achieved as the lower bound of 95% CI (-8.2%) was greater than -6% margin. In the per-protocol population, SVR12 was 97% (95% CI 96%, 99%) in the simplified arm and 98% (95% CI, 96%, 100%) in the standard arm.

Only one participant (simplified monitoring group) discontinued due to an adverse event (AE); no treatment-emergent serious AEs were reported.

“This study has indicated that a simplified monitoring strategy for ’easy-to-manage’ individuals initiated on GLE/PIB is feasible and associated with similar virological outcomes to those of individuals monitored more intensively,” said Principal Investigator, Professor Gregory Dore, from the University of New South Wales in Sydney, Australia.

"Simplified monitoring of new-generation DAAs such as GLE/PIB could enhance the rapid scale-up of treatment, which will help to achieve the WHO's goal of eliminating chronic HCV infection as a major public health threat by 2030".[3,4]

Onsite location reference

Session title: 'Hepatitis C - Treatment and resistance'
Time, date and location of session: 08:00–08:15, 13 April 2019, Main plenary
Presenter: Gregory Dore, Australia
Abstract: Simplified monitoring for hepatitis C virus treatment with glecaprevir plus pibrentasvir: the SMART-C study (PS-178)

Author disclosures

Gregory Dore has received research grants, travel support and fees for speakers bureau and advisory boards from AbbVie, Gilead Sciences, and Merck.

References

1. U.S. National Library of Medicine. Trial of simplified treatment monitoring for 8 weeks glecaprevir/pibrentasvir in chronic hepatitis C patients (SMART-C). Available from: https://clinicaltrials.gov/ct2/show/NCT03117569. Last accessed: March 2019.
2. Mensa FJ, et al. Glecaprevir/pibrentasvir for the treatment of chronic hepatitis C virus infection. Future Microbiol. 2019;14:89–110.
3. World Health Organization. Global health sectors strategy on viral hepatitis 2016–2021: towards ending viral hepatitis (2016). Available from: https://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/. Last accessed: March 2019.
4. Dore GJ, Feld JJ. Hepatitis C virus therapeutic development: in pursuit of "perfectovir". Clin Infect Dis. 2015;60(12):1829–36.

EMBARGO: 00.01 Saturday, 13 April, 2019

Tenofovir associated with a lower risk of hepatocellular carcinoma than entecavir in large hepatitis B study

ILC 2019: Study involving >29,000 individuals with chronic hepatitis B virus infection reports that the risk of hepatocellular carcinoma is at least one-third lower in those treated with tenofovir than in those treated with entecavir.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
A large observational study involving more than 29,000 adults with chronic hepatitis B virus (HBV) infection has reported that the antiviral, tenofovir (TDF), is associated with at least a one-third lower risk of hepatocellular carcinoma (HCC) than entecavir (ETV). The study reported today at The International Liver Congress™ 2019 in Vienna, Austria, confirms previous findings from a Korean research group,[1] suggesting possible advantages of TDF over ETV in terms of HCC prevention.[2]

Hepatitis B virus infection is a common chronic viral infection, with approximately 290 million people estimated to have been infected with HBV globally.[3] Chronic HBV infection leads to liver inflammation, fibrosis and cirrhosis, which may progress to decompensated liver disease and/or the development of HCC.[4] The nucleot(s)ide analogues, TDF and ETV, are the recommended first-line treatments for chronic HBV infection, however, no preferences for either agent are stated in any current guidelines.[5–7]

In the absence of randomized head-to-head comparator trials, high-quality 'real-world' studies are considered to be informative, and, after the Korean study suggested that the risk of HCC was lower in those treated with TDF than in those treated with ETV,1 investigators were urged to explore this issue further.[2]

In the study reported today, 29,123 adults with chronic HBV infection who initially received ETV or TDF for at least 6 months during 2008 to 2018 were identified using inpatient and outpatient databases from all public hospitals and clinics across the Hong Kong territory. Individuals who had cancers or liver transplant before or within the first 6 months of treatment were excluded. The mean age of the study population was 53.7±13.3 years; 18,492 (63.5%) were male; 1,227 (4.2%) initially received TDF, and 27,896 (95.8%) initially received ETV.

With a median (interquartile range [IQR]) follow-up of 3.3 (IQR 1.6–5.0) years, nine (0.7%) TDF-treated individuals and 1,468 (5.3%) ETV-treated individuals developed HCC. The 5-year cumulative incidences (95% confidence interval [95% CI]) of HCC in ETV- and TDF-treated cohorts were 7.5% (95% CI 7.1–7.9%) and 1.3% (95% CI 0.6–2.6%), respectively.

Tenofovir was associated with a lower risk of HCC than ETV before multiple imputation was used to replace missing data (adjusted hazard ratio [aHR] 0.46, 95% CI 0.23–0.91, p=0.027), after multiple imputation with propensity score weighting was used to balance baseline clinical characteristics (weighted HR 0.40, 95% CI 0.18–0.86, p=0.019), and after multiple imputation without propensity score weighting was used (aHR 0.34, 95% CI 0.18–0.66, p=0.001).

"Tenofovir was associated with a significantly lower risk of HCC than entecavir in this large population of adults with chronic HBV infection," said Dr Terry Yip from The Chinese University of Hong Kong, China, who presented the study findings in Vienna. "Although we recognize the inherent limitations of observational data, our findings are consistent with those of the Korean group."

Onsite location reference

Session title: 'Late breaker'
Time, date and location of session: 16:30–16:45, 13 April 2019, Main plenary
Presenter: Terry CF Yip, China
Abstract: Tenofovir treatment has lower risk of hepatocellular carcinoma than entecavir treatment in patients with chronic hepatitis B (LB-03)

Author disclosures

This study is supported by research funding from Gilead Sciences, Inc. (Grant no.: IN-US-988-5290).

References

1. Choi J et al. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. JAMA Oncol. 2019;5(1):30–6.
2. Flemming JA, Terrault NA. Tenofovir vs entecavir for hepatocellular carcinoma prevention in patients with chronic hepatitis B: one of these things is not like the other. JAMA Oncol. 2019;5(1):17–8.
3. Polaris Observatory Collaborators. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. Lancet Gastroenterol Hepatol. 2018;3(6):383–403.
4. Yuen MF, et al. Hepatitis B virus infection. Nat Rev Dis Primers. 2018;4:18035.
5. Terrault NA, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–99.
6. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol. 2017;67(2):370–89.
7. Sarin SK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1–98.

EMBARGO: 00.01 Saturday, 13 April, 2019

'Real-world' effectiveness of elbasvir/grazoprevir confirmed in people with hepatitis C virus infection who inject drugs and/or receive opioid substitution therapy

ILC 2019: 'Real-world' studies confirm the effectiveness of elbasvir/grazoprevir in people with hepatitis C (HCV) genotype 1 infection who inject and/or abuse drugs or who receive opioid substitution therapy.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
Two 'real-world' studies have today confirmed the effectiveness of elbasvir/grazoprevir (EBV/GZR) in the treatment of people with hepatitis C (HCV) genotype (GT) 1 infection who inject or abuse drugs and/or who receive opioid substitution therapy (OST). Investigators in Germany and the USA have reported high sustained virological response rates in these difficult-to-treat populations in whom there has previously been reluctance to use direct-acting antiviral drugs (DAAs).[1]

People who inject drugs (PWID) are at high risk of infection with HCV, with an estimated global HCV prevalence of at least 60–80% in this population.[2] Some people with a history of injecting drugs receive OST for the management of opioid dependence,[3] and this approach has been shown to reduce HCV acquisition by 50%.[4] In clinical studies, DAAs have been effective and well tolerated in individuals receiving OST5 and those with recent injection drug use.6 EBR/GZR was approved in Europe in July 2016,7 with a controlled clinical trial in adults with chronic HCV infection receiving OST reporting a sustained virological response at 12 weeks (SVR12) of 91.5%.5 Currently, little is known about the effectiveness of EBR/GZR in PWID and/or those receiving OST in everyday practice.

