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eViralHepatitis Review
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2011 CONFERENCE COVERAGE OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASE

In this Issue...

As discussed in this review, hepatitis C virus (HCV) infection has overtaken HIV infection as a cause of death in the U.S. Fortunately, treatment of HCV infection continues to improve with the use of the recently approved direct-acting antivirals boceprevir and telaprevir and shorter courses of peginterferon/ribavirin, and a full pipeline of investigational antivirals promises an array of new options and approaches to anti-HCV therapy in short order. In this issue we review findings from epidemiology and HCV treatment studies presented at the 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011). Included in our coverage are new findings on HCV treatment in prior nonresponders, predictors of outcome with telaprevir- and boceprevir-based combination therapy, treatment of patients with HIV/HCV coinfection, and phase 2 clinical trials data on four new drug candidates.

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After participating in this activity, the participant will demonstrate the ability to:

- Identify factors associated with treatment response in prior peginterferon/ribavirin non-responders and previously untreated patients with hepatitis C virus (HCV) infection
- Discuss new clinical trials findings relevant to the management of patients with HCV infection (with and without HIV coinfection)
- Discuss new clinical trials findings relevant to the antiviral management of patients with HIV/HCV coinfection

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THIS ISSUE

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following drugs or products in their presentation: PSI-7977, TMC435, daclatasvir, asunaprevir, and danoprevir.

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COMMENTARY

More than 20 years after the discovery of hepatitis C virus (HCV) as the cause of non-A, non-B hepatitis, this pathogen has emerged as a major cause of morbidity and mortality in many parts of the world, including the United States. Indeed, at the 2011 meeting of the American Association for the Study of Liver Diseases (AASLD), researchers at the Centers for Disease Control and Prevention (CDC) reported that the number of Americans dying of HCV-related disease exceeded the number of deaths attributed to HIV infection in 2007. Consequently, chronic HCV infection represents an urgent public health issue.

However, while the rising tide of deaths from HCV is discouraging, the approval of the first direct-acting antiviral agents (DAAs), boceprevir and telaprevir, in May 2011 marks a major advance in HCV treatment. Treatment with these HCV protease inhibitors in combination with peginterferon and ribavirin is substantially more effective than the prior standard of care and has higher sustained virologic response (SVR) rates in HCV genotype 1-infected persons who have never been treated and those who have failed prior therapy. Consequently, the AASLD updated its practice guidelines for the treatment of HCV genotype 1 infection, establishing boceprevir or telaprevir in combination with peginterferon/ribavirin as the new standard of care.

In parallel to the emergence of boceprevir and telaprevir plus peginterferon/ribavirin, the development of novel oral DAAs for HCV has accelerated dramatically with the presentation of data from studies of new DAAs, both in combination with peginterferon/ribavirin, and importantly, combinations of DAAs in the absence of interferon (i.e., interferon-free regimens). The 2011 AASLD meeting featured cutting-edge scientific presentations on the HCV NS5A replication complex inhibitor, daclatasvir; the second-generation HCV NS3/4A protease inhibitors, TMC-435, BI-1335 and danoprevir; and the potent HCV NS5B nucleotide analog polymerase inhibitor, PSI-7977. The study that generated the greatest interest was unquestionably that of Gane and colleagues, who treated HCV genotype 2/3-infected patients with PSI-7977 plus ribavirin, with or without peginterferon for up to 12 weeks. The results of this small study were stunning: 10 of 10 patients treated with PSI-7977 plus ribavirin for 12 weeks achieved SVR. While these studies are early and much work remains in the development of these novel DAA regimens, 2011 will be remembered as the year the tide was turned on the HCV epidemic.

back to top

THE GROWING BURDEN OF MORTALITY ASSOCIATED WITH VIRAL HEPATITIS IN THE UNITED STATES

Holmberg SD, Ly KN, Xing J, et al. The Growing Burden of Mortality Associated with Viral Hepatitis in the United States, 1999-2007. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 243.

The increasing health burden and mortality attributable to hepatitis B virus (HBV) and to a greater extent hepatitis C virus (HCV) infections are insufficiently appreciated, according to an analysis by Scott Holmberg and colleagues at the U.S. Centers for Disease Control and Prevention (CDC) presented at the 62nd Annual Meeting of the American Association for the Study of Liver Diseases (AASLD 2011).

