Boceprevir and telaprevir are peptidomimetic serine protease inhibitors that have been recently approved for the treatment of HCV chronic infection. The addition of these drugs to the prior standard of care, pegylated interferon and ribavirin, improves sustained virological response rates for treatment-naive and treatment-experienced patients and shortens the duration of treatment for over half of treatment-naive patients. This review describes the clinical data supporting the approval and use of telaprevir and boceprevir, the algorithm for the use of these drugs, their adverse effects, as well as their important drug–drug interactions.

Although agents targeting several sites in the HCV viral life cycle are in development, to date, only telaprevir and boceprevir (drugs that inhibit the NS3/4a serine protease) have been FDA-approved for treatment of chronic hepatitis C. The year 2011 witnessed a dramatic development in the field of therapy for chronic HCV infection with the approval of two protease inhibitors (PIs), telaprevir and boceprevir. These drugs represent the first of an anticipated wave of direct-acting antiviral agents (DAAs) representing several mechanisms of action undergoing ongoing study. Both of the available PIs must be used in combination with pegylated interferon (PEG-IFN) and ribavirin (RBV) and are approved, at this time, only for genotype 1 infection. Pivotal clinical trials demonstrated two important benefits from the addition of these drugs to PEG-IFN and RBV: improved rates of sustained virological response (SVR) and shortened duration of treatment for a substantial proportion of patients with the use of response-guided therapy (RGT).

This review describes the clinical trial data supporting the approval and use of telaprevir and boceprevir for patients with chronic HCV infection, including important findings from early phase studies, results of the pivotal Phase III studies (Tables 1 and 2), and available data related to treatment of historically difficult to cure patients. In addition, this review compares the similarities and differences between the two drugs (Table 3) and provides an algorithm for their use in clinical practice (Figure 1) based on their FDA-approved indications and the latest American Association for the Study of Liver Diseases (AASLD) guidelines for the treatment of HCV [1]. Lastly, the review characterizes the adverse event and drug–drug interaction profiles (Table 4) to help guide safe and appropriate use of these medications.

Overview of serine protease inhibitors
telaprevir and boceprevir

Mechanism and spectrum of action

Both boceprevir and telaprevir are peptidomimetic inhibitors that bind reversibly to the active site of the NS3/4a serine protease enzyme active site [2,3]. They prevent the cleavage of the portion of the genome-derived polypeptide required for the generation of the individual non-structural proteins essential to the HCV viral life cycle. Exposure to either drug results in potent inhibition of viral replication in vitro and in vivo. However, monotherapy results in the rapid emergence of resistant variants (further described in Resistance), resulting in the need for concomitant administration of PEG-IFN and RBV. Although approved only for treatment of HCV genotype 1 and clearly not pangenotypic in their spectrum of activity, variable degrees of suppression of other genotypes may occur, as demonstrated for telaprevir in a recent study in patients with HCV genotype 2 but not genotype 3 [4].
Resistance
NS3/4a protease polymorphisms/substitutions that confer reduced susceptibility to the drugs can be detected prior to treatment by population-based sequencing in 5% of subjects from telaprevir studies of treatment-naïve patients and 7% from boceprevir studies of treatment-naïve patients [3,6]. The presence of these viral variants did not appear to preclude SVR, although this requires further study, particularly in poorly interferon responsive patients [7,8].

Viral variants with mutations in the area of the active drug binding site can also be selected using both drugs in vitro and in vivo [9]. These result in resistance to the drugs, but at the expense of decreased viral fitness [10]. Interferon retains the capacity to suppress all resistant variants and clinical studies have also shown a clear benefit for RBV in preventing the emergence of resistance despite lingering questions about its mechanisms of action [11,12]. In clinical studies, mutations associated with resistance occur more readily with HCV genotype 1a compared with 1b due to a lower genetic barrier to resistance: for two of the amino acid substitutions capable of impairing viral sensitivity to either drug, genotype 1a requires one base pair mutation, whereas 1b requires two to confer resistance [13]. The most common mutations (observed in >10% of subjects with virological failure in clinical trials) include the following: V36M, T54S, R155K for genotype 1a subjects who received boceprevir.

### Table 1. Efficacy results of Phase III studies for HCV treatment-naive patients

<table>
<thead>
<tr>
<th>Study/arm</th>
<th>Subjects, n</th>
<th>RVR, %</th>
<th>eRVR, %</th>
<th>SVR if eRVR, %</th>
<th>SVR, %</th>
<th>Relapse, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boceprevir SPRINT-2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-Black cohort</td>
<td>938</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SOC PEG-IFN/RBV</td>
<td>350</td>
<td>18%</td>
<td>13</td>
<td>93</td>
<td>40</td>
<td>23</td>
</tr>
<tr>
<td>RGT arm</td>
<td>316</td>
<td>60%</td>
<td>47</td>
<td>97</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>FD arm</td>
<td>311</td>
<td>59%</td>
<td>46</td>
<td>96</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td><strong>Boceprevir SPRINT-2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black cohort</td>
<td>159</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>SOC PEG-IFN/RBV</td>
<td>52</td>
<td>8%</td>
<td>6</td>
<td>100</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>RGT arm</td>
<td>52</td>
<td>35%</td>
<td>29</td>
<td>87</td>
<td>42</td>
<td>12</td>
</tr>
<tr>
<td>FD arm</td>
<td>55</td>
<td>40%</td>
<td>37</td>
<td>95</td>
<td>53</td>
<td>17</td>
</tr>
<tr>
<td><strong>Telaprevir ADVANCE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC PEG-IFN/RBV</td>
<td>1,095</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>T8PR RGT arm</td>
<td>364</td>
<td>66</td>
<td>57</td>
<td>83</td>
<td>69</td>
<td>9</td>
</tr>
<tr>
<td>T12PR RGT arm</td>
<td>363</td>
<td>68</td>
<td>58</td>
<td>89</td>
<td>75</td>
<td>9</td>
</tr>
<tr>
<td><strong>Telaprevir ILLUMINATE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>eRVR+24 week arm</td>
<td>162</td>
<td>NA</td>
<td>NA</td>
<td>92</td>
<td>NA</td>
<td>6</td>
</tr>
<tr>
<td>eRVR+48 week arm</td>
<td>160</td>
<td>NA</td>
<td>NA</td>
<td>88</td>
<td>NA</td>
<td>3</td>
</tr>
<tr>
<td>All subjects</td>
<td>540</td>
<td>72</td>
<td>65</td>
<td>As above</td>
<td>72</td>
<td>8</td>
</tr>
</tbody>
</table>

