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Recent Advances in Hepatitis C: Highlights from the 2010 AASLD Meeting

A Review of Selected Presentations from the
61st Annual Meeting of the American Association
for the Study of Liver Diseases
October 29–November 2, 2010
Boston, Massachusetts

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Target Audience: This activity has been designed to meet the educational needs of gastroenterologists, hepatologists, nurses, and other healthcare professionals involved in the treatment of patients with hepatitis C.

Statement of Need/Program Overview: With the commercial launch of 2 new hepatitis C drugs anticipated in the near future, there is a distinct educational need in the hepatology community for an updated understanding of these agents. Throughout the year, various abstracts and posters are presented at major medical meetings that address new treatment strategies, comparisons between different therapies, clinical trial data, retrospective data on real-world clinical experience, etc. Unfortunately, physicians at the major meetings cannot attend all of the poster sessions in their therapeutic area. A compendium of abstracts is vital to help disseminate important new treatment and management options.

Educational Objectives: After completing this activity, the participant should be better able to:

1. Describe effective, individualized treatment strategies for patients with chronic hepatitis C virus (HCV) infection.
2. Explain the latest developments in the treatment of HCV infection.
3. Assess the potential clinical implications of new anti-HCV agents in patients with chronic HCV infection using findings from clinical trials evaluating these agents.

Faculty: Robert S. Brown, Jr., MD, MPH, is Frank Cardile Professor of Medicine and Surgery and Chief of the Center for Liver Disease and Transplantation at Columbia University College of Physicians and Surgeons, New York Presbyterian Hospital/Columbia University Medical Center in New York, New York.

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Introduction

Hepatitis C virus (HCV) infection is a common blood-borne infection that can result in serious long-term consequences, including cirrhosis, hepatocellular carcinoma (HCC), liver failure, and the need for liver transplantation. Approximately 4.1 million individuals in the United States test positive for anti-HCV antibodies, and 3.2 million individuals have chronic HCV infection.[1] The goal of treatment for chronic HCV infection is to achieve sustained virologic response (SVR), defined as undetectable HCV RNA levels 6 months after completing treatment. Attaining SVR has been shown to be durable (ie, equivalent to cure), to slow disease progression, and to reduce mortality.

Currently, standard treatment for HCV infection is combination therapy with peginterferon α-2a or -2b and ribavirin; this treatment is associated with SVR rates of approximately 54–63% in previously untreated patients.[2-4] Response to and duration of treatment varies by genotype. In patients with genotype 2 or 3 HCV infection, a 24-week course of peginterferon and ribavirin induces SVR in nearly 80% of patients.[5] In contrast, patients with genotypes 1 and 4 typically require at least 48 weeks of treatment, and most (50–60%) do not attain SVR.

Since at least half of genotype 1 patients do not achieve SVR with peginterferon and ribavirin, alternative treatments continue to be tested. In recent years, researchers have developed therapeutic agents that directly target HCV. The direct-acting antivirals (DAAs) that have been most widely studied are the protease inhibitors, telaprevir and boceprevir, which inhibit the HCV enzymes NS3/NS4 and NS3, respectively, causing a disruption of HCV replication.

Telaprevir has demonstrated significant efficacy in combination with peginterferon and ribavirin in several large trials. The PROVE1 study evaluated the addition of telaprevir to peginterferon and ribavirin in patients with genotype 1 HCV infection. SVR rates were 41% in patients receiving the combination of peginterferon and ribavirin alone, 61% in patients receiving telaprevir for 12 weeks plus peginterferon and ribavirin for 24 weeks, and 67% in patients receiving telaprevir for 12 weeks plus peginterferon and ribavirin for 48 weeks (P=.02 and P=.002, respectively).[6] The PROVE3 study demonstrated the efficacy of telaprevir in patients with previously treated genotype 1 HCV infection. In this study, patients who did not attain SVR with peginterferon and ribavirin were re-treated with telaprevir plus peginterferon and ribavirin; re-treatment with this triple combination was significantly more effective than re-treating with peginterferon and ribavirin alone.[7]

The other widely studied protease inhibitor, boceprevir, has also demonstrated efficacy in several trials. The SPRINT-1 study was a randomized, open-label, phase II trial evaluating the safety and efficacy of boceprevir plus peginterferon and ribavirin in treatment-naïve patients with genotype 1 HCV infection.[8] In the first part of this study, 520 patients were randomized to receive either a combination of peginterferon and ribavirin alone or 1 of 4 regimens containing boceprevir in addition to peginterferon and ribavirin. Part 2 of this study evaluated the feasibility of using peginterferon with a lower dose of ribavirin, which could help to reduce the risk of anemia-related complications. This study found that all boceprevir-containing regimens were significantly superior to peginterferon and ribavirin alone, with SVR rates of 54–75% versus 38%, respectively, but lower doses of ribavirin were not as effective as full-dose ribavirin with peginterferon and boceprevir.

In 2008, Schiff and colleagues reported on the activity of boceprevir plus peginterferon and ribavirin in select treatment-experienced patients with genotype 1 HCV infection, in particular those with some initial response to peginterferon and ribavirin.[9] In patients who had failed treatment with peginterferon and ribavirin, the combination of peginterferon, ribavirin, and boceprevir was associated with an SVR rate of 14%. In this dose-ranging study, no patients received the full treatment duration of boceprevir (>24 weeks) at the 800-mg dose that is used today. Lower doses of boceprevir were found to be less effective and associated with more resistance, which supported the use of the higher, 800-mg dose. Early response to therapy, defined as undetectable HCV RNA levels within 5 weeks, was a major predictor of SVR.

Another recent area of interest has been the exploration of how genetics influence response to treatment. Individuals of European ancestry are more likely than those of African ancestry to attain SVR with peginterferon and ribavirin, and genetic studies have revealed that approximately half of this difference is explained by a polymorphism near the *interleukin (IL)-28B* gene, which encodes interferon-λ3.[10,11] Thus, recent studies have focused on

assessing the role of IL-28B polymorphisms in determining response to therapy with these new agents.