In the first study reported today, German researchers analysed the German Hepatitis C Registry (DHC-R) records of 992 individuals with HCV GT1 infection who were treated with EBR/GZR ± ribavirin (RBV) for 12–16 weeks.

Of 613 individuals who completed 12 or 24 weeks of follow-up or discontinued treatment early (intent-to-treat [ITT] population), 499 had no former drug use, 67 were PWID on OST, and 47 were former/current drug users not receiving OST. SVR rates were 96.2% (480/499), 89.6% (60/67), and 93.6% (44/47), respectively. In the per-protocol population, SVR rates were 98.6% (484/491), 98.4% (61/62), and 95.7% (44/46), respectively. A significant between-group difference was only observed in the ITT analysis of SVR for the individuals with no former drug use versus those receiving OST.

"In the past, there has been controversy over the use of DAAs to treat HCV infection in PWID1," said Dr Stefan Christensen from the Centre for Interdisciplinary Medicine in Muenster, Germany. "Our findings suggest that any reservations about initiating DAAs in this population is unwarranted, and high rates of SVR can be achieved in clinical practice."

In a second study involving a US Department of Veterans Affairs cohort, 611 individuals with chronic HCV GT1 infection who had received EBR/GZR for >11 weeks and who had either a diagnosis of opioid use disorder or been prescribed medication for opioid dependence were identified. Most individuals (90%) were treatment naïve prior to receiving EBR/GZR and most had chronic kidney disease stage 4–5 (86%). Almost 60% of the cohort had received at least one prescription for an opioid dependence therapy (59%), 90% had a history of drug abuse, and 71% were receiving concomitant psychiatric medication. Most individuals (526/611; 86%) had received EBR/GZR without RBV for 12 weeks; the remaining 85 (14%) had received other EBR/GZR-based regimens.

According to Dr Amy Puenpatom from MSD, a subsidiary of Merck & Co. Inc. Kenilworth, NJ, USA, who presented the study findings on behalf of the investigators (Dr Kramer, Dr Kanwal

and Dr El-Serag), SVR was achieved by 96% (586/611) of individuals. High rates of SVR (94–98%) were achieved across all subgroups analysed, including those with a high baseline viral load (≥800,000 IU/mL), cirrhosis, a history of alcohol or drug abuse, or opioid agonist therapy.

”We are pleased to be presenting these new data at the EASL congress, and look forward to continuing our work to help reduce the global burden of chronic hepatitis C,” said Dr Puenpatom

Onsite location reference

Session title: ‘Viral hepatitis C: Therapy and resistance’
Time, date and location of session: 09:00–19:00, 11 April 2019, Poster Area
Presenter: Stefan Christensen, Germany
Abstract: High real-world effectiveness of elbasvir/grazoprevir in PWID on opioid substitution therapy with HCV genotype 1 infection: Results from the German hepatitis C registry (DHC-R) (THU-125)
Session title: ‘Hepatitis C - Treatment and resistance’
Time, date and location of session: 09:00–09:15, 13 April 2019, Main Plenary
Presenter: Amy Puenpatom, USA
Abstract: Effectiveness of elbasvir/grazoprevir in patients with hepatitis C virus genotype 1 infection who receive opioid agonist therapy: Treatment utilization and the impact of concomitant psychiatric medications (PS-182)

Author disclosures

Stefan Christensen has received honoraria for consulting or speaking at educational events from Abbvie, Gilead, Indivior, Janssen-Cilag, MSD, and ViiV.

The German Hepatitis C-Registry (Deutsches Hepatitis C-Register, DHC-R) is a project of the German Liver Foundation (Deutsche Leberstiftung), managed by Leberstiftungs-GmbH Deutschland in cooperation with the Association of German gastroenterologists in private practice (bng) with financial support from the German Center for Infection Research (DZIF) and the companies AbbVie Deutschland GmbH & Co. KG, Bristol-Myers Squibb GmbH & Co. KGaA, Gilead Sciences GmbH, Janssen-Cilag GmbH, MSD Sharp & Dohme GmbH as well as Roche Pharma AG (financial support until 2017-07-14).

Amy Puenpatom is a director at the Center for Observational and Real-World Evidence, Merck Sharp & Dohme Corp., a subsidiary of Merck & Co Inc, Kenilworth, NJ, USA. Funding for this research was provided by Merck & Co Inc, Kenilworth, NJ USA.

References

1. Asher AK, et al. Clinicians’ Views of Hepatitis C Virus Treatment Candidacy With Direct-Acting Antiviral Regimens for People Who Inject Drugs. Subst Use Misuse. 2016;51(9):1218–23.
2. Nelson PK, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571–83.
3. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2018. J Hepatol. 2018;69(2):461–511.
4. Platt L, Minozzi S, Reed J, Vickerman P, Hagan H, French C, et al. Needle syringe programmes and opioid substitution therapy for preventing hepatitis C transmission in people who inject drugs. Cochrane Database Syst Rev 2017;9:CD012021.
5. Dore GJ, et al. Elbasvir-grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: a randomized trial. Ann Intern Med. 2016;165(9):625–34.
6. Grebely J, et al. Sofosbuvir and velpatasvir for hepatitis C virus infection in people with recent injection drug use (SIMPLIFY): an open-label, single-arm, phase 4, multicentre trial. Lancet Gastroenterol Hepatol. 2018;3(3):153–61.
7. ZEPATIER 50 mg/100 mg film-coated tablets. Summary of Product Characteristics. Merck Sharp & Dohme B.V. June 2018.

EMBARGO: 00.01 Saturday, 13 April, 2019

Burden of alcohol-related liver disease on the increase in Canada: are alcohol harm reduction strategies failing?

ILC 2019: Population-based study finds 'critical increase' in the burden of cirrhosis due to alcohol-related liver disease in Canada, with rising prevalence rates, high rates of late diagnosis, and poor overall survival.

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
Investigators from a large population-based study in Canada have today reported 'critical increases' in the burden of cirrhosis following alcohol-related liver disease, with significant recent rises in the prevalence of the condition, high rates of late diagnosis, and poor overall survival. The study, which was presented at The International Liver Congress™ 2019 in Vienna, Austria, found that middle-aged men appear to be bearing the brunt of that burden.

Liver disease accounts for approximately 2 million deaths annually worldwide, with 1 million deaths due to complications of cirrhosis.[1] Approximately 50% of all cirrhosis-related deaths can be attributed to alcohol,[2] with higher rates of cirrhosis linked to higher rates of alcohol consumption.[3] Over the last two decades, efforts have intensified to increase awareness of the risks associated with heavy drinking and improve access to care for individuals with cirrhosis due to alcohol-related liver disease in Canada4 and many other countries.[5] However, the impact of these efforts on the natural history of alcohol-related cirrhosis have not been fully evaluated.

To shed more light on the effectiveness of national alcohol harm reduction strategies, researchers from the University of Calgary in Canada undertook a study to evaluate changes in the epidemiology of cirrhosis due to alcohol-related liver disease in the Canadian province of Alberta, which has a population of approximately 4.3 million. A number of population-based databases were interrogated to identify all individuals with cirrhosis due to alcohol-related liver disease between 2013 and 2017.

