Advances in the Treatment of Hepatitis C Virus Infection

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Abstract: Therapy for chronic hepatitis C virus (HCV) infection with pegylated interferon α and ribavirin leads to suboptimal rates of viral eradication in patients with genotype 1 HCV, the most common viral strain in the United States and many other countries. Recent advances in the study of viral kinetics, host factors that predict response to antiviral therapy, and viral protein structure have established the foundation of a new era in the treatment of HCV infection. The HCV NS3/4A protease inhibitors boceprevir and telaprevir, the first 2 agents in a new and promising generation of direct-acting antiviral agents to have completed phase III studies, were approved by the US Food and Drug Administration in May 2011. The addition of these HCV protease inhibitors to standard therapy has been demonstrated to dramatically improve sustained virologic response rates, both in treatment-naïve patients and in prior relapsers and nonresponders. These novel agents represent only the beginning of a revolution in HCV therapy, which will include additional protease inhibitors as well as other classes of drugs currently under investigation, such as polymerase inhibitors, NS5A inhibitors, and host factor inhibitors such as cyclophilin antagonists. The future of HCV therapy holds promise for significantly higher sustained virologic response rates with shorter treatment durations, as well as the intriguing potential to achieve virologic cure with interferon-free combination therapy regimens.

Keywords
Hepatitis C virus, genotype 1, boceprevir, telaprevir, direct-acting antiviral agents

Infection with hepatitis C virus (HCV) is a global health concern, with up to 170 million persons infected worldwide.[1] HCV infection is a leading cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma, and it is the most common indication for adult liver transplantation in the United States.[2]

In recent years, standard therapy for HCV infection has consisted of a combination of pegylated interferon α (Peg-IFN-α) and ribavirin (RBV). Over the past decade, clinicians have been able to refine their use of these agents through an increased under-

standing of how viral kinetics predict success or failure of a course of treatment, allowing the duration of therapy to be tailored based on viral response in some patients. However, in most patients with genotype 1 HCV, 48 weeks of treatment has remained the standard therapy. Studies and clinical experience have also established the importance of weight-based RBV for the treatment of patients with genotype 1 HCV infection.

Despite these advances, combination therapy with Peg-IFN-α and RBV (Peg-IFN/RBV) leads to cure in only approximately half of treated patients, and genotype 1 HCV, the most prevalent HCV strain in the United States, remains the most difficult to eradicate with standard therapy. Sustained virologic response (SVR) rates for genotype 1 HCV are approximately 40–50% following 48 weeks of Peg-IFN/RBV; SVR rates are even lower among black patients, individuals with high viral loads, or patients with advanced fibrosis.[3-5]

A culminating event in the era of Peg-IFN/RBV therapy was the discovery of a group of single nucleotide polymorphisms (SNPs) in the region of the interleukin-28B (*IL-28B*; type 3 λ interferon) gene.[6] For reasons that remain a focus of intense investigation among scientists, these SNPs are the most powerful baseline predictors of response to Peg-IFN/RBV therapy identified to date, especially in patients with genotype 1 HCV. There is now a commercially available test for the first described and best studied of these SNPs. With the *IL-28B* test conferring an ability to predict SVR to Peg-IFN/RBV therapy over a greater–than–2-fold range (69% SVR in patients with the CC genotype of the *IL-28B* rs12979860 polymorphism compared to 27–33% in patients with the CT or TT genotype), determination of *IL-28B* genotype had begun to be incorporated into the informed discussion with patients about treatment even before protease inhibitors were approved.

The next leap forward in HCV therapy was marked by the development of direct-acting antiviral (DAA) agents. Recent advances in the understanding of HCV structure and replication facilitated the development of agents that directly inhibit viral enzymes involved in the HCV life cycle. Whereas the mechanism of antiviral effect of Peg-IFN and RBV in the treatment of HCV is nonspecific, DAA agents target HCV-encoded viral proteins. Actual or potential targets include the NS3/4A serine protease, NS5A replication complex protein, NS5B RNA–dependent RNA polymerase, and NS4B and NS3 helicase proteins. Two inhibitors of the NS3/4A serine protease, telaprevir (Incivek, Vertex Pharmaceuticals) and boceprevir (Victrelis, Merck), have now been approved by the US Food and Drug Administration (FDA) based on extensive phase III trials, thus ushering in the era of specifically targeted therapy in the treatment of chronic hepatitis C (CHC). Tables 1 and 2 summarize SVR data from some of these boceprevir and telaprevir trials.

Boceprevir and Telaprevir

Early Boceprevir Studies

Boceprevir is a selective, peptidomimetic, NS3 protease inhibitor that forms a covalent but reversible enzyme-inhibitor complex. It exhibits potent in vitro activity in the HCV replicon system.[7] An early in vivo study further demonstrated viral response to boceprevir in nonresponders with genotype 1 HCV who were treated with Peg-IFN with and without RBV.[8]

SPRINT-1, the phase II, multicenter boceprevir trial, included 520 treatment-naïve, genotype 1 HCV patients recruited at 67 sites in North America and Europe.[9] Patients were randomized to 1 of 5 arms: 2 lead-in arms consisting of 4 weeks of Peg-IFN-α-2b and weight-based RBV (800–1,400 mg daily) followed by the addition of boceprevir (800 mg 3 times daily) for an additional 24 or 44 weeks; 2 no–lead-in arms consisting of boceprevir 3 times daily plus Peg-IFN-α-2b and RBV (800–1,400 mg daily) for 28 or 48 weeks total; and the standard-of-care arm consisting of 48 weeks of Peg-IFN-α-2b plus RBV (800–1,400 mg daily). A second portion of the study evaluated low-dose RBV (400–1,000 mg daily) versus full-dose RBV (800–1,400 mg daily) combined with boceprevir and Peg-IFN-α-2b for a total of 48 weeks.

