TREATMENT STRATEGIES
HEPATOLOGY

Volume 2 Issue 1

- Congress Review
- Hepatic Encephalopathy
- Liver Disease
- Liver Failure
- Liver Transplantaion
- Metabolism

EASL
EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

Includes a Review of the 50th Annual Meeting of the EASL - ILC 2015

Robust protection against recurrent episodes of hepatic encephalopathy (HE)[1]

2-YEAR DATA

6-month data

Daily treatment with XIFAXAN® 550* b.d. plus lactulose significantly reduced episodes† and hospitalisations‡ compared with placebo plus lactulose[1], and improved quality of life[2] in patients with HE.

2-year data

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Xifaxan®550
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* >90% were receiving concurrent lactulose in both treatment arms
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INTERNATIONAL ABBREVIATED PRESCRIBING INFORMATION: XIFAXAN®/ TARGAXAN® 550 mg (rifaximin)
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References: 1. Bass, N.M., *et al.* N Engl J Med, 2010; 362(12): 1071-81. 2. Sanyal, A., *et al.* Aliment Pharmacol Ther, 2011; 34(8): 853-61. 3. Mullen, K.D., *et al.* Clin Gastroenterol Hepatol, 2014; 12(8): 1390-97. 4. TARGAXAN® 550 Summary of Product Characteristics, 2013.

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Welcome...

I am delighted to welcome you to the second edition of *Treatment Strategies - Hepatology*. In this edition we bring you a range of informative articles, papers and reports, as well as an in-depth review of the 50th Annual Meeting of the European Association for the Study of the Liver (EASL) - The International Liver Congress™ (ILC) 2015, which was held in Vienna in April. Our ILC 2015 congress review will provide you with the breaking news, research highlights and the best of the symposia. We really feel that this review will provide you with the not-to-be-missed highlights of the congress.

This edition also features a number of interesting and informative papers on subjects such as Hepatic Encephalopathy, Liver Disease, Liver Failure, Liver Transplantaion and Metabolism. With these papers we aim to bring you new insights into the latest treatment strategies for a number of conditions and diseases, and we hope that you enjoy this carefully chosen content.

So far, 2015 is proving to be a fantastic year for The Cambridge Research Centre, with some exciting changes including Treatment Strategies TV, where you can find footage from the most important scientific conferences, meetings and congresses, as well as interviews, symposia proceedings, roundtable events and much more. We also launched our range of interactive eBooks on iBooks, which is a great new way to read and download our content to your devices. Have you liked our new Facebook page? Here you can find all of the latest news about new projects and upcoming releases, and the Treatment Strategies' team are also all active on Twitter and LinkedIn.

We hope that you enjoy this edition of *Treatment Strategies – Hepatology*, and please do share your thoughts with us on this issue as well as what you would like to see in our next edition, which will feature a review of ILC 2016 - See you in Barcelona.

Nigel Lloyd, Managing Director

The Cambridge Research Centre wishes to thank the following societies for their assistance and involvement in this publication.

CHRONIC LIVER DISEASE

A SLOW, SILENT, BUT PREVENTABLE DEATH

According to the World Health Organization, in 2008, 47.147 Europeans died of liver cancer, and 84.697 Europeans died of liver cirrhosis. These figures combined exceeded breast cancer mortality figures (103,255)[1].

Worldwide, both cirrhosis and liver cancer are on the rise.

THE CAUSES

The major causes of chronic liver disease are:

- Lifestyle (alcohol and overweight/obesity, leading to alcohol- or non-alcohol related fatty liver disease)
- Virus infection (mainly viral hepatitis B and C), and
- Genetic factors including autoimmune diseases

In addition, alcohol consumption by those who are infected with chronic hepatitis B and/or C multiplies the risk of developing cirrhosis and primary liver cancer[2].

ON THE POSITIVE NOTE, THE VAST MAJORITY OF CHRONIC LIVER DISEASE CASES CAN BE PREVENTED AND/OR TREATED

With the recent publication of its manifesto[3], ELPA calls on policymakers to ensure that an integrated approach, from prevention, to early diagnosis of a possible liver problem (e.g. via enzyme testing), to treatment, is taken to deal with the growing burden of liver disease.

ABOUT ELPA:

ELPA emerged from a desire among European liver patient groups to share their experiences. In June 2004, 13 patient groups from 10 European and Mediterranean Basin countries met to create the association. ELPA which formally launched in Paris, on April 14th 2005, now has 29 members from 24 countries.

ELPA and its members are dedicated to multi-level initiatives involving EU and national policymakers, liver specialist associations and public health experts.

European Liver Patients Association

ELPA

For more information about ELPA, please visit our website at **www.elpa-info.org** or contact:

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[1]Blachier M, Leleu H, Peck-Radosavljevic M et al. *The Burden of Liver Disease in Europe: A Review of Available Epidemiological Data*. Geneva: EASL, 2013.
[2]Donato F, Tagger A, Gelatti U et al. *Alcohol and hepatocellular carcinoma: the effect of lifetime alcohol intake and hepatitis virus infections in men and women* Am J Epidemiol 2002, 155:323-331.
[3]http://www.elpa-info.org/elpa-news---reader/items/elpa-briefs-european-elections-candidates-on-chronic-liver-disease.htm

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Sara Montagnese,[1] Jasmohan S. Bajaj,[2] Paolo Angeli[3] and Aleksander Krag[4]

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The International Liver Congress™ 2015

22nd - 26th April - Vienna

50th Annual Meeting of the European Association for the Study of the Liver

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The International Liver Congress™ is the biggest event in the EASL educational calendar.

Every year in April, scientific and medical experts from a broad range of fields including hepatology, gastroenterology, internal medicine, cell biology, transplant surgery, infectious diseases, microbiology and virology, pharmacology, pathology, radiology and imaging, come together from around the world to learn about the latest in liver research.

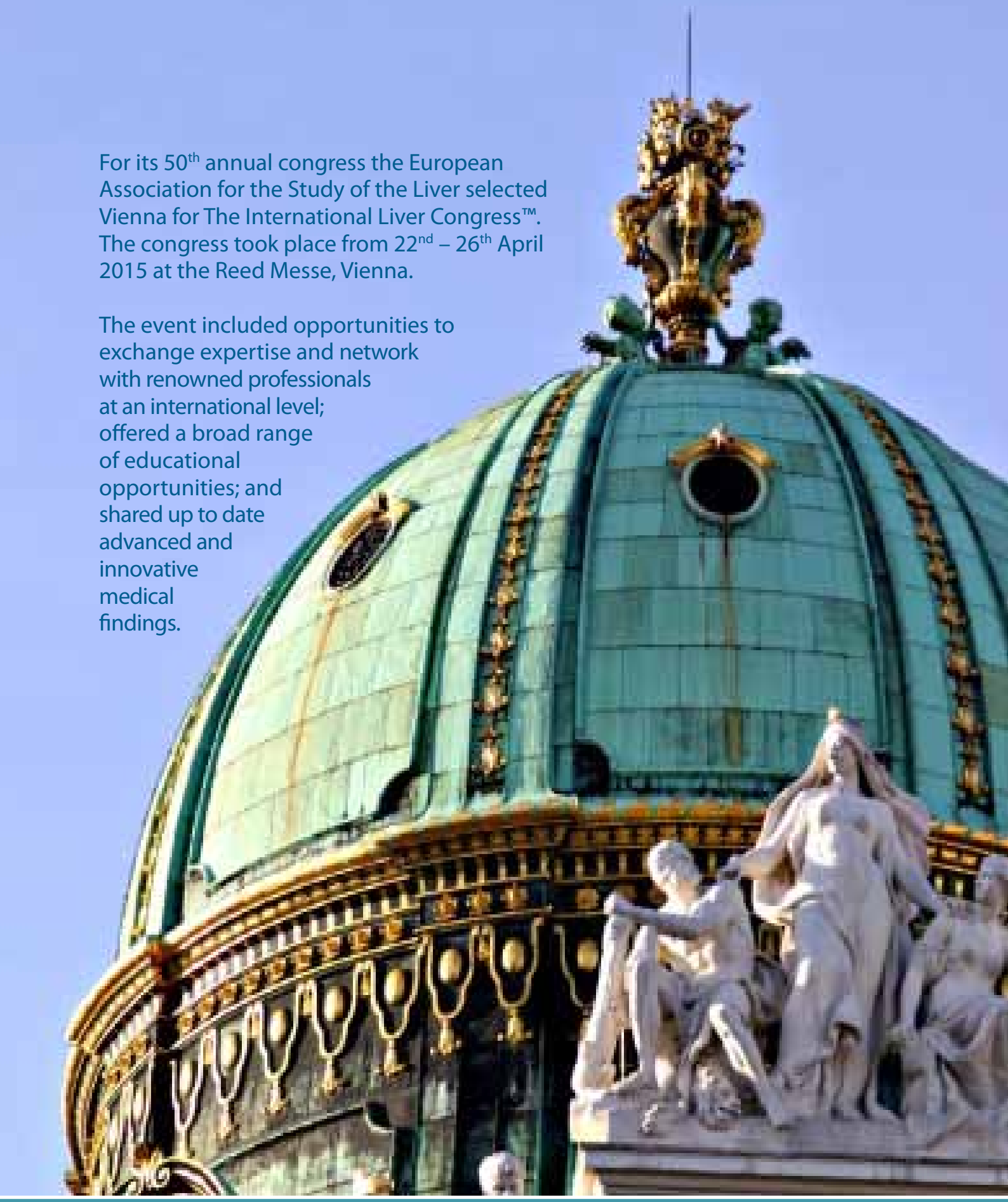
Specialists share their recent data, present their studies and findings, and discuss the hottest topics related to liver disease. Last year, the annual congress attracted almost 11,000 delegates and 250 media representatives from all corners of the planet making this a truly international networking opportunity!

2015 is a very special year for EASL and the hepatology community as it will celebrate its 50th annual meeting and also the 30th birthday of the *Journal of Hepatology*.

The International Liver Congress™ took place April 22nd-26th, 2015 at the Reed Messe congress centre, Vienna, Austria.

For its 50th annual congress the European Association for the Study of the Liver selected Vienna for The International Liver Congress™. The congress took place from 22nd – 26th April 2015 at the Reed Messe, Vienna.

The event included opportunities to exchange expertise and network with renowned professionals at an international level; offered a broad range of educational opportunities; and shared up to date advanced and innovative medical findings.



Vienna, Austria

Austria's capital is famous for its cultural events, imperial sights, coffee houses, cosy wine taverns and the very special Viennese charm.

Vienna's history dates back to the first post-Christian century when the Romans established the military camp Vindobona. Today's cityscape is characterised by the abundance of baroque buildings created mostly under the rule of Empress Maria Theresia and Emperor Franz Joseph, who was largely responsible for the monumental architecture seen around the Ringstraße.

Schönbrunn Palace, the former imperial summer residence, is one of Vienna's most popular sights. The sumptuous palace with its beautifully tended formal gardens, the Gloriette monument, Palm House and zoo attracts hordes of visitors each year. Then there is the huge Hofburg (Imperial Palace), which was the base of the Habsburgs for over six centuries.

The splendid baroque Belvedere Palace today houses the Österreichische Galerie (Austrian Gallery), displaying the largest collection of works by Klimt and Kokoschka, as well as famous paintings by Schiele. Vienna's prime landmarks are the gothic Stephansdom (St. Stephen's Cathedral), the giant big wheel in the Prater (Vienna's old recreational park), and the Spanish Riding School with its famous Lipizzaner horses. In the heart of Vienna, 200m from the State Opera, you'll find a unique, tropical oasis - the Imperial Butterfly House. In one of the world's most beautiful Art Noveau palm houses you can admire around 400 live, free flying butterflies all year round. You can absorb the colours and grace with which they float through the air, past waterfalls and exotic plants, in an environment as true to nature as possible.

Vienna has more museums and galleries of international reputation than you can shake a stick at. Take, for example, the Museum of Fine Arts with the world's largest collection of Bruegel paintings, Museums Quartier with the Leopold Museum, the Museum Moderner Kunst (Museum of Modern Art), Architekturzentrum (Architectural Centre) and the Kunsthalle, all ranking among the city's most important cultural venues.

Vienna owes much of its international fame to the many celebrated composers who lived and worked here, including Strauß, Mozart, Beethoven and Haydn. The Vienna Philharmonic Orchestra is one of the world's best, the State Opera amongst the leading opera houses, not to forget the famous Vienna Boys' Choir.

Talking Head Interviews from The International Liver Congress™ 2015

Professor Ahmet Gurakar, Medical Director, Liver Transplantation, The Johns Hopkins Hospital, Baltimore

Professor Jean Francois Dufour, Head of Hepatology, Bern, Switzerland

50th Anniversary of ILC is 'Landmark' for EASL - Liver Disease

At the opening press conference held at The International Liver Congress™, Markus Peck-Radosavljevic, MD, Secretary-General of the European Association of the Study of the Liver, discussed achievements of EASL and explained that the 50th anniversary of the meeting marks how far the society and the meeting has come over the years.

"This has helped definitely to move liver disease into the lime light because when the society was founded, only one of the viral hepatitis had been identified and now we are actually curing almost all of them."

"I am certain that this 50th EASL celebration will be a memorable event and a huge success, both scientifically and socially"
Serge Erlinger, M.D. Honorary President of The International Liver Congress™ 2015

"The 50th anniversary is a landmark for EASL because the society has had tremendous developments since its first meeting in 1966" said Markus Peck-Radosavljevic, MD, Secretary-General of the European Association of the Study of the Liver (EASL)

Peck also discussed the society's efforts to raise awareness of liver disease to the public through the Liver Works campaign, which was launched at the meeting.

"We launched the Liver Works campaign, which you will see in certain spots throughout Vienna, to make the general public aware of the fact that the liver, which they all know that they have, can be diseased and has to be taken care of."

All-oral, Direct-acting Antiviral Treatment Options for Hepatitis C

Interim data presented at The International Liver Congress™ 2015 from the HCV-TARGET study show that all-oral, direct-acting antiviral therapy for hepatitis C (HCV) is well tolerated and highly effective in patients with decompensated cirrhosis. Sustained virologic response (SVR) at 4 weeks was shown to be: sofosbuvir/ribavirin: 75%; sofosbuvir/simeprevir: 77%; sofosbuvir/simeprevir/ribavirin: 81%.

These results demonstrate that all-oral, direct-acting antiviral regimens are better tolerated and achieve higher rates of SVR in HCV patients with decompensated cirrhosis than older interferon-based therapy.

Importantly, markers of hepatic and synthetic liver function such as bilirubin and albumin values also improved during short-term follow-up. The analyses were restricted to patients with cirrhosis and a MELD score (scoring system to assess the severity of chronic liver disease) of ≥ 10 who had not undergone liver transplantation. Such well tolerated and highly efficacious therapy which can improve liver function presents an excellent option for many patients who do not have access to liver transplantation.

HCV-TARGET is an international research consortium of leading HCV investigators who have established a common research database and are conducting a longitudinal observational study to answer important questions about HCV therapy with direct-acting antiviral agents.

Global Expansion of Hepatitis Vaccination and Treatment is Needed to Make Progress towards Elimination of Hepatitis B

Results revealed at The International Liver Congress™ 2015 demonstrate current treatment and prevention programmes need to be scaled up in order to make elimination of hepatitis B virus (HBV) possible.

The study, conducted by Imperial College Scientists, highlights that if existing interventions, such as infant hepatitis B vaccination and treatment programmes, were scaled up, the number of new chronic HBV infections could be reduced by 90% and mortality levels could be reduced by 65% by 2030. Globally, this would mean 13 million deaths could be prevented, including 6 million cancer cases.

Although universal infant vaccination programmes have proved successful in decreasing the number of new HBV infections, without further intervention the study estimates that the number of people infected with HBV will remain at the current level for the next 40 to 50 years, resulting in 20 million deaths by 2030.

The results were generated using a mathematical model of the worldwide HBV epidemic, which incorporated data on epidemiology, vaccination coverage, treatment, regional demography and the natural history of the virus.

Predictions for incidence of new chronic infections, prevalence and HBV-related mortality were developed for interventions remaining at current levels.

The researchers then explored what scaling up of treatment and prevention would be needed to achieve control and elimination of HBV by 2030.

The study highlights the need to increase current levels of interventions, including the expansion of vaccination and treatment programmes, in order to significantly reduce the transmission of HBV and lower mortality.

NAFLD Patients need a Healthy Lifestyle

In a video perspective from The International Liver Congress™ 2015, Howard Monsour Jr., MD, Chief of Hepatology, Houston Methodist Hospital, Texas, discussed important trends in nonalcoholic fatty liver disease and patients maintaining a healthy lifestyle.

"What's important is identifying genetic factors and thinking how we pick the patient that will progress that we can direct our treatments towards," Monsour said. "Regardless, it will go back to the importance of diet and exercise, which is difficult for Americans to grasp."

Monsour stated that one of the most important things to remember in slowing the progression of NAFLD is a healthy lifestyle.

"Fatty liver disease, unlike hepatitis C, is not going to be cured with a single pill," Monsour said.

Daclatasvir, Sofosbuvir and Ribavirin Combination

Daclatasvir, sofosbuvir and ribavirin combination is highly effective and well tolerated in hepatitis C patients with advanced cirrhosis or post-liver transplant recurrence.

Results from ALLY-1 confirm combination addresses a high unmet therapeutic need for these patients

Phase 3 results presented at The International Liver Congress™ 2015 show that a combination of daclatasvir (DCV), sofosbuvir (SOF) and ribavirin (RBV) for 12 weeks was effective and well tolerated amongst patients with hepatitis C virus (HCV) infection with advanced cirrhosis and post-transplant recurrence.

Sustained virologic response rates at 12 weeks (SVR12) were >90% in patients with Child-Pugh class A or B cirrhosis but lower in Child-Pugh class C. SVR12 was achieved by 94% of liver transplant recipients with HCV recurrence.

ALLY-1 is an open-label study, including treatment-naive or -experienced adults with HCV infection of any genotype.

The most common adverse events (AEs) were headache, fatigue, anaemia, diarrhoea and nausea. There were no treatment-related serious AEs. One post-transplant patient discontinued all therapy after 31 days due to headache but achieved SVR12.

Hepatitis C Screening Essential to Help Catch Patients with Advanced Liver Fibrosis

Study results presented at The International Liver Congress™ 2015 show that the occurrence of advanced liver fibrosis is similar for patients infected with the hepatitis C virus (HCV), whether or not they have been diagnosed.

Most individuals with HCV remain asymptomatic, which makes the diagnosis difficult. The study authors used the hypothesis that individuals whose HCV is not diagnosed are less likely to have advanced fibrosis than those who have been diagnosed. They then compared liver fibrosis between respondents of the National Health and Nutrition Examination Survey (NHANES) in the USA, in patients with diagnosed and undiagnosed HCV infection.

Of the respondents with known HCV infection, the proportion with a high, intermediate and low probability of advanced fibrosis was 14.5%, 40.3%, 45.2%, respectively; in those with undiagnosed HCV the results were 19.1%, 30.9%, 50.0%, respectively.

The study highlights that even if people are unaware they are infected with HCV, the virus affects their liver in the same way, resulting in advanced fibrosis. These results validate the current recommendation that screening for HCV, particularly among high-risk groups, is vital.

EU and Public Health: Hall C (Plenary) Presentation time: 11:30 - 11:45 Presenter: Prowpanga Udompap (United States) Abstract O120: ADVANCED FIBROSIS IS COMMON IN INDIVIDUALS WHOSE HEPATITIS C HAS NOT BEEN DIAGNOSED: RESULTS FROM THE NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY 2001-2012

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Background and Aims

Hepatitis C virus (HCV) infection is a global public health problem - while it is common, its consequences may be severe, including end stage liver disease and hepatocellular carcinoma. Moreover, most individuals with HCV remain asymptomatic, which makes the diagnosis difficult. With the hypothesis that individuals whose HCV is not diagnosed are less likely to have advanced fibrosis than those who have been diagnosed, we compare liver fibrosis between respondents to the National Health and Nutrition Examination Survey (NHANES) with diagnosed and undiagnosed HCV infection.

Methods

Testing for HCV was incorporated in NHANES 2001-2012. In a subgroup of the respondents with HCV infection, follow-up questionnaires were administered. Awareness of HCV infection was assessed by the question whether they had known they had HCV before receiving a letter from NHANES. Liver fibrosis was estimated by the FIB-4 and APRI scores. Based on the published cut-off values for advanced fibrosis, the proportion of respondents with a high probability of advanced fibrosis was compared between respondents with known and undiagnosed HCV.

Results

Out of 30,140 respondents of the NHANES survey, 360 tested positive for HCV RNA. There were 355 participants with complete laboratory data needed for the FIB-4 and APRI scores, of whom 130 had completed the full hepatitis C follow-up questionnaires. Slightly less than half (47.7%, n=62) knew that they had hepatitis C infection before the survey, whereas in the remainder (52.3%), HCV was only discovered from the survey. In the figure, the two groups were comparable with respect to age, sex, aminotransferase and platelet counts. BMI was higher in those with known diagnosed, the significance of which is uncertain. The raw FIB-4 and APRI scores were similar between the two groups. Among the respondents with known HCV infection, the proportion with a high, intermediate, and low probability of advanced fibrosis was 14.5%, 40.3%, 45.2%, respectively. The corresponding data in those with undiagnosed HCV were 19.1%, 30.9%, 50.0%, respectively. A similar pattern was seen with the APRI score.