Dr. Holmberg's team scrutinized nearly 22 million records of multiple-cause deaths from 1999 to 2007 for any mention of HBV, HCV and, for comparison, HIV infection, and assessed age-adjusted mortality rates for each of the three diseases. According to their findings, the number of deaths associated with HCV infection increased significantly each year (+0.18 deaths/100,000 per year), rising to a total of 15,106 deaths in 2007. By comparison, HIV-related deaths declined to 12,734 in 2007. Hepatitis B virus-related mortality remained constant over the study period, at approximately 1800 deaths per year.

Nearly three quarters (73%) of HCV-related deaths and 60% of HBV-related deaths occurred in persons 45 to 64 years old. Several comorbid factors were found to increase the odds of HCV- and HBV-related mortality; these included chronic liver disease (adjusted

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odds ratio [Oradj], 32.1 and 34.4, respectively), coinfection with the other hepatitis virus (Oradj, 29.9 and 31.5, respectively), alcohol-related conditions (Oradj, 4.6 and 3.7, respectively), and HIV-coinfection (Oradj, 1.8 and 4.0, respectively). Speaking to his group's finding that HCV infection had overtaken HIV infection as a cause of death in the U.S., Dr. Holmberg concluded that new policy directions with regard to HCV testing and treatment will be required to achieve declines in mortality similar to those seen with HIV.

back to top

NEW FINDINGS ON HCV TREATMENT WITH APPROVED AGENTS

Pol S, Roberts SK, Andreone P, et al. Efficacy and safety of telaprevir-based regimens in cirrhotic patients with HCV genotype 1 and prior peginterferon/ribavirin treatment failure: subanalysis of the REALIZE phase III study. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 31

Vierling JM, Flamm SL, Gordon SC, et al. Efficacy of boceprevir in prior non-responders to peginterferon/ribavirin: The PROVIDE Study. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract 931

Though we will not be addressing policy initiatives or the topic of screening in this program, the reader is probably aware that important recent developments in the medical management of HCV infection—namely the advent of the approved direct acting antivirals telaprevir and boceprevir—have significantly improved the success of anti-HCV therapy with regard to sustained virologic response (SVR) and cure rates, even in difficult-to-treat scenarios, such as gentotype 1 HCV infection, patients with advanced liver disease (e.g., cirrhosis), and previous nonresponders to standard therapy with peginterferon and ribavirin.

This latter assertion was borne out by a subanalysis of the phase 3 REALIZE study presented at AASLD 2011, in which Stanislas Pol of Université Paris Descartes and colleagues studied the efficacy and safety of telaprevir-based therapy (i.e., telaprevir plus peginterferon/ribavirin) in cirrhotic patients with genotype 1 HCV infection and prior peginterferon/ribavirin treatment failure.

Patients in the REALIZE study were randomized to 48 weeks of standard peginterferon/ribavirin therapy or one of two telaprevir regimens (results for the two telaprevir regimens were pooled in the cirrhosis subanalysis):

• 12 weeks of telaprevir/peginterferon/ribavirin followed by 36 weeks of peginterferon/ribavirin, or

• 4 weeks peginterferon/ribavirin lead-in followed by 12 weeks of telaprevir/peginterferon/ribavirin followed by 32 weeks of peginterferon/ribavirin.

Of the 662 HCV genotype 1-infected patients with prior treatment failure enrolled in the REALIZE study, 143 patients were identified with fibrosis stage 4 (F4) cirrhosis. As a group, cirrhotic subjects were slightly older (54 vs 50 years) and were more likely to be prior peginterferon/ribavirin nonresponders (36% vs 25%), but less likely to be relapsers (43% vs 57%), than their noncirrhotic counterparts. Overall, patients who received telaprevir had significantly higher SVR rates than those who did not. Among cirrhotic patients, SVR was achieved by 49% in the telaprevir group, compared to 8% in the pegintereferon/ribavirin-only control group. Noncirrhotic patients fared much better in the study, however; SVR was achieved by 72% of subjects with absent, minimal, or moderate fibrosis who received telaprevir, versus 20% of subjects who received pegintereferon/ribavirin alone.