The investigators found higher SVR rates in all 4 boceprevir groups (54–75%) compared to standard-of-care treatment (38%), and SVR rates were higher in patients who received a longer treatment duration of boceprevir: 75% in the 48-week boceprevir lead-in group, 67% in the 48-week no–lead-in boceprevir group, 56% in the 28-week boceprevir lead-in group, and 54% in the 28-week boceprevir no–lead-in group. In the second part of the trial, low-dose RBV was shown to be inferior to full-dose RBV, with SVR rates of 36% and 50%, respectively. This observation has had an impact on subsequent drug development programs by reinforcing the importance of standard RBV dosing in investigational regimens with new drugs.

Analysis of adverse events revealed higher rates of anemia in the boceprevir groups (55%) compared to the standard-of-care arm (34%). The use of erythropoietin reduced the discontinuation rate secondary to adverse events from 10–26% to 2–8% in the boceprevir groups; the discontinuation rate in the control arm was 9%. Poordad and colleagues retrospectively analyzed hemoglobin decline during the Peg-IFN/RBV lead-in phase of treatment in SPRINT-1; these results were presented in abstract form at the 2010 Annual Meeting of the American Association

Table 1. Sustained Virologic Response (SVR) Rates of Telaprevir (T) and Boceprevir (BOC) in Treatment-Naïve Patients

Trial	Regimen*	SVR rate (%)
ADVANCE	PR48	44
	T8PR	69
	T12PR	75
SPRINT-2 (nonblack cohort)	PR48	40
	BOC/PR48	68
	RGT	67
SPRINT-2 (black cohort)	PR48	23
	BOC/PR48	53
	RGT	42

*Details of the full dosing regimens can be found in the article.

PR48=pegylated interferon-α/ribavirin for 48 weeks; RGT=response-guided therapy; T8PR=telaprevir for 8 weeks plus pegylated interferon/ribavirin; T12PR=telaprevir for 12 weeks plus pegylated interferon/ribavirin.

Table 2. Sustained Virologic Response (SVR) Rates of Telaprevir (T) and Boceprevir (BOC) in Treatment-Experienced Patients

Trial	Regimen*	SVR rate (%)
REALIZE (overall)	PR48	17
	T12PR	64
	T12PR (with lead-in)	66
Relapsers	PR48	24
	T12PR	83
	T12PR (with lead-in)	88
Partial responders	PR48	15
	T12PR	59
	T12PR (with lead-in)	54
Null responders	PR48	5
	T12PR	29
	T12PR (with lead-in)	33
RESPOND-2 (overall)	PR48	21
	BOC/PR48	66
	RGT	59
Relapsers	PR48	29
	BOC/PR48	75
	RGT	69
Partial responders	PR48	7
	BOC/PR48	52
	RGT	40

*Details of the full dosing regimens can be found in the article.

PR48=pegylated interferon-α/ribavirin for 48 weeks; RGT=response-guided therapy; T12PR=telaprevir for 12 weeks plus pegylated interferon/ribavirin.

for the Study of Liver Diseases (AASLD), held in Boston, Massachusetts.[10] The authors determined that the degree of hemoglobin decline during the lead-in period identified those patients who were at risk for further declines in hemoglobin level following the addition of boceprevir; this finding suggests that those patients might benefit from closer monitoring and, possibly, earlier initiation of erythropoietin therapy.[10] Analysis of adverse events by the SPRINT-1 investigators also demonstrated that patients in the boceprevir groups experienced significantly more dysgeusia compared to controls (27% vs 9%, respectively). Boceprevir was not associated with higher rates of skin rash.

Phase III Boceprevir Studies

The final results of SPRINT-2 were recently published; this study was a phase III, international, multicenter trial of boceprevir in combination with Peg-IFN-α-2b/RBV in 1,097 treatment-naïve genotype 1 HCV patients (938 nonblack and 159 black).[11] All patients received 4 weeks of lead-in therapy with Peg-IFN/weight-based RBV (600–1,400 mg daily) and were then randomized to 1 of the following arms: placebo plus Peg-IFN/RBV for an additional 44 weeks (standard-of-care arm); boceprevir (800 mg 3 times daily) plus Peg-IFN/RBV for an additional 44 weeks (48-week arm); or boceprevir (800 mg 3 times daily) plus Peg-IFN/RBV for an additional 24 weeks, with a further 20 weeks of Peg-IFN/RBV in some patients (response-guided therapy [RGT] arm). Patients in the RGT arm who had undetectable serum HCV RNA levels (as measured by the Roche Taqman v2.0 polymerase chain reaction [PCR] assay) at Weeks 8–24 stopped therapy after a total of 28 weeks; Peg-IFN/RBV therapy was continued for another 20 weeks in those patients who had serum HCV RNA levels that were detectable at any time during Weeks 8–24. All patients with detectable levels of HCV RNA at Week 24 were discontinued from the study. Nonblack and black patient cohorts were analyzed separately.

As expected, SVR rates in the standard-of-care arm were lower in the black cohort (23%) than in the nonblack cohort (40%). In the nonblack cohort, SVR rates were significantly higher in both boceprevir groups compared to the control group: 68% in the boceprevir/Peg-IFN/RBV 48-week treatment group ($P<.0001$ vs control) and 67% in the RGT group ($P<.0001$ vs control). Boceprevir also significantly improved SVR rates in the black cohort: 53% in the boceprevir/Peg-IFN/RBV 48-week treatment group ($P=.004$ vs control) and 42% in the RGT group ($P=.04$ vs control). A modified intent-to-treat analysis

of the black cohort, including only those patients who received at least 1 dose of boceprevir, demonstrated SVR rates of 53% in the boceprevir/Peg-IFN/RBV 48-week group and 47% in the RGT group.

