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THE INTERNATIONAL LIVER CONGRESS™ 2018

APRIL 11-15, PARIS, FRANCE

CONGRESS REVIEW

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The European Association for the Study of the Liver

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INTRODUCTION

INTRODUCTION

The International Liver Congress (ILC) 2018, the 53rd annual meeting of the European Association for the Study of the Liver (EASL), was held this year in Paris, France, and was attended by 9,669 delegates from 121 countries.

The field of hepatology is undergoing dramatic changes, with a major increase in metabolic liver diseases and liver cancer worldwide, highly effective drugs to cure hepatitis C now available, and multiple novel treatment concepts for rare liver diseases and hepatitis B emerging. During the opening ceremony, the ILC 2018 Honorary President, Tilman Sauerbruch, reminded the audience of the huge clinical and scientific advances that have been made in hepatology during the course of his illustrious career. He highlighted that, for example, survival after the first liver transplantations performed by Thomas Starzl in 1963 was just 0–23 days, compared with 1-year survival rates of 85% now, 55 years later. In other areas in the same time period, all viral causes of hepatitis were identified. However, despite these real advances in hepatology, many challenges remain.

Tom Hemming-Karlsen and Tilman Sauerbruch at the opening ceremony of ILC 2018

EASL is committed to addressing these challenges and this ongoing commitment to beating liver disease was reiterated by the Secretary General of the EASL Governing Board, Tom Hemming Karlsen. He highlighted expanded initiatives to educate doctors, nurses and the broader hepatology research community to improve the lives of everyone with liver disease. Such initiatives include clinical practice guidelines, accompanying slide decks, enhanced fellowship programmes, and clinical and basic science schools. In addition, new collaborations are developing, for instance, with diabetologists and oncologists, reflecting the multidisciplinary landscape in which EASL remains the hub.

The annual ILC is an integral part of this commitment, bringing together clinicians, scientists and hepatology associates from all around the world to discuss the latest advances at the frontline of hepatology and related disciplines. This year 2,760 abstracts were submitted. Of these, 1,750 were accepted; 208 as orals and 1,542 as posters. In this report we provide a flavour of the scientific and clinical advances that were shared over the course of the week.


Oral ePoster session

ILC 2018: SCIENTIFIC PROGRAMME HIGHLIGHTS

ILC 2018: SCIENTIFIC PROGRAMME HIGHLIGHTS

LIVER TUMOURS

ILC 2018 was a highly relevant congress for updates on liver tumours. In addition to the specific studies presented, a highlight was the release of the updated EASL hepatocellular (HCC) clinical practice guidelines.

Ongoing debate around DAAs and HCC

The abstracts presented at ILC 2018 on liver tumours covered a broad range of topics, from preclinical models and applications, to results from clinical trials. A number of these reported findings that have real implications for clinical practice, with a key focus on the continued debate on the association between DAAs used to cure HCV and the occurrence or recurrence of HCC in patients with cirrhosis.

A large study in HCV patients with cirrhosis demonstrated that patients treated with DAAs who achieve SVR have a significantly lower rate of first occurrence of HCC (3-year cumulative incidence of 6.0%) compared with those not achieving SVR (30.3%; p<0.0001).[1] An initial increase in HCC compared with those treated with PEG-IFN can be attributed to the profile of patients treated with DAAs; patients were older, had more comorbidities, had poorer liver function and had undergone less rigorous surveillance for HCC prior to treatment with DAAs. What perhaps remain as open questions are whether there is any association between tumour recurrence, whether there is a more aggressive pattern of recurrence in patients with previous HCC treated with DAAs for HCV infection, and whether patients with HCV and HCC should receive DAA therapy prior to liver transplantation. What is clear is that presence of cirrhosis is the main driver of HCC and if the aetiological factor is removed, for example alcohol, the risk of HCC persists.[2] The clear message was that patients with cirrhosis need to undergo continued surveillance for HCC.

Patients with cirrhosis need to undergo surveillance for HCC even if the aetiological driver is removed

Combining therapies to treat HCC

At ILC 2018, there were several reports on studies looking at combining treatment modalities in HCC, although there were no data on new therapeutics under investigation. Sorafenib is the standard first-line therapy for patients with advanced HCC and conventional transarterial chemoembolization (cTACE) is an effective treatment for unresectable HCC.[3] A previous Phase 2 study combining these treatments indicated that this strategy is associated with improved outcomes. However, the subsequent multicentre, open-label,

Professor Joong-Won Park

cTACE + sorafenib does not confer a survival advantage in advanced HCC vs sorafenib alone

1. Nahon P, et al. Abstract PS-020
2. Zangneh HF, et al. Abstract PS-061
3. Park J-W, et al. Abstract GS-003

randomized controlled, Phase 3 STAH trial in 339 patients reported at ILC 2018 failed to confirm these results (median overall survival [OS] 12.8 vs. 10.8 months [p=0.290]). This was despite prolonged time to progression (TTP) and progression-free survival (PFS), greater tumour response rate (TRR), and lower rates of SAEs. In a subgroup analysis a survival benefit was evident in patients who received ≥2 cTACE sessions compared with those receiving sorafenib (18.6 vs. 10.8 months [p=0.006]). The main reasons for dropout after one cTACE session related to adverse events. Those who were able to endure >1 cTACE session had smaller tumours and better-preserved liver function. Professor Joong-Won commented that to really test this result, a second trial would be necessary with limited enrolment according to tumour size and liver function.

In an extended follow-up of 226 patients in a previous randomized controlled trial on the benefits of adjuvant immunotherapy with cytokine-induced killer (CIK) cells for HCC, 5-year progression-free survival was 44.8% among those receiving immunotherapy compared with 33.1% in the control group.[4] Thus, demonstrating that many patients undergoing curative treatment for HCC may benefit from adjuvant CIK cell immunotherapy.

Curative treatment is not an option in many patients with HCC and the results of the palliative cohort of the SORAMIC randomized controlled trial, a study comparing the combination of selective internal radiation therapy (SIRT) with sorafenib vs. sorafenib alone in patients with advanced HCC and not eligible for TACE, were also presented at ILC 2018.[5] Although the primary efficacy endpoint was overall survival in the ITT population, results from the per protocol analysis were presented because significant protocol violations had resulted in unbalanced treatment groups. Although no significant differences were observed in the overall population, subgroup analyses revealed a survival benefit of SIRT + sorafenib in patients ≤65 years of age (HR 0.65; p=0.05), those without cirrhosis (HR 0.46; p=0.02), and those with no alcoholic aetiology (HR 0.63; p=0.012), leading to the hypothesis that SIRT + sorafenib may be of value in certain subgroups of patients. However, the systemic treatment available today remains the standard of care for these patients.

In a further effort to define a role for SIRT in the treatment of advanced HCC, a subgroup analysis of the SARAH study showed that a tumour-absorbed dose of ^{90}Y is significantly associated with overall survival and disease control.[6] The highest response rates were achieved in patients who received ≥100 Gy ^{90}Y (median OS 14.1 months vs. 6.1 months in <100 Gy patients; p<0.0001). In his summary of these data, Professor Fabio Piscaglia asked whether, with the imminent availability of second- and third-line drugs, radioembolization still has a broad application or whether its use will become restricted to specific situations.

HCC is the end stage of many chronic liver diseases, and a significant source of patients with HCC is from those chronically infected with HBV. At ILC 2018, an interesting new approach to treatment using personalized immunotherapy was proposed.[7] Adoptive transfer of T cells engineered to carry HBV-specific T cell receptors showed promising signs of clinical effectiveness in a patient with HCC metastases in the lungs following liver transplant.

4. Lee J-H, et al. Abstract GS-008
5. Ricke J, et al. Abstract LBO-005
6. Hermann A-L, et al. Abstract PS-018
7. Tan A, et al. Abstract PS-017

Advances in classification and risk prediction in cholangiocarcinoma

An interesting study was presented on the integrative molecular classification of cholangiocarcinoma, the second most common primary liver cancer. It is a malignancy of the biliary tree and can be intrahepatic or extrahepatic (eCCA).[8] Genomic derangements vary and differentiation is critical, with implications for clinical management. No effective systemic molecular therapies for eCCA exist and no comprehensive molecular profiling of this cancer has been performed in western patients to inform a more precise therapeutic approach in the clinic. This study reported at ILC represented a first step on this journey. A total of 189 formalin-fixed paraffin-embedded samples from patients with eCCA treated by resection were collected retrospectively. Median survival of the cohort was 48.5 months. Whole gene expression profiling identified four distinct molecular subtypes of eCCA with distinct gene signatures; metabolic (18.7%), proliferation (22.5%), mesenchymal (47.3%), and immune (11.5%). The different clinico-pathological characteristics pave the way for more precise therapeutics targeting these characteristics, potentially nuclear receptor modulators or Wnt antagonists for potential targeted therapies, ERBB-2 mAbs, mTOR inhibitors, CDK4/6 inhibitors or PARP inhibitors for proliferation, HA degradation, hedgehog inhibitors or Bcl-2 inhibitors for mesenchymal and immune checkpoint inhibitors or IL6-JAK-STAT3 inhibitors for immune.

