CLINICAL INVESTIGATION

HCV protease inhibitors: using the evidence to guide clinical practice

The development of direct-acting antivirals with activity against hepatitis C virus (HCV) has been a major breakthrough. The Phase III clinical trials of the protease inhibitors boceprevir and telaprevir have shown that both of these agents substantially improve rates of sustained virological response in patients with genotype 1 HCV infection. However, both agents must be combined with pegylated-IFN and ribavirin and come with their own new, additional side effects. In this review, the data from the clinical trials are reviewed and practical points about using the HCV protease inhibitors in clinical practice are discussed, including: dosing, treatment regimens for naive and experienced patients, the role of a 4-week lead-in phase, the utility of IL-28B testing, drug–drug interactions and antiviral resistance. Major take home messages are highlighted at the end of each section.

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Over the past decade, rigorous efforts have been put forth to develop new antiviral therapies with activity against chronic hepatitis C virus (HCV), which have been referred to as direct-acting antiviral agents (DAAs). Among the first generation of these innovative treatments to complete clinical development are two HCV NS3/4A serine protease inhibitors: boceprevir (BOC) and telaprevir (TVR). The final results of the Phase III trials studying these protease inhibitors (PI) in combination with pegylated-IFN α and ribavirin (RBV) in HCV genotype 1 have demonstrated higher sustained virologic response (SVR) rates than the current standard of care (SOC), comprising pegylated-IFNα and RBV; in treatment-naive patients and those who have failed treatment previously [1–4].

BOC and TVR have been approved in North America and Europe for clinical use and are quickly being adopted into clinical practice. Although much of the emphasis of these therapies has focused on the overall results of the Phase III trials, it is equally important to review the issues involved with bringing these drugs into clinical use, particularly in specific patient populations. In this review, we will examine the available data regarding BOC and TVR to address various practical issues relevant to prescribing physicians. The review focuses on the data from the trials directly, but also highlights how these data have been interpreted by different regulatory agencies, leading to slight differences in drug labeling around the world.

Efficacy of BOC & TVR in triple combination therapy in the treatment-naive

■ BOC

The efficacy of BOC in combination with pegylated-IFNα 2b and RBV (P2bR) in previously untreated patients infected with HCV genotype 1 was evaluated in SPRINT 2, a large Phase III study [1]. In the BOC arms, two strategies were

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examined following a 4-week lead-in period with P2bR. After the lead-in, treatment was either given with BOC plus P2bR for a full 44 weeks; or the duration of therapy was tailored to response (response-guided therapy [RGT]). In the RGT arm, if HCV RNA was undetectable from weeks 8–24, patients received BOC plus P2bR for a total of 24 weeks after the lead-in period (28 weeks total therapy); but if HCV RNA was detectable anywhere between weeks 8 and 24, triple therapy was continued to week 28 and then P2bR alone was continued for an additional 20 weeks (48 weeks total therapy). In this study, the rapid virologic response (early response) was defined as undetectable HCV RNA at week 8 of therapy (4 weeks of lead-in + 4 weeks of BOC/P2bR).

Notably, because of the poorer responses to Peg/RBV in black patients, the study was stratified in black and non-black cohorts. Each cohort was randomized into three groups: Pb2R48 (control), BOC/RGT and BOC/P2bR48 arms.

The SVR rates were significantly higher in the BOC arms for both the non-black and black cohorts. In the non-black cohort, SVR rates were 40% in P2bR48, 67% in the BOC/RGT (p < 0.0001) and 68% in the BOC/P2bR48 (p < 0.0001) (Figure 1); in the black cohort, the SVR rates were 23, 42 (p = 0.04) and 53% (p = 0.004), respectively. The relapse rates were very low in all BOC-treated patients (Figure 1).

Of note, both the US FDA and European Medicines Agency recommended BOC regimens that differed slightly from the trial design for treatment-naive

Figure 1. Treatment results in genotype 1 treatment-naive patients treated with boceprevir with pegylated-IFN and ribavirin.
BOC/RGT: Boceprevir response guided treatment; BOC/P2bR48: Boceprevir and pegylated-IFN α 2b and ribavirin for 48 weeks; SVR: Sustained virological response.
Figures appear in colour online.

patients. In the RGT arm in the SPRINT2 trial, patients who did not have an early reponse but did not meet stopping rules, were treated with a 4-week lead-in followed by 24 weeks of triple combination therapy, at which point the BOC was stopped and P2bR was continued for an additional 20 weeks. Both the FDA and European Medicines Agency approved continuation of BOC to week 36 followed by 12 weeks of P2bR based on modeling data, suggesting that an additional 8 weeks of BOC would compensate for the relatively poor response to P2bR. Notably, Health Canada elected to follow the study design rather than the modeling data and therefore approved the shorter exposure to BOC, indicating that physicians should check country-specific labels for BOC prior to use.

■ Telaprevir
The combination of TVR with pegylated-IFNα 2a – RBV (P2aR) in previously untreated patients infected with HCV genotype 1 was examined in the Phase III trial ADVANCE [3]. The study was designed to evaluate two regimens of TVR of different durations, combined with P2aR. The total duration of treatment was either 24 or 48 weeks. Patients received TVR in combination with P2aR for either 8 or 12 weeks (T8PR, T12PR) followed by continuation of P2aR without TVR. Duration of therapy was tailored to response using the concept of RGT. Patients who had undetectable HCV RNA at week 4 through week 12 of treatment were eligible to shorten treatment to a total of 24 weeks. Patients who did not meet the criteria for the so-called extended rapid virologic response (eRVR) stopped TVR after week 8 or 12 (as per study arm) and continued with Pa2R alone without TVR through to week 48.

The rates of SVR were significantly higher in the TVR treatment arms. Patients were randomized into three groups: T12PR, T8PR and the control PR48 arm, with SVR rates or 75, 69 and 44%, respectively, (p < 0.0001, p < 0.0001) (Figure 2) and correspondingly low relapse rates. The study was not powered to detect differences between the T12PR and T8PR groups, but notably the difference of 6% was not significant.

■ Take home message
In previously untreated adults with chronic HCV genotype 1 infection, the addition of BOC or TVR to standard therapy with pegylated-IFNα and RBV significantly increases the rate of SVR compared to standard (dual) therapy alone. Response-guided therapy allows for the potential to shorten treatment (see below).

Efficacy of BOC & TVR in triple combination

therapy in the treatment experienced
■ BOC
The addition of BOC to combination therapy (P2bR) in previously treated patients infected with HCV genotype 1 was evaluated in the Phase III RESPOND 2 study [2]. This study included partial responders (decrease in HCV RNA >2 log10 IU/ml by week 12, but detectable HCV RNA) or relapsers (undetectable HCV RNA during therapy without subsequent attainment of SVR), but did not include null responders (decrease in HCV RNA <2 log 10 IU/ml by week 12).

All patients received a 4-week lead-in with P2bR. There were two different approaches explored in the BOC arms:

■ Patients received BOC + P2bR for 32 weeks, and those with detectable HCV RNA at week 8 or later, received an additional 12 weeks of P2bR;

■ Patients received BOC + P2bR for 44 weeks.

A total of 403 patients were randomized into three groups: BOC/RGT, BOC/P2bR48, and P2bR48; with SVR rates of 59, 66 and 21%, respectively (p < 0.0001; p < 0.0001) (Figure 3). Previous relapsers responded better than previous partial responders (69/75/29% vs 40/52/7%) (Figure 3).

