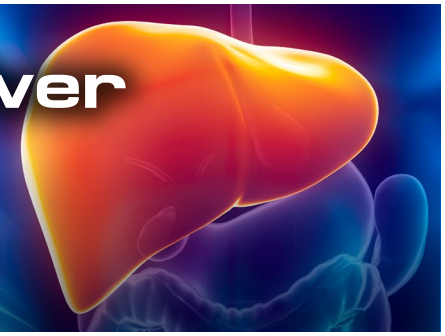
EASL International Liver Congress™ 2015 Conference Review™



Making Education Easy 22-26 April 2015, Vienna, Austria

In this issue:

Abbreviations used in this review:

aHR = adjusted hazard ratio; **AIDS** = acquired immune deficiency syndrome; **AUD** = alcohol use disorders; **CVD** = cardiovascular disease; **GWAS** = genome-wide association study; **HBV** = hepatitis B virus; **HCV** = hepatitis C virus; **HIV** = human immunodeficiency virus; **HR** = hazard ratio; **HVPG** = hepatic venous pressure gradient; **LDL** = low-density lipoprotein; **MELD** = Model for End-Stage Liver Disease; **NAFLD** = non-alcoholic fatty liver disease; **NASH** = non-alcoholic steatohepatitis; **NSBB** = non-selective beta-blockers; **OCA** = obeticholic acid; **OR** = odds ratio; **SVR** = sustained virological response

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Welcome to the 50th International Liver Congress (ILC) of the European Association for the Study of the Liver (EASL), held in April this year in Vienna, Austria.

This meeting brought together specialists from the fields of hepatology, gastroenterology, internal medicine, cell biology, transplant surgery, infectious diseases, microbiology, virology, pharmacology, pathology, radiology and imaging from around the world, to report on and learn about the latest information on liver research.

Associate Professor Golo Ahlenstiel, a Gastroenterologist and Hepatologist at Westmead Hospital, Sydney, attended the congress and has selected presentations relevant to local practice for this review. The EASL recommendations on the treatment of hepatitis C 2015 (published and introduced at the meeting) are also discussed.

We hope you enjoy these selections and look forward to your comments and feedback.

Kind Regards,

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Conference abstracts are available from: https://ilc-congress.eu/abstract_25_04/ILC2015-abstract-book-25-04-Saturday.pdf

EASL recommendations on treatment of hepatitis C 2015

With the publication of new guidelines for HCV treatment, emphasis was placed on interferon-free direct-acting antiviral (DAA) regimens for all HCV genotypes. The guidelines recommend all patients with chronic HCV infection without contraindications to treatment should be offered therapy whether treatment-naïve or treatment-experienced and irrespective of the status of their liver disease, i.e., including decompensated HCV related cirrhosis. The new, very effective therapies, however, are expensive and thus based on availability, prioritisation may be required. EASL recommendations suggest to triage patients based on liver fibrosis stage, risk of progression, extra-hepatic manifestations and likelihood of HCV transmission or HIV or HBV co-infection. Therefore, in the absence of symptoms such as chronic fatigue, patients could defer therapy if they have no significant fibrosis (<F2). Importantly, the new guidelines place interferon-free drug combinations, currently six different regimens, first, with interferon-based combinations only acceptable if interferon-free therapies are not available. This is new and will certainly change the field, and the effects of the guidelines are already altering the way companies are marketing interferon. In contrast, ribavirin will still remain an important part of the treatment combinations, particularly for patients with cirrhosis on the liver transplant waiting list.

HCV guidelines

Liraglutide is effective in the histological clearance of non-alcoholic steatohepatitis in a multicentre, double-blinded, randomised, placebo-controlled phase II trial

Authors: Armstrong MJ et al.