EASL fellowship recipient presents data on integrative molecular classification of eCCA at ILC – potentially paving the way for more precise therapeutics

Dr Robert Montal

CHOLESTASIS AND AUTOIMMUNE

Promising new treatments for PBC without evident increase in pruritus

Some of the most pressing unmet needs in hepatology today are those related to autoimmune disorders and cholestatic disease; there are currently limited treatment options for patients with primary biliary cholangitis or primary sclerosing cholangitis, and diagnosis of autoimmune hepatitis is challenging.

Median survival after a diagnosis of primary biliary cholangitis is 9 years. Although there are some conflicting data, it is largely recognized that ursodeoxycholic acid (UDCA) is associated with prolonged liver transplant-free survival. A study in 3,902 patients reported at ILC 2018 confirmed the impact of UDCA, reporting a 10-year liver transplant-free survival rate of 79.7% compared with 60.7% in untreated patients ($p<0.001$).[9] This survival advantage was observed in all subgroups evaluated, regardless of Rotterdam stage. Of most interest, although less profound, the survival advantage remained evident in patients without improvement in the biochemical measurements of ALP (adjusted HR 0.61, 95%CI 0.46–0.81 [p = 0.0008]) or

8. Montal R, et al. Abstract GS-004
9. Harms M, et al. Abstract PS-008

bilirubin (adjusted HR 0.55, 95%CI 0.45–0.67 [p <0.0001]) after 1 year of UDCA. In 337/3,529 (9.5%) treated patients with neither ALP nor bilirubin improvement, UDCA treatment still showed a trend towards a lower risk of LT/death (HR 0.76, 95%CI 0.55–1.07 [p = 0.113]). This study gives a very clear message: if a patient is given this drug, they are highly likely to experience a benefit. However, what is really required are additional, second-line therapies, as a significant proportion of patients with PBC do not respond to UDCA. Fortunately, as Herbert Tilg highlighted in the ILC wrap-up session, this is a highly active field in hepatology, with several Phase 2 clinical trials underway.

In the first of these trials evaluating new therapeutic approaches in PBC, the selective, potent PPAR-delta agonist, seladelpar, demonstrated sustained anti-cholestatic and anti-inflammatory efficacy over 12 or 26 weeks of administration in patients intolerant or non-responsive to UDCA.[10] Importantly, this efficacy was not associated with transaminase safety signals or an increase in pruritus, a debilitating symptom that can be exacerbated by therapy.

In a second Phase 2 study in a similar PBC patient population, tropifexor, a potent non-bile-acid FXR agonist, was associated with a dose-dependent decrease in GGT, ALP, ALT, and AST.[11] Once again, the lack of any discernible increase in itch could be a major advantage of this FXR agonist, with a resulting positive impact on patient quality of life. In a further study, add-on therapy with budesonide also resulted in improvements in biochemical markers of disease, although no improvements in histology were observed after 36 months of treatment.[12]

Statins are associated with reduced mortality and morbidity in PSC

Management of primary sclerosing cholangitis (PSC) is a medical challenge as there are no approved therapies. Increasing evidence of a beneficial effect of statins in cholestatic liver disease prompted researchers at the Karolinska Institute to conduct a register-based analysis to study the impact of exposure of different drugs, including statins, on death, liver transplantation, and adverse liver events in 2,914 patients with PSC.[13] Of these patients, 94 (3.4%) had undergone liver transplant and 580 (19.9%) had died. Statin use was associated with a reduced risk of all-cause mortality (adjusted HR 0.68, 95% CI 0.54–0.88), reduced mortality and liver transplantation (adjusted HR 0.50, 95% CI 0.28–0.66), and reduced adverse liver events (adjusted HR 0.53, 95%CI 0.36–0.80). UDCA was not associated with a reduced risk of mortality. Despite limitations inherent in register-based studies and underlying confounding factors, such as alcohol use, smoking and obesity, these results are exciting; they are another example of the pleiotropic effects of statins and suggest that they that may be promising candidates for future studies.

Another potential therapeutic option for patients with PSC is NGM282, an engineered, non-tumourigenic FGF19 analogue that potently regulates CYP7A1-mediated bile acid homeostasis.[14] In 62 patients with PSC according to the EASL criteria and ALP >1.5 x ULN, NGM282 potently inhibited bile acid synthesis, decreased markers of hepatic inflammation and significantly improved markers of

10. Hirschfield G, et al. Abstract LBP-002
11. Schramm C, et al. Abstract LBO-007
12. Hirschfield G, et al. Abstract GS-011
13. Stokkeland K, et al. Abstract PS-128
14. Hirschfield G, et al. Abstract LBO-002

fibroblastic response and matrix formation, without an increase in pruritus. However, there was no observed decrease in ALP. Although there was no impact on ALP after treatment for 3 months, the pathways targeted are interesting with respect to PSC as they have a strong immunomodulatory potential and longer trials are warranted with hard endpoints, such as liver biopsy and mortality. It is positive to see such active research in a disease where patient need for new treatment options is high.

Natural history of PSC may complicate evaluation of vedolizumab for PSC

Another attractive treatment option for patients with PSC is vedolizumab (VDZ), owing to its targeting of gut-homing lymphocytes implicated in PSC pathophysiology. Although VDZ has benefits in inflammatory bowel disease, little data exist on its effect in PSC/IBD. The results of a retrospective audit were presented at ILC 2018, which was conducted by the International PSC Study Group and which evaluated its effect in 60 patients with PSC who had received VDZ for IBD.[15] Parameters relevant to PSC and IBD were compared at Baseline, Day 42, and last follow-up. Mean ALP at Baseline was 2.38 x ULN (1.82–2.94) and was not significantly changed at either Day 42 (2.59 x ULN, 1.93–3.24 [p=0.32]), or last follow-up (2.76 x ULN, 2.09–3.44 [p=0.06]. Mean increases in ALT and AST at last follow-up vs. baseline were observed (61.6 IU/L vs. 79.8 IU/L [p=0.0078] and 56. 9 IU/L vs. 71.9 IU/L [p=0.055], respectively). In 44 patients with available data, 25 showed an improved endoscopic IBD response (56.8%), compared with 19 (43.2%) who were unchanged or deteriorated. Of those who had an IBD response, 60.0% had a non-significant ALP drop from baseline to last follow-up compared with only 42.1% in IBD non-responders (p=0.36). The disappointing conclusion is that while VDZ appears moderately effective for IBD in PSC/IBD, there was no effect on ALP response, observations that may be due to the natural course of the underlying PSC.

Serum metabolomic profiling shows diagnostic promise for iCCA

The research activity around cholestatic liver disease was not limited to promising new therapeutics, but also addressed diagnosis and identification of those patients more likely to develop CCA. Despite the recognized predisposition of patients with PSC to intrahepatic cholangiocarcinoma (iCCA), progression to a malignant lesion often escapes detection, with diagnosis occurring at advanced stages.[16] In addition, iCCA can be difficult to differentiate from HCC. The ability to do this is therefore a clear unmet need and non-invasive techniques that can discriminate between iCCA, HCC, and PSC would be a huge advance in cholestatic disease. Chloroform/methanol and methanol extracts obtained from the serum of patients with PSC, iCCA, or HCC and healthy individuals (n=20 in each group) were analyzed using ultra-performance liquid chromatography coupled to mass spectrometry (UHPLC-MS). All samples were obtained from treatment-naïve individuals who had a diagnosis confirmed by histology, without mixed or other

Serum metabolomics profiling may be a promising non-invasive approach to discriminate iCCA, HCC, and PSC

15. Williamson K, et al. Abstract PS-134
16. Banales J, et al. Abstract PS-129

malignancy. A total of 438 metabolites were identified, with significant changes in levels of several compounds evident for each comparison; iCCA vs. control, 52 metabolites; HCC vs. control, 104 metabolites; HCC vs. iCCA, 58 metabolites; PSC vs. control, 151 metabolites; iCCA vs. PSC, 102 metabolites. Of most clinical relevance were the differences between iCCA and PSC, and HCC and iCCA. An algorithm consisting of phosphatidylcholine (PC) (34:3), which demonstrated 100% sensitivity and 80% specificity, + histidine accurately discriminated between PSC and iCCA (area under the receiver operating characteristic curve (AUROC): 0.990 [100% sensitivity, 70% specificity, 85% accuracy]. Similar performance was seen using aspartic acid + glycine (AUROC: 0.885 [95% sensitivity, 65% specificity, 80% accuracy] for differentiation between HCC and iCCA. Although larger validation studies are required to determine diagnostic value, serum metabolomics profiling seems to be a promising non-invasive approach to distinguish iCCA from both HCC and PSC.

