A CME Newsletter

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

EASL 2011
March 30 - April 3, 2011
Berlin, Germany

Course Director

Mark Sulkowski, MD
Associate Professor of Medicine,
Medical Director,
Viral Hepatitis Center
Johns Hopkins University School of Medicine
Baltimore, Maryland

Faculty

Nezam H. Afdhal, MD
Associate Professor of Medicine,
Harvard School of Medicine
Chief of Hepatology, Director of Liver Center,
Beth Israel Deaconess Medical Center
Boston, Massachusetts

Fred Poordad, MD
Chief, Hepatology
Cedars-Sinai Medical Center
Associate Professor of Medicine,
David Geffen School of Medicine at UCLA
Los Angeles, California

K. Rajender Reddy, MD
Professor of Medicine and Surgery,
Director of Hepatology and Medical Director
of Liver Transplantation
University of Pennsylvania
Philadelphia, Pennsylvania

Supported by an unrestricted educational grant from Merck & Co., Inc.

*This coverage is not sanctioned by the conference organizers and is not an official part of the conference proceedings.

Introduction

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL) was held in Berlin, Germany, from March 30-April 3, 2011. This important conference included presentations that provided important new information on evolving treatment options for managing patients infected with hepatitis C virus (HCV), as described in this newsletter.

Updates on HCV Therapy

There were many important updates on treatment issues associated with antiviral therapy and HCV infection. These included the following:

- A study of HCV infection in six European countries concluded that ambitious strategies to treat more persons with chronic HCV and the availability of protease inhibitors (PIs) are expected to have a major impact on HCV-related mortality in the future **[Deuffic-Burban S, et al. Abst. 122]**. The investigators predicted that antiviral treatment in Europe at the current rate will reduce HCV-related mortality by 13% and cirrhosis by 21% until 2025. Further, they concluded that if all treatment-naïve patients and 70% of non-responders were treated with a PI-based regimen, there would be an additional 15% decrease in HCV mortality.
- A multicenter, retrospective cross-sectional study of patients with chronic HCV treated with pegylated interferon/ribavirin (PegIFN/RBV) found that genetic variants in the inosine triphosphatase (ITPA) gene have an impact on the response to treatment of Japanese HCV infection patients **[Sakamoto N, et al. Abst. 469]**. Specifically, the investigators reported that rs1127354, a single-nucleotide polymorphism (SNP) within the ITPA exon that is linked to a deficiency in ITPA, was strongly associated with protection against anemia.
- Researchers in Romania examined the effect of adding fluvastatin (20 mg QD) to treatment of HCV infection with PegIFN/RBV **[Georgescu EF, et al. Abst. 10]**. This study involved 209 treatment-naïve genotype 1b chronic hepatitis C (CHC) patients who received standard 48 week therapy with PegIFN/RBV. Fluvastatin was administered for a total of 72 weeks – 48 weeks in combination with PegIFN/RBV, then an additional 24 weeks by itself. The investigators reported higher rates of early viral response (EVR) (76.0% vs. 61.9%, P=0.041) and sustained viral response (SVR) (63.5% vs. 49.5%, P=0.05) in the fluvastatin + PegIFN/RBV group compared with the PegIFN/RBV alone group. They concluded that statins may support HCV clearance and may be useful in CHC treatment.
- It has been reported that HCV-infected patients with high LDL levels who are treated with PegIFN/RBV achieve higher rates of SVR than patients with low LDL levels. The relationship between elevated LDL and SVR rates in HCV genotype 1 patients was investigated in a retrospective analysis of the PROGRESS study **[Harrison SA, et al. Abst. 431]**. Genotype 1 patients were randomized to 48 weeks of 180 µg PegIFN + RBV either at a dose of 1,200 or 1,400/1,600 mg/day, or 12 weeks of 360 µg PegIFN followed by an additional 36 weeks of 180 µg + RBV either at a dose of 1,200 or 1,400/1,600 mg/day. At the conclusion of the analysis, the investigators reported that intensified dosing of PegIFN increased SVR rates among patients with elevated LDL levels (≥100 mg/dL) but not in patients with LDL levels <100 mg/dL.

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

- Investigators sought to determine the incidence and risk factors for infections in patients receiving PegIFN/RBV therapy in the IDEAL study. 3,070 treatment-naïve, HCV genotype 1 patients were treated for up to 48 weeks with PegIFN-2b or PegIFN-2a + RBV **[Melia M, et al. Abst. 478]**. While on treatment, 1,092 (36%) of patients experienced a moderate to life-threatening infection. In their analysis of the IDEAL study, the investigators reported that decline in lymphocyte count and female gender were the only factors independently associated with moderate to life-threatening infection. Neutropenia was common but changes in neutrophils were not independently associated with moderate to life-threatening infection in the IDEAL study.

Boceprevir Studies

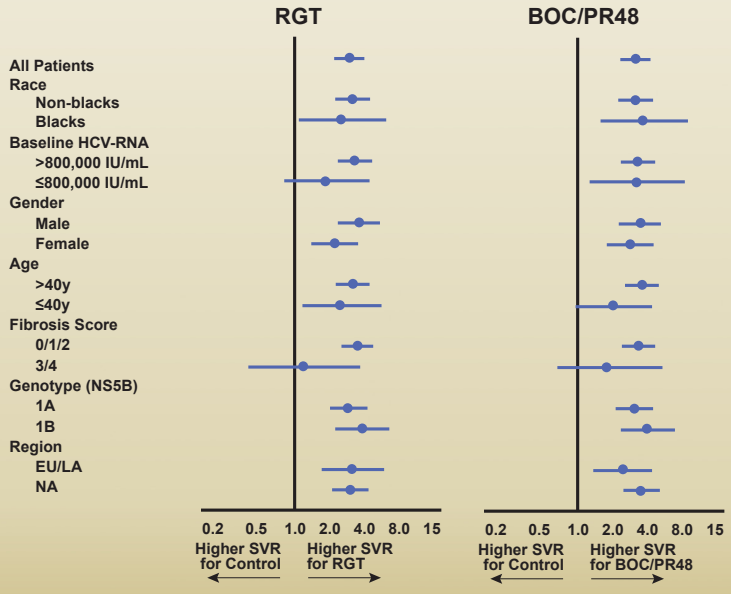
SPRINT-2 and RESPOND-2

EASL featured several important study reports on the use of boceprevir (BOC) for CHC. In an analysis of the SPRINT-2 and RESPOND-2 trials, investigators sought to assess the decline of HCV RNA after 4 weeks of lead-in therapy with PegIFN/RBV as a predictor of SVR **[Vierling JM, et al. Abst. 481]**. Patients in SPRINT-2 (N=1,097) and RESPOND-2 (N=403) were randomized to 4 weeks of PegIFN/RBV, followed by one of three approaches: (1) PegIFN/RBV plus placebo for 44 weeks (PR48); (2) PegIFN/RBV plus response-guided therapy (BOC RGT) – treatment-naïve: for 24 weeks, with additional 20 weeks PegIFN/RBV if detectable HCV RNA during weeks 8-24; previous-treatment-failure: for 32 weeks, with an additional 12 weeks PegIFN/RBV if detectable HCV RNA at week 8; or (3) PegIFN/RBV + BOC for 44 weeks (BOC/PR48).