Finally, recent studies have investigated how to best apply these new agents, either by using them in combination with other therapies, optimizing treatment durations and regimens in different patient populations, and/or identifying factors associated with response to therapy. The results of such studies were presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), which was held October 29–November 2, 2010, in Boston, Massachusetts. Highlights of several key studies are presented in the following pages.

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Importance of Sustained Virologic Response

797 High Correlation Between Week 4 and Week 12 as the Definition for Null Response to Peginterferon Alfa (PEG) Plus Ribavirin (R) Therapy: Results from the IDEAL Trial

F Poordad, MS Sulkowski, JG McHutchison, BR Bacon, J McCone, JM Vierling, S Noviello, N Boparai, JK Albrecht, CA Brass

In the IDEAL study, 3,070 treatment-naïve patients with genotype 1 HCV infection received up to 48 weeks of treatment with 1 of 3 regimens: peginterferon α-2b (1.0 or 1.5 µg/kg/week) plus ribavirin (800–1,400 mg/day) or peginterferon α-2a (180 µg/week) plus ribavirin (1,000–1,200 mg/day). In the current analysis, Poordad and colleagues evaluated data from patients enrolled in the IDEAL study to determine the concordance between virologic response at Weeks 4 and 12. A null response was defined as a failure to achieve an HCV RNA decline of at least 1 $\log_{10}$ IU/mL at Week 4 or a decline of at least 2 $\log_{10}$ IU/mL at Week 12.

The investigators found high positive correlations between the change in HCV RNA levels at Weeks 4 and 12 for all peginterferon and ribavirin regimens. A null response at Week 12 corresponded to an HCV RNA decline of 0.7–1.1 $\log_{10}$ IU/mL at Week 4 in patients receiving peginterferon α-2b (1.5 µg/kg/week) plus ribavirin. The concordance rate for attaining a null or non-null response at both time points was 89% overall, with similarly high rates across the study's 3 treatment arms (Table 1). In a pooled analysis of patients in all 3 treatment arms, concordance rates at Weeks 4 and 12 according to IL-28B genotype were 98% in patients with CC alleles and 83% in patients with CT/TT alleles. The more unfavorable allele was present in almost all patients with a null response at Week 4 or 12.

The investigators concluded that a viral load decline of less than 1 $\log_{10}$ IU/mL at Week 4 is roughly similar to a decline of less than 2 $\log_{10}$ IU/mL at Week 12. Therefore, Week 4 null response may provide an early method of predicting null response, which could help guide early treatment decisions.

213 Impact of Sustained Virologic Response to Pegylated Interferon/Ribavirin on All-Cause Mortality by HCV Genotype in a Large Real-World Cohort: The US Department of Veterans Affairs' Experience

L Backus, DB Boothroyd, BR Phillips, LA Mole

SVR is a well-recognized treatment goal in HCV, but the extent to which SVR reduces the risk of death has not been fully explored in a community setting. Moreover, the effect of SVR on mortality according to genotype has not been well documented. To explore these issues, Backus and colleagues at the Center for Quality Management in Public Health in Palo Alto, California, compared

Table 1. Concordance Between Weeks 4 and 12 Null Response in Peginterferon α and Ribavirin-treated Patients

Outcome	Week 12 null response peginterferon α-2b (1.5 µg/kg/week) and ribavirin			Week 12 null response peginterferon α-2a (180 µg/week) and ribavirin			Week 12 null response peginterferon α-2b (1.0 µg/kg/week) and ribavirin		
	All patients	IL-28B CC	IL-28B CT/TT	All patients	IL-28B CC	IL-28B CT/TT	All patients	IL-28B CC	IL-28B CT/TT
Week 4 null response, n	150	5	68	14	4	70	235	4	113
Week 4 non-null response, n	55	0	30	52	0	9	69	5	31
Concordance	88%	100%	81%	91%	100%	88%	87%	95%	81%

IL=interleukin.

Table 2. Effect of Sustained Virologic Response on Risk of Death from Any Cause in Patients with Hepatitis C Virus (HCV)

	Genotype 1 HCV		Genotype 2 HCV		Genotype 3 HCV	
Analysis	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**	**Hazard ratio (95% CI)**	***P*-value**
Unadjusted	0.45 (0.39–0.52)	<.0001	0.50 (0.38–0.65)	<.0001	0.30 (0.22–0.40)	<.0001
Adjusted for confounding factors	0.67 (0.56–0.79)	<.0001	0.63 (0.45–0.86)	.004	0.45 (0.32–0.65)	<.0001

CI=confidence interval.

outcomes according to SVR status in patients infected with HCV genotypes 1, 2, and 3. All subjects were in the US Department of Veterans Affairs' Clinical Case Registry, had started treatment by June 30, 2007, and had stopped treatment by June 30, 2008. Patients with HIV co-infection or a diagnosis of HCC prior to starting peginterferon and ribavirin treatment were excluded. The main analysis was limited to patients with post-treatment HCV RNA data that indicated whether SVR was attained, although a second analysis included patients without post-treatment data. Mortality outcomes for a period up to December 31, 2009 were obtained from the Veterans Affairs and Social Security Administrations.

A total of 21,836 patients were identified who met all inclusion criteria except a post-treatment HCV RNA test; 75% of patients had genotype 1 HCV infection, 15% had genotype 2 HCV infection, and 10% had genotype 3 HCV infection. The overall SVR rate in an intent-to-treat analysis was 34%; when subdivided by genotype, this rate was 26% for genotype 1 HCV patients, 62% for genotype 2 HCV patients, and 52% for genotype 3 HCV patients. Of the 16,864 individuals with a post-treatment HCV RNA test, the overall SVR rate was 44%, with rates of 35% in genotype 1 HCV patients, 72% in genotype 2 HCV patients, and 62% in genotype 3 HCV patients.

