In this review:

Tenofriv reduces perinatal HBV transmission risk

LDV/SOF+vediprevir for 8 weeks: high SVR in cirrhotic GT1 HCV

Coffee intake improves noninvasive markers of liver disease

REP 2139 shows promise in chronic HBV/HDV co-infection

SOF+velpatasvir for 12 weeks: 99% SVR across HCV strains

Obeticholic acid: therapeutic benefit in PBC

SOF+daclatasvir: potent in GT3 HCV

Outcomes of hepatic decompensation in PBC

Vitamin E for NASH ± diabetes

Albumin resuscitation beneficial in sepsis-induced hypotension

Abbreviations used in this review:

AE = adverse event; DAA = direct-acting antiviral; GT = genotype; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDV = hepatitis D virus; IFN = interferon; LDV = ledipasvir; NALFD = non-alcoholic fatty liver disease; NASH = nonalcoholic steatohepatitis; OR = odds ratio; PBC = primary biliary cirrhosis; RAV = resistance-associated variant; RBV = ribavirin; SOF = sofosbuvir; SVR = sustained virological response; TDF = tenofovir disoproxil fumarate; UDCA = ursodeoxycholic acid.

Welcome to this review of the 66th Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), the premier forum for the exchange of state-of-the-art basic, translational, and clinical research in hepatology.

More than 9,500 hepatologists and hepatology health professionals from across the USA and around the world gathered at The Liver Meeting to exchange the latest liver diseases research, discuss treatment outcomes, and interact with colleagues at this year’s event.

Associate Professor Golo Ahlers, Gastroenterologist and Hepatologist at Westmead Hospital, Sydney, attended this meeting and selected the presentations included in this review.

The Liver Meeting® 2015 abstract supplement, in full text, has been published as a Special Issue online supplement to the journal of Hepatology (October 2015) and can be accessed on the journal’s website: http://onlinelibrary.wiley.com/doi/10.1002/hep.v62.21/issuetoc. Late-breaking abstracts have been published in the December issue of Hepatology: http://onlinelibrary.wiley.com/doi/10.1002/hep.v62.6/issuetoc.

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

Kind Regards,

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Tenofriv disoproxil fumarate (TDF) reduces perinatal transmission of hepatitis B virus in highly viremic mothers: a multi-center, prospective, randomized and controlled study

Presenter: Calvin Q. Pan, NYU Langone Medical Center, NYU School of Medicine, New York

Summary: This study recruited 200 pregnant women who were hepatitis B e antigen (HBeAg)-positive and had hepatitis B virus (HBV) DNA >200,000 IU/mL at baseline (mean >8 log IU/mL). They were randomised to receive either tenofriv disoproxil fumarate (TDF) 300 mg starting at gestation week 30–32 and continuing through postpartum week 4, or no antiviral treatment. All women were followed-up until postpartum week 28. 180 women completed the study. All infants received immunoprophylaxis. At postpartum week 28, the mother-to-child transmission (MTCT) rate was significantly lower in infants from TDF-treated mothers versus those from non-treated mothers. The safety profile was similar between groups, with no difference in birth defect rates. HBV DNA levels decreased to <200,000 IU/mL in 66 of 97 TDF-treated mothers before delivery compared to only 2 of 100 non-treated mothers (p<0.001). HBV serological outcome did not differ between groups.

Comment: Mother-to-child transmission of HBV infection remains a significant problem, particularly in high prevalence countries such as China with transmission rates of up to 30% despite adequate immunoprophylaxis in mothers with high levels of HBV. However, data regarding the impact of chemoprophylaxis using tenofriv are limited. In this randomised controlled trial from China, HBeAg-positive mothers with high viral load (n=200) received tenofriv commencing between weeks 30 to 32, or no therapy. There was a significant reduction in infant infections in the tenofriv group versus untreated mothers (0% vs 6.8% in per protocol and 5.2% vs 18% in intention-to-treat analysis). Importantly, there was no significant increase in birth defects or congenital malformations between babies born to treated and untreated mothers (2.11% vs 1.14%); these included 1 case each of torticollis and umbilical hernia in the tenofriv group, and 1 case of hypospadias in the untreated group. Tenofriv therapy reduced HBV DNA levels below 200,000 IU/mL in 68% versus only 2% in the untreated group. Mothers tolerated tenofriv therapy well, though there was a higher incidence of elevated transaminases and creatinine kinase levels. This study suggests that chemoprophylaxis with tenofriv in the third trimester is efficacious and safe in pregnant females with high HBV load.

Viral Hepatitis Plenary. Abstract 209.