Conclusions

While more than half of survey respondents did not know of their HCV infection, their liver fibrosis was no less advanced than those whose HCV had been diagnosed prior to participation in the survey. These data further justify the current recommendation for HCV screening in asymptomatic individuals.

Disclosure of Interest

P. Udompap: : None Declared, A. Mannalithara: : None Declared, N.-Y. Heo: : None Declared, W. R. Kim: Consultant: Gilead, BMS

New Study Shows Cancer Rates Higher in Patients with HCV vs. General Population

Results announced at The International Liver Congress™ 2015 show that cancer rates in patients with the hepatitis C virus (HCV) were significantly increased compared to the non-HCV cohort. The researchers suggest an extrahepatic manifestation of HCV may be an increased risk of cancer.

The aim of the study was to describe the rates of all cancers in the cohort of HCV patients compared to the non-HCV population. Known cancer types associated with hepatitis C include non-Hodgkin's lymphoma, renal and prostate cancers, as well as liver cancer.

A retrospective study at Kaiser Permanente, Southern California, USA, was conducted. The study authors recorded all cancer diagnoses in patients over 18 years of age with or without HCV during 2008-2012. Within the timeframe of the study 145,210 patient years were included in the HCV cohort, and 13,948,826 patient years were included in the non-HCV cohort.

In the HCV cohort there were 2,213 cancer diagnoses (1,524/100,000) during the 5-year period and 1,654 cancer diagnoses when liver cancer was excluded (1,139/100,000). In the non-HCV cohort there were 84,419 cancer diagnoses (605/100,000) during the same 5-year period and 83,795 (601/100,000) when liver cancer was excluded. When all cancers are considered the rate is 2.5 times higher in the HCV cohort; when liver cancers are excluded, the rate is still almost 2 times higher.

Lisa Nyberg, MD, MPH, Kaiser Permanente, Southern California, senior author of the study, explains: "The results suggest that cancer rates are increased in the cohort of hepatitis C patients versus the non-hepatitis C patients, both including and excluding liver cancers. These findings certainly point to the suggestion that hepatitis C may be associated with an increased risk of cancer. However, the findings must be interpreted with caution, as the study also showed that confounding factors such as alcohol abuse, tobacco, obesity, and diabetes modified the results."

Dr Laurent Castera, Vice-Secretary, European Association for the Study of the Liver, commented: "This data adds to the evidence bank linking hepatitis C with an increased risk of cancer, and highlights that there is still a long way to go in order to fully understand this complex and devastating disease."

Delaying HCV Therapy Worsens Treatment Efficacy

Delaying treatment for hepatitis C virus infection until an increased fibrosis-4 score is reached negatively impacted the efficacy of the treatment among veterans, according to data presented at the 2015 International Liver Congress™.

Jeffrey S. Mc Combs, PhD, associate professor at the University of Southern California School of Pharmacy, Los Angeles, California, and colleagues, analysed data of 187,860 veterans with HCV from the electronic medical records at Veteran Affairs between 1999 and 2010.

The patients selected for analysis had one or more reported fibrosis-4 (FIB-4) values, which the researchers looked at to estimate the impact on patient risk of treatment initiation before and after the patient's FIB-4 values increased, and to conclude whether or not treatment can or should be delayed.

The impact of time to treatment initiation and time to three different definitions of an elevated FIB-4 level were estimated using time-dependent Cox proportional hazards models, according to the research.

"What we have done is go back and look at the treatment of VA patients over a 10-year period ending in 2010 before the new medications and ask questions about what we can learn about the way treatment proceeded prior to new drugs," Mc Combs said during his presentation.

"We are building a story about essential need for new medications. It grew into an analysis [where we asked] can we come up with ways of allocating the scarce resources in a way that we can all get through this crisis and arrive at a point where we can eradicate this disease and not break the bank, so to speak."

"What we have done is go back and look at the treatment of VA patients over a 10-year period ending in 2010 before the new medications and ask questions about what we can learn about the way treatment proceeded prior to new drugs"

According to the results, beginning HCV therapy prior to a patient reaching a FIB-4 value greater than 1.00 reduced morbidity by 41% and mortality by 36%.

Beginning treatment after FIB-4 reached 1.00 was effective, but decreased the reduced morbidity risk to 30%. However, this did not occur if treatment initiation was delayed until after reaching a FIB-4 value greater than 3.25.

The risk reductions associated with treatment initiation before reaching a FIB-4 of more than 3.25 were 34% for the composite event and 45% for mortality. However, if treatment was initiated after a FIB-4 value of over 3.25 was attained, these risks decreased to 11% and 25%, respectively.

These adverse effects of delaying treatment until after reaching a FIB-4 value greater than 3.25 were because patients already treated would have viral load suppression and a reduced impact of viral load suppression on morbidity, according to Mc Combs' presentation.

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Disclosures

The researchers report no relevant financial disclosures.

Late-Breaking Oral Presentation Highlights RG-101's Potent, Durable and Pan-Genotypic Effects in Diverse HCV Population

Regulus Therapeutics Inc., a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, presented new data strengthening the profile of RG-101, a wholly-owned, GalNAc-conjugated anti-miR targeting microRNA-122 ("miR-122") for the treatment of HCV, during an oral late-breaking session at ILC 2015 in Vienna, Austria.

Extended follow-up results evaluating a single subcutaneous administration of either 2 mg/kg or 4 mg/kg of RG-101 as monotherapy in HCV patients with varied genotypes, liver fibrosis status and treatment history showed that 10/22 patients had HCV RNA levels below the limit of quantification ("BLOQ") at 12 weeks and 70 % of those patients remained BLOQ at 20 weeks (7/10). In addition, the positive results that were previously reported from the completed clinical study of RG-101 were reviewed during the oral late-breaker.

Regulus also made several poster presentations highlighting the pharmacokinetics and pharmacodynamics of RG-101 in healthy volunteers, the preclinical pharmacokinetics, pharmacodynamics, and toxicity of RG-101, and the efficacy of RG-101 in a preclinical model of HCV. The ILC 2015 oral presentation slides and posters related to RG-101 will be accessible at www.regulusrx.com.

"With multiple presentations at this year's ILC meeting, Regulus is pleased to tell the complete development story of RG-101, our unique microRNA therapeutic for the treatment of HCV, with positive preclinical results through impressive data in our first-in-human clinical trial," said Paul Grint, MD, Chief Medical Officer of Regulus. "All told, we believe that RG-101 is the most potent, durable and versatile compound in development to treat HCV. In the near term, we look forward to testing the ability of RG-101 to shorten the duration of treatment to just four weeks in combination with oral agents, which is a key goal to advance the program under our 'Clinical Map Initiative' strategy."

"ILC 2015 is an extremely important meeting to advance the treatment of HCV and we are pleased to present such significant data on RG-101 in the oral late-breaking session," said Hendrik W. Reesink, M.D., Ph.D., Associate Professor in the Department of Gastroenterology and Hepatology at the Academic Medical Center in The Netherlands. "Having so many patients with undetectable levels of virus after just a single administration so many months out is truly remarkable and these findings continue to suggest the clinical benefit of RG-101's ability to improve upon current therapies in a wide range of HCV patients. I look forward to seeing RG-101 progress into future clinical studies."

REGULUS THERAPEUTICS™

Transgene Presents New Data With TG1050, An Immunotherapy Being Developed To Treat Chronic Hepatitis B

Transgene SA announced that new pre-clinical data with TG1050, an immunotherapy being developed for the treatment of chronic hepatitis B, were presented at The International Liver Congress™ 2015.

The TG1050 data were presented as part of a Liver Immunology session in an oral presentation entitled: TG1050, A Novel Immunotherapeutic to Treat Chronic Hepatitis B, can Control HBsAg and Provoke HBsAg Seroconversion in HBV-persistent Mouse Models (Abstract O031).

The data presented demonstrates the antiviral potential of TG1050 in a persistent hepatitis B virus (HBV) in vivo model.

In this model, TG1050 was shown to significantly reduce circulating HBV DNA, to reduce the circulating HBV surface antigen (HBsAg), and to trigger seroconversion to HBsAg (i.e., to develop anti-HBsAg antibodies). The development of anti-HBsAg antibodies has been associated with HBV cure.

The presentation is available on Transgene's website in the "Our Pipeline/Publications" section at http://www.transgene.fr/?page_id=10487#TG1050.

"TG1050 was designed by Transgene's scientific and medical teams and it is exciting to see it entering the clinic" said Eric Quéméneur, PhD, Executive Vice President and Vice President, Research & Development.

"The pre-clinical data presented today provide strong proof of concept and further support the clinical development plan for TG1050 in the treatment of chronic hepatitis B.

The first-in-humans clinical trial, which is expected to begin patient enrollment in mid-2015, will evaluate the safety of TG1050 in combination with current standard-of-care antiviral therapy."

Preliminary Results Show Civacir® Prevents Recurrence of Hepatitis C in Liver Transplant Patients

Phase III data demonstrate prophylactic efficacy of Civacir® in patients who undergo antiviral therapy prior to transplantation.

New data from an ongoing Phase III trial revealed at The International Liver Congress™ 2015 show that the use of hepatitis C immune globulin (HCIG, Civacir®) can effectively prevent hepatitis C virus (HCV) recurrence in patients following a liver transplant (LT). The data demonstrate that intravenous Civacir given both peri- and post-LT prevents HCV-reinfection in patients who also received antiviral therapy (AVT) before their transplant operation.

Civacir is a hepatitis C immune globulin (HCIG) produced from pooled plasma from hundreds of screened donors who have high antibody titers against HCV. In this trial, patients received AVT before their LT and those in the active treatment groups received 16 infusions of Civacir in the peri- and immediate post-LT period for 10 weeks. The control group received current standard of care (no treatment) post-LT.

The preliminary results suggest that Civacir provides an effective alternative approach as compared to current standard of care to prevent HCV recurrence in post-LT patients. Civacir was well tolerated with no drug-related serious adverse events observed during the study.

Hepatitis C virus (HCV) remains the leading cause for liver transplantation (LT) and recurrent HCV disease is the most frequent cause of graft loss. Prevention of recurrence independent of genotype and severity of cirrhosis is highly desirable because it simplifies post-LT management.

AbbVie Presents Late-Breaking, Preliminary Phase 3b Data with VIEKIRAX® + EXVIERA®

AbbVie announced new, preliminary safety and efficacy data from the first cohort of its ongoing, Phase 3b RUBY-I study. RUBY-I is evaluating VIEKIRAX® (ombitasvir/paritaprevir/ritonavir tablets) + EXVIERA® (dasabuvir tablets) with or without ribavirin (RBV) in treatment-naïve, non-cirrhotic, genotype 1 (GT1) chronic hepatitis C patients with severe renal impairment (stage 4 or 5), including those on hemodialysis.

The primary endpoint of the study is the percentage of patients achieving sustained virologic response at 12 weeks post-treatment (SVR12). Patients who reached post-treatment week four to date (n=10 of 20 enrolled) achieved 100% SVR4 (n=10/10).[1] RUBY-I was presented as a late-breaker at The International Liver Congress™ (ILC) 2015.

"Treating hepatitis C patients with severe renal impairment may be a concern, particularly in those patients on hemodialysis," said Paul J. Pockros, M.D., director of Liver Disease Center Scripps Clinic and director of clinical research at Scripps Translational Science Institute in La Jolla, California. "With limited data currently available on the safety and efficacy of interferon-free treatments for patients with renal impairment, the preliminary results seen in RUBY-I show promising initial SVR rates with the VIEKIRAX® + EXVIERA® regimen in a dedicated study for this often difficult-to-treat patient population."

Additionally, RUBY-I data showed no virologic failures to date.[1] Preliminary safety analyses reported that patients experienced mainly mild or moderate adverse events when receiving VIEKIRAX® + EXVIERA® with or without RBV, most commonly (>20%) anemia, fatigue, diarrhea, nausea, dizziness and headache.[1] To date, eight of 13 genotype 1a (GT1a) patients had a RBV dose interruption.[1]

"RUBY-I is part of AbbVie's broader Phase 3b program and demonstrates our continued focus on people living with hepatitis C that have specific needs," said Scott Brun, M.D., vice president, pharmaceutical development, AbbVie. "Studies in our Phase 3b program will help to further expand our knowledge of the utility of VIEKIRAX® + EXVIERA® in special populations encountered in clinical practice."

Additional Phase 3b studies from AbbVie presented at ILC 2015 included MALACHITE-I and MALACHITE-II data, and the TOPAZ-I and TOPAZ-II study design. The MALACHITE studies evaluate adult patients with GT1 chronic HCV infection without cirrhosis receiving VIEKIRAX® + EXVIERA® with or without RBV compared to treatment with telaprevir with pegylated-interferon and RBV, which remains the standard of care in many regions of the world.[2,3]

The TOPAZ studies will evaluate the effect of SVR12 on long-term outcomes, five years following treatment with VIEKIRAX® + EXVIERA® with or without RBV in adults with GT1 chronic HCV infection.[4]

> "Studies in our Phase 3b program will help to further expand our knowledge of the utility of VIEKIRAX® + EXVIERA® in special populations encountered in clinical practice" Scott Brun, M.D., vice president, pharmaceutical development, AbbVie

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Norgine Presents PROSPER Study - First Ever Real World Evidence Study in Hepatic Encephalopathy Patients Taking Rifaximin-α 550mg

Norgine B.V. presented the study design of PROSPER, a real world outcomes study of hepatic encephalopathy patients' experiences on rifaximin-α 550mg at The International Liver Congress™ (ILC) 2015. PROSPER is an observational, multicentre study among 550 patients in Europe and Australia. It has been designed to monitor the clinical effectiveness of rifaximin-α and its impact on health care resources utilisations.[1]

Hepatic encephalopathy places a significant burden on patients and their caregivers, with the burden increasing as the severity of the disease progresses.[2,3] Furthermore, patients with hepatic encephalopathy have significantly more hospitalisations, emergency hospital admissions, and primary care contacts compared with patients with severe liver disease without hepatic encephalopathy.[4]

It is anticipated that the findings of this study will provide important real world evidence, as well as potentially providing a better understanding of the burden and natural history of hepatic encephalopathy as well as the variability in disease management in individual units.

Donna McVey, Chief Development Officer, Norgine said: "The announcement of this study is a milestone in our journey in hepatology and demonstrates our commitment to patients with hepatic encephalopathy; helping to improve the understanding of the impact of rifaximin-α 550mg in the real world, beyond what we see in controlled clinical trials. This study will help us and healthcare decision-makers to improve the treatment of hepatic encephalopathy and ensure effective use of rifaximin-α 550mg to minimise the burden of this disease on patients, their carer and healthcare budgets."

Hepatic encephalopathy is a serious and potentially life-threatening neuropsychiatric condition associated with advanced liver cirrhosis that affects around 248,000 people in Europe and Australia combined.[5,6,7,8]

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Herbal Remedy Derived from Milk Thistle Demonstrates Efficacy in Non-alcoholic Steatohepatitis

Silymarin results in resolution of non-alcoholic steatohepatitis and improvement in fibrosis. Results from a double-blind, placebo-controlled study of silymarin, which is derived from the milk thistle plant, have shown that this herbal remedy may be a useful treatment option for non-alcoholic steatohepatitis (NASH). An interim analysis of the study, revealed at The International Liver Congress™ 2015, shows a significantly higher percentage of patients experienced NASH resolution and improvement in fibrosis after 48 weeks of treatment with silymarin compared to placebo. NASH occurs when the liver becomes inflamed due to the accumulation of fat. Over time, persistent inflammation can lead to the formation of fibrous scar tissue in the liver and around its blood vessels, which can eventually cause cirrhosis.

A total of 64 patients (silymarin = 30, placebo = 34) with biopsy-proven NASH had completed the study at the time of interim analysis. Silymarin has already demonstrated anti-oxidant, anti-inflammatory and anti-fibrotic properties, and these latest study results show that it may be a useful treatment for NASH.

Gilead Announces Results From Studies Evaluating Sofosbuvir-based Regimens in Chronic Hepatitis C Patients With Genotypes 2-5

Gilead Sciences, Inc. announced results from two studies evaluating the safety and efficacy of investigational uses of sofosbuvir-based regimens in chronic hepatitis C virus (HCV)-infected patients with genotypes 2, 3, 4 and 5. Results from the BOSON study of Sovaldi® (sofosbuvir 400 mg) in combination with ribavirin (RBV) or with pegylated interferon (PEG)/RBV demonstrated high cure rates across all patients with genotypes 2 and 3. Separately, results from a Phase 2 study demonstrate the safety and efficacy of Harvoni® (ledipasvir 90 mg/sofosbuvir 400 mg) in patients with genotypes 4 or 5 infection. Data from both studies were presented in oral sessions at the 50th Annual Meeting of the European Association for the Study of the Liver (The International Liver Congress™ 2015) in Vienna, Austria.

Sovaldi and Harvoni are each approved in the United States for the treatment of chronic HCV infection. Sovaldi is used in combination with other agents and its efficacy has been established in patients with genotypes 1-4; Harvoni is indicated for patients with genotype 1.

BOSON (Study GS-US-334-0153, #LB05), a randomized Phase 3 study of 592 patients, evaluated the safety and efficacy of Sovaldi plus RBV for 16 or 24 weeks compared with Sovaldi plus PEG/RBV for 12 weeks among treatment-naïve or treatment-experienced genotype 3 patients with and without cirrhosis and treatment-experienced genotype 2 patients with cirrhosis. Thirty-seven percent of study participants had cirrhosis.

Among genotype 3 patients, rates of sustained virologic response 12 weeks after treatment (SVR12) were highest among those receiving Sovaldi plus PEG/RBV for 12 weeks (93%, n=168/181), compared to those receiving Sovaldi plus RBV for 24 weeks (84%, n=153/182) or for 16 weeks (71%, n=128/181). Treatment-experienced genotype 3 patients with cirrhosis receiving Sovaldi plus PEG/RBV demonstrated SVR12 rates of 86% (30/35).

Genotype 2 patients also demonstrated high SVR12 rates across all treatment arms. SVR12 rates among patients receiving Sovaldi plus PEG/RBV were 94% (15/16), and 100% (17/17) and 87% (13/15) for those receiving Sovaldi plus RBV for 24 and 16 weeks, respectively.

Sovaldi plus PEG/RBV and Sovaldi plus RBV were well tolerated. The most common adverse events in the study were fatigue, headache, insomnia and nausea. Overall, six patients (1%) discontinued treatment due to adverse events, one of whom was treated with Sovaldi plus PEG/RBV.

"It remains difficult to achieve a virological response in genotype 3, which is one of the most prevalent genotypes in the world, with higher prevalence in Europe and Asia," said Graham R. Foster, FRCP, PhD, Professor of Hepatology, The Liver Unit, Queen Mary's University of London, Barts Health, London, United Kingdom. "These results are compelling because they represent the highest cure rates observed among treatment-experienced, cirrhotic genotype 3 patients in any Phase 3 clinical trial to date."

In a separate open-label Phase 2 study of Harvoni conducted in France (Study GS-US-337-1119, O056), results demonstrated high SVR rates in both treatment-naïve and treatment-experienced patients with chronic HCV genotypes 4 or 5 infection, 50% of whom had cirrhosis.

Ninety-three percent of patients with genotype 4 (41/44) and 95% of patients with genotype 5 (39/41) achieved SVR12. Response rates were similar among both treatment-naïve and -experienced patients and regardless of cirrhosis.

The most common adverse events (affecting more than 10% of patients) were asthenia, headache and fatigue. Most adverse events were mild or moderate in severity and none resulted in treatment discontinuation. There were no grade 3 or 4 clinical laboratory abnormalities.

"HCV genotype 4 and 5 are less prevalent than other genotypes and therefore have traditionally not been closely studied," said Armand Abergel, MD, PhD, Department of Hepatology and Gastroenterology, Centre Hospitalier Universitaire-Estaing, Université d'Auvergne, Clermont-Ferrand, France. "These data provide important evidence that the all-oral, ribavirin-free Harvoni regimen is both safe and effective for many patients with genotype 4 or 5, regardless of prior treatment experience."

The safety and efficacy of these investigational uses of Harvoni and Sovaldi have not been established.

Sofosbuvir/Ledipasvir + Ribavirin Cures Most Hepatitis C Patients with Advanced Liver Disease

An oral regimen of sofosbuvir/ledipasvir (Harvoni) and ribavirin taken for 12 or 24 weeks produced sustained virological response rates of 85%-88% for genotype 1 hepatitis C patients with decompensated cirrhosis and 95%-98% for liver transplant recipients with less advanced liver damage, according to preliminary results from the SOLAR-2 study presented at the European Association for the Study of the Liver (EASL) 50th International Liver Congress™.

Direct-acting antiviral agents used in interferon-free regimens have revolutionised hepatitis C treatment, curing most patients including those traditionally considered difficult to treat. But challenges remain for people with advanced liver disease, including those with decompensated cirrhosis (when the liver can no longer carry out its vital functions) and patients who are awaiting or have received liver transplants.

Michael Manns from Hannover Medical School in Germany and fellow investigators with the SOLAR-2 trial (GS-US-337-0124) evaluated the safety and efficacy of the nucleotide HCV polymerase inhibitor sofosbuvir and NS5A inhibitor ledipasvir, taken as a once-daily fixed-dose coformulation, plus daily ribavirin for people with advanced liver disease.

This Phase 2 study enrolled more than 300 chronic hepatitis C patients in Europe, Canada, Australia and New Zealand. Three-quarters were men, more than 90% were white, and the median age was nearly 60 years. Most had HCV genotype 1 (about half with 1a and 40% with 1b), while about 10% had genotype 4. About 80% had received prior treatment without being cured.