Summary: This multicentre, double-blinded, randomised, placebo-controlled phase II trial histologically assessed the efficacy of the long-acting GLP-1 analogue, liraglutide 1.8 mg/day, in 52 patients (mean age 51 years, 60% male, 33% type II diabetes) with non-alcoholic steatohepatitis (NASH; 52% F3/F4 Kleiner fibrosis stage). In total, 45 patients received end-of-treatment liver biopsies; of 23 patients receiving liraglutide, 9 (39%) had resolution of definite NASH versus 2 (9%) of 22 patients receiving placebo ($p = 0.019$). Two (9%) liraglutide recipients had worsening of fibrosis versus 8 (36%) placebo recipients ($p = 0.026$). Liraglutide also reduced weight (-5.3 vs -0.6 kg, $p = 0.001$), BMI (-1.8 vs -0.3 kg/m^2, $p = 0.003$), and fasting glucose (-1.0 vs -0.7 mmol/L, $p = 0.005$) versus placebo. No serious adverse events occurred in liraglutide recipients; 2 (8%) of 26 patients withdrew from treatment because of drug-related gastrointestinal (nausea, diarrhoea) adverse events.

Comment: NASH has seen a rapid increase in incidence over the last few decades and is now one of the commonest causes for chronic liver disease. To date, treatment options are limited, particularly with respect to pharmacological intervention. The Liraglutide Efficacy and Action in NASH (LEAN) trial studied the effect of the glucagon-like peptide-1 (GLP-1) analogue, liraglutide, currently licensed in diabetes mellitus type II and obesity therapy, in patients with biopsy-proven NASH who were overweight. In this small trial (52 patients randomised), NASH resolution occurred in 39% of patients receiving liraglutide versus 9% in the placebo group. While the results are very encouraging with respect to pharmacological therapy of NASH in patients with diabetes and/or obesity, it remains unclear if and to what extent these results apply to non-diabetic, non-obese patients with NASH and how much liraglutide induced weight loss may have contributed to these results.

Abstract # G01

Statin use significantly decreases decompensation and death in veterans with hepatitis C-related compensated cirrhosis

Authors: Mohanty A et al.

Summary: In an analysis of data from the Veteran Affairs clinical case registry (n = 342,157) the effect of statin use on decompensation and mortality was examined in a cohort of HCV mono-infected patients with compensated cirrhosis; 685 statin users were propensity score matched, using demographics, year of index visit, site of statin prescription, site prescribing pattern, number and type of lipid tests, laboratory data including liver tests, and comorbid conditions, with 2062 non-users. The discrimination of the propensity score model was 0.92. A lower risk of decompensation was associated with statin use (HR 0.55; 95% CI 0.39-0.77) or death (HR 0.56; 95% CI 0.46-0.69). The association was retained after adjustment for age and Child score (decompensation HR 0.53; 95% CI 0.37-0.74; death HR 0.54; 95% CI 0.44-0.66) or age and MELD score (decompensation HR 0.53; 95% CI 0.38-0.75; death HR 0.54; 95% CI 0.44-0.66).

Comment: While statins are often avoided in patients with chronic liver disease due to their risk of hepatotoxicity, recent data suggest they may actually be beneficial in patients with cirrhosis by reducing portal pressure resulting in better survival of patients with a history of variceal bleeding. This retrospective analysis of the Veteran Affairs clinical case registry compared patients with HCV related liver cirrhosis with and without statin therapy over a time frame of 14 years. Statin use was associated with lower risk of decompensation (HR 0.55) or death (HR 0.56) compared to non-users, suggesting that statin use in HCV cirrhosis may lower the risk of hepatic decompensation and death by more than 40%. While this study is retrospective and will have to be confirmed in a prospective, randomised trial including its safety profile, it may suggest patients who should be on statins for other reasons should not necessarily avoid them just because they have cirrhosis. Given that statins are generally inexpensive, they would be an attractive adjunct to current therapies if their efficacy and safety were proven by a randomised trial.

Abstract # 0072

The burden of cardiovascular disease and mortality across a spectrum of non-alcoholic fatty liver disease: a 14-year follow-up population study of 929,465 individuals

Authors: Mann JP et al.

Summary: This retrospective analysis of data from 929,465 patients in a UK hospital activity-analysis register examined the overall burden of cardiovascular disease (CVD) and all-cause mortality risk associated with non-alcoholic fatty liver disease (NAFLD). Over 14-years, 2701 patients were diagnosed with NAFLD-spectrum conditions including 1294 with NAFLD, 122 with non-alcoholic steatohepatitis (NASH), and 1285 with cirrhosis. Male patients predominated (56–58%) and 78–80% were Caucasian. All-cause mortality was higher in patients with NASH than with NAFLD (22.1% vs 14.5%; $p = 0.025$), and was higher in patients with cirrhosis than with NAFLD (53.1% vs 14.5%; $p < 0.001$). Congestive cardiac failure had a lower prevalence in patients with NAFLD than in those with NASH ($p = 0.001$) and cirrhosis ($p < 0.001$). Type II diabetes, atrial fibrillation, hyperlipidaemia, and chronic kidney disease all had higher prevalence in the advanced stages of NAFLD.