Data from [17,27,28]. *Week 8: after 4 weeks of triple therapy. eRVR, extended rapid virological response; FD, fixed duration; NA, not applicable; PEG-IFN, pegylated interferon; RBV, ribavirin; RGT, response-guided therapy; RVR, rapid virological response; SOC, standard of care; SVR, sustained virological response; T8PR, triple therapy for 8 weeks; T12PR, triple therapy for 12 weeks.

### Table 2. Efficacy results of Phase III studies for HCV treatment-experienced patients

<table>
<thead>
<tr>
<th>Study/arm</th>
<th>Subjects, n</th>
<th>Overall RVR (RVR by relapse, partial response, null response, %)</th>
<th>Overall SVR (SVR by prior relapse, partial response, null response, %)</th>
<th>Relapse (relapse by prior relapse, partial response, null response, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boceprevir RESPOND-2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC PEG-IFN/RBV</td>
<td>80</td>
<td>9% (Un, Un, NA)</td>
<td>100</td>
<td>21 (29, 7, NA)</td>
</tr>
<tr>
<td>RGT arm</td>
<td>162</td>
<td>46% (Un, NA)</td>
<td>86</td>
<td>59 (60, 40, NA)</td>
</tr>
<tr>
<td>FD arm</td>
<td>161</td>
<td>52% (Un, Un, NA)</td>
<td>88</td>
<td>66 (75, 52, NA)</td>
</tr>
<tr>
<td><strong>Telaprevir REALIZE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOC PEG-IFN/RBV</td>
<td>133</td>
<td>2% (3, 0, 3)</td>
<td>Un</td>
<td>17 (24, 15, 5)</td>
</tr>
<tr>
<td>48 week arm</td>
<td>266</td>
<td>57% (89, 65, 26)</td>
<td>Un</td>
<td>64 (85, 59, 29)</td>
</tr>
<tr>
<td>Lead-in 48 week arm</td>
<td>264</td>
<td>59% (70, 65, 41)</td>
<td>Un</td>
<td>66 (88, 54, 33)</td>
</tr>
</tbody>
</table>

Data from [31,33]. *Treatment week 8 (after 4 weeks triple therapy). †Treatment week 8 for lead-in arm, week 4 for others. FD, fixed duration; NA, not applicable; PEG-IFN, pegylated interferon; RBV, ribavirin; RGT, response-guided therapy; RVR, rapid virological response; SOC, standard of care; SVR, sustained virological response; Un, unavailable.
T54A/S, V55A, A156S and I/C170A for genotype 1b subjects who received boceprevir, V36M and R155K for genotype 1a subjects who received telaprevir, and V36A/L, T54A/S and A156S/T for genotype 1b subjects who received telaprevir [5,6]. These mutations confer cross-resistance of telaprevir and boceprevir to each other as well as to several other investigational HCV PIs [14].

Clinical trial data and recommended use of boceprevir and telaprevir

Because there has been no clinical trial comparing the efficacy of telaprevir and boceprevir head-to-head, the clinical data regarding these two drugs will be reviewed separately for treatment-naive and treatment-experienced patients. The limited available data related to treatment of historically difficult to cure patients, such as those of Black race or those with HIV or advanced fibrosis, will be discussed. Limited or no data exist about telaprevir’s and boceprevir’s safety and efficacy in paediatric and geriatric patients or in patients with end stage renal disease or on haemodialysis, moderate to severe hepatic impairment, solid organ transplantation, HBV coinfection, or in patients who failed therapy with other HCV PIs. Use of boceprevir and telaprevir in these populations is therefore not recommended at this time, although studies in some of these groups are planned or ongoing.

Table 3. Comparison between boceprevir- and telaprevir-based HCV treatment

<table>
<thead>
<tr>
<th>Feature</th>
<th>Boceprevir</th>
<th>Telaprevir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of action</td>
<td>Serine protease inhibitor</td>
<td>Serine protease inhibitor</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Aldo-keto reductase, CYP3A,</td>
<td>CYP3A, P-glycoprotein</td>
</tr>
<tr>
<td></td>
<td>P-glycoprotein</td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>800 mg (four 200 mg capsules)</td>
<td>750 mg (two 375 mg tablets)</td>
</tr>
<tr>
<td>Food restrictions</td>
<td>3 times daily (every 7–9 h)</td>
<td>3 times daily (every 7–9 h)</td>
</tr>
<tr>
<td>PEG-IFN/RBV dual therapy lead-in</td>
<td>With meal or light snack</td>
<td>With meal or snack containing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>approximately 20 g of fat</td>
</tr>
<tr>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Duration triple therapy</td>
<td>24–44 Weeks depending on</td>
<td>24–48 Weeks depending on</td>
</tr>
<tr>
<td></td>
<td>response, cirrhosis status and</td>
<td>response, cirrhosis status and</td>
</tr>
<tr>
<td></td>
<td>prior treatment status*</td>
<td>prior treatment status*</td>
</tr>
<tr>
<td>Total treatment duration</td>
<td>28–48 Weeks depending on</td>
<td>24–48 Weeks depending on</td>
</tr>
<tr>
<td></td>
<td>response, cirrhosis status and</td>
<td>response, cirrhosis status and</td>
</tr>
<tr>
<td></td>
<td>prior treatment status*</td>
<td>prior treatment status*</td>
</tr>
<tr>
<td>Groups approved for response-guided therapy</td>
<td>Treatment-naive, relapsers*,</td>
<td>Treatment-naive, relapsers</td>
</tr>
<tr>
<td>Rules for stopping treatment based on futility</td>
<td>HCV RNA&gt;100 IU/ml at 12 weeks,</td>
<td>HCV RNA&gt;1,000 IU/ml at 4 or 12 weeks,</td>
</tr>
<tr>
<td></td>
<td>detectable at 24 weeks</td>
<td>detectable at 24 weeks</td>
</tr>
<tr>
<td>Side effects seen in excess of</td>
<td>Anaemia, neutropaenia,</td>
<td>Rash, fatigue, pruritis, gastrointestinal effects,</td>
</tr>
<tr>
<td>PEG-IFN/RBV in controlled clinical trials</td>
<td>gastrointestinal effects, dysgeusia,</td>
<td>anaemia, anorectal symptoms, dysgeusia</td>
</tr>
</tbody>
</table>

