Boceprevir and Telaprevir in the Management of Hepatitis C Virus–Infected Patients

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Recent approval of direct-acting antiviral agents (DAAs) against hepatitis C virus (HCV) offers a major advance in the management of HCV infection. These DAAs, boceprevir and telaprevir, when given with pegylated interferon alfa (Peg-IFN) and ribavirin (RBV), result in a much higher sustained virologic response rate compared with Peg-IFN and RBV. The DAA-containing regimens are approved for HCV genotype 1 infection in HCV treatment–naive and HCV treatment–experienced patients. In this review, we present an overview of pharmacology, efficacy, adverse events, and emergence of resistance-associated variants with the use of these agents. As with all drugs, especially newly approved drugs, clinicians must consult the package insert for detailed prescribing information, list of all reported adverse events, contraindications, and drug interactions.

Chronic infection with hepatitis C virus (HCV) is a prevalent and expensive condition affecting more than 1.3% of the US population at a cost of >$5.5 billion annually. Available data show that successful antiviral treatment slows liver disease progression and improves survival. However, despite the wide availability of antiviral treatments, the proportion of HCV-infected patients eligible for treatment and the rates of treatment initiation and completion is very low [1, 2]. Response to treatment is measured by achievement of sustained virologic response (SVR), defined as absence of demonstrable viral replication 6 months after completion of a full course of treatment. With the current standard of care regimen using pegylated interferon alfa (Peg-IFN) and ribavirin (RBV), only 54%–56% of subjects achieve an SVR, with lower rates reported for those infected with HCV genotypes 1 and 4 (~40%) [3–5]. Thus, a significant proportion of infected patients remains at risk for progression to advanced liver disease or cirrhosis.

Treatment for HCV infection reduces the risk of complications such as hepatocellular carcinoma and improves overall survival. Risk reduction is greatest among those who achieve an SVR or complete a full course of treatment, but benefit is seen in most treated patients [6, 7]. HCV is also associated with a higher risk of diabetes, with a reduction in risk seen among treated persons who achieve SVR [8].

Early-generation serine protease inhibitors (including boceprevir and telaprevir) were developed based on the structure of NS3 protease of HCV genotype 1. HCV genotype 1 is the dominant genotype in North America and Western Europe, and also the most difficult to treat. Therefore, the recent Food and Drug Administration (FDA) approval of the new direct-acting antiviral agents (DAAs) against HCV genotype 1 is welcome news. Although these agents demonstrate some activity against HCV genotype 2, there is very little efficacy against genotype 3. Hence, the approved indication for these drugs is for HCV genotype 1 infection only.

**LIFE CYCLE AND TARGETS FOR ANTI-HCV DRUGS**

The life cycle of HCV begins with the entry of HCV into the host hepatocytes via receptor-mediated endocytosis.
This is followed by uncoating of the virus with the release of single-stranded HCV RNA in the cytoplasm. The HCV RNA attaches to the endoplasmic reticulum, where it is translated into a single large polyprotein. This polyprotein is then processed by viral and host proteases into several structural and nonstructural proteins (Figure 1). The structural proteins assemble new viral particles, and the nonstructural proteins participate in viral replication. The major enzymes involved in posttranslational processing are the NS2-3 protease and the NS3/4A protease. Once the viral genome has been translated, viral replication starts. Viral replication is mediated largely by the nonstructural protein NS5B RdRp (RNA polymerase). This is followed by assembly of virions and release from the infected cells [9, 10].

All of these steps serve as potential targets for DAAs. Both boceprevir and telaprevir directly and specifically inhibit the HCV NS3/4A serine protease, thereby preventing cleavage of the HCV polyprotein chain and halting viral replication [9, 10]. Numerous other agents, including nucleoside, nonnucleoside, and nucleotide RNA polymerase inhibitors, entry inhibitors, and Toll-like receptor 7 agonists are also in development.

**CLINICAL PHARMACOLOGY**

The mechanism of (NS3) protease inhibition involves formation of a stable reversible covalent bond between the ketoamide of the drug and the NS3 protease active site serine, which is the protease that mediates the cleavage of the HCV polyprotein to form the functional proteins essential for viral propagation.