Similar virologic response rates were observed in a separate study in which HCV genotype 1-infected patients who had previously failed pegintereferon/ribavirin therapy were subsequently started on 44 weeks of boceprevir/peginterferon/ribavirin triple therapy. John Vierling of Baylor College of Medicine and his colleagues enlisted 48 subjects who had received at least 12 weeks of pegintereferon/ribavirin in one of two other comparative

treatment studies (SPRINT-2, RESPOND-2) and failed to achieve a SVR (<2 log10 copies/mL decline in HCV RNA at week 12). The results of a preliminary subset analysis of these previous null responders in the ongoing PROVIDE study were presented at AASLD 2011 by coinvestigator Michelle Treitel.

The study group was 65% male, 67% white; mean age was 51 years (range, 25-66 years). Mean baseline viral load was 6.5 log10 IU/mL, and 87% of patients had baseline HCV RNA levels >800,000 IU/mL; 48% had HCV genotype 1a, 30% genotype 1b, and 22% undetermined subtype 1. There was little advanced liver disease in the study group; only 8% of patients had fibrosis scores > F2.

Patients were treated with boceprevir 800 mg three times daily with food, peginterferon 1.5 µg/kg/week by subcutaneous injection, and weight-based twice-daily ribavirin (600-1400 mg/day). Patients who had been off pegintereferon/ribavirin for more than two weeks received four weeks of peginterferon/ribavirin induction therapy before adding boceprevir. The primary endpoint was undetectable HCV RNA (< 9.3 IU/mL) on triple therapy at weeks 24 and 44 (end of treatment [EOT]). Results are summarized in the table below.

TABLE 1. Previous Null Responders with Undetectable HCV RNA

Weeks of Boceprevir	% (n/N) with HCV RNA (<9.3 IU/mL)
12	48 (20/42)
24	45 (19/42)
44 (EOT)	41 (17/41)

On the basis of these findings, the investigators concluded that prior null responders retreated with peginterferon/ribavirin plus boceprevir frequently achieve viral negativity. Further, Dr. Treitel reported that virologic responses at week 4 of peginterferon/ribavirin induction therapy were predictive of SVR rates, with 50% of patients who experienced a 1 log10 or greater drop in HCV RNA achieving SVR, compared with 34% of patients with viral load reductions < 1 log10 after 4 weeks of peginterferon/ribavirin.

back to top

PREDICTORS OF OUTCOME OF THERAPY FOR HCV INFECTION

Bacon BR, Bruno S, Schiff ER, et al. Predictors of Sustained Virologic Response (SVR) among Poor Interferon (IFN) Responders when Boceprevir (BOC) Is Added to Peginterferon Alfa-2b/Ribavirin (PR). 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011). San Francisco, November 4-8. 2011. Abstract 33.

T Berg, P Andreone, S Pol, et al. Predictors of Virologic Response with Telaprevir-based Combination Treatment in HCV Genotype 1-infected Patients with Prior Peginterferon/ribavirin Treatment Failure: Post-hoc Analysis of the Phase III REALIZE Study. 62nd Annual Meeting of the American Association for the Study of Liver Disease (AASLD 2011). San Francisco, November 4-8. 2011. Abstract 32.

Though virologic response during the peginterferon/ribavirin induction phase of treatment is a strong predictor of eventual SVR with boceprevir triple therapy, approximately one-third of boceprevir-treated patients with poor induction phase responses do go on to achieve and sustain HCV negativity through the end of treatment. In a post hoc analysis of pooled patient data from the two boceprevir studies described above, Bruce Bacon from St. Louis University School of Medicine and his colleagues looked at factors that predicted eventual SVR among 192 treatment-naive patients and 90 previously treated patients (in the SPRINT-2 and RESPOND-2 studies, respectively) who exhibited poor early virologic responses to the four-week peginterferon/ribavirin induction phase of therapy (i.e., < 1 log10 decline in HCV RNA).

