

## New Developments in the Treatment of Hepatitis C Virus Infection from Digestive Disease Week 2011

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With commentary by

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### Special Reporting on:

Response During Lead-In Period Predicts SVR Following Treatment  
with Boceprevir Plus Peginterferon and Ribavirin

Risk of Hepatocellular Carcinoma Is Reduced in HCV-Treated  
Patients Who Achieve SVR

*IL-28B* Genotype Affects SVR Rates Following Treatment with  
Telaprevir Plus Peginterferon and Ribavirin

Efficacy and Safety of Boceprevir in Combination with  
Peginterferon  $\alpha$ -2a and Ribavirin

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## Response During Lead-In Period Predicts SVR Following Treatment with Boceprevir Plus Peginterferon and Ribavirin

In an oral session at the 2011 Digestive Disease Week (DDW) conference, Dr. John Vierling presented results from a pooled analysis of 2 randomized, phase III trials—SPRINT-2 and RESPOND-2—both of which evaluated the efficacy and safety of boceprevir, used in combination with peginterferon  $\alpha$ -2b and ribavirin, in patients with genotype 1 hepatitis C virus (HCV) infection.<sup>1</sup> Both trials demonstrated that adding boceprevir to peginterferon  $\alpha$ -2b and ribavirin significantly increases sustained virologic response (SVR) rates compared to treatment with peginterferon and ribavirin alone (Table 1). While both trials involved similar drug regimens, the SPRINT-2 trial enrolled treatment-naïve patients, whereas the

RESPOND-2 trial enrolled patients who had failed previous treatment.<sup>2,3</sup>

In both trials, patients received 4 weeks of peginterferon and ribavirin alone before starting boceprevir. The rationale for this 4-week lead-in period is several-fold: It may optimize peginterferon and ribavirin steady-state concentrations before exposure to a direct-acting antiviral (DAA) agent; it may reduce viral load before the patient is exposed to the DAA agent; it allows for a determination of the patient's tolerance to, and compliance with, peginterferon and ribavirin; and it may predict the likelihood of attaining SVR with boceprevir-based triple therapy.

Previous studies have demonstrated a correlation between SVR rates and initial response to therapy among

patients treated with peginterferon and ribavirin. In the IDEAL trial, a phase III study of peginterferon  $\alpha$ -2a versus peginterferon  $\alpha$ -2b in patients with genotype 1 HCV infection, reductions in HCV RNA levels during the initial 4 weeks of therapy significantly predicted SVR.<sup>4</sup> Similar findings were observed during the SPRINT-1 trial, a phase II study that evaluated boceprevir plus peginterferon and ribavirin in treatment-naïve patients; specifically, patients with a decline in HCV RNA level of at least 1.0 log<sub>10</sub> following a 4-week lead-in period with peginterferon and ribavirin had an SVR rate of 75%, compared to an SVR rate of 38% in patients whose initial decline in HCV RNA level was less than 1.0 log<sub>10</sub>.<sup>5</sup>

**Table 1.** Sustained Virologic Response (SVR) Rates According to Response Following 4-Week Lead-In Therapy with Peginterferon and Ribavirin (PR)

Lead-in HCV-RNA decline log <sub>10</sub> *	SVR, n/N (%)					
	Treatment-naïve			Previous treatment failure		
	48 PR n=363	BOC RGT n=368	BOC/PR48 n=366	48 PR n=80	BOC RGT n=162	BOC/PR48 n=161
<1.0	3/83 (3.6)	27/97 (27.8)	36/95 (37.9)	0/12 (0)	15/46 (32.6)	15/44 (34.1)
<0.5	0/25 (0)	13/47 (27.7)	11/37 (29.7)	0/4 (0)	4/13 (30.8)	1/8 (12.5)
0.5–<1.0	3/58 (5.2)	14/50 (28.0)	25/58 (43.1)	0/8 (0)	11/33 (33.3)	14/38 (38.9)
≥1.0	133/260 (51.2)	203/252 (80.6)	200/254 (78.7)	17/67 (25.4)	80/110 (72.7)	90/114 (78.9)
1–<1.5	12/56 (21.4)	33/47 (70.2)	29/48 (60.4)	0/11 (0)	15/21 (71.4)	15/28 (53.6)
1.5–<2	13/40 (32.5)	20/31 (64.5)	18/25 (72.0)	3/17 (17.6)	11/20 (55.0)	15/15 (100)
2–<3	25/56 (44.6)	44/55 (80.0)	42/57 (73.7)	3/17 (17.6)	18/26 (69.2)	30/37 (81.1)
3–<4	21/36 (58.3)	47/53 (88.7)	48/54 (88.9)	3/10 (30.0)	18/23 (78.3)	11/14 (78.6)
≥4	33/42 (78.6)	42/47 (89.4)	45/50 (90.0)	6/10 (60.0)	18/20 (90.0)	17/18 (94.4)
Undetectable	29/30 (96.7)	17/19 (89.5)	18/20 (90.0)	2/2 (100)	0/0 (0)	2/2 (100)

\*Patients missing HCV RNA assessment at Treatment Week 4 were not included.

BOC=boceprevir; HCV=hepatitis C virus; RGT=response-guided therapy.

## ABSTRACT SUMMARY Response-Guided Therapy with Boceprevir

Response-guided therapy involves modifying total treatment duration based on whether patients attain HCV RNA undetectability early in the course of therapy. Both SPRINT-2 and RESPOND-2 included response-guided therapy arms; the duration of treatment was determined based on virologic responses at Weeks 8 and 12 in RESPOND-2 and at Weeks 8–24 in SPRINT-2. In the current analysis, Manns and colleagues further analyzed the outcomes from both of these response-guided therapy arms.<sup>1</sup>

In the SPRINT-2 trial, 57% of patients in the response-guided therapy arm (208 of 368 patients) had undetectable levels of HCV RNA at Week 8. These early responders received treatment for a total duration of 28 weeks; 88% of these patients achieved SVR, compared to an SVR rate of 90% in the patients who received 4 weeks of peginterferon and ribavirin followed by 44 weeks of boceprevir-based triple therapy.

Most subgroup analyses showed similar SVR rates for response-guided therapy compared to 48 weeks of

boceprevir-based triple therapy; an exception occurred in patients with advanced fibrosis (F3/F4), in whom SVR rates were 79% among patients who received response-guided therapy versus 93% among patients who received 48 weeks of boceprevir-based triple therapy. However, there were fewer than 15 patients per group in this category. Among the 44% of boceprevir-treated patients who attained undetectable levels of HCV RNA at Weeks 8–24, the SVR rate was 96% in both the response-guided therapy arm and the 48-week, boceprevir-based triple therapy arm. Again, subgroup analyses showed similar SVR rates among all subgroups except patients with advanced fibrosis, in whom the number of patients was small.