Treatment-naive patients

Clinical trial data and recommended use of boceprevir for treatment-naive patients

Boceprevir early phase study findings

Initial Phase I and II studies to explore the safety and dosing of boceprevir were actually conducted in treatment-experienced subjects. They established the most effective dose of boceprevir (800 mg three times daily) and showed that boceprevir yielded greater reductions in viral load when given with PEG-IFN [15,16]. Monotherapy resulted in viral breakthrough related to the selection of resistant viral mutants [15] and RBV use improved outcomes [16]. It was also observed that a rapid response to treatment predicted SVR and that subjects who demonstrated some interferon-responsiveness (that is, 1–2 log decrease during PEG-IFN/RBV dual therapy) were more likely to achieve SVR with triple therapy [16]. In the Phase II study, a 1–2 g/dl incremental increase in anaemia was observed with boceprevir use [16].

Incorporating lessons learned from that study, SPRINT-1 was an international, multicentre randomized clinical trial in treatment-naive genotype 1 patients that compared multiple boceprevir treatment strategies with PEG-IFN-α2b plus RBV standard of care (SOC). This study explored 28- versus 48-week treatment durations, utilization of a PEG-IFN/RBV lead-in
Figure 1. Recommended treatment algorithms that incorporate response during treatment, cirrhosis status and prior treatment status

Duration of pegylated interferon (PEG-IFN)/ribavirin (RBV) dual therapy is depicted in light grey, duration of triple therapy including protease inhibitor in dark grey and stopping rules are in clear hexagons. (A) Treatment algorithms for patients eligible for response-guided therapy (RGT). (B) Treatment algorithms for patients not eligible for RGT. *RGT approach approved by the FDA not the EMA.
The first wave: HCV NS3 protease inhibitors telaprevir and boceprevir

Antiviral Therapy 17.6 Pt B

versus simultaneous start of all three drugs and, as a way of minimizing side effects, low dose versus standard RBV. SPRINT-1 showed that adding boceprevir improved SVR rates compared with SOC PEG-IFN/RBV, but that SVR rates were substantially higher with 48 weeks treatment compared with 28 weeks and with standard versus low dose RBV [12]. The rationale for using a 4-week PEG-IFN/RBV dual therapy lead-in prior to adding boceprevir was to establish steady-state and reduce HCV viral load, thus decreasing the odds of subsequent development of boceprevir resistance. The 48-week arms had higher SVR rates than the shorter duration arms, and the 48-week arm with the lead-in phase had the highest SVR rate (75%). It was additionally observed that the degree of virological response during the lead-in was predictive of SVR [12]. Moreover, there was a trend toward lower rates of virological breakthrough in the lead-in arms. This strategy of treating with a PEG-IFN/RBV lead-in prior to adding boceprevir was incorporated into all arms of the Phase III studies.

Boceprevir Phase III study data
The Phase III study, SPRINT-2, confirmed the superior efficacy of boceprevir plus PEG-IFN/RBV to PEG-IFN/RBV and provided support for the use of RGT (28–48 weeks determined by treatment response; Table 1) [17]. This randomized, double-blind, placebo-controlled trial, compared triple therapy with boceprevir (800 mg three times daily) plus PEG-IFN/RBV, given for either a duration to be determined by treatment response (RGT) or a fixed duration (FD), to SOC PEG-IFN/RBV in both a Black and non-Black cohort of patients \( n=938 \) non-Black and \( n=159 \) Black). Subjects randomized to RGT all received 4 weeks PEG-IFN/RBV lead-in followed by 24 weeks of triple therapy. At this point, those subjects who had achieved a rapid virological response (RVR; defined as undetectable HCV RNA after 4 weeks triple therapy (week 8 treatment) and maintained undetectable HCV RNA stopped treatment. Those with detectable HCV RNA during that period continued on PEG-IFN/RBV for an additional 20 weeks unless HCV RNA was detectable at treatment week 24, which comprised a stopping rule. FD subjects received 4-week lead-in PEG-IFN/RBV followed by 44 weeks of boceprevir/PEG-IFN/RBV. SVR rates achieved in both the boceprevir RGT and FD groups were superior to PEG-IFN/RBV with respective SVR rates of 67% and 68% versus 41% in the non-Black cohort and 42% and 53% versus 23% in the Black cohort. Notably,
in the RGT arms, 60% of the non-Black and 35% of the Black cohort were undetectable at week 8 (RVR), with those who remained undetectable qualifying for shortened therapy. Of these subjects with RVR, 89% of patients in the non-Black cohort and 78% of patients in the Black cohort achieved SVR. Overall, SVR rates were 36% in subjects without an RVR [17]. Although not powered to determine non-inferiority of RGT to FD, the FDA concluded RGT was justified based on this data and recommend RGT in treatment-naive patients without cirrhosis.