Comment: There is a known association between NAFLD and an increased risk for CVD, particularly in NASH. The research team used electronic medical records from patient hospital encounters between 2000 and 2013 and identified 1294 patients with fatty liver disease, 122 with non-alcoholic steatohepatitis, and 1285 with NASH related cirrhosis. A caveat is that for the purpose of their analysis, NAFLD cirrhosis was identified by the code for cryptogenic cirrhosis and may thus have included non-NASH cases. All-cause mortality was significantly lower with fatty liver (14.5%) alone as compared to steatohepatitis (22.1%) and cirrhosis (53.1%). Importantly, congestive cardiac failure was significantly lower in patients with fatty liver disease (3.8%) than in patients with steatohepatitis (9.0%) or cirrhosis (6.6%). Similar effects were noted for type II diabetes, hyperlipidaemia, atrial fibrillation and chronic kidney disease. After adjustment for a variety of confounders, mortality remained 5-fold higher in patients with cirrhosis. Overall, it means that risk for cardiovascular complications and mortality are high in patients with NASH, particularly in NASH-related cirrhosis, and need to be carefully screened for and managed.

Abstract # G12

The confounding role of severe comorbidities and alcohol use disorders on prognosis in chronic hepatitis C virus infection: an analysis of the 2008–2012 French national hospital discharge database

Authors: Schwarzinge M et al.

Summary: Data from 28,953,755 hospitalised French patients were used to compare the prognostic value of chronic HCV infection and alcohol use disorders (AUD) in the general population. Chronic HCV infection was found in 0.39% of the hospitalised patients (n = 112,146), and AUD in 2.44% (n = 705,259); chronic HCV infection and AUD occurred in 0.08% of patients (n = 23,351). The aHR for in-hospital death was 1.90 (95% CI 1.86-1.94) for chronic HCV infection and 3.13 (95% CI 3.10-3.15) for AUD; a negative interaction was observed between chronic HCV infection and AUD (aHR 0.93; 95% CI 0.90-0.97). Withdrawal or abstinence from alcohol was associated with a lower mortality risk (HR 0.66; 95% CI 0.65-0.67). Chronic HCV infection was associated with higher mortality risks only in presence of severe comorbidities (HIV/AIDS; liver, kidney or other solid organ transplant, non-Hodgkins lymphoma; cancer; cryoglobulinemia, chronic kidney disease; end stage liver disease or other severe comorbidity [Charlson Index]). AUD was associated with higher mortality risks in all prognostic subgroups.

Comment: To investigate the impact of concomitant alcohol use on chronic HCV infection, patient's encounters due to admission to hospitals in metropolitan France between 2008–2012 were analysed; this identified 112,146 patients with chronic hepatitis C, 705,259 patients with chronic alcohol use and 23,351 with both. The adjusted HR of in-hospital death was 1.9 for chronic hepatitis C and 3.1 for chronic alcohol use with a negative interaction. More than 80% of all liver complications/deaths in HCV patients occurred in those with concurrent alcohol use or other severe conditions. Alcohol withdrawal or abstinence was associated with a significantly reduced rate of liver complications or mortality by ~30%. While there was extensive discussion around whether these results indicate that treating alcohol addiction is more important than HCV eradication with potentially expensive drugs, another important aspect of this study is that a) concomitant alcohol abuse remains common in patients with chronic hepatitis C, and b) it is important to screen for and treat alcohol abuse in these patients given its substantial impact on liver related complications and mortality.

Abstract # G16

Independent commentary by Associate Professor Golo Ahlenstiel, Gastroenterologist & Hepatologist at Westmead Hospital, Sydney. After completing his medical and doctoral degrees at the University of Bonn, Germany, Golo Ahlenstiel received research fellowships from the National Institutes of Health (NIH, USA) and the German Research Foundation (DFG, Germany) to pursue research into the immune-pathogenesis of viral hepatitis at the National Institutes of Health, Bethesda, MD, USA. Apart from his clinical duties as a staff specialist at Westmead Hospital, he also leads a Liver Immunology group at Westmead Millennium Institute.