Boceprevir is rapidly absorbed and eliminated (mean plasma half-life, related to metabolism, of 3–5 hours). Exposure to boceprevir increases in a dose-related, but not a dose-proportional, manner over the range of 200–800 mg 3 times per day. Food significantly increases the bioavailability of boceprevir (40%–60%) regardless of fat content, and boceprevir should be administered with meals. Once absorbed, it is extensively metabolized, primarily by aldo-keto reductase and to a lesser degree by CYP3A4/5 enzymes. The predominant metabolic pathway produces inactive, ketone-reduced stereoisomers. Boceprevir and metabolites are eliminated primarily by hepatic clearance. Special population studies concluded that no dose adjustment was needed for subjects with mild or moderate hepatic impairment or with renal impairment. Boceprevir is eliminated predominantly in the feces (~80%) with lesser amounts eliminated in the urine (~9%).

Telaprevir is also rapidly absorbed and has a half-life of 58 minutes [11]. It is taken up by the liver on first-pass metabolism, resulting in high liver concentrations [12]. The systemic exposure to telaprevir was increased by 237% when telaprevir was administered with a standard fat meal compared with fasting state. Because the type of meal significantly affects exposure to telaprevir, it should always be taken with food with at least 20 grams’ fat content. Telaprevir is extensively metabolized in the liver, primarily by cytochrome P450 CYP3A4. Telaprevir is a strong inhibitor of CYP3A4 and a substrate and inhibitor of P-glycoprotein. After oral administration, telaprevir is moderately bound to plasma proteins, primarily to alpha-1-acid glycoprotein and albumin. This binding is concentration dependent, decreasing with increasing concentrations of
CLINICAL TRIALS

Both telaprevir and boceprevir have been evaluated in phase 3 clinical trials. Boceprevir trials include SPRINT-2 in treatment-naive subjects and RESPOND-2 in treatment-experienced subjects [13, 14]. Telaprevir trials include ADVANCE and ILLUMINATE in treatment-naive subjects and REALIZE in treatment-experienced subjects (Table 1) [15–17].

Boceprevir Trials

The SPRINT-2 and RESPOND-2 trials evaluated the efficacy and safety of boceprevir in treatment-naive (n = 1097) and previously treated (n = 403) subjects with HCV genotype 1 [13, 14]. Subjects were randomly assigned to 1 of 3 groups in both trials, including a control group (with Peg-IFN and RBV for 48 weeks) and 2 combination treatment groups (with boceprevir, Peg-IFN, and RBV) (Table 1). These trials employed a “lead-in” strategy during which all study groups received Peg-IFN and RBV for 4 weeks. The rationale for the lead-in phase was to lower the HCV RNA levels before exposure to boceprevir, thereby reducing the risk of viral breakthrough or resistance to the DAA [18]. Subsequently, the control group received Peg-IFN and RBV for the remaining 44 weeks. One of the 2 boceprevir groups received boceprevir plus Peg-IFN–RBV for 44 weeks (Boc-PR fixed-dose group), whereas the second boceprevir group received response-guided treatment (RGT; Boc-PR RGT group); treatment was stopped early (at 28 and 36 weeks in treatment-naive and treatment-experienced subjects, respectively) if subjects had rapid and extended virologic response (undetectable RNA at week 8 that stayed negative through week 24). Those who did not have a response continued Peg-IFN–RBV for an additional 20 weeks to a total of 48 weeks of treatment. The primary end point was the proportion of subjects with an SVR.

Figure 2 displays results from the boceprevir trials. The SVR rate was significantly higher in the boceprevir groups than in the control group for treatment-naive as well as treatment-experienced subjects. Sixty-three percent and 66% of treatment-naive subjects and 60% and 64% of treatment-experienced subjects achieved an SVR with Boc-PR RGT and Boc-PR fixed dose, respectively, compared with 53% and 51% in the control group (P < .0001 for both). A total of 44% of subjects in the RGT group were early responders (undetectable HCV RNA level at weeks 8 through 24) and received a 28-week course of treatment.