Detailed subgroup analysis was undertaken to compare SVR rates in the 2 boceprevir groups in SPRINT-2.[11,12] In the nonblack cohort, not only were overall SVR rates similar in the 2 groups, but SVR rates were similar in those patients who achieved persistently undetectable HCV RNA levels during Weeks 8–24 (96% vs 97%, respectively). In nonblack patients with HCV RNA levels that were detectable during Weeks 8–24 (but undetectable at Week 24) who received more than 28 weeks of therapy, SVR rates were identical (74%) whether patients received 24 or 44 weeks of boceprevir en route to a total of 48 weeks of therapy. As reported in the FDA briefing document, when both cohorts were pooled, it was found that late responders (patients with HCV RNA levels that were detectable after Week 8 but undetectable at Week 24) had SVR rates of 75% and 66% in the 48-week treatment group and the RGT group, respectively.[13] This result was interpreted as a potentially clinically meaningful difference. Along with the results of the HCV RESPOND-2 study in treatment-experienced patients (see below), which involved 32 weeks of triple therapy out of 48 weeks total therapy, this analysis led to the now FDA-approved regimen for late responders: 32 weeks of boceprevir (not 24 weeks, as in the SPRINT-2 trial) plus Peg-IFN/RBV after the 4-week lead-in period, followed by a 12-week tail of Peg-IFN/RBV.

Additional analyses demonstrated that the degree of HCV RNA decline at the end of the 4-week lead-in phase was the strongest predictor of SVR.[14] In patients with a decline of less than 1 $\log_{10}$ in HCV RNA level, SVR rates were 39% and 29% in the 48-week and RGT arms, respectively, versus 82% and 83%, respectively, in patients with better responsiveness to Peg-IFN. Similarly, the degree of Peg-IFN responsiveness was predictive of the risk of emergence of resistant viral variants.[15]

Discontinuation of therapy secondary to adverse events in SPRINT-2 was similar across the 3 arms: 16% for both the standard-of-care group and the 48-week boceprevir/Peg-IFN/RBV group, versus 12% for the RGT group. As first observed during SPRINT-1, anemia was more common in boceprevir-treated patients (49%) compared to control patients (29%). While dose reduction secondary to anemia was required more often in patients receiving boceprevir compared to control patients (21% vs 13%), treatment discontinuation was rare in all arms (2% vs 1%, respectively). Overall, nearly twice as many boceprevir-treated patients than control patients had a hemoglobin level below 9.5 g/dL or a requirement for erythropoietin (43% vs 24%, respectively). Dysgeusia was more than twice as common in boceprevir-treated patients. In addition, grade 3 neutropenia (absolute neutrophil count [ANC] of 500 to <750/mm^3) occurred in 24% of boceprevir-treated patients versus 14% of control patients (P<.001), while grade 4 neutropenia (ANC <500/mm^3) occurred in 7% of boceprevir-treated patients versus 4% of control patients.

While SPRINT-2 focused on treatment-naïve patients with genotype 1 HCV, the contemporaneously published HCV-RESPOND-2 trial provided hope for patients who had been previously treated with Peg-IFN/RBV.[16] Enrolled patients included partial responders, who had at least a 2-$\log_{10}$ reduction in HCV RNA level by Week 12 of prior therapy but persistent viremia at Week 24, and relapsers, who attained undetectable HCV RNA levels at the end of treatment but did not achieve SVR. The control and experimental regimens were similar to those of SPRINT-2 except that the period of triple therapy was longer in the RGT group: Patients received either Peg-IFN/RBV for 48 weeks (control); 4 weeks of lead-in therapy with Peg-IFN/RBV followed by boceprevir plus Peg-IFN/RBV for 44 weeks; or 4 weeks of lead-in therapy followed by RGT, which consisted of either boceprevir plus Peg-IFN/RBV for an additional 32 weeks if serum HCV RNA levels were undetectable at Week 8, or boceprevir plus Peg-IFN/RBV for an additional 32 weeks followed by 12 more weeks of Peg-IFN/RBV if serum HCV RNA levels were detectable at Week 8. All patients with detectable levels of HCV RNA at Week 12 were discontinued from the study.

The poor SVR rate in the control group (21%) was significantly improved in both the 48-week boceprevir group (66%) and the RGT group (59%). As expected, prior relapsers had higher SVR rates than prior nonresponders in all 3 arms (29% in the control group, 75% in the 48-week group, and 69% in the RGT group). The authors further showed that the highest SVR rate occurred in patients who achieved a decline in HCV RNA level of at least 1 $\log_{10}$ at the end of the 4-week lead-in period ("good response to Peg-IFN") and received 44 weeks of boceprevir plus Peg-IFN/RBV: 79%, versus 73% in the RGT group. Patients in the boceprevir groups with a decline of less than 1 $\log_{10}$ in HCV RNA level during the lead-in period ("poor response to Peg-IFN") had significantly higher SVR rates than similar patients in the control group (34% and 33%, respectively, vs 0% in the control group).

Discontinuation secondary to adverse events was reported in 12% of patients in the 48-week group, 8% of patients in the RGT group, and 2% of control patients. Anemia was more common in the boceprevir groups (43–46%) versus the control group (20%), although treatment discontinuation secondary to anemia was rare in all groups (0% in the control group and 0–3% in the boceprevir groups).

