61st Annual Meeting of the American Association for the Study of Liver Diseases

Conference Review™

The Liver Meeting® 29 Oct–2 Nov 2010 Boston, MA, USA

In this review:

Welcome to our review of the 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), held recently in Boston, Massachusetts.

AASLD was founded in 1950 and is the leading organisation of scientists and healthcare professionals committed to preventing and curing liver disease. AASLD's Liver Meeting® this year attracted 7,500 physicians, surgeons, researchers, and allied health professionals from around the world and provided a forum for the exchange of research in diseases of the liver and biliary tract, and in liver transplantation. Dr Alexander Thompson a Gastroenterologist and Head of Hepatology Research at St. Vincent's Hospital, Melbourne, attended the conference and considered the following 10 studies to be of particular interest. These and other abstracts presented at The Liver Meeting® can be found online in a special Hepatology supplement: http://www.aasld.org/news/100710/Pages/HEPSupplement.aspx.

We hope you find our review of The Liver Meeting® interesting and useful in your clinical practice.

Kind regards

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IL28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with HCV with HCV infection

Authors: Charlton MR et al

Summary: This study evaluated the impact of IL28B gene polymorphism among liver transplant donors and recipients. 189 consecutive patients with hepatitis C virus (HCV) who underwent liver transplantation at the Mayo Clinic from 1995–2005 were enrolled. DNA genotyping showed that IL28B polymorphism (CC variant) in liver transplant recipients slowed the time to histological recurrence of HCV (p=0.0081), and the presence of IL28B CC variant in either the recipient or donor liver was associated with increased SVR rate (p=0.0095). IL28B genotype had no significant impact on overall survival or liver-related survival. In conclusion, livers from donors with the IL28B gene polymorphism might preferentially be allocated to patients with HCV infection.

Comment: This abstract presented data identifying a role for IL28B polymorphism in predicting SVR rate in patients with post-transplant HCV infection who are treated with peg-interferon and ribavirin. The "good responder" genotype (here CC for rs12979860) was associated with higher SVR rate. This was true for both recipient and donor IL28B genotype, and, despite small numbers, the benefit appeared to be additive in the setting of both donor + recipient carrying the "good response" genotype. The results are consistent with very similar data from a Japanese group (Fukuhara, Gastroenterology 2010;139(5):1577-85). Data were also presented suggesting that IL28B polymorphism may influence HCV recurrence post-transplant. The data suggest a potential role for IL28B genotyping in donor selection protocols for patients with chronic hepatitis C (CHC) on transplant waiting lists.

Reference: Hepatology 2010;52(suppl): abstract 1

The effect of treatment group, HCV genotype, and IL28B genotype on early HCV viral kinetics in a phase 2a study of PEG-interferon lambda (PEG-IFN-λ) in hepatitis C patients

Authors: Freeman JA et al

Summary: This report presented early HCV viral kinetic data collected in a phase 2a study of PEG-interferon lambda (PEG-IFN-λ). 57 treatment naïve patients with HCV infection (genotype 1, 2, 3 or 4) were randomly allocated to receive 80, 120, 180, or 240µg PEG-IFN-λ or 180µg peginterferon alfa-2a (PEG-IFN-α2a) for 12 weeks. A multivariable linear regression model was used to evaluate the effects of HCV genotype, IL28B genotype, and treatment group on early HCV viral kinetics (first and second phase slopes). Rates of viral decline were faster in PEG-IFN-λ (120, 180, or 240µg) recipients than in PEG-IFN-α2a recipients, independent of host and virus genotype. HCV viral decline was faster in patients with a CC IL28B genotype, independent of HCV genotype. The first and second phase slopes of PEG-IFN-λ in patients with a CT/TT IL28B genotype approached those seen in PEG-IFN-α2a recipients with a CC IL28B genotype. In conclusion, the rates of viral decline in patients with HCV infection treated with 120, 180, or 240µg PEG-IFN-λ may be at least equivalent to those seen in PEG-IFN-α2a recipients.

Comment: PEG-IFN-λ (or PEG-IL29) is a member of the recently identified type 3 IFN family, and is currently in phase 2 development as an alternative to PEG-IFN-α for the treatment of HCV. An HBV development program is also planned. Expression of the PEG-IFN-λ-receptor is restricted compared with the ubiquitous type 1 IFN receptor, with the potential for a more favourable side effect profile. This interim analysis of week 12 data showed that kinetics of viral decline are similar for PEG-IFN-λ compared to PEG-IFN-α. Interestingly, there was a clear difference in viral kinetics according to IL28B genotype for patients treated with PEG-IFN- λ, where patients carrying the "good response" IL28B genotype displayed more rapid virological decline. HCV RNA response rates were lower with HCV genotype 1/4 vs 2/3. PEG-IFN- λ was associated with less cytopenia.