A more detailed analysis of the patients with complete SVR data showed the presence of significant comorbidities, including a history of tobacco use (52%), hypertension (52%), diabetes (20%), chronic obstructive pulmonary disease (15%), and coronary artery disease (12%). Significant percentages of patients had also recently received (within the prior 12 months) a diagnosis of depression (36%), alcohol abuse (24%), and/or hard drug use (12%).

During a mean follow-up period of 3.7 years following completion of the post-treatment HCV RNA test, a total of 1,535 patients (9.1%) died. Patients who attained SVR were significantly less likely to die during the follow-up period than patients who did not attain SVR, with relative risk reductions of 55% in genotype 1 patients, 50% in genotype 2 patients, and 70% in genotype 3 patients (Table 2). SVR remained independently associated with a reduced risk of death from any cause in all 3 genotypes even after a multivariate analysis adjusted for age; sex; race; body mass index; creatinine clearance; hepatitis B virus co-infection; comorbidities; treatment duration; year of treatment initiation; and levels of albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, hemoglobin, platelets, and sodium. The degree of benefit again varied by genotype; there was a 33% reduction in risk of death among patients with genotype 1 infection, a 47% reduction in genotype 2 patients, and a 55% reduction in genotype 3 patients. These results underscore the importance of achieving SVR even in patients with competing risk factors.

899 The Effect of Hepatitis C Treatment Response on Medical Costs: A 5-Year Longitudinal Analysis in a Managed Care Setting

JA Darbinian, F Velez, CP Quesenberry, GT Ray, B Deniz, M Manos

Another aspect of SVR that has not been well studied is its effect on healthcare costs and resources. To investigate this issue, Darbinian and colleagues conducted a 5-year longitudinal analysis assessing the effects of response to HCV treatment on medical costs in a managed care setting. The analysis included 2,464 adults in the Northern California Kaiser Permanente Medical Care Program who received treatment for HCV between 2002 and 2007. Patients had to have received at least 4 weeks of antiviral therapy with peginterferon and ribavirin and must have been members of this program for a continuous period from 1 year prior to treatment through 1 year post-treatment.

Of the 1,924 evaluable patients, 62.9% were male, 58.4% were white, 13.7% were Hispanic, 9.5% were Asian, and 8.9% were black. Patients had a mean age of 50 years at the end of treatment. Genotype 1 HCV infection was most common (62.1%), followed by genotype 2 (22.1%) and genotype 3 (15.8%). Almost half of patients

(48.2%) attained SVR. The mean treatment duration was 31.6 weeks; treatment durations ranged from 4–20 weeks (20.3% of patients), 21–26 weeks (29.1%), 27–44 weeks (17.7%), and 45–60 weeks (32.9%).

Compared to patients who attained SVR, patients who did not attain SVR incurred higher average annual costs in the first 5 years after treatment, with an average total cost difference of $2,648 per year in the complete analysis. A truncated analysis that included only outcomes within the 99th percentile was conducted to provide a more precise estimate; in this analysis, the annual difference was $1,946. This difference included hospital costs ($842 per year) and outpatient costs ($998 per year). This difference was observed in patients with genotype 1 infection and genotype 2/3 infections, with total annual truncated cost differences of $1,968 and $2,257, respectively. In the first 4 years after treatment, total costs were 24–56% higher among patients who did not attain SVR compared to those who attained SVR. Outpatient costs, both pharmacy and nonpharmacy costs, were also higher in the first 3 years post-treatment.

Patients who attained SVR were also significantly less likely than patients who did not attain SVR to utilize healthcare services. In Years 2–5 after treatment, patients who did not attain SVR were 10–145% more likely to be hospitalized, 70–130% more likely to require outpatient liver-related laboratory tests, 55–70% more likely to require other tests, and 20–40% more likely to visit an internal medicine or gastrointestinal clinic. Clearly, attaining SVR not only benefits each patient's clinical outcome but also confers significant cost and resource savings in the years after treatment.

Boceprevir

LB-4 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

F Poordad, J McCone, BR Bacon, S Bruno, MP Manns, MS Sulkowski, IM Jacobson, K Reddy, N Boparai, V Sniukiene, CA Brass, JK Albrecht, J Bronowicki

Poordad and colleagues presented final results of the randomized, double-blind, international, phase III SPRINT-2 trial, which evaluated peginterferon (1.5 µg/kg/week) plus ribavirin (600–1,400 mg/day) with or without boceprevir (800 mg 3 times per day) in patients with previously untreated genotype 1 HCV infection. All patients underwent a 4-week lead-in treatment period with peginterferon and ribavirin, after which patients were randomly assigned to 1 of 3 treatment arms: peginterferon and ribavirin plus placebo for 44 weeks; response-guided therapy (RGT), in which patients received boceprevir plus peginterferon and ribavirin for 24 weeks, with an additional 20 weeks of peginterferon and ribavirin for patients with detectable HCV RNA levels during Weeks 8–24; or fixed-duration triple therapy with boceprevir plus peginterferon and ribavirin for 44 weeks. Treatment was discontinued in patients with detectable HCV RNA levels at Week 24. At baseline, 92% of patients had HCV RNA levels above 400,000 IU/mL and 9% had F3/4 fibrosis confirmed by biopsy.