■ Telaprevir
The combination of TVR with P2aR in previously treated patients infected with HCV genotype 1 was examined in a Phase III trial (REALIZE) [4]. This study included previous relapsers, partial responders and null responders. There was no adjustment of treatment duration based on response to therapy and all patients received 48 weeks of treatment.

Patients were randomized to three groups: T12PR, T12PR with a 4-week lead-in of P2aR, and P2aR (control); with SVR rates of 64, 66 and 17%, respectively (p < 0.0001; p < 0.0001) (Figure 4). SVR rates were significantly higher in the TVR groups compared with the control arms among the previous relapsers (83% in T12PR48, 88% in lead-in T12PR48 and 24% in the PR48 group), partial responders (59, 54 and 15%, respectively), and null responders (29, 33 and 5%, respectively) (p < 0.001 for all comparisons) (Figure 4). The prior treatment response was the strongest predictor of treatment outcome with TVR-based therapy with prior relpasers showing SVR rates above those achieved in a treatment-naive population, while prior null responders had low rates of SVR, particularly in the setting of cirrhosis. There was no advantage in terms of rates of SVR with a lead-in phase with TVR-based therapy.
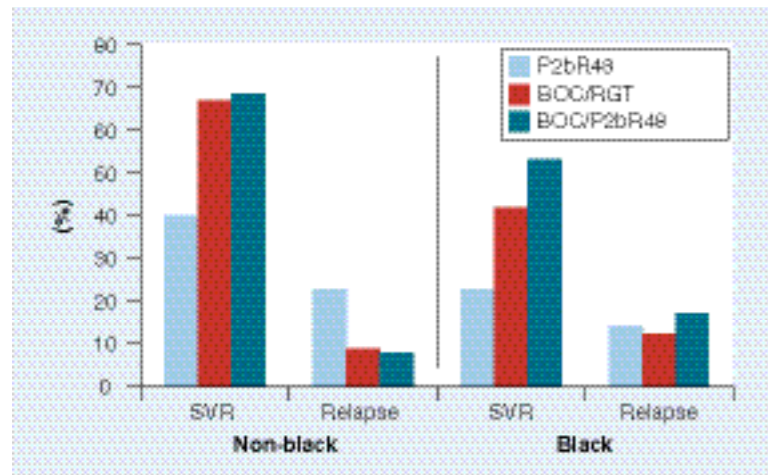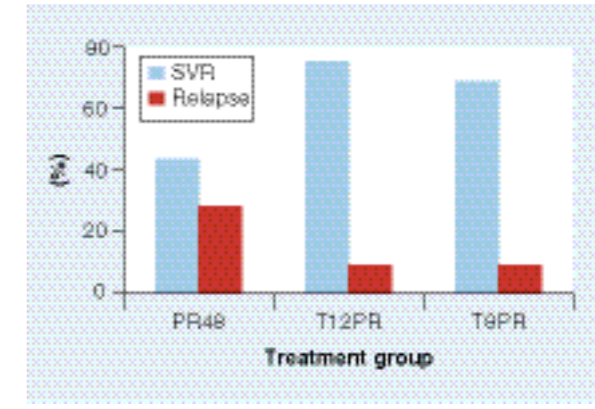

Figure 2. Treatment results in genotype 1 treatment-naive patients treated with telaprevir with pegylated-IFN and ribavirin.
PR48: Pegylated IFN and ribavirin for 48 weeks; SVR: Sustained virological response; T12PR: Telaprevir for 12 weeks, pegylated IFN α 2a and ribavirin for 48 weeks; T8PR: Telaprevir for 8 weeks, pegylated IFN α 2a and ribavirin for 48 weeks.
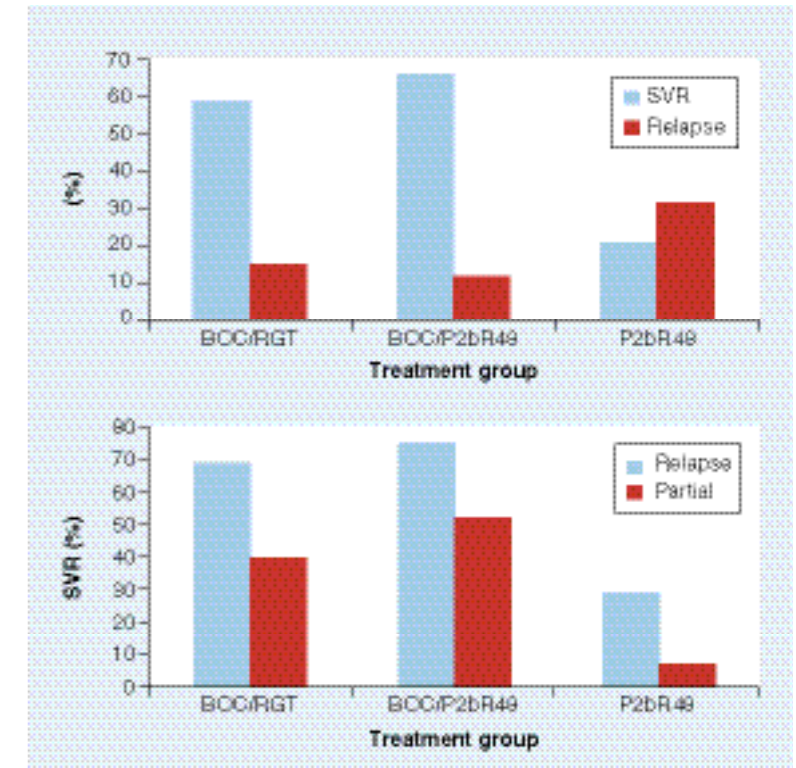

Figure 3. Treatment results in genotype 1 treatment-experienced patients treated with boceprevir with pegylated-IFN and ribavirin.
BOC/RGT: Boceprevir response guided treatment; BOC/P2bR48: Boceprevir and pegylated IFN α 2b and ribavirin for 48 weeks; P2bR48: Pegylated IFN α 2b and ribavirin for 48 weeks; SVR: Sustained virological response.
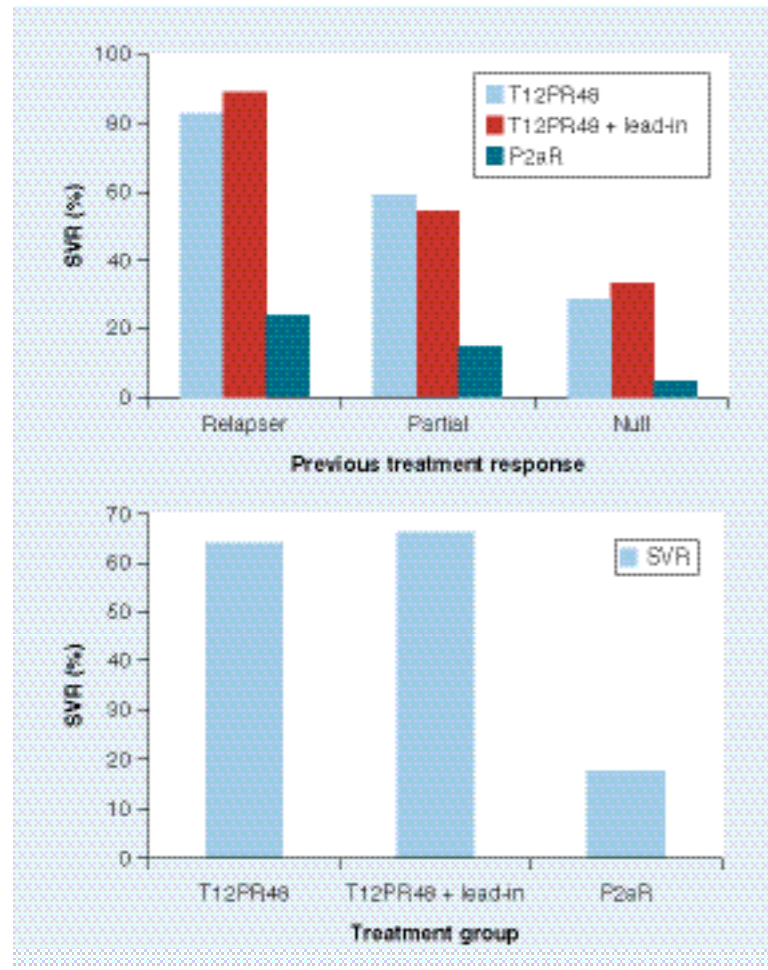
Figure 4. Treatment results in genotype 1 treatment-experienced patients treated with telaprevir with pegylated-IFN and ribavirin. P2aR: Pegylated IFN α 2 and ribavirin; T12PR48: Telaprevir for 12 weeks, pegylated IFN α 2a and ribavirin for 48 weeks; SVR: Sustained virological response.