Reference: Hepatology 2010;52(suppl): abstract 831

Telaprevir in combination with peginterferon alfa2a and ribavirin for 24 or 48 weeks in treatment-naïve genotype 1 HCV patients who achieved an extended rapid viral response: final results of phase 3 ILLUMINATE Study

Authors: Sherman KE et al

Summary: The ILLUMINATE study compared the efficacies of 24- and 48-week telaprevir-based regimens in patients with HCV who achieved an extended rapid viral response (eRVR) at week 12. 540 treatment-naïve genotype 1 HCV patients received oral telaprevir 750mg q8h with PEG-IFN-α2a 180 µg/week and ribavirin 1000-1200 mg/day for 12 weeks. 322 patients who achieved eRVR at week 12 were randomised (1:1) at week 20 to continue receiving the telaprevir-based regimen for 24 or 48 weeks of total treatment. SVR rates 24 weeks post-treatment were 92% and 87.5% with the 24- and 48-week regimens, respectively. One patient (0.6%) in the 24-week treatment group and 20 patients (12.5%) in the 48-week treatment group discontinued after week 20 because of adverse events. In conclusion, a 24-week telaprevir-based regimen was non-inferior to a 48-week regimen in HCV patients who achieved eRVR at week 12.

Comment: This randomised study supports 24 weeks of telaprevir-based therapy for patients who attain eRVR. The ILLUMINATE study randomised treatment-naïve patients who attained eRVR to 24 vs 48 weeks of therapy at week 20 (in the ADVANCE study, all eRVR patients were treated for 24 weeks). The rate of eRVR was 65%. Amongst patients achieving eRVR and who were randomised at week 20, the SVR rate with 24 weeks of treatment was 92% vs 87.5% with 48 weeks. The SVR rate was 64% in those patients who did not attain eRVR and were randomised at week 20. The overall discontinuation rate for adverse events was 17%. 100 patients stopped therapy prior to randomisation at week 20 (62 for adverse events, 12 for virological failure, and 26 other - the SVR rate in this group was 23%).

Reference: Hepatology 2010;52(suppl): abstract LB-2

Boceprevir (BOC) combined with peginterferon alfa-2b/ribavirin (P/R) for treatment-naïve patients with hepatitis C virus (HCV) genotype (G) 1: SPRINT-2 final results

Authors: Poordad F et al

Summary: The double-blind SPRINT-2 study investigated the efficacy and safety of PEG-IFN-α2b/ribavirin (P/R) ± boceprevir (BOC) in treatment-naïve patients with genotype 1 HCV. After a 4-wk lead-in (LI) period with P 1.5 µg/kg SC per week and R 600-1400 mg/day given bid (P/R), patients were randomised to 1 of 3 treatment groups: P/R plus placebo for 44 wks (48P/R); response-guided BOC regimen, comprising P/R plus oral BOC 800mg tid for 24 wks, with another 20 wks of P/R if detectable HCV RNA during wk 8-24 (RGT); or P/R plus BOC for 44 wks (LI+44 P/R/BOC). 938 non-black and 159 black patients were enrolled. SVR rates in non-black patients 24 weeks post-treatment were 40% for 48P/R, 67% for RGT ($p<0.0001$) and 68% for LI+44 P/R/BOC ($p<0.0001$). Corresponding SVR rates in black patients were 23%, 42% ($p=0.044$) and 53% ($p=0.004$). Overall, 16%, 12% and 16% of patients in the respective groups discontinued because of adverse events. In conclusion, P/R+BOC significantly increased SVR compared with standard of care in treatment-naïve patients with HCV genotype 1.

Comment: This abstract presented the final results of the phase 3 boceprevir study for treatment-naïve patients. In the Caucasian patients, the rate of SVR in the 48-week BOC-containing regimen (68%) and the response-guided BOC regimen (67%) were significantly higher than PR alone (40%) [overall SVR rates were 66%, 63% and 38%]. RGT was associated with a similar rate of SVR compared to the 48-week BOC regimen. 47% of Caucasians had persistently undetectable HCV RNA from week 8–24 of treatment and were eligible for short duration therapy (28 weeks). Less than 1 log virological decline during the 4-week lead-in phase predicted for lower SVR rates and higher rates of drug resistance. The major side effects of treatment were anaemia and dysgeusia; anaemia (Hb<10g/dL) occurred in 49% of patients treated with BOC-containing regimens compared to 29% of controls; EPO therapy was common (43% of patients treated with BOC vs 24% of patients treated with P/R).