Similarly, 69% and 75% of previous relapers had SVR with Boc-PR RGT and Boc-PR fixed dose, respectively, compared with 29% in those receiving Peg-IFN and RBV (P < .001) (Figure 2). Forty percent and 52% of previous partial responders had SVR with Boc-PR RGT and Boc-PR fixed dose, respectively, compared with 7% in those receiving Peg-IFN and RBV. Among African Americans, the SVR rates were 42% versus 23% in treatment-naive subjects and 61% versus 8% in treatment-experienced subjects. Too few subjects had cirrhosis to make any reasonable comparisons in the SVR rates. Previous relapers responded better than previous nonresponders (ie, subjects with a >2 log_{10} decrease who kept detectable HCV RNA levels throughout therapy). A total of 42% of subjects in the RGT group were early responders (undetectable HCV RNA level at weeks 8–24) and received a 36-week course of treatment.

Telaprevir Trials

The ADVANCE and REALIZE trials evaluated the efficacy and safety of telaprevir in treatment-naive (n = 1088) and previously treated (n = 662) subjects with genotype 1, respectively [15, 17]. Subjects were randomized to 3 arms, including the current standard of care with Peg-IFN and RBV for 48 weeks (control group) or to 1 of the 2 combination treatment arms including telaprevir plus Peg-IFN and RBV (Table 1).

In the telaprevir arms, subjects received 8 or 12 weeks of telaprevir in addition to Peg-IFN and RBV (T8PR or T12PR, respectively) followed by Peg-IFN and RBV up to study week 24 (ie, additional 16 or 12 weeks of Peg-IFN and RBV, respectively). Treatment-naive subjects who achieved undetectable levels of HCV RNA at week 4 that extended to week 12 (ie, extended rapid virologic response [eRVR]) stopped therapy at study week 24, whereas those who did not meet these criteria received an additional 24 weeks of Peg-IFN and RBV. All previously treated subjects continued treatment to a total of 48 weeks regardless of eRVR.

Among treatment-naive subjects with genotype 1 HCV infection (ADVANCE trial), the rates of SVR for the T12PR and T8PR groups were 79% and 75%, respectively, compared with 46% in the control group (P < .0001) (Figure 2). Fifty-eight percent of treatment-naive subjects had eRVR and thus could stop treatment early. Telaprevir was efficacious across several subgroups. Specifically, the SVR rate in African Americans was 62%; a similar proportion of subjects with cirrhosis achieved SVR. However, only a small number of subjects were enrolled in these key subgroups.

The ILLUMINATE trial was designed to determine whether there was any additional benefit to extending therapy from 24 to 48 weeks in subjects with eRVR receiving combination treatment [16]. In this study, the SVR rates in the subjects with an eRVR who were randomized to 24 weeks versus 48 weeks of telaprevir were 92% and 88%, respectively, showing that there is no benefit to extending therapy.

Addition of telaprevir to Peg-IFN and RBV similarly improved SVR in treatment-experienced subjects (REALIZE trial) (Figure 2) [17]. Lead-in treatment for 4 weeks with Peg-IFN and RBV before telaprevir treatment in a prior treatment failure
Table 1. Study Designs for the Phase 3 Trials Evaluating the Safety and Efficacy of Direct-Acting Antiviral Agents for Hepatitis C Virus Infection