■ **Take home message**

In patients with HCV genotype 1 infection who have previously failed treatment with pegylated-IFNα and RBV, BOC or TVR combination therapy results in significantly higher rates of SVR compared with PR therapy. The most important predictive factor for SVR in treatment-experienced patients using BOC or TVR combination therapy is the history of the prior response (relapse, partial or null) to PR therapy.

Proportion of patients eligible for shortened duration of therapy

One of the major strengths of using BOC or TVR in combination with PR is the potential for shortening treatment duration. By using RGT, patients may stop therapy earlier without compromising the rates of SVR, as demonstrated by the Phase III studies [1–3].

In addition, decreasing the duration of treatment can eliminate the risk of developing potential adverse effects, decrease drug costs, and likely improve adherence. Importantly, not all patients will qualify for shortened treatment and particular groups (e.g., those with cirrhosis), as well as those who respond slowly, will require a full 48-week course of therapy.

■ **BOC**

The benefit of RGT for BOC has been demonstrated in both treatment-naive (SPRINT 2) and experienced patients (RESPOND 2) [1,2]. Of the treatment-naive patients in the RGT arm, 44% were eligible for shortened therapy.

In the treatment-experienced cohorts, those eligible to shorten therapy to 36 weeks were required to have undetectable HCV RNA at both 8 and 12 weeks. In RESPOND-2, 46–52% of patients in the BOC arms were shortened therapy with no reduction in SVR compared with those treated for 48 weeks (Figure 5).

Available data suggest that certain populations may benefit from a full 48-week course of therapy. Patients with cirrhosis, whether treatment-naive or -experienced, had better rates of response with a lead-in followed by 44 weeks of triple combination therapy than with the RGT algorithms. In SPRINT2, patients with cirrhosis had SVR rates of 42% in the BOC48 arm compared with 31% with the RGT approach [1], which were similar to the results in the pegylated-IFNα/ribavirin control arm (38%); however, very few patients with cirrhosis were included in the study. Similarly, in RESPOND2, fixed duration of therapy led to SVR rates of 68% compared with 44% with RGT [5]. Patients with a poor response during the lead-in phase (<1-log decline from baseline) also did better with an additional 44 weeks of BOC/P/R than with RGT [1,5]. Based on these data, despite the limited numbers, both the US FDA and European Medicines Agency have recommended extended therapy (BOC48) for patients with cirrhosis and those with a <1-log decline in HCV RNA during the lead-in phase. Therefore, it is critical to assess the level of hepatic fibrosis in all patients prior to starting therapy to determine the length of treatment, as well as the need for ongoing follow-up after SVR. Although neither regulatory agency recommended excluding black patients from an RGT approach, it is notable that the SVR rate for black patients with RGT was only 42 compared to 53% with the BOC48 approach. However, the number of black patients was relatively limited and most poor-responding patients would be identified by following the lead-in phase response as a guide to therapy.

Notably, the FDA and European Medicines Agency

differed in their recommendations regarding previous relapsers treated with BOC/P/R combination therapy. The FDA followed the protocol in the RESPOND2 trial allowing for an RGT approach in non-cirrhotic patients with discontinuation of therapy at 36 weeks of treatment for those who had undetectable HCV RNA by week 8 through week 24. In contrast, the European Medicines Agency recommended that such patients stop BOC at week 36 but continue PR for an additional 12 weeks. Country-specific guidelines should be reviewed to clarify appropriate treatment duration.

■ **Telaprevir**

Although RGT was used in the ADVANCE study, there was no direct comparison with a 48-week course of therapy because all patients in the T12PR and T8PR groups who achieved eRVR were permitted to shorten therapy. To specifically evaluate the role of RGT, the ILLUMINATE study randomized patients who achieved an eRVR to 24 or 48 weeks of therapy [6]. The rate of SVR was 92% with 24 weeks of therapy compared to 88% with 48 weeks of therapy for those with an eRVR, suggesting that RGT is an appropriate approach in treatment-naive patients treated with TVR. In addition, fewer adverse events and treatment-discontinuations were noted with 24 weeks of therapy. Notably, 65% of patients who entered the trial achieved an eRVR (Figure 5). Of patients with cirrhosis who achieved an eRVR, 18 were randomized to stop at week 24 and 12 to continue to week 48. Only 12 of 18 (66%) who stopped at week 24 achieved SVR, while 11 of 12 (92%) who received 48 weeks of therapy went on to SVR. Despite the limited numbers, regulatory agencies have recommended 48 weeks of therapy for all patients with cirrhosis regardless of on-treatment response.

In treatment-experienced patients, no studies have looked at shortening therapy with TVR. Nonetheless, the FDA has recommended an RGT approach with TVR combination therapy for previous relapsers to PR therapy without cirrhosis because of the high rates of SVR reported, as well as data from the Phase II trials showing high response rates with 24 weeks of therapy in this population [101]. Both the FDA and European Medicines Agency have recommended that all previous null or partial responders be retreated with TVR combination therapy for 48 weeks.

■ **Take home message**

In treatment-naive patients, an RGT-approach will allow a significant proportion of patients to shorten therapy with BOC (44%) and TVR (58–65%) to a total of 24–28 weeks. In treatment-experienced
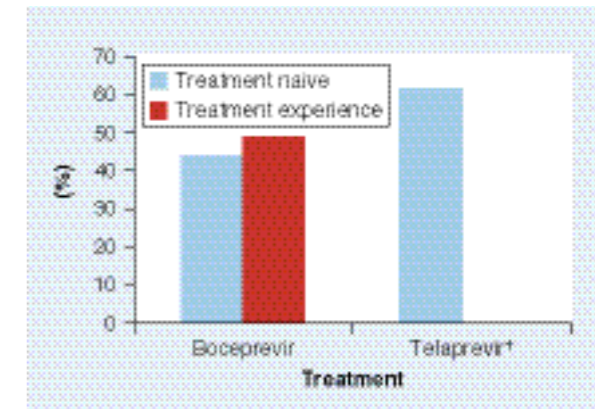

Figure 5. Proportion of patients qualifying for shortened therapy based on response-guided therapy using boceprevir or telaprevir in treatment-naive and treatment-experienced patients (for boceprevir only). †Based on combined results of patients who qualified for response-guided therapy in ILLUMINATE and ADVANCE.

patients, prior relapsers can use the RGT strategy with either TVR or BOC. All patients with cirrhosis should receive 48 weeks of total therapy. Therefore, evaluation of the degree of fibrosis with either liver biopsy or noninvasive methods is critical to establish or exclude the presence of cirrhosis prior to starting therapy. Patients responding poorly (<1-log decline) in the lead-in phase prior to BOC-based therapy should receive 44 additional weeks of triple therapy. FDA and European Medicines Agency recommendations differ and do not follow the study protocols precisely. Country-specific labels for both agents should be reviewed for each specific patient population.