SVR rates were greater in patients with ≥1.0 $\log_{10}$ declines in HCV RNA after lead-in than in poor interferon responders (defined by <1.0 $\log_{10}$ declines): 80% vs. 33% in treatment-naïve and 76% vs. 33% in previous treatment-failure patients. The investigators concluded that in both studies, the greater the decline in HCV RNA after a 4-week lead-in on PegIFN/RBV, the higher the rate of SVR. They noted that while HCV RNA response to lead-in therapy predicted SVR, it should not be used to predict futility, because one third of poor responders to PegIFN/RBV lead-in achieved SVR with BOC combination therapy.

In another analysis of SPRINT-2, investigators assessed several host and viral factors associated with SVR **[Reddy KR, et al. Abst. 466]**. They found that SVR rates in BOC arms were numerically higher than PegIFN/RBV for each of the baseline factors examined (Figure 1). SVR in non-black patients (n=938) was 40% for PR48 and significantly higher (*P*<0.0001) in both BOC arms: BOC RGT was 67%, and BOC/PR48 was 68%; corresponding SVRs in black patients (n=159) were 23%, 42% (*P*=0.044), and 53% (*P*=0.004). Multivariate stepwise logistic regression analysis including baseline factors in the overall population identified BOC treatment and 3 baseline factors – HCV RNA ≤400,000 IU/mL (OR=3.7, *P*<0.001), absence of advanced fibrosis (OR=1.9, *P*=0.004), and non-black race (OR=0.5, *P*<0.001) – as significantly associated with SVR. When on-treatment response at treatment week 4 was added to this model (decline in viral load after lead-in: ≥1 log vs. <1 log), it was found to be the strongest predictor of SVR (OR=9.3, CI 6.5-13.3, *P*<0.0001), and race was no longer significant. The investigators concluded from their analysis of SPRINT-2 that BOC + PegIFN/RBV was superior to PegIFN/RBV alone for each of the subgroups. BOC RGT and BOC/PR48, low baseline viral load, low fibrosis score and non-black race were predictors of SVR, but when added to the model, treatment week 4 response was the strongest predictor of SVR, demonstrating that patients with ≥1 log decline in HCV RNA at treatment week 4 had significantly higher chances of achieving SVR regardless of race.

Figure 1. SPRINT-2 Subgroup Analysis and SVR



Response-Guided Therapy

An analysis by Manns and associates examined whether response-guided therapy (RGT) was able to reduce treatment duration in early responders in SPRINT-2 and RESPOND-2 **[Manns MP, et al. Abst. 448]**. The investigators reported that in treatment-naïve patients, 56% (208/368 in BOC RGT and

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

204/366 in BOC/PR48) had undetectable HCV RNA at week 8 and were eligible for shorter therapy if they remained HCV RNA negative for the remaining treatment period. These patients attained high SVR rates in both the BOC RGT and BOC/PR48 arms (88% and 90%, respectively). Similarly, comparable lower SVR rates were reported in patients with detectable HCV RNA at week 8 in the BOC RGT and BOC/PR48 arms (36% and 40%). In previous-treatment-failure patients, approximately half (74/162 BOC RGT and 84/161 BOC/PR48) of patients in the BOC arms had undetectable HCV RNA at week 8 and were eligible for shorter therapy. These patients attained similarly high SVR rates in both arms (86% [64/74] BOC RGT and 88% [74/84] BOC/PR48). As was seen in treatment-naïve patients, lower SVR rates were reported in previous-treatment-failure patients with detectable HCV RNA results at week 8 in the BOC RGT and BOC/PR48 arms (40% and 43%). Based on these findings, the investigators concluded that BOC RGT reduced treatment duration in patients with early HCV RNA negativity at week 8 who remained continuously HCV RNA negative in both treatment-naïve and previous-treatment-failure patients. These findings suggest that many patients may only need to take BOC therapy for 24 weeks (if treatment naïve) or 32 weeks (in previous-treatment-failure patients) to achieve a good outcome.

Advanced Fibrosis/Cirrhosis

Investigators also examined the benefit of BOC in HCV genotype 1 patients with advanced fibrosis/cirrhosis in a subgroup analysis of SPRINT-2 and RESPOND-2 **[Bruno S, et al. Abst. 7]**. There is interest in this question because both treatment-naive and patients who have previously failed treatment who have advanced fibrosis/cirrhosis due to HCV genotype 1 infection have low rates of SVR with standard of care (PegIFN/RBV - SOC) therapy and because cirrhotic patients are at the greatest risk for end-stage liver disease and death and have the most to benefit with SVR.

SPRINT-2 and RESPOND-2 randomized 100 and 78 patients with advanced fibrosis/cirrhosis (METAVIR score F3/4), respectively. In SPRINT-2, different response patterns emerged based on the patient's METAVIR score. In patients with scores of F0/1/2, SOC patients had an SVR of 38%, while both BOC treatment arms had an SVR of 67%. In patients with METAVIR scores of F3/4, 37.5% of patients in the SOC arm had an SVR, while 41.2% of patients in the BOC RGT arm had an SVR – a difference that was not statistically significant. In the BOC/PR48 group, 52.4% of F3/4 patients had an SVR, which was statistically significantly better than the SOC arm (P<0.04).

Similar results were reported in RESPOND-2: for F0/1/2 patients, SVR was 23% for SOC, 66% for BOC RGT, and 68% for BOC/PR48 patients. For F3/4 patients, SVR was 13.3% in the SOC arm, 43.8% in the BOC RGT arm, and 67.7% in the BOC/PR48 arm; however, the differences between F3/4 patients in both BOC arms and the PegIFN/RBV arm were statistically significant: P<0.04 for BOC RGT vs. SOC, and P<0.0005 for BOC/PR48 vs. SOC.

In addition, investigators reported that in SPRINT-2, SVR was higher in both BOC treatment arms vs. SOC in patients with <1 $\log_{10}$ HCV RNA decline at week 4. In RESPOND-2, there was a discrepancy in treatment week 8 response between the two BOC regimens, attributable to baseline characteristics and small sample size. However, SVR according to treatment week 8 response was equivalent. The investigators concluded that in treatment-naive or previous-treatment-failure patients with HCV genotype 1 infection and advanced fibrosis/cirrhosis, addition of BOC to PegIFN/RBV in 48-week treatment arms was associated with enhanced SVR.