The investigators identified several baseline and early treatment factors that were predictive of eventual SVR in poor interferon responders. In both study populations, patients with HCV subtype 1b (vs subtype 1a) were significantly more likely to achieve SVR (P=0.028 [SPRINT-2]; = 0.001 [RESPOND-2]). Among treatment-naive patients (SPRINT-2), those with mild to moderate or no liver fibrosis (≤ F2) at baseline were more likely to achieve SVR than patients with advanced fibrosis and cirrhosis (P = 0.025). Virologic response at treatment week 8 (i.e., four weeks after the addition of boceprevir) was highly predictive of SVR; no patient in either study with < 3 log10 decline in HCV RNA at week 8 went on to achieve SVR.

A similar post *hoc* study of baseline and on-treatment predictors of SVR to telaprevir-based triple therapy was presented by Thomas Berg of Universitätsklinikum Leipzig. Dr. Berg and his colleagues examined the effect of baseline patient characteristics and on-treatment responses at weeks 4 and 12 on SVR rates among HCV genotype 1-infected patients with prior peginterferon/ribavirin failure who received combination therapy with telaprevir plus peginter-feron/ribavirin or peginterferon/ribavirin alone in the pivotal REALIZE study.

Data were available for 578 subjects, of whom 28%, 19% and 53% were prior null responders, partial responders, or relapsers, respectively; 69% were male; 5% were black; mean age was 51 years. Eighty-eight percent of patients had HCV RNA levels ≥ 800,000 IU/mL and 25% had cirrhosis. Mean low density lipoprotein (LDL) level was 2.6 mmol/L.

Baseline factors predictive of SVR included prior response to peginterferon/ribavirin (relapse vs. null or partial response; P < 0.0001), LDL level (P < 0.0001), and fibrosis stage, the effect of which was most prominent in prior nonresponders retreated with telaprevir (OR = 0.60 [0.45, 0.81]) and prior relapsers retreated with peginterferon/ribavirin (OR = 0.41 [0.20,0.81]). Baseline HCV RNA levels were predictive of SVR in patients who did not receive telaprevir, irrespective of type of prior response (P < 0.05), but was not significant among telaprevir-treated patients. On-treatment response, as defined by eRVR (undetectable HCV RNA at weeks 4 and 12), was found to be the strongest predictor of SVR (OR = 7.8 [4.7,12.9]).

back to top

TREATMENT OF HIV/HCV COINFECTED PATIENTS

Sherman KE, Rockstroh JK , Dieterich DT, et al. Telaprevir Combination with Peginterferon Alfa-2a/Ribavirin in HCV/HIV Coinfected Patients: 24-Week Treatment Interim Analysis. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8. 2011. Abstract LB-8.

Labarga P, Téllez M, Barreiro P, et al. The PERICO Trial: A Multicenter Randomized Controled Trial Comparing High Ribavirin (RBV) Induction vs. Standard RBV Dosing in the

Treatment of Chronic Hepatitis C in HIV-Coinfected Patients. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, November 4-8. 2011. Abstract 247.

Patients who are coinfected with both HIV and HCV tend to experience more rapid HCV disease progression and do not respond as well to standard interferon-based therapy. In a late breaking study presented at AASLD 2011, Kenneth Sherman from the University of Cincinnati College of Medicine and his colleagues sought to examine whether improvements in SVR rates achieved with telaprevir triple therapy in genotype 1 HCV monoinfected patients would extend to patients coinfected with HIV.

Dr. Sherman presented a 24-week interim analysis from an ongoing trial comparing telaprevir triple therapy versus standard peginterferon/ribavirin therapy in HIV/HCV coinfected patients. The study enrolled two groups of patients: antiretroviral therapy (ART)-naive patients with CD4 cell counts > 500 cells/mm3 (Part A) and patients receiving stable ART with either efavirenz or boosted atazanavir plus tenofovir/emtricitabine (Part B); patients in the latter group had undetectable HIV RNA and CD4 cell counts >300 cells/mm3. No patient in either group had been previously treated for HCV.

In both parts participants were randomly assigned to receive either telaprevir triple therapy or peginterferon/ribavirin therapy for 48 weeks. Triple therapy consisted of telaprevir 750 mg (1125 mg for patients taking efavirenz) thrice daily plus 180 mcg/week pegylated interferon alfa-2a plus ribavirin 800-1200 mg/day. Standard therapy consisted of the same doses of peginterferon and ribavirin. According to predefined futility rules, treatment was discontinued for patients who failed to show adequate responses to therapy (i.e., viral breakthrough or < 2 log10 decline in HCV RNA at week 12).