VIRAL HEPATITIS

Promising treatment options in patients with HDV/HBV infection are welcomed

As with previous years, viral hepatitis was a key focus at ILC 2018. There were several presentations on how best to use the expanding treatment options available to manage patients with chronic hepatitis B and C, and promising new options were presented for HDV/HBV coinfection, for which there is currently no approved drug therapy. This is a significant unmet medical need as an estimated 10–20 million people around the world are infected with this most severe form of viral hepatitis, characterized by rapid progression to cirrhosis and a 5–7-fold increased likelihood of developing HCC compared with HBV-monoinfected patients.

Promising, albeit early, results from Phase 2 studies demonstrated significant virological suppression in response to two potential treatment options for HDV – the HBV entry inhibitor myrcludex B (MyrB) and the prenylation inhibitor lonafarnib.

Professor Heiner Wedemeyer

Although HDV RNA reduction/suppression is associated with improved long-term clinical outcomes, it is only achieved in 25–30% of patients after a 48-week course of PEG-IFNα 2a and late relapses may occur in more than half of patients. The final results of a multicentre, open-label Phase 2b clinical trial of MyrB, an entry inhibitor that blocks the HBV/HDV receptor NTCP, in 120 patients treated with TDF were presented at ILC 2018.[17] After 24 weeks of treatment, dose-dependent decreases in median HDV RNA levels were observed (−1.75 log [2 mg], −1.60 log [5 mg], −2.70 log [10 mg]) that were not observed with TDF alone (−0.18 log). HDV RNA declined by ≥2 log or was undetectable in 46%, 47%, 77%, and 3% of patients, respectively, and correlated with intrahepatic decrease of HDV RNA replication on histology.

17. Wedemeyer H, et al. Abstract GS-005

ALT normalized in 43%, 50%, 40%, and 7% and liver stiffness declined. At follow-up, 12 weeks after stopping treatment, HDV RNA relapse occurred in 60%, 80%, and 83% of HDV RNA responders and ALT levels increased correspondingly. Apart from an increase in bile acids that is expected with the mode of action of MyrB, tolerability was good. Of particular interest, despite an increase in serum bile acid concentrations, no patients reported itching, suggesting that bile acids *per se* do not cause pruritus. These results are highly promising.

MyrB also reduced intrahepatic levels of HDV RNA and HDV antigen-positive cells in a dose-dependent manner.[18] This finding together with the concomitant reduction in ALT reduction and of inflammatory cytokines suggests that reducing HDV infection serves to diminish liver inflammation. However, although sustained HDV control after 24 weeks of therapy was possible in individual patients, longer treatment durations, perhaps for 2–3 years, or even maintenance therapy, need to be investigated in future trials and a combination trial with PEG-IFNα 2a is already underway.

Previously published data from the LOWR HDV-2 study, in patients with chronic HDV, demonstrated an antiviral response against HDV with multiple combinations of lonafarnib and ritonavir (RTV), with or without PEG-IFNα, for 12 to 48 weeks.[19] A subanalysis of this study, in 33 patients completing 24 weeks of treatment, evaluated virological response rates as a function of baseline viral loads and demonstrated that while lonafarnib-based regimens (25 or 50 mg plus RTV) achieved virological responses in most patients, the all oral combination of lonafarnib 50 mg BID plus RTV 100 mg BID appeared to be a particularly effective option for patients with low baseline viral load, with a 100% (7/7) response. Although triple therapy with lonafarnib in combination with RTV and PEG-IFNα appears to be the best choice of therapy, investigators are considering evaluation of two further approaches: to evaluate whether response is sustained upon stopping all oral treatment after 3 months or whether there is viral rebound and clearance, or, again after 3 months of treatment, to have a washout period followed by a second block of treatment.

Refining our knowledge on how best to treat patients with chronic hepatitis C

With many effective drugs available and able to cure most patients with chronic hepatitis C, the focus is now on evaluating response in real-world cohorts to include populations frequently under-represented in clinical trials, refining treatment approaches, and managing patients failing on DAA therapy. There were presentations on all of these topics at ILC 2018, many of which are reflected in the updated HCV clinical practice guidelines.

HCV updated clinical practice guidelines focus on simplified patient management

Several reports were presented on the efficacy of glecaprevir/pibrentasvir. The results from the ENDURANCE-5, -6 study reported SVR12 rates of 97% in patients infected with GT 5 or GT 6, without or with cirrhosis.[20] These patients are historically under-represented in clinical trials and the cure rates and tolerability profile observed in this study were in line with those reported in registration trials. The efficacy of

18. Allweiss L, et al. Abstract PS-162
19. Yurdaydin C, et al. Abstract PS-161
20. Asselah T, et al. Abstract GS-012

this regimen was confirmed in real-world studies, including from the German Hepatitis Registry (DHC-R) study (100% SVR12 in the mITT population),[21] an ongoing, non-interventional, multicentre, prospective registry study, and the Italian Navigator-II study (98% SVR12),[22] both of which also reported a good tolerability profile. High rates of SVR12 were observed across all genotypes assessed, regardless of presence of cirrhosis, previous exposure to DAAs, or historic or active intravenous drug use. Real-world data also confirmed the effectiveness of sofosbuvir/velpatasvir in patients with HCV GT 3, a patient population in which cure rates have not been as high as with other genotypes. In two separate studies, SOF/VEL for 8 weeks was shown to be highly effective in patients with significant cirrhosis on daily supervised OST.[23] Similar results were observed with 12 weeks of treatment in NS5A-naïve patients with cirrhosis.[24]

Professor Tarik Asselah

Professor Thomas Berg

As well as real-world studies, additional clinical trials on some regimens looking to reduce the duration of treatment reported data on the efficacy of elbasvir/grazoprevir in patients chronically infected with HCV GT 4.[25] HCV GT 4 is endemic in the Middle East and Africa, and increasing in prevalence in Europe as a result of immigration and injecting drug use. Reducing duration of treatment, in particular in those actively injecting drugs, could expand access and adherence to treatment, something considered crucial to achieve elimination targets, particularly in countries with high prevalence and low resources. The current minimum recommended treatment regimen with the once-daily fixed-dose combination of elbasvir (EBR) 50 mg and grazoprevir (GZR) 100 mg in chronic HCV GT4 infection is 12 weeks. However, a Phase 4 study in F0–F2 patients presented at ILC 2018 reported SVR12 rates of 93% in those with available data (26/28).

Against a background of very high SVR12 rates after first-line therapy with many DAAs in many different subpopulations, it is easy to forget that some patients are not cured after their first treatment and require subsequent lines of therapy. At ILC 2018, data were presented on the management of this relatively small but potentially challenging patient population. In a Phase 3b, open-label, randomized, pragmatic study of glecaprevir/pibrentasvir +/– ribavirin (RBV) for HCV GT 1 subjects who previously failed an NS5A Inhibitor + SOF therapy, G/P resulted in very high rates of SVR12 in those with available data, regardless of presence of cirrhosis or treatment duration for 12 or 16 weeks.[26] There are also retreatment options in patients who fail G/P therapy; in the ongoing Phase 3 Magellan-3 study, preliminary data show that retreatment with G/P + SOF + RBV for 12 or 16 weeks was well tolerated and has demonstrated a high rate of SVR12, regardless of HCV genotype or baseline resistance-associated substitutions.[27] In a further study, real-world data from the Frankfurt Resistance Database suggested SOF/VEL/VOX to be an effective rescue

21. Berg T, et al. Abstract GS-007
22. D'Ambrosio R, et al. Abstract GS-013
23. Boyle A, et al. Abstract PS-034
24. Buti M, et al. Abstract PS-035
25. Asselah T, et al. Abstract GS-006
26. Lok A, et al. Abstract LBO-008
27. Wyles D, et al. Abstract PS-040

therapy in patients with prior DAA treatment failure despite the presence of high-level RASs and/or multiple previous DAA therapies.[28]

All these data show that DAAs are highly effective in clearing active HCV infection. However, there has been a lack of evidence of the impact they have on severe liver-related morbidity at a population level. Data presented at ILC 2018 confirmed the long-term benefits of achieving SVR, with data from the Scottish HCV Clinical Database demonstrating that following the introduction of DAAs, an immediate and considerable reduction in the incidence of HCV-related decompensated cirrhosis was apparent.[29] Furthermore, in an analysis of the pre-transplant cohorts of the SOLAR-1 and -2 studies, and the ASTRAL-4 study,[30] SOF/LDF or SOF/VEL therapy in patients with decompensated cirrhosis was found to result in significantly decreased mortality (-54%) by Day 365, an observation that was consistent with real-world data from over 4,000 patients in the HCV-RESIST cohort receiving a variety of DAAs.[31] In addition, an analysis of DALTON cirrhosis registry data presented at ILC 2018 aimed to evaluate durability of SVR and the clinical progression or reversal of liver disease reversal among patients who had achieved SVR.[32] The study showed that SVR was maintained in almost 100% of patients, and among patients who achieved SVR the incidence of HCC was very low over 120 weeks of follow-up. Although uncommon, HCC occurred most often in patients with decompensated cirrhosis. However, most patients maintained or improved their Child–Pugh category relative to baseline in response to treatment through 96 weeks of follow-up, improvements in liver stiffness occurred early and were sustained. In line with all these studies, a decline in the number of patients requiring a liver transplant as a result of chronic HCV infection was also shown at ILC 2018.[33]

Promising therapeutic agents for HBV at ILC 2018

Therapy for patients with chronic hepatitis B has looked largely the same for over 2 decades. However, potential new therapeutic targets are being studied and some promising results with some novel therapies were presented at ILC 2018. RO7049389 is a small-molecule, Class I HBV core protein allosteric modulator (CpAM) that induces formation of abnormal hepatitis B virus (HBV) core aggregates, resulting in defective capsid assembly and thereby suppressing HBV replication. In a key plenary at ILC 2018, results from the ongoing Phase 1 study investigating the safety, tolerability, pharmacokinetics, and anti-HBV activity of RO7049389 showed attendees that in healthy volunteers, RO7049389 was rapidly absorbed and eliminated from plasma, and was well tolerated across doses.[34] In patients with chronic HBV infection, robust and continued HBV DNA declines from pre-dosing levels were observed over 28 days, with median (maximal) decline being 2.7 (3.4) log10 IU/ml and below the limit of detection in 3/6 patients. These preliminary but promising results suggest that RO7049389 is well tolerated and demonstrates excellent anti-HBV activity.