In the RESPOND-2 trial, which enrolled patients who had previously failed treatment, 46% of patients in the response-guided therapy arm (74 of 162 patients) achieved undetectable levels of HCV RNA by Week 8 and maintained HCV undetectability at Week 24, making them eligible for a

shortened course of therapy. These patients received treatment for a total duration of 36 weeks and achieved an SVR rate of 86%. The SVR rate in patients treated with 48 weeks of boceprevir-based triple therapy was 88%. Only 2 subgroups showed lower SVR rates with response-guided therapy compared to 48 weeks of boceprevir-based triple therapy: previous nonresponders to peginterferon and ribavirin (78% vs 90%); and patients with advanced (F3/F4) fibrosis (80% vs 90%).

Based on their analysis, the authors suggested that response-guided therapy may be preferable to fixed-duration treatment both in previously untreated patients and in patients who previously failed treatment, as response-guided therapy provides comparable efficacy with a shorter treatment duration.

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In the current analysis, Vierling and colleagues used data from the SPRINT-2 and RESPOND-2 trials to assess the relationship between interferon responses following 4 weeks of peginterferon and ribavirin therapy and SVR rates. The SPRINT-2 trial enrolled 1,099 previously untreated patients; in all 3 arms of this study, patients received 4 weeks of lead-in treatment with peginterferon and ribavirin. Following the lead-in period, patients received 1 of 3 regimens: In Arm 1, the lead-in period was followed by 44 weeks of placebo plus

peginterferon and ribavirin. In Arm 2 (the response-guided therapy arm), the lead-in period was followed by 24 weeks of boceprevir plus peginterferon and ribavirin; patients who showed undetectable HCV RNA levels between Weeks 8 and 24 could stop therapy at Week 28, while patients with detectable HCV RNA levels at Week 24 received an additional 20 weeks of placebo plus peginterferon and ribavirin. In Arm 3, the lead-in period was followed by 44 weeks of treatment with boceprevir plus peginterferon and ribavirin.

Patients with a detectable level of HCV RNA at Week 24 stopped therapy due to futility.

The RESPOND-2 trial enrolled 403 patients who had previously failed treatment, but the study design specifically excluded null responders. Again, all groups received a 4-week lead-in with peginterferon and ribavirin, after which patients received 1 of 3 treatments: placebo plus peginterferon and ribavirin for 44 weeks; response-guided therapy with boceprevir plus peginterferon and ribavirin; or boceprevir plus peginterferon

## ABSTRACT SUMMARY Predictive Value of Historical Response to Peginterferon and Ribavirin Versus Response During 4-Week Lead-In Period

The RESPOND-2 trial evaluated boceprevir plus peginterferon and ribavirin in patients who had failed prior treatment; patients in this study included prior non-responders (patients who had an HCV RNA reduction  $\geq 2.0 \log_{10}$  by Week 12 but who did not achieve HCV RNA undetectability) and prior relapsers (patients who attained undetectable levels of HCV RNA at the end of treatment but who did not subsequently attain SVR). The RESPOND-2 trial excluded patients who failed to achieve at least a  $2.0 \log_{10}$  decline in HCV RNA level by Week 12. In the current analysis, Esteban and colleagues compared patients' historical response to peginterferon and ribavirin with the response to peginterferon and ribavirin observed during the 4-week lead-in period of the RESPOND-2 trial.<sup>1</sup> Both historical responses and lead-in responses were correlated with SVR rates to determine which were predictive of SVR.

Among the 144 nonresponders in the RESPOND-2 trial, SVR rates were 52% in patients who received 4 weeks of peginterferon and ribavirin followed

by 44 weeks of boceprevir-based triple therapy, 40% in patients who received response-guided therapy, and 7% in patients who received peginterferon and ribavirin alone. SVR rates among the 259 relapsers were 75%, 69%, and 29%, respectively. In an exploratory analysis, an HCV RNA reduction of at least  $0.91 \log_{10}$  at Week 4 was found to be most predictive of SVR among boceprevir-treated patients.

Interestingly, many patients with a well-documented history of previous interferon responsiveness did not attain at least a  $1.0 \log_{10}$  decline in HCV RNA level by Week 4 of the RESPOND-2 trial. Of the 394 patients with available data, 102 patients (26%) had a decline in HCV RNA level that was less than  $1.0 \log_{10}$  at Week 4. This poor interferon response was more common in historical non-responders than in historical relapsers (39% vs 18%).

Despite the significant association between lower SVR rates and a less-than- $0.91 \log_{10}$  reduction in HCV RNA level at Week 4, the authors suggested that HCV RNA response following the

4-week lead-in period should not be used to define futility, as 33–34% of patients with an HCV RNA decline less than  $1.0 \log_{10}$  at Week 4 were able to attain SVR when treated with boceprevir plus peginterferon and ribavirin. Also, among patients who achieved a HCV RNA decline of at least  $1.0 \log_{10}$  by Week 4, 64–66% attained HCV RNA undetectability at Week 8; in the response-guided therapy arm, achieving this benchmark meant that patients were eligible for a 36-week course of therapy. Finally, a multivariate analysis found that Week 4 response to peginterferon and ribavirin (HCV RNA reduction  $\geq 1.0 \log_{10}$  vs  $<1.0 \log_{10}$ ) was a stronger predictor of SVR than historical treatment response.

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and ribavirin for 44 weeks. In the response-guided therapy arm, patients with undetectable HCV RNA levels at Week 8 could stop therapy after a total of 36 weeks; patients with detectable HCV RNA levels received an additional 12 weeks of placebo plus peginterferon and ribavirin. In this study, a detectable level of HCV RNA at Week 12 was a stopping rule for futility.

The percentage of patients who showed an HCV RNA decline at Week 4, following the peginterferon and ribavirin lead-in period, was

20–25% in the SPRINT-2 trial and 15–28% in the RESPOND-2 trial. Among patients with poor responses during lead-in therapy, SVR rates were quite low if patients subsequently received peginterferon and ribavirin alone; however, the addition of boceprevir to peginterferon and ribavirin substantially increased SVR rates in these patients. The highest SVR rates were observed in patients who attained an HCV RNA decline of at least  $1 \log_{10}$  after the 4-week lead-in period.

In the SPRINT-2 trial, SVR rates for patients with an HCV RNA decline less than  $1 \log_{10}$  after the 4-week lead-in period were 3% among patients treated with peginterferon and ribavirin alone, 28% among patients who received response-guided boceprevir plus peginterferon and ribavirin, and 38% in patients who received 48 weeks of boceprevir-based triple therapy. The addition of boceprevir to peginterferon and ribavirin in patients with an HCV RNA decline of at least  $1 \log_{10}$  after

the 4-week lead-in period yielded a response rate of 80–90%.