SOLAR-2 included 160 people with decompensated cirrhosis who were either awaiting or had received liver transplants. They were classified as Child-Pugh-Turcotte (CPT) class B or C, an index of liver disease severity based on total bilirubin and albumin levels, blood clotting capacity, and presence of ascites or hepatic encephalopathy. About one-quarter of the CPT B/C patients had a MELD score greater than 15 (another measure of liver disease severity).

The study also included 168 liver transplant recipients with recurrent HCV who had less severe liver disease – CPT Class A and absent to advanced liver fibrosis (stage F0-F3).

Participants were randomly assigned to receive sofosbuvir/ledipasvir plus ribavirin for either 12 or 24 weeks. Manns explained that when the study was designed it was not yet known how well sofosbuvir/ledipasvir without ribavirin would work for patients with advanced disease, so there was no ribavirin-free arm.

Results

• After 12 weeks of post-treatment follow-up, the CPT B/C patients had sustained virological response (SVR12) rates of 85% with 12 weeks of treatment and 88% with 24 weeks.
• In the CPT A group, SVR12 rates were 95% and 98%, respectively.
• A single genotype 1 CPT A patient, 6 genotype 1 CPT B/C patients, and 3 genotype 4 CPT B/C patients relapsed after finishing treatment.
• Overall cure rates were similar for 12 and 24 weeks of therapy.
• Participants with CPT B responded somewhat better than those with CPT C, and within the CPT C group, pre-transplant patients did better than post-transplant patients.
• Looking only at genotype 1 patients, SVR12 rates were similar to the overall rates.
• Among genotype 4 CPT B/C patients, however, only 57% were cured with 12 weeks of therapy, rising to 86% with 24 weeks; the corresponding rates were 91% and 100% for genotype 4 CPT A patients.
• Sustained viral suppression was associated with improved liver function: almost all CPT class A participants remained the same, 35% of those initially classified as class B reverted to class A, while 48% of those classified as class C reverted to class B and 5% to class A.
• CPT and MELD scores fell largely due to decreased bilirubin and improved ability to synthesize proteins such as albumin.
• Given that this was a population with advanced disease, almost all participants experienced some adverse events.
• About 15% of CPT A patients and 28% of CPT B/C patients had serious adverse events, but only a few cases were deemed related to the study drugs.
• 12 participants died during the study – mostly due to liver-related complications – but no deaths were considered treatment-related.
• 6 patients discontinued treatment due to adverse events, all but 1 of whom had decompensated cirrhosis.
• The most common adverse events were fatigue, anaemia, nausea, and headache.

Sofobuvir/ledipasvir plus ribavirin "resulted in high SVR2 rates in HCV patients with advanced liver disease, irrespective of transplantation status," the researchers concluded. They added that this regimen "was generally safe and well-tolerated in patients with advanced liver disease, pre- and post-liver transplantation." Manns cautioned that the genotype 4 numbers were too small to

make meaningful comparisons, but suggested that 24 weeks is probably preferable for genotype 4.

Looking at another group of patients with advanced liver disease, a late-breaking poster presentation by Xavier Forns and colleagues described 11 participants in SOLAR-1 and SOLAR-2 who developed fibrosing cholestatic hepatitis, a rare severe form of recurrent hepatitis that can occur after liver transplantation. All these patients achieved SVR12 after 12 or 24 weeks of treatment with sofosbuvir/ledipasvir plus ribavirin, according to a press release issued by manufacturer Gilead Sciences. "The patients included in these analyses are among the most difficult to both treat and cure and, until now, have had limited or no treatment options," Manns stated in the release, commenting on both studies. "These data demonstrate that, even among these difficult-to-treat patient groups, sofosbuvir-based oral therapy offers the potential of high cure rates, improves outcomes and is generally well tolerated with a favourable safety profile."

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Researchers Highlight Need for Better Evidence to Guide European Efforts to Increase Hepatitis B and C Testing

The apparent dearth of research on hepatitis B and C testing in many European countries could be hampering efforts to identify infected individuals, according to results from a comprehensive review of 136 studies presented at The International Liver Congress™ 2015.

The systematic review concluded that the current evidence base on hepatitis B and C testing appears to be lacking in many European countries. At present it is informed primarily by published articles and conference abstracts from just 6 out of 53 member countries of the World Health Organization (WHO) European Region: Turkey, Germany, Italy, France, The Netherlands and the United Kingdom.

The results indicate that some high-risk populations have been studied much more than others, but mostly only in a small number of countries. The results also appear to show high median testing uptake levels across Europe. However, since almost all of the studies used methodologies that required or encouraged study participants to undergo testing, high median testing uptake levels are not likely to be representative of the overall testing uptake in most populations. "It's clear from our review that there are crucial gaps in our knowledge on hepatitis B and C testing – we do not yet have enough information to plan effective public health responses in Europe," commented Professor Jeffrey Lazarus, Professor of International Health Systems at Copenhagen University, Denmark. "Our research team is particularly concerned about the low numbers of published studies looking at migrants, prison inmates and men who have sex with men – all populations that might benefit greatly from targeted hepatitis testing interventions."

> **"It's clear from our review that there are crucial gaps in our knowledge on hepatitis B and C testing" Commented Professor Jeffrey Lazarus, Professor of International Health Systems at Copenhagen University, Denmark**

Professor Tom Hemming Karlsen, Scientific Committee Member, European Association for the Study of the Liver, added: "Viruses that affect the liver, such as hepatitis B and C, can cause real problems if not identified and treated early. We need to raise awareness of the threat posed by these viruses and actively encourage testing across Europe. This is not only vital to diagnosis and treatment but also to prevention – to stopping the viruses spreading through populations and generations to come."

New Real World Data Show Sofosbuvir/Daclatasvir Combination is an Effective Treatment Option for Difficult-to-treat Hepatitis C Patients

Results presented at The International Liver Congress™ 2015 show that the sofosbuvir (SOF)/daclatasvir (DCV) treatment combination is effective amongst hepatitis C virus (HCV) genotype-1 mono-infected patients. These results are significant because whilst other combinations have been widely reported on, there have been few data until now regarding the use of SOF/DCV combination in real world situations.

Overall, the sustained virologic response rate at 4 weeks (SVR4) for SOF/DCV was 81.6% after 12 weeks of treatment and 93.9% following 24 weeks of treatment. The SVR4 rate for SOF/DCV with ribavirin (RBV) was 100% and 96.6% after 12 and 24 weeks, respectively. The 12-week combination of SOF/DCV/RBV achieved a 100% SVR4 rate in cirrhotic patients without the additive effect of extension of the treatment to 24 weeks with or without RBV (95.7% and 92.5%, respectively), and this was also true in experienced patients. All non-cirrhotic patients achieved 100% SVR4 at 12 weeks, demonstrating that the 12-week combination of SOF/DCV is a proven therapeutic option. Importantly, the SVR12 rate was 100% for SOF/DCV/RBV after both 12 and 24 weeks.

"The cohort study has found that the sofosbuvir/daclatasvir combination is associated with a high rate of SVR4 in difficult-to-treat patients infected by genotype-1 hepatitis C. We also found that the combination with ribavirin increases the SVR rate in cirrhotic or experienced patients without the additive effect of the extension of the treatment from 12 to 24 weeks. We hope that this helps support further treatment options for difficult-to-treat patients," said Professor Stanislas Pol, Hôpital Cochin, Paris, France, principal investigator of the French ANRS CO-22 Hepather cohort.

409 HCV genotype-1 mono-infected patients were given a combination of SOF (400 mg/d) and DCV (60 mg/d) without ribavirin (n=318) or with ribavirin (1-1.2 g/d, n=91). 318 patients had cirrhosis and 306 were previously treated with peginterferon-ribavirin (PR) (n=134) or PR + a first generation protease inhibitor (PI) (n=172). "This study shows very positive results for hepatitis C genotype-1 mono-infected patients. This is one of the first real-life studies looking into sofosbuvir/daclatasvir combinations and has demonstrated that this is a good therapeutic option for these patients. It represents another treatment option to help patients beat hepatitis C," said Professor Tom Hemming Karlsen, Scientific Committee Member, European Association for the Study of the Liver. Serious adverse events were reported in 9% of patients and treatment discontinuation related to adverse events in 3.1%.

Pooled Analysis Confirms Vitamin E as a Treatment for Non-alcoholic Steatohepatitis

A study found that vitamin E is a safe and effective treatment for both adults and children.

Results revealed at The International Liver Congress™ 2015 show that vitamin E (d-alpha-tocopherol) is an effective treatment for non-alcoholic steatohepatitis (NASH). NASH occurs when the liver becomes inflamed due to the accumulation of fat. Over time, persistent inflammation can lead to the formation of fibrous scar tissue in the liver and around its blood vessels, which can eventually cause cirrhosis.

A pooled analysis of data from two randomised trials comparing vitamin E versus placebo, and the placebo group from another trial comparing vitamin E use versus non-use, demonstrates that the efficacy of vitamin E is comparable to other treatments for NASH, including pioglitazone, metformin and obeticholic acid. In addition, treatment with vitamin E is associated with significant improvements in both NASH histology (45% vs 22% in those not treated with vitamin E) and resolution of disease (38% vs 20% in those not treated with vitamin E). There was no increase in cardiovascular events and no adverse lipid profiles were observed with vitamin E treatment.

A total of 347 patients (155 treated with vitamin E, 192 not treated with vitamin E) were included in the analysis which compared data from three clinical trials that investigated the efficacy and safety of vitamin E as a treatment for NASH: the PIVENS, TONIC and FLINT trials. Histologic improvement was defined as ≥ 2 point improvement in NAS with no worsening of fibrosis, and NASH resolution measured effectiveness.

The study supports the use of vitamin E as a treatment for NASH.

Once-daily Grazoprevir/Elbasvir is Effective and Well-tolerated in Patients Infected with Chronic Hepatitis C Virus

Results presented at The International Liver Congress™ 2015 show that a 12-week oral regimen of once-daily single tablet grazoprevir/elbasvir (GZR/EBR) is effective and well-tolerated in treatment-naive (TN) patients infected with chronic hepatitis C virus (HCV) genotypes (GT)-1, -4 or -6, including those with compensated cirrhosis.

Based on preliminary results from 316 GZR/EBR recipients in the immediate treatment arm, 299 patients (95%) achieved a sustained virologic response at 12 weeks (SVR12).

"These initial results show that once-daily grazoprevir/elbasvir offers significant advantages over older treatments, demonstrating the ideal combination of high efficacy with good tolerability and convenience in treatment-naive patients infected with chronic HCV," said Rajender Reddy, MD, FAASLD Professor of Medicine, Professor of Medicine in Surgery, Director of Hepatology, Medical Director of Liver Transplantation, University of Pennsylvania, USA.

Serious adverse events (AEs) occurred in 9 (3%) and 3 (3%) patients in the active (immediate treatment) and placebo (deferred treatment) arms, respectively.

"Newer antiviral regimens such as the combination of grazoprevir/elbasvir offer much hope to people living with hepatitis C. They have shown great efficacy and tolerability for the treatment of this chronic infection," said Dr Laurent Castera, Vice-Secretary, European Association for the Study of the Liver.

C-EDGE TN is an international, randomised, blinded, placebo-controlled, parallel-group trial of an oral fixed-dosed combination of GZR 100 mg/EBR 50 mg once-daily in TN patients infected with HCV GT-1, -4 or -6, including cirrhotic and non-cirrhotic patients.

Drinking Just One or Two Alcoholic Drinks a Day Linked to Liver Disease

New data highlights why reducing heavy drinking should be considered an important target for public health monitoring and policies. According to the World Health Organization, excessive alcohol drinking is the most common cause of cirrhosis worldwide.

A new worldwide study presented at The International Liver Congress™ 2015 has shown the significant influence of daily drinking on this disease burden.

New data shows that the cirrhosis burden caused by alcohol increased by 11.13% when moving from the moderate to heavy daily drinking (up to one drink/day for women; two drinks/day for men) classification ($p<.001$).

Most studies assessing the prevalence of alcohol abuse as a risk factor for alcoholic cirrhosis focus on total annual amount drunk per person. However, the researchers highlight that clinical studies suggest that it is a high daily consumption which is the strongest predictor of alcoholic cirrhosis. This new research concluded that heavy daily drinkers most significantly and independently influence a country's cirrhosis burden.

According to the World Health Organization's Global Status Report on Alcohol and Health, around 6% of global deaths are caused by drinking alcohol, the majority from alcoholic cirrhosis - scarring of the liver as a result of continuous, long-term liver damage. Half of all cases of cirrhosis are caused by alcohol. The researchers analysed the WHO's Global Status Report on Alcohol and Health, which included parameters of alcohol consumption and drinking patterns from 193 countries. Reducing heavy drinking should therefore be considered as an important target for public health monitoring and policies.

Non-alcoholic Steatohepatitis Associated with a 50% Higher Chance of Death Compared with Non-alcoholic Fatty Liver Disease

Large population-based cohort provides important new insights into mortality and cardiovascular disease over the non-alcoholic fatty liver disease spectrum.

Results from a large population-based cohort of almost a million people in the UK found that the chances of dying from non-alcoholic steatohepatitis (NASH), over a 14-year period, was approximately 50% higher than for those with non-alcoholic fatty liver disease (NAFLD).

Reported at The International Liver Congress™ 2015, the large study analysed the overall burden of cardiovascular disease and all-cause mortality across the spectrum of NAFLD. The four stages of NAFLD are steatosis (or simple fatty liver), non-alcoholic steatohepatitis (NASH), fibrosis and cirrhosis.

Data from over 900,000 patients in England was obtained from a local computerised hospital activity analysis register. Data was processed to identify patients with NAFLD, NASH and NAFLD cirrhosis throughout the study period. Cardiovascular comorbidities were coded and their prevalence were analysed over 14 years.

During the 14-year study period, 2,701 patients were diagnosed with NAFLD-spectrum conditions: 1,294 with NAFLD, 122 with NASH and 1,285 with cirrhosis. All-cause mortality was higher in people with NASH than NAFLD (22.1% vs 14.5%) and in those with cirrhosis than NAFLD (53.1% vs 14.5%). Congestive cardiac failure was less prevalent in NAFLD than NASH and cirrhosis.

Dr Jake Mann, University of Cambridge, UK, concluded: "Non-alcoholic fatty liver disease is recognised as a risk factor for cardiovascular disease. Our results suggest that non-alcoholic steatohepatitis conveys an even greater risk. This study provides important new insights into mortality and burden of cardiovascular disease in patients across the non-alcoholic fatty liver disease spectrum."

Dr Laurent Castera, Vice-Secretary, European Association for the Study of the Liver, commented: "In non-alcoholic fatty liver disease, fat builds up in the liver which can cause inflammation and, eventually, lead to permanent scarring. Non-alcoholic fatty liver disease has four stages and these findings clearly link the severity of the disease with the increased risk of cardiovascular disease and death. It is therefore imperative that we identify people in the early stages of non-alcoholic fatty liver disease so they can be treated through diet and lifestyle interventions before their condition becomes potentially deadly."

Use of Pocket-sized Ultrasound Device Helps Reduce the Need for Further Testing in a Variety of Clinical Settings

A pocket-sized ultrasound device (PUD) use assists physicians in making more accurate diagnoses.

Results from a study presented at The International Liver Congress™ 2015 demonstrate that the use of a pocket-sized ultrasound device (PUD) helps to reduce the need for further testing in both the inpatient and outpatient setting.

The study evaluated the effectiveness of the PUD when testing for the following conditions: biliary-duct dilation, gallstones, ascites, splenomegaly, pleural effusion, pericardial effusion, urinary retention, urinary stones, abdominal mass and aortic aneurysm.

PUDs offer a comparable performance to standard ultrasonography, however the accuracy of a physical examination is often poor meaning that further tests are required. This study assessed whether adding the use of PUD to physical examination could lead to a reduction in the rate of additional tests required.

Of the 1,962 patients included in the study:

- 726 (37%) were inpatients, 510 (26%) were hepatology outpatients and 726 (37%) were recruited from GPs
- Gallstones (37%), ascites - excessive accumulation of fluid in the abdominal cavity (17%), pleural effusion (13%), urinary stones (13%) and urinary retention (12%) accounted for more than 90% of the clinical questions, confirmed by PUD in 66% of cases
- The overall frequency of further tests needed after PUD was 37%
- The rate of agreement between findings of the PUD and additional tests was 89%

This study found that after basic training, the use of a PUD offers a simple and effective way to improve the accuracy of diagnosis and reduce the number of tests a patient needs.

Hilton Barcelona Avenida Diagonal

Hilton Barcelona Avenida Diagonal

Hilton Diagonal Mar

The International Liver Congress™ 2016...

13th to 17th April, Barcelona, Spain

Treatment Strategies takes a look at a number of the finest hotels Barcelona has to offer...

HILTON BARCELONA AVENIDA DIAGONAL
Location - 589-591, BARCELONA, 08014, SPAIN

Experience the city at your leisure from the conveniently located Hilton Barcelona. Situated on Barcelona's main avenue, Avenida Diagonal, this hotel offers easy access to a range of activities. The hotel is within minutes of the largest stadium in Europe, home to FC Barcelona, two shopping centres with exceptional boutiques, El Palacio de Congresos de Catalunya (PCC) and a running circuit.

Hilton Barcelona is just 10 minutes from the city centre and is a fantastic base to discover all the main attractions. Barcelona International Airport El Prat is just 15 minutes away and Sants Railway Station is only 5 minutes from the hotel.

Stay in a newly designed room, with décor inspired by famous Catalan architect Antoni Gaudí and panoramic views of the city. All rooms at Hilton Barcelona feature work desks and WiFi for business convenience. Enhance your stay and upgrade to an Executive room or a spacious suite, with access to a private Executive Floor offering Executive Lounge access with a choice of complimentary Spanish and international newspapers, breakfast, evening hors d'oeuvres and refreshments.

Unwind after a busy day at The Vibe Bar & terrace. Discover the unique atmosphere of Barcelona while tasting our famous tapas and enjoying a delicious cocktail. Enjoy the innovative menu in The Mosaic Restaurant – inspired by Mediterranean cuisine and showcasing local produce.

HILTON DIAGONAL MAR BARCELONA
Location - PASSEIG DEL TAULAT 262-264, BARCELONA, 08019, SPAIN

Only a 10 minute walk from the beach, the Hilton Diagonal Mar Barcelona offers stunning views of the sea and the rising sun. Enjoy a fun family beach holiday, have a cultural Barcelona City break or spend a romantic weekend in Catalonia's capital. Less than 25 minutes from the airport, this Barcelona hotel is just a few stops from the city centre via Tram or metro. The hotel faces the largest shopping centre in Barcelona, Diagonal Mar.

Spacious contemporary rooms overlook the sea or Barcelona's sky line. WiFi or wired internet access, flat screen LED TV,

safe and mini bar are available. Some of the rooms can be connected to other rooms for your convenience as well. Guests also lounge in the luxury seasonal outdoor pool, play with their children in the paddling pool, or try one of the four-star facilities.

The spacious Executive Lounge offers a place to relax with spectacular city and sea views from its 15th floor terrace. As an Executive Guest, you will benefit from exclusive services in the lounge such as complimentary internet access, all day refreshments, breakfast and afternoon snacks.

Dine at the Hilton Indigo Restaurant for delicious International and Catalan food, or unwind at the seasonal poolside bar and restaurant 'Brisa' with Mediterranean dishes to be enjoyed on its beautiful terrace. The Pistaccio Lounge Bar is the perfect venue for cocktail lovers wishing to start or end their evening in a relaxed atmosphere.

Alexandra Barcelona, a DoubleTree by Hilton Hotel
Location - Calle Mallorca, 251, Barcelona, 08008, Spain

Boasting innovative design and contemporary amenities, Alexandra Barcelona, a DoubleTree by Hilton Hotel, is centrally located in the commercial area of Paseo de Gracia in the heart of Barcelona - it is walking distance from Passeig de Gràcia and is within Rambla de Catalunya.

This stylish Barcelona hotel is near several famous modernist works and buildings, including La Pedrera and Casa Batlló and guests can enjoy easy access to the finest entertainment and shopping areas in the city.

The friendly staff look forward to welcoming you with a DoubleTree chocolate chip cookie on arrival.

Feel at home in a comfortable guest room at this Barcelona hotel, equipped with a variety of thoughtful amenities, including an ultra-slim LED TV and complimentary WiFi. For additional space and amenities, upgrade to a junior suite, many of which feature a private balcony or terrace. Host a meeting or celebration for up to 200 people with four meeting spaces, including a spacious, multi-purpose room and the latest A/V technology.

A 24-hour business centre is also available, offering a variety of useful services and amenities.

Da Luca Restaurant, Cafe & Bar is the perfect place to savour traditional Italian cuisine, including authentic specialities from the Liguria region, expertly prepared using the finest and freshest ingredients.