Administration of BOC & TVR

The administration of BOC and TVR will be based on the design of their respective Phase III trials, which used combination therapy including pegylated-IFN α 2a or 2b, and RBV.

■ **BOC**

BOC is given three times-daily (7–9 h apart) at a dose of 800 mg (4 × 200 mg capsules) in combination with pegylated-IFNα 2b (1.5 µg/kg/week) and weight-based RBV (0.8–1.4 g/day). BOC should be taken with food to maximize drug exposure, although bioavailability is similar regardless of food type (e.g., fat vs non-fat) or timing (just prior, during or following completion of meal) [102]. It is recommended to use a 4-week lead-in phase with PR in all BOC-treated patients with HCV RNA testing at week 4. After the lead-in, BOC is added. For patients with a less than 1-log decline during the lead-in and for those with cirrhosis, PR

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and BOC should be continued for an additional 44 weeks. Patients without cirrhosis who have undetectable HCV RNA at week 8 of therapy after a >1-log decline during the lead-in (4-week lead-in plus 4 weeks of BOC/P/R therapy) can safely stop all treatment at week 28. Patients who do not qualify for shortened therapy should receive either an additional 20 weeks of PR therapy after stopping BOC at week 28 (trial design and Health Canada recommendations) or should continue BOC to week 36 followed by 12 weeks of PR alone (FDA and European Medicines Agency recommendations) (Figure 6).

In treatment-experienced patients, after an initial 4-week lead-in phase with PR, BOC is added. For previous partial responders and relapsers who achieve an early response (undetectable week 8 through week 24), the FDA recommends continuing BOC/PR for 32 additional weeks and stopping all therapy at week 36. For patients who do not achieve an early response, after stopping BOC at week 36, PR should be given for an additional 12 weeks. The European Medicines Agency recommends the additional 12 weeks of PR beyond week 36 (total 48 weeks therapy) for all treatment-experienced patients. Although use of BOC in null responders was not studied in the Phase III trials, the FDA and European Medicines Agency have recommended that such patients receive a full 48 weeks of therapy (4-week lead-in plus 44 weeks of BOC/PR) if therapy is considered in this population

(Figure 6) [102]. All treatment-experienced patients with cirrhosis should also receive 44 weeks of triple therapy after the 4-week PR lead-in for a full 48-week course of therapy.

■ Telaprevir
TVR is given three-times-daily (7–9 h apart) at a dose of 750 mg (2 × 375 mg tablets) in combination with pegylated-IFN and weight-based RBV (1–1.2 g/day). Like BOC, TVR should be taken with food, however the fat content of the food is very important. Patients should take TVR with 20 g of fat to maximize bioavailability [101]. In treatment-naive patients, triple combination therapy (T/P/R) is administered for the first 12 weeks of treatment followed by PR. In patients who attain eRVR (HCV RNA undetectable weeks 4 through 12), PR is continued for 12 additional weeks for a total duration of 24 weeks. Patients who do not attain eRVR require an additional 36 weeks of PR treatment for a total duration of 48 weeks (Figure 7). All patients with cirrhosis should receive 12 weeks of TVR and a total of 48 weeks of PR.

In treatment-experienced patients with previous null or partial response, triple combination therapy is administered for 12 weeks with the continuation of PR for an additional 36 weeks (48 weeks total). In previous relapsers, the same RGT protocol used in treatment-naive patients can be used (Figure 7). As with treatment-naive patients, all patients with

Figure 6. Treatment algorithms for boceprevir (based on clinical trial design and Canadian but not US FDA or European Medicines Agency guidelines).
B: Boceprevir; P: Pegylated IFN; R: Ribavirin; RVR8: Undetectable hepatitis C virus RNA at week 8 of therapy (4 weeks of lead-in, plus 4 weeks of boceprevir/pegylated IFN α 2b and ribavirin).

cirrhosis should receive 12 weeks of TVR and a total of 48 weeks of PR.

■ Take home message
Both BOC and TVR must be taken every 7–9 h (not three times-daily) with food. TVR should be taken with 20 g of fat. The prior response, lead-in phase (BOC) and presence of cirrhosis determine the duration of PI therapy. An RGT approach should not be used in patients with cirrhosis and those with a poor lead-in phase response (BOC).

BOC & TVR use with either pegylated-IFNα 2a or 2b
The Phase III trials studied BOC and TVR specifically with pegylated-IFNα 2a and 2b, respectively; however, subsequent data have shown that either pegylated-IFN is effective with either PI.

■ BOC with pegylated IFNα 2a
The use of BOC in combination with pegylated-IFNα 2a and ribavirin (P2aR) was evaluated in an unpublished, double-blind, randomized, controlled trial that included prior nonresponders and relapsers [7]. These patients both received 4-week lead-in therapy with P2aR followed by the addition BOC or placebo for 44 weeks. The BOC arm resulted in superior SVR rates (64 vs 21%; p < 0.0001) compared with placebo, and similar to the SVR rates observed with pegylated-IFNα 2b, RBV and BOC, suggesting that BOC can be combined with either pegylated-IFN [2]. Although there are no data of BOC with Peg2a in treatment-naive patients, there is no reason to believe that this would not be a successful approach.

■ TVR with pegylated-IFNα 2b
An open-label study in HCV genotype 1 treatment-naive patients assessed the efficacy of TVR used at difference doses (750 mg Three-times-daily vs 1125 mg twice-daily) with either pegylated-IFNα 2a or 2b [8]. Among the different regimens, similar SVR rates were observed with no statistically significant differences in virologic response at week 4, week 12 and at the end of treatment, irrespective of the type of pegylated-IFNα used.
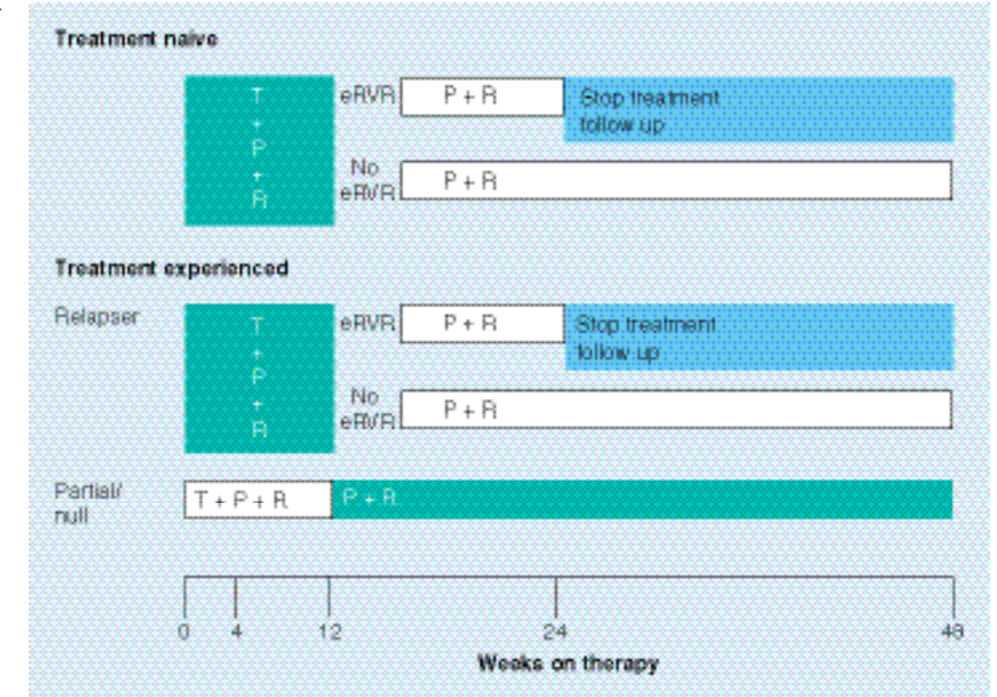