Similar findings were observed in a subgroup analysis of the SPRINT-2 trial data in which outcomes were analyzed according to race. In the 940 nonblack subjects enrolled in the study, SVR rates among patients with an HCV RNA decline less than  $1 \log_{10}$  after the 4-week lead-in period were 5% in the control arm, 29% in patients who received response-guided therapy with boceprevir plus peginterferon and ribavirin, and 39% in patients treated with 48 weeks of boceprevir-based triple therapy. A similar trend was observed in the 159 enrolled black patients; among those with HCV RNA declines less than  $1 \log_{10}$  after 4 weeks of lead-in therapy, SVR rates were 0%, 25%, and 31%, respectively. In both subgroups, SVR rates were higher among patients who achieved greater declines in HCV RNA level by Week 4.

The investigators also evaluated the association between SVR rates and response following the 4-week lead-in period among the 403 treatment-failure patients enrolled in the RESPOND-2 trial. Among patients whose reduc-

tion in HCV RNA level was less than  $1 \log_{10}$  after 4 weeks of peginterferon and ribavirin treatment, SVR rates were 0% in patients who were subsequently treated with peginterferon and ribavirin, 33% in patients who received response-guided boceprevir plus peginterferon and ribavirin, and 34% in patients who received 48 weeks of boceprevir-based triple therapy. As was seen in other groups, response rates were higher among patients who showed greater declines in HCV RNA level, with SVR rates exceeding 70% in some instances.

Among patients with a reduction in HCV RNA level of at least  $1.0 \log_{10}$  after the 4-week lead-in period, the positive predictive value of attaining SVR was 80% in SPRINT-2 and 76% in RESPOND-2. However, the negative predictive value—which reflects the likelihood of not attaining SVR if the patient's reduction in HCV RNA level was less than  $1 \log_{10}$  after the lead-in period—was only 67% in both SPRINT-2 and RESPOND-2. This finding indicates that nearly one third of patients with a poor virologic response during lead-in therapy

still attain SVR when subsequently treated with boceprevir plus peginterferon and ribavirin. Dr. Vierling concluded that responses during the lead-in period can facilitate individualized patient discussions about the probability of overall treatment response in both treatment-naïve patients and patients who previously failed treatment.

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## Risk of Hepatocellular Carcinoma Is Reduced in HCV-Treated Patients Who Achieve SVR

Previous studies have suggested that HCV treatment reduces the risk of developing hepatocellular carcinoma (HCC), irrespective of cirrhosis. Meta-analyses have reported a risk reduction of approximately 55–57% with interferon treatment versus no treatment, including a 52% risk reduction among nonresponders versus untreated patients.<sup>1,2</sup> Although informative, these studies have focused on the effect of interferon mono-

therapy; they have not evaluated the benefit of more current regimens, such as pegylated interferon or combination therapy with peginterferon plus ribavirin. Moreover, these analyses have primarily been single-center studies conducted in Japan and Europe, and the number of patients in these studies has been small.

To better understand the correlation between HCV treatment and HCC risk, Kramer and colleagues

conducted a retrospective, observational, cohort study of HCV-infected individuals with and without cirrhosis.<sup>3</sup> This analysis included data from 1996 through 2006 extracted from the Veterans Affairs (VA) HCV Clinical Case Registry, a clinical database of all HCV-infected patients receiving care across 128 VA facilities.

To be included in this analysis, patients had to have an HCV index date between 1998 and 2005, detect-

**ABSTRACT SUMMARY Analysis of Healthcare Costs Associated with HCV Infection**

The estimated cost of HCV infection in the United States was nearly \$5.5 billion in 1997, and this cost is expected to increase over the next several decades.<sup>1,2</sup> To estimate the incremental effects of HCV infection on healthcare costs in a real-world setting, McCombs and colleagues analyzed data from a US health insurer.<sup>3</sup>

In this study, the researchers identified patients with newly diagnosed HCV infection between 2003 and 2008, and cost analyses were conducted on data from patients with at least 2 years of uninterrupted eligibility. A 2-year observation period was defined for each patient, starting from the first observed HCV diagnosis or the start of drug therapy. To determine the incremental cost effect of HCV infection, costs incurred by these HCV-infected patients were compared with costs incurred by a cohort of matched indi-

viduals without HCV infection. Exclusion factors included hepatitis B virus infection, HIV infection, cirrhosis, liver cancer, or liver transplantation in the past year.

The database included 60,806 patients with HCV infection, all of whom had at least 2 HCV-related diagnoses or a single diagnosis plus a prescription for an interferon-based HCV medication or ribavirin. Of this group, 11,165 patients (18%) had a full year of eligibility prior to the index date. In addition to these patients, 408,631 control patients with at least 2 years of continuous eligibility were identified. Using data from these 419,796 patients, a logistic model identified several factors that were significantly associated with HCV infection: age (with incidence peaking at 45–55 years;  $P < .0001$ ); male gender ( $P < .0001$ ); living in the South ( $P < .0001$ ); and use of specific prescription drugs, including

beta blockers, CCI, insulin, hypotension medications, and loop diuretics ( $P < .05$ ).

The average cost of healthcare in the first year after HCV diagnosis or initiation of therapy was significantly higher in the HCV-infected patients than the control group (\$37,390 vs \$13,575;  $P < .0001$ ); this difference translated into an incremental cost of nearly \$24,000 in the first year (Table 1). Adverse events that occurred at significantly higher rates in HCV-infected patients included hospitalization (odds ratio [OR], 2.3), depression (OR, 2.0), cirrhosis (OR, 82.2), hepatic cancer (OR, 25.8), and liver transplantation (OR, 58.4;  $P < .0001$  for each).

Given the significant healthcare costs associated with HCV infection and the risk of multiple adverse events, the authors concluded that more effective and better-tolerated treatments for HCV infection could provide both health improvements and cost savings.

**Table 1. Costs Associated with New Hepatitis C Virus (HCV) Diagnosis**

Cost in first year	HCV-infected	Non-HCV-infected	Observed incremental cost	P-value
Total	\$37,390	\$13,575	\$23,815	<.0001
Medical	\$28,484	\$11,738	\$16,746	<.0001
Ambulatory	\$14,286	\$6,811	\$7,475	<.0001
Hospital	\$11,468	\$4,016	\$7,452	<.0001
Prescriptions	\$8,907	\$1,837	\$7,070	<.0001

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able viremia, and more than 1 visit to a VA facility. Patients who started peginterferon after September 2005 were excluded, as were patients with HCC prior to or within 1 year of the HCV index date. VA administrative files from January 2007 through September 2010 were queried to deter-

mine the incidence of HCC based on ICD-9 codes; VA vital status files were searched to determine dates of death. To evaluate the significance of cirrhosis, patients with cirrhosis were identified based on the presence of a validated ICD-9 code. HCV treatment was defined as at least 2 pre-

scriptions for peginterferon plus ribavirin, with the first dose administered prior to September 30, 2005. SVR was defined as all HCV RNA results being negative after the completion of treatment, with 1 negative test result at least 12 weeks after the completion of treatment.