Due to known differences in response for different ethnic groups, separate analyses were conducted for the

Table 3. Efficacy Outcomes with Peginterferon (PEG) and Ribavirin (RBV) with or without Boceprevir (BOC) in the SPRINT-2 Trial

Outcome	Nonblack patients			Black patients		
	BOC (RGT) + PEG/RBV (n=316)	BOC (44 weeks) + PEG/RBV (n=311)	PEG/ RBV (n=311)	BOC (RGT) + PEG/RBV (n=52)	BOC (44 weeks) + PEG/RBV (n=55)	PEG/ RBV (n=52)
SVR, %						
• Overall	67	68	40	42	53	23
• Patients with Week 4 HCV RNA decline <1 $\log_{10}$ IU/mL, %	29	39	5	25	31	0
• Patients with Week 4 HCV RNA decline ≥1 $\log_{10}$ IU/mL, %	82	82	52	67	61	46
Relapse, %	9	5	23	12	17	14

HCV=hepatitis C virus; RGT=response-guided therapy; SVR=sustained virologic response.

159 black patients and the 936 nonblack patients. In both groups, SVR rates were significantly higher in the boceprevir-containing treatment arms than the control arm. Among nonblack patients, SVR rates were 67% in patients who received RGT, 68% in patients who received 44 weeks of boceprevir, and 40% in patients who received peginterferon and ribavirin alone (P<.0001 for each boceprevir-containing treatment arm vs control). In black patients, SVR rates were 42%, 53%, and 23%, respectively (P=.044 for RGT vs control; P=.004 for 44 weeks of boceprevir therapy vs control). Other efficacy outcomes are described in Table 3.

In the overall study population, discontinuations due to adverse events were similar among the 3 treatment arms; discontinuations occurred in 16% of patients in the peginterferon and ribavirin arm, 12% of patients in the RGT arm, and 16% of patients in the 44-week boceprevir plus peginterferon and ribavirin arm. Anemia occurred in 49% of patients receiving boceprevir and 29% of patients receiving peginterferon and ribavirin, resulting in dose reductions in 13% and 21% of patients, respectively. However, treatment discontinuations due to anemia were rare, occurring in only 1% and 2% of patients, respectively.

801 Frequencies of Resistance-Associated Amino Acid Variants Following Combination Treatment with Boceprevir Plus PEGINTRON (PegInterferon Alfa-2b)/Ribavirin in Patients With Chronic Hepatitis C (CHC), Genotype 1 (G1)

JM Vierling, PY Kwo, E Lawitz, J McCone, ER Schiff, D Pound, M Davis, JS Galati, SC Gordon, N Ravendhran, L Rossaro, F Anderson, IM Jacobson, R Rubin, L Pedicone, EI Chaudhri, X Tong, P Qiu, RJ Barnard, CA Brass, JK Albrecht, P Mendez, R Ralston

Vierling and colleagues presented an analysis of HCV variants associated with resistance to boceprevir in the SPRINT-1 study. At baseline, resistance-associated mutations were present in 24 of 595 patients (4%); 17 of these 24 patients (71%) attained SVR. Sequencing was performed on samples from 219 patients (37%) after baseline, which showed that resistance-associated mutations developed during treatment in 109 patients (50%); 2 of these patients achieved SVR. Among the 212 patients with evaluable resistance data, reasons for not attaining SVR included nonresponse (34%), relapse (33%), viral breakthrough on treatment (30%), and incomplete virologic response (28%). The incidence of resistance-associated mutations in these groups was 37%, 27%, 90%, and 67%, respectively.

The highest rate of resistance-associated mutations was observed in patients receiving low-dose ribavirin (41%). In contrast, the lowest rate of mutations was observed in patients who received peginterferon and ribavirin during a 4-week lead-in period followed by 44 weeks of treatment with boceprevir plus peginterferon and ribavirin (11%).

The prevalence of different resistance-associated mutations in patients who did not attain SVR varied by genotype. Resistance-associated mutations included V36M, T545, and R155K in patients with genotype 1a infection and T54A, T54S, A165S, and V170A in patients with genotype 1b infection. Lead-in therapy appeared to reduce the incidence of the T545 resistance mutation.

933 Hemoglobin Decline During Lead-In Phase as an Early Predictor of Anemia After the Addition of Boceprevir: A Retrospective Analysis of HCV SPRINT-1

F Poordad, JM Vierling, R Esteban, PY Kwo, J Long, EI Chaudhri, L Pedicone, JK Albrecht

Ribavirin is known to cause reductions in hemoglobin levels, and the addition of boceprevir to peginterferon and ribavirin can lead to further declines in hemoglobin, on the order of 1.0–1.5 g/dL. In an analysis from the SPRINT-1 trial, Poordad and colleagues retrospectively evaluated whether hemoglobin reductions during the peginterferon and ribavirin lead-in phase predicted nadir hemoglobin levels during subsequent combination therapy with boceprevir, peginterferon, and ribavirin.

The investigators found that hemoglobin nadir levels were similar in the 2 treatment arms that had a 4-week lead-in period, regardless of the overall duration of treatment. Hemoglobin nadirs below 9.5 g/dL developed in 27–29% of patients. Among all boceprevir-treated patients, 17% developed hemoglobin levels below 10 g/dL by Week 8 of treatment (including the 4-week lead-in period), and 17% of patients had received erythropoietin (EPO) by this time.

The investigators reported a correlation between the degree of hemoglobin decline during the lead-in period and the hemoglobin nadir observed during combination therapy, suggesting that patients who are at higher risk of anemia could be closely monitored and promptly treated with EPO if needed. This proactive management may minimize the extent to which anemia causes a need for ribavirin dose reductions below effective concentrations or discontinuations.

Table 4. Efficacy of Boceprevir (BOC) Plus Peginterferon (PEG) and Ribavirin (RBV) in Genotype 1 Patients Who Were Previous Peginterferon and Ribavirin Nonresponders or Relapsers

	BOC (44 weeks) + PEG/RBV (48 weeks) (n=161)	BOC (RGT) + PEG/RBV (n=162)	PEG/RBV (48 weeks) (n=80)
End of therapy response	77%	70%	31%
SVR			
• All patients	67% (107/161)	59% (95/162)	21% (17/80)
• Previous nonresponders	52% (30/58)	40% (23/57)	7% (2/29)
• Previous relapsers	75% (77/103)	69% (72/105)	29% (15/51)
• Patients with null response at Week 4	34% (15/44)	33% (15/46)	0% (0/12)
• Patients with non-null response at Week 4	80% (90/114)	73% (80/110)	26% (17/66)
Relapse rate	12%	15%	32%

RGT=response-guided therapy; SVR=sustained virologic response.