The overall annual age/sex-adjusted incidence of cirrhosis due to alcohol-related liver disease was found to be 38.9 cases/100,000 for women and 55.6 cases/100,000 for men; the highest incidence rate was observed among men aged 40–59 years (97.4/100,000). While incidence rates remained stable across the study period, prevalence rates increased significantly from 107.7 to 158.2 cases/100,000 between 2013 and 2017 ($p<0.01$). The prevalence rate was highest among men aged 60–79 years (309.5 cases/100,000). Survival rates at 1, 3, and 5 years were 66.9%, 60.7%, and 55.1%, respectively, with more than 70% of newly-diagnosed individuals presenting with decompensated cirrhosis at the time of diagnosis.

"This study highlights a critical increase in the prevalence and burden of cirrhosis due to alcohol-related liver disease in this representative Canadian population," said Dr Hassan Azhari from the University of Calgary in Canada, who presented the study findings today. "The risk of developing cirrhosis due to alcohol-related liver disease was highest among middle-aged men, and survival rates were poor across the entire cohort, primarily because of the late diagnosis. We need to develop more effective preventative strategies and better surveillance practices to detect individuals with alcohol-related liver disease earlier."

"Indeed, EASL recommends the implementation of population-level strategies such as raising prices on alcohol through excise taxes and pricing policies," said Professor Helena Cortez-Pinto from the Hospital Universitário de Santa Maria, Lisbon, Portugal, and an EASL Governing Board member. "Canada has been making efforts in this direction, although it may not be enough. There is also a need for screening for liver disease among patients with alcohol-related problems, in order to diagnose the disease before cirrhosis is present."

"Indeed, EASL recommends the implementation of population-level strategies such as raising prices on alcohol through excise taxes and pricing policies," said Professor Helena Cortez-Pinto from the Hospital Universitário de Santa Maria, Lisbon, Portugal, and an EASL Governing Board member. "Canada has been making efforts in this direction, although it may not be enough. There is also a need for screening for liver disease among patients with alcohol-related problems, in order to diagnose the disease before cirrhosis is present."

Onsite location reference

Session title: 'Alcohol related liver disease'
Time, date and location of session: 09:00–09:15, 13 April 2019, Lehar 4
Presenter: Hassan Azhari, Canada
Abstracts: The burden of alcoholic cirrhosis is critically increasing in Canada: A population-based study (PS-175)

Author disclosures

Hassan Azhari has no relevant disclosures.

References

1. Asrani SK, et al. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151–71.
2. Stein E, et al. Heavy daily alcohol intake at the population level predicts the weight of alcohol in cirrhosis burden worldwide. J Hepatol. 2016;65(5):998–1005.
3. Rehm J, et al. Global burden of alcoholic liver diseases. J Hepatol. 2013;59(1):160–8.
4. Canadian Centre on Substance Abuse. Reducing Alcohol-Related Harm in Canada: Toward a Culture of Moderation. Recommendations for a National Alcohol Strategy. April 2007. Available from: http://www.ccdus.ca/Eng/topics/alcohol/Pages/default.aspx. Last accessed: February 2019.
5. World Health Organization. Global status report on alcohol and health 2018. Available from: https://apps.who.int/iris/bitstream/handle/10665/274603/9789241565639-eng.pdf. Last accessed: February 2019.

EMBARGO: 00.01 Saturday, 13 April, 2019

Emricasan fails to meet primary endpoint in ENCORE-PH study but shows potential benefits in high-risk individuals

ILC 2019: ENCORE-PH study of emricasan in nonalcoholic steatohepatitis (NASH)-related cirrhosis and severe portal hypertension (PH) fails to meet primary endpoint, but benefits reported in individuals at high risk of decompensation

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
The ENCORE-PH study of emricasan in the treatment of nonalcoholic steatohepatitis (NASH)-related cirrhosis with severe portal hypertension (PH), has failed to meet its primary endpoint, but meaningful reductions in portal pressure were observed in a subgroup of individuals with high-risk disease. The first results of the Phase 2b study, which were presented today at The International Liver Congress™ 2019 in Vienna, Austria, demonstrated that, although emricasan did not reduce the hepatic venous pressure gradient (HVPG) across the entire cohort of study participants, meaningful reductions were reported in those with compensated cirrhosis and a high baseline HVPG of ≥16 mmHg.

Portal hypertension is a frequent complication of liver cirrhosis and is characterized by an increased pressure gradient between the portal vein and the hepatic vein – the so-called portal pressure gradient or HVPG.[1] An HVPG >10 mmHg defines clinically-significant PH and, in those with cirrhosis, predicts the development of decompensated disease and severe clinical complications.[1] An HVPG >12 mmHg is defined as severe PH,[1] with pressures >16 mmHg associated with a very high risk of major clinical events and death.[2,3] Studies have demonstrated that if portal pressure of high-risk patients can be reduced sufficiently (e.g. by ≥20%), the risk of development or progression of decompensation and death can be greatly reduced in individuals with PH.[4]

Emricasan is an oral pan-caspase inhibitor that ameliorated portal hypertension and improved survival in animal models of cirrhosis[5–8] and reduced HVPG among individuals with compensated cirrhosis and severe PH in a previously-reported open-label study.[7] The aim of the ENCORE-PH study reported today was to confirm the results reported in this open-label study.

The randomized, double-blind, placebo-controlled ENCORE-PH study enrolled 263 subjects with NASH cirrhosis and a baseline HVPG ≥12 mmHg (severe PH). All subjects were randomized to receive oral emricasan 5 mg, 25 mg, 50 mg or placebo twice-daily (bid) for 48 weeks. Most study participants (201/263, 76%) had compensated cirrhosis at the time of enrollment, while a smaller proportion (62/263, 24%) had early decompensated disease. The primary endpoint of the study was the mean change in HVPG from baseline to Week 24 across the entire study cohort.

'In the overall primary endpoint analysis, which included patients with compensated and early decompensated cirrhosis, although reductions in HVPG were seen in all emricasan treatment groups, the differences compared with placebo were not statistically significant', said investigator, Professor Guadalupe Garcia-Tsao from Yale University in Connecticut, USA. Relative reductions of 3 to 5 U/L in ALT and 2 to 6 U/L in AST were also observed in the emricasan treatment groups compared with placebo ($p<0.05$ in all but one group).

A post hoc analysis of data from the ENCORE-PH study demonstrated that, for participants with compensated cirrhosis and an HVPG ≥16 mmHg, emricasan resulted in meaningful reductions in HVPG compared with placebo. The mean changes from baseline at Week 24 with emricasan were –1.6 mmHg (5 mg bid), –1.7 mmHg (25 mg bid), –1.5 mmHg (50 mg bid) compared with an increase of 0.5 mmHg with placebo ($p<0.05$ vs placebo for all comparisons).

"Although the primary endpoint was not met in this study, the reductions in HVPG observed in patients with compensated NASH cirrhosis and very severe PH are encouraging and support additional exploration in these patients", said Prof. Garcia-Tsao. "This group of patients is at greatest risk of progressing to decompensation and there are currently no approved treatments available to them".

"There is a significant unmet need for new therapies in patients with cirrhosis due to NAFLD," said Professor Philip Newsome, Vice-Secretary of EASL, "and this study shows that emricasan may be of potential value in this setting.

Further studies are required to confirm the effectiveness of emricasan in patients with more advanced portal hypertension."