Figure 7. Treatment algorithms for telaprevir (based on clinical trial design and Canadian but not US FDA or European Medicines Agency guidelines).
eRVR: Hepatitis C virus RNA undetectable at weeks 4 through 12; P: Pegylated IFN; R: Ribavirin; T: Telaprevir.

■ Take home message
Current data suggest that BOC and TVR can be effectively used with either available pegylated-IFNα formulation.

Dosing of BOC & TVR
As both BOC and TVR require three times-daily dosing, concerns regarding noncompliance have arisen. The previously mentioned TVR study assessed the effect of decreased frequency of dosing showing no difference in SVR rates when TVR was used at a dose of 750 mg every 7–9 h compared with 1125 mg twice-daily [8]. However, the study population included only treatment-naive patients with a very small percentage of black patients and cirrhotics. There are no published data evaluating decreased dosing frequency of BOC, but based on its short half-life, it likely requires three daily doses.

■ Take home message
BOC and TVR should be administered every 8 h until future studies have clearly shown the option of twice-daily dosing has no effect on SVR in all populations.
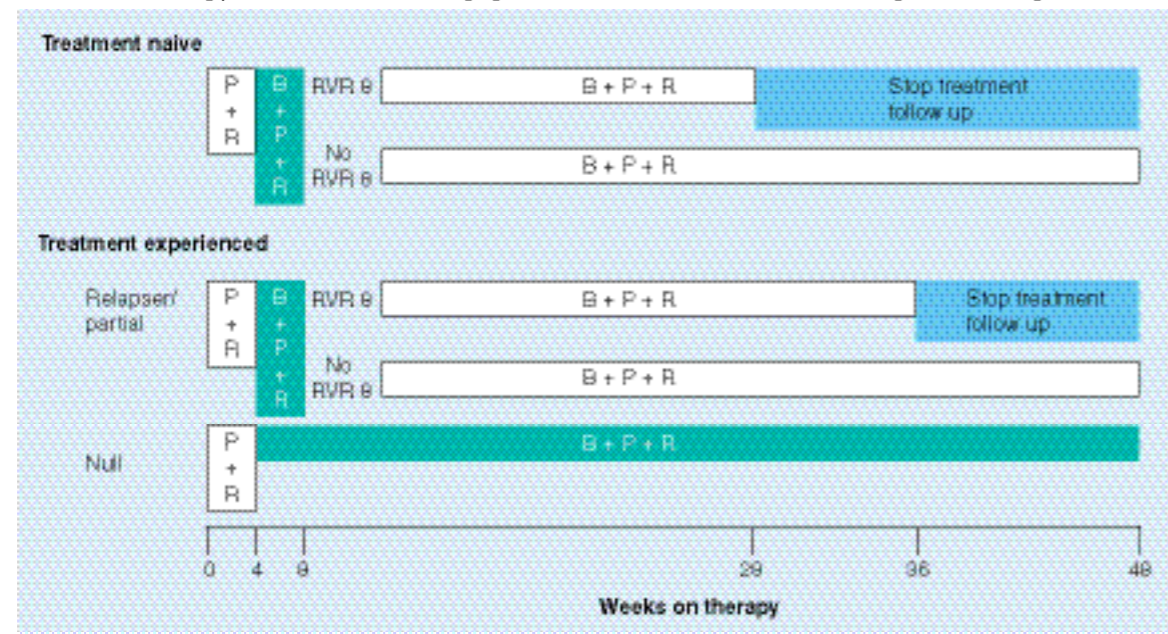
The benefit of the lead-in phase

The 4-week lead-in approach with PR was chosen for all BOC Phase III trials based on findings from the Phase II clinical development, which suggested that this approach produced slightly better rates of SVR and modestly lower rates of viral breakthrough compared with treatment without a lead-in phase [9]. Other theoretical advantages to a lead-in phase include the potential for a reduced risk of viral resistance and to allow time for PR to reach steady-state prior to the addition of the PI.

Despite the theoretical advantages, the lead-in phase has not been shown to increase rates of SVR or reduce the risk of resistance with either BOC or TVR [4]. However, the lead-in phase does provide important information, which may affect treatment decisions. The greatest utility of the lead-in phase is to provide a real-time evaluation of interferon-responsiveness. In treatment-experienced patients, the previous treatment response is the strongest predictor of response to BOC or TVR-based therapy. Similarly, the response during lead-in phase predicts subsequent rates of SVR and may even alter the decision to treat. Patients with a poor lead-in phase response (<1-log decline in HCV RNA) were less likely to achieve SVR and more likely to have emergence of resistance, leading to the recommendation that such patients should not use the RGT treatment algorithms, but rather should receive an additional 44 weeks of BOC/P/R therapy. Alternatively, for patients who suppress virus to undetectable levels during the lead-in phase (RVR), the addition of the BOC or TVR may not be necessary as high rates of SVR can be achieved with just 24 weeks of therapy. Notably, however, whether the addition of a protease inhibitor would increase the rates of SVR further in RVR patients is unknown.

Although the lead-in phase did not lead to higher rates of SVR in patients treated with a lead-in phase with TVR in the REALIZE trial, there may still be some advantages. The lead-in was particularly helpful for prior null responders. Null responders with a less than 1-log decline in HCV RNA during the lead-in phase had an SVR rate of 15%, while those with a greater than 1-log decline had an SVR rate of 54%. Therefore, for null responders, although not required, one may elect to use a lead-in with TVR and to stop therapy if there is a less than 1-log decline given the low chance of SVR. For partial responders and relapsers, the lead-in phase was less clinically useful and is not necessary when treating with TVR.

The lead-in phase can further help assess both compliance and tolerability, including treatment-related side effects, before exposure to a class of drugs to which resistance can develop.

■ **Take home message**
The lead-in phase provides important information relating IFN responsiveness to probability of SVR. A less than 1-log decline in HCV RNA during the lead-in phase indicates poor IFN responsiveness, which is associated with lower rates of SVR and should therefore lead to avoidance of an RGT approach to therapy.

Stopping rules
Stopping rules have been established for both BOC and TVR combination therapies based on the Phase III trials. After careful examination of the trial data, the FDA and European Medicines Agency adopted slightly different stopping rules from those used in the studies. It is of critical importance that the stopping rules be followed carefully to avoid unnecessary PI exposure and to prevent the emergence of PI-resistant virus with increased replicative fitness [3,4,101,102].