Hepatology. 2015;62(Suppl 1):316-7A.
Comment: In patients with hepatitis C coinfection who reduced their alcohol consumption by 5 g/day, as well as those who increased it by 5 g/day, the increase in CAP was 15% (p=0.04) and the decrease was 10% (p=0.02), respectively. This study highlights the importance of monitoring alcohol consumption in patients with hepatitis C.

Parallel 37: Hepatitis C: Pre-Approval Clinical Studies II. Abstract 247.

Coffee consumption reduces liver stiffness in those with hepatitis C and a non-invasive marker of steatosis in those with non-alcoholic fatty liver disease

Presenter: Alexander Hodge, Gastroenterology and Hepatology, Monash Medical Centre, Monash University, Clayton, VIC, Australia

Summary: These researchers examined whether coffee intake improves intrahepatic triglyceride content using transient elastography (TE) in patients with hepatitis C infection. Coffee consumption reduced liver stiffness by 1.5–7 log in 12 patients (undetectable in 6 patients). In 10 patients with detectable α2a, the decrease was 9% (p=0.032). In the NAFLD cohort, the decrease in liver stiffness was significant (9%) (p=0.02). Coffee consumption did not affect CAP in other patient groups. The most frequent AEs were headache, rash, and sinusitis.

Comment: Coffee consumption reduces liver stiffness in those with hepatitis C and a non-invasive marker of steatosis in those with non-alcoholic fatty liver disease. It may be possible.


Update on the safety and efficacy of REP 2139 monotherapy and subsequent combination therapy with pegylated interferon alpha-2a in chronic HBV / HDV co-infection in Caucasian patients

Presenter: Michel Bazinet, Replicor Inc., Montreal, Canada

Summary: Outcomes are reported for 12 Caucasian patients with chronic HBV/HDV co-infection treated with once-weekly REP 2139-Ca (calcium chelate complex) at a dose of 500 mg via 2h IV infusion for 15 weeks, followed by 15 weeks of combined therapy with 250 mg of REP 2139-Ca and 180 ug of pegylated interferon (Peg-IFN) α-2a, then 33 weeks with Peg-IFN alone. The time of this report, serum hepatitis B surface antigen (HBsAg) was reduced by 1–6 log in 11 patients (5 with serum HBsAg <1 IU/mL) and HDV RNA was reduced 1.5–7 log in 12 patients (undetectable in 6 patients). In 10 patients with detectable anti-HBs, levels were <10 mIU/mL in 6 patients, and after combined treatment with REP 2139 plus Peg-IFN, anti-HBs titres were substantially increased from 50 to >800 mIU/mL in 5 patients.

Comment: Co-infection with HBV/HDV is associated with an increased risk of cirrhosis and treatment for HDV is challenging in the absence of potent therapeutic options. Nucleic acid polymers (NAPs) can be used to block HBV particle assembly and release. REP 2139 has shown to clear HBsAg and improve response to immunotherapy to HBV. The current study is a phase II proof-of-concept trial in HBV/HDV co-infection with patients receiving REP 2139 for 15 weeks followed by 15 weeks of combined therapy with REP 2139 and IFN and then 33 weeks of IFN monotherapy. The exciting result of this is that HDV RNA has become undetectable in 6/12 patients, is reduced >1.5 log in 12/12 patients and anti-HBs is detected in 10/12 patients. REP 2139 was well tolerated with only mild and quickly resolving reactions to IV infusion. The results of this phase II trial hold promise for not only successful viral suppression but actual eradication in the future.

Parallel 6: Imaging and Noninvasive Markers of Liver Disease. Abstract 47.

Coffee consumption reduces liver stiffness in those with hepatitis C and a non-invasive marker of steatosis in those with non-alcoholic fatty liver disease.
The selective farnesoid X receptor agonist obeticholic acid (OCA) promotes bile acid secretion. OCA was designed particularly for patients unresponsive to the standard and only other therapy for PBC, ursodeoxycholic acid (UDCA). The presented data was a follow-up of the original 12-week, phase 2, double-blind, placebo-controlled study testing OCA as monotherapy in PBC. 28 patients enrolled in a long-term safety extension, with 19 patients still enrolled after 4.5 years and 8 of these having added UDCA. Long-term OCA treatment resulted in sustained reductions in ALT, AST, GGT and ALP, whereas conjugated bilirubin remained unchanged. Pruritus was the most common AE, affecting 25 out of 28 patients. AE's caused 7 patients to stop OCA. Decreases in HDL resulted in lower total cholesterol levels and were not considered clinically significant. Given that biochemical response is considered a good marker for long-term prognosis, the sustained response and the generally reasonable AE profile and tolerability, OCA may become a useful therapeutic option for PBC.