In a further study, the novel capsid assembly modulator (CAM) JNJ-56136379 (JNJ-6379) showed promise as a potential therapeutic option in treatment naïve patients with chronic hepatitis B without cirrhosis.[35] In this ongoing, randomized,

28. Vermehren J, et al. Abstract THU-347
29. Hutchinson S, et al. Abstract GS-017
30. Kim WR, et al. Abstract PS-151
31. Calvaruso, et al. Abstract PS-149
32. Mangia A, et al. Abstract GS-018
33. Perricone G, et al. Abstract LBP-021
34. Gane E, et al. Abstract LBO-003
35. Zoulim F, et al. Abstract LBO-004

double-blind, placebo-controlled Phase 1b study in 36 HBeAg-positive and -negative patients, substantial reductions from baseline in HBV DNA and HBV RNA were observed in patients treated with 25 mg, 75 mg, or 150 mg for 1 month. The drug also showed no dose-limiting toxicities, with exposure increasing in a dose-dependent manner. Once again, although preliminary, these data are promising for new therapeutic options in patients with chronic hepatitis B.

CIRRHOSIS AND COMPLICATIONS

In her wrap-up presentation during the last general session, Professor Dominique Thabut highlighted that cirrhosis is still a major public health concern that represents a heavy burden of disease across Europe and the rest of the world, something that was also stressed in the Jean-Pierre Benhamou clinical state-of-the-art lecture given by Professor Jaime Bosch. He noted the number of individuals with cirrhosis at around 2.8 million and highlighted the broad spectrum of disease represented by cirrhosis, and the varying treatment goals at different stages of disease.

Urgent action is required to combat multi-drug resistant bacterial infections in patients with cirrhosis

In patients with cirrhosis, bacterial infections are a common and life-threatening complication. However, despite this, little is known about the epidemiology and outcomes. Some welcome light was shed on this in the first general session of ILC this year with presentation of results of the multicentre intercontinental study in hospitalized patients with cirrhosis promoted by the International Club of Ascites.[36] The most common infections were spontaneous bacterial peritonitis (SBP; 27%), urinary tract infections (UTI; 22%), and pneumonia (19%). From a total of 1,302 patients, 740 (57%) had at least one positive culture and 959 microorganisms were isolated (58% Gram negative; 38% Gram positive; 4% fungi). The variation between countries in terms of multi-drug resistant (MDR) bacteria was striking; from 16% in the USA to 73% in India against a global prevalence of 34%. Independent risk factors for MDR infections, in addition to infection in Asia and South America, were antibiotic use in the 3 months prior to hospitalization, the category of infection, site of infection, and skin and soft tissue infection. Infections due to MDR bacteria were associated with a lower rate of response to empirical antibiotic treatment, a higher incidence of shock, and incident organ failure. Susceptibility *in vitro* is highly clinically relevant in this patient population as this is the strongest predictor of in-hospital mortality. The relevant differences in the aetiology across the world, particularly with respect to MDR bacteria, highlight the need to develop tailored empirical antibiotic strategies.

Empirical antibiotic strategies are required in response to global variations in MDR bacteria

This is a highly relevant issue across Europe, with high rates of immigration from countries with high rates of MDR

36. Piano S, et al. Abstract GS-001

However, Dr Salvatore Piano, who presented the data, stressed that the hepatology community cannot afford to wait for this to happen. In the meantime, efforts must be increased to reduce the spread of MDR bacteria in patients with cirrhosis. In particular, adherence to EASL-recommended treatment has been associated with better outcomes.[37] However, what is particularly concerning is that only around 60% of patients were treated in accordance with these recommendations.

Dr Salvatore Piano

Bacterial infection in patients with cirrhosis is often treated with beta-lactam antibiotics. Previous studies in patients without cirrhosis have suggested that continuous infusion of beta-lactams may improve outcome. A sub-study of the European prospective, multicentre, observational 'bloodstream infection in cirrhotic patients (BICHROME)' study assessed the impact of continuous infusion versus intermittent administration of piperacillin-tazobactam or carbapenems in patients with cirrhosis and bloodstream infection.[38] After 30 days of follow up, mortality was significantly lower among patients receiving continuous infusion compared with those receiving intermittent administration.

Important data shown for the daily clinical management of patients with infections and advanced liver disease

Inflammation in patients with cirrhosis

Systemic inflammation, characterized by increased levels of cytokines and oxidative stress, plays a major role in the pathogenesis of ACLF in patients with decompensated cirrhosis. However, the factors triggering this process remain elusive. An interesting presentation at ILC suggested that one of these triggers could be oxidized albumin (HNA1), which may exert its effect through the p38 MAP kinase pathway.[39] These findings provide a rationale for the removal and replacement of these molecules in the prevention and treatment of organ failure in patients with decompensated cirrhosis.

Inflammatory response profiles following treatment with albumin correlated with 6-month survival

In a complementary study, differential inflammatory response profiles following treatment with albumin were found to correlate with survival at 6 months.[40] In the ATTIRE feasibility study, 79 patients with cirrhosis were given albumin for 14 days. Patients with acute decompensation/acute-on-chronic liver failure (AD/ACLF) were stratified by survival and immune function tested *ex vivo* at baseline and at intervals for 2 weeks. The study found that immune function was restored following albumin infusion to healthy levels in both survivors and non-survivors. Interestingly the group found that there is a distinct immune restoration phenotype associated with differences in survival: they concluded that a more gradual restoration of immune function with albumin confers better survival and outcomes than a rapid restoration. The worse clinical outcome was mirrored by a hyperinflammatory phenotype in non-survivors, according to CRP

37. Piano S, et al. Abstract PS-080
38. Bartoletti M, et al. Abstract PS-077
39. Quiles JA, et al. Abstract PS-012
40. Becares N, et al. Abstract PS-013

levels. The ATTIRE trial is continuing to the end of the year and future studies will investigate underlying molecular mechanisms and whether immune effects of human albumin solution differ according to inflammatory profile.


Dr Marco Di Pascoli

The clinical benefit of long-term administration of human albumin for treating ascites is debated. A prospective, single-centre study carried out in Padova, Italy provided convincing evidence that long-term albumin treatment of patients with cirrhosis and refractory ascites reduces the probability of inpatient hospitalizations and improves survival.[41] The study compared albumin 20 g twice per week, plus hydro-saline restriction and maximum tolerated doses of diuretics (n=45), against standard-of-care treatment alone (n=25). Over a study period of 2 years, 33% of patients who received albumin treatment remained free from hospitalization compared with none of the patients receiving only standard-of-care treatment (p=0.008). Patients treated with albumin also showed a reduction in the incidence of overt hepatic encephalopathy and infections and had reduced mortality compared with patients receiving standard-of-care (cumulative incidence 42% versus 66%; p = 0.032).

Potential therapeutic value of manipulating the gut microbiome

Diet can profoundly affect the gut microbiome, which in turn is associated with outcomes such as hepatic encephalopathy, infections, hospitalizations, and death in patients with liver cirrhosis. In a study on the gut microbiome in patients with acute on chronic liver failure, 200 patients with cirrhosis, either AD or ACLF, were studied prospectively with DNA extracted from stool samples.[42] Gene richness (as measured by gene count and number of metagenomic species) was markedly reduced in patients with liver cirrhosis compared with healthy subjects and strikingly reduced with disease severity and progression to ACLF. Antibiotic use reduced gene richness more so but not significantly. *Enterococcus* species correlated with disease severity, particularly with ACLF and was associated with poor prognosis. Human DNA was also found in more abundance in the patients with ACLF and was found to be highly positively correlated with disease severity. Though the significance of this finding is uncertain, it was thought to be due to inflammatory bowel disease.