216 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

BR Bacon, SC Gordon, E Lawitz, P Marcellin, JM Vierling, S Zeuzem, F Poordad, N Boparai, M Burroughs, CA Brass, JK Albrecht, R Esteban

The double-blind, placebo-controlled RESPOND-2 trial evaluated the safety and efficacy of boceprevir plus peginterferon and ribavirin in patients with genotype 1 HCV infection who had previously not responded to peginterferon and ribavirin or whose disease had relapsed after such treatment. A total of 403 patients received 4 weeks of lead-in therapy with peginterferon and ribavirin followed by 1 of 3 treatment regimens: RGT with peginterferon and ribavirin plus boceprevir (800 mg 3 times per day) for 32–44 weeks; 44 weeks of boceprevir, peginterferon, and ribavirin; or 44 weeks of peginterferon and ribavirin alone. Patients with detectable HCV RNA levels at Week 12 discontinued treatment.

The patient population was 67% male and 12% black; 12% of patients had cirrhosis. Overall, the boceprevir-containing treatment regimens were significantly more effective than the control regimen; at 24 weeks post-treatment, SVR rates were 59% for patients who received RGT and 67% for patients who received 44 weeks of triple therapy with boceprevir, compared to 21% for patients who received peginterferon and ribavirin alone. The best outcomes were observed in patients who showed at least 1 $\log_{10}$ decline in HCV RNA levels at Week 4 (after the 4-week lead-in period) and who then received 44 weeks of the boceprevir-containing regimen; this group had an SVR rate of 80% (Table 4). Approximately 28% of all patients assigned to a boceprevir-containing regimen had a null response after the 4-week lead-in period. Although overall response rates were lower in patients with a null response at 4 weeks, boceprevir still appeared to be beneficial in this group; SVR rates in this subset of patients were higher in the boceprevir-containing arms than the control arm. Discontinuations due to adverse events were more common among patients assigned to the boceprevir-containing treatment regimens, with discontinuations reported in 12% of patients receiving boceprevir for 44 weeks, 8% of patients receiving RGT with boceprevir, and 3% of patients receiving peginterferon and ribavirin only.

Telaprevir

211 Telaprevir in Combination with Peginterferon and Ribavirin in Genotype 1 HCV Treatment-Naïve Patients: Final Results of Phase 3 ADVANCE Study

IM Jacobson, JG McHutchison, GM Dusheiko, AM Di Bisceglie, R Reddy, NH Bzowej, P Marcellin, AJ Muir, L Bengtsson, A Dunne, N Adda, S George, RS Kauffman, S Zeuzem

Jacobson and colleagues presented the final results of the randomized, placebo-controlled, phase III ADVANCE trial, which evaluated the addition of telaprevir to peginterferon and ribavirin in treatment-naïve patients with genotype 1 HCV infection. A total of 1,088 patients

were randomly assigned to receive either peginterferon (180 µg/week) and ribavirin (1,000–1,200 mg/day) or peginterferon and ribavirin plus telaprevir (750 mg every 8 hours) for the first 8 or 12 weeks of treatment. Patients in the telaprevir-containing arms who achieved an extended rapid viral response (eRVR), defined as undetectable HCV RNA levels at Weeks 4 and 12, received a total of 24 weeks of therapy; other patients received a total of 48 weeks of therapy. Patients were stratified by baseline HCV RNA level (<800,000 IU/mL vs ≥800,000 IU/mL) and by viral subtype (1a vs 1b).

In this difficult-to-treat population, 77% of patients had HCV RNA levels at or above 800,000 IU/mL, 58% had genotype 1a infection, 58% were male, 11% were Latino or Hispanic, 9% were black, and 21% had bridging fibrosis or compensated cirrhosis. The primary endpoint of the study was SVR, which was defined as undetectable HCV RNA levels 24 weeks after the last planned treatment dose. Rates of SVR were significantly higher in both telaprevir-containing treatment arms than in the control arm. In an intent-to-treat analysis, SVR rates were 75% following 12 weeks of telaprevir treatment, 69% following 8 weeks of telaprevir treatment, and 44% in the control arm (P<.0001).

Adverse events occurring in more than 25% of patients in the telaprevir-containing treatment arms included fatigue, pruritis, nausea, headache, anemia, rash, influenza-like illness, insomnia, pyrexia, and diarrhea. Adverse events led to discontinuation of treatment in 8% of patients who received telaprevir for 8 weeks, 7% of patients who received telaprevir for 12 weeks, and 4% of patients in the placebo arm. Discontinuation rates due to rash were 0.5%, 1.4%, and 0%, respectively, and discontinuation rates due to anemia were 3.3%, 0.8%, and 0.6%, respectively.

LB-11 Clinical Virology Results from Telaprevir Phase 3 Study ADVANCE

TL Kieffer, DJ Bartels, J Sullivan, BS Adiwijaya, EZ Zhang, A Tigges, J Dorrian, J Spanks, S De Meyer, G Picchio, N Adda, AD Kwong

In a related presentation, Kieffer and colleagues presented clinical virologic results from the ADVANCE study. For this analysis, HCV RNA measurements and population sequencing of the *NS3-4A* gene were performed at baseline, during treatment, and during follow-up among patients who did not attain SVR. The investigators attempted to identify amino acid substitutions associated with resistance to telaprevir.