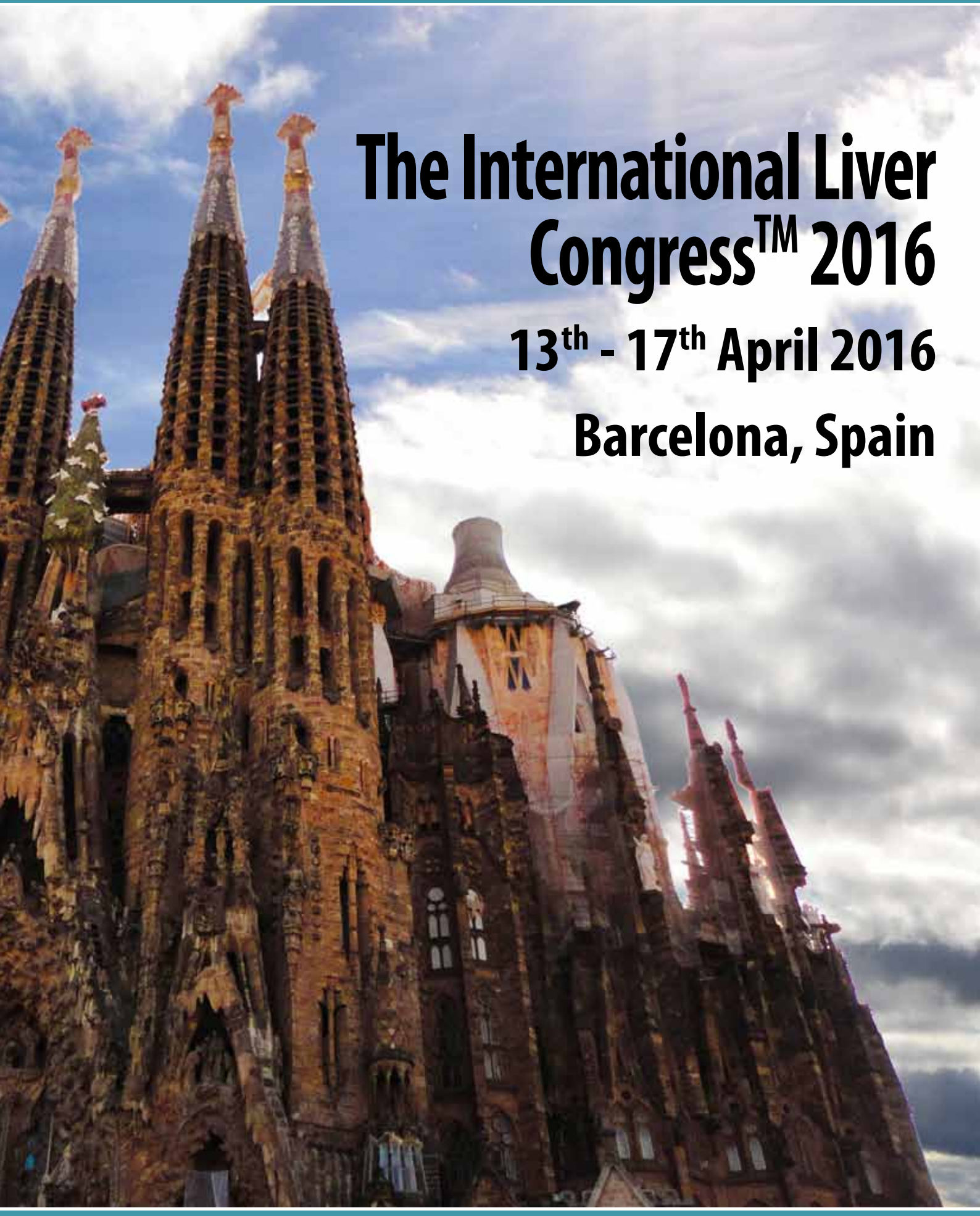
Enjoy coffee and a sandwich or meet with friends to sip cocktails on the terrace. Keep active in the exercise room or unwind in the 'wellbeing area', which features a dry Finnish Sauna and a restful massage room.

For more information please visit **www3.hilton.com**


Hilton Diagonal Mar


Alexandra Barcelona, a DoubleTree by Hilton Hotel


Alexandra Barcelona, a DoubleTree by Hilton Hotel



The International Liver Congress™ 2016

13th - 17th April 2016

Barcelona, Spain

Real-World Evidence: Does it Really Change Clinical Practice?

Summary of Presentations from the Norgine-sponsored Satellite Symposium at The International Liver Congress™ 2015, 50th Annual Meeting of the European Association for the Study of the Liver, Vienna, Austria, 22nd – 26th April 2015

Sara Montagnese,[1*] Jasmohan S. Bajaj,[2] Paolo Angeli[3] and Aleksander Krag[4]

1. Reader in Medicine and Honorary Consultant Physician, University of Padova, Padova, Italy; 2. Associate Professor of Medicine, Virginia Commonwealth University and McGuire VA Medical Center, Richmond, VA, USA; 3. Associate Professor of Internal Medicine, University of Padova, Padova, Italy; 4. Professor of Hepatology, University of Southern Denmark and Head of Hepatology, Odense University Hospital, Odense, Denmark

Dr Sara Montagnese is a Reader in Medicine and Honorary Consultant Physician at the University of Padova, Italy. Her research interests are in hepatic encephalopathy, and in the sleep and circadian disorders of patients with cirrhosis. Dr Montagnese has considerable scientific and clinical experience in these areas and has published extensively.

Dr Jasmohan S. Bajaj is an Associate Professor of Medicine at Virginia Commonwealth University and McGuire VA Medical Center in Richmond, Virginia, USA. He has served as a principal investigator or co-investigator for numerous clinical trials in areas such as hepatic encephalopathy, chronic liver disease and microbiome. Dr Bajaj is the Chairperson of the Acute-on-Chronic Liver Failure Special Interest Group at the American Association for the Study of Liver Disease and for the North American Consortium for the Study of End-Stage Liver Disease.

Prof. Paolo Angeli is an Associate Professor of Internal Medicine at the University of Padova, Italy. He is also Head of the Unit of Hepatic Emergencies and Liver Transplantation, a research group working on the pathophysiology and treatment of acute, chronic and acute-on-chronic liver diseases, and on liver transplantation. He is the present Secretary of the International Club of Ascites. Prof. Angeli has previously contributed to guidelines and/or positional papers on the management of ascites, bacterial infections and acute kidney injury in patients with cirrhosis for the European Association for the Study of the Liver. He also contributed to the new diagnostic criteria for acute kidney injury in patients with cirrhosis, which resulted from a consensus process involving almost all the international experts in this field.

Prof. Aleksander Krag is Professor of Hepatology at the University of Southern Denmark and Head of Hepatology at Odense University Hospital, a 1200-bed teaching hospital serving a population of 1.5 million people in Odense, Denmark. He holds a PhD from the University of Copenhagen and has completed the 'Pasteur programme' on leadership and project management at Harvard Business School, USA. Prof. Krag is also a member of the Scientific Committee of Baveno VI and the Executive Committee of the International Club of Ascites.

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Introduction

Randomised clinical trials are the gold standard in the development of new medications or interventions and are essential to prove efficacy; however they usually employ tightly defined inclusion/exclusion criteria and rigid treatment protocols. As such, they differ from everyday clinical practice, where patients are more diverse and complex in terms of clinical characteristics and treatment is tailored on an individual basis. Even when protocols and checklists are in place to help optimise patient care in clinical practice, they are not necessarily implemented in the way in which they were devised to be used and tested during clinical trial development.[1] Furthermore, the incidence of clinical events observed in randomised controlled trials may not reflect true event rates in clinical practice. For example, the incidence of venous thromboembolism in ambulatory patients with cancer appears to be higher in clinical practice (up to 13.5%) than data from clinical trials would suggest (3–4% in the placebo arms of trials for thromboembolism prophylaxis).[2] This is perhaps due to the selection of lower-risk patients in clinical trials and/or the detection of asymptomatic venous thromboembolism in real-world studies that are conducted over longer time periods than clinical trials.[2] Similarly, the benefits of carotid endarterectomy in the 'real world' have been shown to be greater than data from clinical trials had originally indicated,[3] largely because a small group of high-risk patients had not been identified and analysed separately. Issues such as these have fuelled wider debate about the validity of clinical trial data and directed attention to real-world, personalised and precision medicine.[4,5]

Selection of patients for clinical trials typically involves exclusion of those with high levels of comorbidity, since this can confound findings and hamper the discernment of a treatment effect. However, in clinical practice, the presence of comorbidity must be taken into account

when making treatment decisions. This is illustrated by the results from a study of 276 patients referred to a specialist clinic for suspected hepatic encephalopathy (HE) or for pre-transplant screening.[6] The patients underwent thorough diagnostic evaluation and, if needed, cerebral imaging.[6] Overall, 177/276 patients were found to be neuropsychiatrically impaired, but less than half of these (n=82; 46.3%) were deemed to have only HE, since the remaining patients (n=95; 53.7%) had comorbidities that could contribute to, or fully explain, their neurological/psychiatric profiles.[6]

It is therefore apparent that real-world studies are needed to complement evidence from randomised clinical trials, by providing information on the effectiveness (as opposed to efficacy) of a new intervention, together with pragmatic guidance on its expected risks and benefits when used in everyday clinical practice.

This article will focus on the challenges and benefits of setting up real-world studies in patients with liver disease, and discuss the importance of robust methodology and the inclusion of quality measures to ensure that such studies provide data that are both useful and relevant to clinical practice.

Setting Up an Inpatient Database: Patients with Cirrhosis – Lessons Learned from America

Dr Jasmohan S. Bajaj

The Role of Consortia in Clinical Research

The formation of consortia allows the collection of large amounts of data from a range of centres. As such, they are able to provide stronger evidence than a single centre alone, even if that centre comprises a large cohort of patients, since they represent a greater breadth of clinical practice experience. This is important because, even when practice guidelines are adhered to, there is still considerable variation between centres in the way in which clinical practice is conducted, due to differences in how physicians are trained and the guidelines are implemented. Consortia contribute substantially to clinical research, as evidenced by the high proportion of publications that are derived from such collaborations, and can be powerful tools to improve clinical medicine and inform future research. These are particularly valuable during the middle phases of translational research, when an intervention is being assessed for its potential implications in diagnosis and clinical practice, and for population health (T2 and T3 stages; Figure 1).[7] Since patients from tertiary-care and community-based centres are usually excluded from clinical trial populations by criteria designed to minimise the impact of confounding factors, data from randomised controlled trial populations are typically not reflective of the underlying real-world population. Consortia therefore provide a valuable means of bridging the evidence gap between clinical trials and clinical practice.

Setting up an Inpatient Database: the North American Consortium for the Study of End-Stage Liver Disease (NACSELD)

Inpatient databases provide a means of assessing how clinical trial data and evidence-based guidelines translate into real-world clinical practice. Before setting up a consortium for an inpatient database, several initial questions must be addressed. Firstly, it is important to ascertain whether there is a particular research question that needs to be answered which cannot be answered at a single centre. The collection of data in itself is not valuable unless the research objective is clearly defined. Secondly, it must be established whether there are other centres that are trying to address the same issue and, if so, they should be invited to join the consortium. It is important to try and involve a variety of centres from a range of geographical locations to ensure that a diverse patient population is represented. Thirdly, it must be established whether the necessary data can be collected easily, since the logistical implications of data collection can be substantial. Ease of data collection is primarily dependent on the design of the study, which must be carefully considered at the outset. Furthermore, it must be established whether or not there is funding available to help support the work. Funding can be difficult to obtain when initially setting up a project, but is often more forthcoming once the project is seen to be yielding useful information.

In the field of liver cirrhosis, it was recognised that there are many important questions that have not been addressed beyond the randomised controlled trial and single-centre settings. Consequently, NACSELD was set up as a consortium of tertiary-care hepatology centres that prospectively collects data on hospitalised patients with cirrhosis. The initial research question that NACSELD was set up to address was to identify the determinants of outcomes in cirrhotic patients hospitalised with bacterial infections.[8] This was recognised as a pressing need in North America and patients began to be enrolled only 5 months after initial discussions had taken place. NACSELD enrolled almost 600 patients from 17 sites in the USA and Canada for this project, with no specific funding [Bajaj, personal communication]. The current research objective of NACSELD

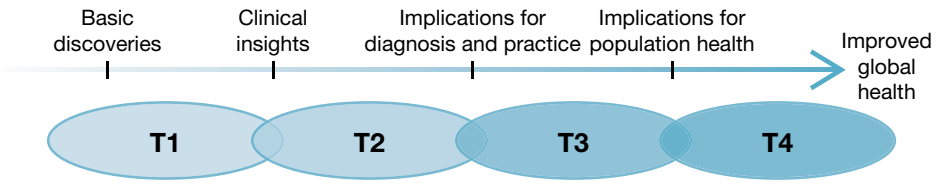


Figure 1. Translational research objectives through databases.

('NACSELD-II') is to identify the determinants of outcomes in cirrhotic patients hospitalised for non-elective purposes, for which over 1500 patients from 16 sites in the USA and Canada have currently been enrolled, with funding provided by a pharmaceutical company (Grifols) and the National Institute of Diabetes and Digestive and Kidney Diseases [Bajaj, personal communication]. Funding was provided on the basis of the results from the initial unfunded study and this has allowed the database to become much larger and more powerful than the original database, with samples (such as urine, serum and stools) being collected alongside patient data. The initial unfunded period was therefore a crucial first step in the overall progress and success of NACSELD.

The NACSELD protocol and data collection sheets were formulated and finalised during a meeting of the American Association for the Study of Liver Diseases (AASLD) acute-on-chronic liver failure (ACLF) special interest group. This provided an opportunity for all those involved to agree the project's objectives and ensure that their needs and concerns were addressed, thereby maximising the likelihood of active participation in data collection. The database was created and set up at the Virginia Commonwealth University Medical Center, using Research Electronic Data Capture (REDCap) software.[9] REDCap is a freely available resource allowing the creation of an online, anonymised database that can be adapted for each centre's use and made accessible to all researchers in the study. Once approved by local ethics boards, each centre recruits patients prospectively and enters anonymised data in the REDCap database. Importantly, each centre only has access to its own data, which can be used as that centre wishes (e.g. to publish abstracts). However, only the biostatistician, chairperson and database managers have access to the entire database, which is solely used to answer the specific question(s) agreed at the project's outset. The database is monitored and specific aspects of the clinical question(s) are extracted, analysed and published at a central location by an experienced biostatistician. Consequently, only the outputs of the database (as opposed to the actual data) are released and available for all participants to analyse and publish from.

Data from NACSELD have resulted in the publication of five original manuscripts to date, concerning second infections in patients with cirrhosis hospitalised with infection,[8] infection-related ACLF,[10] validation of the new consensus definitions for acute kidney injury,[11] the characterisation of risk factors for subsequent infections within 6 months of discharge in patients with cirrhosis originally hospitalised with infection,[12] and the risk and predictors of delisting or death in patients with cirrhosis hospitalised with infection.[13] NACSELD data have also been presented in 12 congress abstracts, including five oral presentations and three posters of distinction.

Other databases and consortia that are providing valuable information relating to cirrhosis include the European Association for the Study of the Liver-Chronic Liver Failure (EASL-CLIF) consortium, which has undertaken multiple studies concerning prognosis in patients with cirrhosis and ACLF;[14] the Acute Kidney Injury Network (AKIN), which aims to develop and facilitate international and interdisciplinary research initiatives in the diagnosis, prevention and treatment of acute kidney injury;[15] the Hepatitis C Therapeutic Registry and Research Network (HCV-TARGET), an international consortium of leading HCV investigators who have established a common research database and are conducting a longitudinal observational study to address issues relating to HCV therapy with direct-acting antiviral agents;[16] and the Chronic Hepatitis Cohort Study (CHeCS), a prospective, longitudinal, observational cohort study of data from four integrated healthcare systems, which has been undertaken to assess the clinical impact of chronic viral hepatitis in the USA.[17]

Lessons Learned from NACSELD

Experience from setting up NACSELD has shown that such projects are highly feasible. A coherent question is required at the outset and this must take into account the ease of putting patients into the study and collecting the necessary data – a balance is required between level of detail and practicality. Focused strategies need to be developed through discussions among the team members. The database must be carefully designed, data collection tools must be accessible to all those involved, and data must be entered into the database with care and accuracy (since 'garbage in = garbage out'). It should be remembered that not everyone who initially agrees to participate in such an endeavour will actually do so; sites have to be fully committed to the project in order for it to work, particularly if funding is not available. Most importantly, it is essential that there is confidence in the overall goal (to increase knowledge) and trust between colleagues regarding data collection, analysis and publication.

Setting Up an Outpatient Database: How Outpatient Data Informed Improvement in the Care of Patients with Cirrhosis

Professor Paolo Angeli

The Need for Improved Models of Care

The economic weight of cirrhosis on the healthcare system is substantial for several reasons. Firstly, the rate of hospitalisation associated with cirrhosis and its complications is high. For example, data from the Nationwide Inpatient Sample (NIS), a large nationally representative administrative database in the USA, have shown that the overall rate of hospitalisation for complications of cirrhosis (such as HE, ascites or variceal bleeding) between 1998 and 2003 was 23.6 per 100,000 people annually.[18] Secondly, hospitalisation is expensive: during the period of the NIS study, the average charge per hospitalisation for patients with complications of cirrhosis increased from US $19,775 to US $27,979.[18] In Italy, the corresponding average charge per hospitalisation, but without accounting for liver transplantation, has been estimated to

be US $12,647 [Angeli, personal communication]. Thirdly, the rate of hospital readmission in patients with cirrhosis is high. For example, a retrospective audit of over 400 patients with decompensated cirrhosis treated at a single academic transplant centre in the USA found that, over a median post-discharge follow-up period of 398 days, the rate of hospital readmission was 37% after 1 month and 69% overall (excluding patients with elective readmissions).[19] There is therefore a pressing need for new models of care for patients with cirrhosis to improve patient outcomes and reduce the substantial burden on healthcare systems of hospitalisation and readmission.

Factors Affecting Quality of Care

Quality of care can be measured using outcome indicators such as survival rate, hospital readmission rate, quality of life and perceived quality of care. However, such outcome measures are the final step in a ladder of patient management comprising access of patients to care, adherence to guideline recommendations and the model of care employed. Access to care for patients with decompensated cirrhosis varies between and within countries due to economic and demographic factors, such as race.[20] Although it is unclear whether patients with chronic diseases fare better as a result of specialist caregiving,[21] in the field of hepatology there is evidence to suggest that patients followed up by a specialist physician are more likely to be managed according to recommended guidelines than those who are followed up under non-specialist care. For example, a study that assessed whether recommendations for surveillance for hepatocellular carcinoma in high-risk patients (those with cirrhosis or non-cirrhotic hepatitis B) were being utilised in clinical practice found that surveillance rates were significantly higher among patients followed in subspeciality gastroenterology clinics compared with those followed in primary-care clinics (51.7% vs. 16.9%; $p<0.001$).[22] However, adherence to guideline recommendations alone is not sufficient to ensure good quality of care. This is illustrated by a prospective, randomised controlled study that compared a chronic disease management model with usual care in patients with chronic liver failure treated at a single hepatology unit in Australia.[23] Although adherence to recommended guidelines (e.g. screening for hepatocellular carcinoma, hepatitis A and B vaccination) was significantly higher in the chronic disease management model group compared with the usual care group, there were no significant differences between groups in terms of hospital admission rates, risk of death, Child-Turcotte-Pugh scores or quality of life.[23] It is therefore apparent that an effective overall model of care (rather than just adherence to guideline recommendations) is required in order to improve patient outcomes.