Reference: Hepatology 2010;52(suppl): abstract LB-4

Merry Christmas

and happy New Year from all of us at Research Review

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Dual, triple, and quadruple combination treatment with a protease inhibitor (GS-9256) and a polymerase inhibitor (GS-9190) alone and in combination with ribavirin (RBV) or PegIFN/RBV for up to 28 days in treatment naïve, genotype 1 HCV subjects

Authors: Zeuzem S et al

Summary: This study investigated combinations of the novel protease inhibitor GS-9256 and the polymerase inhibitor GS-9190 when administered for up to 28 days in treatment naïve patients with genotype 1 HCV. In part A, 31 patients were randomised to receive GS-9256 (75mg bid)/GS-9190 (40mg bid) alone or in combination with ribavirin (1000-1200 mg/day divided bid) for up to 28 days. Median maximal declines in HCV RNA were 4.1 and 5.1 log10 IU/mL for the respective regimens. The antiviral activity of GS-9256/GS-9190 was enhanced by combination with ribavirin, and virologic breakthrough was reduced. In part B, patients who had suboptimal response or virologic breakthrough prior to day 28 had PEG-INF (180µg weekly) added. Patients treated in part B achieved HCV RNA ≤ 25 IU/mL within 14 days without breakthrough. In conclusion, GS-9256/GS-9190/ribavirin produced substantial viral suppression, and the addition of PEG-IFN led to rapid and complete viral suppression in patients with genotype 1 HCV.

Comment: Patients were randomised to 9256/9190, 9256/9190 + RBV or 9256/9190 + RBV + PEG. Combination 9256/9190 therapy was associated with median HCV RNA reduction at d7 of –4.1 log, compared to –5.1 for 9256/9190 + RBV and –5.7 for quadruple therapy. Week 4 RVR rates were 7%, 38% and 100%, however, largely due to the development of antiviral resistance and virological breakthrough. In most patients in the 9256/9190 arm, double mutants in the NS3 and NS5B regions were observed. This was disappointing and points to the lower barrier to the emergence of multiple mutations in HCV compared to HBV. RBV increased antiviral potency and dramatically decreased the emergence of resistant mutants. Quadruple therapy was most potent and no resistance was seen. The data suggest that in the short/medium term, IFN and RBV will remain a necessary component of combination regimens.

Reference: Hepatology 2010;52(suppl): abstract LB-1

IL28B genotype is not associated with advanced hepatic fibrosis in chronic hepatitis C patients enrolled in the IDEAL study

Authors: Thompson AJ et al

Summary: This study evaluated the association between IL28B genotype and hepatic fibrosis in patients with chronic hepatitis C. 1329 participants in the IDEAL study, with METAVIR fibrosis stages F0 (2%), F1 (73%), F2 (15%), F3 (4%) and F4 (7%), were included in the analysis. Multivariate logistic regression showed that there was no relationship between IL28B genotype and advanced hepatic fibrosis (F3-4). Predictors of advanced fibrosis were METAVIR activity, age >40 years, hepatic steatosis, LDL cholesterol level, BMI and fasting hyperglycaemia. In conclusion, IL28B genotype was not associated with advanced hepatic fibrosis in this cohort of patients with chronic hepatitis C.

Comment: In this retrospective cross-sectional analysis of the large, well-characterised IDEAL pharmacogenetics cohort, there was no association observed between IL28B genotype and fibrosis stage, or estimated fibrosis progression rate (METAVIR stage/estimated duration of infection, yrs). Although the study was limited by the lack of prospective follow-up, and the fact that >70% of the patients were judged to have METAVIR F1 stage fibrosis, the data are reassuring for patients with the `poor response' IL28B genotypes who are having treatment deferred until the availability of direct-acting antivirals.