Predictors of response to treatment included baseline HCV RNA < 400,000 IU/ml, age ≤ 40 years, absence of cirrhosis and statin use. The lead-in phase was also observed to be a valuable predictor of treatment response: 79–81% of subjects with a >1 log decrease during the lead-in phase achieved SVR compared with 28–38% SVR in those who did not [17]. Subsequent analyses also showed a more favourable response in subjects with genotype 1b versus 1a and host IL28B (genetic polymorphism on chromosome 19, rs 12979860) genotype CC versus CT or TT [18]. However, boceprevir therapy sharply decreased the differential rates of SVR between CC patients and those with the T allele.

**Boceprevir for difficult to cure populations: Black/African American**

As described above, Black patients benefited from the addition of boceprevir with SVR rates of 42% with RGT and 53% with FD compared with 23% in the SOC arm [17]. When the intent-to-treat analysis was limited to non-cirrhotic Black subjects, more similar response rates were observed with RGT and FD (50% versus 54%) [19]. In addition, with a modified intent-to-treat analysis evaluating only patients who received at least one dose of boceprevir, the SVR rates in the boceprevir arms were 47% and 53% for RGT and FD, respectively.

**Boceprevir for difficult to cure populations: advanced fibrosis**

Subgroup analyses of the Phase III study revealed that triple therapy including boceprevir was also superior to SOC in the 10% of Caucasian patients with advanced fibrosis (Metavir score 3 or 4), with SVR rates of 50% with boceprevir versus 39% with SOC [17]. In subjects with cirrhosis, higher response rates were observed with FD (43%) versus RGT (31%). Although numbers of subjects were small, this resulted in the FDA recommending 48-week treatment (no RGT) for subjects with cirrhosis.

**Boceprevir for difficult to cure populations: HIV coinfection**

SVR rates in patients with HIV coinfection have not yet been published, but a study comparing 48 weeks of boceprevir/PEG-IFN/RBV with PEG-IFN/RBV for patients with HIV showed promising preliminary results. In the boceprevir arm, 61% of subjects achieved SVR12 compared with 27% with PEG-IFN/RBV [20]. Although this study excluded efavirenz use and did not evaluate RGT, a Phase III study will explore the use of boceprevir in HIV treatment-naive and treatment-experienced subjects, including RGT for treatment-naive patient without cirrhosis.

**Boceprevir treatment strategy recommended for treatment-naive patients**

Boceprevir has been FDA- and European Medical Agency (EMA)-approved for treatment of HCV genotype 1 only in combination with PEG-IFN and RBV. The algorithm in Figure 1 demonstrates the recommended strategy for using boceprevir including decision points and stopping rules. After giving a 4-week lead-in treatment with PEG-IFN/RBV, boceprevir 800 mg three times a day (every 7–9 h) is added. Treatment duration is then guided by response. Those with undetectable HCV RNA at week 8 receive a total duration of 28 weeks (4 weeks PEG-IFN/RBV followed by 24 weeks triple therapy), and those with detectable HCV RNA at week 8 that becomes undetectable by week 24 receive 48 weeks total treatment (4 weeks PEG-IFN/RBV followed by 32 weeks triple therapy and then 12 weeks PEG-IFN/RBV). The latter regimen differs from the regimen used in clinical studies described above, as it contains an extra 8 weeks of boceprevir. This was based upon the findings that in patients with late response across both the non-Black and Black cohorts, SVR occurred in 66% of those receiving RGT (with 24 weeks of boceprevir and a 20-week PEG-IFN/RBV ‘tail’) and in 75% of those receiving a full 44 weeks of boceprevir after the PEG-IFN/RBV lead-in. RGT is not recommended for patients with cirrhosis, who should receive 48 weeks of therapy. Also different from the pivotal trial is the stopping rule of detectable HCV RNA at week 24 in the SPRINT-trial, the recommended stopping rule in clinical practice is HCV RNA ≤ 100 IU/ml at week 12 or detectable HCV RNA at week 24.

Clinicians should be aware that the basis for the application of RGT is complete undetectability of HCV RNA at week 8 and beyond. If HCV RNA is detectable but below the lower limit of quantification, the opportunity for RGT does not apply.

**Clinical trial data and recommended use of telaprevir for treatment-naive patients**

**Telaprevir early phase findings**

Phase I studies established telaprevir dosing (750 mg every 8 h), demonstrated the potency of telaprevir as monotherapy (all subjects given 750 mg dosing had a >3 log decrease in HCV RNA) and revealed that virological breakthrough with selection of viral mutations with decreased susceptibility to telaprevir would occur
with monotherapy [21–23]. They also established that these resistant variants could be cleared subsequently with Peg-IFN and RBV, thereby confirming the necessity of combination therapy [22–24].

Two Phase II multicentre, randomized, double-blind, placebo-controlled studies, PROVE1 and PROVE2, established the safety of telaprevir in combination with Peg-IFN and RBV and superior efficacy over Peg-IFN/RBV for treatment-naive subjects in the US and Europe [11,25]. In addition to establishing superiority over Peg-IFN/RBV, PROVE1 established the foundation for what has become known as RGT by showing that in those with RVR, SVR rates with 24 weeks were similar to that of 48 weeks. It also showed that relapse rates were unacceptably high if Peg-IFN/RBV was discontinued as early as 12 weeks, leading to a recommended treatment duration of at least 24 weeks [25]. In addition to establishing superiority over SOC, PROVE2, which contained a RBV-free arm of equivalent size to the other treatment arms, demonstrated that RBV was essential to combination therapy and that baseline HCV RNA was predictive of response to triple therapy [11]. PROVE1 and PROVE2 showed that virological breakthrough during telaprevir treatment was associated with selection of resistance mutants and demonstrated that subjects with genotype 1a were more likely to develop resistance than 1b given its lower genetic barrier to resistance. In both studies, anaemia and a potentially treatment-limiting rash emerged as important side effects that occurred more frequently with triple therapy than SOC [11,25].