A New Model of Specialist Caregiving for Patients with Cirrhosis and Ascites

The need for real-world data to help guide clinical practice is not only important when evaluating the effectiveness of new treatments, but also when assessing new models of care. In many countries, the intervention of a specialist physician for outpatients with cirrhosis is 'on demand', the examination being undertaken on the basis of the results of laboratory investigations conducted 1–3 weeks previously. Since there has been increasing recognition that this approach to patient management is inappropriate, a new model of care was progressively developed for patients with cirrhosis and ascites discharged from the General Hospital of Padova, Italy. Recently, a study was conducted to compare this new 'care management programme' (CMP) with 'standard outpatient care' (SOC).[24] With SOC, the management of outpatients was undertaken by the primary physician with the support of a specialist physician who checked the patients 'on demand', without the availability of data from laboratory examinations and instrumental procedures in real time. Patients had the option of attending a 'day hospital' for specialist caregiving (e.g. paracentesis, banding ligation of oesophageal varices, blood transfusion), but not necessarily with the same specialist physician who had previously visited them as an outpatient. With the CMP, patients were followed up by a team comprising a consultant hepatologist, dedicated nurses and physicians-in-training at the hospital unit for outpatients. In patients who underwent a 'care management check-up', data from laboratory examinations, liver ultrasound and upper endoscopy were obtained in real time, and dietary, pharmacological and other treatment approaches (e.g. staging and treatment of hepatocellular carcinoma, scheduling for liver transplantation) were agreed. The support of other specialist physicians (such as toxicologists and psychiatrists) was also available, as required. All information was shared in real time with each patient's general practitioner and follow-up check-up dates were scheduled. As with SOC, CMP patients had the option of attending a day hospital for specialist caregiving, but they were seen at the day hospital by the same team responsible for their care management check-up. The potential advantages of the CMP were that clinical decisions were made in real time, there was the potential for the development of educational programmes for patients and their families, invasive procedures could be scheduled, information could be transferred to the patient's primary physician in real time, and adherence to treatment recommendations (e.g. recommendations for moderate dietary sodium restriction) could be optimised. Patients in the two groups were individually matched for eight variables chosen for their potential effect on outcomes: age, gender, type of ascites (responsive vs. refractory or recurrent), Model for End-stage Live Disease score, Child-Turcotte-Pugh score, aetiology of cirrhosis, local/non-local residence and comorbidities (Charlson index).[24]

In total, 40 and 60 patients were assigned to the CMP and SOC groups, respectively, and one patient from each group was lost to follow-up.[24] There were no significant differences between groups in terms of demographic, clinical and laboratory features, or causes of emergent hospital admission at the time of inclusion.[24] The study found that 12-month mortality from any cause was significantly lower for the CMP

group than for the SOC group (23.1% vs. 45.7%; p<0.025), as was 12-month mortality from liver-related causes (15.4% vs. 35.6%; p<0.05).[24] Regression analysis demonstrated that the probability of 1-year survival was significantly higher in the CMP group versus the SOC group (p=0.0086; Figure 2).[24] The rate of 30-day hospital readmission was significantly lower in the CMP group versus the SOC group (15.4% vs. 42.4%; p<0.01), as was the rate of readmission during the 12 months of follow-up (46.2% vs. 71.2%; p<0.025).[24] In addition, the mean number of days of hospital stay per patient-month of life was significantly lower in the CMP group versus the SOC group (2.9 vs. 6.0 days; p<0.025).[24] The causes of hospital readmission during follow-up were generally similar between groups, except that the readmission rate for massive ascites was significantly lower in the CMP group than in the SOC group (23.9% vs. 36.8%; p<0.05).[24] Although the costs associated with specialist caregiving and day hospital attendance were significantly higher in the CMP group than in the SOC group, the overall global costs attributable to management per patient-month of life were significantly lower for the CMP group than for the SOC group (€1479 vs. €2816; p<0.05), primarily because the costs of emergent hospitalisation were significantly reduced (€1347 vs. €2768; p<0.05).[24]

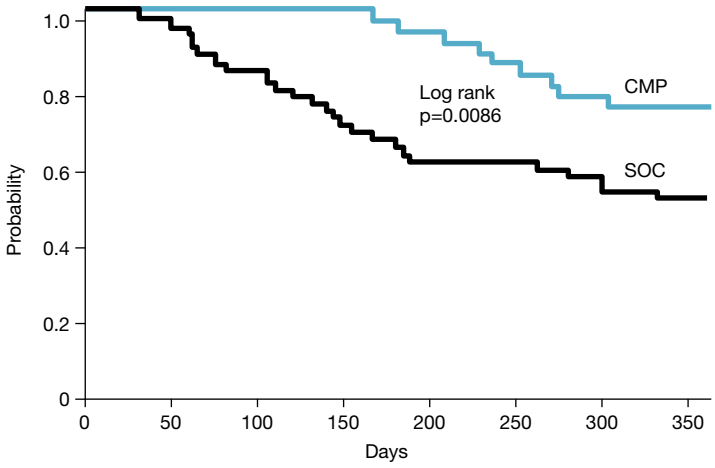


Figure 2. Probability of 1-year survival in patients with cirrhosis and ascites admitted to the CMP group or SOC group. Adapted from Morando F, *et al.*, 2013 with permission from Elsevier.[24]
CMP, care management programme; SOC, standard outpatient care.

In summary, this outpatient study demonstrated that the CMP can improve the quality of care and 12-month survival of patients with cirrhosis and ascites.[24] Moreover, the CMP's favourable cost profile, due to more rational use of hospital services, provides further evidence of its potential value in the care of outpatients with decompensated cirrhosis.[24] These findings illustrate that real-world evidence can be important in informing future clinical practice.

A New Prospective Observational Study in Hepatic Encephalopathy: PROSPER

Professor Aleksander Krag

Definition, Classification, Epidemiology and Burden of HE

HE is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting that manifests as a wide spectrum of neurological or psychiatric abnormalities, ranging from subclinical alterations to coma.[25] The neuropsychiatric symptoms of HE are thought to result from elevated blood levels of gut-derived neurotoxins (particularly ammonia), which enter the brain due to the inability of the cirrhotic liver to remove them from the blood.[26] The severity of HE is classified according to the West Haven criteria in a range from 'minimal' through grade 1 to 4, and the current EASL/AASLD guideline categorises 'covert HE' as West Haven minimal and grade 1 HE, and 'overt HE' as West Haven grades 2 to 4 HE.[25] Since HE represents a continuum of fluctuating and reversible symptoms, it may only be detected when it manifests as an overt episode, unless specific efforts are made to detect it in its covert stages.[27] Covert HE occurs in 20–80% of patients with cirrhosis and overt HE will occur in 30–40% of patients with cirrhosis at some time during their clinical course.[25] In the EASL-CLIF Consortium Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study, which involved over 1300 patients with cirrhosis and acute decompensation, approximately one third of patients (34%) had overt HE at the time of enrolment.[28]

HE increases the risk of mortality[28,29] and is one of the most debilitating complications of liver disease, negatively affecting the lives of both patients and caregivers.[25,30] In a population-based cohort study of 466 Danish patients diagnosed with alcoholic cirrhosis, the 1-year and 5-year mortality rates for patients with overt HE were 64% and 85%, respectively, substantially higher than for patients with ascites and/or variceal bleeding.[29] For example, 5-year mortality rates were 59%, 64% and 80% for patients with ascites alone, variceal bleeding alone and ascites plus variceal bleeding, respectively.[29] HE is associated with a substantial economic burden, due both to direct healthcare costs and the indirect costs associated with, for example, lost productivity.[25]

Rifaximin-α 550 mg in the Management of HE

Rifaximin-α 550 mg is a locally acting antibiotic that is minimally absorbed in the gut to reduce intestinal flora, including ammonia-producing species.[31] It is indicated in Europe for the reduction in recurrence of episodes of overt HE in patients aged ≥18 years.[32] In Australia, it has the same indication, but is restricted to where other treatments have failed or are contraindicated.[33] The efficacy of rifaximin-α 550 mg was demonstrated in a randomised controlled trial, in which rifaximin-α 550 mg twice daily reduced the relative risks of recurrence of overt HE and HE-related hospitalisation by 58% and 50%, respectively, compared with placebo (absolute risk reductions: 24%

and 9%, respectively).[34] In a subsequent extension study, long-term treatment (≥24 months) with rifaximin-α 550 mg provided a continued reduction in the rate of HE-related and all-cause hospitalisation, without an increased rate of adverse events.[35] As randomised controlled trials are conducted in carefully defined patient populations using rigid treatment protocols to ensure that a specific clinical hypothesis can be tested, real-world data are required to determine how the efficacy of rifaximin-α 550 mg translates into effectiveness in clinical practice.

Design of the Prospective Real-world Outcomes Study of HE Patients' Experience on Rifaximin-α 550 mg (PROSPER)

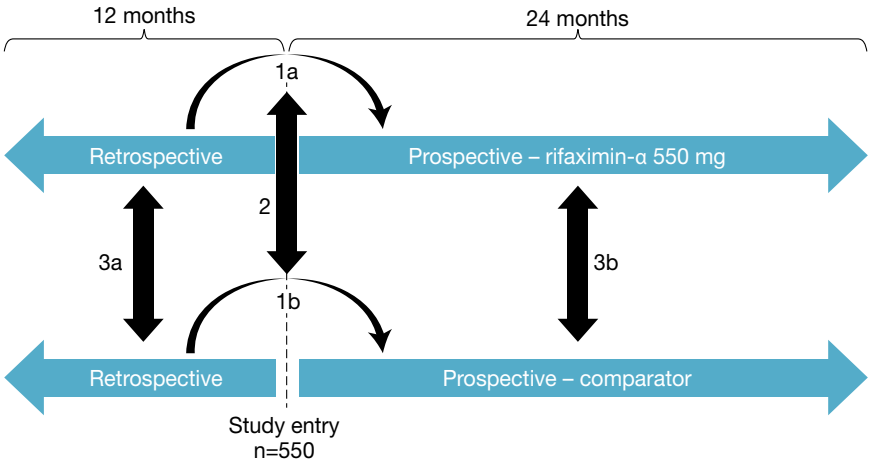
PROSPER is a multinational, multicentre, observational study that will be conducted in secondary- and tertiary-care centres across Europe and Australia.[36] It was designed in order to complement clinical trial evidence; its aim being to evaluate the 'real-world' clinical effectiveness of rifaximin-α 550 mg and its impact on healthcare resources when used for management of HE in routine clinical practice. PROSPER will be conducted under real-world clinical practice conditions, since no changes to management practice for HE patients will be made for the purposes of the study. In addition, it will employ very few inclusion and exclusion criteria in order to represent the heterogeneity of HE patients encountered in clinical practice. The study design will comprise two phases: a retrospective phase of up to 12 months, involving the review of patients' medical records and admissions data, and a prospective phase of up to 24 months, during which data will be collected for all patients receiving rifaximin-α 550 mg ('rifaximin-α 550 mg cohort') or not receiving rifaximin-α 550 mg ('comparator cohort'). The primary endpoint of the study is the rate of HE- and liver-related hospitalisation, and the resulting duration of hospitalisation (in terms of bed-days). Secondary assessments will include other measures of efficacy, effectiveness, safety, quality of life and work productivity impairment.[36]

Although 'real-world' studies have greater generalisability to clinical practice than clinical trials, they are associated with a greater potential for bias. Therefore, PROSPER has been purposely designed to minimise as much bias as possible.[36] A key factor in reducing bias will be the incorporation into the study design of three comparative approaches (Figure 3).[36] Statistical analyses will include multivariable methods (e.g. modelling or propensity score analysis) to minimise bias associated with observational study design. Count data, such as hospitalisation rates, will be assessed using regression analysis, which will account for the duration of exposure to rifaximin-α 550 mg and the influence of competing risks (such as death), and adjust for underlying differences between the two cohorts (i.e. confounding factors). In addition to the study's main assessments, exploratory analyses will be conducted to provide further insights into the natural history of HE. PROSPER aims to enrol approximately 550 patients. An interim analysis will be performed after 12 months of data collection and the full dataset should be available for analysis by July 2018.[36]

In summary, PROSPER may provide important real-world evidence of the effectiveness of secondary prophylaxis with rifaximin-α 550 mg and its impact on healthcare resource utilisation in Europe and Australia.[36] It could also provide a better understanding of the burden and natural history of HE and variability in HE management practice. Since PROSPER's design and robust statistical methodology will help minimise bias associated with real-world observational studies, its findings should be highly relevant to clinical practice and will complement clinical trial data in informing future HE management practice.[36]

Panel Discussion

The CMP model of patient care was devised for use in a teaching hospital and there was discussion regarding its applicability in the district hospital setting, where resources and staffing are less comprehensive. It was felt that the most important aspect of the CMP model is the testing of laboratory parameters in real time for patients with decompensated cirrhosis. Liver ultrasound in real time for such patients is also important, but the other aspects of the CMP model



In order to minimise the influence of confounding factors on results, study outcomes will be compared between treatment cohorts in three ways: (1) comparison of outcomes before and after study entry ('pre/post' comparisons) for each cohort (comparisons 1a and 1b); (2) comparison of changes across the two cohorts, i.e. the difference between the cohorts in pre/post changes (comparison 2); and (3) clinical characterisation of study population based on retrospective chart review (comparison 3a), followed by comparison of outcomes between the cohorts following study entry, after statistical adjustment on the basis of findings from comparison 3a (comparison 3b).

Figure 3. PROSPER study design.[36]

(such as upper endoscopy in real time and other specialist caregiver support), although useful, were not considered to be essential.

Responsibility for data collection is an important consideration when first setting up an inpatient database, such as NACSELD, since this can be very time-consuming. When funding is not available, the database should be 'lean and mean', so that the requested data are as focused and concise as possible, allowing hospital staff (e.g. nurses and fellows) to collect the data. When funding is available, someone can be employed specifically to collect data and the requested information can therefore be broader and more extensive. Quality assurance is also an important consideration. With NACSELD, Dr Bajaj conducts quality assurance testing on data from every third patient; further quality assurance testing is conducted by the study's biostatistician once the data are shared with the research group. It is imperative to build such safeguards into the process, since the study's leader/s is/are ultimately responsible for the quality of the data. Hospital staff are primarily motivated to collect data by abstract publication. Although each site only has access to its own data (only four people have access to the complete NACSELD database), these data can be used as the site wishes. This not only includes independent research publication, but also the provision of evidence of the site's performance (e.g. adherence to guideline recommendations) as a potential means of effecting change in local management practice.

In conclusion, there is a need for real-word evidence to complement findings from clinical trials. However, the setting up of real-world studies requires careful consideration to avoid potential bias and ensure that the data are applicable to wider clinical practice.

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Systems Biology Using Metabolic Profiling of Urine for the Earlier Diagnosis and Monitoring of Liver Disease

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Background

The initial stages of liver damage or the early signs of liver cancer can be difficult to detect using routine clinical and imaging diagnostic tests.[1] However, the diseased liver may cause specific and early changes in how nutrients are metabolised or how drugs and toxins are broken down, and such differences may be detected by changes in the low molecular weight metabolite profiles of either blood or urine.[2] Subtle chemical changes in body fluids can be assessed by a range of state-of-the-art analytical chemistry methods, including mass spectrometry and/or proton (1H) nuclear magnetic resonance (NMR) spectroscopy.[3] In this short review we outline urinary metabolic profiling studies using 1H NMR spectroscopy applied to hepatocellular carcinoma and treatment of liver cirrhosis, which illustrate the potential of the technique and show the scope for using the results to develop robust and specific urinary dipstick tests as well as improving understanding of disease mechanisms.

Dr I. Jane Cox is a Senior Scientist at the Institute of Hepatology, London and she leads the Metabonomic and Proteomic Group. She is particularly interested in using state-of-the-art analytical chemistry techniques for improving diagnosis and monitoring of liver disease. Prior to joining the Foundation for Liver Research, Dr Cox held an academic position in the Imaging Sciences Department at Imperial College London during which time she developed and applied *in vivo* and *in vitro* clinical magnetic resonance spectroscopy techniques.

Professor Roger Williams is Director of the Institute of Hepatology, London and of the Foundation for Liver Research. Before that, he had established over a period of 30 years, the world renowned Institute of Liver Studies at King's College Hospital. He is a Fellow of the Academy of Medical Sciences and is the recipient of numerous honorary fellowships, medals and prizes including the American Society of Transplantation Senior Achievement Award in 2004, a Hans Popper Lifetime Achievement Award in 2008, the Distinguished Service Award of the International Liver Transplant Society in 2011 and, in 2013, the Distinguished Achievement Award of the American Association for the Study of Liver Disease. His main clinical and research interests are in acute liver failure, liver transplantation, complications of cirrhosis and management of viral hepatitis.

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Metabolic Profiling by 1H NMR Spectroscopy

Urine is a particularly useful body fluid to study because it is straightforward to collect and to subsequently store at -80°C. Urine samples can be transported easily, nationally or internationally, from the sample collection site to the NMR centre for sample analysis.

The low molecular metabolites detected by 1H NMR metabolic profiling are in the micromolar concentration range and upwards. These metabolite peaks are of much lower signal intensity than the signal from water, the main component of urine, but a range of NMR sequences are available for suppressing the water resonance so that the metabolite peaks can be more easily visualised. The 1H NMR peak positions are determined by the chemical composition of each metabolite. Therefore each metabolite present has a characteristic fingerprint 1H NMR profile. The 1H NMR fingerprints from similar types of metabolites, however, can be overlapping. The peak area or peak height relates to the concentration of the metabolite in the urine sample. Importantly, the urinary 1H NMR spectrum includes resonances from metabolites related to host cellular metabolism as well as gut microbial metabolism. This allows urinary 1H NMR profiling to provide a window into alterations of gut microbiota composition and function.

The NMR equipment (Figure 1) is based on a superconducting magnet with a magnetic field strength often more than 100,000 stronger than the earth's magnetic field. Subtle changes in the local magnetic field within a sample, caused by the metabolites present, are detected by radiofrequency and the NMR spectrometer is used to generate and detect the NMR signal. The multitude of resonances in an 1H NMR spectrum can be assigned with reference to published and freely available databases, for example the Human Metabolome Database (HMDB).[4] A representative urinary NMR spectrum is illustrated in Figure 2 and resonances can be assigned to metabolites involved in renal function, gut microbial co-metabolites, tricarboxylic acid cycle

intermediates, skeletal muscle turnover, branched chain amino acid metabolism as well as liver metabolism.

Factors that may need to be considered when interpreting a urinary 1H NMR spectrum include gender, diet, alcohol intake and medication, particularly over-the-counter analgesics such as paracetamol.[5;6] Paracetamol metabolites and ethanol are readily identified in a urinary 1H NMR spectrum, for example, but without knowledge of a detailed dietary and medication history then interpretation of a 1H NMR spectral change to a specific disease process may be misleading. Gut microbial co-metabolites, for example trimethylamine, dimethylamine, phenylacetylglutamine, hippurate and trimethylamine-N-oxide,[7] contribute to the 1H NMR spectral profile, which adds to the complexity of spectral interpretation.

Figure 1. This photograph illustrates a high-resolution nuclear magnetic resonance spectroscopy system, which includes an extremely strong magnet (typically 100,000 times stronger than the earth's magnetic field).

The NMR signal, generated after applying a radiofrequency pulse, is detected and processed by the spectrometer into an NMR spectrum.

Subtle differences in urinary chemical composition, highlighted by changes between NMR spectra, can be assessed using multivariate statistical analyses.

Urinary 1H-NMR Studies of Hepatocellular Carcinoma

A recent study on urinary markers of hepatocellular carcinoma (HCC), undertaken in collaboration with the Jos University Teaching Hospital in Nigeria, showed creatinine, carnitine, creatine and acetone most strongly contributed to a multivariate model distinguishing urinary profiles from hepatitis B surface antigen-positive patients with HCC, hepatitis B surface antigen-positive patients with cirrhosis and hepatitis B surface antigen-negative controls.[8] Importantly, a similar change in the urinary profile was observed in an Egyptian cohort of hepatitis C virus infected patients with HCC and cirrhosis compared to healthy controls.[9] Urinary 1H NMR metabolic profiling from 16 Egyptian patients diagnosed with HCC, 14 Egyptian patients with clinically or histologically confirmed cirrhotic liver disease and 17 healthy Egyptian control subjects showed the sensitivity and specificity of using the urinary profile to distinguish Egyptian patients with HCC tumours from healthy controls and from patients with cirrhosis was 100%/94% and 81%/71% respectively. The metabolites that were most influential in discriminating the Egyptian groups of patients included creatinine, creatine, carnitine, citrate, hippurate, trimethylamine-N-oxide and glycine. The urinary profiles from Egyptian and Nigerian patients with HCC were indicative of the tumour effects on physiology, energy production and aberrant chromosomal methylation. These studies have recently been extended and expanded in a study of West Africans and a urinary metabolite panel, comprising inosine, indole-3-acetate, galactose, and an N-acetylated amino acid (NAA), showed a high sensitivity (86.9%) and specificity (90.3%) in the discrimination of HCC from cirrhosis.[10] A number of metabolites were significantly increased in the urine of HCC patients and correlated with clinical stage of HCC and these included NAA, dimethylglycine, 1-methylnicotinamide, methionine, acetylcarnitine, 2-oxoglutarate, choline and creatine.[10] Documentation of urinary biomarkers at different stages will be important to establish whether such metabolic changes can be used to diagnose HCC at a sufficiently early stage when curative options are still possible. This is particularly relevant for under-resourced regions of the world where a robust, sensitive and cost-effective test would be of value in early diagnosis.

Urinary 1H-NMR Studies of Cirrhosis

Proton pump inhibitors (PPI), such as omeprazole, have been associated with infectious complications in cirrhosis but their impact on distal gut microbiota composition and function is unclear. In collaboration with Dr Jasmohan Bajaj's group at the Hunter Holmes McGuire Veteran Affairs Medical Centre we have studied urinary 1H-NMR metabolic profiling changes in patients with cirrhosis and healthy controls after omeprazole therapy and results were compared with stool microbiota composition and function.[11] Serum gastrin concentrations significantly increased after PPI both in cirrhosis and controls and a significant microbiota change was seen in both controls and cirrhosis after omeprazole. Relative Streptococcaceae abundance, normally present in saliva, was significantly increased post-omeprazole

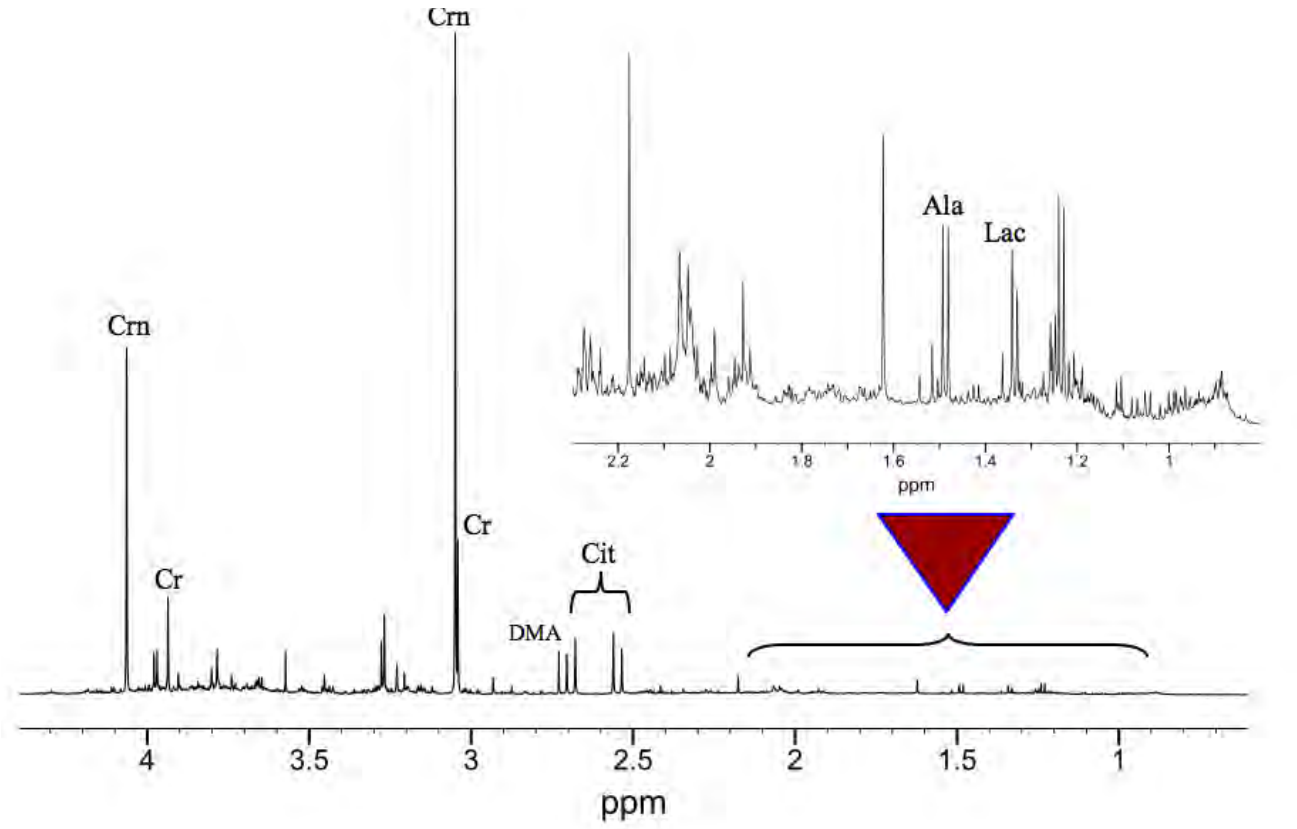

Figure 2A. The aliphatic region of an illustrative urinary 1H NMR spectrum showing assignment of the prominent peaks to creatinine (Crn), creatine (Cr), citrate (Cit), dimethylamine (DMA), lactate (Lac) and alanine (Ala).