Diet affects gut microbiota and modulates hospitalization risk in an international cirrhosis cohort

In a separate study in an international cirrhosis cohort, diversity of gut microbiota was related to hospitalization risk.[43] The study, which compared dietary habits and clinical outcomes in age-matched healthy controls and outpatients with compensated and decompensated cirrhosis, revealed some interesting differences between the USA and Turkey. Individuals from Turkey, including those with cirrhosis, had a significantly higher microbial diversity than their counterparts in the USA. In the US cohort microbial diversity was further reduced in patients with more severe disease. Notably

41. Di Pascoli M, et al. Abstract PS-076
42. Sole C, et al. Abstract PS-015
43. Bajaj JS, et al. Abstract PS-016

there was a greater proportion of commensal bacteria in Turkish patients with decompensated cirrhosis and a greater proportion of potentially pathogenic bacteria, such as *Enterococcaceae*, in American patients with decompensated cirrhosis. These differences seemed to be associated with diet, with a Mediterranean-style diet rich in in vegetables and fermented milk products, along with coffee, tea and chocolate, being associated with greater gut microbial diversity and a lower risk of hospitalization. The potential for manipulation of the gut microbiome was an emerging theme at ILC 2018 but was not restricted to patients with cirrhosis.

ILC theme: the emerging role of the microbiome. The studies reported here were among several hinting at the potential for manipulating the gut microbiome. Investigators in the USA identified a gut microbiome-derived metabolite as a potential biomarker for severity of NAFLD,[44] researchers in Europe detected a distinct faecal microbiome signature in patients with PSC[45] and autoimmune hepatitis,[46] and investigators in China presented data suggesting that changes in the gut microbiota could be an underlying mechanism in thrombus formation in PVT.[47]

METABOLISM, ALCOHOL AND TOXICITY

Explosion of research into therapeutic interventions for NASH

There is no doubt that over the coming years the contribution of non-alcoholic fatty liver disease (NAFLD) to the burden of chronic liver diseases will increase and accordingly, NAFLD was a hot topic at ILC 2018, with many studies presented on potential future therapies for non-alcoholic steatohepatitis (NASH). This is extremely exciting as NASH is a disease with high unmet need without any approved pharmacological interventions.

Professor Vlad Ratziu

According to the first of these, the Phase 2b CENTAUR study, the anti-fibrotic effects of cenicriviroc (CVC) previously reported in patients with a well-defined histological diagnosis of NASH were sustained at 2 years.[48] Anti-fibrotic effects (improvement by ≥1 stage) were evident in 26% of patients receiving CVC for 2 years compared with 20% receiving placebo (p=0.03) and were most pronounced in those with more advanced disease at diagnosis. In a novel study design, 289 patients were randomized 2:1:1 to CVC 150 mg:placebo:placebo, with patients in one of the placebo arms switching to the same dose of CVC after 1 year. This was the first global study with centrally analyzed biopsies at 3 time points: Baseline, Year 1 and Year 2. Of the original cohort,

Sustained anti-fibrotic effect reported with cenicriviroc in NASH

44. Caussy C, et al. Abstract PS-050
45. Liwinski T, et al. Abstract FRI-200
46. Liwinski T, et al. Abstract FRI-201
47. Huang X, et al. Abstract FRI-232
48. Ratziu V, et al. Abstract GS-002

242 continued after Year 1, with paired biopsies at Baseline and Year 2 available for 213. Among non-responders to placebo who switched to CVC, fibrosis improvement without worsening of NASH was seen in 24% compared with 17% of those remaining on placebo (p=0.36). Over 2 years a greater proportion of patients on CVC achieved ≥2-stage fibrosis improvement and no worsening of NASH. However, a fluctuating course of fibrosis was observed in patients in the placebo group.

In a second study, MGL-3196, a selective thyroid hormone receptor-beta agonist significantly decreased hepatic fat in 125 NASH patients at 12 weeks compared with placebo.[49] In patients with biopsy-proven NASH, 75% of those receiving a prespecified high dose achieved at least a 30% decrease in hepatic fat as well as significant reductions in multiple atherogenic lipids, in particular LDL-C levels, plus decreases in AST and ALT and a significant decrease in blood pressure. In a key sub-study in patients with paired biopsies at Baseline and 12 weeks, MGL-3196-treated patients showed statistically significant improvements in CT1, a known correlate of inflammation, as well as reductions in ELF and Pro-C3. This was particularly apparent in patients with more advanced fibrosis at Baseline. Dr Harrison commented that histopathological assessment at 36 weeks will allow for correlations with the baseline biopsy and multiple 12-week and 36-week non-invasive imaging and biomarkers.

Potential NASH therapeutics improve liver fat content and metabolic markers

NGM282, a non-tumourigenic FGF19 analogue, is also under investigation in NASH. In a Phase 2 study in 22 patients with biopsy-confirmed NASH, NGM282, administered for 12 weeks demonstrated significant and clinically meaningful reductions in non-invasive markers of liver disease: all patients had a reduction in absolute liver fat content (LFC) of ≥5%; 67% had a mean decrease in relative LFC at 12 weeks and 100% achieved a clinically meaningful decrease of ≥30.[50] These changes in liver fat content were accompanied by substantial anti-fibrotic activity; 42% of patients had improved fibrosis ≥1 stage (3 patients went from being F3 to F1) and 68% of patients had improved histology after 12 weeks of treatment. These findings, although preliminary, generated a great deal of excitement among the audience.

Another early-phase trial in NASH evaluating SGM-1019, a first-in-class novel small molecule modulator of inflammasome activity in NASH, was presented at ILC 2018.[51] The NLRP3 inflammasome drives fibrogenesis in NASH and P2X7 is a NLRP3 inflammasome activator. In preclinical studies, the P2X7 inhibitor SGM-1019 decreased inflammation, fibrosis, and liver injury in models of NASH. In healthy volunteers, SGM-1019 was well tolerated and substantially inhibited P2X7 at all doses up to 1,500 mg twice daily in a 14-day study. Because of differences in the fibrotic process, it is currently unclear as to whether a greater anti-fibrotic effect will be required to show clinical benefit in humans than in animals. However, evaluation of the drug continues and a Phase 2a study of SGM-1019 in NASH is currently being initiated.

49. Harrison S, et al. Abstract GS-009
50. Harrison S, et al. Abstract GS-014
51. Dabbagh K, et al. Abstract PS-111

Negative trials were also given a prominent platform at ILC 2018. In the late-breaking session results were presented from the Phase 2 trial of JKB-121, a weak antagonist of the TLR-4 receptor shown to prevent NASH in preclinical models.[52] In this multicentre, randomized, double-blind, placebo-controlled study in 65 adults with biopsy-proven NASH there was no difference in LFC by MRI-PDFF and/or serum ALT at 24 weeks compared with placebo.

Combination therapy with therapeutics targeting fibrosis, inflammation, and fat metabolism is an attractive approach to managing patients with NAFLD/NASH; it is likely to be necessary to target metabolism, inflammation, fibrosis, apoptosis, and oxidative stress. In a proof-of-concept study, the potential for combination therapy with an anti-inflammatory/anti-apoptotic ASK1 inhibitor (selonsertib), and either an ACC inhibitor targeting lipotoxicity (GS-0976) or an FXR agonist (GS-9674) was assessed in 70 patients with NASH.[53] After 12 weeks, both combinations led to improvements in hepatic *de novo* lipotoxicity and steatosis, liver biochemistry and fibrosis markers. However, similar responses were observed with monotherapy and studies of longer duration with histological assessment are required to better characterize the efficacy of 2- or 3- drug combinations versus monotherapy in NASH and a Phase 2, 48-week study with histological assessment is ongoing.

While it is promising to see so much exciting early clinical phase research in NAFLD, all that is available for patients with NAFLD/NASH now is lifestyle advice, which experience has shown is difficult for patients to maintain long term. In an interesting study conducted in Italy, a web-based educational intervention aimed at instigating lifestyle changes was found to be as good as standard group counselling in helping patients lose weight.[54] Among the 716 patients with NAFLD studied, BMI decreased similarly in patients undertaking the web-based counselling and the standard group counselling, with a target 10% weight loss, an important endpoint that is associated with improvement in NAFLD histology, attained in 8.6% (web group) vs. 10.0% (standard group) and accompanied by reduced calorie intake and increased physical activity. Liver enzymes and surrogate markers of steatosis and fibrosis similarly improved in both groups. The key however, is for patients to be motivated. In such individuals the web-based approach seems to be a useful addition to the educational efforts to help NAFLD control, ensuring that all patients can be accessed.

Welcomed focus on management of liver disease associated with alcohol use

It was encouraging to see increased activity around the management of alcohol-related liver disease at ILC 2018, exemplified by the introduction of the updated clinical practice guidelines from EASL. During a Public Health session it was highlighted that stigma needs to be removed around this chronic liver disease, a disease that is responsible for more mortality and morbidity globally than all other chronic liver diseases combined. In addition, as well as preventing alcohol-related morbidity and mortality through initiatives such as the

Reduced stigma associated with liver disease related to alcohol is required

52. Diehl AM, et al. Abstract LBO-006
53. Lawitz E, et al. Abstract PS-105
54. Mazzotti A, et al. Abstract PS-112

minimum unit pricing scheme, it is critical to effectively manage existing patients with alcohol-related disease.