Analysis of SVR rates by *IL-28B* subtype was undertaken in the 62% and 66% of patients with available genetic testing results in SPRINT-2 and RESPOND-2, respectively.[17] Overall, 29% of patients in the 2 boceprevir studies were *IL-28B* subtype CC, 54% were CT, and 18% were TT. In the control group of SPRINT-2, SVR rates were found to be 50–51% higher in patients with the favorable CC genotype compared to patients with the CT or TT genotype. The CC patients in the boceprevir treatment arms had SVR rates 9–27% higher than CT or TT patients, but the proportional increase in SVR was much greater in the CT and TT patients. Among prior treatment failure patients in RESPOND-2, SVR rates in the control group were not clearly impacted by *IL-28B* genotype. The addition of boceprevir was noted to significantly increase SVR rates across all *IL-28B* genotypes. The authors concluded that viral response at the end of the 4-week Peg-IFN/RBV lead-in period superseded the predictive value of *IL-28B* for SVR in both treatment-naïve and treatment-experienced patients.

Early Telaprevir Studies

Telaprevir is a selective, peptidomimetic, NS3 protease inhibitor that forms a covalent, reversible enzyme-inhibitor complex that has shown potent in vitro antiviral activity in HCV replicon systems.[18] Subsequent research demonstrated that in vivo antiviral activity of telaprevir was augmented by Peg-IFN coadministration.[19]

The efficacy of telaprevir in combination with Peg-IFN/RBV in treatment-naïve patients with genotype 1 HCV was evaluated in PROVE 1 and PROVE 2, the initial, phase IIb North American and European multicenter telaprevir trials.[20-23] PROVE 1 included 263 patients who were randomized to 1 of 3 telaprevir arms or standard-of-care therapy. In the experimental groups, telaprevir was given orally (1,250 mg twice daily for 1 day followed by 750 mg every 8 hours thereafter) for a total of 12 weeks in combination with Peg-IFN-α-2a (180 mcg weekly) and RBV (1,000–1,200 mg daily) administered for a total of 12 weeks (T12PR12), 24 weeks (T12PR24), or 48 weeks (T12PR48). The standard-of-care patients received Peg-IFN-α-2a (180 mcg weekly) and RBV (1,000–1,200 mg daily) for 48 weeks total plus placebo for the first 12 weeks. Patients in the T12PR24 and T12PR48 groups had significantly higher SVR rates than the standard-of-care group: 61% and 67% versus 41%, respectively. Patients in the T12PR12 group had a 35% SVR rate; while this rate was lower than the SVR rate in the control group, it provided proof-of-concept for curability of HCV infection with a short (12-week) duration of protease inhibitor–based therapy in some patients.

Adverse events leading to discontinuation of therapy occurred significantly more often in the telaprevir groups (21%) versus the control group (11%). The most significant adverse event in the telaprevir groups was severe rash, occurring in 7% of telaprevir-treated patients versus 1% of control patients.

In the PROVE 2 study, 334 patients were randomized to standard-of-care therapy or telaprevir (1,250 mg daily for 1 day followed by 750 mg daily thereafter) for a total of 12 weeks in combination with either Peg-IFN-α-2a alone for 12 weeks (T12P12) or Peg-IFN-α-2a and weight-based RBV for a total of 12 weeks (T12PR12) or 24 weeks (T12PR24). Patients in the standard-of-care arm received Peg-IFN-α and weight-based RBV for 48 weeks total plus placebo for the first 12 weeks (PR48). Patients in the T12PR24 and T12PR12 groups had significantly higher SVR rates (69% and 60%, respectively) compared to the standard-of-care group (46%). The importance of concomitant RBV administration in future HCV treatment regimens was illustrated by the low SVR rate (36%) in the T12P12 arm. Even more than the finding in SPRINT-1 that reduced RBV dosing impairs SVR, this finding in the PROVE 2 study has had the profound impact of demonstrating the importance of RBV in regimens containing DAA drugs, despite the relative inactivity of RBV when given as monotherapy to patients with HCV infection.

Similar to PROVE 1, PROVE 2 showed that telaprevir was well tolerated overall, although there were significantly more adverse events in the telaprevir group. The most notable adverse event was again skin rash, leading to discontinuation of therapy in 7% of patients who received the 3-drug regimens (T12PR24 and T12PR12). Rashes were noted to be severe (grade III) in 6% of telaprevir-treated patients.

The final phase IIb telaprevir study, PROVE 3, investigated telaprevir in combination with Peg-IFN-α-2a/RBV in genotype 1 CHC patients who were prior nonresponders (patients who never achieved undetectable HCV RNA levels on prior therapy) or relapsers to Peg-IFN/RBV therapy.[24] Patients were randomized to 1 of 4 groups: standard-of-care therapy with Peg-IFN-α-2a/RBV for 48 weeks (PR48); telaprevir (750 mg every 8 hours) plus Peg-IFN-α-2a alone for 24 weeks (T24/P24); 12 weeks of telaprevir plus Peg-IFN-α-2a/RBV followed by 12 additional weeks of Peg-IFN-α-2a/RBV (T12/PR24); or 24 weeks of telaprevir plus Peg-IFN-α-2a/RBV followed by 24 additional weeks of Peg-IFN-α-2a/RBV (T24/PR48).