Reference: Hepatology 2010;52(suppl): abstract 229

Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naïve patients: final results of phase 3 ADVANCE study

Authors: Jacobson IM et al

Summary: The phase 3 ADVANCE study compared the use of two telaprevir (TVR)-based response-guided regimens with that of a regimen of PEG-IFN-α2a 180µg per week plus ribavirin 1000-1200 mg/day (P/R) in treatment-naïve patients with chronic genotype 1 HCV infection. Patients were randomised (1:1:1) to 1 of 3 treatment arms and received TVR 750mg q8h + P/R for 8 or 12 wks, followed by additional wks of P/R; or P/R for 48 weeks (control group). TVR recipients who achieved an eRVR at wks 4 and 12 stopped at week 24; those who did not received a total of 48 weeks' therapy. SVR at 24 weeks after the last planned dose was 69% and 75% with the 8- and 12-week TVR regimens, respectively, compared with 44% with the P/R regimen (p<0.0001). The safety and tolerability of TVR was similar to that reported previously. In conclusion, these results confirm the clinical benefit of TVR reported in phase 2 studies of treatment-naïve patients with genotype 1 HCV infection.

Comment: This abstract presented the final results of the primary phase III telaprevir study. The SVR rates in the TVR8/P/R (69%) and TVR12/P/R (75%) regimens were significantly higher than P/R alone (44%). Patients who achieved an eRVR with TVR were treated for 24 weeks, otherwise 48 weeks total. The rates of eRVR were 58%, 57% and 8% for the TVR12, TVR8 and P/R arms; SVR rates were then 89%, 83% and 97%. Approximately 40% of telaprevir-treated patients required 48 weeks of therapy. There was a ~5% higher rate of on-treatment virologic failure during the P/R treatment phase in the TVR8/P/R arm compared to the TVR12/P/R arm, suggesting that 12 weeks of TVR is superior to 8 weeks. SVR rates were significantly higher in cirrhotic patients (62%, 53% and 33%). The major adverse events due to telaprevir were rash (biopsies = eczema), anaemia and diarrhoea, but discontinuation rates were lower than in the phase 2 studies.

Reference: Hepatology 2010;52(suppl): abstract 211

A prospective and open-label study for the efficacy and safety of telbivudine(Ltd) in pregnancy for the prevention of perinatal transmission of hepatitis B virus (HBV) to the infants

Authors: Han G et al

Summary: This study evaluated the use of telbivudine (Ltd) during late pregnancy for the reduction of HBV transmission in highly viremic HbeAg-positive mothers. 190 pregnant Asian women with HbeAg-positive chronic hepatitis B who were 20–32 weeks' gestation and who had HBV DNA >1.0 x 6log10 c/mL received either Ltd 600 mg/day from w20–32 of gestation to w4 postpartum, or no treatment. All infants received 200 IU of HBIg within 24 hours postpartum and 20mg recombinant HBV vaccine at 0, 1 and 6 months. At birth, significantly fewer infants in the Ltd arm than the control arm were HBsAg+ (6.32% vs 30.43%; p<0.001). At w28, 2.11% vs 13.04% of infants in the Ltd and control arms, respectively, were HbsAg-positive and/or had detectable HBV DNA (p=0.004). No women in the Ltd arm discontinued because of adverse events and no congenital deformities were noted. In conclusion, Ltd safely reduced perinatal HBV transmission when used during late pregnancy in highly viremic mothers with chronic hepatitis B.

Comment: This was an open-label study of the use of telbivudine (Ltd) in late pregnancy (in addition to post-partum HBIg and vaccine) for preventing vertical transmission of HBV. HBeAg+ mothers with HBV DNA >200,000 IU/mL were eligible for enrollment and treated with either Ltd 600 mg/d from W20-32 of gestation to W4 postpartum or no treatment. The use of Ltd was associated with a reduced rate of vertical transmission vs controls (HbsAg-positive +/- HBV DNA: 2% vs 13%). Treatment appeared to be safe for both mother and infant. Postpartum flare occurred in 13% of Ltd patients after stopping at week 4, but no severe hepatitis occurred (ALT > 10x ULN).