Adverse Events with Boceprevir

Investigators also reported at EASL on the overall safety profile of BOC in SPRINT-2 and RESPOND-2 **[Manns MP, et al. Abst. 449]**. Treatment-emergent adverse events (AEs) occurred in >98% of patients in all arms of both studies. In SPRINT-2, the median duration of treatment (days) was 203 (PR48), 197 (BOC RGT), and 335 (BOC/PR48). Serious adverse events (SAE) were reported in 9%, 11%, and 12% of the three arms, respectively. In previous-treatment-failure patients (RESPOND-2), the median duration of treatment was 2.4- to 3.2-fold longer in the BOC arms compared with control. SAEs were reported in 5%, 10%, and 14% of the three arms, respectively. The most common AEs reported in both studies were fatigue, headache and nausea and were comparable in all arms. In treatment-naïve patients, anemia occurred in 29% of PR48 and in 49% of each of the BOC arms; erythropoietin (EPO) use was 24% in PR48 and 43% in each of the BOC arms. In previous-treatment-failure patients, anemia occurred in 20% of PR48 and 43%-46% of the BOC arms; EPO use was 21% in PR48 and 41%-46% in the BOC arms. The only AE that was specifically attributed to BOC was dysgeusia. In both treatment-naïve and previous-treatment-failure patients, all BOC arms did not show increase in bilirubin levels over PR48 arms.

Another analysis examined anemia in the SPRINT-2 and RESPOND-2 studies **[Sulkowski MS, et al. Abst. 476]**. While it is known that the addition of BOC to PegIFN/RBV causes increased anemia, the relationship with SVR is unknown. Anemia was defined as hemoglobin (Hb) <10 g/dL. The investigators reported that in SPRINT-2, anemia occurred in 49.4%, and EPO use was reported in 43.3% of patients in the BOC/PegIFN/RBV arm, while anemia occurred in 29.7%, and

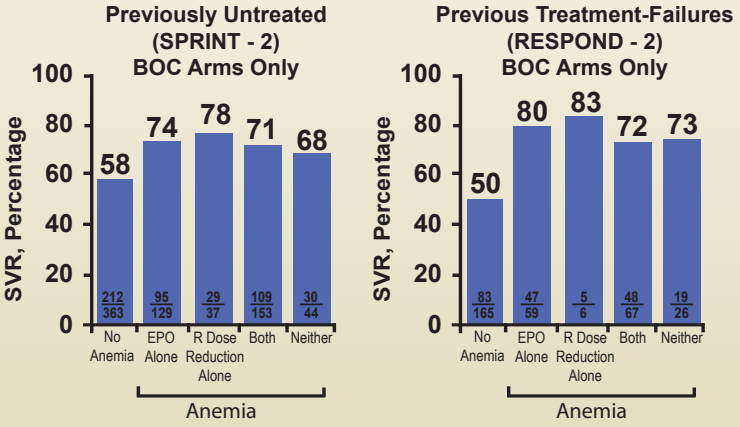
The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

EPO use was reported in 24.0% of patients in the control (PegIFN/RBV) arm. In both control and BOC groups, it was found that SVR was more frequent in patients who developed anemia compared to those who did not (P<0.001). In previous-treatment-failure patients (RESPOND-2), anemia and EPO use occurred in 48.6% and 43.3%, respectively, of the BOC-treated patients and 25% and 21.2%, respectively, of the PegIFN/RBV group. In the BOC group, SVR was significantly more frequent in patients who developed anemia compared to those who did not (P<0.001). In both patient groups, EPO was prescribed in 78.5% of anemic patients treated with BOC and 68.0% of those in the PegIFN/RBV control group. It was reported that in patients with anemia in SPRINT-2 and REPOND-2, the SVR rates in both BOC arms managed with RBV dose reductions alone were comparable to those in patients managed with EPO, with or without RBV dose reduction (Figure 2).

Figure 2. SVR According to EPO Use and Ribavirin Dose Reduction



IL28B and Virologic Response

In another interesting study presented at EASL, patients in SPRINT-2 and RESPOND-2 were tested for IL28B polymorphisms to assess IL28B genotype as a predictor of treatment week 4 responses and SVR **[Poordad E, et al. Abst. 12]**. The investigators found that among treatment-naïve patients, SVR was 50%-51% higher in CC controls compared with CT and TT, while in the BOC arms SVR was 9%-27% higher in CC patients compared with CT and TT. For previous-treatment-failure patients, there was a clear advantage for BOC in all categories (CC, CT, and TT). In black patients (n=94), SVR rates were higher with BOC in all IL28B groups. In all IL28B genotypes with <1 log treatment week 4 response, the addition of BOC had a notable impact, particularly in the non-CC patients. Only 3% of CC patients did not achieve a 1 log decline at treatment week 4 with PegIFN/RBV, compared to 25% CT, and 44% TT. IL28B genotype was a stronger predictor than other baseline variables including subtype, race, age and fibrosis score; however, it was not a significant predictor when treatment week 4 response was included in the model. The investigators concluded that IL28B was a strong baseline predictor of SVR even in the presence of BOC. However, treatment week 4 response to PegIFN/RBV remains a stronger predictor of SVR compared with baseline variables, including IL28B genotype.

Treatment with Peginterferon α-2a

Investigators sought to determine the safety and efficacy of combining BOC with PegIFN α -2a (PEG2a) and RBV in patients who met identical entry criteria to patients in RESPOND-2 **[Flamm S, et al. Abst. 1366]**. This study randomized 201 HCV genotype-1 relapsers and non-responders to two arms: patients in Arm 1 (control) received a 4-week lead-in of PEG2a/RBV followed by placebo + PEG2a/RBV for 44 weeks. Arm 2 received a 4-week lead-in of PEG2a/RBV followed by BOC + PEG2a/RBV for 44 weeks. Therapy was discontinued if HCV RNA was detectable (undetectable HCV RNA <9.3 IU/mL) at week 12. The primary endpoint was SVR 24 weeks post-therapy. The addition of BOC after a 4-week lead-in with PEG2a/RBV significantly increased SVR: 21% in Arm 1 vs. 64% in Arm 2 (P<0.0001). SVR for patients with poor interferon responsiveness (<1 $\log_{10}$ decrease in HCV-RNA after 4-week lead-in) was 0% in Arm 1 and 39% in Arm 2. For patients responsive to interferon (≥1 $\log_{10}$ decrease in HCV RNA after a 4-week lead-in), SVR was 25% in Arm 1 and 71% in Arm 2. Discontinuation due to AEs occurred in 4% and 17% of patients in Arms 1 and 2, respectively. Rates of serious AEs were 10% in Arm 1 and 13% in Arm 2. The frequencies of anemia (<10.0 g/dL) were 27% in arm 1 vs. 49% in Arm 2; neutropenia (WHO grade 3-4 [<750/mm^3]) 21% vs. 43%; EPO use 30% vs. 47%. Based on their findings, the investigators concluded that lead-in with PEG2a and ribavirin followed by addition of BOC resulted in high SVR rates similar to those observed using an identical treatment regimen with PegIFN alfa-2b and that therapy was generally well-tolerated. Taken together with the findings from RESPOND-2, this trial demonstrated that BOC can be combined with either PEG2a or PEG2b to significantly increase SVR in patients who failed prior therapy.