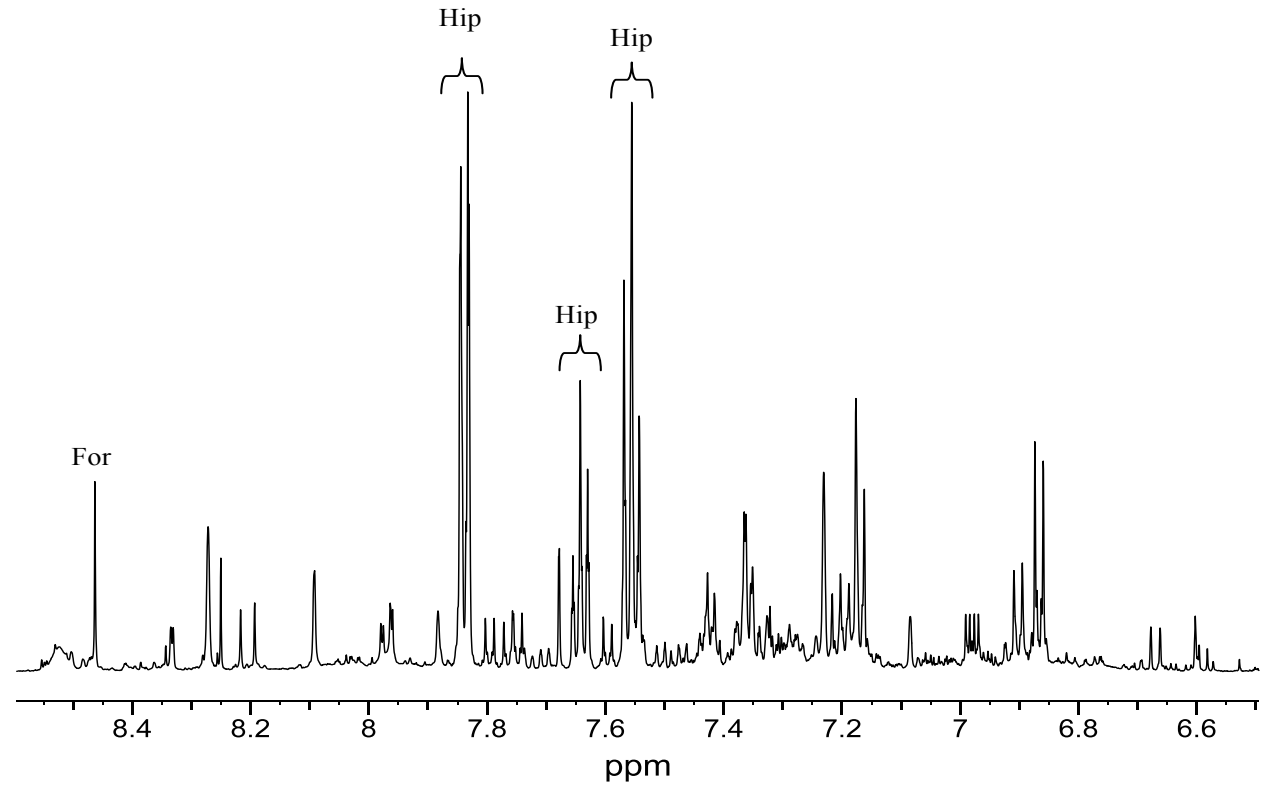

Figure 2B. The aromatic region of an illustrative urinary 1H NMR spectrum showing resonances assigned to hippurate (Hip) and formate (For) for example.

in controls (1 vs. 5%) and cirrhosis (0 vs. 9%) and was correlated with serum gastrin levels ($r = 0.4$, $P = 0.005$). The urinary 1H NMR spectroscopy data showed significantly reduced hippurate in cirrhosis versus controls both pre- and post-omeprazole and increased lactate in both groups post- versus pre-omeprazole, whereas dimethylamine decreased in cirrhosis only. Using correlation network analysis, changes in linkages of bacteria with metabolites were observed post-omeprazole compared with pre-PPI in cirrhosis patients. This study concluded that omeprazole was associated with a microbiota shift and functional change in the distal gut in patients with compensated cirrhosis and that this could result in bacterial overgrowth.[11]

Summary

As metabolic profiling studies of both urine and plasma, using either NMR techniques or mass spectrometry methodologies, continue to expand, the relevance of specific metabolic profiles in different disease phenotypes is being better understood. In addition to the two studies highlighted in this short review, plasma or urine metabolic fingerprints have been identified for various causes and stages of liver disease, including fatty liver disease[12] and obesity,[13] and hepatic encephalopathy.[14]

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Definitions of Acute-on-chronic Liver Failure: The Past, The Present and the Future

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Introduction

Chronic liver diseases (CLD) are defined by the following triad: 1) prolonged course of a hepatic disease >6 months; 2) inflammatory and/or degenerative morphological findings; and 3) uncertain prognosis.[1] CLD consist of several aetiologies and different states of functional and/or morphological liver deterioration. Nevertheless, regardless of the aetiology, CLD could lead to both histological modifications of the liver and chronic liver insufficiency. CLD caused by steatohepatitis (alcohol or obesity) or chronic viral hepatitis leads to morphological changes in the liver. These changes could be attributed to four processes: 1) cell damage and degeneration; 2) cell death and necrosis; 3) liver regeneration; and 4) fibrogenesis. Cirrhosis is the consequence and final stage of various CLD.[2] Associated to this phenomenon, in cirrhotic patients, increased intrahepatic vascular resistances leads to portal hypertension and its complications, namely gastrointestinal (GI) bleeding from varices and/or ascites. Moreover, major functions of the liver are also impaired such as immunological function with increased infection sensibility and several perturbations in anabolism and catabolism liver function. Unfortunately, there are no correlations between morphological changes and the severity of functional impairment. Nevertheless, put together, all these perturbations, often asymptomatic when cirrhosis is 'compensated', become symptomatic when the cirrhosis is 'decompensated'.

Natural history of the disease could be progressive, with a slow decrease of liver function but without the potential for full recovery leading to end-stage of cirrhosis. End-stage of cirrhosis is characterised by chronic decompensation of the liver. At which point, the only definitive treatment is liver transplantation (LTx). Patients with CLD may have acute decompensation (AD) that is usually precipitated by an event that represents a direct or indirect hepatic insult. For example, indirect insult could be infection or extra-hepatic surgery. Direct insult could be new viral hepatitis infection (like virus Delta or E), viral hepatitis reactivation, or hepatotoxic drug misuse. In case of AD, partial or full recovery to the original liver function level is assumed after treatment. In those patients, short-term mortality increases dramatically when extra-hepatic organ failures are present. Three clinical scenarios are possible regarding the natural history of the CLD: CLD without cirrhosis and AD, CLD with cirrhosis and AD, and CLD with cirrhosis and end-stage liver disease. These three categories of patients are different in terms of mechanism and prognosis (Figure 1).

Acute-on-chronic liver failure (ACLF) is a complex syndrome with an acute deterioration of liver function superimposed on CLD. Both the exact definition and underlying pathogenesis of ACLF remain unclear. Instead of using the term 'acute decompensation', ACLF is used to define and classify all acute events of liver decompensation in patients with CLD or cirrhosis regardless of the presence of other organ failure. In >20 years, this syndrome has taken several different definitions, leading different outcomes according to mortality. From all the available definitions, three common points are emphasised: 1) Presence of CLD; 2) Rapid deterioration but theoretically reversible liver function; and 3) high short-term mortality. ACLF is associated with a short and medium-term mortality of 50-90%.[3,4] A new definition and classification will allow to better stratify patients with ACLF. Nevertheless, proposed definitions by Asian and Americano-European Study of the Liver societies are not clear with the definition of the CLD. On the other hand, new classifications proposed by the European and North American studies focus only on cirrhotic patients and define the patient principally with extra-hepatic failure which could be confusing too. None of those definitions or classifications takes into account the probability of liver function recovery. Unfortunately, despite recent efforts to well define this syndrome, there is no universally accepted definition.

New approaches, more global and biological, of this polymorphic syndrome are needed. 'Omic' approaches, such as metabolomic, are probably interesting biological approaches to help clinicians to best define and classify the patients with this syndrome and predict liver function recovery. In this review, we discuss the evolution and accuracy

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of the different definitions of the ACLF and propose the need for 'biological' approaches of this syndrome.

ACLF Definitions: the Past

The term 'acute-on-chronic liver failure' appears for the first time in 1995.[5] It gains interest at the end of the last century probably as a consequence of the development of the different kinds of liver support. Initially, it describes a condition with superimposed insult on the liver in patients with CLD. On the other hand, it describes the notion that an organ (the liver in this case) with chronic impairment could have superimposed acute impairment but with possible return to the previous state. Then, patients with chronic liver failure (CLF) and acute liver failure (ALF) should be treated by liver support as a bridge to the recovery of their function or to the LTx. Unfortunately, despite the first meta-analysis, which showed decreased mortality in the ALCF group, no controlled trials have been able to support this hypothesis.[6,7] Subsequently, several definitions were proposed to define this syndrome. At the beginning, all of them focused on the loss of liver function with various clinical and biological signs (Table 1). Few definitions take into account organs other than the liver in the definition. High short-term mortality of this syndrome (between 50-90%) was common in all of them. The presence of a large panel of definitions is a problem for the interpretation of the studies regarding outcomes or therapeutic trials on patients with ACLF. Taking into account this point and the increase of interest for these patients, notably regarding the LTx, more consensual definitions were raised at the beginning of the new century. Typically two definitions, especially due to the difference of CLD aetiology, from the 'Western countries' and 'Eastern countries' (i.e. mainly Asian) were proposed.

ACLF Definitions: the Present

Two definitions of the ACLF are mostly used. One is proposed by the Asian-Pacific Association of the Study of the Liver and the others by the American Association for the Study of the Liver (AASLD) and the European Association for the Study of the Liver (EASL).[8,9] The Asian definition focuses exclusively on liver failure. ACLF is defined asacute hepatic insult manifesting as jaundice (with bilirubin ≥5 mg/dl), coagulopathy (with international normalised ratio ≥1.5 or prothrombin activity <40%), and complicated within 4 weeks by ascites and/or hepatic encephalopathy with previously diagnosed or undiagnosed CLD. Current definition of ACLF proposed by EASL-AASLD symposium includes the notion of high mortality and extra-hepatic organ failure. ACLF is then defined as an "acute deterioration of pre-existing CLD, usually related to a precipitating event and associated with increased mortality at 3 months due to multi-organ failure." The precipitating event may be an extra-hepatic insult such as sepsis, or GI bleeding. It may also be a direct hepatic mechanism with viral infestation or reactivation, or drug induced liver injury.[3] Two points should be clarified; first, all patients with CLD are included in those definitions and not only patients with cirrhosis. CLD without cirrhosis does not have the same clinical presentation, treatment, or prognosis when compared to CLD with cirrhosis. Consensual definition of CLD is lacking. Future works are needed to establish new criteria (clinical, radiological, biological, and/or histological) to best define it. Moreover, those criteria of CLD will probably be also helpful to best recognise unknown underlying CLD and distinguish

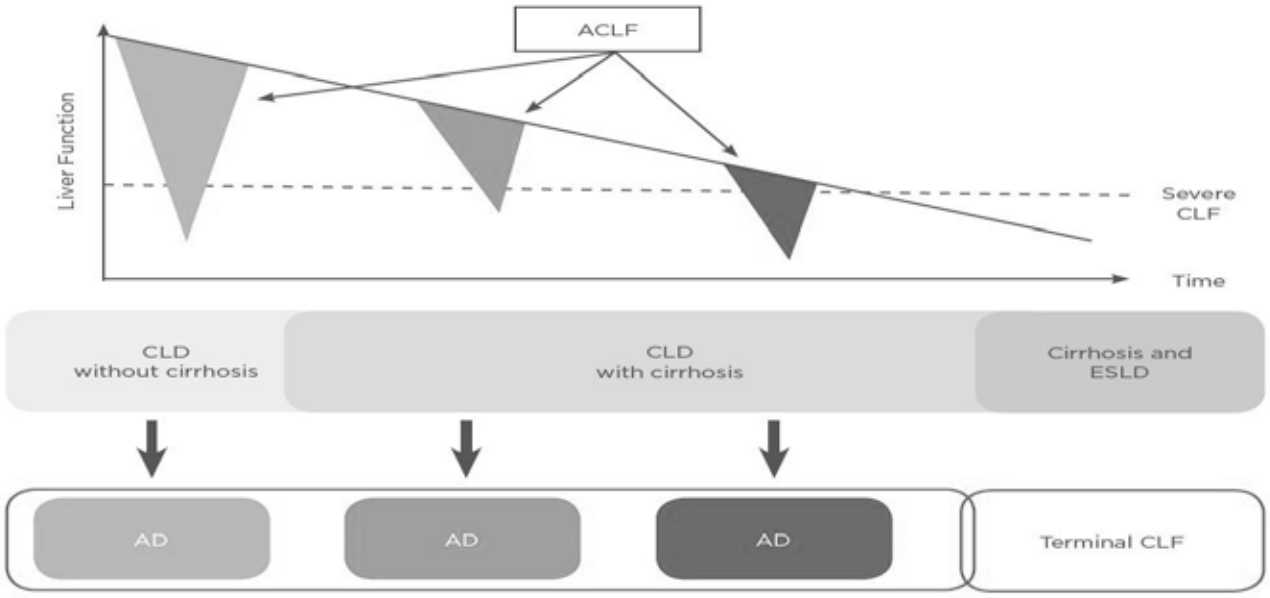

Figure 1. Schematic representation of natural history of chronic liver disease (CLD), acute decompensation (AD), and end-stage liver disease (ESLD). This figure describes the concept of acute-on-chronic liver failure (ACLF) in CLD patients with or without cirrhosis, chronic liver failure (CLF), and ESLD. It also describes arbitrary evolution of CLD with cirrhosis, at the top of the figure, progressive decreases of the liver function leading to terminal liver failure and, on the bottom of the figure, three categories of patients: CLD without cirrhosis, CLD with cirrhosis, and cirrhosis and ESLD. ACLF (at the top) is characterised by acute liver impairment but with partial or total recovery of the liver function after treatment.

patients with ALF from a patient with ALF or CLF. Second, the notion of recovery is lacking in both of them. How so you differentiate between impairment of liver function that leads to end-stage disease or from the ones which will recover?

To address the first issue, Jalan et al.[10] attempted to classify patients with CLD. They proposed a new classification of ACLF in three categories (A, B, or C) according to underlying presence of cirrhosis and for the cirrhotic patient, history of pervious decompensation. Group A includes CLD patients without cirrhosis. Group B includes well-compensated cirrhosis, and group C includes patients with advanced cirrhosis with previous decompensation. Prospective evaluation of this new classification is necessary to determine its accuracy. Recently, two large studies have tried to better classify ACLF patients: one from EASL– Chronic Liver Failure Consortium (EASL-CLIF) Consortium in Europe, called the CLIF Acute On Chronic Liver Failure in Cirrhosis (CANONIC) study, and the other from the North-American Consortium for the Study of End-Stage Liver Disease study.[11,12] The first study included around 1,400 patients hospitalised with cirrhosis for an AD. This study classified ACLF based on mortality (Table 2).

In the CLIF classification (CLIF-ACLF Grades), cirrhotic patients were classified according to organ failure, mainly kidney and brain (i.e. hepatic encephalopathy) failure. The North American Study proposes classification of ACLF specific to cirrhotic patients with sepsis (infection-related acute-on-chronic liver failure [I-ACLF]). The goal of this classification is to help the clinician with bedside decision-making to accurately identify potential survivors for cost-effective healthcare resource utilisation. I-ACLF is defined as a cirrhotic patient with suspected or documented infection and at least one organ failure (hepatic encephalopathy Grade 2/3, renal replacement therapy, mechanical ventilation, shock). Approximately 500 patients were included in this multicentre prospective study. As expected, for both studies, mortality was well correlated with the number of organ failures. Major points of the new classifications are: 1) they included only patients with proven or strongly suspected liver cirrhosis; 2) they included all aetiologies of cirrhosis; 3) they included well-documented cirrhotic patients hospitalised for an acute event; 4) for one of them (European study), there is external validation of the accuracy of the classification.[13] The interesting point with these classifications is that they best stratify cirrhotic patients with ACLF according to the risk of death. The major implication is for its use in the inclusion criteria to have a more homogenous population for future randomised clinical trials. However, consensual definition of ACLF is still lacking. The ambiguity and variability in the definition/classification of ACLF does not allow the clinician to make rapid and proper diagnoses of ACLF, to distinguish between patients with ACLF that require transplantation and those that require only intensive medical treatment. Specific biomarkers that confirm the diagnosis, exclude other diseases, and best predict patients with poor outcome should be stated to best define ACLF.

ACLF Definition: the Future

Bioclinical classification as proposed by Moreau et al.[12] is probably a major improvement concerning the characterisation of the ACLF according to its prognosis. Nevertheless, the score used is complex and not readily adaptable to clinical care. The view of the ACLF syndrome as a systemic syndrome with extra-hepatic organ failures responsible of increased mortality is interesting, but it is also counterintuitive to define an 'acute hepatic failure' as 'extra-hepatic

	Definition	Aetiology of CLD	Ref
1	Acute insult manifesting as jaundice (bilirubin ≥10 mg/dl) and coagulopathy (PTA <40%), complicated within 4 weeks with ascites and/or HE with previously diagnosed or undiagnosed chronic hepatitis B (with or without cirrhosis).	Hepatitis B virus	[illegible]
2	Acute deterioration of liver function in established and compensated CLD following a life-threatening complication (HE or ascites or bleeding or HRS) in patient with or without cirrhosis.	Hepatitis B virus	[illegible]
3	Defined as a rise in MELD score of >5 points within 4 weeks before transplantation.	Various	[illegible]
4	Acute decompensation of cirrhosis manifested by increased jaundice.	Various	[illegible]
5	ACLF was diagnosed in cirrhotic patients with acute hepatitis A or E presenting with clinical evidence of liver failure (significant ascites and/or HE).	Various	[illegible]
6	Defined as acute decompensation of CLD with severe liver dysfunction and high grade of HE (2 or more).	Hepatitis B virus	[illegible]
7	Cirrhotic patient with decompensation such as GIB, HE, admitted to ICU required organ support	Various	[illegible]

Table 1. Different definitions of acute-on-chronic liver failure (ACLF) found in the literature. PTA: prothrombin activity; HE: hepatic encephalopathy; CLD: chronic liver disease; HRS: hepatorenal syndrome; MELD: model for end-stage liver disease; GIB: gastrointestinal bleeding; ICU: intensive care unit.