<table>
<thead>
<tr>
<th>Characteristics of Study Participants</th>
<th>Boceprevir Trials</th>
<th>Telaprevir Trialsa</th>
<th>Boceprevir Trials</th>
<th>Telaprevir Trialsa</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of participants</td>
<td>1 097</td>
<td>403</td>
<td>1 088</td>
<td>662</td>
</tr>
<tr>
<td>Race, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>82</td>
<td>85</td>
<td>89</td>
<td>93</td>
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<tr>
<td>African American</td>
<td>14</td>
<td>12</td>
<td>9</td>
<td>4.5</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>60</td>
<td>60.5</td>
<td>58</td>
<td>69</td>
</tr>
<tr>
<td>Cirrhosis, %</td>
<td>9</td>
<td>12</td>
<td>6</td>
<td>25.5</td>
</tr>
<tr>
<td>Baseline viral load of ≳800,000 IU/mL, %</td>
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<td>87.5</td>
<td>77</td>
<td>88</td>
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<tr>
<td>Response to prior treatment, %</td>
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<td></td>
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<tr>
<td>Null response</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
<td>28</td>
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<tr>
<td>Partial response</td>
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<td>36</td>
<td>NA</td>
<td>19</td>
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<tr>
<td>Relapse</td>
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<td>64</td>
<td>NA</td>
<td>53</td>
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<tr>
<td>Study design</td>
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<tr>
<td>Group 1 (control)</td>
<td>PR for 48 weeks</td>
<td>PR for 48 weeks</td>
<td></td>
<td></td>
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<tr>
<td>Group 2</td>
<td>Lead-in PR for 4 weeks, then boceprevir plus PR for additional 44 weeks</td>
<td>Lead-in PR for 4 weeks, then boceprevir plus PR for additional 44 weeks</td>
<td>Telaprevir plus PR for 8 weeks, then additional weeks of PR based on response</td>
<td>Telaprevir plus PR for 12 weeks, then additional weeks of PR based on response</td>
</tr>
<tr>
<td>Group 3</td>
<td>Lead-in PR for 4 weeks, then boceprevir plus PR for 24 weeks with or without additional weeks of PR based on response</td>
<td>Telaprevir plus PR for 12 weeks, then additional weeks of PR based on response</td>
<td>Telaprevir plus PR for 12 weeks, then additional weeks of PR based on response</td>
<td>Telaprevir plus PR for 12 weeks, then additional weeks of PR based on response</td>
</tr>
<tr>
<td>Study drugs</td>
<td>Peg-IFN 2b</td>
<td>Peg-IFN 2b</td>
<td>Peg-IFN 2a</td>
<td>Peg-IFN 2a</td>
</tr>
<tr>
<td>Interferon type</td>
<td>1.5 µg/kg/week</td>
<td>1.5 µg/kg/week</td>
<td>1.0–1.2 g/day</td>
<td>1.0–1.2 g/day</td>
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<tr>
<td>Interferon dose</td>
<td>0.6–1.4 g/day</td>
<td>0.6–1.4 g/day</td>
<td>0.6–1.4 g/day</td>
<td>0.6–1.4 g/day</td>
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<tr>
<td>Ribavirin dose</td>
<td>800 mg every 8 hours</td>
<td>800 mg every 8 hours</td>
<td>750 mg every 8 hours</td>
<td>750 mg every 8 hours</td>
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<tr>
<td>DAA dose</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Treatment duration</td>
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<tr>
<td>Triple therapy duration</td>
<td>24 or 32 weeks</td>
<td>32 weeks</td>
<td>8 or 12 weeks</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Treatment duration if early responseb</td>
<td>28 weeks</td>
<td>36 weeks</td>
<td>24 weeks</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Treatment duration if no early responseb</td>
<td>48 weeks</td>
<td>48 weeks</td>
<td>48 weeks</td>
<td>48 weeks</td>
</tr>
<tr>
<td>Stopping rules</td>
<td>HCV RNA level of ≥100 IU/mL at treatment week 12, or detectable HCV RNA at treatment week 24</td>
<td>HCV RNA level of ≥100 IU/mL at treatment week 12, or detectable HCV RNA at treatment week 24</td>
<td>HCV RNA level of &gt;1000 IU/mL at treatment week 4, HCV RNA level of &gt;1000 IU/mL at treatment week 12, or detectable HCV RNA at weeks 24–40</td>
<td>HCV RNA level of &gt;1000 IU/mL at treatment week 4, HCV RNA level of &gt;1000 IU/mL at treatment week 12, or detectable HCV RNA at weeks 24–40</td>
</tr>
</tbody>
</table>

Abbreviations: DAA, direct-acting antiviral agent; HCV, hepatitis C virus; NA, not applicable; Peg-IFN, pegylated interferon alfa; PR, pegylated interferon alfa and ribavirin.

a The table does not include the ILLUMINATE trial. The study design and results from the ILLUMINATE trial are discussed in the text.

b The definition of early virologic response to guide response-guided therapy varied for the 2 agents. For telaprevir, it was defined as undetectable levels of HCV RNA at week 4 extended to week 12 of treatment (extended rapid virologic response). These patients were eligible to receive 24 total weeks of therapy. Those who did not meet the criteria but had undetectable HCV RNA levels at week 24 received 48 total weeks of therapy. For boceprevir, early virologic response was defined as undetectable levels of HCV RNA at treatment week 8. If this was extended to week 24 of treatment, then patients were eligible to receive 28 weeks (if treatment naive) or 36 total weeks of therapy (if previously treated). Those who did not have early response continued Peg-IFN–ribavirin for additional weeks to 48 total weeks of treatment.
population did not improve SVR rates over a simultaneous start (groups pooled in the FDA analyses). SVR rates were 86% in prior relapers, 59% in partial responders, and 56% in null responders in the telaprevir group, versus 22%, 15%, and 5% respectively. Furthermore, both trials employed different definitions for early response or treatment futility. Boceprevir trials allowed Subjects who did not achieve SVR to receive further treatment, whereas telaprevir trials did not.