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Telaprevir Studies

There were several presentations at EASL that provided important new information on the use of telaprevir (TVR) for patients with HCV infection. One of these focused on ADVANCE, a study that assessed the efficacy and safety of two TVR-based, response-guided regimens in combination with PegIFN α-2a and RBV in treatment-naïve patients with chronic genotype 1 hepatitis C (HCV) infection **[Marcellin P, et al. Abst. 451]**. The two TVR treatment groups were those that received TVR for 8 weeks (T8PR) or 12 weeks (T12PR).

Marcellin and colleagues compared SVR rates in the two TVR-based regimens and with PegIFN/RBV in pre-defined subgroups of patients. They reported that patients in the TVR-treated patients achieved SVR rates of 75% (T12PR) and 69% (T8PR) compared with 44% in patients receiving PegIFN/RBV in the full analysis (intention-to-treat) population ($P<0.0001$ for both TVR-based regimens versus PegIFN/RBV).

All subgroup analyses revealed higher response rates with TVR than with PegIFN/RBV alone. In an analysis of SVR by HCV genotype, it was found that genotype 1b patients had a slightly higher SVR than genotype 1a patients. This difference in response may have been due to genetic barriers to resistance in 1b versus 1a: the number of mutations required for the 1a virus to escape from the PIs is one, while the number of mutations for 1b is two. Specifically, SVR occurred in 71% and 79% of genotype 1a and 1b patients in T12PR, 66% and 74% in T8PR and 41% and 48% in PegIFN/RBV, respectively. While the difference between the two genotypes is small, it is worthwhile for clinicians to note the subtype of each patient.

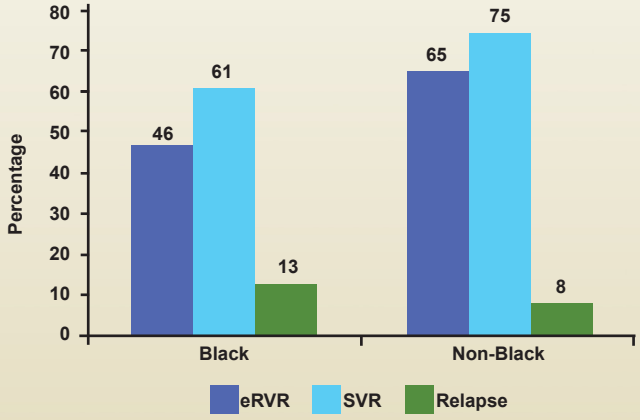
Another issue that was examined was viral load. While viral load can have a significant impact on treatment response with standard PegIFN/RBV treatment, in the ADVANCE study the difference in SVR between patients with HCV RNA levels ≥800,000 IU/mL and <800,000 IU/mL was not large, with 74% of patients with levels ≥800,000 IU/mL having SVR and 78% of patients with <800,000 IU/mL achieving SVR. In ADVANCE, the PI significantly helped the high viral load patients. When fibrosis stage was analyzed, a similar pattern emerged, in that TVR treatment increased SVR vs. PegIFN/RBV, but the response was higher in patients with a score of F0/1/2 (78%) vs. those with F3/4 (62%).

Telaprevir and Patient Characteristics

A study by Dusheiko and colleagues evaluated the effect of race on the response to treatment with TVR-based therapy **[Dusheiko GM, et al. Abst. 415]**. In this analysis, patients who received 12 weeks of response-guided TVR-based therapy for a total treatment duration of 24 or 48 weeks (ADVANCE N=903 and ILLUMINATE N=540) were compared to ADVANCE patients who received 48 weeks of PegIFN/RBV alone (N=361). Race and ethnicity were self-reported and were not mutually exclusive.

The investigators reported that TVR-based therapy provided a substantial improvement in SVR rates in African American and Latino patients, who are known to achieve lower SVR rates when treated with PegIFN/RBV alone (Figure 3) However, SVR for black patients taking TVR-based therapy (61%) was less than that for non-black patients (75%). The same was true for the rate of extended rapid viral response (eRVR) (46% vs. 65% in non-black patients), and the relapse rate was higher (13% vs. 8% in non-black patients). Some of these differences may be explained by the IL28B polymorphism, although other factors may be involved that need to be investigated.

Figure 3. ADVANCE/ILLUMINATE: Viral Response According to Race



Another study presented at EASL examined the impact of the IL28B genotype on SVR rates in the ADVANCE trial **[Jacobson IM, et al. Abst. 1369]**. In this study, the IL28B genotype was determined in de-identified left-over specimens available from ADVANCE sites. Because of the limited number of patients of non-white race and the requirements of the de-identification procedure, only samples from white patients were tested. 454/1088 (42%) patients had IL28B test results available. Of these, 150/454 (33%) were CC, 224/454 (49%) CT, and 80/454 (18%) TT.

The investigators reported SVR rates for each subgroup by arm, as shown in Figure 4. 72%, 54% and 48% of CC, CT and TT TVR patients respectively, had undetectable HCV RNA at weeks 4 and 12 (eRVR) compared with 16%, 3% and 0% of PegIFN/RBV patients. Among eRVR TVR patients, 91% achieved SVR (97% of CC, 88% of CT/TT) with 24 weeks

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

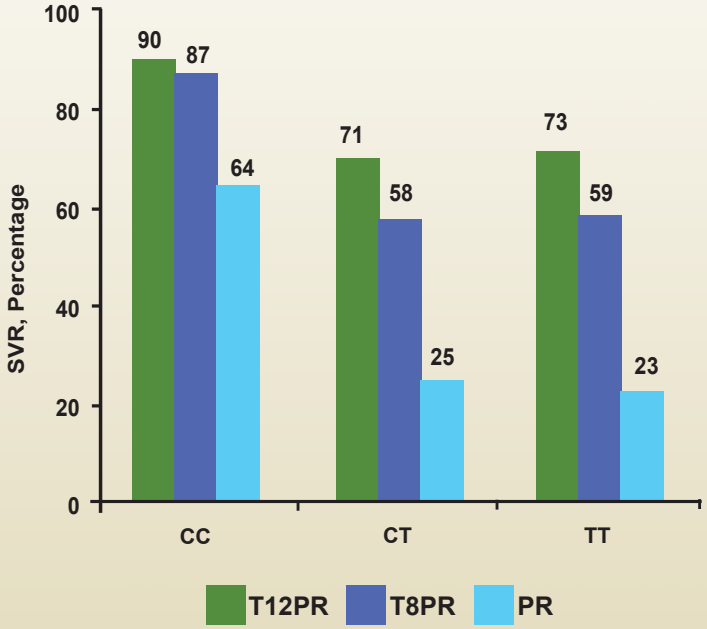
Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

of therapy, while 45% of non-eRVR TVR patients had SVR (67% of CC, 38% CT/TT) with 48 weeks of therapy.