Poster Sessions: Abstract 628.

Hepatology. 2015;62(Suppl 1):114A.

All-or-treatment with daclatasvir (DCV) plus sofosbuvir (SOF) plus ribavirin (RBV) for 12 or 16 weeks in HCV genotype (GT) 3-infected patients with advanced fibrosis or cirrhosis: The ALLY-3+ phase 3 study

Presenter: Vincent Leroy, CHU de Grenoble, La Tronche, France

Summary: ALLY-3+ enrolled 50 treatment-naïve or -experienced patients with genotype 3 chronic HCV infection. Over a quarter (28%) had advanced fibrosis (stage F3) and 72% had compensated cirrhosis (stage F4). About half had high HCV viral load at baseline (>6 million IU/mL). Participants were randomised to receive 12 weeks (n=24) or 16 weeks (n=26) of daclatasvir 60 mg and sofosbuvir 400 mg once-daily plus 1,000 to 1,200 mg/day weight-based ribavirin. An intent-to-treat analysis demonstrated no significant between-group difference for overall SVR12 rates, which were 88% in the 12-week treatment arm and 92% in the 16-week arm. All patients with advanced fibrosis achieved SVR12 in both treatment arms. In patients with cirrhosis, SVR12 rates were 83% in the 12-week arm and 89% in the 16-week arm. SVR12 rates were 92% for the treatment-naïve cohort (88% for treatment-naïve cirrhotics) and 89% for treatment-experienced patients (86% for treatment-experienced cirrhotics). No viral breakthroughs occurred during treatment. Treatment was well tolerated. The most common AEs were insomnia (30%), fatigue (26%), and headache (24%). One patient developed grade 3 anaemia.

Comment: In the era of DAAs, HCV genotype 1 infection as the previously difficult-to-treat HCV genotype 18 has been at the initial treatment of attention. This has resulted in therapeutic options for genotype 3 being limited so far. The ALLY-3 study was an open-label, phase 3b study in HCV GT3-infected treatment-naïve or -experienced patients with compensated advanced fibrosis or cirrhosis treated with 12 or 16 weeks daclatasvir, sofosbuvir and ribavirin. Overall SVR at 4 weeks post-treatment was 92%, with 88% and 96% for 12- and 16-week arms, respectively. Relapse occurred in 3 patients (2 in 12- and 1 in 16-week arms). Interestingly, 4 of 5 patients with prior relapse to sofosbuvir and ribavirin achieved SVR. One death was considered not treatment-related. Resistance-associated HCV variants were found in 8 patients at baseline, with 7 of them achieving SVR. However, all relapers had resistance-associated HCV variant NS5A–Y93H at the time of relapse. There were no discontinuations due to AEs. This new drug combination is very potent for HCV genotype 3 patients, even in the context of cirrhosis, allowing cure rates above 90%.

Late-Breaking Abstract Posters. Approved HCV Drugs. LB-3.

Hepatology. 2015;62(Suppl 1):1380-1A.

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.


Introducing VIEKIRA PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir) and VIEKIRA PAK-RBV (ombitasvir/paritaprevir/ritonavir + dasabuvir + ribavirin) for the treatment of patients with GT1 chronic HCV.1,2

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HCV=Hepatitis C Virus. RNA=Ribonucleic Acid. SVR=Sustained Virologic Response. GT1=Genotype 1. RBV=Ribavirin.

* Cure defined as <25 IU/mL HCV RNA 12 weeks post end-of-treatment (SVR12) in 97% HCV GT1 patients with or without cirrhosis (pooled analysis Phase III trial cohorts, n=1096)

A NEW FACE OF CURE* IN CHRONIC HCV: INTRODUCING VIEKIRA PAK1,2

Overall cure* rates in patients receiving the recommended dosing regimen in a pooled analysis of Phase III clinical trials1,2

97% (n=1062/1096) achieved SVR12
Incidence and impact of decompensating events in primary biliary cirrhosis: Results of an international follow up study of 3030 patients

Presenter: Maren H. Harms, Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands

Summary: These researchers examined long-term follow-up data (median 8.4 years) from 2,938 patients with PBC treated with UDCA at 17 North American and European centers. Decompensation was defined as a first event of ascites,variceal bleeding, or encephalopathy, whichever came first. A decompensating event occurred in 275 patients: ascites: 167 (61%), variceal bleeding: 76 (27%), encephalopathy: 24 (9%), and multiple: 8 (3%). Survival did not differ significantly between different types of events: 1-, 3- and 5-year transplantation-free survival with or without event was 59% vs 99%, 35% vs 97% and 19% vs 94% respectively (time-dependent HR 40.6; 95% CI, 29.6 to 55.7). In multivariable analysis, factors found to be predictive of survival at time of first event included age at time of event (per 10 years) (HR 1.39; 95%CI, 1.09 to 1.63), calendar year of event (HR 0.97; 95%CI, 0.94 to 0.99), bilirubin >2x upper limit of normal (ULN) (HR 2.98; 95%CI, 1.99 to 4.45) and normal albumin (HR 1.68; 95% CI 1.12 to 2.53). Patients with normal albumin and bilirubin <2xULN at time of event had significantly better survival compared with those with abnormal albumin and/or bilirubin >2xULN (p<0.001) (median 4.0 vs 0.8 years).