Onsite location reference

Session title: 'Late breaker'
Time, date and location of session: 16:00–16:15, 13 April 2019, Main plenary
Presenter: Guadalupe Garcia-Tsao, USA
Abstract: Double-blind, placebo-controlled, randomized trial of emricasan in subjects with NASH cirrhosis and severe portal hypertension (PH) (LB-01)

Author disclosures

Gudalupe Garcia-Tsao is a consultant for Biovie, Conatus, Enterome, Galectin, Genfit, Intercept and has received research grant funding from Intercept. Conatus funded the present study.

References

1. Bosch J, Iwakiri Y. The portal hypertension syndrome: etiology, classification, relevance, and animal models. Hepatol Int. 2018;12(Suppl 1):1–10.
2. Silva-Junior G, et al. The prognostic value of hepatic venous pressure gradient in patients with cirrhosis is highly dependent on the accuracy of the technique. Hepatology. 2015;62(5):1584–92.
3. Berzigotti A, et al. Prognostic value of a single HVPG measurement and Doppler-ultrasound evaluation in patients with cirrhosis and portal hypertension. J Gastroenterol. 2011;46(5):687–95.
4. Berzigotti A. Advances and challenges in cirrhosis and portal hypertension. BMC Med. 2017;15(1):200.
5. Barreyro FJ, et al. The pan-caspase inhibitor emricasan (IDN-6556) decreases liver injury and fibrosis in a murine model of non-alcoholic steatohepatitis. Liver Int. 2015;35(3):953–66.
6. Gracia-Sancho J, et al. The pan caspase inhibitor emricasan improves the hepatic microcirculatory dysfunction of CCl4-cirrhotic rats leading to portal hypertension amelioration and cirrhosis regression. Hepatology. 2016;64:1043A.
7. Eguchi A, et al. Emricasan, a pan-caspase inhibitor, improves survival and portal hypertension in a murine model of common bile-duct ligation. J Mol Med (Berl). 2018;96(6):575–83.
8. Garcia-Tsao G, et al. Emricasan (IDN-6556) lowers portal pressure in patients with compensated cirrhosis and severe portal hypertension. Hepatology. 2019;69(2):717–28.

EMBARGO: 00.01 Saturday, 13 April, 2019

Hepatitis B core protein inhibitor, ABI-H0731, produces promising results in Phase 2a studies

ILC 2019: Interim data from two Phase 2a studies of ABI-H0731 suggest good tolerability and enhanced antiviral efficacy in combination with standard-of-care in chronic hepatitis B infection

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
An interim analysis of data from two ongoing Phase 2a studies investigating the hepatitis B core protein inhibitor (CI), ABI-H0731, reported today at The International Liver Congress™ 2019, found that, when administered in combination with nucleos(t)ide analogues (Nucs), ABI-H0731 was well tolerated and provided early and enhanced antiviral activity in both treatment-naïve and virologically-suppressed individuals.

Hepatitis B virus (HBV) infection remains a major global public health challenge and is associated with significant morbidity and mortality.[1] The main goals of treatment for individuals with chronic HBV infection are to improve survival and quality of life by preventing disease progression and the development of hepatocellular carcinoma.[1] Standard-of-care in chronic HBV infection is the long-term administration of Nucs,1 which suppress viremia and improve liver health, but are rarely curative.[1,2]

Hepatitis B core protein inhibitors are novel small molecules designed to target the HBV core protein, which is involved in multiple steps of the HBV lifecycle.[3] ABI-H0731 is a potent and selective oral HBV CI that is being developed in an effort to improve functional cure rates (i.e. clearance of residual viremia and antigens1) in chronic HBV infection.[4] A recently-reported Phase 1 study found that ABI-H0731 was well tolerated and associated with dose-dependent anti-HBV activity when used as monotherapy over 28 days in viremic individuals with chronic HBV infection.[5]

In interim analyses from the two randomized, double-blind, placebo-controlled Phase 2a studies presented today, ABI-H0731 was administered in combination with Nucs in two different study cohorts:

1) Individuals with chronic HBV infection (hepatitis B e antigen [HBeAg]-positive or negative) already suppressed on standard-of-care Nucs (n=73) who received add-on ABI-H0731 300 mg once-daily (qd) or placebo (Study ABI-H0731-201)

2) Treatment-naïve HBeAg positive individuals (n=25) who were initiated on either entecavir (ETV) + ABI-H0731 300 mg qd or ETV + placebo (Study ABI-H0731-202).

The primary efficacy endpoints of the two studies are the log10 reduction in HBsAg/HBeAg at Week 24 (Study ABI-H0731-201) and the log10 reduction in HBV DNA at Weeks 12 and 24 (Study ABI-H0731-202).

According to Dr Jacob Lalezari from Quest Clinical Research in San Francisco, USA, who presented the interim analyses, “ABI-H0731 has been well tolerated so far and few treatment-emergent adverse events (AEs) or laboratory abnormalities have been reported. Most AEs have been mild or moderate in intensity and none have led to treatment discontinuation.”

In Study ABI-H0731-201, the interim analysis includes 64/73 suppressed individuals that have completed the Week 12 assessment and 9 that have completed week 24 assessments. Those receiving ABI-H0731 in combination with a Nuc had significant reductions in HBV RNA levels of 2.34 log10 IU/ml compared with 0.05 log10 IU/ml in the group receiving Nuc + placebo at Week 12 ($p<0.001$). The reductions at Week 24 were 2.20 vs 0.15 log10 IU/ml, respectively ($p=0.012$). Additionally, DNA viremia was persistent at the limits of quantitation in subjects on Nuc monotherapy, while subjects on combination therapy showed a further reduction in viral DNA to below the limits of a

highly sensitive PCR assay (2–5 copies).

In Study ABI-H0731-202, 24 treatment-naive individuals have completed Week 12 assessments, and 12 have completed Week 24. At Week 12, HBV DNA declines in the combination arm were 4.54 log10 IU/ml, compared with 3.29 log10 IU/ml for the group receiving ETV + placebo ($p<0.011$). HBV RNA declines in the combination arm were 2.27 log10 IU/ml, compared with 0.44 log10 IU/ml for the group receiving ETV + placebo ($p<0.005$).

At week 24, HBV DNA declines in the combination arm were 5.94 log10 IU/ml, compared with 3.99 log10 IU/ml in the group receiving ETV + placebo ($p<0.005$). HBV RNA declines were 2.54 log10 IU/ml in the combination arm compared with 0.61 log10 copies/ml in the group receiving ETV + placebo ($p<0.005$).

'This interim analysis of two studies supports that ABI-H0731 in combination with Nucs appears to provide rapid, enhanced anti-HBV activity,' said Dr Lalezari. 'Although decreases in HBeAg and HBsAg in some individuals have been observed in both studies, it is too early to draw meaningful conclusions about this endpoint. The accelerated decline and significant loss of baseline RNA and DNA viremia suggest that combination therapy with a core inhibitor + Nuc may enhance loss of cccDNA and viral antigen once residual viremia has been fully cleared.'

'It is great to see that new HBV treatments are being developed,' said Professor Markus Cornberg from Hannover Medical School in Germany, a member of EASL's governing board. 'This Hepatitis B core protein inhibitor shows an effect on HBV RNA levels and thus an additional antiviral efficacy. However, it too early to conclude if this treatment could lead to HBV cure.'

Onsite location reference

Session title: 'Late breaker'
Time, date and location of session: 17:15–17:30, 13 April 2019, Main plenary
Presenter: Jacob Lalezari, USA

Abstract: Interim safety and efficacy results of the ABI-H0731 Phase 2a program exploring the combination of ABI-H0731 with NUC therapy in treatment-naive and treatment-suppressed chronic hepatitis B patients (LB-06)

Author disclosures

Dr Jacob Lalezari currently serves as a consultant to Assembly Biosciences.