Grade	No ACLF	ACLF Grade 1	ACLF Grade 2	ACLF Grade 3
Definition	No organ failure or single organ failure (coagulation, circulation, or respiration) and creatininaemia <1.5 mg/dl and no hepatic encephalopathy	Single kidney failure or single organ failure (coagulation, circulation, or respiration) and creatininaemia between 1.5 and 1.9 mg/dl or hepatic encephalopathy and creatininaemia between 1.5 and 1.9 mg/dl	Two organ failures	Three organ failures
1 and 3 months mortality	4.7% and 14%	22.1% and 40.7%	32% and 52.3%	76.7 and 79.1%

Table 1. Definition of chronic liver failure consortium - acute-on-chronic liver failure (CLIF-ACLF) grades. Coagulation failure is defined by the international normalised ratio >2.5 or platelet count <20 g/l; circulation failure is defined by use of any dose of terlipressin, dopamine, dobutamine, epinephrine, or norepinephrine. Lung failure is defined by PaO2/FiO2 ratio <200 or SpO2/FiO2 ratio <89. Kidney failure is defined by creatininaemia >2 mg/dl or need to renal replacement therapy. Hepatic encephalopathy Grade >2 defines neurological failure.

failure'. To better define ACLF syndrome, new biomarkers or biological fingerprints could probably be helpful. Nevertheless, it is now widely accepted that the search for a single biomarker that can be used in routine clinical practice to diagnosis patients with ACLF is probably unrealistic. Future definition and characterisation of this systemic syndrome could probably be completed and clarified using the 'omic' concept, and specifically, the metabolomic approach. Metabolomics, which is the study of metabolic changes in an integrated biological system using multiparametric analyses, may help identify biomarkers that characterise the metabolic profiles of a disease, and/or evaluate metabolic modifications after treatment has been initiated.[14] Metabolomics, using proton nuclear magnetic resonance (1H-NMR) spectroscopy, when applied to liver disease, has shown a close relationship between metabolic abnormalities and the severity of the disease in sera and tissues.[15,16] Recently, a serum metabolite fingerprint for ACLF, obtained with 1H-NMR, was identified.[17]

The hypothesis in this study was that cirrhotic patients with acute events have had a specific metabolic response as compared to cirrhotic patients with stable cirrhosis. Metabolomic profiles of the sera of 93 patients with compensated or decompensated cirrhosis (CLF group) but stable liver function, and 30 patients with cirrhosis and hospitalised for the management of an acute event who may be responsible of ACLF (i.e. ACLF group) were analysed. Both groups were well-separated using a multivariable statistic method and the specific metabolomics fingerprint of patients in intensive care unit was identified. Several metabolites were identified and reflected major changes in liver function, such as energy metabolism, urea metabolism, or amino acid metabolism, but also major extra-liver function changes, such as renal impairment, or were related to inflammation/necrosis. This primary results are interesting but should be confirmed by a large multicentric population including various aetiologies.

Conclusion

Despite major efforts, recent definitions and classifications proposed by leading organisations or studies are still confusing for the clinician notably to make difference between ACLF and CLD or ACLF in cirrhotic patient and cirrhosis decompensation. Future research should produce an accurate 'universal' definition of this complex syndrome, in-patients with CLD, and including cirrhotic patients. In the same way, a study of the variations of different biomarkers or biological fingerprints could be interesting in order to best classify and define the prognostics of those patients. An interesting way to find it could be a biological approach using the 'omic' platforms.

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Liver Transplantaion for Alcoholic Liver Disease – Time for a Paradigm Shift?

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Introduction

Excessive alcohol consumption is responsible for 4% of mortality and presents the third leading risk factor for disease and disability worldwide.[1] Alcoholic liver disease (ALD) is the most prevalent liver disease in Europe and is the second most common indication for liver transplantation (LT) in Europe and the United States.[2,3] It comprises of a wide range of hepatic manifestations including alcoholic fatty liver disease, alcoholic steatohepatitis (ASH), and liver cirrhosis complicated by portal hypertension. LT has been well established as a life-saving treatment for end-stage ALD. However, as determined by the shortage of donor livers, alcoholic cirrhosis as an indication for LT is discussed controversially. Since alcoholism is a life-long disease and is not cured by LT, optimal selection of patients with a low risk of alcohol relapse, as well as continuous monitoring and support after LT, are essential.

Diagnosis of Alcohol Addiction and ALD

Alcohol dependence has to be differentiated from alcohol abuse (DSM-IV), or hazardous and harmful drinking (WHO),[1] as well as from sporadic drinking episodes.[4,5] This classification is of particular importance within the transplant setting, since patients may be denied LT in the case of suspected alcohol abuse. Moreover, alcohol relapse in transplant recipients has to be detected at an early stage to provide psychomedical support and preserve long-term graft function. Clear diagnosis of alcohol consumption and ALD is complicated by the lack of definite cut-off values of ethanol, identified as harmful in certain populations.

Hepatic steatosis was found in 60% of patients with regular alcohol intake >60 g/day.[6,7] Liver cirrhosis was confirmed by liver biopsy in 29% of a large series of patients with alcoholism.[8] In a meta-analysis the daily consumption of >25 g ethanol has been associated with an increased risk of liver cirrhosis and its complications.[9]

Recently, increased risk of mortality due to liver cirrhosis was even found with consumption <25 g of ethanol per day (12-24 g/day).[10] Thus, patients might be put at risk even if ethanol levels are below the current public recommendations for alcohol consumption. Differential diagnosis to non-alcoholic fatty liver (NAFL) and steatohepatitis (ethanol cut-off: 20 g/day for women, 30 g/day for men), and the assessment of alcohol as an additional hit to the liver in other liver diseases are difficult.

Risk for Alcohol Relapse and Impact on Outcome

Outcome of LT for ALD in Europe is similar to other indications with a 5 and 10-year survival of 73%, and 59%, respectively.[11] Relapse of alcohol consumption occurs in 10-50% of patients undergoing LT for end-stage ALD.4,[12-14] Of these, 10-36% of patients resume drinking heavily.[5,14,15] Graft dysfunction can be found in up to 17% of patients.[16]

Cuadrado *et al*.[17] reported significantly reduced 10-year survival rates of 45% versus 86% in transplant recipients returning to alcohol use. Similarly, a recently published study - investigating alcohol relapse rates in living donor LT (LDLT) in Japan - described 10-year survival rates of 22% (versus 74%) in patients with alcohol relapse.[18] Of note, in contrast to patients with recurrence of heavy drinking, who suffer from subsequent organ dysfunction due to recurrent ALD and have mainly liver-related mortality, the majority of patients with low-to-moderate alcohol consumption (in the absence of other liver diseases), or those who are long-term abstainers, die from de novo malignancies, cardiovascular disease, or infections.[13]

Reports studying non-adherence to immunosuppression in patients with alcohol relapse show a wide range of 3-47%.[19-21] However, non-adherence is not directly associated with alcohol relapse, but rather with each patient's personality.[22] Unexpectedly, patients with LT due to ALD have, in general, a lower rejection risk than patients transplanted due to other indications, suggesting an immune-inhibitory effect of alcohol.[3,23,24]

Lower social support, psychobehavioural comorbidities, family history

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of alcoholism,diagnosis of alcohol dependence, repeated attempts at rehabilitation, non-compliance with clinic visits after LT, and smoking were all identified as risk factors for alcohol relapse after LT, along with pre-transplant abstinence period;[4,25,26] protective factors include patient insight and perception of the negative consequences of alcohol.[24,26] Therefore, thorough evaluation of psychosocial influencing factors and psychobehavioural disorders should be considered the core of the risk assessment prior to transplantation.

Eligibility for LT

The '6-Month Rule'

Originating from the fact that alcohol abstention can lead to dramatic improvement in liver function to a point where LT is no longer necessary, most transplant centres require a 6-month abstention period before patients become listed for LT. Above all, plausible abstention ≥6 months has been used as a surrogate parameter for long-term sobriety after LT to identify patients who will most benefit from LT. However, data on the '6-month rule' are controversial and a clear rationale is lacking.[27] Although shorter sobriety periods prior to LT are predictive of future relapses,[4,13,28] sobriety becomes robust only after 5 years of alcohol abstention.[29,30] On the one hand, this may be a result of inconsistent definition of alcohol use and alcohol dependence used in these studies, on the other hand, this may be due to the difficulty in evaluation and detection of alcohol abuse and relapse. Therefore, the UK Liver Transplant Group, rather than using a specified period of abstinence, agreed on certain contraindications for listing, including: alcoholic hepatitis, repetitive episodes of non-compliance with medical care, returning to drinking followingfull professional assessment, and concurrent illicit drug use.[31-33]

LT for Alcoholic Hepatitis

The discussion concerning selection criteria of patients with ALD becomes even more controversial in the context of alcoholic hepatitis. Historically, patients suffering from acute ASH have been denied LT due to active alcohol consumption.[34] However, mortality in patients failing to respond to corticosteroids in comparison to responders is veritably high (28-day survival 53% versus 91%, 6-months survival 30%).[35] Particularly, recent reports on favourable outcomes after LT for severe ASH have led to a change in therapeutic algorithms, and according to the European Association for the Study of the Liver (EASL) guidelines, LT could be a treatment option for highly selected patients.[36] Singal *et al.*[37] demonstrated similar 5-year patient survival rates in patients transplanted for ASH compared to patients transplanted for alcoholic liver cirrhosis (73% versus 78%). Furthermore, a case-control study by Mathurin *et al.*[38] showed a dramatically improved survival at 6-month follow-up for patients who had received LT in comparison to patients who had received medical treatment, but who only partially responded or were non-responders (77% versus 23%). Only patients without prior episodes of ASH, as well as patients with good family support, lack of relevant comorbidities, and commitment to alcohol abstention, were included in the study. Of note, only 3 of 26 patients relapsed to alcohol consumption after 2 years.

On the other hand, in the context of organ shortage, major ethical concerns may be raised. Frequently, alcoholism is seen as a self-inflicted disease not only by the public, but also among medical personnel, and LT for ALD has led to sustained controversies. Unselected organ distribution can thus result in decreasing donor numbers. Therefore, transparent selection criteria for LT patients with ALD, and particularly ASH, are mandatory.[39]

Monitoring Consumption and Managing Relapse

Identification of patients at risk of alcohol relapse displays a challenge for multidisciplinary transplant teams. Alcohol relapse, in contrast to temporary slips (which are recognised by the patient as potentially harmful and may foster a new abstinence), is defined by abusive consumption (at least four drinks per day or one drink in ≥4 consecutive days).[40,41] In a patient population where optimal selection is difficult, the treating physicians in particular must be aware of signs of recidivism. Whereas alcohol relapse prior to LT may preclude patients from the waiting list,[42,43] good psychosocial and medical support of patients may be decisive to prevent or to detect the signs of alcohol relapse earlier after LT in order to support long-term graft survival.[44] As such, most centres have implemented regular follow-up visits by addiction specialists after LT,[42,45] thereby achieving a significant reduction of recidivism;[20,46] intervention trials were only of limited success.[47,48]

To guarantee optimal patient selection for LT and best psychological and medical support, in addition to assessment by experienced addiction professionals, objective tools for alcohol detection are mandatory. In fear of negative socioeconomic consequences or of being denied LT, patients frequently do not admit alcohol consumption, adapt their drinking patterns to scheduled hospital visits (in order to be able to provide negative alcohol tests), or do not indicate actual amounts of alcohol intake.[43,49] To face these challenges some centres have implemented random alcohol testing without prior notice for patients on the waiting list.[50,51]

The National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health (Bethesda, MD) recommend a combination of carbohydrate deficient transferrin (CDT), mean corpuscular volume (MCV), and gamma glutamyl transferase (GGT) for alcohol screening,[52] reaching a sensitivity and specificity of 88% and 95%, respectively.[53-55] However, MCV and GGT, as well as the commonly used liver enzymes such as alanine-amino transferase (ALT) and aspartate-amino transferase (AST), have only low specificity in patients with end-stage liver disease or LT recipients.[43,56] Besides self-reporting questionnaires, such as Alcohol Use Disorders Identification Test (AUDIT-C),[57,58] and interviews by addiction specialists, a combination of alcohol markers

in the blood (CDT), urine (urinary ethylglucuronide [uEtG]), and hair (hEtG) have been reported to be of high value in this patient cohort.[43,50] In particular, EtG in hair - a metabolite of ethanol - has the advantage of differentiating between excessive drinking (<60 g ethanol/day), moderate alcohol consumption (10-40 g ethanol/day), and teetotallers or very moderate drinkers (<10 g ethanol/day) for up to 6 months before, independent of the severity of liver disease.

Importantly, since a recent study proved the negative effect of excessive alcohol consumption on long-term patient survival regardless of the indication for LT, screening for alcohol consumption also in non-ALD transplant recipients should be included.[59] Due to the potentiated negative effect of alcohol in hepatitis C, we should be especially aware of alcohol consumption in this patient population.[2]

Conclusion

LT for alcoholic cirrhosis is a matter of continuous controversy since Starzl *et al*.[60] first drew attention to successful outcomes of LT for ALD. The most relevant concerns within the context of ALD and LT are the reliable pre and post-transplant perceptions of alcohol dependence and relapse. Universally applicable criteria for the evaluation of patient eligibility for LT border their limits when it comes to the individual patient, and the frequently applied '6-month rule' should be reconsidered. Moreover, in highly selected patients where spontaneous recovery of liver function cannot be expected, such as acute alcoholic hepatitis not responding to medical treatment, the '6-month rule' is not applicable. To develop an individual risk profile based on psychosocial factors in combination with the analysis of drinking patterns seems to be more decisive. In addition to routine visits by a multidisciplinary transplant team, including an addiction specialist prior to and after LT, screening for alcohol consumption and relapse by the use of biomarkers in blood, urine, and/or hair should be performed on a regular basis. Early detection of recurrence of harmful drinking and alcohol dependence is mandatory to preserve long-term graft function.

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Hepatic-based Inborn Errors of Metabolism

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Introduction

Inborn errors of metabolism (IEMs) are a vast, diverse, and heterogeneous set of genetic disorders that are caused by alterations of a specific chemical reaction in metabolism. The term was coined by Sir Archibald Garrod in 1902.[1] Although individually rare, IEMs are collectively common with an estimated incidence >1:1,000.[2] There are hundreds of different IEMs mapped to date, and the number will probably continue to grow until all variants of enzymes and transporters that specify homeostatic mechanisms in humans are identified.[3,4] IEMs are a significant cause of morbidity and mortality, especially in childhood. A vast number of key metabolic reactions occur in the liver. This review focuses on the most common hepatic-based IEMs where transplantation (Tx), either as whole organ or as isolated hepatocytes, may be an option. Based on data from the European Liver Transplant Registry, familial amyloid polyneuropathy (FAP), Wilson's disease (WD), and alpha-1 antitrypsin deficiency (A1ATD) combined accounts for ~55% of all liver transplants for IEMs (Table 1).[5-13] In phenylketonuria (PKU), due to its relative frequency, arduous management, and grave complications, hepatocyte transplantation (HTx) is being investigated.[14]

Familial Amyloid Polyneuropathy

FAP is caused by a mutation in the gene that encodes transthyretin (TTR), and was first described by Mario Corino de Andrade in 1952.[15] There are >100 mutations in the TTR gene associated with disease,[16] the most common being V30M. FAP is an autosomal dominant disease found throughout the world, but not all carriers develop the disease. For example, Northern Sweden has a high carrier frequency of the V30M mutation - 1.5% of the population - but only 5% develop symptoms before the age of 40 years. In contrast, endemic areas in Portugal have ten times lower carrier frequency (0.18%), but high penetrance (87% before the age 40).[17] Unexpectedly, homozygote carriers do not have more severe disease than heterozygotes.[17] TTR transports thyroxin and retinol in serum and cerebrospinal fluid, and is secreted by hepatocytes.[18] TTR is a significant plasma protein (approximately 25 mg/dl),[19] and has a tendency to form amyloid in essentially all vascular organs. These amyloid deposits are found, to some degree, in 25% of the population older than 80 years,[20] usually without clinical significance. In TTR V30M, a single amino acid substitution results in a structural change of the protein, causing altered metabolism and enhanced amyloid fibril formation,[21] resulting in neuro and cardiomyocyte-toxicity at a younger age.

FAP is characterised by progressive peripheral and autonomic neuropathy or cardiomyopathy in early adulthood and results in severe disability and death within 10-15 years.[22] It is caused by deposits of mutant TTR displacing normal cellular structures, resulting in impairment of organ function.[16] Clinically, FAP should be considered in patients with a progressive axonal polyneuropathy of unknown origin, especially when associated with autonomic dysfunction or cardiac manifestation. Biopsy of an affected organ may then confirm the diagnosis. Family history is of paramount importance.[23] Medical treatment options for FAP are evolving. The working hypothesis is that if one can stabilise TTR in its tetrameric form, amyloid formation may be prevented. Tafamidis, a meglumine salt, has been shown to slow the neurological deterioration in FAP,[24] and has been approved in Europe and Japan. Another strategy is inhibition of TTR synthesis on the RNA level. Again, mainly two strategies for this exist; degradation of mRNA by antisense oligonucleotides or gene silencing using small interfering RNAs. Phase I studies for both strategies have recently been completed, and Phase II/III studies are ongoing. Both strategies appear safe, and efficiently reduce the amount of circulating TTR.[25-27]

Liver transplantation (LTx) has been performed as treatment for FAP since the early 1990s. Worldwide, over 2,000 liver transplants have been registered (www.fapwtr.org), of which 1,200 have been performed in Europe alone.[5] The overall 5-year patient survival in Europe following Tx is 76%, but 100% 10-year survival has been reported by a Japanese group.[28] TTR is not hepatotoxic, meaning that the explanted liver from a FAP patient can be transplanted into another

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patient with terminal liver failure. The first such 'domino' procedure was performed in 1995.[29] The V30M liver will indeed continue to produce mutant TTR, but the generally slow progression of the disease may justify the use in older recipients.[30] There is mainly one drawback with LTx for FAP (aside from the necessity of immunosuppression and risks of surgery): the transplanted liver continues to produce normal TTR, which, in some patients, continues to be incorporated into existing fibril deposits, especially in the heart.[31] Combined heart-liver Tx has been performed in patients with FAP,[32] but is not likely to become a widely available treatment option.

Wilson's Disease

WD is caused by mutations in the gene encoding ATP7B, and was first described Samuel Alexander Kinnier Wilson in 1912.[33] There are >500 mutations associated with WD in the ATP7B gene (http://www.hgmd.cf.ac.uk/ac/gene.php?gene=ATP7B). WD is an autosomal recessive disorder with a prevalence of about 1:30,000 to 1:100,000,[8] but the prevalence may be considerably higher in some areas, e.g. East Asia.[34] Genotype-phenotype correlations in WD have yet to be established, as the number of homozygotes is exceedingly small, and the prevalence of compound heterozygotes is high.[35]

ATP7B is found exclusively in the hepatocyte and permits the efficient excretion of copper into the bile. Copper is an important cofactor for many proteins, but the average diet provides an abundance and the majority ends up being excreted.[36] The most common effect of mutation in ATPB7 is protein misfolding. This misfolding causes altered metabolism, decreased stability, and loss of copper-transport activity.[37,38] The resulting copper accumulation is toxic, especially in the liver and brain.[39] Recently, it has been shown that copper is required for tumour growth and signalling in some cancers, however, the rate of hepatobiliary malignancies in WD is very low.[40,41] WD is characterised by liver disease in the second decade, followed by neuropsychiatric disorders in the third decade, but the clinical presentation is highly heterogeneous and may include Fanconi syndrome, cardiomyopathy, osteomalacia, and anaemia.[39] The median delay in diagnosis is reported to be 2 years.[42] Clinically, a diagnostic scoring system has been developed[43] with a high sensitivity and specificity.[44] It combines clinical findings, lab results, liver biopsy, and mutation analysis. Pragmatically, the presence of low serum caeruloplasmin and higher urine copper is sufficient to conclude the diagnosis of WD in most cases.

Kayser-Fleischer rings are present in about 50% of cases of WD at diagnosis.[8] Liver biopsy is used to define liver status in cases with ambiguous biochemical parameters and to evaluate hepatic copper levels with specific stains.[45] Medical treatment of WD include copper-chelators (penicillamine or trientine) and zinc salts, with the goal to establish and maintain normal copper homeostasis. Medical treatment can generally prevent and even reverse symptoms of copper overload, at least when initiated at an early stage in the disease.[46] However, non-responders or lack of compliance to the drug treatment may result in disease progression and acute liver failure with mortality approaching 100%. Sporadically, therapeutic plasma exchange and various forms of albumin dialysis have been reported as effective techniques for rapidly reducing serum copper levels in WD crisis, delaying or even preventing the need for LTx.[47] HTx has been proven safe, and at least transciently effective, in treating other IEMs, and could conceivably be utilised as support until chelation treatment shows its effect.[48] LTx is the treatment modality of choice in most cases of WD crisis. In Europe, >800 patients with WD have been transplanted. The 5-year overall survival rate is 85%.[5]

Disorder	Incidence	No. of transplants performed
Familial amyloid polyneuropathy	1:500 to 1:100,000[5,6]	1280[7]
Wilson's Disease	1:30,000 to 1:100,000[8]	812[7]
Alpha-1 antitrypsin deficiency	1:2,000 to 1:5,000[9]	542[7]
Hereditary haemochromatosis	1:200 to 1:300[10]	468[7]
Primary hyperoxaluria	1:120,000[11]	230[7]
Tyrosinaemia Type 1	1:100,000[12]	98[7]
Homozygous hypercholesterolaemia	1:1,000,000[13]	21[7]

Table 1. Hepatic-based inborn errors of metabolism (IEMs) and liver transplantation in Europe from 1988-2009. NB: Transplants for non-hepatic-based IEMs are excluded.