The 2 telaprevir-containing treatment arms showed similar rates of virologic failure at Weeks 4 and 12; virologic failure occurred in 2.7% of patients in the 8-week telaprevir group and 3.3% of patients in the 12-week telaprevir group. However, the incidence of virologic failure assessed after Week 12 was approximately 5% higher among patients treated with 8 versus 12 weeks of telaprevir (10.2% vs 5.0%). The 8-week telaprevir treatment duration was also associated with emergence of both wild-type virus and lower-level telaprevir-resistant variants. These outcomes suggest that extending the telaprevir treatment duration from 8 to 12 weeks reduces the risk of virologic failure.

Modeling analyses developed using data from the phase II trials PROVE1 and PROVE2 support this hypothesis, with these studies showing that a minor population of low-level telaprevir-resistant variants may exist after 8 weeks of treatment but are cleared with additional treatment. An analysis of 91 patients with telaprevir-resistant variants showed that the resistant virus was cleared by the end of the study; the median follow-up period for this study was 45 weeks. The median time required to fully clear these variants ranged from 13 weeks for T54 to 44 weeks for R155.

LB-2 Telaprevir in Combination with Peginterferon Alfa-2a 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

KE Sherman, SL Flamm, NH Afdhal, DR Nelson, MS Sulkowski, GT Everson, MW Fried, K Kleber, M Martin, AJ Sankoh, RS Kauffman, S George, CI Wright, F Poordad

The phase III ILLUMINATE study was designed to evaluate the feasibility of RGT for telaprevir-containing regimens, which could allow for shorter treatment durations in patients who attain rapid, durable responses and longer treatment durations in other patients. In this open-label, multicenter study, patients with previously untreated genotype 1 HCV infection received telaprevir (750 mg every 8 hours) plus peginterferon α-2a (180 µg/week) and ribavirin (1,000–1,200 mg/day) for the first 12 weeks, followed by treatment with peginterferon and ribavirin alone during Weeks 12–20. Patients attaining eRVR, defined as undetectable HCV RNA levels (<25 IU/mL) at Weeks 4 and 12, were randomly assigned at Week 20 to either discontinue peginterferon and ribavirin at Week 24 or to continue peginterferon and ribavirin until Week 48. Patients who did not attain eRVR received peginterferon and ribavirin for 48 weeks. Patients who did not attain a 2 $\log_{10}$ reduction in HCV RNA levels at Week 12 and patients with detectable HCV RNA levels at Week 24 were considered to have virologic failure and therefore discontinued treatment. The trial was statisti-

cally powered to detect the noninferiority of the shorter treatment duration.

A total of 540 patients were enrolled across 74 study centers; 60.2% of study participants were male, 79.1% were white, and 11.3% had cirrhosis. The median HCV RNA level at baseline was 6.5 $\log_{10}$ IU/mL. Rapid viral response was attained in 389 patients (72%), and eRVR was attained in 352 patients (65.2%). Of the patients attaining eRVR, 322 were randomized 1:1 to receive treatment for a total of either 24 weeks (n=162) or 48 weeks (n=160). The investigators reported no significant differences in efficacy between the 2 treatment durations; SVR rates were 92% and 87.5% among patients receiving treatment for 24 and 48 weeks, respectively. In an intent-to-treat analysis, this RGT approach was associated with an overall SVR rate of 71.9%. Only 6.7% of patients discontinued treatment because of virologic failure.

Another 17.4% of patients discontinued all treatment drugs because of adverse events, most commonly fatigue or anemia. Treatment discontinuations due to adverse events primarily occurred in later treatment weeks. In patients attaining eRVR who were assigned to 48 weeks of treatment, the discontinuation rate due to adverse events was 12.5%. Only 1 patient (0.6%) in the 24-week treatment arm discontinued treatment due to an adverse event after Week 20; during the first 12 weeks of treatment while on telaprevir, 3 patients (0.6%) discontinued treatment due to anemia and 6 patients (1.1%) discontinued treatment due to rash.

The investigators concluded that these data support the use of RGT for telaprevir-based regimens in treatment-naïve patients. RGT should allow for shorter treatment durations in nearly two thirds of patients, and it appears to be as effective as the longer treatment duration but avoids the toxicity associated with longer treatment periods.

828 Activity of Telaprevir Monotherapy or in Combination with Peginterferon-Alfa-2a and Ribavirin in Treatment-Naïve Genotype 4 Hepatitis-C Patients: Final Results of Study C210

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A large meta-analysis previously showed that treatment with peginterferon and ribavirin is associated with an SVR rate of 72% in patients with genotype 4 HCV infection.[1] To improve this rate, researchers have been examining the possibility of adding other agents to the treatment regimen. Preclinical data suggest that telaprevir could be active in patients with genotype 4 HCV infection, although it may not have the same activity as it does in patients with genotype 1 HCV infection.

To explore the safety and efficacy of telaprevir in patients with genotype 4 HCV infection, Benhamou and colleagues conducted the randomized, partially blinded study C210. A total of 24 patients with previously untreated genotype 4 HCV infection were randomly assigned to receive 2 weeks of treatment with either telaprevir monotherapy (750 mg every 8 hours), telaprevir plus peginterferon α-2a [40 kD] (180 µg/week) and ribavirin (1,000–1,200 mg/day), or peginterferon and ribavirin alone. All patients subsequently received 46 weeks of treatment with peginterferon and ribavirin, resulting in a total treatment period of 48 weeks.

Of the 24 patients randomized to treatment, 53% were male, 67% were white, and 33% were black; the patients' median age was 45.5 years. The median baseline HCV RNA level was 5.9 $\log_{10}$ IU/mL, and HCV RNA levels were at or above 800,000 IU/mL in 54% of patients. No patients showed evidence of cirrhosis.