References

1. Fricker ZP, Lichtenstein DR. Primary sclerosing cholangitis: a concise review of diagnosis and management. Dig Dis Sci. 2019;64(3):632–42.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–72.
3. Khanna A, Jones DE. Novel strategies and therapeutic options for the management of primary biliary cholangitis. Therap Adv Gastroenterol. 2017;10(10):791–803.

EMBARGO: 00.01 Saturday, 13 April, 2019

Elafibranor demonstrates significant anticholestatic effects in the treatment of primary biliary cholangitis

ILC 2019: Phase 2 study reports significant reductions in alkaline phosphatase and high responder rates among individuals with primary biliary cholangitis treated with elafibranor

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria: A Phase 2 study investigating the peroxisome proliferator-activated receptor (PPAR)-α/α agonist, elafibranor, has today reported significant anticholestatic effects among individuals with primary biliary cholangitis (PBC) treated for 12 weeks. The study reported at The International Liver Congress™ 2019 in Vienna, Austria, found that elafibranor was associated with significant decreases in alkaline phosphatase (ALP) and other biochemical markers of PBC compared with placebo.

Primary biliary cholangitis is a chronic autoimmune condition that causes damage to the bile ducts, leading to impairment of bile flow and the development of cirrhosis and end-stage liver disease.[1,2] A large proportion of individuals with PBC are identified incidentally through imaging findings or the detection of elevated liver enzymes such as ALP and gamma-glutamyl transferase, although symptoms including fatigue, pruritus, and jaundice are sometimes present.[1,2] Current treatment options for PBC are relatively limited, with European guidelines recommending life-long treatment with ursodeoxycholic acid (UDCA), with additional options including obeticholic acid, fibrates, and budesonide.[2]

Elafibranor is an investigational oral treatment that has anti-inflammatory properties and decreases the synthesis and toxicity of bile acids.[3] The study presented today is the first to investigate elafibranor in the treatment of PBC.[3]

"The development of new treatments for PBC is critical because many patients either do not respond sufficiently to current therapies or cannot tolerate them," explained Dr Velimir Luketic from the Virginia Commonwealth University School of Medicine in Richmond, USA, who presented the study results today.

The Phase 2 study involved 45 individuals with PBC without cirrhosis who had not responded adequately to UDCA treatment (defined as an ALP >1.67 x upper limit of normal [ULN]) and were randomized to receive 12 weeks of add-on oral elafibranor at a dose of 80 mg/day or 120 mg/day or to placebo. The primary endpoint of the study was the percentage change from baseline in ALP at Week 12 relative to placebo.

According to Dr Luketic, both doses of elafibranor significantly decreased mean ALP compared with placebo ($p<0.001$), with reductions of 48% with the 80 mg/day dose, 41% with the 120 mg/day dose, and an increase of 3% with placebo. At Week 12, 67% and 79% of participants who received elafibranor 80 mg/day and 120 mg/day, respectively, had an ALP <1.67 x ULN, a reduction in ALP >15%, and a total bilirubin within normal limits compared with 6.7% of participants who received placebo. Significant improvements in lipid and inflammatory markers and a trend in decreased pruritis were also observed.

"Twelve weeks of elafibranor treatment was well tolerated and produced marked improvements in ALP and other biochemical markers of PBC in this Phase 2 study,' said Dr Luketic. 'These results suggest the treatment has substantial anticholestatic efficacy that we hope will translate into long-term benefits for patients."

"An optimal therapy for PBC has yet to be discovered; however the current study is of major significance, since it opens the path for a new molecule to be used in the clinical setting" said Professor Marco Marzioni from the Università Politecnica delle Marche, Ancona, Italy, and an EASL Governing Board Member. "Although this is still a phase II study, the results are solid and very promising; a sign of a

better future for our patients."

Onsite location reference

Session title: 'Late breaker'
Time, date and location of session: 16:15–16:30, 13 April 2019, Main plenary
Presenter: Velimir Luketic, USA
Abstract: Elafibranor, a peroxisome proliferator-activated receptor alpha and delta agonist demonstrates favourable efficacy and safety in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid treatment (LB-02)

Author disclosures

Velimir Luketic has been a consultant for Genfit and an investigator on sponsored clinical trials by AbbVie, BMS, Exalenz, Genfit, Gilead, Intercept, Merck and Novartis.

References

1. Fricker ZP, Lichtenstein DR. Primary sclerosing cholangitis: a concise review of diagnosis and management. Dig Dis Sci. 2019;64(3):632–42.
2. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: The diagnosis and management of patients with primary biliary cholangitis. J Hepatol. 2017;67(1):145–72.
3. Khanna A, Jones DE. Novel strategies and therapeutic options for the management of primary biliary cholangitis. Therap Adv Gastroenterol. 2017;10(10):791–803.

EMBARGO: 00.01 Saturday, 13 April, 2019

Givosiran and lanreotide produce encouraging results in studies of rare liver diseases

ILC 2019: Promising results reported with givosiran in acute hepatic porphyria (AHP) and lanreotide in polycystic liver disease (PLD) associated with autosomal dominant polycystic kidney disease (ADPKD)

EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER (EASL)

13 April 2019, Vienna, Austria:
Two studies involving individuals with rare liver diseases have reported encouraging findings with investigational agents; givosiran, for the treatment of acute hepatic porphyria (AHP), and long-term lanreotide in polycystic liver disease (PLD) associated with autosomal dominant polycystic kidney disease (ADPKD). The studies, which were presented today at The International Liver Congress™ 2019 in Vienna, Austria, provide new evidence of the clinical benefits of these two treatments in liver conditions in which current treatment options are limited.

The first study was a Phase 3, randomized, double-blind, placebo-controlled study (ENVISION) that evaluated the investigational RNA interference (RNAi) agent, givosiran, in AHP[1] – a rare and serious genetic condition caused by problems with the normal liver production of heme (a molecule required for the function of haemoglobin and some other proteins).[2,3] The treatment has been designed to reduce levels of the enzyme, hepatic delta aminolevulinic synthase 1 (ALAS1) which, when induced, results in the build-up aminolevulinic acid (ALA) and porphobilinogen (PBG), toxic intermediaries of heme synthesis responsible for the potentially life-threatening, recurrent neurovisceral attacks and debilitating chronic symptoms of AHP.[1]

"The ENVISION study enrolled individuals diagnosed with AHP who were experiencing recurrent neurovisceral attacks" explained Manisha Balwani MD MS, Associate Professor of the Department of Genetics and Genomic Sciences and Department of Medicine at the Icahn School of Medicine at Mount Sinai and principal investigator of the ENVISION study. "Participants were randomized to receive subcutaneous (sc) givosiran 2.5 mg/kg or placebo once-monthly for 6 months. The primary endpoint of the study was the annualized rate of attacks requiring hospitalization, urgent care, or intravenous administration of hemin treatment at home in AIP patients. Secondary endpoints included urine levels of ALA and PBG; rate of hemin usage, a medication used to treat acute porphyria attacks; rate of attacks in AHP patients; symptoms and quality of life measures."[1]

Givosiran significantly lowered the mean annualized rate of composite attacks by 74% relative to placebo (p=6.04 x 10-9). Furthermore, the median annualized rate of composite attacks was lowered by 90% relative to placebo, and 50% of patients treated with givosiran were attack-free compared with 16.3% for placebo. In addition, givosiran treatment resulted in significant reductions in levels of urinary ALA and PBG, and the usage of hemin, relative to placebo. Adverse events were reported for most patients (80.4% with placebo; 89.6% with givosiran), and serious adverse events were reported in 20.8% of givosiran and 8.7% of placebo patients. There was one discontinuation from treatment in a patient on givosiran due to a transaminase elevation, per protocol criteria. No deaths were reported on study. Ninety-three of 94 patients enrolled in the open-label extension phase of the study.