The interim analysis was based on data from 60 of 62 patients enrolled who received at least one dose of study drug: 13 in Part A (no ART) and 47 in Part B (ART). Forty-four patients reached week 24 on the study drug. Mean age was 46 years; 88% were male, 27% were black, 68% had subtype 1a; 3.3% had cirrhosis. At baseline, 92% and 81% of Part A and B patients had HCV RNA ≥ 800,000 IU/ml; mean CD4 counts were 690 cells/mm3 and 562 cells/mm3, respectively.

Of the 16 patients who did not reach week 24 on the study drug, six met a futility rule (including two HCV breakthroughs on telaprevir). Three telaprevir-treated patients in Part B experienced a serious adverse event (cholelithiasis, jaundice, hemolytic anemia) that led to discontinuation of one or more study drugs.

Overall, at 24 weeks, significantly higher on-treatment responses were observed in patients treated with telaprevir-based triple therapy compared to standard therapy; the results are summarized in Table 2.

TABLE 2. Patients with Undetectable HCV RNA at Week 24 (%)

	Telaprevir Triple Therapy	Standard Therapy
No ART	86	33
Efavirenz-based ART	75	50
Atazanavir-based ART	67	75
Total	**71**	**55**

Generally, patients who received telaprevir triple therapy experienced more side effects than patients who received standard therapy. Adverse events that occurred ≥ 10% more frequently among patients receiving telaprevir included abdominal pain, vomiting, nausea, pyrexia, dizziness, depression, and pruritus. Bilirubin adverse events occurred more frequently in ATV/r patients (27% vs. 0%), as did indirect hyperbilirubinemia. No severe rashes were reported.

Another approach to achieving higher SVR rates among patients with HIV/HCV coinfection proved less fruitful. Vincent Soriano from Hospital Carlos III in Madrid and his colleagues

investigated whether greater ribavirin exposure, particularly early in the course of therapy, might improve virologic outcomes in HIV/HCV coinfected patients.

The PERICO study included 365 HIV/HCV coinfected participants who were randomized to receive peginterferon alfa-2a 180 mcg/week plus ribavirin 1000-1200 mg/day (weight-adjusted) or ribavirin 2000 mg/day. Patients in the high-dose ribavirin arm took the 2000 mg/day dose, along with weekly erythropoietin injections, for four weeks, at which point ribavirin was reduced to standard 1000-1200 mg/day doses and erythropoietin was discontinued. Patients with rapid virologic response (RVR) at week 4 were treated for the standard duration of 24 weeks (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4); patients without RVR were treated for 48 or 72 weeks, respectively. Treatment was discontinued in the event of an inadequate virologic response or HCV RNA breakthrough at weeks 12 or 24.

Overall, there was no significant difference in efficacy between the high-dose induction and standard ribavirin arms: SVR rates at 24 weeks were 43% and 47%, respectively, by intent-to-treat analysis and 53% and 57%, respectively, in the on-treatment analysis. Treatment was discontinued early by approximately half of patients in both arms, primarily because of virologic failure.

As expected, better virologic responses in both arms were associated with HCV genotype (82% for genotype 2/3 vs. 36% for genotype 1/4), IL28B gene pattern (74% for CC vs.

35% for CT/TT), and baseline HCV RNA <500,000 IU/mL (61% vs. 39% for HCV RNA ≥ 500,000 IU/mL). Rapid virologic response at week 4 and completion of the planned duration of therapy were most strongly correlated with SVR in this study population, regardless of ribavirin dose.

back to top

INVESTIGATIONAL AGENTS FOR THE TREATMENT OF HCV INFECTION

Hezode C, Hirschfield GM, Ghesquiere W, et al. BMS-790052, A NS5A Replication Complex Inhibitor, Combined with Peginterferon Alfa-2a and Ribavirin in Treatment-Naive HCV- Genotype 1 or 4 Patients: Phase 2b AI444010 Study Interim Week 12 Results. 62nd Annual Meeting of the American Association for the Study of Liver Disease. San Francisco, November 4-8, 2011. Abstract 227.