Urgent action is required to reduce alcohol consumption and EASL has the opportunity to drive policy by being the authoritative medical voice in the public debate around alcohol use

One interesting study evaluated the quantitative assessment of fibrosis using collagen proportionate area (CPA).[55] This measure has already been shown to predict clinical outcomes in patients with chronic hepatitis C and NAFLD, and has also been shown to subclassify cirrhosis. This study found the measure to be a useful predictor of outcomes in patients with alcoholic hepatitis as well. In a retrospective analysis of 141 patients with biopsy-proven AH, CPA correlated significantly with fibrosis stage across the whole spectrum of fibrosis and along with abstinence and ABIC score, was an independent predictor of 30-day mortality (OR 0.496, p = 0.05).

End-stage alcoholic cirrhosis is preceded by years of subclinical progressive fibrogenesis driven by hepatic inflammation.[56] Biomarkers that can be used to monitor acute alcoholic hepatic inflammatory activity are a significant unmet need. Researchers from Denmark presented their work on the value of M30, a cytokeratin-18 based novel biomarker, in the detection of subclinical liver inflammation. In their prospective study they assessed biopsies from outpatients with an ongoing or prior excessive alcohol intake for M30, ActiTest, and AST/ALT levels. They found that M30, ActiTest, and whether patients were actively drinking at inclusion independently predicted increasing grade of hepatic inflammation, while AST:ALT ratio did not. M30 diagnosed presence of severe hepatic inflammation (score 4–5) with excellent accuracy (M30 AUROC 0.90, 0.85–0.94), was significantly better than ActiTest or AST:ALT ratio (AUROC 0.77 and 0.74; P < 0.001), and is a promising biomarker for grading subclinical, alcoholic hepatic inflammation and in detecting severe hepatic inflammation.

There are few treatment options for patients with alcohol-related chronic liver disease, despite the fact that alcohol misuse is responsible for hundreds of thousands of deaths per year across Europe.[57] In France in March 2014, a temporary recommendation was made to use the GABA-B agonist baclofen (up to a maximum of 300 mg/day) to reduce alcohol consumption or to maintain abstinence after alcohol withdrawal. In a very important study by the National Observatory of patients treated with baclofen for alcohol dependence in hepato-gastroenterology units, the value of baclofen treatment for these reasons was evaluated in over 200 patients. Researchers found that at 1 year, use of baclofen, combined with medical and psychosocial monitoring, helped two-thirds of patients with and without cirrhosis reduce or stop their alcohol consumption.

Hepatologists should use drugs like baclofen to promote abstinence and should work closely with alcohol and addiction clinics

55. Misas MG, et al. Abstract PS-070
56. Thorhauge KH, et al. Abstract PS-071
57. Barrault C, et al. Abstract PS-072

Critically, liver function among 77 patients with cirrhosis improved. Interestingly, the incidence of adverse events seemed to decrease with longer use. These observations are highly relevant as many clinicians are reluctant to use these types of treatments in patients with cirrhosis on safety grounds. However, there is now concern that modification of the upper limit of baclofen to 80 mg/day will make it very difficult for patients to reach a level of indifference towards alcohol.

GENERAL HEPATOLOGY

A wide variety of topics were covered in the General Hepatology track. In particular liver transplantation (LT), and associated issues, was a focus that was echoed in a new category this year at ILC, Liver Transplant and Surgery. The changing indications for LT were discussed, with transplants as a result of chronic hepatitis C becoming less frequent, while alcohol-related disease and fatty liver disease as indications for transplant are becoming increasingly common.

In line with this, the first large dataset on the European study on LT associated with NASH was presented at ILC 2018.[58] Outcomes after LT for NASH are seldom reported. This retrospective cohort study used data from the European Liver Transplant Registry database to evaluate clinical outcomes for adult patients undergoing LT for NASH versus other indications (2002–2016). The proportion of LTs carried out for patients with NASH is increasing year on year. Patients with NASH undergoing LT were more likely to be older (median age 60 vs. 55, $p<0.001$), have a greater BMI (32.6 ± 4.6 kg/m^2 vs. 25.8 ± 4.4 kg/m^2, $p<0.001$), and have concomitant HCC (39.1% vs. 28.9%, $p<0.001$). Patient and graft survival were comparable in those with NASH versus other common indications and after adjusting for recipient (age, sex, BMI, blood group, presence of HCC) and donor (age, BMI, blood group, type of donor) factors, NASH was not an independent predictor of outcome (HR 1.07, $p=0.18$). Within the NASH cohort, age, BMI, MELD, donor blood group, and organ type were predictors of post-transplant survival.

A retrospective study of consecutive patients undergoing LT at a single French centre (2011–2016) developed a model to simultaneously analyze longitudinal exposure to tacrolimus and the risk of developing CKD within the first year after LT.[59] CKD was defined as a calculated glomerular filtration rate (eGFR) <60 mL/minute/1.73m^2 (MDRD-4 formula), during three consecutive months. Overall, 46 (25.5%) of patients developed CKD within 1-year post-LT. Seven risk factors were pre-selected using random survival analysis to predict the risk of CKD. Longitudinal tacrolimus exposure was not a significant predictor of post-LT CKD, whereas eGFR Month 1 and acute kidney injury were associated with CKD. These two factors remained significant after adjustment for longitudinal exposure to tacrolimus. This is the first study to use a time-to-event model to investigate the individual factors, including tacrolimus longitudinal exposure, associated with the development of CKD with the first year of LT. Larger studies are required to validate these findings.

58. Haldar D, et al. Abstract PS-041
59. Maurel P, et al. Abstract PS-044

An interesting study discussed the risk of donor specific antibodies (DSA) after LT.[60] There is an ongoing controversy about the importance of DSA, their prevalence and consequences for graft, and patient survival after LT. An analysis of clinical and demographic data of 430 LT recipients was used to determine the association of DSA with complications following LT and the relevance of antibody subspecies. Compared with DSA-negative patients, those who developed DSA (18.8% [81/430]) experienced a significantly higher rate of cirrhosis after LT (18.5 versus 8.8%, p≤0.027), and numerically higher rate of overall complications (75.3% versus 72.8%, p=0.67), *de novo* autoimmune hepatitis (10.0% vs. 4.3%, p=0.055) and acute rejections (24.7% versus 16.6%, p=0.076). Detectable DSA are primarily HLA class II. There was no significant difference in the frequency of complications stratified by HLA class and mean fluorescence intensity DSA (i.e. level of antibodies) was not predictive of complications after LT.

Towards improving availability of organs for liver transplantation

An interesting theme apparent in several presentations at ILC 2018 was the different approaches to increasing donor availability for liver transplant and promoting graft survival. As well as expansion of current criteria and consideration of use of livers from patients with active HCV infection in the era of curative therapy, some novel approaches were introduced.

In a proof-of-concept study, transplanting mouse-rat chimeric livers into baby rats demonstrated potential for growing transplantable patient-like organs in animals.[61] Mouse-rat chimeric livers were created by transplanting Lewis rat hepatocytes into FRG® mice. The chimeric organs were then transplanted into 3-week old Lewis rats. Under calcineurin inhibitor monotherapy all chimeric liver recipients survived in good health with normal development and weight gain. Four months after transplant the chimeric livers were partially repopulated by rat cholangiocytes and portal endothelial cells. Generation of transplantable patient-like organs in animals could ultimately solve the problem of organ shortage and extend the indications for liver transplantation. This is the first report of robust survival of orthotopically transplanted chimeric livers and is particularly encouraging, since the transplanted organs were able to grow and develop normally in the host animals.

First report of robust survival of orthotopically transplanted chimeric livers at ILC 2018

Describing a technology that could ultimately be used in the field of liver transplantation, Dr Luca Frenguelli from UCL, London, described a key advance in the development of personalized 3-dimensional (3D) technologies for the study of regenerative medicine and models of liver disease.[62] A common limitation of hepatic lineages derived from iPSCs is a blunted phenotype compared with primary hepatocytes. However, decellularized scaffolds composed by natural liver extracellular matrix (ECM) may help maintain the phenotype of primary cells and promote cell survival, proliferation and differentiation of stem cells. Dr Frenguelli's group demonstrated

60. Willuweit K, et al. Abstract PS-045
61. Lacotte S, et al. Abstract PS-125
62. Frenguelli L, et al. Abstract PS-104

that hepatocyte-like cells derived from iPSC technology can differentiate and mature using human liver 3D ECM and, critically, that efficiency of this differentiation is improved when culturing cells from an earlier stage of development, e.g. hepatoblasts – the first time that this has been demonstrated at such an early stage.