Reference: Hepatology 2010;52(suppl): abstract 212

Shorter duration and lower dose of peginterferon alfa-2a therapy results in inferior HBeAg seroconversion rates compared with the duration and dose of 48 weeks and 180 µg: NEPTUNE study

Authors: Liaw Y et al

Summary: The double-blind NEPTUNE study evaluated the use of PEG-IFNα-2a given for 24 or 48 weeks at either 90 or 180µg weekly in HBeAg-positive patients with chronic hepatitis B (CHB). 551 adults with HBeAg-positive CHB were randomised to 1 of 4 treatment groups and received PEG-IFNα-2a for 24 wks at 90µg per wk (24/90) or 180µg per wk (24/180), or for 48 wks at 90µg per wk (48/90) or 180µg per wk (48 /180). The rate of HBeAg seroconversion 24 weeks post-treatment (primary endpoint) was 14.1% in the 24/90 group, 22.9% in the 24/180 group, 25.8% in the 48/90 group and 36.2% in the 48/180 group. Logistic regression analysis stratified for genotype showed that the two null hypotheses of inferiority for 24 weeks' duration and 90µg dosage were retained. In conclusion, 24 weeks' treatment with PEG-IFNα-2a was inferior to 48 weeks' treatment, and 90µg was inferior to 180µg in patients with chronic hepatitis B.

Comment: This abstract confirmed that, in patients with HBeAg-positive chronic hepatitis B, 48 weeks of PEG-IFN-alpha-2a, at a dose of 180mg weekly, results in superior rates of HBeAg seroconversion compared to lower dose (90mg) or shorter duration (24 weeks). Superior virological (<2,000 IU/mL) and biochemical (ALT< ULN) were also observed. 84–88% of the patients were Asian. A separate study presented similar data for PEG-IFN-alpha-2b (abstract 133).

Reference: Hepatology 2010;52(suppl): abstract 215

HCV RESPOND-2 final results: high sustained virologic response among genotype 1 previous non-responders and relapsers to peginterferon/ribavirin when re-treated with boceprevir plus PEGINTRON (peginterferon alfa-2b)/ribavirin

Authors: Bacon BR et al

Summary: The double-blind RESPOND-2 trial investigated the efficacy and safety of the oral HCV-NS3 protease inhibitor boceprevir (BOC) when added to PEGINTRON (P) and ribavirin (R) in the re-treatment of previous non-responders and relapsers to P/R therapy. 403 patients with genotype 1 HCV who had not responded to P/R treatment were randomised 1:2:2 to receive either P/R control (arm 1), 4 wks of P/R (lead-in) then RGT with P/R + 800mg BOC tid (arm 2), or P/R lead-in for 4 wks then 44 wks of P/R + 800mg BOC tid (arm 3). The SVR rates at 24 weeks' post-treatment were 21%, 59% and 67% in arms 1, 2, and 3, respectively ($p<0.0001$ for arms 2 and 3 vs arm 1). Previous relapsers had higher SVR than previous non-responders in all treatment groups. 3%, 8% and 12% of patients in the respective arms discontinued because of adverse events. In conclusion, BOC added to P/R resulted in high SVR rates in patients with genotype 1 HCV who were previous non-responders and relapsers to P/R treatment.

Comment: This abstract presented the final results for the phase 3 BOC trial that enrolled patients who had previously failed P + R therapy. Non-response was defined as a 2 log reduction in HCV RNA levels at week 12, but failure to ever become undetectable. Week 12 non-responders (< 2 log drop) were excluded. Relapse was defined as undetectable HCV RNA at the end of treatment, but failure to achieve SVR. The rate of SVR in the 48-week BOC-containing regimen (67%) and the response-guided BOC regimen (59%) were significantly higher than P/R alone (21%). Approximately 45% of patients were eligible for shorter treatment in the RGT arm. Rates of SVR were higher in relapsers compared to prior non-responders. Virological decline during the 4-week lead-in phase predicted for SVR (SVR if >= 1 log decline: 79%, 73% vs 25% for 48-week BOC, RGT and PR; SVR if < 1 log decline: 34%, 33% and 0%). 26% of patients had a < 1 log HCV RNA reduction at week 4. The major AE was anaemia (EPO use 46%, 41% vs 21%). Neutropenia was also more common with BOC treatment (< 750: 27%, 25% vs 13%).

Reference: Hepatology 2010;52(suppl): abstract 216

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AASLD Conference Review

Selection and review of the research was carried out independently by *Dr Alexander Thompson, a Gastroenterologist and Head of Hepatology Research at St. Vincent's Hospital, Melbourne. He is also a Neil-Hamilton Fairley NHMRC Research Fellow at the University of Melbourne, and consultant to the Victorian Infectious Diseases Reference Laboratory (VIDRL). Gaining gastroenterology training in Melbourne before completing a PhD in the immunovirology of chronic hepatitis B infection at VIDRL, Alexander recently returned from a post-doctoral fellowship with the McHutchison group at the Duke Clinical Research Institute, Duke University, NC, USA, where he was investigating genetic predictors of treatment outcome in chronic hepatitis C.*