Another Phase II study explored whether telaprevir could be administered every 12 h as the three times a day dosing was chosen based on monotherapy and not on studies of telaprevir combined with Peg-IFN/RBV. In this open-label study, which also evaluated Peg-IFN-a2a versus Peg-IFN-a2b, no significant difference in SVR rates were observed between subjects who received telaprevir every 12 or every 8 h and were similar regardless of Peg-IFN. However, telaprevir every 12 h dosing needs to be explored further in larger studies before being considered as SOC and such studies are in progress [26].

Telaprevir Phase III study data

Two pivotal Phase III studies established the safety and efficacy of telaprevir for purposes of FDA registration and informed the current use of telaprevir (Table 1). The randomized, double-blind, placebo-controlled, FDA registration trial, ADVANCE (n=1,088), studied two telaprevir dosing strategies, triple therapy for 8 (T8PR) or 12 (T12PR) weeks followed by response-guided Peg-IFN/RBV, and compared them with Peg-IFN/RBV [27]. The goal of studying two different durations of telaprevir dosing was to determine whether a shorter duration of telaprevir would decrease the frequency of side effects (for example, rash) while preserving efficacy. Unlike the Phase II studies, ADVANCE included patients with advanced fibrosis (bridging fibrosis or compensated cirrhosis) and took a response-guided approach to the duration of therapy for all subjects. Subjects in the telaprevir arms with undetectable HCV RNA from weeks 4 to 12, referred to as an extended rapid virological response (eRVR), received 24 weeks of treatment, whereas those who took longer to become undetectable received 48 weeks. SVR rates were 69% and 75% in the two telaprevir groups and were superior to SOC (44%). In addition, 57% and 58% of T8PR and T12PR subjects met the criteria for eRVR and received 24 weeks of total treatment resulting in SVR rates of 89% and 83%, respectively. Although a lower incidence of rash was observed in the T8PR arm, the T12PR arm experienced a higher SVR rate that was consistent among subgroup analysis as well as a lower incidence of virological failure during the dual therapy phase of treatment. For these reasons, 12 weeks of triple therapy became the approved treatment strategy.

The other Phase III study of telaprevir conducted in treatment-naive subjects, ILLUMINATE (n=540), sought to establish the non-inferiority of RGT by randomizing subjects with eRVR to 24 versus 48 weeks. In this supportive, multicentre, randomized, open-label clinical trial, 65% of subjects achieved an eRVR with SVR rates of 92% and 88% in the 24 and 48 week groups, respectively – meeting the statistical criteria for non-inferiority and providing firm evidence to support the approach of RGT in treatment-naive patients [28].

Telaprevir for difficult to cure populations: Black/African American

Although Black patients represented only 9% of subjects in ADVANCE and 15% in ILLUMINATE, a pooled analysis of subjects assigned to receive 12 weeks of triple therapy as part of either RGT or FD in these studies was conducted to examine the effect of race on treatment response and resistance rates [29]. It revealed overall SVR rates of 62% in 127 Black subjects versus 77% in 1,124 non-Black subjects. In the 46% of Black subjects with eRVR, 85% achieved SVR, whereas the rate was 90% in the 65% of non-Black patients with eRVR. Because this analysis included subjects assigned to either RGT or FD, it cannot answer if RGT is non-inferior to FD for Black patients in particular. However, in support of RGT, SVR rates were similar for Black subjects with eRVR in ILLUMINATE (88% and 94% achieving SVR in the 24-week and 48-week arms, respectively [28]). Although the numbers were small, on-treatment virological failure and relapse both occurred more frequently in Black patients compared with non-Black patients (virological failure in 11% versus 7% and relapse in 7% versus 3%, respectively) [29].
Telaprevir for difficult to cure populations: advanced fibrosis

In ADVANCE, SVR rates were superior to SOC in telaprevir-treated subjects with advanced fibrosis with 62% achieving SVR versus 33% in SOC. However, in ILLUMINATE, although numbers were small, SVR rates appeared diminished in cirrhotic subjects assigned to 24 weeks compared with 48 weeks, with 12/18 (67%) versus 11/12 (92%) achieving SVR, respectively. Although data is insufficient to conclude the inferiority of RGT in this population, guidelines recommend strong consideration of 48 weeks duration of therapy for previously treatment-naive cirrhotics with eRVR.

Telaprevir for difficult to cure populations: HIV coinfection

Preliminary data from a Phase II study of HIV–HCV-coinfected patients revealed promising SVR 12 responses of 74% in telaprevir-treated compared to 45% with PEG-IFN/RBV alone [30]. Subjects were on no antiretroviral therapy or on antiretroviral regimens including the combination of tenofovir/etrcrecitabine plus either ritonavir-boosted atazanavir or efavirenz. Intensive week 4 pharmacokinetic (PK) evaluation showed that telaprevir exposure was comparable across these antiretroviral regimens and that only modest changes occurred in the PK of the antiretrovirals. Phase III studies for treatment-naive and treatment-experienced HIV–HCV-infected persons that include RGT for treatment-naive are underway.