A two-stage genome-wide association study identifies TM6SF2 and MBOAT7 as risk loci for alcohol-related cirrhosis

Authors: Buch S et al.

Summary: In this study a two-stage genome-wide association study (GWAS) compared patients with alcohol-related cirrhosis to alcohol dependent controls without liver disease. In stage one, separate GWAS were conducted on German (410 cases vs 1119 controls) and UK patients (302 cases vs 347 controls) combined via meta-analysis; in stage two, GWAS hits were validated though independent analyses of German (529 cases vs 761 controls) and Belgian (619 cases vs 161 controls) cohorts. The strongest association in the stage one meta-analysis was rs738409 variants in PNPLA3 (OR = 2.38; P_{meta} = b1.17 x 10^{-28}); 102 separate variants at the PNPLA3 locus were associated with genome-wide significance ($P_{threshold}$ <5 x 10^{-8}). Nine independent loci were of borderline significance. Validation genotyping confirmed disease association for rs738409 in PNPLA3, and lead markers identified MBOAT7: rs641738 and TM6SF2: rs10401969.

Comment: Alcohol abuse is a not only common cause of liver disease and cirrhosis in the Western world, but also often contributes to disease progression in chronic viral hepatitis. Phenotypically, however, less than 20% of patients with chronic alcohol abuse develop significant liver disease. This would suggest that genetic predisposition may play a role in this context similarly to what has been observed for chronic HCV infection and IFNL3 polymorphisms, which were originally identified by GWAS. Polymorphisms of the PNPLA3 have been previously associated with alcoholic liver disease, but no GWAS have been done so far. The current study performed by a multinational collaboration was designed as a two-stage GWAS comparing cases with alcohol-related cirrhosis with alcohol dependent controls with no evidence of liver disease. The strongest association was found with PNPLA3 rs738409. Numerous other associations, however, were also identified including MBOAT7 rs641738 and TM6SF2 rs10401969. These results are exciting in that they may allow risk-stratifying patients at risk for alcoholic liver cirrhosis and support an important role of lipid metabolism in fibrosis progression in chronic alcoholism. Furthermore, lessons learned from these studies may also apply to other chronic liver disease conditions such as NASH or HCV infection, given the overlapping role of these enzymes in these diseases.

Abstract # L06

Obeticholic acid for NASH: benefits in a high-risk subgroup and the effects of concomitant statin use

Authors: Neuschwander-Tetri B et al.

Summary: This study reports secondary analyses to determine the effect of obeticholic acid (OCA; n = 85) versus placebo (n = 77) in a subgroup of patients with more severe NASH (stage 2-3 fibrosis or stage 1 fibrosis with diabetes, obesity or ALT ≥60 [associated with fibrosis progression]) enrolled in the 72-week placebo-controlled, double-blind FLINT (Farnesoid X Receptor Ligand Obeticholic Acid in NASH Treatment) trial. NASH improved by ≥2 points in 50% of OCA recipients versus 31% of placebo recipients (p = 0.001), NASH resolution occurred in 18% vs 6.5% of patients (p = 0.03), and fibrosis regressed by at least one stage in 39% vs 22% (p = 0.012). Fibrosis progression with OCA was also attenuated (16% vs 29%; p = 0.047). LDL cholesterol increased during OCA treatment in patients receiving statins at baseline, but these levels did not exceed those of placebo-treated patients not receiving statins. Initiation of statin therapy while receiving OCA reduced LDL levels to below the pre-OCA baseline.

Comment: The Farnesoid X receptor ligand OCA was recently reported in the FLINT Trial to improve liver histology including fibrosis in NASH but was also associated with pruritus and total and LDL cholesterol elevations (Neuschwander-Tetri, Lancet 2014). Given the alterations in lipid profile the role of statins in this context warranted further sub-analysis: Mean LDL levels were lower at baseline in patients on statin therapy (92 mg/dL vs 124 in untreated), but increased to 109 mg/dL on OCA therapy. However, these LDL levels remained substantially below that of patients without any statin therapy at all on OCA (135 mg/dL). Statin initiation during OCA treatment reversed LDL to below pre-OCA baseline levels (121 mg/dL at baseline vs 104 mg/dL at week 72). Secondly, this sub-analysis looked specifically at patients with more severe NASH; OCA therapy resulted in significant greater histologic improvements in NASH and NASH resolution, and greater fibrosis regression. Thus, statin therapy can ameliorate or reverse OCA induced LDL rise and OCA therapy is particularly effective in high-risk NASH patients.