Collectively, these data show that the addition of either DAA to Peg-IFN–RBV results in significantly higher rates of SVR in treatment-naive as well as previously treated subjects with chronic genotype 1 infection, compared with Peg-IFN–RBV alone. However, there are several differences across the trials that limit any direct comparisons. These trials used different formulations of Peg-IFN, different doses of RBV, and different durations of treatment. Furthermore, both trials employed different definitions for early response or treatment futility. Boceprevir trials allowed erythropoietin for anemia; telaprevir trials did not. Given these differences, the results of these trials are not directly comparable.

### TOXICITY AND ADVERSE EVENTS

The effectiveness of these new agents in clinical practice is expected to be partially offset by new challenges with increased adverse events (AEs) and early discontinuation due to these AEs. In all phase 3 trials above, AEs were significantly more frequent in the treatment arms.

Anemia was the most significant AE associated with boceprevir-containing regimens. Approximately one-half (49%) of the subjects receiving boceprevir in the SPRINT-2 trial had anemia (vs 29% in the Peg-IFN–RBV group), requiring erythropoietin administration in 43% (vs 24% in the Peg-IFN–RBV group) [14]. Dysgeusia occurred more than twice as often in boceprevir recipients. Neutropenia (85%) and thrombocytopenia (~30%) were also more common in boceprevir recipients. In pooled analyses, the frequency of discontinuation owing to an AE did not differ significantly between subjects receiving boceprevir and those receiving standard therapy (13% vs 12%).

The most common AEs with telaprevir were pruritis and skin rash. One-half of the subjects receiving telaprevir had pruritis and 56% reported a rash compared with 28% and 34%, respectively, of subjects treated with Peg-IFN and RBV alone [15–17]. The rash is typically eczematous, maculopapular, and papular-lichenoid; occurs within the first 16–20 days of treatment; and generally resolves over 4–6 weeks after completion. The rash was severe in approximately 5% of subjects. Anemia also occurred frequently in subjects receiving telaprevir (37% vs 19% in the control group). Fourteen percent of subjects had a hemoglobin value of <8.5 g/dL with telaprevir compared with 5% with Peg-IFN–RBV. Anorectal AEs (eg, hemorrhoids, rectal burning, and pruritus) were experienced by 29% of subjects receiving telaprevir versus 7% of controls. In pooled analyses, overall treatment discontinuation rates were 17% in the telaprevir arms and 4% in the Peg-IFN–RBV arms.

### RESISTANCE

Due to a very high replication rate and lack of effective proof-reading, it is estimated that every possible nucleotide variant of HCV is produced each day in a given host [19]. Resistance-associated variants (RAVs) are present in small numbers (0.3%–2.8%) in treatment-naive subjects and rapidly emerge as dominant strains after initiation of treatment [20]. The following variants have been reported in treatment-naive subjects: V36M (frequency, 0.9%), R155K (0.7%), V170A (0.2%), and R109K (0.2%) [21]. There are differences in prevalence of RAVs by HCV subtype; individuals infected with HCV genotype 1a strains exhibit a much higher prevalence of

| Table 2. Primary Mutations and Frequencies in Clinical Trials of Subjects Treated With Telaprevir- or Boceprevir-Based Regimens |
|---------------------------------|----------------|----------------|
| **Primary Resistance-Associated Variant** | **Telaprevir** | **Boceprevir** |
| V36A/M<sup>a</sup> | ... | ... |
| T54A/S<sup>a</sup> | ... | ... |
| R155K/T<sup>a</sup> | ... | ... |
| A156S<sup>a</sup> | ... | ... |
| A156T/V<sup>b</sup> | ... | ... |
| V36M<sup>a</sup> | ... | ... |
| T84A<sup>a</sup> | ... | ... |
| R155K<sup>a</sup> | ... | ... |
| V170A<sup>a</sup> | ... | ... |
| A156T<sup>b</sup> | ... | ... |