The study cohort included 123,319 patients with chronic HCV infection. Patients' mean age was 50 years, and 97% were male. Thirty-nine percent of patients were white, and 25% were black; data on race and/or ethnicity were missing for 31% of patients. Almost half of patients (47%) had HCV genotype 1 or 4 infection, 11% had genotype 2 or 3 infection, and the genotype was unknown in 42% of patients. Cirrhosis was reported in 13% of patients.

A total of 3,500 cases of HCC were observed during nearly 8 years of follow-up, yielding an overall rate of HCC in this cohort of 3.7 per 1,000 person-years. The incidence of HCC was 1.4 per 1,000 person-years in patients who underwent treatment and attained SVR, 4.9 per 1,000 person-years in patients who received treatment but did not attain SVR, and 3.6 per 1,000 person-years in patients who received no treatment. In the subset of patients with cirrhosis, the incidence of HCC was 16.8 per 1,000 person-years for all patients with cirrhosis, 6.9 per 1,000 person-years in treated patients who attained SVR, 16.6 per 1,000 person-years in treated patients who did not attain SVR, and 17.6 per 1,000 person-years in untreated patients.

**Table 2.** Risk of Hepatocellular Carcinoma in Various Groups as Determined by Cox Multivariate Models

Model	Variable	Hazard ratio	95% CI	P-value
Overall cohort (n=123,319)	HCV treatment with SVR	0.29	0.22–0.39	<.0001
	HCV treatment without SVR	0.95	0.86–1.06	.33
Cirrhosis cohort (n=16,301)	HCV treatment with SVR	0.34	0.23–0.48	<.0001
	HCV treatment without SVR	0.83	0.72–0.96	.01

CI=confidence interval; HCV=hepatitis C virus; SVR=sustained virologic response.

In a multivariate analysis that controlled for significant demographic factors and comorbidities—including medical issues, mental health issues, and substance abuse—the risk of HCC was found to be reduced by 71% in treated patients who achieved SVR versus untreated patients (hazard ratio, 0.29;  $P<.0001$ ; Table 2). In the overall cohort, no HCC risk reduction was seen for treated patients who did not achieve SVR versus untreated patients. Among patients with cirrhosis, HCV treatment that yielded SVR was associated with a 66% reduction in the risk of HCC compared to no treatment,

and treatment that did not achieve SVR was associated with a 17% reduction in the risk of HCC.

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## IL-28B Genotype Affects SVR Rates Following Treatment with Telaprevir Plus Peginterferon and Ribavirin

Single nucleotide polymorphisms (SNPs) near the interleukin (IL)-28B gene are highly associated with responses to peginterferon and ribavirin in patients with genotype 1 HCV infection.<sup>1,2</sup> To evaluate the significance of *IL-28B* polymorphisms as a predictor of response to telaprevir-based regimens, Jacobson and col-

leagues compared SVR rates among *IL-28B* genotypes in patients from the ADVANCE trial.<sup>3</sup> The ADVANCE trial was a randomized, double-blind, placebo-controlled, phase III trial that evaluated telaprevir in combination with peginterferon and ribavirin in treatment-naïve patients with genotype 1 HCV infection. A total

of 1,088 patients were randomly assigned to 1 of 3 treatment arms: telaprevir plus peginterferon and ribavirin for 12 weeks, followed by peginterferon and ribavirin alone for 12 or 36 weeks, depending on the patient's extended rapid virologic response (eRVR) status; telaprevir plus peginterferon and ribavirin for

8 weeks, followed by peginterferon and ribavirin for 16 or 40 weeks depending on eRVR status; or peginterferon and ribavirin alone for 48 weeks. SVR was defined as undetectable levels of HCV RNA at the end of treatment and 24 weeks after the last planned dose of study drug.

The investigators verified that their diagnostic assay could provide consistent genotype determinations for the rs12979860 SNP. Using 72 control samples divided evenly among each genotype, the researchers found 100% correspondence. The assay performance was subsequently confirmed using more than 2,500 independent tests, which showed that the assay was highly reproducible.

In the current analysis, *IL-28B* genotype was determined for 454 of the 1,088 patients (42%) in the ADVANCE trial who were enrolled at study sites in the United States. The analysis included only white patients, due to the small number of nonwhite individuals enrolled in the study and the requirements of the deidentification procedure. The most common genotype was C/T (49%), followed by C/C (33%), and then T/T (18%).

The investigators reported that adding telaprevir to the treatment regimen substantially improved SVR rates across all *IL-28B* genotypes (Table 3). The differences were most dramatic in patients with the C/T and T/T alleles, in whom SVR rates were more than doubled with telaprevir-containing therapy versus peginterferon and ribavirin alone. In general, SVR rates were similar among patients with C/T and T/T genotypes.

In the ADVANCE trial, eRVR (defined as HCV RNA negativity at Weeks 4 and 12) resulted in assignment to a shorter duration of therapy. The duration of therapy appeared to have a greater effect in patients with the T allele than in patients with the C/C genotype; in the former group, an additional 4 weeks of therapy were associated with at least a 10% increase

in SVR. When data from the 2 telaprevir-containing arms were pooled, an analysis showed that most telaprevir-treated patients who attained eRVR also attained SVR: 97% of patients with the C/C genotype, 88% of patients with the C/T genotype, and 85% of patients with the T/T genotype. In contrast, SVR rates were low

among patients who did not attain eRVR: 63% of patients with the C/C genotype, 33% of patients with the C/T genotype, and 46% of patients with the T/T genotype.

Dr. Jacobson concluded that HCV treatment consisting of telaprevir plus peginterferon and ribavirin increases SVR rates across all *IL-28B*

### ABSTRACT SUMMARY Telaprevir May Extend Patients' Life Span and Reduce Long-Term Complications Associated with HCV

Brogan and colleagues presented results of a decision-analytic model designed to assess the potential long-term clinical value of telaprevir-based therapy in patients with genotype 1 HCV infection.<sup>1</sup> The researchers used Microsoft Excel to develop a model with a treatment phase and a post-treatment phase that could estimate long-term outcomes following treatment with telaprevir plus peginterferon and ribavirin versus peginterferon and ribavirin alone. The patient population included in the model consisted of a group of treatment-naïve patients and a group of treatment-experienced patients who had received prior therapy with peginterferon and ribavirin. Patients were modeled through a 72-week decision-tree treatment phase mirroring the ADVANCE and REALIZE clinical trials, then were moved through a long-term, post-treatment phase. The probability of adverse clinical outcomes and mortality risks were obtained from the published literature and US life tables.