Telaprevir alone demonstrated modest antiviral activity in these patients, with a median decline in HCV RNA levels of 0.77 $\log_{10}$ IU/mL between baseline and Day 15. In comparison, treatment with peginterferon and ribavirin was associated with a decline in HCV RNA levels of 1.58 $\log_{10}$ IU/mL, and treatment with telaprevir plus peginterferon and ribavirin was associated with a median decline of 4.32 $\log_{10}$ IU/mL. This finding suggests that the 3 agents may achieve a synergistic effect when used together. The investigators noted that IL-28B genotypes were not investigated in this study; thus, imbalances in the frequency of these genotypes cannot be excluded as a potential explanation for the differences among the 3 groups.

No significant differences in outcomes among the 3 groups were noted at the end of the peginterferon and ribavirin treatment period. In an intent-to-treat analysis, the proportion of patients with undetectable HCV RNA levels was 75% in the group treated with telaprevir plus peginterferon and ribavirin, 75% in the group treated with peginterferon and ribavirin alone, and 88% in the group treated with telaprevir alone followed by peginterferon and ribavirin for 46 weeks. SVR rates were 50%, 63%, and 63%, respectively.

Viral breakthrough developed in 5 patients receiving telaprevir monotherapy. Viral sequencing was performed on samples from 4 of these patients, revealing variants in 2 patients that are known to be associated with reduced telaprevir susceptibility in genotype 1 HCV infection. However, 3 of the 4 patients with viral breakthrough attained SVR after completion of the second treatment phase.

The safety of telaprevir was similar to previous reports. The most commonly reported adverse event in the 2-week investigational treatment phase was an influenza-like illness, reported in 38% of patients receiving telaprevir, 50% of patients receiving peginterferon and ribavirin, and 88% of patients receiving all 3 agents. The second most common adverse event was asthenia, reported in 0%, 38%, and 75% of patients, respectively. The only difference in adverse event rates during the overall treatment phase was an increased incidence of influenza-like illness among patients receiving telaprevir plus peginterferon and ribavirin.

Interferon-Lambda: A Potential New Agent

821 Pegylated Interferon Lambda (PEG-IFN-λ) Phase 2 Dose-Ranging, Active-Controlled Study in Combination with Ribavirin (RBV) for Treatment-Naïve HCV Patients (Genotypes 1, 2, 3 or 4): Safety, Viral Response, and Impact of IL-28B Host Genotype Through Week 12

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While much attention is being given to telaprevir and boceprevir, interferon-λ is another new agent being evaluated as a possible treatment for HCV. Because it uses a receptor with more limited expression, interferon-λ may have a better safety profile than interferon-α. Muir and colleagues therefore performed a phase II, dose-ranging, active-control study of interferon-λ plus ribavirin in treatment-naïve patients with genotype 1, 2, 3, or 4 HCV infection. A total of 55 patients were randomly assigned to receive a single dose of interferon-λ at doses of 80, 120, or 240 μg (n=45) or interferon-α at 180 μg (n=10) for pharmacokinetic analysis, followed 2 weeks later by interferon-λ or interferon-α plus ribavirin for 24 weeks (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4).

Interferon-λ was found to induce rapid viral declines, with the degree of decline varying based on HCV genotype and IL-28B genotype. At the 3 highest doses of interferon-λ, 71% of patients with genotype 1 or 4 HCV infection and an IL-28B genotype of CC had undetectable HCV RNA levels at Weeks 2 and 4. The virologic response rates were lower among patients with a CT or TT genotype than among patients with a CC genotype; in the former group, virologic response rates were 8% at Week 2 and 25% at Week 4.

Clinical adverse events at or above grade 2 in severity were less frequent with interferon-λ compared to interferon-α (33% vs 50%), in particular hematologic toxicity. Grade 2 anemia (hemoglobin levels ≤10 g/dL) developed in 2% of patients receiving interferon-λ versus 20% of patients receiving interferon-α, resulting in more ribavirin-associated dose reductions in the interferon-α arm. Interferon-λ was also associated with less neutropenia than interferon-α, with median reductions in neutrophil levels of 0.86×10^9 cells/L and 2.4×10^9 cells/L, respectively. Other adverse events included grade 2 or 3 ALT and/or AST elevations, which occurred with both interferon-λ (20%) and interferon-α (30%) and led to interferon-λ dose reductions in 3 patients (7%). All ALT and/or AST elevations resolved within 1 week, with levels remaining stable thereafter. One patient receiving interferon-α required a dose reduction due to depression. Treatment discontinuations due to adverse events were reported in 4 patients, including 1 patient receiving interferon-α and 3 patients receiving interferon-λ.

Reference

1. Khuroo MS, Khuroo MS, Dahab ST. Meta-analysis: a randomized trial of peginterferon plus ribavirin for the initial treatment of chronic hepatitis C genotype 4. *Aliment Pharmacol Ther.* 2004;20:931-938.

Commentary

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Without a doubt, 2010 was an exciting year in hepatitis C research. Phase III data were presented for the 2 protease inhibitors that are furthest along in development, telaprevir and boceprevir, and we expect that these 2 drugs will receive approval from the US Food and Drug Administration within the coming year. The addition of a protease inhibitor as a DAA agent to peginterferon and ribavirin has now increased SVR rates in many genotype 1 HCV patient populations above 60–70%. It has also enabled us to shorten therapy in over half of genotype 1 HCV patients to 24 weeks, which is the same duration of therapy we currently use to treat genotypes 2 and 3 HCV infection. Additionally, we have new paradigms for using early virologic clearance to facilitate RGT, genetic markers that predict patients' likelihood of responding to interferon-based regimens, new options for treating prior nonresponders and relapsers, and additional data supporting the value of HCV clearance for improving long-term outcomes. With these new drugs will come new challenges and potential pitfalls we must avoid; one such pitfall is the development of antiviral resistance, which will require closer monitoring of patient responses and HCV RNA levels. New side effect management strategies will also be required. Finally, while the goal of eliminating peginterferon or ribavirin from our HCV treatment regimens remains desirable, this is a future goal that we are not yet close to attaining.