Telaprevir treatment strategy recommended for treatment-naive patients

Based on the data presented above, telaprevir has been FDA- and EMA-approved for treatment of chronic HCV genotype 1 only in combination with PEG-IFN and RBV. Telaprevir 750 mg three times a day (every 7–9 h) plus PEG-IFN/RBV is given for 12 weeks followed by PEG-IFN/RBV for 12 or 36 weeks duration as determined by treatment response. Those having an eRVR defined as HCV RNA undetectable at weeks 4 and 12, receive a total duration of 24 weeks (12 weeks triple therapy followed by 12 weeks PEG-IFN/RBV) and those without an eRVR receive 48 weeks total treatment (12 weeks triple therapy followed by 36 weeks PEG-IFN/RBV). RGT is not recommended for patients with cirrhosis who should receive 48 weeks of therapy. The algorithm in Figure 1 demonstrates the recommended strategy for using telaprevir including decision points and futility stopping rules. Of note, these stopping rules differ from those applied in Phase III trials, with an HCV RNA level >1,000 IU/ml at weeks 4 and 12 mandating discontinuation of all therapy. Again, complete HCV RNA undetectability at weeks 4 and 12 is required for application of RGT.

Treatment-experienced patients

When considering treatment-experienced patients, the most important predictor of treatment response is prior treatment response. Patients for whom treatment failed previously are typically categorized as one of the following: relapers (HCV RNA became undetectable during treatment but detectable HCV RNA recurred after cessation of treatment), partial responders (HCV RNA decreased ≥2 log IU/ml at week 12 but did not become undetectable by 24 weeks) or null responders (HCV RNA decreased <2 log IU/ml at week 12). Subjects were stratified by these categories in the Phase III studies described below.

Clinical trial data and recommended use of boceprevir for treatment-experienced patients

Boceprevir clinical trial data

RESPOND-2 (n=403), the Phase III, randomized, double-blind, parallel group, study of boceprevir with PEG-IFN/RBV for treatment-experienced subjects included patients with prior partial response or relapse, but not null response to prior PEG-IFN/RBV treatment (Table 2). It was designed similar to the treatment-naive study in that the boceprevir arms included a 4-week lead-in of PEG-IFN/RBV and compared RGT and FD with SOC PEG-IFN/RBV. However, in this study, the regimens for the RGT arm differed from the treatment-naive study with subjects achieving an eRVR completing 32 weeks of triple therapy (36 weeks of total treatment), whereas those still detectable at week 8 completed 32 weeks of triple therapy followed by an additional 12 weeks of PEG-IFN/RBV (48 weeks total therapy). Boceprevir triple therapy arms were superior to SOC PEG-IFN/RBV with 66%, 59% and 21% achieving SVR in the FD, RGT, SOC arms, respectively [31]. SVR rates were highest amongst subjects who were relapers (69–75%) compared with partial responders (40–52%). Again, undetectable HCV RNA after 4 weeks of triple therapy was highly predictive of SVR; 86–88% of subjects with RVR in the boceprevir arms achieved SVR compared with 40% in subjects without RVR. Other predictors of response included lower baseline HCV RNA and absence of cirrhosis. A <1 log decrease during the lead-in also predicted a poorer response to treatment; however, even these subjects had improved response rates compared with SOC PEG-IFN/RBV (33–34% versus 0%) [31]. Thus, it is not recommended that the lead-in response be used as a rationale to discontinue treatment.

Although RESPOND-2 did not include prior null responders, a subsequent, single arm rollover study (PROVIDE) enrolled null responders from the Phase III treatment studies. An interim assessment of data...
from 45 of 48 subjects (3 were not dosed with boceprevir) revealed that 16 (36%) achieved SVR with boceprevir [32]. The number of cirrhotics in this open-label study was small. This rate is similar to that observed in RESPOND-2 subjects with poor interferon responsiveness (<1 log decrease at week 4). When treatment failed, resistance mutations were present frequently; 44% of tested subjects without SVR had resistant variants detected.

Boceprevir for difficult to treat populations: Black/African American
Of the 49 Black patients enrolled in RESPOND-2, 53–61% achieved SVR with boceprevir. This was similar to the study population as a whole and far superior to the 8% who achieved SVR with PEG-IFN/RBV [31].

Boceprevir for difficult to treat populations: advanced fibrosis
Subgroup analysis showed benefit in subjects with cirrhosis re-treated with boceprevir compared with SOC, where none achieved SVR. However, in comparing RGT versus FD strategies, the SVR rate was noted to be much lower in the RGT arm (35% versus 77%) [31]. This, along with the small number of patients studied and the importance of ‘erring’ on the side of optimizing therapy in cirrhotics, has contributed to the package insert guideline that cirrhotics, whether treatment-naive or treatment-experienced, should receive a full 48 weeks of therapy with a 4-week lead-in period of PEG-IFN/RBV and 44 weeks of triple therapy with boceprevir.

Boceprevir treatment strategy recommended for treatment-experienced patients
The FDA approved RGT for relapers and partial responders without cirrhosis (Figure 1). This entails giving a 4-week PEG-IFN/RBV lead-in followed by 32 weeks of triple therapy for patients with undetectable HCV RNA at week 8. Patients without detectable HCV RNA at week 8 in whom HCV RNA becomes undetectable by week 24, and are therefore eligible for completion of therapy, require an additional 12 weeks of PEG-IFN/RBV from weeks 36 to 48. The EMA did not approve RGT for these patients, instead endorsing a fixed 48-week duration of treatment for all relapers and partial responders (4-week PEG-IFN/RBV lead-in, followed by 32 weeks of triple therapy and then 12 weeks of PEG-IFN/RBV). For null responders, limited clinical data exists regarding boceprevir use. As described above, a recent small open-label study of null responders derived from the control arms of the boceprevir trials showed an SVR rate of approximately 36%, with the analysis nearly completed [32]. If boceprevir is chosen for a prior null responder, 48 weeks of treatment, including 4 weeks PEG-IFN/RBV followed by 44 weeks triple therapy, is recommended. Similarly, 48 weeks of treatment is recommended for patients with poor interferon response (defined as <1 log at end of PEG-IFN/RBV lead-in phase) or, as above, cirrhosis. The stopping rules for futility of treatment are identical to those for treatment-naive subjects (Figure 1).