**Frequency on treatment, %**

- **Treatment-naive subjects**: 12 vs 22 vs 80 vs 22 vs 54 vs 48 vs 92 vs 41
- **Subjects who did not achieve SVR**: Treatment-experienced subjects
- **Subjects with HCV genotype 1a**: 12 vs 22 vs 80 vs 22 vs 54 vs 48 vs 92 vs 41
- **Subjects with HCV genotype 1b**: 12 vs 22 vs 80 vs 22 vs 54 vs 48 vs 92 vs 41
- **Subjects with viral breakthrough**: 12 vs 22 vs 80 vs 22 vs 54 vs 48 vs 92 vs 41
- **Subjects with incomplete response**: 12 vs 22 vs 80 vs 22 vs 54 vs 48 vs 92 vs 41
- **Subjects who were relapers**: 12 vs 22 vs 80 vs 22 vs 54 vs 48 vs 92 vs 41

**Abbreviations**: HCV, hepatitis C virus; SVR, sustained virologic response.

<sup>a</sup> These confer low-level resistance (3–25-fold decrease in median inhibitory concentration for telaprevir and boceprevir, respectively).

<sup>b</sup> These confer high-level resistance (≥50-fold decrease in median inhibitory concentration for telaprevir and boceprevir, respectively).
RAVs compared with those infected with HCV genotype 1b (8.6% vs 1.4%) [20].

In both biochemical and replicon assays, emergence of the following mutations confers moderately reduced susceptibility to boceprevir: V36M/A, T54A/S, R155K/T, V170A, V55A, V158I, and M175L. Significant reduction in susceptibility occurs with A156T and A156V mutations, although it is noteworthy that the replicons carrying the A156T mutation are significantly less fit than replicons carrying other resistance mutations [19]. Double mutations conferred a multiplicative (rather than merely additive) increase in resistance. In phase 3 trials, RAVs were detected at baseline in 7% of subjects, although this did not affect SVR significantly. Emergence of RAVs during treatment was significantly associated with virologic breakthrough or failure.

In subjects receiving a telaprevir-containing regimen, telaprevir-resistant variants were observed in 12% of treatment-naive groups and 22% of treatment-experienced groups. Resistance-associated variants were detected in up to 80% of those who do not achieve an SVR, and this proportion decreased after telaprevir was stopped. Resistance usually emerges during the first 12 weeks of telaprevir use, and RAVs tend to be replaced by wild-type virus over time in the absence of telaprevir selective pressure. (Table 2).

There are likely differences in response to treatment based on the precise RAVs present. It has been suggested that those RAVs which confer low-level resistance (eg, V136M and V170A) may be overcome by high concentration of drugs achieved by the regimens used in recent trials, whereas RAVs that confer...
high-level resistance may only be partially suppressed at best [20, 21]. Further data from recently concluded trials are awaited.

**SPECIAL POPULATIONS**

Currently, there are no published phase 3 studies of DAAs in persons with HCV–human immunodeficiency virus (HIV) co-infection, persons with chronic kidney disease, or children. Based on previous clinical trials using Peg-IFN and RBV, it is likely that these agents, when used in combination with Peg-IFN and RBV, will substantially improve SVR in the HCV–HIV coinfected population, although perhaps not quite to the degree in the HCV mono-infected population. Phase 2 clinical trials as well as pharmacologic studies of these agents in HIV-infected persons, with particular emphasis on drug interactions with antiretrovirals used to treat HIV infection, are ongoing. Data are also lacking in persons with acute HCV infection, decompensated cirrhosis, organ transplant, and hepatitis B virus coinfection.

The use of DAAs is likely to be very limited in patients with chronic kidney disease for reasons of toxicity, particularly of RBV. Because both boceprevir and telaprevir potentiate RBV-associated anemia, the combination has the potential to further aggravate anemia to life-threatening levels. Patients with cirrhosis pose a significant challenge because they are less likely to achieve an SVR compared with those with a lesser degree of fibrosis. Longer treatment duration with the DAAs in combination with Peg-IFN and RBV has been suggested.