ILC theme: the potential of pluripotent stem cells. The study from Dr Frenguelli and colleagues was one of several reports of *in vitro* disease models on the potential for using patient-specific induced pluripotent stem cells (iPSCs) in modelling or regenerative medicine in liver disease. In one such study, effectiveness and the mechanism of action, of transplantation of human pluripotent stem cells as a treatment for advanced cirrhosis and portal hypertension were demonstrated, observations that open up the possibility of evaluating the possible beneficial effects of human stem cells in patients with chronic liver disease.[63] In a further study, modelling NAFLD using human induced pluripotent stem cells was able to mimic the mechanisms of hepatocyte steatosis and lipotoxicity associated with NAFLD progression, including the inflammatory and fibrotic response, and may be an important step towards model NAFLD *in vitro*.[64]

63. Fernández-Iglesias A, et al. Abstract PS-009
64. Morell CM, et al. Abstract PS-052

NEW AT ILC 2018

NEW AT ILC 2018

Several new sessions were introduced at ILC this year, with highlights including interactive research think tanks and meet the expert sessions, as well as the public health category, in recognition of the growing number of public health abstract submissions and the importance of the topic.

PUBLIC HEALTH

A very welcome addition was the public health category, which addressed pressing issues from a more societal perspective. Sessions covered a range of topics in viral hepatitis and NAFLD/NASH. Health state transition models predicted lower morbidity and mortality with early treatment of HCV with DAAs and lower lifetime costs; that ultrasound surveillance for HCC was shown to be cost effective in HCV-related cirrhosis after SVR, but was unlikely to be so in F3. Molecular phylogenetic analyses were able to link cases of an HAV outbreak among MSM in Italy to three European outbreaks, suggesting that efforts to increase HAV vaccine coverage in high-risk groups are required.

The HEPAHEALTH project report, released at ILC 2018

In a thought-provoking presentation, very low food security was shown to almost triple the risk of developing advanced liver fibrosis in people with both diabetes and NAFLD, highlighting that as well as the established risk factors for advanced fibrosis, socioeconomic factors must be considered.

In other Public Health sessions delegates were urged to become activists and the authoritative voice in the debate around alcohol use to help to reduce one of the more frequent and preventable liver diseases. The need for such action was evidenced by the HEPAHEALTH report released during ILC 2018, which provided an up-to-date status report of the burden of liver disease across Europe.

Professor Francesco Negro and Dr Laura Pimpin reporting the key findings from the HEPAHEALTH report, released at ILC 2018

RESEARCH THINK TANKS

The research think tanks were a new initiative at ILC 2018 and will be key sessions in future meetings. These sessions provided a forum for academic debate between different organizations with shared objectives, supporting EASL's commitment to identifying new research pathways to improve the lives of all patients living with liver disease. The programmes for each of the think tanks were developed by research interest groups or consortia, and were coordinated by EASL. The research think tanks covered a broad range of topics, for example, two on viral hepatitis considered the barriers preventing elimination of HCV and the need for a vaccine in an era where infection can be cured in most patients. Messages that came across loud and clear were the need to focus on improved multidisciplinary cooperation, screening programmes, and education to effectively reach and treat key populations. Other hot topics were effective integration of services and task shifting to allow more people to access care.

Research Think Tank – NAFLD: targets and pharmacotherapy in NASH

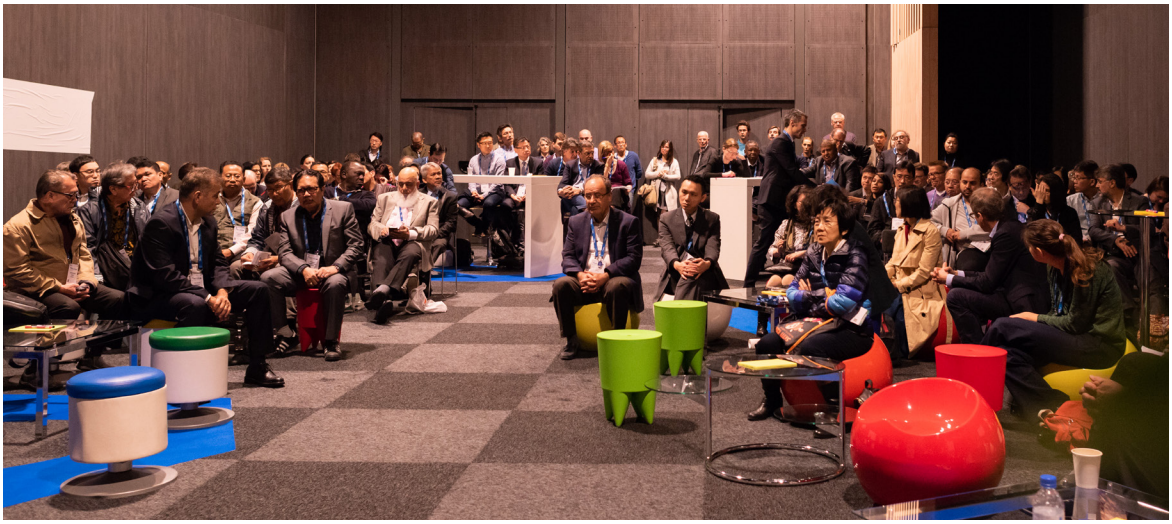
Similarly, in the NAFLD research think tank, collaboration between hepatologists and diabetologists was identified as a key need. In this session and in the chronic liver failure research think tank, participants also discussed the need for new biomarkers for differential diagnoses, prognosis, and individual tailoring of new treatments. In the portal hypertension think tank new concepts related to the link between the coagulation cascade and chronic liver disease were underlined. Other points of discussion were how to optimize the design of clinical trials for the prevention and treatment of portal vein thrombosis, and which drugs could be suitable for trials over the next few years.

MEET THE EXPERTS

Professors Michael Manns and Olivier Chazouillères in the meet the expert session: management of autoimmune hepatitis

Delegates had the opportunity to meet face-to-face with top experts in their fields of interest at several meet the expert sessions throughout the week. The sessions covered HCV infection in patients with HCC, difficult cases in HCV, cirrhosis after HCV cure, whether patients with chronic hepatitis B infection should be treated, when nucleoside analogue therapy can be stopped in HBV, management of HDV, management of HEV, prevention of decompensation in cirrhosis, antibiotic stewardship in cirrhosis,

hepatorenal syndrome, achieving alcohol abstinence, portal vein thrombosis, alpha-1-antitripsin deficiency, autoimmune hepatitis, Wilson disease, and non-invasive tests in liver diseases. Experts were kept busy with challenging questions that they could answer in more depth than in a standard scientific session. The more informal setting was conducive to relaxed, interactive discussion of the most pressing issues in hepatology today.



The new meet the expert sessions proved very popular with delegates at ILC 2018

ALSO AT ILC 2018

ALSO AT ILC 2018

Other stimulating sessions at ILC 2018 included state-of the-art lectures, the clinical postgraduate course on viral hepatitis, basic science seminars on targetable pathways in liver disease, skills in hepatology, and industry-sponsored symposia.

STATE-OF-THE-ART LECTURES

The basic science state-of-the-art lecture, delivered by Richard Blumberg, highlighted how the neonatal Fc receptor has emerged as an important clinical target in adult life that is currently under evaluation in several clinical scenarios. He introduced the functions of this receptor in regulating IgG and albumin, its two main ligands, and the clinical opportunities that are emerging from this understanding.

In the clinical state-of-the art presentation, Professor Jaime Bosch proposed that due to the array of causes, inaccurate diagnosis, and often negative connotations, the term 'cirrhosis' be substituted to "advanced chronic liver disease". This was suggested at the 2015 Baveno VI consensus conference on portal hypertension and serves to better distinguish the substages of the disease and hence, the goals of treatment.

POSTGRADUATE COURSE

The topic for this year's postgraduate course was viral hepatitis, which was structured in the form of six clinical case discussions: two in HBV, two in HCV and one each in HDV and HEV. The aim of the course was to promote discussion around the clinical management of complex cases, as well as the WHO target to eliminate viral hepatitis by 2030.

The postgraduate course on viral hepatitis focused on six clinical cases

BASIC SCIENCE SEMINARS

The basic science seminar on targetable pathways in liver disease served as a timely reminder of the lab-based research that underpins the clinical advances reported at ILC each year. Each seminar was organized as a workshop with a presentation from a senior scientist and a young investigator, followed by lively discussion. Topics this year were identifying targetable pathways in liver disease, new targets in metabolism, inflammation and fibrosis, and liver tumours, and progression from targetable pathways to the clinics.

SKILLS IN HEPATOLOGY

The new skills in hepatology category included two symposia and several practical, hands-on sessions. The symposia were dedicated to ultrasound, held in collaboration with the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB), and to invasive methods and procedures in hepatology. The hands-on sessions complemented the symposia content, with an additional session on emerging therapies.

Hands-on training in the new skills in hepatology sessions

INDUSTRY SYMPOSIA

During ILC 2018 there were 12 satellite symposia covering the management of HCV, HBV, HCC, NASH, hepatic encephalitis, and PBC.

HCV

From treatment simplification to HCV elimination: Effective multi-stakeholder care

This symposium organized by AbbVie explored simplified regimens targeting the evolving HCV treatment landscape, with a focus on advances in treatment attributes, overcoming the barriers to HCV care, and the strategies and key stakeholders that can contribute to HCV elimination.