Clinical trial data and recommended use of telaprevir for treatment-experienced patients
Telaprevir clinical trial data
REALIZE (n=662), the Phase III study of telaprevir for treatment-experienced subjects, differed from the boceprevir Phase III treatment-experienced study in that no RGT regimen was studied (Table 2). REALIZE also included patients with null response as well as partial response and relapse to SOC PEG-IFN/RBV. REALIZE utilized a randomized, double-blind, placebo-controlled study design to compare two regimens of telaprevir in combination with PEG-IFN/RBV to SOC PEG-IFN/RBV. Both telaprevir-based treatments lasted 48 weeks and consisted of 12 weeks of triple therapy followed by 36 weeks of PEG-IFN/RBV. One arm utilized a 4-week lead-in treatment of PEG-IFN/RBV treatment, whereas the other started all drugs simultaneously. The overall SVR rates were superior in both telaprevir-containing arms (65% combined arms) compared with the SOC arm (17%).

In subjects who received telaprevir, response correlated to prior interferon responsiveness, with 86% of relapers, 57% of partial responders and 31% of null responders achieving SVR [33]. However, among 50 null responder cirrhotics, the SVR rate was only 7/50 (14%). By contrast, the presence of cirrhosis had no significant effect on rates of SVR in prior relapers and a more modest effect in partial responders.

The majority of subjects (76%) in triple therapy arms with virological failure or relapse developed mutations associated with reduced susceptibility to telaprevir [33]. No difference was observed between the two strategies of telaprevir, lead-in or simultaneous start (66% versus 64%, respectively). Similar to boceprevir studies, <1 log IU/ml HCV RNA decrease during the 4-week PEG-IFN/RBV lead-in predicted lower likelihood of SVR. A subsequent analysis revealed that among null responders, a <1 log reduction in HCV RNA at week 4 of lead-in therapy resulted in an SVR rate of 15% compared with 54% in those with a better response at week 4. This has led some clinicians to adopt the ‘off-label’ approach of a 4-week PEG-IFN/RBV lead-in when treating prior null responders, and discontinuing therapy in the face of a poor interferon response. The rationale for this approach is to minimize the risk of emergent resistance in the face of a poor likelihood of success and,
at centres where clinical trials are performed, to preserve the eligibility of such patients for trials of novel agents in null responder populations. Other predictors of response to telaprevir-based treatment include low-density lipoprotein, HCV genotype subtype, alanine aminotransferase and aspartate aminotransferase levels, HCV RNA and fibrosis stage [34].

**Telaprevir for difficult to cure populations: Black/African American**

Although only 4% of subjects in REALIZE were Black, they had similar response rates as the group as a whole (63% overall SVR). Further study is needed to accurately determine response rates for treatment-experienced Black patients.

**Telaprevir for difficult to cure populations: advanced fibrosis**

Subgroup analysis of REALIZE revealed that more advanced fibrosis predicted poorer response to treatment, particularly in the patients with poorer interferon responsiveness during past treatment. In the combined telaprevir arms, 34% of prior partial responders with cirrhosis and only 14% of prior null responders with cirrhosis achieved SVR.

**Telaprevir treatment strategy recommended for treatment-experienced patients**

As with treatment-naive subjects, telaprevir for treatment-experienced subjects is administered in combination with PEG-IFN/RBV for 12 weeks followed by PEG-IFN/RBV with the duration depending on prior treatment history and on treatment response. Although not explicitly studied, the FDA and EMA endorse a recommendation that prior relapers may be considered for RGT similar to treatment-naive patients (Figure 1). This recommendation is based on the high degree of interferon responsiveness in relapers, by definition, and the high actual SVR rates in relapers, including Phase II studies in which subjects with rapid response received 24 weeks of treatment [35]. RGT is not recommended for partial and null responders. They should be given 48 total weeks of treatment including 12 weeks of triple therapy followed by 36 weeks of PEG-IFN/RBV. The stopping rules for futility of treatment are identical to those for treatment-naive subjects (Figure 1).

**Side effects of boceprevir and telaprevir**

Not surprisingly, because both telaprevir and boceprevir are given in addition to PEG-IFN and RBV in the studies described above, the frequency of adverse events was greater in the arms that included these PIs. Combined data from controlled treatment-naive studies revealed that more boceprevir-treated subjects than PEG-IFN/RBV-treated subjects experienced the following side effects: anaemia, neutropaenia, dysgeusia, vomiting and chills (experienced by >10% of subjects and ≥5% more than SOC) [5,6]. Data from combined, controlled clinical trials of telaprevir showed that rash, anaemia, pruritus, anorectal complaints (described variously as hemorrhoids, discomfort and pruritis), nausea, diarrhoea, vomiting and dysgeusia occurred in at least 5% more of telaprevir-treated subjects compared with PEG-IFN/RBV-treated subjects [5,6].

The two common side effects of greatest potential concern include anaemia and rash. Although anaemia during treatment is primarily driven by RBV through its effect on red blood cell haemolysis, both boceprevir and telaprevir contribute to anaemia. Both drugs induce an incremental degree of haemoglobin decrease of 1–1.5 g beyond that observed with PEG-IFN/RBV. In treatment-naive studies SPRINT-1 and SPRINT-2, haemoglobin levels <10 g/dl and <8.5 g/dl occurred more frequently in the boceprevir-treated patients (49% and 6%) compared with SOC (29% and 3%) [6]. Erythropoetin (EPO) use and dose modifications of RBV due to anaemia occurred approximately twice as frequently in boceprevir arms in Phase II and III studies, but treatment discontinuations due to anaemia were rare with or without boceprevir (1%) [6]. Preliminary data suggested that the anaemia management strategy (EPO versus dose reduction) did not affect SVR rates with boceprevir use. However, subjects with anaemia did experience higher SVR rates [36]. In Phase III telaprevir studies, haemoglobin <10 g/dl and <8.5 g/dl also occurred more frequently with 12 weeks of telaprevir (36% and 14%) compared with SOC (17% and 5%) [5]. The telaprevir studies did not permit EPO use, so RBV dose reduction was the preferred strategy. RBV dose reductions due to anaemia occurred in 36% but, as with boceprevir, were not associated with reduced rates of SVR (76% if reduction versus 72% without) [37]. The package insert for boceprevir recommends dose reduction of RBV for haemoglobin <10 g/dl and discontinuation of RBV for haemoglobin <8.5 g/dl, whereas the telaprevir package insert recommends dose reduction in the event of anaemia as per the RBV prescribing information [5,6].