Before PI treatment is initiated, the wild-type (WT) virus is more fit than the baseline PI-resistant virus and will be the dominant population. When PI treatment starts, PI-resistant virus gains a significant fitness advantage over the suppressed WT virus, and thus emerges as the dominant virus in the population. If the PI is continued despite the presence of a significant PI-resistant viral population, the PI-resistant virus will continue to naturally evolve over time through the occurrence of random mutations. Some of these random mutations may compensate for the fitness loss associated with the original PI-resistance mutations leading to a more fit PI-resistant population. Over time, with multiple compensatory mutations, PI-resistant virus may improve its fitness to the point that it is able to compete favorably with WT virus. If such a scenario occurs, PI-resistant virus is likely to persist even after the PI is stopped, which may limit future treatment options.

Because the stopping rules are based on the presence of very low levels of virus (1000 or 100 IU/ml), there may be a temptation to continue patients with HCV RNA levels that are only slightly above these thresholds. However, it is important to recognize that these thresholds were chosen very carefully such that no SVRs would have been missed in the Phase III trials had these rules been applied. In most cases, patients with viral levels above the specified thresholds have viral titres that are rising rather than falling. For example, a drop from 6 logs at baseline to 1500 IU at week 4 with T/PR therapy may seem like a very favorable response. However, it is most likely that if a week 2 sample were available it would show that the HCV RNA titre was actually below 1500 IU/

ml and the week 4 titre is on the way up (not down), due to the presence of resistant virus.

■ **BOC**
Stop all medications if:
■ HCV RNA ≥ 100 IU/ml at week 12;
■ HCV RNA detectable at week 24.

Although not endorsed as a formal stopping rule by FDA or European Medicines Agency, one may consider stopping all medications for patients with a poor lead-in phase response (<1 log decline in HCV RNA) and <3 log decline in HCV RNA by week 8 because none of the 44 such patients achieved SVR in Phase III trials.

■ **Telaprevir**
Treatment-naive
Stop all medications if:
■ HCV RNA >1000 IU/ml at week 4 or 12;
■ HCV RNA detectable at week 24.

■ **Take home message**
The application of established stopping rules is critical for patients on triple therapy to limit unnecessary PI exposure and to prevent emergence of PI-resistant virus with increased replicative fitness. HCV RNA levels above defined thresholds for futility likely indicate rising viral titres with resistant virus and should lead to prompt treatment discontinuation.

Role of IL-28B
Genome-wide association studies have made a major contribution to the treatment of hepatitis C with the discovery of SNP around the gene that encodes for IL-28B on chromosome 19 [10–12]. The single nucleotide polymorphism (rs12979860) has been strongly associated with SVR in patients with HCV genotype 1 infection treated with PR therapy.

■ **Treatment-naive**
Retrospective analyses of the Phase III PI trials in treatment-naive patients have demonstrated that the IL-28B genotype is a strong baseline predictor of SVR [13,14]. The addition of a PI was of greatest benefit in patients with the unfavorable CT and TT genotypes. Both BOC and TVR clearly increased rates of SVR in patients with non-CC genotypes. For patients with the CC genotype, the benefit of the PI was less clear. In CC patients in the ADVANCE study, the rate of SVR was 90% in TVR-treated patients compared with 64% in the PR control group. By contrast, in the SPRINT2 trial, the SVR was 80% with the addition of

BOC compared to 78% in the PR control arm. On the surface it would appear that TVR improves rates of SVR for CC patients while BOC does not. However, it is notable that the response rates among CC patients in the control arms of these studies differed markedly (78 vs 64%). The 64% figure in the ADVANCE study is considerably lower than most previous reports of SVR rates in CC patients with PR therapy. The results with the addition of TVR in CC patients would have been less remarkable if the expected 80% SVR rate had been seen in the control arm. However, CC patients still benefited from the addition of PI because they were more likely to qualify for shortened therapy (72–89%) compared with non-CC patients (48–52%) [13,14]. Overall, in treatment-naive patients the addition of a PI is of most benefit for non-CC patients, but increases the likelihood of shortening therapy for patients with the CC genotype. Future studies are underway to explore if CC patients can shorten treatment duration.

■ **Treatment-experienced**
The relationship between the IL-28B genotype and response was evaluated in a subset of treatment-experienced patients treated with both BOC and TVR [13,15]. As expected in trials of previous treatment failures, there were significantly more non-CC patients compared with the studies involving treatment-naive patients (TVR 82 vs 67%; BOC 70 vs 64%) [13–15].

In patients who had previously failed treatment, there was no difference observed in SVR in the TVR arms among the three IL-28B genotypes when controlled for previous treatment response (null,
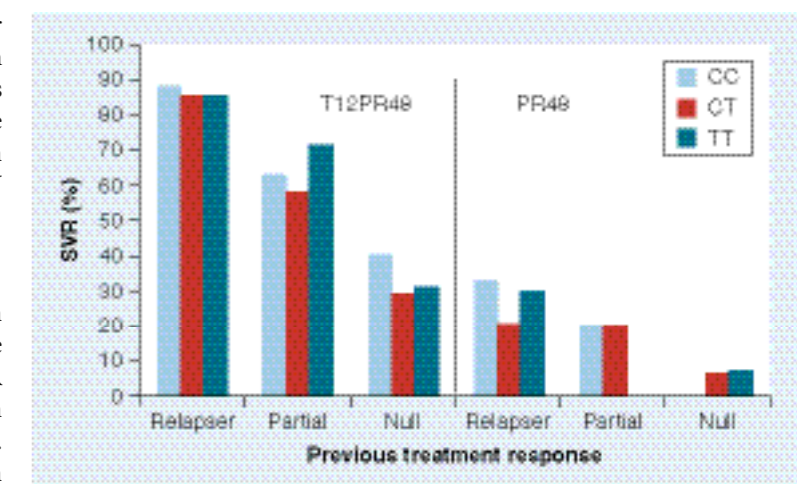

Figure 8. Utility of IL-28B genotype in outcome in previously treated patients receiving telaprevir-based triple therapy.
PR48: Pegylated IFN α 2a and ribavirin for 48 weeks; SVR: Sustained virological response; T12PR48: Telaprevir for 12 weeks, pegylated IFN α 2a and ribavirin for 48 weeks.

partial or relapse) (Figure 8) [15]. These results suggest that prior response to treatment is a more significant predictor of SVR in treatment-experienced patients with limited utility for IL-28B genotyping. The data from patients in the RESPOND2 trials also showed that previous treatment response was more important than IL-28B genotype in treatment-experienced treated with BOC. Similarly, the response in the lead-in phase was a better predictor of treatment outcome than IL-28B genotype in both treatment-naive and treatment-experienced patients.