Shaping tomorrow together – from aspiration to achievement in HCV care

During this symposium organized by Gilead, an eminent panel of hepatologists and virologists encouraged delegates to engage across disciplines and the wider community to move towards HCV elimination by establishing short-term, achievable targets and goals.

HCV unsymposium: your meeting, your agenda!

In this session organized by AbbVie, the expert panel discussed the audience's top five topics selected from a range of trending themes, such as the HCV care cascade, HCV elimination, and management of high-risk populations.

A future without hepatitis C: what will it take?

In this symposium organized by MSD, the panel explored the feasibility of reaching the WHO's target for HCV elimination by 2030 and considered the action needed to effect global change: programmes that improve awareness and prevention, and that help to remove current barriers to diagnosis and treatment.

HBV

Shaping tomorrow together: advances driven by commitment in HBV care

In this symposium organized by Gilead, the expert panel explored future possibilities and priorities for the management of hepatitis B, how our current experience can best be used to shape that future, and whether the prospect of moving from virological control to the elimination of HBV infection is a realistic proposition.

HCC

Treatment sequencing and maximizing survival – uHCC in 2018

This symposium organized by Bayer highlighted the importance of effective treatment sequencing in unresectable hepatocellular carcinoma (uHCC) and provided practical guidance for the management of patients on systemic treatment, while exploring how the sorafenib–regorafenib sequence has impacted the uHCC treatment paradigm.

Emerging horizons in HCC: from palliation to cure

This symposium organized by Celsion challenged the audience to reconsider current treatment paradigms in HCC, particularly for patients once only considered for palliative treatment who can now be targeted for cure. New developments in treating intermediate-size HCC were discussed, including the role of tyrosine kinase inhibitors and immuno-oncology.

NASH

Advanced NASH and HCC – the new frontiers

During this symposium organized by Bristol-Myers Squibb, the pathophysiology and potential complications of advanced NASH and HCC were discussed with delegates, providing insights into treatment innovations including immunotherapy, targeted therapies, and combination therapies.

Game changers in NASH management

The GENFIT symposium provided a comprehensive overview of current challenges in NASH medical and educational fields, especially regarding awareness, diagnosis, and treatment.

Shaping tomorrow together – addressing the challenges in the management of advanced fibrosis due to non-alcoholic steatohepatitis (NASH)

In this symposium organized by Gilead, an expert panel examined the evolving burden of NASH-related liver disease and the challenges faced by today's clinicians, and discussed current and future research into improving diagnostics and treatment options to manage this growing patient population.

Hepatic Encephalitis

Driving change to optimize the HE patient journey

In this symposium organized by Norgine, the panel discussed the challenges of effective long-term management of hepatic encephalitis (HE) and the requirement for coordinated multi-disciplinary care, emphasizing the positive impact that proactive and practical solutions can have in preventing deterioration and recurrence of HE episodes.

Primary biliary cholangitis

Primary biliary cholangitis: old disease, new perspectives

This symposium organized by Intercept was an exploration of best practice in PBC care, focusing on the second-line therapy obeticholic acid for patients with inadequate response to standard-of-care therapy. Delegates gained insight from a patient group representative, and heard about new long-term study results and real-world data.

EASL, THE HOME OF HEPATOLOGY

Multidisciplinary collaboration and integration of care were buzzwords at this year at ILC. In line with this, EASL is committed to mutually beneficial collaborations with international societies that can help in its mission to beat liver disease. Delegates had the opportunity to hear about what is happening in these collaborations and the specific efforts that are being made together. The collaborative symposia were an exciting evolution of the 'Home of Hepatology' concept. Over the course of ILC

The speaker panel for the joint EASL–WHO symposium on meeting the 2030 goals for viral hepatitis elimination

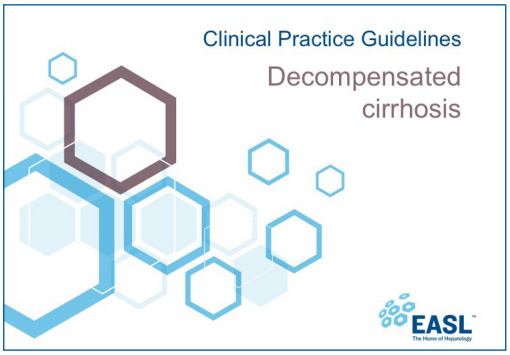
2018, the EASL–CDC symposium discussed the decentralization and integration of HCV diagnostics, care, and treatment services in low- and middle-income countries, the EASL–EASD symposium discussed testing strategies and pathways in NAFLD, the EASL–APASL symposium discussed ACLF and critical care in hepatology, the EASL–WHO symposium discussed barriers to meeting the 2030 elimination goals of the WHO viral hepatitis strategy, urging everyone to 'find the missing millions', the EASL–ALEH symposium debated diagnostic dilemmas in metabolic liver disease, and the EASL–ESMO symposium stressed the need for collaboration between medical oncologists and hepatologists to boost therapeutic advances in liver cancer.

EASL RECOGNIZES THE ROLE OF NURSES AND ASSOCIATES

At ILC 2018 there was a new focus on the role of nurses and associates in the management of liver diseases. For the first time there was a specific research poster area for nurse-led research and two Nurses and Associates Forums. Together these highlighted the integral role that nurses play in delivering quality care in chronic liver disease; from education of those individuals at risk of liver disease, through continuity of care throughout the course of their illness, to end-of-life support. The sessions highlighted the need for cross-disciplinary collaboration to deliver the highest quality care for patients to improve outcomes. It was clear that nurses welcomed the opportunity to get involved and to give their perspective.

The integral role of nurses and associates in hepatology care was highlighted in two forums and a number of nurse-led research posters

MAJOR EASL CLINICAL PRACTICE GUIDELINE RELEASES



Updated EASL clinical practice guidelines on the management of patients with decompensated cirrhosis were released during ILC 2018

Seven EASL clinical practice guidelines and recommendations (CPG) were presented during ILC: 'Management of hepatocellular carcinoma', 'Management of patients with decompensated cirrhosis', 'Nutrition in chronic liver disease', 'HEV infection', 'Management of drug-induced liver injury', 'Management of alcohol-related liver disease' and 'Treatment of hepatitis C'. For the first time in EASL history, accompanying slide decks were produced that the liver community are able to use freely in their own presentations. These can be downloaded here: www.ilc-congress.eu/slide-decks.

ILC 2018: AWARDS AND STATS

ILC 2018 IN NUMBERS

9,669 delegates attended, from **121** countries

2,760 abstracts submitted, abstracts accepted **1,750**

23 prizes awarded

7 CPGs released

Programme sponsors **17**

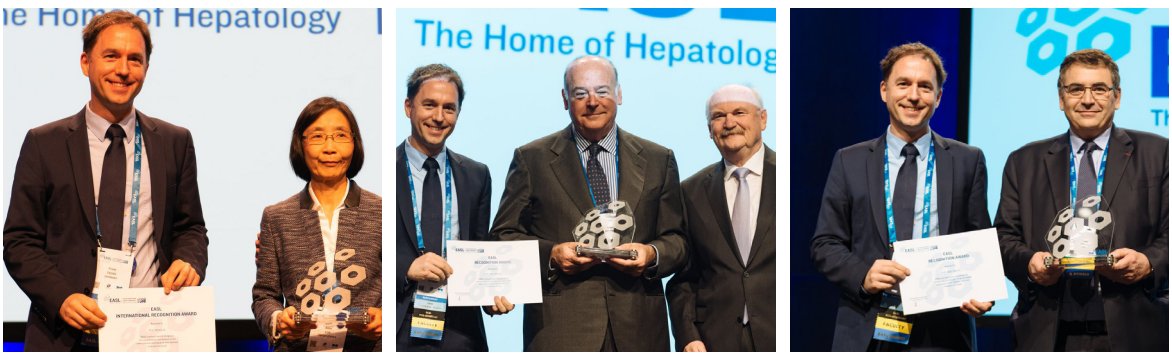
82 exhibitors

13 Biotech Village sponsors

18 skills learning centre sponsors

EASL RECOGNITION AWARDS 2018

During ILC 2018 EASL recognized the men and women who are writing the history of EASL with outstanding contributions to liver disease care and research in Europe.



Professors Anna Lok, Mario Mondelli and Didier Samuel being awarded EASL Recognition Awards for their contributions to liver disease care and research

AFTER ILC 2018

AFTER ILC 2018

ILC 2018 was an exciting meeting covering many topics in both basic and clinical science in hepatology. The congress didn't end with the closing ceremony, delegates can stay in touch through the EASL social channels: Twitter, Facebook, LinkedIn and can continue to explore educational materials via the EASL websites for Best of ILC 2018 slide decks and debrief videos, access to the latest EASL clinical practice guidelines and their summary slide decks, and for webcast presentations from the meeting.

EASL
The Home of Hepatology

THE INTERNATIONAL LIVER CONGRESS™ 2019

APRIL 10 - 14, VIENNA, AUSTRIA

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