Based on these findings, Jacobson and his research team stated that TVR-based therapy improved eRVR and SVR rates across all IL28B genotypes. Specifically, TVR-based therapy more than doubled the rates of SVR in CT/TT patients, and substantially increased SVR rates in those with CC genotype, as compared with PegIFN/RBV therapy alone. Non-attainment of eRVR was associated with lower SVR rates across all IL28B genotypes, with the largest decrement in CT/TT patients.

Figure 4. ADVANCE: SVR According to IL28B Genotype



A report from EASL that reviewed data from ADVANCE and ILLUMINATE (another phase 3 study that evaluated safety and efficacy of TVR in genotype 1 HCV treatment-naïve patients) consisted of a retrospective pooled analysis, in which efficacy outcomes were assessed based on anemia and RBV dose reductions **[Sulkowski MS, et al. Abst. 477]**. In this analysis, ADVANCE and ILLUMINATE patients who received 12 weeks of TVR-based regimen (T12PR) in combination with either 24 or 48 weeks of PegIFN/RBV were compared to ADVANCE patients who received 48 weeks of PegIFN/RBV (control group), based on their eRVR. All randomized patients who received at least one dose of study medication and underwent hemoglobin measurement at baseline and at least once during the treatment phase were included.

Of the 1,239 patients included in the analysis, 41% (361/885) and 26% (92/354) of patients in the T12PR and PegIFN/RBV groups, respectively, developed anemia during treatment. 74% (267/361) and 50% (46/92) of T12PR and PegIFN/RBV patients with anemia, respectively, achieved SVR. 73% (384/524) and 41% (108/262) of T12PR and PegIFN/RBV patients without anemia, respectively, achieved SVR. 72% (260/361) and 58% (53/92) of T12PR and PegIFN/RBV patients with anemia, respectively, had RBV dose reduction due to adverse events compared to 11% (60/524) and 6% (16/262) of T12PR and PegIFN/RBV patients without anemia, respectively. SVR was achieved by 76% (243/320) and 54% (37/69) of patients with RBV dose reduction in the T12PR and PegIFN/RBV groups, respectively; compared with 72% (408/565) and 41% (117/285) of patients without RBV dose reduction in the T12PR and PegIFN/RBV groups, respectively.

It should be noted that in these studies, EPO was not permitted to be used and the primary management strategy for patients with anemia was RBV dose reduction or discontinuation. These findings showed that anemia was more frequent in patients who received TVR than in patients in the control group. However, in patients treated with TVR, anemia and RBV dose reduction had no effect on SVR rates compared with patients treated with PegIFN/RBV alone.

Results from REALIZE

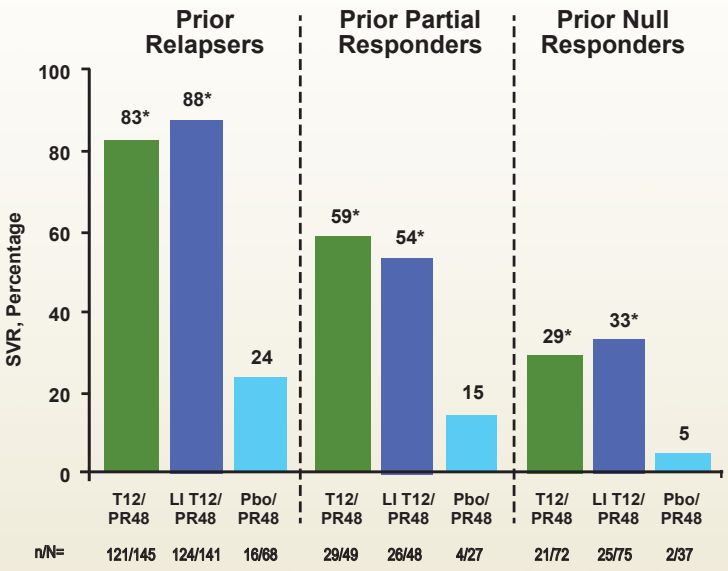
REALIZE was another study with TVR presented at EASL **[Zeuzem S, et al. Abst. 5]**. REALIZE was designed to evaluate the efficacy, safety and tolerability of TVR + PegIFN/RBV compared with PegIFN/RBV alone in genotype 1 HCV-infected patients with prior PegIFN treatment failure, including non-responders (null- and partial-responders) and relapsers. Treatment arms were: 1) TVR/PegIFN/RBV for 12 weeks, followed by PegIFN/RBV for 36 weeks (T12/PR48); 2) PegIFN/RBV for 4 weeks followed by TVR/PegIFN/RBV for 12 weeks, then PegIFN/RBV for 32 weeks (Lead-in T12/PR48); or 3) PegIFN/RBV for 48 weeks (Pbo/PR48). The primary objective was to evaluate the superior efficacy of the TVR + PegIFN/RBV arms for non-responders and relapsers. Secondary objectives included the evaluation of a lead-in and efficacy in prior null- and partial-responders separately. As shown in Figure 5, TVR/PegIFN/RBV demonstrated superior efficacy compared with PegIFN/RBV in all prior-treatment-failure populations studied, including null- and partial-responders.

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Figure 5. REALIZE: SVR in Prior Relapsers, Prior Partial Responders and Prior Null Responders



*P<0.001 vs. Pbo/PR48

SVR by Lead-in Phase Response in REALIZE

A poor therapeutic response to PegIFN/RBV is defined as a <1 $\log_{10}$ decline in viral load at week 4, while a null response (NR) to a current or prior course of PegIFN/RBV is defined as a <2 $\log_{10}$ decline in HCV RNA at week 12. The FDA adopted the week 12 NR definition in a recent draft guidance. The REALIZE study uniquely enrolled classically defined prior null responders, partial responders and relapsers, and included an arm with a PegIFN/RBV lead-in phase. This design allowed a comparison of on-treatment response after 4 weeks of PegIFN/RBV with prior response categories, including a comparison of 'null response', as well as the relationship between <1 or ≥1 $\log_{10}$ HCV RNA decline and SVR in response to TVR/PegIFN/RBCV treatment. A subanalysis of the REALIZE trial examined SVR in terms of prior response to therapy and week 4 response to PegIFN/RBV lead-in **[Foster GR, et al. Abst. 6]**.