■ Take home message
Addition of either BOC or TVR improves response rates in patients with all IL-28B genotypes with the greatest benefit seen in patients with the non-CC genotypes. In treatment-experienced patients, previous treatment response is a better predictor of SVR with limited utility for IL-28B genotype. The response during the 4-week lead-in phase is a better predictor of treatment outcome than the IL-28B genotype

Adverse effects
■ BOC
The main side effect associated with BOC use is the potential to develop anemia. A significantly higher proportion of patients treated with BOC compared to SOC required the use of erythropoietin (EPO) in both SPRINT-2 (43 vs 24%) and RESPOND-2 (41–46 vs 20%) [1,2]. Anemia occurs relatively early on in therapy with at least a 1–1.5 g/l drop in hemoglobin by week 6–8 in most patients receiving BOC. Anemia may be a significant issue in clinical practice because of limitations on the availability of EPO as well as its significant costs and potential for side effects. A study comparing RBV dose reduction (200–400 mg/day) and EPO use showed identical rates of SVR (71%) in treatment-naive patients treated with BOC and, hence, RBV dose reduction is the preferred first-line strategy for anemia management. Although RBV should be started at full dose, no effect on SVR was seen in patients who had RBV dose reductions for anemia. In all studies with BOC, the development of anemia was associated with SVR, possibly reflecting higher drug exposure and compliance. If necessary, anemia can also be managed with blood transfusion. Importantly, prescribers should not reduce the dose of BOC to manage anemia.

The second notable reported adverse event with BOC use is dysgeusia (alteration of taste). Although this was a troublesome side effect, it did not lead to treatment discontinuations in the clinical trials and hopefully will be a manageable side effect in clinical

practice. Some strategies including chewing gum and drinking chocolate milk with the pill have been anecdotally advocated (Table 1).

■ Telaprevir
Dermatologic issues are the main side effects associated with TVR use. In controlled clinical trials, rash events (all grades) were reported in 56% of subjects who received TVR treatment compared with 34% of subjects who received SOC [101]. In most cases the rash was not severe, however rare cases of DRESS (drug reaction with systemic signs) and Stevens-Johnson syndrome have been reported, but fortunately with no associated deaths. In the clinical trials, rash led to discontinuation of TVR alone in 6% of patients and to discontinuation of all treatment in 1%. Rash most frequently began during the first 4 weeks, but could occur at any time during TVR treatment. Improvement of rash occurred after discontinuation, but could take weeks for complete resolution. The rate of treatment discontinuation due to rash decreased in more recent trials, suggesting that, with experience, investigators were more comfortable continuing therapy. A careful rash management plan was also developed for the Phase III trials, which will also be very useful in clinical practice (Table 1) [101].

Pruritus even in the absence of rash occurred significantly more in patients treated with TVR compared with SOC [3,4]. Pruritus rarely led to discontinuation of treatment (<1%). A variety of different techniques for the management of pruritus have been suggested, including: moisturizing creams, topical cleansing regimens, topical steroidal creams and oral antihistamines (Table 1).

The overall incidence and severity of anemia is also increased with TVR combination therapy compared with SOC (36 vs 17%) [3,4]. A decrease in hemoglobin levels occurred during the first 4 weeks of treatment, with lowest values reached at the end of TVR dosing. The use of EPO was not allowed in the Phase III TVR trials, but will likely play a minor role in clinical practice because of the short duration of TVR therapy (12 weeks). Notably, in the Phase III trials with TVR, anemia was managed with RBV dose reduction down to 600 mg daily, according to the RBV product monograph. A retrospective analysis of the trials showed that the RBV dose reductions had no effect on SVR [16]. Blood transfusions were required in 7% of patients treated with TVR and were more likely in older patients with low body-mass index and low baseline hemoglobin.

A significant number of anorectal adverse events (e.g., hemorrhoids, anorectal discomfort, anal pruritus and rectal burning) occurred in the

Table 1. Management of adverse effects

Drug	Adverse effect	Management
BOC	Anemia	Ensure Fe/folate and B12 replete; reduce RBV dose to 600 mg OD with TVR-based therapy and by 200–400 mg/day with BOC-based therapy; supplement with EPO (as second-line); consider further RBV dose reductions as needed; do not reduce dose of BOC; transfuse if necessary Low threshold for pretreatment cardiac testing
BOC	Dysgueusia	Chewing gum; chocolate milk
TVR	Rash	Serious skin reactions (e.g., DRESS/Stevens Johnson syndrome), discontinue all three drugs; emergency dermatology consultation Mild–moderate rash: good skin care; treat with topical corticosteroids and oral antihistamines; if rash progresses or systemic symptoms develop, discontinue TVR; after discontinuation of TVR, if rash does not improve after 7 days, discontinue pegylated-IFN and RBV
TVR	Pruritus	Good skin care – moisturizing creams; topical corticosteroids; oral antihistamines
TVR	Anemia	See above – BOC anemia
TVR	Anorectal symptoms	Ensure adequate cleansing; hemorroidal steroid creams (e.g., anusol); lidocaine gel PR; sitz baths; fiber/metamucil

BOC: Boceprevir; DRESS: Drug rash with eosinophilia and systemic symptoms; EPO: Erythropoietin; OD: Once daily; PR: Peginterferon/ribavirin; RBV: Ribavirin; TVR: Telaprevir.

TVR-treated patients compared with those who received SOC (29 vs 7%) [101]. The majority of these events were mild–moderate in severity and led to treatment discontinuation in <1%. All patients had resolution of symptoms following discontinuation. However, the reported numbers in the clinical trials may be somewhat lower than will be seen in clinical practice because patients have not volunteered these symptoms. Based on anecdotal clinical experience and expert opinion, anorectal adverse events can be managed with supportive topical therapies (hemorrhoidal creams, sitz baths and so forth).

Data from ADVANCE showed that treatment-naive patients treated with 12 weeks of TVR, as compared to 8 weeks, had better overall results in all subgroups, albeit nonsignificant, including: higher rates of response, lower rates of virologic failure and decreased emergence of resistance-associated variants [3]. The improved results in the T12PR are probably attributable to more efficient elimination of the virus as a result of an additional 4 weeks of TVR therapy, supporting a T12PR treatment model. However, because the results were not significant, patients experiencing significant TVR-related adverse events can shorten TVR therapy to 8 weeks and maintain good results.

■ Take home message
Significant adverse events related to BOC include anemia and dysgeusia. Significant adverse events related to TVR include rash, anemia and anorectal signs and symptoms. If necessary, TVR can be

reduced to 8 weeks without significant effect on rate of SVR. Careful monitoring of side effects in clinical practice will be essential.

Drug interactions
The family of cytochrome P450 (CYP) enzymes, mainly found in hepatocytes, are responsible for the metabolism of many different drugs. Both BOC and TVR are substrates (partly metabolized) and strong inhibitors of CYP3A4 [101,102]. Because CYP3A4 is involved in the metabolism of numerous drugs, there is potential for a significant number of drug interactions.

Drugs metabolized primarily by CYP3A4 may have increased exposure when coadministered with BOC or TVR, thereby increasing or prolonging their therapeutic and adverse effects. Similarly, drugs that induce or inhibit CYP3A4 could decrease or increase exposure to BOC and TVR. As such, BOC and TVR coadministration is contraindicated with drugs that are potent inducers of CYP3A4 and drugs that are highly dependent on CYP3A4 for clearance. Among contraindicated medications identified by the FDA are several commonly used drugs, including: oral midazolam, sildenafil, anticonvulsants (carbamazepine, phenytoin and phenobarbitol) and statins (lovastatin, simvastatin and atorvastatin) [101,102]. Other potential drug interactions can be found using reputable and up to date drug databases [103,104].

Future prescribers will need to carefully review all medications, including herbal and over-the-counter preparations, used by the patient as well as any new

drugs that maybe coadministered during treatment to help identify potential important drug interactions and ideally prevent serious adverse events.

■ Take home message

There are numerous potential drug interactions involving the coadministration of BOC or TVR. Future prescribers will need to review in detail any coadministered medications to identify possible interactions and contraindications.