"Givosiran represents a novel approach to the treatment of this rare liver disease, for which there is a considerable unmet need," said Dr Balwani.

The second study presented today evaluated the long-term efficacy of the somatostatin analogue, lanreotide, in PLD associated with ADPKD.

Polycystic liver disease is the most common extra-renal manifestation of this rare genetic

condition,[4] and is characterized by the development of fluid-filled liver cysts that cause progressive and symptomatic liver enlargement.[5]

'Lanreotide has been shown in previous PLD studies to reduce liver volume,6,7 however, there are no robust data on the long-term volume-reducing effects of this or other somatostatin analogues,' explained Dr René van Aerts from Radboud University Medical Center in Nijmegen, the Netherlands. The study presented by Dr van Aerts involved a subanalysis of data from the DIPAK-1 study, which was a 120-week, randomized, open-label study to compare the renoprotective effect of lanreotide with standard-of-care (SOC) (i.e. blood pressure reduction measures) in 305 individuals with ADPKD.8 The new analysis included 175 individuals from the DIPAK-1 study who had PLD (93 received lanreotide 120 mg sc every 4 weeks, 82 received SOC).

At 120 weeks, the height-adjusted total liver volume (hTLV) decreased 1.99% (95% CI –4.21, 0.24) in the lanreotide treatment group, while it increased by 3.92% (95% CI 1.56, 6.28) in the SOC group (treatment difference: 5.91% (95% CI –9.18, –2.63; (p<0.001). A beneficial treatment effect was still evident 4 months after the last injection (hTLV –3.87%; 95% CI –7.55, –0.18; p=0.04). Lanreotide resulted in an even greater reduction in height-adjusted total liver and kidney volume compared to SOC (-7.18%, CI -10.25 to -4.12; p<0.001).

'This study has provided the robust evidence we needed that lanreotide is associated with sustained reductions in liver growth in patients with PLD due to ADPKD,' said Dr van Aerts. 'The benefits of treatment were apparent even after treatment cessation. In patients with symptomatic PLD, long-term treatment with lanreotide should be considered. A patient-centered approach is needed to decide whether prolonged administration is warranted, based on individual liver volume-reducing effect, effect on symptoms, tolerability, and expected gender- and age-based disease progression.'

'To perform clinical studies in rare diseases is always very challenging, since the task of enrolling an adequate number of patients is quite complex,' said Professor Marco Marzioni from the Università Politecnica delle Marche, Ancona, Italy, and an EASL Governing Board Member. 'The authors of these two studies are thus to be congratulated, since they were able to design and complete very solid studies that contribute to the need of our patients, namely the possibility of receiving a better cure.'

Onsite location reference

Session title: 'General session 3'
Time, date and location of session: 10:15–10:30, 13 April 2019, Main plenary
Presenter: Manisha Balwani, USA
Abstract: 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 (GS-14)
Session title: Clinical developments in rare liver disease
Time, date and location of session: 08:00–08:15, 13 April 2019, Strauss 3
Presenter: René van Aerts, the Netherlands
Abstract: Lanreotide reduces liver growth in autosomal dominant polycystic kidney disease: Data from a 120-week randomized clinical trial (PS-192)

Author disclosures

Manisha Balwani (the Principal Investigator in the ENVISION study) receives financial compensation as an advisory board member for Alnylam (the study sponsor and manufacturer of the study drug givosiran). The Icahn School of Medicine at Mount Sinai ("ISMMS") holds issued and pending patents related to the study drug givosiran and has licensed these patents to Alnylam. As part of the license to Alnylam, ISMMS will receive payments from Alnylam, including a payment when givosiran entered Phase 3 clinical studies, as well as future payments if givosiran becomes a marketed treatment for acute hepatic porphyria. ISMMS, as well as the ISMMS faculty that are named inventors on the licensed patents, will benefit financially.René van Aerts has no relevant disclosures.

1. Sardh E, et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. N Engl J Med. 2019;380(6):549–58.
2. Bissell DM, et al. Porphyria. N Engl J Med. 2017;377(9):862–72
3. Wang B, et al. Acute hepatic porphyrias: review and recent progress. Hepatol Commun. 2018;3(2):193–206.
4. de Miranda Henriques MS, de Morais Villar EJ. The Liver and Polycystic Kidney Disease. In: Li X, editor. Polycystic Kidney Disease [Internet]. Brisbane (AU): Codon Publications; 2015 Nov. Chapter 17. Available from: https://www.ncbi.nlm.nih.gov/books/NBK373392/.Last accessed: February 2019.
5. van Aerts RMM, et al. Clinical management of polycystic liver disease. J Hepatol. 2017;68(4):827–37.
6. van Keimpema L, et al. Lanreotide reduces the volume of polycystic liver: a randomized, double-blind, placebo-controlled trial. Gastroenterology. 2009;137(5):1661-8.e1-2.
7. Chrispijn M, et al. The long-term outcome of patients with polycystic liver disease treated with lanreotide. Aliment Pharmacol Ther. 2012;35(2):266–74.
8. Meijer E, et al. Effect of lanreotide on kidney function in patients with autosomal dominant polycystic kidney disease: The DIPAK 1 randomized clinical trial. JAMA. 2018;320(19):2010–9.

ICE-HBV International Coalition to Eliminate HBV
PROMOTING GLOBAL COLLABORATION IN HBV CURE RESEARCH

Doherty Institute

THE UNIVERSITY OF MELBOURNE

The Royal Melbourne Hospital

A joint venture between The University of Melbourne and The Royal Melbourne Hospital

MEDIA RELEASE

UNDER EMBARGO until Wednesday, 10 April 2019, 11.30am CEST

Coalition launches Global Scientific Strategy to Cure Hepatitis B

The ICE-HBV Global Scientific Strategy, published today in The Lancet Gastroenterology and Hepatology, lays the groundwork for the momentum behind hepatitis B (HBV) cure research and the long-term implementation of HBV cure preparedness worldwide.

HBV is a global public health challenge on the same scale as tuberculosis, HIV and malaria. More than 257 million people worldwide are chronically infected with HBV and nearly 900,000 people died from the disease in 2017.

Worldwide efforts to eliminate HBV have been boosted today by the launch of a Global Scientific Strategy to Cure Hepatitis B (the ICE -HBV Strategy) by the International Coalition to Eliminate HBV (ICE-HBV), a global group of researchers, patient representatives and health organisations.

The ICE-HBV Strategy, published simultaneously in The Lancet Gastroenterology and Hepatology, was released and webcast live on the opening day of the The International Liver Congress taking place in Vienna, and hosted by the European Association for the Study of the Liver (EASL).

HBV is a viral infection that attacks the liver and can cause both acute and chronic disease. The virus is transmitted through contact with the blood or other body fluids of an infected person. Today, more people die from chronic hepatitis B (CHB) virus infection than from malaria.

CHB causes almost 40 per cent of hepatocellular carcinoma, which is the second leading cause of cancer-related mortality worldwide.