Terrault N, Cooper C; Balar LA, et al. High Sustained Virologic Response (SVR24) Rates with Response-Guided Danoprevir (DNV; RG7227) Plus PegIFN α-2a (40KD) and Ribavirin (P/R) in Treatment-naive HCV Genotype 1 (G1) Patients: Results from the ATLAS Study. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, November 4-8. 2011. Abstract 79.

Fried M, Buti M, Dore GJ, et al. TMC435 in Combination with Peginterferon and Ribavirin in Treatment-Naive HCV Genotype 1 Patients: Final Analysis of the PILLAR Phase IIb Study. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, November 4-8. 2011. Abstract LB-5.

Lawitz E, Lalezari JP, Hassanein T, et al. Once-Daily PSI-7977 Plus Peg/RBV in Treatment-naïve Patients with HCV GT1: Robust End of Treatment Response Rates are Sustained Post-treatment. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, November 4-8. 2011. Abstract 225

The sessions and studies presented at AASLD 2011 evidenced an HCV drug pipeline fully loaded with second-generation direct-acting antiviral agents (DAA) that promise to continue the relegation of standard interferon-based therapy's efficacy problems to the past. Data from phase 2 trials of four investigational direct-acting antiviral agents (DAA) used in conjunction with pegintereferon/ribavirin were separately presented.

Christophe Hézode of CHU Henri Mondor, Creteil, France, presented interim data from the international AI444010 study of the NS5A replication complex inhibitor daclatasvir plus peginterferon/ribavirin as initial therapy for HCV infection. The analysis included 395 previously untreated patients, most of whom with HCV genotype 1 (75% had genotype 1a). Patients were randomized to once-daily daclatasvir 20 mg, daclatasvir 60 mg or placebo plus peginterferon/ ribavirin for either 24 or 48 weeks. Patients with good virologic responses at weeks 4 (HCV RNA < 25 IU/mL) and 10 (undetectable HCV RNA) were randomized a second time to either triple therapy for another 12 weeks (24 weeks total) or 12 weeks of peginterferon/ribavirin alone.

The majority of patients in the daclatasvir 20 mg (71%) and 60 mg (72%) arms were eligible for shorter therapy. Of patients who received 12 weeks of triple therapy followed by 12 weeks of peginterferon/ribavirin alone, 96% and 94% had undetectable HCV RNA at week 24 in the daclatasvir 20 mg and 60 mg arms, respectively. Of patients who received triple therapy for all 24 weeks, end-of-treatment response rates were 88% and 100%, respectively. The safety profile of daclatasvir at both dosages was comparable to placebo.

Similar outcomes were found in a similarly designed trial of triple therapy including the HCV NS3/4A protease inhibitor danoprevir. Norah Terrault from the University of California at San Francisco presented the final results of the ATLAS trial, which evaluated danoprevir at doses of 300 mg thrice-daily, 600 mg twice-daily, and 900 mg twice-daily versus placebo, all in combination with peginterferon/ribavirin. Two-hundred twenty-five treatment-naive genotype 1 patients were included in the analysis, of whom 60% were male, 10% were black, 82% had baseline HCV RNA ≥ 800,000 IU/mL; and 62% were infected with HCV genotype 1a. All patients received triple therapy (or placebo) for 12 weeks, followed

by an additional 12 weeks of peginterferon/ribavirin. Patients with extended rapid virologic response (eRVR), defined as undetectable HCV RNA (< 15 IU/mL) throughout weeks 4 to 20, stopped all treatment at week 24; patients without eRVR continued on peginterferon/ribavirin through week 48. Overall, very high SVR rates were achieved with response-guided danoprevir triple therapy. The results are summarized in Table 3.

TABLE 3. Virologic Responses to Danoprevir or Placebo (%)

	DNV 300mg	DNV 600mg	DNV 900mg	PBO
Overall SVR-24	68	83	76	43
eRVR (DVR arms only)	65	79	18	N/A
SVR-24 in eRVR patients	87	95	89	N/A

The 900 mg danoprevir dose was discontinued early because of exposure-related, reversible alanine aminotransferase (ALT) elevations. Studies are currently being conducted with lower doses of danoprevir boosted with ritonavir to reduce overall danoprevir exposure while retaining the drug's potent antiviral activity.