Alpha-1 Antitrypsin Deficiency

A1ATD is an autosomal recessive disease caused by mutations in the SERPINA1 gene. The disease was discovered in 1963 by Carl-Bertil Laurell.[49] In the SERPINA1 gene there are >120 mutations identified, but the majority of patients with severe disease are homozygous for the Z mutation.[9] A1ATD has an estimated prevalence of 1:2,000 – 5,000.[9] Not all develop disease: it is estimated that 10-35% of patients with ZZ genotypes do not exhibit any clinical symptoms.[50] In an epidemiological study carried out in Sweden over 40 years, <10% of the 127 infants that were identified had clinically significant liver disease over the first four decades of life.[51,52]

A1AT is mainly synthesised by hepatocytes and to a small degree in the lungs. The physiologic serum concentration of A1AT for adults ranges from 1.0-1.7 g/l, but as an acute phase protein, it is up-regulated during inflammation, infection, cancer, and pregnancy.[53] The most important function of A1AT is inactivation of released proteolytic enzymes in the lungs. In patients with the ZZ variant, A1AT proteins have a single amino acid substitution causing structural change, accumulation in the rough endoplasmic reticulum and decreased secretion.[54] The function of A1AT is also reduced.[55] In this sense, A1ATD is similar to the amyloidoses (e.g. FAP). As a result of decreased secretion of A1AT, overt protease activity ensues in the lungs, resulting in destruction of lung matrix components, alveolar structures, and blood vessels. Injury to liver cells also occurs, but susceptibility to disease is determined by processing abilities for misfolded A1AT. Interindividual differences in this cellular machinery are thought to be responsible for the different susceptibility to chronic liver disease.[56] Higher rates of liver cancer are found in A1ATD due to hepatic inflammation and increased liver cell turnover.[57] A1ATD typically appears with chronic obstructive pulmonary disease (COPD), emphysema, and disseminated bronchiectasis, usually between the forth and the fifth decade, but earlier onset may occur, especially in smokers.[58] In younger patients there is often a long lapse before A1ATD is diagnosed,[59] as the symptoms are attributed to a more likely diagnosis of asthma. The progression to liver cirrhosis in patients with A1ATD is usually slow. However, some patients develop early end-stage disease, with the need for LTx at a young age.

Diagnosis of A1ATD is usually made by measurement of serum A1AT concentration in combination with determination of C-reactive protein (the latter to exclude ongoing inflammation), and established with genotyping. Treatment of A1ATD lung manifestations does not differ from standard treatments of COPD.[60] Substitution therapy with A1AT derived from pooled human plasma is performed in some European countries, but robust evidence of efficacy is so far limited.[61] Recently, a Phase I/II clinical trial with an adeno-accosiated virus as vector delivering human A1AT complementary DNA (cDNA) has been completed,[62] and may usher in a new era in the treatment of A1ATD. For hepatic manifestations, the anticonvulsive drug carbamazepine is currently being evaluated in a Phase III clinical trial.[63,64] Carbamazepine has been shown to enhance autophagy and perhaps other intracellular mechanisms for degrading deposits of misfolded A1AT. For advanced liver disease, Tx is the treatment of choice. More than 500 patients have been transplanted for A1ATD in Europe, and the 5-year overall patient survival is 85%.[5]

Phenylketonuria

PKU is an autosomal recessive disease caused by mutations in the phenylalanine hydroxylase (PAH) gene. The disease was first described by Asbjorn Folling.[65] In the PAH gene >500 mutations have been mapped, and most have effects on PAH activity.[66] Established genotype-phenotype correlations are emerging.[67] PKU has a prevalence of about 1:10,000 in Europe, but for some areas it is higher.[68] PAH converts phenylalanine (Phe) into tyrosine, and is found exclusively in the liver.[69] Loss of PAH activity results in increased concentrations of Phe in the blood. Phe is an essential amino acid, and its entry into the brain is mediated by the large neutral amino acid carrier L-type amino acid transporter 1 (LAT1). Two other amino acids—tyrosine (precursor of dopamine and noradrenaline) and tryptophan (precursor of serotonine), also enter the brain via the LAT1 carrier. Since they compete for the same carrier, high concentrations of Phe in the blood impairs brain uptake of tryptophan and tyrosine.[70] Accordingly, cerebral protein synthesis rate is decreased in PKU patients when concentration of Phe is high.[71] Furthermore, animal studies haveshown that high concentration of Phe and its metabolites (principally phenyl lactate and phenylacetate) exert deleterious effects on markers of bioenergetics activity in neural tissue.[72] Together with the deficiency of tyrosine and its downstream products, these factors may explain the neurotoxicity in PKU.

PKU is classified by the severity of hyperphenylalaninaemia. The normal range of blood Phe concentrations is 0.8–1.8 mg/dl; concentrations above 20 mg/dl denote classic PKU.[73] Clinically, untreated PKU leads to disturbed brain development with profound retardation, microcephaly, epilepsy, and other neurologic symptoms. Most countries have a newborn screening programme, and early detection and implementation of a Phe-restricted diet widely prevents neurological symptoms. However, the diet regimen is arduous and even patients with well-controlled PKU exhibit a variety of subtle physical, cognitive, and behavioural symptoms.[67,74-76] Perhaps unsurprisingly, it has been shown that patients with PKU spend considerably more time managing their disease than patients with Type 1 diabetes.[77] Sapropterin dihydrochloride, a pharmaceutical form of the chaperone PAH cofactor tetrahydrobiopterin, lowers plasma Phe concentrations for up to half of patients with PKU.[78] Responders reportedly also experience increases in Phe tolerance[79] and increased quality of life (QoL).[80]

One patient with PKU has received a LTx for reasons unrelated to PKU, and the patient's blood Phe level normalised after transplant.81 HTx has been performed in one patient who had poor dietary control, with temporary improvement of blood Phe levels.[82] Clinically, HTx involves isolation of hepatocytes from livers rejected for solid organ Tx, and is performed with an infusion of the cells via a portal catheter into the liver, in a manner much resembling that of islet Tx. It is minimally invasive, and generally performed under local anesthesia. In the case of PKU, the cells need only improve a single enzyme deficiency. A clinical trial with hepatocytes for PKU is currently ongoing in the United States.[14]

Conclusion

Even though IEMs are regarded as simple mendelian diseases, clear genotype-phenotype correlations are rarely seen.[4] It is increasingly recognised, partly through the advent of next-generation sequencing, that multiple causative alleles, modifier alleles, or both, are common.[83] Hopefully improvements in our understanding of these genetic mechanisms will result in robust methods that can identify patients needing treatment before devastating symptoms occur. Gene therapy, and cellular Tx have the potential of dramatically improving the QoL of patients suffering from IEMs in the near future. For now, improved medical treatments and whole organ LTx may increasingly be considered in hepatic based IEMs.

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Upcoming Congresses and Meetings

The Global Viral Hepatitis Summit

26-28 June 2015

Berlin, Germany

At this, the 15th international symposium, attendees can enjoy a programme of lectures, discussions and exhibitions on diagnosis, developments and therapies for hepatitis. The meeting will be held alongside the 12th annual meeting of the German national network of competence on viral hepatitis and the 1st International Symposium of the Hepatitis Section of the German Center for Infection Research.

http://www.isvhld2015.org/

European Society for Medical Oncology (ESMO) 17th World Congress on Gastrointestinal Cancer.

1-4 July 2015

Barcelona, Spain

The ESMO World Congress on Gastrointestinal Cancer provides a platform for discussion on all aspects of gastrointestinal cancer, including screening, diagnosis and tumour management. Register before 18 June for a discounted fee.

Visit http://www.esmo.org/Conferences/World-GI-2015-Gastrointestinal-Cancer for further details

ILTS 21st International Annual Congress

8-11 July 2015

Chicago, IL, USA

This annual congress will review recent innovative liver transplantation techniques, promote understanding of perioperative management controversies and provide a platform for scientists, physicians, surgeons and other liver specialists to engage and discuss the latest therapies.

Registration opens at 6.30am on 8 July or pre-register online. Find out more here: http://2015.ilts.org/

World Congress on Hepatitis

20-22 July 2015

Orlando, Florida, USA

This is a multidisciplinary conference, covering a range of topics from patient management to clinical application. There will be scientific and clinical presentations from experts in the field for an educational forum to benefit everyone from senior physicians to junior investigators.

http://hepatitis.omicsgroup.com/

9th Annual Conference of the International Liver Cancer Association

4-6 September 2015

Paris, France

Aimed at experts from all liver cancer disciplines, this congress links research and practice, through lectures, symposia, exhibitions and general sessions. This year there will also be a pre-conference workshop on immunopathogenesis and immunotherapy in HCC.

http://www.ilca-online.org/

The Viral Hepatitis Congress

10-12 September 2015

Frankfurt, Germany

Following unprecedented advances in the treatment of hepatitis, such progress is hoped for other liver conditions. The Viral Hepatitis Congress seeks to continue to process the latest data and share this information in a relaxed and informative event.

www.viral-hep.org

Cardiovascular and Interventional Radiological Society of Europe (CIRSE)

26-30 September 2015

Lisbon, Portugal

CIRSE is a non-profit association that places emphasis on investing in high-quality educational and scientific programmes, thereby offering great value to participants. CIRSE 2015 will be the organisation's 30th anniversary, and to mark this, it will have a special focus on awards and new members of the IR community. The popular "CIRSE Meets…" session will host a delegation from China.

http://cirse2015.org

22nd International Symposium on Hepatitis C Virus and Related Viruses

9-13 October 2015

Strasbourg, France

This congress will showcase a series of abstracts, lectures, exhibitions and poster presentations, covering topics including molecular virology, pathogenesis and innate immunity. The programme also includes an evening 'Discovering Strasbourg' for visitors to find out more about the beautiful city they are in.

http://www.hcv2015.org/

The Liver Meeting

13-17 November 2015

AASLD says the programming for this meeting has been refined as part of a major initiative to reflect the rapid advances in hepatology. More than 9500 hepatology experts will be attending this winter conference, to discuss treatments and developments in this field.

http://www.aasld.org/

3rd World Congress on Controversies in Gastroenterology

December 2015

Paris, France

This conference offers the chance for leaders in this field to debate the latest treatments in gastroenterology and endoscopy. Bringing together experts from across the world, the very latest issues will be discussed and analysed in a series of lectures and group sessions.

http://www2.comtecmed.com/cigi

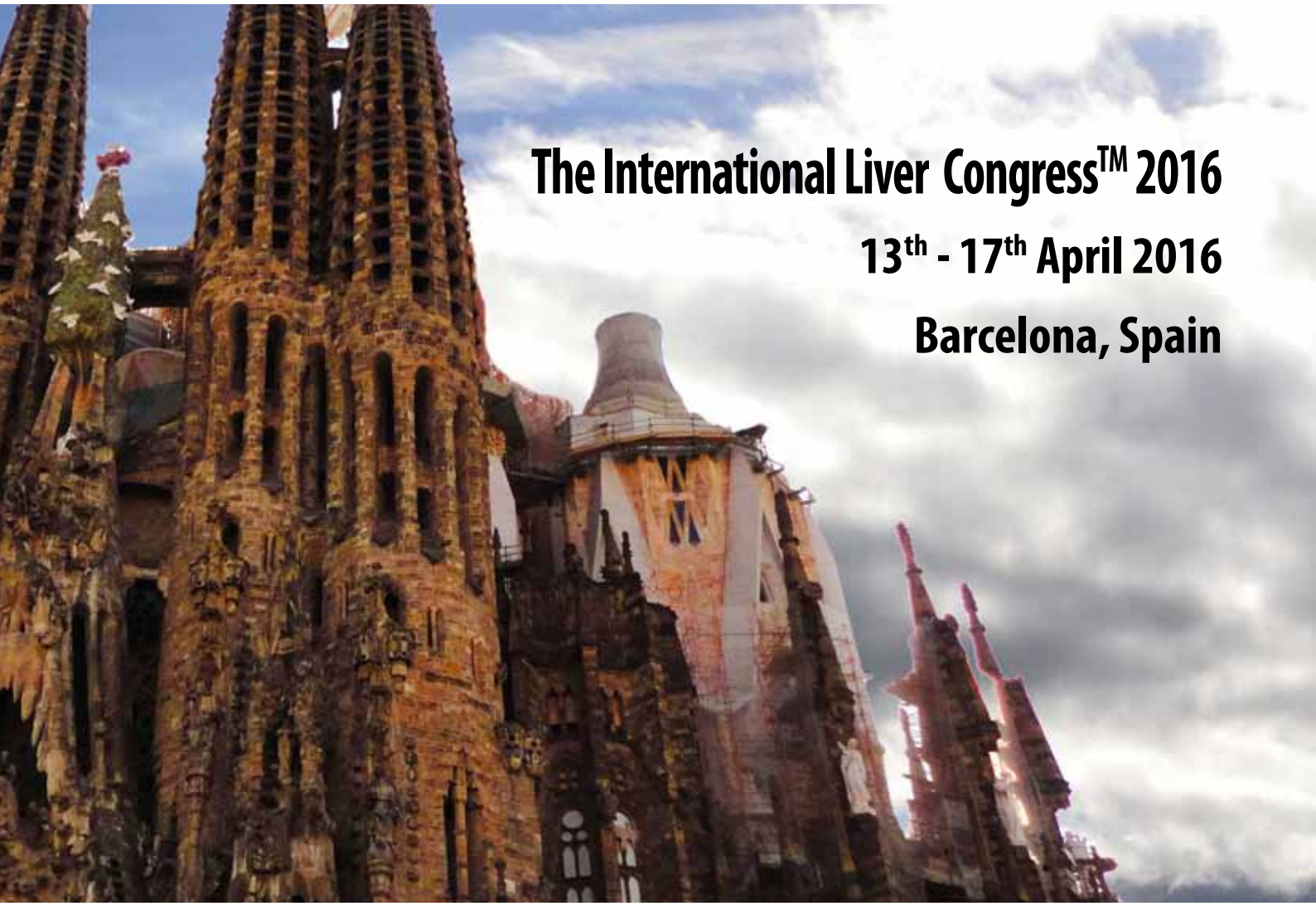
51st Intrenational Liver Congress ILC - EASD

13-17 April 2016

Barcelona, Spain

This Congress will attract specialists from around the world to discuss and analyse the latest developments in the clinical management and basic science aspects of liver diseases.

Building on the success of the ICL 2015, the scientific programme will offer a wide range of symposia, workshops, postgraduate courses, forums, and webcasting services to pique the interest of all its participants.



Robust protection against recurrent episodes of hepatic encephalopathy (HE)[1]

2-YEAR DATA

6-month data

Daily treatment with XIFAXAN® 550* b.d. plus lactulose significantly reduced episodes† and hospitalisations‡ compared with placebo plus lactulose[1], and improved quality of life[2] in patients with HE.

2-year data

The reduction in hospitalisations compared to placebo plus lactulose observed over 6 months is maintained over 2 years in patients treated with XIFAXAN® 550 b.d. plus lactulose.[1,3] The 2-year infection rates are lower than those observed in patients treated with XIFAXAN® 550 b.d. plus lactulose for 6 months, and the rates of adverse events are similar.[3]

Xifaxan®550
Targaxan®550
Rifaximin-α

* >90% were receiving concurrent lactulose in both treatment arms
† p<0.001 ‡ p=0.01

INTERNATIONAL ABBREVIATED PRESCRIBING INFORMATION: XIFAXAN®/ TARGAXAN® 550 mg (rifaximin)
Presentation: Blister pack containing 14 film-coated, pink tablets of 550 mg rifaximin for oral administration. **Indication:** Reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age. **Dosage and administration:** 550 mg twice a day orally with a glass of water, with or without food. No specific dosing adjustment is necessary for patients with hepatic insufficiency or for the elderly. **Contraindications:** Hypersensitivity to rifaximin, rifamycin derivatives or any of the excipients. Cases of intestinal obstruction. **Warnings and precautions:** The safety and effectiveness of rifaximin for the prevention of recurrence of hepatic encephalopathy have not been established in patients under 18 years of age. Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out. Caution is advised in patients with impaired renal function. Concomitant administration of rifaximin with other rifamycins is not recommended. Caution should be exercised when administering rifaximin to patients with severe hepatic impairment (Child-Pugh C) and in patients with MELD (Model for End-Stage Liver Disease) score >25. The effectiveness of oral oestrogenic contraceptives could decrease after rifaximin administration. Additional contraceptive precautions are recommended, in particular if the oestrogen content is less than 50 µg. Rifaximin may cause a reddish discolouration of the urine. **Interactions:** No experience administrating rifaximin to subjects taking another rifamycin to treat a systemic bacterial infection. In vitro data show rifaximin did not inhibit major cytochrome P450 (CYP) drug metabolizing enzymes. Rifaximin did not induce CYP1A2 and CYP 2B6 but was a weak inducer of CYP3A4. In healthy subjects studies demonstrated rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however in hepatic impaired patients rifaximin may decrease exposure of CYP3A4 substrates administered concomitantly (e.g. warfarin, antiepileptics, antiarrhythmics) due to higher systemic exposure. It is unknown whether concomitant drugs inhibiting P-glycoprotein and/or CYP3A4 increase systemic exposure of rifaximin. **Pregnancy and lactation:** No or limited data on the use of rifaximin in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus. Use of rifaximin during pregnancy is not recommended . It is unknown whether rifaximin/metabolites are excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy. **Undesirable effects:** Adverse effects observed in the placebo-controlled study RFHE3001 and long-term study RFHE3002: Common (≥1/100 to <1/10): Depression, dizziness, headache, dyspnoea, abdominal pain upper, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, oedema peripheral. Prescribers should consult country approved prescribing information for further information in relation to undesirable effects. **Overdose:** No case of overdose has been reported. In patients with normal bacterial flora, rifaximin in dosages of up to 2,400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage. In case of accidental overdosage, symptomatic treatments and supportive care are suggested. **Price and pack sizes:** PVC-PE-PVDC/Aluminium foil blisters in cartons of 28 or 56 tablets. Contact local distributor for price. **Legal category:** POM. **Prescribing information:** Medicinal product subject to medical prescription. **Marketing authorisation holder:** Norgine Pharmaceuticals Ltd. Norgine House, Widewater Place, Moorhall Road, Harefield, Middlesex UB9 6NS, UK. **Product licence number:** PL20011/0020. **ATC code:** A07AA11. **Date International Prescribing Information prepared:** 15 December 2014. **Company reference:** GL/XIF/1214/0080.

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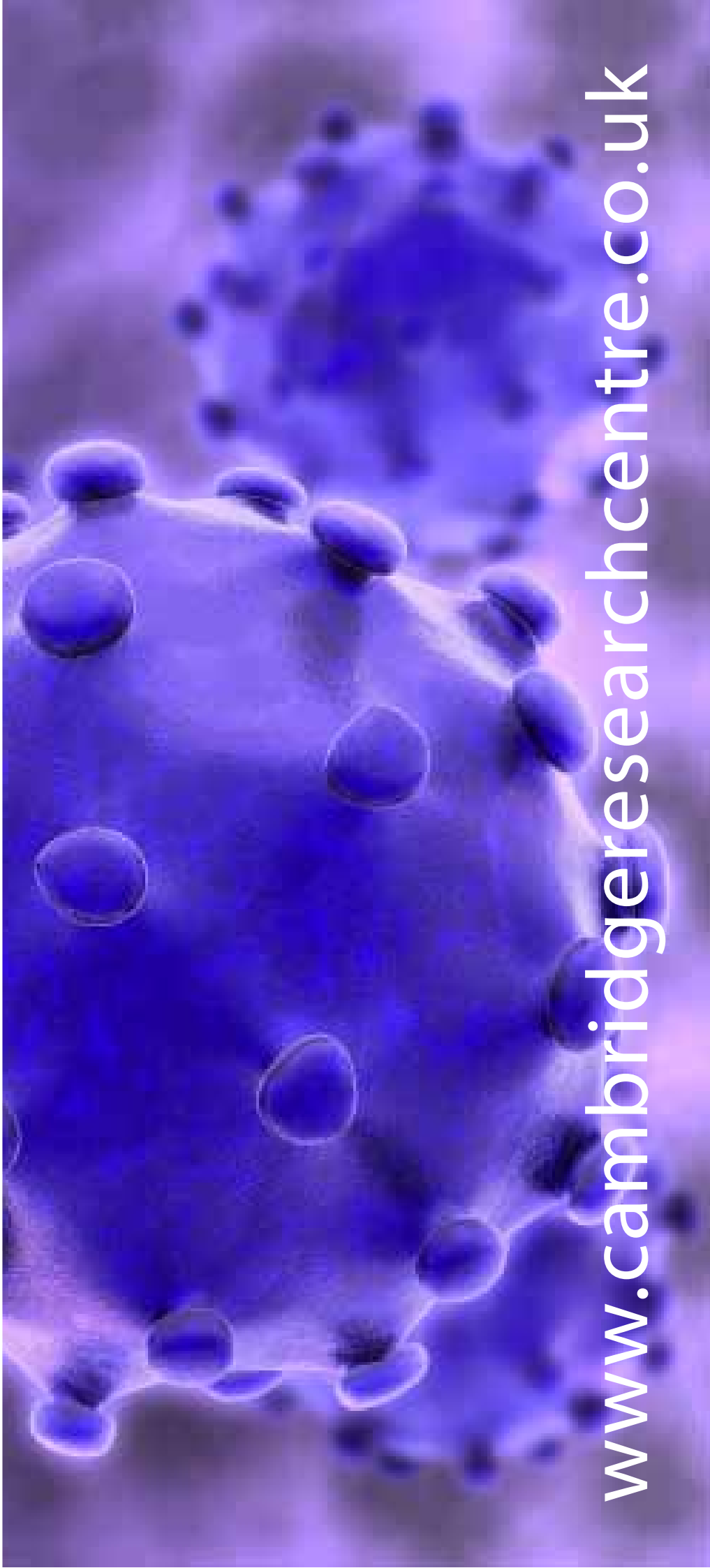

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