In this subanalysis, patients in the lead-in arm (n=240) received 4 weeks of PegIFN/RBV followed by TVR (750 mg every 8 hours) for 12 weeks combined with PegIFN/RBV followed by 32 weeks of PegIFN/RBV alone. Control patients (n=121) received 48 weeks of PegIFN/RBV. All patients received PegIFN α-2a. The investigators reported that 10% of prior relapsers and 31% or 40% of partial responders had <1 $\log_{10}$ decline in HCV RNA at week 4 in the control and lead-in arm, respectively. SVR rates in the TVR lead-in arm among prior relapsers and partial responders were higher (62% and 56%, respectively; combined SVR=58%) than in prior week 12 null responders who experienced <1 $\log_{10}$ decline in HCV RNA (15%). Although patients with ≥1 $\log_{10}$ response at the end of the lead-in phase had the highest SVR rates, SVR in TVR/PegIFN/RBV patients with <1 $\log_{10}$ was considerably higher (62%-15%) than control (0%).

The researchers summarized the study by noting that poor interferon responders on treatment (<1 $\log_{10}$ decline in HCV RNA at week 4) are not the same as prior PegIFN/RBV NR (<2 $\log_{10}$ at week 12). SVR rates in TVR/PegIFN/RBV-treated patients were higher than controls, irrespective of their response (<1 or ≥1 $\log_{10}$) at the end of the lead-in phase.

IL28B Genotype and SVR Rates in REALIZE

Investigators conducted a retrospective analysis to characterize the relationship between IL28B genotype and SVR in REALIZE **[Pol S, et al. Abst. 13]**. To collect the appropriate information, patients were asked to consent to genetic testing. 527/662 (80%) patients enrolled in REALIZE agreed to allow such testing. This represented 72%, 76% and 98% of the total relapsers, partial responders, and null responders, respectively. Genotype rs12979860 was determined using a TaqMan allelic discrimination assay validated against Sanger sequencing on 50 independent samples. This was a retrospective study based on patients who consented to genetic testing prior to the discovery of IL28B, so sample size was not based on formal statistical considerations.

Overall, 94% of patients in the analysis were white and 4% were black. 18% of patients were IL28B CC, 61% CT and 21% TT. By prior response category, the highest proportion of IL28B TT patients was among prior NRs (28%), while the highest frequency of CC patients occurred among prior relapsers (27%). IL28B genotypes were well balanced across all arms with exception of a higher frequency of TTs in the placebo arm. Since no differences were observed between the two T arms, a pooled analysis was conducted.

The analysis showed that differences in SVR rates among IL28B CC, CT and TT patients were only evident when the three patient subpopulations were pooled; however, SVR among CT and TT patients were still high (Figure 6).

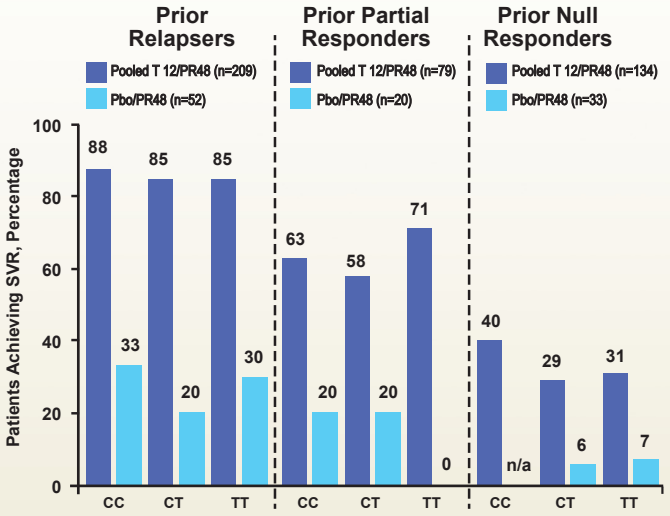
It is worth noting that CC patients who are null responders or partial responders are unusual. They are not like CC patients who have never been treated; when a CC patient fails, it suggests that other factors may be involved. The investigators concluded that IL28B genotype did not contribute to outcome prediction in prior-treatment-experienced patients treated with a TVR-based regimen and thus may be of limited utility in this patient population.

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

Figure 6. SVR Rates by IL28B Genotype and Prior Response in REALIZE



Telaprevir and Methadone

Many HCV-infected patients are, or have been, injection drug users and receive methadone maintenance therapy. Therefore, investigators sought to determine the pharmacokinetic interaction between methadone and TVR and the effect on the pharmacodynamics of methadone **[van Heeswijk R, et al. Abst. 1244]**.

To investigate this topic, researchers conducted an open-label, single-sequence clinical trial in HCV-negative volunteers on methadone maintenance therapy. TVR 750 mg every 8 hours was co-administered with methadone for 7 days. Pharmacokinetic profiles of R- and S-methadone were measured over the 24-hour dosing interval on Day 1 (methadone alone, reference) and on Day 7 of TRV co-administration (test). The unbound fraction of R-methadone was measured in pre-dose samples before and during TVR co-administration. Least square means and associated 90% confidence intervals (CIs) of treatment ratios (test/reference) were calculated based on log-transformed pharmacokinetic parameters.

Eighteen volunteers were enrolled in the study; 2 discontinued prior to receiving TVR. The least square means ratio (90% CIs) of the Cmin, Cmax and AUC24h for R-methadone was, respectively, 0.69 (0.64-0.75), 0.71 (0.66-0.76) and 0.71 (0.66-0.76). The AUC ratio of S-/R-methadone was comparable before and during co-administration of TRV (0.90, 90% CIs 0.86-0.94), indicating lack of a stereo-specific effect. The median unbound fraction of R-methadone increased from 7.92% to 9.98% during co-administration of TVR. The estimated median unbound Cmin of R-methadone, however, was comparable before (10.63 ng/mL) and during co-administration of TVR (10.45 ng/mL). There were no discontinuations due to adverse events. During co-administration of TVR, fewer volunteers experienced withdrawal symptoms and the median resting pupil diameter was smaller, compared with treatment with methadone alone.

Although total exposure to R-methadone (active form) was reduced by approximately 30% during TVR co-administration, there was no indication of opioid withdrawal. This is consistent with the observation that unbound minimal concentrations of R-methadone were not affected by TVR. The investigators concluded that these findings suggest that no adjustment of methadone is required when initiating TVR. However, clinical monitoring is recommended as individual dose modifications may be necessary.

Novel Therapies and Strategies

There were many reports on studies investigating new HCV drugs in development. These included the following:

PROTON

The nucleotide analog (NA) PSI-7977 is being studied in PROTON, a phase 2b dose-ranging study with PegIFN α-2a/RBV in treatment-naïve patients with HCV genotypes 1, 2, or 3. In PROTON, patients were stratified by IL28B genotype.