Strong virologic outcomes were demonstrated with another HCV NS3/4A protease inhibitor, TMC435. Michael Fried of the University of North Carolina at Chapel Hill presented final results of the PILLAR trial, which evaluated two once-daily doses of TMC435 (75 mg and 150 mg) versus placebo. Within each TMC435 dosing group, patients were randomly assigned to receive 12 or 24 weeks of the drug. All patients were also given peginterferon/ribavirin at standard doses for at least the first 24 weeks of the study. Patients with unquantifiable HCV RNA at week 4 and sustained undetectable HCV RNA levels from weeks 12 through 20 could stop treatment at that point; patients who did not meet this criteria continued on peginteferon/ribavirin for an additional 24 weeks (48 weeks total). The primary endpoint was SVR at week 72 (24 weeks post-therapy). A second efficacy endpoint was complete early virologic response (cEVR) at week 12.

Three hundred eighty-six previously untreated patients with HCV genotpye 1 infection were enrolled in the study. Overall, patients in the four TMC435 arms had significantly higher cEVR and SVR rates, as summarized in the table below.

TABLE 4. Virologic Response Rates With TMC435 or Placebo

	cEVR at Week 12 (%)	SVR at Week 72 (%)
TMC435 75 mg, 12 weeks	91	82
TMC435 75 mg, 24 weeks	93	75
TMC435 150 mg, 12 weeks	94	81
TMC435 150 mg, 24 weeks	95	86
Control	56	65

The highest response rates were seen in patients who qualified for shorter treatment: 82%, 81%, 79%, and 86% of patients in the four TMC435 arms, respectively, met the criteria for shorter treatment; of these, 91%, 85%, 93%, and 96% achieved SVR. TMC435 was generally safe and well tolerated, with fewer discontinuations occurring in the treatment arms than in the control arm.

Eric Lawitz from Alamo Medical Research, San Antonio, Texas, presented an analysis of 121 treatment-naive HCV genotype 1-infected patients enrolled in the PROTON study of the once-daily uridine nucleotide analog HCV polymerase inhibitor, PSI-7977.

Participants were randomized to receive 200 mg (n = 48) or 400 mg (n = 47) once-daily PSI-7977 or placebo (n = 26) plus peginteferon/ribavirin for 12 weeks. Patients with extended rapid virological responses (eRVR), defined as undetectable HCV RNA levels throughout week 4 to week 12, continued with another 12 weeks of peginterferon/ribavirin (24 weeks total); patients who did not meet this criterion continued on peginteferon/ribavirin for an additional 36 weeks (48 weeks total).

Overall, very high RVR, end-of-treatment (week 12) response, and SVR rates were achieved with response-guided triple therapy with PSI-7977. All but one patient who received PSI-7977 at either dose qualified for the shorter treatment course. Ninety-eight percent and 91% of patients in the two PSI-7977 arms had undetectable HCV RNA at weeks 4 and 12, respectively, compared with 19% and 50% of patients in the control arm. Sustained virologic response rates at 12 weeks post-treatment were 88% and 91% in the 200 mg and 400 mg PSI 7977 arms, respectively. (Patients in the control arm were still undergoing follow-up for SVR.) The superior efficacy of the 400 mg over the 200 mg dose was demonstrated by three viral breakthroughs (which occurred during weeks 12 and 24 of peginterferon/ribavirin treatment) and one relapse in the 200 mg group, compared with no breakthrough or relapse in the 400mg group. The safety profile of PSI-7977 was comparable to placebo in this study.

back to top

ON THE PATH TO INTERFERON-FREE THERAPY FOR HCV INFECTION

Gane EJ, Stedman CA, Hyland RH, et al. Once Daily PSI-7977 plus RBV: Pegylated interferon-Alfa not required for Complete Rapid viral response in Treatment-naive Patients with HCV GT2 or GT3. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, November 4-8. 2011. Abstract 34.