The most robust responses were observed in the triple therapy groups. Notably, 48 weeks of triple therapy did not appear to be superior to 24 weeks of triple therapy, with virtually equivalent SVR rates of 51% in the T12/PR24 group and 53% in the T24/PR48 group, both of which were significantly higher than the 14% SVR rate in the standard-of-care group. Patients in the RBV-sparing group

again fared less well, with an SVR rate of 24% in the T24/P24 group. Prior relapsers had the best response to retreatment with a telaprevir-based regimen, with SVR rates of 69% and 76% in the T12/PR24 and T24/PR48 groups, respectively, compared to 20% in the standard-of-care arm and 42% in the RBV-sparing arm. Patients with prior viral breakthroughs who were treated with triple therapy also had increased SVR rates: 57% in the T12/PR24 group and 62% in the T24/PR48 group, compared to 40% and 36% in the standard-of-care group and the RBV-sparing group, respectively. Even prior nonresponders who were treated with triple therapy had significantly improved SVR rates: 39% and 38% in the T12/PR24 and T24/PR48 groups, respectively, versus 9% in the standard-of-care arm and 11% in the RBV-sparing arm.

The safety profile of telaprevir in PROVE 3 was similar to that of PROVE 1 and PROVE 2. Discontinuation of therapy because of adverse events was again more common in patients who received a telaprevir-based regimen compared to the control group (15% vs 4%, respectively). Skin rash was the most notable adverse event, occurring in 51% of patients in the telaprevir arms, with severe rash noted in 5% of telaprevir-treated patients. In addition, in all the phase II studies, telaprevir induced an incremental degree of hemoglobin decline of 1.0–1.5 g/dL relative to that associated with Peg-IFN/RBV alone.

Phase III Telaprevir Studies

In the pivotal phase III ADVANCE study, RGT regimens with telaprevir were compared to standard-of-care therapy in 1,088 patients with genotype 1 CHC.[25] Patients were randomized to 1 of 3 treatment arms: telaprevir (750 mg every 8 hours) plus Peg-IFN-α-2a/RBV for 8 weeks followed by additional weeks of Peg-IFN-α-2a/RBV (T8); telaprevir plus Peg-IFN-α-2a/RBV for 12 weeks followed by additional weeks of Peg-IFN-α-2a/RBV (T12); or standard-of-care therapy consisting of Peg-IFN-α-2a/RBV for 48 weeks (PR48). Patients in the telaprevir arms who achieved undetectable levels of HCV RNA at Weeks 4 and 12 as measured by the Roche Taqman v2.0 PCR assay (ie, extended rapid viral response [eRVR]) were treated for a total of 24 weeks, whereas those who did not achieve eRVR were treated for a total of 48 weeks.

Treatment with telaprevir led to significantly higher SVR rates, with 75% and 69% of patients in the T12 and T8 groups achieving SVR, respectively, compared to 44% of patients in the PR48 group (P<.0001). Patients in the telaprevir arms were much more likely to have undetectable levels of HCV RNA at Weeks 4 and 12 (eRVR): 58% in T12 and 57% in T8, versus 8% in PR48. Achieving eRVR was highly predictive of SVR in all groups (89%, 83%, and 97% in the T12, T8, and PR48 groups, respectively). SVR rates were significantly improved with the addition of telaprevir in patients of all races. In black patients, SVR rates were increased to 62% and 58% in the T12 and T8 groups, respectively, from 25% in the PR48 group. Telaprevir also significantly improved SVR rates in patients with bridging fibrosis or cirrhosis: 62% in the T12 group versus 33% in controls.

For patients with an undetectable viral load at the end of therapy, relapse rates were 9%, 9%, and 28% in the T12, T8, and PR48 groups, respectively. In this study, virologic failure was defined as (1) meeting a stopping rule (telaprevir was stopped if HCV RNA levels were above 1,000 IU/mL at Week 4, while all therapy was stopped if the decline in HCV RNA level at Week 12 was less than 2 $\log_{10}$ or there was a detectable HCV RNA level at Week 24); (2) having an HCV RNA level above 1,000 IU/mL at Week 12; or (3) having a detectable HCV RNA level at the end of treatment. Virologic failure was lower in the telaprevir-treated patients than control patients (8% in the T12 group and 13% in the T8 group vs 32% in the PR48 group). Virologic failure was more common in patients with genotype 1a than genotype 1b because of the lower barrier to resistance of genotype 1a to telaprevir (a property shared with boceprevir).

Discontinuation of therapy due to adverse events over the entire course of treatment was more common in the telaprevir groups: 10% in both the T8 and T12 groups versus 7% in the PR48 group. Discontinuation was most commonly secondary to anemia or rash in the telaprevir groups. Grade III rash occurred in 6% of patients in the T12 group versus 4% of patients in the T8 group. The overall discontinuation rates secondary to adverse events were lower than in the PROVE trials, most likely owing to sequential rather than simultaneous discontinuation of study drugs when severe rash occurred in the ADVANCE trial, unlike in earlier telaprevir studies. Anemia (hemoglobin level <10 g/dL) was more common in the telaprevir groups: 36% in the T12 group and 40% in the T8 group versus 14% in the PR48 group. Anemia led to discontinuation of study drugs in 1%, 3%, and less than 1% of patients in the T12, T8, and PR48 groups, respectively. As suggested in earlier studies, telaprevir was associated with an incremental decline in hemoglobin of 1.0–1.5 g/dL relative to Peg-IFN/RBV alone during the period of telaprevir dosing. Of note, anorectal complaints under several descriptors were common in telaprevir-treated patients, occurring at a rate of 29% in the telaprevir groups versus 7% in controls.

The phase III, open-label ILLUMINATE study was a supportive trial intended to solidify the foundation for RGT with telaprevir, which was strongly suggested by the ADVANCE trial. All patients were treated with 12 weeks of telaprevir plus Peg-IFN-α-2a/RBV; patients who achieved eRVR (undetectable HCV RNA levels at Treat-

ment Weeks [TW] 4 and 12) were then randomized to either 24 or 48 weeks (total) duration of Peg-IFN-α-2a/RBV.[26] Of the 540 enrolled patients, approximately 60% achieved eRVR with 12 weeks of telaprevir-based therapy. The investigators found the 24-week telaprevir-based regimen to be noninferior to the 48-week regimen, with SVR rates of 92% versus 87.5%, respectively. The overall SVR rate was 71.9%. Discontinuation of all study medications secondary to adverse events occurred in 17.4% of patients; discontinuations secondary to anemia and rash occurred in 0.6% and 1.1% of patients during the telaprevir treatment phase, respectively.