Efficacy and safety of vitamin E in nonalcoholic steatohepatitis patients with and without diabetes: Pooled analysis from the PIVENS and FLINT NIDDK NASH CRN trials

Presenter: Kris V. Kowdlely, Swedish Medical Center, Seattle, Washington, USA

Summary: The PIVENS randomised controlled trial (RCT) examined the efficacy of vitamin E for the treatment of NASH in non-diabetic adults, and the FLINT RCT compared obeticholic acid with placebo in diabetic and non-diabetic adult patients with nonalcoholic steatohepatitis (NASH). This presentation compared outcomes for vitamin E in diabetic NASH with pooled data from non-diabetic NASH patients in the PIVENS RCT vitamin E and placebo groups and from non-diabetics in the FLINT placebo arm. For this analysis, histologic improvement was defined as a ≥2-point improvement in NASH with no worsening of fibrosis or NASH resolution. In both trials, a total of 105 patients received vitamin E and 145 did not; 53 had diabetes and 197 were non-diabetic. All had baseline and end-treatment liver biopsies. Vitamin E was associated with histologic improvement in diabetic (OR 4.4; 95% CI, 1.1 to 18.0; p=0.04) and non-diabetic patients (OR 3.1; 95% CI, 1.7 to 5.8; p<0.001), but not a significantly greater rate of NASH resolution in diabetic (OR 1.8; 95% CI 0.3 to 12.2; p=0.55) or non-diabetic patients (OR 1.7; 95% CI 0.9 to 3.3; p=0.09). The incidence of cardiac events did not differ significantly between diabetics using and those not using vitamin E (0% vs 12%; p=0.19), nor between non-diabetics using vitamin E versus not using vitamin E (12% vs 9%; p=0.51). Net changes from baseline in total cholesterol, HDL cholesterol, LDL cholesterol and triglycerides did not differ significantly between treatment groups.

Comparison and outcomes of 5% albumin vs 0.9% normal saline fluid resuscitation in cirrhosis presenting with sepsis-induced hypotension: A randomized controlled trial - Fluid Resuscitation In Septic Shock In Cirrhosis (FRISC Protocol)

Presenter: Cyriac A. Philips, Hepatology and Transplant Medicine, Institute of Liver and Biliary Sciences, New Delhi, India

Summary: This study randomly assigned cirrhotic patients with sepsis-induced hypotension to receive human albumin 5% as a 250 mL bolus over 15 minutes (n=154) or normal saline (30 mL/kg over 30 minutes; n=154). Albumin administration resulted in significantly higher proportions of patients achieving an increase from baseline in mean arterial pressure (MAP) >65 mm Hg at 1 hour (25.3%) and maintaining MAP at 3 hours (11.7%) compared with saline administration (14.3% and 3.2%, respectively; p<0.001). Albumin was associated with a superior, sustained reduction in heart rate (p=0.01), although the increase from baseline in urinary output at 3 hours was similar between treatment groups (p=0.142). There was a greater change in lactate acid concentration with albumin compared with saline administration (p<0.01), with better clearance of lactic acid with albumin over saline (p<0.001). Finally, albumin demonstrated superior overall survival at 1 week (p=0.05).

Comment: Albumin is commonly used in the context of large-volume paracentesis in patients with decompensated liver cirrhosis to minimise the risk for hepatorenal syndrome. While albumin has been suggested to be useful for fluid resuscitation in patients with liver cirrhosis and variceal bleeding or sepsis-induced hypotension, actual evidence regarding the superiority of albumin over regular fluids such as normal saline is scarce. This randomised study compared human albumin with normal saline in 308 patients with liver cirrhosis and sepsis-induced hypotension. Not necessarily surprisingly, but importantly, albumin was superior in terms of haemodynamics, tissue perfusion and early survival as compared to normal saline. The overall survival at day 1, 5 and 7 was better with albumin (96.8/65.6/43.5%) as compared to normal saline (87/44.2/38.3%). Further study is required, but already the current results call for similar research in patients with variceal bleeding.


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