**PRESCRIBING DAAs**

Boceprevir is dosed at 800 mg 3 times per day in combination with Peg-IFN plus RBV. Boceprevir should be taken with food, because this increases boceprevir exposure. In treatment-naive patients, after a lead-in phase of 4 weeks with Peg-IFN and RBV alone, boceprevir is added to Peg-IFN and RBV for 24 weeks (to week 28) (Figure 3). If patients have an undetectable HCV RNA level at week 8 of therapy, then treatment can be stopped at 28 weeks. If HCV RNA is detectable at week 8, then triple therapy is continued for an additional 8 weeks (to week 36) followed by an additional 12 weeks of Peg-IFN–RBV (to week 48).

Treatment-experienced patients are separated into partial responders and relapsers or null responders. Previous partial responders and relapsers receive a lead-in phase of 4 weeks with Peg-IFN–RBV followed by triple therapy for 32 weeks (to week 36). If HCV RNA is undetectable at week 8, then all treatment can be stopped at week 36. If HCV RNA is detectable at week 8, then Peg-IFN–RBV is continued for an additional 12 weeks (to week 48). Patients with a prior null response (ie, those who had a <2 log_{10} decrease in HCV RNA level by week 12 of treatment), as well as those with compensated cirrhosis, should receive a lead-in phase of Peg-IFN and RBV for 4 weeks

![Figure 3](https://academic.oup.com/cid/article-abstract/54/1/96/369063)
followed by 44 weeks of triple therapy (to week 48). Additionally, treatment-naive patients who show a poor response to Peg-IFN–RBV lead-in after 4 weeks (\(\leq1\log_{10}\) decrease in HCV RNA level) should also be considered for an additional 44 weeks of triple therapy. These patients may also need to be monitored closely to determine who may benefit from better therapies, once they are available. Conversely, in treatment-naive patients with undetectable HCV RNA levels after the lead-in period, boceprevir administration may not result in a higher rate of SVR than that achieved with the use of Peg-IFN and RBV alone. If the patient has an HCV RNA level of \(\geq100\) IU/mL at week 12, or a confirmed, detectable HCV RNA level at week 24, then triple drug therapy should be discontinued, because these patients are unlikely to achieve an SVR and are at a higher risk for developing resistant mutations.

Telaprevir is dosed at 750 mg 3 times per day (every 7–9 hours) in combination with Peg-IFN plus RBV. Telaprevir should be taken with at least 20 grams of fat. As shown in Figure 4, for treatment-naive patients and prior relapers, the overall duration of treatment is determined by response at weeks 4 and 12. In treatment-naive patients, telaprevir is administered for the first 12 weeks of therapy. In patients who achieve eRVR, Peg-IFN–RBV is administered for an additional 12 weeks for a total duration of 24 weeks; other patients continue Peg-IFN–RBV for a total duration of 48 weeks. In treatment-experienced patients with prior partial or null response, telaprevir is administered for 12 weeks in combination with Peg-IFN–RBV, and treatment with Peg-IFN–RBV is then continued for a total of 48 weeks. Discontinuation of therapy is recommended in patients with HCV RNA levels \(\leq1000\) IU/mL at treatment week 4 or 12 and in those who have a confirmed detectable HCV RNA level at treatment week 24. These patients are unlikely to achieve SVR and are at higher risk for resistance.

Neither DAA should be administered as monotherapy and must only be prescribed with both Peg-IFN and RBV. Dose reductions are not recommended. In patients who fail to eradicate the infection with one DAA, retreatment with the second agent is not recommended because of high risk of resistance.

**FUTURE DIRECTIONS**

The approval of boceprevir and telaprevir offers major advances in the treatment of HCV-infected persons. However, many questions remain, specifically on the use of newer agents for non–genotype 1 HCV–infected persons and the precise roles of interleukin 28B and inosine triphosphatase polymorphisms in the screening and selection of patients. Finally, Peg-IFN and RBV–sparing regimens are in early clinical trials and would represent the next advance in HCV treatment.

**CONCLUSIONS**

Results from the recently reported clinical trials show that the addition of direct-acting protease inhibitors to Peg-IFN plus RBV strongly improves the chance to achieve an SVR in patients with genotype 1 HCV infection. Although these new agents...
will vastly expand the pool of patients who may demand antiviral therapy, advanced physical and mental co-morbidity will continue to be a challenging clinical issue. The benefits of new agents may also be further offset by increased viral resistance and AEs. Despite these considerations, these new additions to the armamentarium against HCV are changing our approach to treatment.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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