The phase III REALIZE trial evaluated the role of telaprevir in Peg-IFN/RBV-experienced patients.[27] A total of 662 genotype 1 HCV-infected patients who were relapsers, partial responders, or null responders (<2-$\log_{10}$ decline in HCV RNA level at Week 12 of prior therapy) were prospectively enrolled and randomized into the control arm or 1 of 2 telaprevir-based treatment arms: telaprevir (750 mg every 8 hours) plus Peg-IFN-α-2a/RBV for 12 weeks followed by Peg-IFN-α-2a/RBV for 36 weeks (simultaneous start arm); or Peg-IFN-α-2a/RBV for 4 weeks, followed by telaprevir (750 mg every 8 hours) plus Peg-IFN-α-2a/RBV for 12 weeks, followed by Peg-IFN-α-2a/RBV for an additional 32 weeks (delayed start arm). The latter arm was the only regimen with a lead-in phase of Peg-IFN-α-2a/RBV in the entire development program for telaprevir. Control patients were treated with 12 weeks of placebo plus Peg-IFN-α-2a/RBV followed by 36 weeks of Peg-IFN-α-2a/RBV alone. Among relapsers, the SVR rate was 86% overall (88% in the delayed start arm and 83% in the simultaneous start arm) compared to 24% in the control group. Among prior partial responders, the SVR rate was 57% (54% and 59% in the delayed start arm and the simultaneous start arm, respectively), versus 15% in the control arm. Finally, 31% of null responders achieved SVR: 33% in the delayed start arm and 29% in the simultaneous start arm, versus 5% in the control arm. The authors concluded that, while both telaprevir-based regimens were superior to standard-of-care therapy, the lead-in (delayed start) regimen did not significantly improve SVR rates over the simultaneous start regimen.

An analysis of the impact of hepatic fibrosis on SVR in the REALIZE trial demonstrated that fibrosis had minimal effect on SVR in relapsers, even if cirrhosis was present, but that cirrhosis did result in decreased SVR rates among partial responders and null responders. The effect of hepatic fibrosis was most dramatic in the latter group, among whom SVR rates were 41% and 39% if mild or bridging fibrosis was present, respectively, compared to only 14% of patients with cirrhosis. Genotype 1 subtype also had an impact on SVR rates, with 10–15% lower SVR rates in prior nonresponders with genotype 1a versus genotype 1b.

Yet another analysis of the lead-in arm of the REALIZE trial evaluated the association between the degree of HCV RNA decline after 4 weeks of Peg-IFN-α-2a/RBV therapy and the subsequent chance of SVR. If HCV RNA level declined by less than 1 $\log_{10}$ at Week 4, relapsers had an SVR rate of 62%, versus 94% with a decline of 1 $\log_{10}$ or greater. For partial responders, SVR rates were 56% and 50%, respectively. The greatest impact was in null responders, who had SVR rates of 15% and 54%, respectively.[28]

Further subgroup analyses of SVR rates by *IL-28B* genotype were undertaken in both the ADVANCE and REALIZE trials.[29,30] In ADVANCE, 42% of patients, all of whom were white, had *IL-28B* testing results available for analysis. Of these patients, 33% were *IL-28B* subtype CC, 49% were CT, and 18% were TT. Telaprevir improved SVR rates in all *IL-28B* subtypes, with an SVR rate of 90% in the CC group and an SVR rate above 70% in the T allele groups. The largest proportionate increase in efficacy was observed in CT and TT patients. Patients with the CC genotype were more likely to achieve eRVR and thereby be eligible for shortened duration of therapy.

In the REALIZE study, a total of 80% of enrolled patients underwent genetic testing. Of these patients, 18% were *IL-28B* subtype CC, 61% were CT, and 21% were TT. The authors concluded that *IL-28B* genotype was not predictive of response in this patient population; thus, *IL-28B* genotype appears to be of limited use in assessing previously treated patients who will be re-treated with a telaprevir-based regimen.

Protease Inhibitor Prescribing Information

With the FDA's approval of boceprevir and telaprevir, practitioners now have official prescribing information for both medications. There are some notable differences between this information and the regimens used in the previously described studies.

Boceprevir is approved for the treatment of genotype 1 CHC; it is available in oral tablets at a dose of 800 mg and is to be taken 3 times daily in combination with Peg-IFN/RBV.[31] Per package instructions, all patients are to receive a 4-week lead-in period of Peg-IFN/RBV, with the addition of boceprevir (3 times daily) in combination with Peg-IFN/RBV thereafter. Treatment duration is determined by RGT criteria, which assess HCV RNA levels at TW8, TW12, and TW24. For treatment-naïve patients with undetectable HCV RNA levels at TW8 and TW24, 3-drug therapy is terminated at TW28. In treatment-naïve patients with detectable HCV RNA levels at TW8 and undetectable HCV RNA levels at TW24, the 3-drug regimen is continued through TW36, followed by

Peg-IFN/RBV alone through TW48. In previous partial responders or relapsers with undetectable HCV RNA levels at TW8 and TW24, the 3-drug regimen is continued through TW36. Patients with HCV RNA levels that are detectable at TW8 and undetectable at TW24 are treated with the extended course of the 3-drug regimen (through TW36), followed by Peg-IFN/RBV alone through TW48. Treatment is determined to be futile if the patient's HCV RNA level is 100 IU/mL or greater at TW12 or detectable at TW24, at which point the 3-drug regimen is to be discontinued. (These recommendations apply to treatment-naïve and treatment-experienced patients.) Package instructions state that RGT was not studied in patients who had a decline of less than 2 $\log_{10}$ in HCV RNA level during prior Peg-IFN/RBV therapy. If boceprevir is used in these null responders, providers are advised to treat for the longer duration of therapy: Peg-IFN/RBV for 4 weeks followed by 44 weeks of the 3-drug regimen. This longer, 48-week duration of triple therapy is also suggested for patients with poor Peg-IFN responsiveness at Week 4 or those with compensated cirrhosis.