“Some 900,000 people dying unnecessarily of hepatitis B every year is simply unacceptable,” said Professor Peter Revill, ICE-HBV Chair and Royal Melbourne Hospital Senior Medical Scientist at the Doherty Institute.

“Inexplicably, despite the huge human and economic toll of chronic hepatitis B, HBV research remains largely underfunded, to the point of being compared to a neglected tropical disease. HBV cure research could make all the difference and prevent adverse outcomes in all people infected with the virus, allowing them to live treatment-free, fully productive lives and reduce the stigma associated with this chronic infection.”

If we have a vaccine and drugs for treating hepatitis B why do we need to research a cure?

A safe and effective vaccine to prevent HBV infection exists and its universal delivery is essential for the elimination of HBV as a public health threat. Lifelong treatment is also needed for those already chronically infected but currently is only accessed by some eight per cent of the millions of people who need it, partly due to the complexity of disease monitoring. The ICE-HBV Strategy argues strongly for the need for appropriate cure research and preparedness to complement the World Health Organization’s global elimination strategy, the HBV vaccine and the well-tolerated but poorly-accessed therapy.

The current treatment regime helps keep HBV under control, but it is not a cure because it cannot completely clear the virus from infected cells. cccDNA (covalently closed circular DNA) is a special DNA structure that arises during the propagation of HBV in the cell nucleus and may remain permanently there. Following HBV infections, cccDNA can remain in liver cells following clinical treatment and can even reactivate.

Even with ongoing treatment, people are still at a higher risk of developing liver cancer, particularly those with underlying cirrhosis due to CHB. It raises issues of medication adherence and requires considerable investment for ongoing monitoring, adding to the challenges of achieving elimination.

Twin-pronged approach

To achieve the goal of HBV cure, the ICE-HBV Strategy proposes and describes in detail two main approaches; curing of HBV infection without killing infected cells, and inducing immune control to safely eliminate infected cells. The ICE-HBV Strategy argues that each of these approaches will need to be underpinned by coordinated clinical studies to advance HBV cure.

The ICE-HBV Strategy also cites emerging evidence that the HBV disease 'time-clock' commences ticking earlier than previously appreciated and that HBV DNA integrations are associated with liver cancer – hence treatment might be advisable at a much earlier stage than currently recommended.

that the HBV disease 'time-clock' commences ticking earlier than previously appreciated and that HBV DNA integrations are associated with liver cancer – hence treatment might be advisable at a much earlier stage than currently recommended.

New collaborations are key

"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 257 million of us living with hepatitis B are desperate for this to be reality to stop the needless suffering and deaths. We applaud the ICE-HBV Strategy as a sign of the commitment to scale up the necessary research and collaboration to get us there. "We believe if the same kind of fervour and investment is given to HBV that was poured into hepatitis C therapeutic development, we would dramatically expedite the timeline to a cure. 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."

A more universal health coverage approach

Recent scientific progress and the momentum created by the discovery of a cure for the hepatitis C virus (HCV) has created a sense of hope to find a cure for HBV.

ICE-HBV is calling for increased investments in HBV cure research and cure preparedness to save the lives of the 257 million people living with CHB worldwide, most of whom are unaware of their infection.

While ICE-HBV supports both the World Health Organization global health sector strategy on viral hepatitis and the World Hepatitis Alliance's 'Find the Missing Millions' campaign, it urges a more universal health coverage approach to the HBV response.

"We strongly believe that public health and research agencies need go beyond the existing objectives and work together to discover and ensure access to curative treatment regimens for people living with HBV," said Professor Fabien Zoulim, ICE-HBV Deputy Chair, Vice-president of the scientific advisory board and head of the HBV cure programme at the French National Agency for Research on HIV and Viral Hepatitis (ANRS) in Paris, France.

Recommendations

The ICE-HBV Strategy sets out a series of research priority areas to tackle HBV, which include:

HBV Elimination

- Developing standardised methods to quantify cccDNA and study mechanisms of cccDNA homeostasis and processes affecting its biogenesis, homeostasis, structure, transcriptional control and decay.
- Define mechanisms determining HBV infection establishment: characterise all steps from cell entry to cccDNA mini-chromosome formation and maintenance.
- Improve methodologies for the study of cccDNA processing and virus-host interactions to reveal new targets for therapeutic approaches to clear cccDNA, by applying state of the art 'omics' approaches (e.g. genomics, transcriptomics, proteomics, metabolomics, kinomics) to increase understanding of HBV-host interactions at a genome-wide level.
- Develop and validate new serum markers (e.g. core-related antigens (HBcrAgs), HBV-RNA) as reliable biomarkers of cccDNA activity in the liver. Once markers are identified and characterised, ensure they are standardised.
- Develop methods to specifically degrade HBV cccDNA.
- Develop methods to prevent transcription of cccDNA and integrated HBV DNA. Continue to develop methods to inhibit the additional key steps of the viral replication cycle, that may be included in combination strategies to cure the infection.
- Develop efficient and convenient in vitro functional cccDNA systems.
- Develop convenient in vivo model systems, particularly immunocompetent non-human primate and mouse models susceptible to HBV infection.

HBV Immunity

- Clinical studies with existing immune interventions.
- The relative contribution of different components of the immune system to viral clearance versus viral persistence, immunopathology and treatment response among neonates, children, adolescents and adults.

- The mechanisms of T cell exhaustion and the extent to which T cell restoration is reversible, durable and needed for viral control.
- The role of B cells in the natural history of disease and how they can be effectively monitored for research and clinical trials.
- The impact of liver microenvironment on the composition and function of innate and adaptive cells and identification of biomarkers in the blood that best reflect the intrahepatic immune response.
- The number of infected hepatocytes in each category of patients and the degree of immune mediated destruction that is required for clearance but can still be tolerated before hepatic decompensation occurs.

Implementation

- Increase funding for individual and collaborative cure-related research projects by governmental and private funding agencies and philanthropic benefactors. Consideration should be given to establishing international research consortia, similar to the Martin Delaney Collaboration for HIV research managed by the NIH in the USA. HBV cure research investment strategies should be prioritised in national HBV plans globally.
- The WHO Hepatitis Elimination Strategy should be funded in full, with particular focus on delivery of birth dose vaccines and substantially increased investments in HBV research and the improvement of point-of-care diagnostics for treatment and cure roll-out.
- Concentrate on the discovery of interventional strategies that will permanently reduce the number of productively infected cells or permanently silence the cccDNA in those cells and also stimulate HBV-specific T cells and the production of neutralising antibodies that will prevent viral spread to uninfected cells, mimicking spontaneous resolution of acute HBV infection.
- Establish repositories of standardised HBV reagents and protocols and facilitate access to all researchers across the world and support the development of in vivo models of HBV infection.

ENDS

About the International Coalition to Eliminate Hepatitis B (ICE-HBV)

ICE-HBV is an international research-driven forum, which is coordinating, promoting and establishing public-private collaborative partnerships to accelerate the discovery of a chronic hepatitis B (CHB) cure. ICE-HBV aims to fast-track the discovery of a safe, effective, affordable and scalable cure to benefit all people living with CHB, including children and people living with hepatitis C, hepatitis D and HIV co-infection. ICE-HBV intends to contribute to the elimination of CHB as a global public health challenge. ICE-HBV is a non-profit initiative initially created in 2016 by academic researchers from the ANRS (France Recherche), the Peter Doherty Institute for Infection and Immunity and the International HBV Meeting. Its growing list of individual members and member organisations now spans the globe.