Abstract # LP18

Ledipasvir/sofosbuvir with ribavirin is safe and efficacious in decompensated and post liver transplantation patients with HCV infection: Preliminary results of the prospective SOLAR 2 trial

Authors: Manns M et al.

Summary/Comment: Eradication of HCV infection in patients with decompensated liver cirrhosis or after liver transplantation is notoriously difficult. The SOLAR 2 trial studied efficacy and safety of ledipasvir/sofosbuvir (LDV/SOF) fixed dose combination with ribavirin (RBV) in HCV genotype 1 and 4 infected patients with decompensated liver disease or post-liver transplantation irrespective of prior treatment failure or not. Patients were randomised to receive 12 or 24 weeks of treatment stratified into six groups based on Child-Pugh-Turcotte (CPT) score and whether they were pre- or post-transplant. Of 327 patients 80% were IL28B non-CC (i.e. non-responder genotype), 159 (49%) were infected with HCV genotype 1a, 131 (40%) with genotype 1b and 37 (11%) with genotype 4. Notably, 18% of patients with cirrhosis had a MELD score >15. While only 68% of patients have completed study treatment at this time, treatment itself was well tolerated with only 12 discontinuations and only 62 patients experiencing serious adverse events in this very morbid patient cohort. Only eight of these serious adverse events were deemed to be medication related. Importantly, SVR4 rates so far are >90 in all arms except for patients with CPT C cirrhosis regardless of whether they were pre- or post-transplant. Overall, these data A) underline the importance of treating HCV early post-transplant, B) support the safety thereof and C) suggest very high efficacy in this group. In the long run the new therapies should result in more patients having HCV eradicated prior to transplant or otherwise straight after and thus, result in better preservation of graft function.

Abstract # G02

Rifaximin and propranolol combination therapy is more effective than propranolol monotherapy in the hepatic venous pressure gradient response and propranolol dose reduction – a pilot study

Authors: Baik SK et al.

Summary/Comment: Non-selective beta-blockers (NSBB) are the mainstay of pharmacological therapy to reduce the portal pressure and thus risk for variceal bleeding. Their clinical efficacy, however, is limited and comes with significant side effects complicating their clinical application. Bacterial translocation in patients with liver cirrhosis and associated endotoxaemia has been reported to have a negative impact on portal pressures. This raises the question whether addition of rifaximin may be beneficial in this context. Rifaximin is an antibiotic used to treat small bowel overgrowth or treatment-resistant hepatic encephalopathy, as it results in gastrointestinal decontamination without significant side effects, as it is not absorbed. The current study investigated whether addition of rifaximin to NSBB therapy may improve portal pressures. While small, this study was nevertheless randomised with two arms: NSBB only (n = 48) and NSBB + rifaximin (n = 17). Monotherapy recipients received propranolol titrated to a maximum of 320 mg/day with a target of 25% heart rate reduction. Combination therapy recipients also received propranolol titrated according to the heart rate, however, the maximum dose was limited to 160 mg/day and rifaximin 1200 mg/day was administered. Patients with hepatic venous pressure gradient (HVPG) reduction by ≥20% or to less than 12 mmHg were defined as responders. As expected, portal pressures dropped significantly in both groups by more than 10 mmHg. Combination therapy, however, showed better HVPG response rates than NSBB only (82% vs 50%, p = 0.018) and the mean reduction in HVPG was larger (5.8 mmHg vs 3.5 mmHg, p = 0.038). This is notable because propranolol doses were significantly (p = 0.033) lower in the combination group (127 mg vs 152 mg) and reduction in heart rate significantly (p = 0.001) less (7.4% vs 20.5%). These results are interesting, as both medications are often prescribed together in patients with advanced cirrhosis. Secondly, it would suggest that rifaximin may allow using a lower dose of NSBB with presumably less side effects. Further studies with larger patient numbers and equal NSBB dosing are required to clarify whether combination therapy influences clinical endpoints such as variceal bleeding.

Abstract # G03

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