- 25 treatment-naïve, non-cirrhotic HCV genotypes 2 and 3 patients with HCV RNA >50,000 IU/mL were studied in PROTON **[Lalezari J, et al. Abst. 61]**. Patients received PSI-7977 400 mg QD with PegIFN/RBV for 12 weeks. One subject was lost to follow-up after day 1. All of the remaining 24 subjects completed 12 weeks of therapy. The investigators reported that after 12 weeks of therapy, all (100%) of the remaining patients had an HCV RNA less than the limit od detection (<LOD), for an ITT response rate of 96%.
- Patients with HCV genotype 1 were randomized 2:2:1 to receive PSI-7977 200 mg, 400 mg, or placebo, plus PegIFN/RBV for 12 weeks, followed by 12 or 36 weeks PegIFN/RBV in a response-guided regimen **[Nelson DR, et al. Abst. 1372]**. In a blinded ITT analysis of the 95 genotype 1 patients receiving PSI-7977 200 mg or 400 mg, significant and consistent antiviral activity was observed with HCV RNA <LOD (15 IU/mL) as early as day 3, in 93/95 by week 4 (RVR 98% vs. 19% control). By week 12, 100% of the 200 mg and 92% of the 400 mg PSI-7977 patients had HCV RNA <LOD. The investigators concluded that PSI-7977 + PegIFN/RBV demonstrated potent on-treatment antiviral activity in treatment-naïve patients with HCV genotype 1 for an overall RVR of 96% with no viral breakthrough.

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

NUCLEAR

This study combined PSI-7977 and PSI-938, another NA **[Lawitz E, et al. Abst. 1370]**. This combination was the first purine + pyrimidine combination explored for HCV. Complementary resistance profiles, high barriers to resistance, broad genotype coverage, and independent phosphorylation pathways characterize this promising direct acting antiviral (DAA) combination. The NUCLEAR study consisted of treatment-naïve, non-cirrhotic patients with HCV genotype 1 who received: 1) PSI-938 for 14 days; 2) PSI-938 days 1-7 and PSI-938 + PSI-7977 days 8-14; 3) PSI-7977 days 1-7 and PSI-938 + PSI-7977 days 8-14; or 4) PSI-938 + PSI-7977 for 14 days. 10 patients per cohort (2 placebo) received PSI-938 300 mg QD and/or PSI-7977 400 mg QD. There were no clinically relevant pharmacokinetic interactions between PSI-7977 and PSI-938. Monotherapy PSI-938, monotherapy PSI-7977, or combination PSI-938 + PSI-7977 provided profound and consistent reductions in HCV RNA with HCV RNA <LOD (15 IU/mL) as early as day 3 of monotherapy. Monotherapy with either NA provided profound antiviral responses rivaling the best antiviral responses reported by combinations employing 2 or more DAAs. This early and short duration study was a good proof of concept that a dual nucleotide strategy has potential and is both safe and effective.

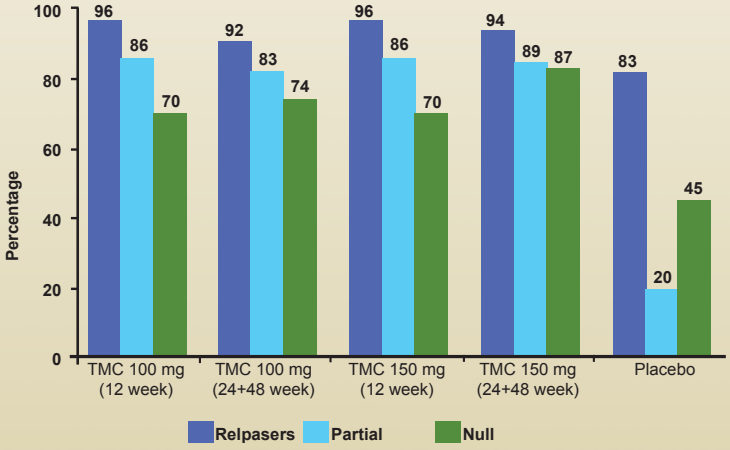
ZENITH

The ZENITH study is assessing the safety, tolerability and antiviral activity of VX-222 (a non-nucleoside polymerase inhibiter [NNPI]) with TVR – alone (DUAL) or with PegIFN α-2a and RBV (QUAD) in chronic HCV genotype 1 treatment-naïve patients **[Di Besceglie AM, et al. Abst. 1363]**. 106 patients have been randomized to 1 of 4 arms: A (n=18): VX-222 100 mg, TVR 1125 mg BID; B (n=29): VX-222 400 mg, TVR 1,125 mg BID; C (n=29): VX-222 100 mg, TVR 1,125 mg BID, PEG 180 µg/week, RBV 1,000-1,200 mg/day; and D (n=30): VX-222 400 mg, TVR 1,125 mg BID with the same doses of PegIFN and RBV, for 12 weeks. Additional 12 or 24 weeks of PegIFN/RBV treatment is dependent on viral responses at week 2 and 8. Results presented at EASL showed that both DUAL arms were terminated after patients experienced on-treatment viral breakthrough (vBT). No vBT has been observed in either QUAD arm. Median time to undetectable HCV RNA was 4 and 2 weeks in Arms C and D, respectively. The majority of patients in arm D had undetectable HCV RNA by week 2; RVR rates were high in both QUAD arms.

ASPIRE

TMC435 is an oral, once-daily, HCV NS3/4A protease inhibitor. ASPIRE is a randomized, double-blind, placebo-controlled trial investigating the efficacy, tolerability, safety and pharmacokinetics of TMC435 administered with PegIFN/RBV **[Zeuzem S, et al. Abst. 1376]**. Results of a week 24 interim analysis were presented at EASL. The study enrolled genotype 1 HCV patients with evidence of null-response, partial response or relapse following ≥1 course of PegIFN/RBV therapy. Patients were randomized to one of seven treatment arms (all TMC435 once-daily): TMC435 (100 mg or 150 mg) + PegIFN/RBV for 12 weeks, followed by PegIFN/RBV + placebo for 36 weeks; TMC435 (100 mg or 150 mg) + PegIFN/RBV for 24 weeks, followed by PegIFN/RBV + placebo for 24 weeks; TMC435 (100 mg or 150 mg) + PegIFN/RBV for 48 weeks; or PegIFN/RBV + placebo for 48 weeks. vBT was observed in 9% patients in TMC435 arms. As shown in Figure 7, relapsers had the best treatment responses in all TMC435 treatment groups (92%-96%), followed by partial responders in TMC435 treatment groups (83%-89%). Null responders had the worst responses in all TMC435 treatment groups (70%-87%). For each group, responses with PegIFN/RBV were less than any TMC435-treated group. Partial responders had an especially poor response with PegIFN/RBV (20%). The investigators stated that treatment-experienced patients who failed PegIFN/RBV achieved significantly greater virologic response rates following treatment with a TMC435-containing regimen compared with placebo. There were no relevant differences in safety or tolerability between TMC435 and placebo groups.