Website: ICE-HBV.org
Twitter: @ICE-HBV
#ICEHBV

About the Peter Doherty Institute for Infection and Immunity

Finding solutions to prevent, treat and cure infectious diseases and understanding the complexities of the immune system requires innovative approaches and concentrated effort. This is why The University of Melbourne – a world leader in education, teaching and research excellence – and The Royal Melbourne Hospital – an internationally renowned institution providing outstanding care, treatment and medical research – have partnered to create the Peter Doherty Institute for Infection and Immunity (Doherty Institute); a centre of excellence where leading scientists and clinicians collaborate to improve human health globally.

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BACKGROUND INFORMATION

Alcohol-Related Liver Disease

Alcohol can damage or even destroy liver cells and, although the liver can regenerate and repair itself, drinking more alcohol than the liver is able to process can lead to serious damage and loss of function. Alcoholic liver disease or alcohol-related liver disease (ALD) is damage to the liver caused by excessive alcohol consumption, resulting in serious and life-threatening complications.

Europe is the heaviest drinking region in the world in terms of the prevalence of alcohol consumption and ALD is therefore is an important issue for Europe to address.

ALD is a complex disease that encompasses a spectrum of conditions, including:

- Simple steatosis (accumulation of fat in the liver)
- Alcoholic fatty liver disease (or alcoholic steatohepatitis)
- Alcoholic hepatitis (inflammation of the liver)
- Cirrhosis (scarring of the liver)
- Liver cancer

The consequences of ALD can be grave. Severe alcoholic hepatitis is life-threatening, and people who develop cirrhosis and fail to stop drinking are 50% more likely to die in the next five years.

Intake of alcohol is the biggest risk factor for ALD and this risk increases significantly for men who drink more than 40 grams of alcohol a day for more than ten years. The development of cirrhosis in men is usually associated with consumption of more than 80 grams of alcohol a day for more than ten years. Men who drink in excess of 230 grams of alcohol a day for 20 years have approximately a 50% risk of developing liver cirrhosis. Abstinence from alcohol is a critical goal for patients as it improves the clinical outcomes of all stages of ALD.

EASL recommends screening for liver cancer in patients with liver cirrhosis, as well as alcohol-induced damage in organs including the heart, kidney, nervous system and pancreas. A liver transplant may be considered for patients who have liver failure that has not improved after both treatment and long-term alcohol abstinence.

However, not all chronic alcohol abusers develop liver disease and factors beyond alcohol intake, such as gender, genetic factors and nutrition, are thought to be involved. Women are more susceptible to ALD than men, even when body size is taken into account. ALD often runs in families and therefore genetic causes play a part in its development. Both obesity and a diet that is high in unsaturated fat are risk factors for ALD. Other factors, such as infection with the hepatitis C virus, also play a part in ALD risk.

EASL is involved in a range of public affairs initiatives aimed at raising awareness among European decision makers about the need to tackle liver disease in a comprehensive manner. The most cost-effective policies to reduce alcohol-related harm are those that affect the availability of alcohol, either through pricing, hours and places of sale, or minimum age purchase laws.

Cirrhosis

Liver or hepatic disease comprises a wide range of complex conditions that affect the liver. Amongst these is cirrhosis, which is the late, symptomatic stage of chronic liver disease which occurs when scar tissue (fibrosis) largely replaces healthy liver tissue, compromising the function of the organ and predisposing it to liver cancer. Chronic liver diseases induce cirrhosis in approximately 633,000 patients per year globally.

Complications of cirrhosis are serious and include, among others, the accumulation of fluid in the abdominal cavity (ascites), jaundice, gastrointestinal bleeding (rupture of gastroesophageal varices), severe bacterial infections, and hepatic encephalopathy. The complications of cirrhosis were the leading cause of adult liver transplants in Europe, with 67,208 being carried out between 1988 and 2015.

Cirrhosis can eventually lead to liver failure, where the liver stops working, which can be fatal. It is estimated that in 2013, liver cirrhosis resulted in 170,000 deaths in Europe. The liver damage caused by cirrhosis can rarely be undone. However, if liver cirrhosis is diagnosed early and the cause is treated, further damage can be limited and also reversed in a minority of cases.

The risk factors associated with cirrhosis include, the excessive consumption of alcohol, obesity and viral hepatitis. Cirrhosis can take multiple years to develop and can do so without many noticeable symptoms, until the damage to the liver becomes very serious.

Liver Cancer (HCC)

Although the exact causes of liver cancer are unknown, most cases are associated with damage and scarring of the liver known as cirrhosis. Liver cancer is a frequent tumour that starts in the main types of liver cells. The most common primary liver cancer is hepatocellular carcinoma (HCC), which starts in the hepatocytes.

Worldwide, liver cancer is the sixth most common cancer, with 63,500 new cases of liver cancer being diagnosed in Europe in 2012. The incidence of it increases with age, with around 9 out of 10 cases occurring in those over the age of 55. The lifetime risk of developing liver cancer is around 1 in 120 for men and 1 in 215 for women.

There are two categories of liver cancer. The first is primary liver cancer, where the cancer begins in the cells of the liver itself. The most common forms of these are hepatocellular carcinoma (HCC), hepatomas and cholangiocarcinoma. HCC is one of the most serious outcomes of cirrhosis and is responsible for 90% of primary liver cancer cases. The second category is secondary liver cancer, which begins in the cells of other organs of the body but then spreads to the liver.

Symptoms of liver cancer can include weight loss, jaundice, itching, loss of appetite, pain in your abdomen or your right shoulder and a lump in the right side of your abdomen. Maintaining a healthy weight, drinking alcohol in moderation, if at all, and being cautious with chemicals at home or work, can all help to reduce the risk of cirrhosis and liver cancer.

Non-alcoholic Fatty Liver disease (NAFLD)

NAFLD is a condition in which fat builds up in the liver. It is often associated with obesity and diabetes. In some people NAFLD can progress to non-alcohol related steatohepatitis (NASH), a more aggressive form that can lead to cirrhosis, and to primary liver cancer.

A healthy liver should contain little or no fat. However, increasingly unhealthy western diets have seen a rise in NAFLD around the world, making it the most common liver disorder in western countries. Currently, NAFLD affects approximately 20-30% of the population worldwide, with as many as 52 million people in the EU suffering from some form of NAFLD.

A small group of people with NAFLD attain a more serious condition named non-alcohol steatohepatitis (NASH). It is estimated that between 10-30% of patients with NAFLD have NASH that can progress into cirrhosis. NASH is a serious condition that may progress into serious liver scarring and cirrhosis. Cirrhosis causes irreversible damage to the liver and is ultimately the most severe stage of NASH.

NAFLD can affect a wide range of people. However, being overweight or obese can heighten your chances of developing NAFLD. The prevalence of NAFLD is also higher in individuals with other features of metabolic syndrome including diabetes and hypertension. These factors also increase the likelihood that individuals will develop more advanced forms of NAFLD, including fibrosis and NASH.

Hepatitis C is also transmitted through contact with infected blood or other bodily fluids, which can result in acute or chronic disease. The number of people chronically infected with Hepatitis C worldwide is estimated to be about 71 million.

Currently, no vaccine is available for the Hepatitis C virus.

Hepatitis D is caused by the hepatitis delta virus, which is again transmitted through contract with infected blood or other bodily fluids. This form only occurs in people who are also infected with Hepatitis B. The majority of patients infected with Hepatitis D virus have a progressive disease which over time evolves into cirrhosis.

Hepatitis E is caused by the Hepatitis E virus and is transmitted through contaminated water or raw swine meat. Every year there are an estimated 20 million Hepatitis E infections and 44,000 Hepatitis E-related deaths.

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