Telaprevir has also been approved for the treatment of genotype 1 CHC; it is available in oral tablets at a dose of 750 mg and is to be taken 3 times daily in combination with Peg-IFN/RBV.[32] Package instructions state that patients must receive the 3-drug regimen for 12 weeks, followed by either 12 or 36 additional weeks of Peg-IFN/RBV therapy; duration of RGT depends on both viral response and prior response. Among treatment-naïve patients and prior relapsers, those patients with undetectable HCV RNA levels at Weeks 4 and 12 complete 12 more weeks of Peg-IFN/RBV. The exception to this guideline is that treatment-naïve patients with cirrhosis who have undetectable HCV RNA levels at Weeks 4 and 12 "may benefit" from an additional 36 weeks of Peg-IFN/RBV. Prior nonresponders, whether partial responders or null responders, should receive a total of 48 weeks of therapy (T12PR48). Treatment futility mandating medication discontinuation is defined as an HCV RNA level above 1,000 IU/mL at Week 4 or Week 12 or a detectable HCV RNA level at Week 24 in all categories of patients.

Both telaprevir and boceprevir are at least partially metabolized by, and are potent inhibitors of, CYP3A. For this reason, both drugs are contraindicated in patients taking other medications that are also highly dependent on CYP3A clearance and in which elevated concentrations are associated with serious adverse events. The statin class is an important example of this potential interaction. Specifically, lovastatin and simvastatin are contraindicated with both boceprevir and telaprevir; atorvastatin is also contraindicated with telaprevir. Similarly, protease inhibitors are contraindicated with medications that strongly induce CYP3A, in order to avoid loss of efficacy of the protease inhibitor. Clinicians are strongly advised to become familiar with these drugs and to have drug-drug interaction information readily available in the practice setting when patients are seen. Dose reduction and monotherapy with either medication are also prohibited so as to minimize the emergence of viral resistance.

Future Directions

The FDA approval of telaprevir and boceprevir, while a major leap forward, is not the end of the evolution of HCV therapy. Other potent protease inhibitors that have shown promising results in early trials are in development, including agents given once or twice daily (telaprevir is currently being studied at a dose of 1,125 mg twice daily); also in development are polymerase inhibitors (both nucleoside and non-nucleoside) and a newer class of agents that target the NS5A protein of HCV, which is a crucial element of viral replication.

Results from a phase IIb study of a novel NS3/4a protease inhibitor, TMC435, in combination with Peg-IFN/RBV were presented at AASLD 2010.[33] Investigators randomized 386 treatment-naïve genotype 1 CHC patients to 1 of 5 study arms, 4 of which contained variable doses (75 mg or 150 mg) or durations of RGT with the protease inhibitor. Patients in the TMC435 arms who had HCV RNA levels below 25 IU/mL (detectable or undetectable) at Week 4 and undetectable HCV RNA levels at Weeks 12, 16, and 20 had treatment discontinued at Week 24; the remainder of patients completed 48 weeks total therapy with Peg-IFN/RBV. The authors reported that 79–86% of patients in the TMC435 arms were able to end therapy at Week 24 according to the experimental protocol. SVR rates in patients who were able to shorten therapy were 88–97%. Of particular note, there was no significant difference in adverse events between TMC435-treated patients and patients in the placebo arm, with discontinuation of therapy secondary to adverse events occurring in 7.1% and 7.8% of study participants, respectively. Hyperbilirubinema in the absence of any evidence of necroinflammation, attributed to a transporter effect, was reported with the 150-mg dose of TMC435, which was chosen as the dose for further development in ongoing, phase III trials. Promising preliminary results have been reported in nonresponders and in patients who received TMC435 with other protease inhibitors, including BI201335 and danoprevir.[34,35]

The potential of polymerase inhibitors is illustrated by the recently presented phase II data on RG7128, a nucleoside analogue.[36] Preliminary results from the JUMP-C trial were presented at the 2011 Annual Meeting of the European Association for the Study of the

Liver (EASL), held in Berlin, Germany. Of those patients treated with RG7128 plus Peg-IFN/RBV who achieved eRVR and received 24 weeks of therapy, 76% went on to achieve SVR12 (undetectable HCV RNA levels 12 weeks after cessation of therapy). There was a 24% relapse rate after a total of 24 weeks of therapy, suggesting that a longer duration of therapy may be needed to optimize results with this drug. Preliminary results from PROPEL, a second study on RG7128, showed that the combination of RG7128 plus Peg-IFN/RBV was safe and well tolerated, yielding rapid virologic response (RVR; defined as undetectable HCV RNA levels at TW4) rates of 39–63% and complete early virologic response (cEVR; defined as undetectable HCV RNA levels at TW12) rates of 68–87% in patients with genotype 1 or 4 HCV, 20% of whom were cirrhotic.[37]

Another novel and exciting polymerase inhibitor, PSI-7977, has also demonstrated promising SVR rates in genotype 1 HCV patients, many of whom had poor predictors of Peg-IFN responsiveness, when used in combination with Peg-IFN/RBV.[38] Of 121 treatment-naïve patients, 75% of whom had genotype 1a HCV and 60% of whom had *IL-28B* genotype CT or TT, SVR12 rates were 88% in those who received PSI-7977 (200 mg) plus Peg-IFN/RBV and 91% in those who received the higher dose of PSI-7977 (400 mg) plus Peg-IFN/RBV. There was no observed viral breakthrough. This drug is being further evaluated both in combination with Peg-IFN/RBV and in Peg-IFN–free combinations with other potent agents.