According to this model, telaprevir-based therapy would extend patients' life span by an average of 2.0 years in treatment-naïve patients and 3.4 years in treatment-experienced patients, compared to treatment with peginterferon and ribavirin alone. Quality-adjusted life-years would be extended by 2.4 years and 3.8 years, respectively.

Over patients' remaining lifetime, telaprevir-based therapy would be expected to reduce the risk of compensated cirrhosis, decompensated cirrhosis, HCC, and liver transplantation by approximately half compared to treatment with peginterferon and ribavirin alone. Telaprevir-based therapy would also reduce the risk of HCV-related death by nearly half: from 24.8% to 12.6% in treatment-naïve patients, and from 42.0% to 21.6% in treatment-experienced patients.

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**Table 3.** Sustained Virologic Response (SVR) Rates in the ADVANCE Trial According to Interleukin-28B Genotype

Patient population	SVR rate		
	T12PR	T8PR	PR
All white patients in ADVANCE trial	75%	80%	46%
C/C genotype	90%	84%	64%
C/T genotype	75%	57%	25%
T/T genotype	73%	59%	23%

PR=peginterferon and ribavirin; T8PR=8 weeks of triple therapy including telaprevir, followed by peginterferon and ribavirin alone; T12PR=12 weeks of triple therapy including telaprevir, followed by peginterferon and ribavirin alone.

genotypes. SVR rates were higher in patients without the T allele, but telaprevir-based therapy yielded the greatest incremental benefit in SVR rates for patients with the T allele. eRVR rates were also higher across *IL-28B* genotypes with telaprevir-based therapy compared to peginterferon and ribavirin therapy. Most patients who attained eRVR subsequently attained SVR, but even in this

group, SVR rates varied somewhat across genotypes; SVR rates were slightly higher in patients with the C/C genotype compared to the C/T or T/T genotype. This trend toward higher SVR rates in patients with the C/C genotype was more pronounced among patients who did not attain eRVR. Further studies, including those in nonwhite patients, are needed to confirm these findings.

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## Efficacy and Safety of Boceprevir in Combination with Peginterferon $\alpha$ -2a and Ribavirin

In previous trials of boceprevir, such as SPRINT-2 and RESPOND-2, this agent was evaluated in combination with peginterferon  $\alpha$ -2b and ribavirin. Although the IDEAL trial showed no significant differences between peginterferon  $\alpha$ -2a and peginterferon  $\alpha$ -2b in terms of SVR rates or tolerability, the combination of boceprevir plus peginterferon  $\alpha$ -2a and ribavirin has not been evaluated in a clinical trial. To investigate the efficacy and safety of this combination, Flamm and colleagues therefore undertook Protocol 05685, a randomized trial of peginterferon  $\alpha$ -2a and ribavirin with or without bocepre-

vir in patients with genotype 1 HCV infection who previously failed treatment.<sup>1</sup>

The entry criteria for this study were identical to those used for RESPOND-2, and patients were similarly categorized as being either relapsers or nonresponders; prior relapsers achieved undetectable levels of HCV RNA yet failed to achieve SVR, while prior nonresponders achieved at least a 2  $\log_{10}$  decrease in plasma HCV RNA level by Week 12 but never reached undetectability. Patients who failed to achieve at least a 2  $\log_{10}$  decline in HCV RNA level by Week 12 were excluded from the current study.

Patients were randomly assigned 1:2 to receive 4 weeks of peginterferon and ribavirin followed by 44 weeks of peginterferon and ribavirin plus either placebo (n=67) or boceprevir (n=134). Stratification was based on response to prior treatment (nonresponse vs relapse) and HCV genotype (1a vs 1b). Patients with detectable levels of HCV RNA at Week 12 stopped treatment due to futility.

Patients in this study had a mean age of 53 years and were primarily male (64% and 72% in the control and boceprevir-treated groups, respectively). Approximately two thirds of patients were prior relapsers, and nearly

## ABSTRACT SUMMARY Determining Effective Durations of Telaprevir and Peginterferon-Plus-Ribavirin

Clinical trials evaluating the efficacy and safety of telaprevir have used varying durations of treatment; in addition to testing various durations of telaprevir, these studies have also experimented with different durations of peginterferon and ribavirin. Using data from phase III studies in treatment-naïve patients, Adiwijaya and colleagues generated a viral dynamic model to determine the optimal durations of each drug.<sup>1</sup> In general, the prospectively predicted SVR rates from the current study were comparable to the SVR rates observed in clinical trials.

According to the current model, 8 weeks of telaprevir in treatment-naïve patients is associated with a predicted SVR rate of 62–70%; the corresponding SVR rate observed in the ADVANCE trial was 69%.<sup>2</sup> Similarly, a 12-week treatment duration of telaprevir is associated with a predicted SVR rate of 72–78%; observed SVR rates in the ADVANCE and ILLUMINATE trials were 75% and 72%, respectively.<sup>2,3</sup> According to the model, extending the treatment duration to 24 weeks did not appear to increase the SVR rate (predicted range, 73–79%).

In treatment-experienced patients, the predicted SVR rate was 43–51% with

8 weeks of telaprevir and 59–66% with 12 weeks of telaprevir. Again, extending the treatment duration to 24 weeks did not improve the predicted SVR rate (61–69%). This finding is in agreement with the PROVE-3 trial, which found no substantial improvement in SVR rates with 24 weeks versus 12 weeks of telaprevir therapy.<sup>4</sup> Notably, the PROVE-3 trial did find an increase in treatment discontinuations with longer therapy; during the final 12 weeks of treatment, 8% of patients discontinued treatment due to adverse events.

In patients who achieved eRVR (defined as an undetectable level of HCV RNA at Weeks 4 and 12), the model predicted a 1% increase in SVR rate if peginterferon and ribavirin treatment was used for 24 weeks versus 48 weeks. This trend was observed in the ILLUMINATE trial among patients who attained eRVR; SVR rates were 92% in patients who received 24 weeks of peginterferon and ribavirin and 88% in patients who received 48 weeks of peginterferon and ribavirin therapy. In this patient population, treatment discontinuation rates due to adverse events were 1% with 24 weeks of treatment and 12% with 48 weeks of treatment.

The researchers concluded that their model supports the use of telaprevir for 12 weeks in treatment-naïve and treatment-experienced patients; it also supports the use of peginterferon and ribavirin for 24 weeks in treatment-naïve patients who attain eRVR.

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one fourth of patients had advanced fibrosis (METAVIR F3/F4). Patients were primarily from North America (72% in the control group and 69% in the boceprevir-treated group), with the remainder being European. Black individuals comprised only 9% and 12% of the control and boceprevir-treated groups, respectively. More than half of patients in each group had

subtype 1a infection (56% and 57%, respectively), and approximately two thirds had an HCV RNA level above 800,000 IU/mL (75% and 81%, respectively).