Chayama K, Takahashi S, Kawakami Y, et al. Dual Oral Combination Therapy with the NS5A Inhibitor BMS-790052 and the NS3 Protease Inhibitor BMS-650032 Achieved 90%

Sustained Virologic Response (SVR12) in HCV Genotype 1b-Infected Null Responders. 62nd Annual Meeting of the American Association for the Study of Liver Diseases. San Francisco, November 4-8. 2011. Abstract LB-4

The most talked-about study results presented at AASLD 2011 were from two trials that explored the use of all-oral, interferon-free anti-HCV regimens in previously untreated patients with HCV genotype 2/3 infection (ELECTRON Study) and in prior null responders with HCV genotype 1b infection (Study AI447-017), respectively.

Edward Gane from the New Zealand Liver Transplant Unit in Aukland, New Zealand, presented 12-week post-treatment (SVR-12) data from the ELECTRON study, in which 40 treatment-naive, noncirrhotic patients with HCV genotype 2 or 3 received 400 mg PSI-7977 and ribavirin once daily for 12 weeks, plus 4, 8, or 12 weeks peginterferon or no interferon at all (total, 4 arms). The intent of the study was to determine the shortest duration of interferon therapy that would prove effective in conjunction with dual PSI-7977/ribavirin therapy. The answer, it turned out, was that interferon appeared to be superfluous in this relatively easy-to-treat population: 10 of 10 (100%) patients randomized to interferon-free PSI-7977/ribavirin therapy achieved and sustained SVR through 12 weeks post-treatment (100% SVR-12 rates were achieved in all four treatment arms, regardless of interferon exposure). Results are summarized in the table below.

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Table 5. Virologic Response Rates with PSI-7977/Ribavirin Plus/Minus Interferon

	PSI-7977/RBV							
	12 weeks PEG		8 weeks PEG		4 weeks PEG		No PEG	
Time (Week)	n	%<LOD	n	%<LOD	n	%<LOD	n	%<LOD
2	9/11	82	7/8	88	8/9	89	8/10	80
4	11/11	100	10/10	100	9/9	100	10/10	100
8	11/11	100	10/10	100	9/9	100	10/10	100
12	11/11	100	10/10	100	9/9	100	10/10	100
SVR4	11/11	100	10/10	100	9/9	100	10/10	100
SVR12	11/11	100	10/10	100	9/9	100	10/10	100

Gane and colleagues concluded that once-daily PSI-7977 400 mg administered with ribavirin for 12 weeks was very well tolerated, with no attributable safety issues observed and no discontinuations and was highly potent in patients with HCV genotype 2/3 infection, of whom 100% (40/40) achieved rapid (week 4) and sustained virologic responses in this study, irrespective of interferon use. The absence of any viral breakthrough in this and other studies of PSI-7977 is also encouraging, evidencing a high barrier to resistance.

Finally, Kazuaki Chayama from Hiroshima University, Hiroshima, Japan, presented 48-week data from an ongoing open-label trial (AI447-017) of an interferon-free, dual oral combination of the NS5A replication complex inhibitor daclatasvir plus the NS3 protease inhibitor asunaprevir in noncirrhotic Japanese adults with HCV genotype 1b infection who had previously failed to respond to peginterferon/ribavirin therapy. Participants received oral daclatasvir/asunaprevir for 24 weeks and were followed for another 24 weeks. Though the study was small (n = 10), the findings were striking: 9 of 10 (90%) patients completed 24 weeks of treatment and had persistently undetectable HCV RNA levels through 24 weeks post-treatment (SVR-24). The remaining patient, who stopped treatment after two weeks because of grade 4 hyperbilirubinemia, also had undetectable HCV RNA after 24 weeks' follow-up, despite having detectable viremia at the time of discontinuation. One other patient experienced a grade 3 adverse event (pyrexia) and two patients had mild and transient ALT elevations; diarrhea and headache were the most common complaints among patients in this study. There was no instance of viral breakthrough during the study and no correlation was found between baseline resistance-related polymorphisms and virologic outcomes.

Chayama and colleagues concluded that daclatasvir/asunaprevir therapy was generally well tolerated, with a side-effect profile that compared favorably with historical experience with interferon-based therapy, and that high cure rates are achievable with combination DAA therapy—without interferon—in patients with HCV genotype 1b infection.

back to top

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