The ability to use early viral clearance to facilitate RGT has been a major paradigm shift in HCV treatment, as this strategy allows us to maximize treatment efficacy while minimizing side effects. Between the phase II PROVE study and the phase III ILLUMINATE and ADVANCE studies, we have seen that 12 weeks of telaprevir in combination with 24–48 weeks of peginterferon and ribavirin shows excellent efficacy in both treatment-naïve patients and patients who previously failed treatment. Similar results were seen in the SPRINT and RESPOND trials for triple combination therapy consisting of boceprevir plus 28–48 weeks of peginterferon and ribavirin.

The ILLUMINATE study established that 12 weeks of triple therapy with telaprevir, peginterferon, and ribavirin followed by an early RGT tail consisting of peginterferon and ribavirin is equivalent to a fixed-duration, 48-week course of therapy. Patients who achieved eRVR—defined as an undetectable HCV RNA level at Weeks 4 and 12—could be treated for a total of 24 weeks and achieve an SVR rate of 92%. Patients who attained eRVR comprised 65% of the total study group. Patients who did not achieve eRVR received 48 weeks of therapy and had a lower SVR (64% in the ILLUMINATE study and 58% in the ADVANCE trial), but RGT with telaprevir still proved superior to 48 weeks of treatment with peginterferon and ribavirin alone.

RGT was also used in the SPRINT-2 study, the phase III trial of boceprevir. In the boceprevir trials, patients received peginterferon and ribavirin alone during the 4-week lead-in period, followed by an additional 24 or 44 weeks of triple therapy including boceprevir. White patients who maintained undetectable HCV RNA levels during Weeks 4–20 of triple therapy (ie, Weeks 8–24 of overall therapy) could receive treatment for just 28 weeks and achieve an SVR of 89%. Patients with a positive viral load at Week 8 received 48 weeks of therapy and had a lower response rate (37%). Efficacy was lower in black patients, with SVR rates of 42–53% overall, but these rates were still approximately twice the SVR rate achieved with peginterferon and ribavirin alone, and black subjects with undetectable HCV RNA levels at Week 8 achieved an SVR rate of 80%. In addition, treatment with telaprevir or boceprevir plus peginterferon and ribavirin can yield SVR rates of 75–86% in prior relapsers and approximately 50% in prior nonresponders when patients receive 48 weeks of therapy. Thus, all patient groups are likely to benefit from the addition of DAA agents.

While both these new DAA agents are likely to prove quite beneficial, clinicians should bear in mind their differences. One important consideration is the different treatment regimens used with these 2 protease inhibitors. Boceprevir involves a 4-week lead-in period with peginterferon and ribavirin followed by RGT with all 3 drugs for an additional 24–44 weeks. Telaprevir regimens use triple combination therapy at initiation for 12 weeks followed by 12–36 weeks of treatment with peginterferon and ribavirin alone. The rules for RGT also differ for these 2 drugs; the ability to truncate therapy is determined by a negative viral load at Weeks 8–24 for boceprevir and by eRVR or negative viral load at Weeks 4 and 12 for telaprevir.

The side effect profiles of these drugs also differ. For telaprevir, the major challenge is rash, which can occur in up to 56% of patients, although rash was also reported

in 37% of patients in the ADVANCE study who were treated with peginterferon, ribavirin, and placebo. An improved rash management plan—with sequential stopping of telaprevir and then ribavirin prior to stopping all therapy—decreased the need to stop telaprevir to under 10% and the need to stop all drugs to under 2%. For boceprevir, the major challenge is anemia. In all of the boceprevir trials, anemia and ribavirin dose reductions were more frequent with boceprevir, peginterferon, and ribavirin, despite the use of EPO at the investigators' discretion; discontinuations due to anemia were uncommon, however, and EPO was used in approximately 40% of subjects.

In addition to demonstrating the efficacy of telaprevir and boceprevir, the studies highlighted in this monograph also reinforce earlier data showing that full-dose ribavirin and peginterferon are required in order to achieve maximal results. Thus, it is unlikely that protease inhibitors will eliminate the need for peginterferon and ribavirin in the near future. A number of other protease and polymerase inhibitors have shown promising early data, so it is likely that we will eventually have several agents from which to choose. This should allow for quadruple combinations to increase response rates in difficult-to-treat patients and nonresponders. Once we have more DAA agents, the possibility of eliminating peginterferon or ribavirin from our treatment regimen may be within reach.

Questions still remain as to the role of the lead-in phase with peginterferon and ribavirin and how to utilize this phase for patient management. The role of EPO to manage the anemia seen with protease inhibitors is also under active study. In addition, challenges remain regarding how to educate clinicians on optimal use of DAA agents, including how to prevent and monitor for resistance, new stopping rules, and increased side effect management. Unlike peginterferon and ribavirin, DAA agents cannot be dose reduced without increasing the risk of resistance; thus, clinicians must either manage patients' side effects or stop the medication. As more agents are developed, the need to understand mechanisms of action and cross-resistance will also be necessary. While telaprevir and boceprevir will not be used in combination, nucleoside and non-nucleoside polymerase inhibitors may be combined in the future.

Finally, increasing data have established that achieving SVR is equivalent to cure and is associated with significant health benefits. An accumulating body of data shows that patients who achieve SVR have decreases in liver-related complications, mortality, and healthcare costs. SVR is associated with a less-than-1% chance of long-term relapse, lower morbidity and mortality, and less need for diagnostic testing and liver disease therapies. Our biggest obstacles remain those related to patient identification, although improved screening, better awareness of therapy, and increased tolerability of and access to existing antiviral therapy should improve this situation.

In summary, we are making progress despite substantial ongoing challenges. Within the year, we expect that patients with genotype 1 HCV infection will be able to achieve an approximately 75% chance of viral cure and sustained clinical benefits, with over half of these patients needing only 6 months of therapy. For HCV, the future is bright and becoming brighter every day.


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