Figure 7. ASPIRE: Virologic Responses at Week 24



Tegobuvir (GS-9190) + GS-9256 ± PegIFN/RBV or RBV

GS-9256, a non-covalent NS3 protease inhibitor, and tegobuvir (GS-9190, TGV), a non-nucleoside NS5B polymerase inhibitor, were studied after initiating follow-up therapy with Peg/RBV alone **[Foster G, et al. Abst. 425]**. The study consisted of treatment-naïve patients with genotype 1a/1b HCV who received GS-9256/TGV (n=15), GS-9256/TGV/RBV (n=13), or GS-9256/TGV/PegIFN/RBV (n=14) for up to 28 days. All 42 patients completed the 28 day oral antiviral phase of the study and initiated PegIFN/RBV standard of care. At week 24,

The 46th Annual Meeting of the European Association for the Study of the Liver (EASL)

Advances in Chronic Hepatitis C Management and Treatment

Jointly sponsored by the Postgraduate Institute for Medicine and ViralEd, LLC.

the percentage of patients who achieved HCV RNA <25 IU/mL was 67% for the GS-9256/TGV only group (n=15), 100% for the GS-9256/TGV + RBV group (n=13) and 92% for the GS-9256/TGV + PegIFN/RBV group (n=14). When GS-9256 and TGV were used for 4 weeks without PegIFN or RBV, it is interesting to note that the virologic response was very low – only 20% of patients achieved HCV RNA <25 IU/mL, compared to 62% with GS-9256/TGV + RBV and 100% with GS-9256/TGV + PegIFN/RBV.

Alisporivir

Alisporivir (DEB025) is an oral cyclophilin inhibitor that targets host proteins with potent pan-genotypic anti-HCV activity. A study reported at EASL evaluated the efficacy and safety of alisporivir combined with PegIFN α-2a/RBV in genotype 1, treatment-naïve CHC patients **[Flisiak R, et al. Abst. 4]**. 288 patients were randomized to receive DEB025 + PegIFN/RBV for 48 weeks (DEB48), DEB025 + PegIFN/RBV for a fixed 24 weeks of treatment (DEB24), DEB025 + PegIFN/RBV in response-guided treatment (DEB-RGT) of 24 weeks for RVR <LOD (HCV RNA ≤10 IU/mL) and 48 weeks for non-RVR patients, or DEB025 placebo + PegIFN/RBV for 48 weeks (control). The endpoint was sustained virological response at 24 weeks (SVR24) of follow-up. SVR24 was reported at EASL to be 79% in the DEB48 arm vs. 55% in the control arm (P=0.008), despite a lower proportion of the IL28B Rs12979860 CC allele in the DEB48 arm (19% vs. 33%, respectively). SVR24 was 69% in the DEB-RGT and 53% in the DEB24 arms respectively. Among patients with at least 12 weeks of treatment, there were no (0/196) null responders in the DEB025 arms versus 10% (7/71) in the control arm. These results demonstrate the superiority of alisporivir combined with PegIFN/RBV in achieving SVR24 in genotype 1 treatment-naïve patients. Treatment with alisporivir was well tolerated and associated with low viral breakthrough.

SILEN-C

This study investigated BI201335, a potent and specific once daily HCV NS3/4A protease inhibitor with antiviral activity in chronic HCV genotype 1 infection **[Sulkowski M, et al. Abst. 66]**. In this trial, 290 HCV genotype 1 patients with non-response to at least 12 weeks of previous PegIFN/RBV treatment (relapsers excluded) received 240 mg BI201335 once daily (QD) with a 3 day lead-in (LI) of PegIFN/RBV (240 mg QD/LI); 240 mg BI201335 once daily (240 mg QD); or 240 mg BI201335 twice daily with a 3 day LI (240 mg BID/LI). In each group, BI201335 was given for 24 weeks together with PegIFN/RBV for 24 or 48 weeks. SVR was assessed at week 12 (SVR12) and week 24. The majority of analyzed patients had CT or TT IL28B genotype (90%). After 24 weeks, the overall response rate (SVR) was 27% in the 240 mg QD/LI group, 41% in the 240 mg QD group, and 31% in the 240 mg BID/LI group. Null responders had a lower SVR than partial responders in all three treatment groups. At 24 weeks, eRVR was similar in all three groups. Adverse events were highest in the 240 mg BID group, with jaundice and rash being the most common.

JUMP-C

Mericitabine (RG7128, MCB) is a selective nucleoside inhibitor of the HCV NS5B RNA-dependent RNA polymerase with activity across all HCV genotypes. Results were presented on the JUMP-C trial, an ongoing phase 2b study in treatment-naïve patients with HCV genotypes 1/4 **[Pockros P, et al. Abst. 1359]**. The trial objective was to compare a RGT regimen of MCB plus PegIFN α-2a/RBV (Arm A) with PegIFN/RBV alone (Arm B). Patients randomized to Arm A achieving an eRVR (HCV RNA <15 IU/mL from weeks 4-22) received MCB (1,000 mg BID) plus standard doses of PegIFN/RBV for 24 weeks. Those not achieving an eRVR in Arm A received 24 weeks of MCB plus PegIFN/RBV followed by a further 24 weeks of PegIFN/RBV. Patients randomized to Arm B received PegIFN/RBV for 48 weeks. The planned interim analysis was presented at EASL. At 24 weeks, virological suppression (HCV RNA <15 IU/mL) was achieved in 74/81 (91%) patients receiving MCB plus PegIFN/RBV compared to 53/85 (62%) receiving PegIFN/RBV alone. In Arm A, 49/81 patients (60%) achieved an eRVR compared with 11/85 (13%) of Arm B. SVR12 was achieved in 37/49 (76%) of patients in Arm A achieving an eRVR; however, an important finding was a relapse rate of 24% (12/49). Among patients in Arm A who consented to host IL28B genotyping, eRVR was achieved in 15/18 CC patients, and 12/15 achieved SVR-12, while 18/33 nonCC patients achieved eRVR, and 13/18 achieved SVR-12. The investigators noted that a good tolerability and safety profile, strong antiviral potency and no evidence of resistance-related breakthrough makes MCB appropriate for further study, including in combination with other DAAs.

BMS-790052 + BMS-650032 ± PegIFN/RBV

A phase IIa study by Lok and associates generated a lot of interest at EASL **[Lok A, et al. Abst. 418]**. The investigators studied the use of two experimental agents: BMS-790052 (an NS5A inhibitor) + BMS-650032 (an HCV PI) ± PegIFN/RBV in HCV genotype 1 null responders to PegIFN/RBV, N=21. Patients received one of two treatments for 24 weeks: BMS-790052 60 mg QD + 1 BMS-650032 600 mg BID, or BMS-790052 60 mg QD + BMS-650032 600 mg BID + PegIFN/RBV. After 24 weeks of therapy, 36.4% (4/11) patients receiving dual therapy (BMS-790052 + BMS-650032) had an SVR, and 100% (10/10) of patients on quad therapy (BMS-790052 + BMS-650032 + PegIFN/RBV) had an SVR. This study was the first to show SVR can be achieved without the use of PegIFN/RBV; however, the efficacy was limited in persons with subtype 1a in which only 2 of 9 subjects achieved SVR. Nonetheless, these data support the pursuit of novel combinations of DAAs for the treatment of HCV in the absence of interferon alfa.