SVR rates at 24 weeks post-treatment were significantly higher in patients treated with boceprevir plus peginterferon  $\alpha$ -2a and ribavirin compared to those treated with pegin-

terferon  $\alpha$ -2a and ribavirin alone. This finding held true for the overall population (64% vs 21%;  $P < .0001$ ), prior nonresponders (47% vs 5%), and prior relapsers (70% vs 28%; Figure 1). Relapse rates were also lower among patients treated with boceprevir plus peginterferon  $\alpha$ -2a and ribavirin compared to those treated with peginterferon  $\alpha$ -2a and

### ABSTRACT SUMMARY Resistance-Associated Amino Acid Variants in Boceprevir-Treated Patients

In the phase II SPRINT-1 study, resistance-associated amino acid variants (RAVs) were identified that were associated with differential responses to boceprevir.<sup>1</sup> In the current analysis, Howe and colleagues expanded on this finding by performing a longitudinal analysis of RAVs identified in patients from the SPRINT-1 study.<sup>2</sup> The current analysis included 6 patients who attained SVR and 23 patients who did not attain SVR (15 with genotype 1a infection and 8 with genotype 1b infection).

The investigators used population sequencing to detect amino acid variants at boceprevir resistance loci in the NS3/4A protease, and broad-spectrum 454 sequence analysis was used for detailed analyses of variants at specific NS3 amino acid positions. Initial samples were obtained at baseline and/or at 1–4 time points postbaseline; follow-up samples were obtained after

Week 72 from eligible patients who were enrolled in the long-term follow-up study. Approximately 2,200 clones were sequenced at each time point.

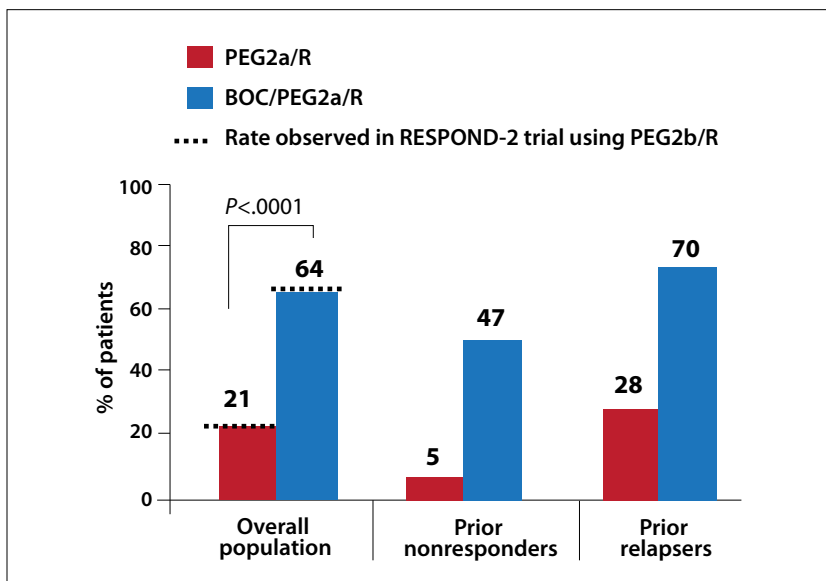
Overall, most of the RAVs identified through population sequencing occurred at a frequency of 10–20% according to 454 sequencing. However, 454 sequencing identified variants occurring at a lower rate (approximately 2.5–5.0%) that were not detected by population sequencing.

Among patients with genotype 1a infection, the most common RAVs in patients with incomplete virologic responses were V36, R155, and T54. RAVs were also detected in patients with breakthrough responses. In patients with genotype 1b infection, commonly detected RAVs included T54, A156, V158, and V170. Variants at T54, A156, and V170 were also found in patients with breakthrough responses.

The analysis revealed no new RAVs at baseline, though the limit of detection was 2.5%. The authors noted that 2 RAVs—V36M and R155K—appeared to be linked, as they were detected at a frequency approaching 100% in several subjects. Finally, as has been previously reported, the researchers found that some patients did attain SVR despite having RAVs at baseline, including T45S and R155K.

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2. Howe JA, Qiu P, Ogert RA, et al. Frequencies of resistance-associated amino acid variants detected by 454 sequencing during combination treatment with boceprevir plus peginterferon (peginterferon alfa-2B)/ribavirin in HCV (G1)-infected patients. Presented at Digestive Disease Week; May 7–10, 2011; Chicago, Illinois. Abstract Su1874.



**Figure 1.** Sustained virologic response at 24 weeks post-treatment.

BOC=boceprevir; PEG=peginterferon; R=ribavirin

ribavirin alone; again, this finding held true in the overall study population (12% vs 33%), prior nonresponders (30% vs 67%), and prior relapsers (6% vs 28%).

As has been observed in other clinical trials of boceprevir, HCV RNA reductions after the 4-week lead-in period were associated with overall responses to therapy, although a proportion of patients with poor responses to interferon still attained SVR with boceprevir-containing therapy. Among patients with a decline in HCV RNA level of less than 1 log<sub>10</sub> after the lead-in period, SVR rates were 39% with boceprevir plus peginterferon and ribavirin versus 0% with peginterferon and ribavirin alone. Corresponding SVR rates among patients who achieved a Week 4 HCV

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## ABSTRACT SUMMARY Safety of Boceprevir-Based Therapy

Manns and colleagues presented the results of a boceprevir safety analysis that included data from the SPRINT-1, SPRINT-2, and RESPOND-2 trials.<sup>1</sup> Safety was assessed in patients who received at least 1 dose of any study medication; the analysis included 1,548 patients who received boceprevir plus peginterferon and ribavirin and 547 patients who received peginterferon and ribavirin alone. The duration of therapy exceeded 24 weeks in 78% of patients, and total boceprevir exposure was approximately 840 patient-years.

Serious adverse events occurred in 11% of boceprevir-treated patients and 8% of patients who received peginterferon and ribavirin alone, and the adverse event profile observed in this study reflected toxicities that are known to be associated with peginterferon and ribavirin. However, boceprevir was associated with an increase in hematologic effects and dysgeusia. Common treatment-related adverse events that occurred at equal or higher rates in patients receiving boceprevir-based triple therapy compared to patients receiving peginterferon and ribavirin alone included fatigue (57% of both groups), anemia (49% vs 29%, respectively), headache (44% vs 43%, respectively), and nausea (45% vs 40%, respectively). Table 1 shows adverse events for which the difference in incidence between arms was at least 5%.