In Phase II/III studies, approximately half of telaprevir-treated patients developed a rash with >90% being of mild-to-moderate severity and commonly resolving after telaprevir discontinuation. Rash was judged severe in these trials if it involved >50% of body surface area in the judgment of the investigator. Approximately 50% of rashes occurred within the first 4 weeks and the other 50% between weeks 5–12 with median onset at day 25 [38]. In Phase III studies, the implementation of a rash management plan resulted in less PEG-IFN/RBV discontinuations due to rash (1% in Phase III versus
Drug–drug interactions

Attention to drug–drug interactions with HCV PIs is essential for the clinician who may be unaccustomed to this concern after years of experience with PEG-IFN/RBV therapy. Both telaprevir and boceprevir are potent inhibitors of cytochrome p450 3A4/5 (CYP3A) and P-glycoprotein. Other medications that rely on these pathways for clearance require increased monitoring for adverse events if coadministered, or they are contraindicated for use with boceprevir and telaprevir if increased drug levels are associated with serious or life-threatening events. Of additional concern, boceprevir and telaprevir are also metabolized by pathways including CYP3A (Table 3), thus leading to the potential for coadministered medications that induce these enzymes to lower their levels and effectiveness. Table 4 includes medications and supplements that are known to be contraindicated for use during treatment with boceprevir and/or telaprevir for these reasons. Some commonly used drug classes concerning for interactions with boceprevir and telaprevir include, but are not limited to, antiretrovirals, anticonvulsants, antiarrhythmics, calcium channel blockers, HMG-CoA reductase inhibitors, oral contraceptives, immunosuppressants, PDE5 inhibitors, sedatives and inhaled corticosteroids. A small study of subjects on stable methadone replacement revealed about a 20% decrease in unbound methadone levels with coadministration of telaprevir, although not generally necessary dose adjustments may be needed in some patients [39]. Both boceprevir and telaprevir may compromise the effectiveness of hormonal contraception, with decreased exposure to ethinyl estradiol and increased exposure to drosperinone [5,6,40]. Because these drugs are always given with RBV, a known teratogen, two forms of non-hormonal contraception should be used by women of childbearing capacity until at least 2 weeks after discontinuation of the PI, whereupon the longstanding requirement of two methods of contraception (including hormonal) until 6 months after cessation of RBV is still in effect. Additional information on drug interactions can be found in the package inserts or through online drug interaction software.

For HIV-infected patients, drug–drug interactions are of particular concern as many antiretrovirals inhibit, induce or are metabolized by the CYP3A pathway. The antiretroviral regimen in use may ultimately dictate the particular HCV PI and the dose of the PI that is most suitable for the patient. For instance, telaprevir is not recommended for use with lopinavir/ritonavir, darunavir or fosamprenavir, and may require an increased dose when coadministered with efavirenz [5]. The FDA and EMA also recently released warnings about coadministration of boceprevir with HIV PIs due to drug–drug interactions. Additional information on drug interactions with antiretrovirals is expected from ongoing and planned clinical trials. Because the safety and efficacy of these drugs has not yet been established for HIV-infected persons, treatment through a clinical trial is advisable and early data do suggest favourable on-treatment response rates [20,30]. If a clinical trial is not available, recently published guidelines may be helpful in determining the appropriateness of their off-label use [41].

Conclusions

Clinical trial evidence supports and guidelines now endorse a PI, either telaprevir or boceprevir, along with PEG-IFN/RBV as the new SOC for both treatment-naive and treatment-experienced adults with genotype 1 chronic HCV infection. However, guidelines do not
address prioritization of patients to receive telaprevir- or boceprevir-based treatment based on predictors of response. For instance, a PI-based regimen offers a treatment-naive patient a high likelihood of cure as well as being eligible for shorter treatment. By contrast, for a patient with a prior null response together with cirrhosis, SVR rates are quite low with approved PIs and failure is likely to result in the development of resistance. This latter patient may benefit from a regimen including more than one DAA, available only through clinical trials currently.

With the use of telaprevir and boceprevir, some common themes have emerged including those related to RGT, interferon responsiveness, drug resistance, adverse events and drug–drug interactions. With both telaprevir and boceprevir, treatment duration is guided by response for treatment-naive and relapsers, and results in shorter duration of therapy for half or more of patients. For treatment-experienced subjects, the highest SVR rates occur in prior relapers, followed by partial and then null responders. The majority of patients in whom treatment fails develop mutations associated with resistance, with failure occurring mostly in frequently in prior null responders, especially cirrhotics. The long-term implications of drug resistance remain unclear, but available data show a reassuring tendency toward decrease in resistant viral variants over time [42–45]. This provides a rationale for not categorically denying therapy to patients with negative prognostic factors, although the decision to re-treat certain patients, such as null responders with cirrhosis, should be individualized. Adverse effects are more frequent than with PEG-IFN/RBV alone, but not treatment-limiting in most cases. Drug interactions are common due to the metabolic pathway for both drugs.

As the arsenal of drugs to treat HCV grows, these lessons learned with boceprevir and telaprevir, the first wave of DAAs, will be of great value in further progressing the treatment of chronic HCV infection.

Disclosure statement

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