The first SVR12 data on BMS790052, a potent NS5A inhibitor, in genotype 1 HCV-infected patients were presented at EASL 2011.[39] The 2 higher doses of this drug (10 mg and 60 mg daily) were given with Peg-IFN/RBV for 48 weeks; SVR12 rates were 92% and 83%, respectively, compared to 25% with Peg-IFN/RBV alone. Adverse events were similar across all treatment groups.

In addition to focusing on direct inhibition of viral proteins, a recent study demonstrated that drugs that target cellular elements used by HCV during its replicative process, such as cyclophilins, can yield suppressive effects on HCV replication.[40] One such cyclophilin inhibitor, alisporivir, has demonstrated favorable SVR rates in combination with Peg-IFN/RBV.[41] As presented at EASL 2011, 288 treatment-naïve genotype 1 HCV-infected patients were randomized to receive 1 of 4 regimens: alisporivir plus Peg-IFN/RBV for 48 weeks; alisporivir plus Peg-IFN/RBV for 24 weeks; alisporivir plus Peg-IFN/RBV for 24 or 48 weeks (24 weeks for patients achieving RVR and 48 weeks for those who did not); or placebo plus Peg-IFN/RBV for 48 weeks. SVR rates were 76%, 53%, and 69% in the treatment groups, respectively, versus 55% in the control group. Of note, the 48-week alisporivir group had a disproportionately low number of *IL-28B* CC patients compared to the control group (19% vs 33%), possibly leading to an underestimation of the improvement in SVR rates with alisporivir.

Recent attention has begun to focus on alternative approaches to HCV drug development. Given the tolerability profile of Peg-IFN–based regimens, it has been debated for some time whether HCV could be eradicated with Peg-IFN–free regimens that combine DAA agents. The INFORM-1 study evaluated the combination of a protease inhibitor, RG7227 (now called danoprevir), and RG7128, a nucleoside polymerase inhibitor, at varying doses in over 70 genotype 1 CHC patients; this study demonstrated marked viral suppression over a 2-week period with no virologic breakthrough due to resistance.[42] Recently presented studies at AASLD 2010 and EASL 2011 that evaluated combinations of pure antiviral drugs have yielded intriguing early results concerning the principles of Peg-IFN–free regimens. Oral DAA agents can, in fact, confer marked viral suppression; however, dual combinations, at least, appear to require that 1 component should be a drug with a high barrier to resistance, such as a nucleoside analogue, in order to optimize response.

Barring such a component, RBV appears to be a potentially valuable adjunctive third drug, as demonstrated in a trial of a protease inhibitor and a non-nucleoside polymerase inhibitor that featured breakthroughs in the absence of RBV (as a third drug) but showed a protective effect of RBV in another arm.[43] Breakthroughs also occurred in a combination trial involving a protease inhibitor and a potent NS5A inhibitor in prior nonresponders to Peg-IFN/RBV; these breakthroughs were probably related to the fact that each of these drug classes is characterized by a lower genetic barrier to resistance when used alone.[44] In another study of a protease inhibitor and a non-nucleoside polymerase inhibitor, breakthroughs were not seen when RBV was used as a third drug.[45]

One of the most intriguing studies to come out in the past year presented further data from the aforementioned study combining asunaprevir (previously known as BMS-650032), a protease inhibitor, with daclatasvir (previously known as BMS-790052), a potent NS5A inhibitor in 11 null responder patients.[46] When treated for 24 weeks with the 2-drug combination, 7 of the 11 patients (63.6%) achieved RVR, with 5 of the 11 patients remaining undetectable at the end of 24 weeks and 4 of the 11 patients achieving SVR12 with the Peg-IFN–free regimen. These findings provide the eagerly awaited proof-of-concept that HCV infection can be cured without Peg-IFN. In another arm of the same study, 10 of 10 patients who received these drugs plus Peg-IFN and RBV achieved SVR, creating a clear mandate for further studies of such regimens, particu-

larly in more refractory patients, even as Peg-IFN–free studies are expected to expand in scope.

The formulation and initiation of such trials is proceeding at a pace that many did not anticipate until very recently, and if the SVR proof-of-concept is reinforced in Peg-IFN–free trials in the near future, the direction of the field will shift dramatically. At the present time, however, it is important for patients to be informed that the new drugs generating so much interest still require the concomitant administration of Peg-IFN/RBV.

These exciting developments will lead to a mandate for the education of practitioners who treat HCV regarding the optimal use of new agents, including management of side effects, prevention and management of resistance, and awareness of drug-drug interactions. Detailed, ongoing discussions with patients about the timing of treatment (or re-treatment, in treatment-experienced patients) and selection of regimens will undoubtedly be required. We also anticipate numerous new studies of novel HCV therapies in patient populations that have not been included in initial studies, such as HIV co-infected patients (such studies are in progress with protease inhibitors), transplant recipients, and patients with decompensated liver disease. Proper use of these novel agents is expected to have enormous global impact on decreasing the burden of advanced liver disease due to HCV infection.

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