Rates of treatment-emergent neutropenia due to boceprevir were higher in previously untreated patients compared to patients who had previously failed treatment (25% vs 14%, respectively); this finding is likely due to

the fact that previously treated patients were excluded from RESPOND-2 if their absolute neutrophil count was less than 1,500 cells/mm<sup>3</sup> (<1,200 cells/mm<sup>3</sup> for

black patients). The investigators noted that boceprevir-treated patients were more likely to receive granulocyte colony-stimulating factor than patients

**Table 1. Adverse Events Occurring at Least 5% More Frequently with Addition of Boceprevir to Peginterferon and Ribavirin**

Adverse event	Boceprevir plus peginterferon and ribavirin (n=1,548)	Peginterferon and ribavirin (n=547)
Anemia	49%	29%
Nausea	45%	40%
Dysgeusia*	37%	15%
Diarrhea	23%	18%
Neutropenia	23%	18%

\*Described as metallic taste, earthy aftertaste, and bitter taste.

**Table 2. Duration of Treatment-Related Adverse Events with Response-Guided Treatment Versus 48-Week Treatment with Boceprevir Plus Peginterferon and Ribavirin\***

Adverse event	Mean duration of adverse event (weeks)	
	Response-guided treatment (n=282)	48-week boceprevir plus PR (n=288)
Any adverse event	36	44
Fatigue	32	38
Insomnia	28	39
Arthralgia	26	26
Headache	20	25
Anemia	19	26
Depression	16	28
Neutropenia	15	20
Nausea	15	20
Chills	8	10
Diarrhea	7	12
Suicidal ideation	2	6

\*Only includes patients with undetectable levels of hepatitis C virus RNA at Week 8. PR=peginterferon plus ribavirin.

(Abstract Summary continues on the following page.)

**ABSTRACT SUMMARY (Continued) Safety of Boceprevir-Based Therapy**

receiving peginterferon and ribavirin alone (9% vs 6%). However, rates of infection were similar in both groups (18% vs 17%). Finally, thrombocytopenia was reported in 4% of patients receiving boceprevir and 1% of patients receiving peginterferon and ribavirin alone (grade 3/4: 3% vs 1%).

Toxicity did not appear to limit treatment duration. Discontinuations due to adverse events occurred in only 1% of patients receiving boceprevir and 0% of patients in the control arm. However, dose modifications (of any study drug) were sometimes required;

adverse events led to dose modifications in 13% of patients receiving boceprevir plus peginterferon and ribavirin and 8% of patients receiving peginterferon and ribavirin, though peginterferon accounted for most of the modifications.

Finally, this study found that response-guided therapy appears to provide a safety benefit by decreasing exposure to all drugs in qualifying patients. A combined analysis of patients in the SPRINT-2 and RESPOND-2 trials who attained HCV RNA negativity at Week 8 showed a shorter duration

of treatment-related adverse events with response-guided therapy compared to 48-week boceprevir-based triple therapy. This analysis showed a shorter mean duration of any adverse event (36 weeks vs 44 weeks, respectively), as well as shorter durations for specific adverse events (Table 2).

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RNA decline of at least  $1.0 \log_{10}$  were 71% and 25%, respectively.

The highest SVR rates in this study were observed in boceprevir-treated patients with undetectable levels of HCV RNA at Weeks 8 and 12 (89%), followed by control patients with undetectable levels of HCV RNA at Weeks 8 and 12 (44%). Among patients with detectable levels of HCV RNA at Week 8 but undetectable levels at Week 12, SVR rates were 42% in boceprevir-treated patients and 16% in the control group.

In terms of adverse events, this study revealed no safety findings that had not been previously reported with boceprevir plus peginterferon  $\alpha$ -2b and ribavirin. Adverse events that occurred at least 10% more frequently in the boceprevir-treated group compared to the control group included anemia (50% vs 33%), nausea (39% vs 27%), dysgeusia (39% vs 15%), neutropenia (31% vs 18%), diarrhea (25% vs 7%), and rash (23% vs 7%). Overall, boceprevir is the only protease inhibitor to have demonstrated effi-

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## Commentary

Steven L. Flamm, MD

Chronic HCV infection is a worldwide scourge—afflicting approximately 170 million people—and it is responsible for significant morbidity and mortality. Standard therapy for HCV consists of peginterferon  $\alpha$  and ribavirin, but SVR rates with this treatment are poor for patients with genotype 1 HCV infection (approximately 40–45%). Many patients do not respond to therapy, and many others relapse after attaining negative viral titers during therapy. Furthermore, many patients opt to defer therapy because the SVR rates associated with treatment are relatively low and side effects are considerable, despite the fact that achieving SVR is thought to diminish the chances of advanced liver disease and/or death. Overall, the number of patients who have failed therapy or who refuse therapy is substantial. This unmet medical need has provided the impetus for research efforts to improve treatment outcomes for patients with HCV infection, hopefully in the setting of acceptable tolerability.

Fortunately, many classes of medications are currently under investigation, the most advanced of which include DAA agents. Two products, telaprevir and boceprevir, have been the subject of phase II and pivotal phase III trials, data from which have been presented previously, and both products were recently approved by the US Food and Drug Administration (FDA) for use in treatment-naïve and treatment-experienced patients with genotype 1 HCV infection. Important presentations discussed in this supplement represent additional analyses from these studies, as well as a new presentation of a phase III trial of boceprevir in treatment-experienced patients. These presentations represent attempts to further delineate pretreatment and on-treatment

predictors of success, explain the ramifications of treatment failure, understand safety and tolerability issues, and define the impact of therapy on adverse outcomes such as HCC and pharmacoeconomics.

Pretreatment variables that are known to influence treatment outcomes with peginterferon  $\alpha$  and ribavirin include gender, baseline viral load, histologic status, HIV status, and other factors. In recent years, researchers also noted that allelic differences near the *IL-28B* gene are the strongest predictors of SVR. Some physicians have used this test to help make treatment decisions such as whether to treat patients or whether to continue therapy in patients with a low likelihood of response and an unfavorable *IL-28B* genotype. An unanswered question has been whether *IL-28B* polymorphisms have the same predictive value in patients treated with protease inhibitors.

Jacobson and colleagues sought to assess the predictive value of *IL-28B* polymorphisms in patients from the ADVANCE trial who were treated with telaprevir-based regimens. Jacobson reported that patients of all *IL-28B* genotypes benefited from the addition of telaprevir, compared to treatment with peginterferon  $\alpha$  and ribavirin alone; patients with the C/T and T/T genotypes benefited the most. In the treatment group that received 12 weeks of telaprevir, patients with the C/C genotype had the best outcome (90% SVR), but the difference in SVR rates compared to the other genotypes (75% with C/T and 73% with T/T) was not as significant as it was in the control group (64% SVR for C/C, 25% for C/T, and 23% for T/T).

This study also found that eRVR was an important predictor of SVR regardless of *IL-28B* genotype. For patients without eRVR, however, higher SVR rates were present in the C/C genotype compared to the C/T or T/T genotype. It is important to note that only white patients were included in this assessment, so the results may

not be applicable to other patient populations. In white patients, *IL-28B* testing appears to provide limited prognostic information for patients on telaprevir-based regimens. However, this information appears unlikely to affect treatment decisions, and therefore such testing cannot be advocated at this time. Additional investigation is necessary to confirm these findings, particularly in nonwhite patients.

An on-treatment predictor of SVR with peginterferon  $\alpha$  and ribavirin is HCV RNA levels at Week 4 of therapy. Patients with an HCV RNA reduction greater than  $1 \log_{10}$  by Week 4 have a significantly increased likelihood of SVR compared to patients who have a decline less than  $1 \log_{10}$ . Boceprevir-based regimens employ a lead-in strategy in which triple therapy with the protease inhibitor is preceded by a 4-week course of peginterferon  $\alpha$  and ribavirin. An outstanding question has been whether the virologic response at the end of the lead-in period predicts subsequent response.

Vierling and colleagues sought to determine the relationship between interferon responsiveness at Week 4 and SVR using data from the phase III SPRINT-2 and RESPOND-2 trials. In treatment-naïve patients with genotype 1 HCV infection, patients who attained a less-than- $1 \log_{10}$  decline in HCV RNA levels at Week 4 benefited greatly from the addition of boceprevir. Such patients benefited the most from a predetermined course of 44 weeks of triple therapy, as opposed to a response-guided therapy regimen (3% SVR with control therapy, 28% with response-guided therapy, and 38% with 44 weeks of triple therapy). Based on these findings, the FDA has recommended that clinicians consider a 44-week regimen of triple therapy for treatment-naïve patients with poor interferon responsiveness, rather than response-guided therapy. In treatment-experienced patients, the addition of boceprevir also greatly enhanced SVR in patients with poor interferon

responsiveness (0% with control therapy, 33% with response-guided therapy, and 34% with 44-week triple therapy). Conversely, the positive predictive value of HCV RNA declines greater than 1 log<sub>10</sub> by Week 4 with subsequent addition of boceprevir was excellent, with SVR rates of 80% in treatment-naïve patients and 76% in treatment-experienced patients. Because approximately 33% of patients who exhibited poor interferon responsiveness still attained SVR, Week 4 HCV RNA response does not represent an appropriate discontinuation point for futility.

Esteban and coworkers studied the effect of historical response (partial response vs relapse) in comparison to interferon responsiveness at Week 4 as a predictor of SVR in previously treated patients on boceprevir-based regimens in the RESPOND-2 trial. Multivariate analysis showed that interferon responsiveness at Week 4 was a stronger predictor of SVR than historical treatment response. It is important to note that HCV RNA assessment at Week 4 does not represent a decision time-point for boceprevir-based regimens, with the possible exception of deciding to extend triple therapy to 44 weeks in treatment-naïve patients with poor interferon responsiveness. Rather, assessment at Week 4 provides prognostic information for individual patients on antiviral therapy.

To date, all phase III trials with telaprevir have involved peginterferon  $\alpha$ -2a and ribavirin, and phase III trials with boceprevir have involved peginterferon  $\alpha$ -2b and ribavirin. In a presentation at this year's DDW conference, I reported on the final results of a phase III trial investigating boceprevir in combination with peginterferon  $\alpha$ -2a and ribavirin in patients who previously failed therapy with peginterferon  $\alpha$  and ribavirin alone (partial responders or relapsers). Patients either received re-treatment with peginterferon  $\alpha$  and ribavirin or treatment with boceprevir (4-week lead-in with peginterferon  $\alpha$  and ribavirin followed by 44 weeks

of triple therapy). The findings nearly replicated the results of the previously reported RESPOND-2 trial, which involved the same patient populations. SVR significantly increased with the addition of boceprevir (47% in the boceprevir arm vs 5% in the control arm for previous partial responders; 70% in the boceprevir arm vs 28% in the control arm for previous relapsers). Furthermore, no new adverse events were reported. This study confirms the efficacy of boceprevir in patients who previously failed therapy, and it endorses the efficacy and safety of boceprevir with either of the peginterferon  $\alpha$  products.

Although SVR is much higher with protease inhibitors, some patients still do not respond. A new concern in patients who receive DAAs but do not respond is the development of RAVs. Many variants are present at baseline, and others may develop during therapy. A previous report regarding telaprevir-related RAVs suggested that the frequency of RAVs returned to baseline in less than 1 year after discontinuation of antiviral therapy. At this year's DDW conference, Howe and colleagues presented an analysis of RAVs in patients treated with boceprevir. Definitive RAVs were present in patients with incomplete virologic response and breakthrough as detected by population sequencing (10–20%) and broad-spectrum 454 sequencing (2.5–5%). There was some overlap but also differences in RAV profiles among HCV genotypes 1a and 1b. The authors noted that some patients with baseline RAVs still achieved SVR. These preliminary reports are important, but additional investigation is necessary to understand the implications of resistance in incomplete virologic responders and patients with breakthrough. For example, a study is needed to assess the possible development of multimutation RAVs and their significance.

On a different note, previous studies have suggested that interferon therapy reduces the risk of HCC in

patients with chronic HCV infection. Meta-analyses have indicated a significant risk reduction (52%) even among nonresponders compared to untreated patients. However, these studies have generally been single-center studies comprised of small numbers of patients. Kramer and colleagues reported on a retrospective, clinical database assessment of more than 123,000 patients with HCV in which they sought to determine the effect of antiviral therapy on the risk of HCC. The study was plagued by the issues often encountered in retrospective database assessments, such as missing data and unclear treatment regimens (HCV treatment was defined as having a minimum of 2 prescriptions of peginterferon  $\alpha$  and ribavirin). However, multivariate analysis revealed that the risk of HCC was reduced by 71% in treated patients versus untreated patients. Furthermore, there was no HCC risk reduction in treated patients without SVR compared to untreated patients. In cirrhotic patients, SVR was associated with a 66% reduction in the risk of HCC, while treatment without SVR was associated with a 17% reduction in risk. This provocative study suggests that SVR provides an important favorable long-term outcome, both overall and in cirrhotic patients, and that treatment is beneficial in cirrhotic patients.

These reports help us understand how to interpret pretreatment and on-treatment predictors of response to telaprevir- and boceprevir-based antiviral regimens, and they have direct implications for clinical practice. Increased SVR may result in decreased rates of HCC and lower rates of decompensated liver disease. This is the dawn of a new age for antiviral therapy for genotype 1 HCV infection. In the long term, regimens with other small molecules will also be assessed. Regimens with 4 drugs—peginterferon  $\alpha$ , ribavirin, a protease inhibitor, and a second small molecule such as a polymerase inhibitor or an NS5a inhibitor—and interferon-free regimens are also under investigation.

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