Use of TVR or BOC combination therapy in specific populations with HCV genotype 1 infection

Because of higher efficacy rates and the potential for shorter duration of therapy, BOC and TVR will become attractive considerations for physicians contemplating HCV treatment in specific populations infected with genotype 1; particularly those at risk for progression to severe liver disease and hepatic complications. These populations include: cirrhotics, HIV coinfection, renal insufficiency (creatinine clearance <50 ml/min) and liver transplant recipients.

■ Cirrhosis

In the Phase III trials, only a small number of patients with cirrhosis were included and all had very well compensated disease. More patients with cirrhosis were included in the TVR-naive and -experienced trials (n = 247) than in the trials of BOC [1–4]; however, although the data may be somewhat more robust for TVR, for both agents true estimates of efficacy and more importantly safety in this population are lacking. Although the numbers are small, the data with both agents suggest that patients with cirrhosis should receive a full 48 weeks of therapy. Response rates were lower in patients with cirrhosis than in those with earlier stages of fibrosis, with the exception of prior relapsers, in whom the rates of SVR were equivalent from F0 through to F4. Prior null responders with cirrhosis had very low rates of SVR and treatment should be considered carefully in this population. Patients with cirrhosis were at higher risk of anemia and require careful monitoring for all adverse effects. Patients with even very early hepatic decompensation were excluded from all Phase III trials. Although it may be reasonable to consider treating patients with very early decompensation in centers with extensive experience and access to liver transplantation, further decompensation and other severe complications, including death, must be discussed with the patient prior to starting therapy.

■ HIV/HCV coinfection

There are significant drug–drug interactions with PIs and some classes of antiretroviral medications for HIV. Currently trials are ongoing with both TVR and BOC in HIV-infected patients and early results look promising in terms of both efficacy and safety.

■ Renal failure

Although neither drug is renally cleared, there are no safety data in patients with significant renal impairment. Until further data are available, these patients should be treated in clinical trials only.

■ Post-liver transplantation

The use of new therapies in the treatment of liver transplant recipients raises complex issues concerning drug–drug interactions. A recent open-label Phase 1 nonrandomized study in healthy volunteers designed to assess the effect of TVR coadministration, on the pharmacokinetics of a single dose of either cyclosporine or tacrolimus [17], found that TVR coadministration significantly increased cyclosporine (4.6-fold) and tacrolimus exposure (70-fold). In addition, the elimination half-life of these drugs was decreased by four- to five-fold. These results suggest a potential significant risk to transplant recipients from drug toxicities with TVR coadministration. Recent reports suggest that BOC also affects the levels of calcineurin inhibitors, but not to the degree seen with TVR. The use of either TVR or BOC in organ transplant patients is not recommended until needed studies have been completed and regulatory approval has been obtained.

■ Take home message

BOC or TVR should not be used in patients with decompensated cirrhosis, HIV coinfection, renal insufficiency or previous liver transplantation, until future studies in these populations have been performed.

Role of BOC/TVR in the treatment of nongenotype 1 HCV

Clinical studies involving TVR have demonstrated strong antiviral activity against genotype 2, modest activity against genotype 4, and limited activity for genotype 3 [18,19]. There are no published studies investigating BOC antiviral activity in patients with nongenotype 1 infection but there is some suggestion that BOC may have some activity against genotype 3 HCV. Until further clinical studies involving patients with nongenotype 1 are performed, the standard of care in these patients will remain combination pegylated-IFNα and RBV.

■ Take home message

In patients with HCV nongenotype 1 infection, combination pegylated-IFNα and RBV remains the standard of care.

Resistance

Most failures to eradicate HCV infection on triple combination therapy are due to an inadequate anti-viral response to PR on the background of a dominant resistant viral population to the administered PI at the time of viral breakthrough or relapse [3]. Upon withdrawal of PI therapy, follow-up studies have shown ongoing dynamic changes in the viral population with a progressive replacement of the resistant variants with the WT population after several weeks to months [20,21]. Although the resistant populations were not detectable in the majority of these patients by population sequencing, it is unlikely that they have truly disappeared. Population sequencing detects variants that account for at least 25% of the viral population, while less frequent variants will not be detected.

One factor reported to contribute to the likelihood of resistance development is HCV genotype subtype [22]. For example, two nucleotide substitutions are necessary for a genotype 1b virus to develop the resistant variant R155K, whereas only one substitution is necessary to develop this variant in a genotype 1a backbone. As expected, the rate of emergence of resistance in the clinical trials was higher in patients with genotype 1a than 1b (Figure 9).

Another important issue regarding resistance development relates to cross-resistance. *In vitro* data indicate cross-resistance among all first-generation NS3/4A protease inhibitors, including BOC and TVR [23–25]. Therefore, patients resistant to BOC cannot be treated with TVR and vice versa. Fortunately, DAAs from other classes are active against PI-resistant variants.

Significant efforts should be undertaken to reduce the likelihood of emergence of resistance. Compliance will be a major issue for patients and must be stressed and monitored carefully, as sub-optimal drug levels increase the risk of resistance. Timing of administration will need to be emphasized to maximize bioavailability and ensure optimal efficacy, but may be difficult to implement as PI's will need to be taken every 8 h while RBV is given twice-daily.

Pegylated-IFN and RBV are important for the suppression of pre-existing PI-R virus. Strategies to improve pegylated-IFN responsiveness will be
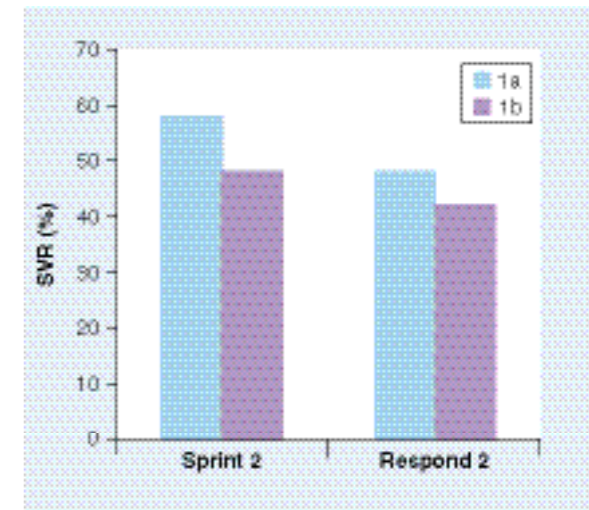

Figure 9. Differences in sustained virological response rates between patients infected with genotype 1a and 1b receiving boceprevir-based triple therapy.
SVR: Sustained virological response.

important to lower the probability of resistance. Such strategies include: weight loss, adequate dosing and possibly novel approaches such as vitamin D or coffee supplementation [26–28].

Lastly, as discussed above, strict application of stopping rules should be enforced to prevent beneficial compensatory mutations in the PI-R viruses.

■ Take home message

The majority of patients who fail HCV therapy using triple combination therapy is attributed to inadequate antiviral response to pegylated-IFNα and RBV with a dominant viral population resistant to the administered protease inhibitor. PI-resistant variants are less likely to emerge in patients with genotype 1b compared to genotype 1a. There is extensive intra- but not inter-class cross-resistance.

Implications of treatment failure on the efficacy of future therapy

It is not known whether the development of resistant variants to BOC and TVR in patients who fail triple combination therapy will significantly impact the efficacy of future DAA-based treatment. However results with DAA-combination therapies look very promising and will likely provide options for patients who fail PI-based therapy.

Conclusion

The new SOC treatment for HCV genotype 1 is triple combination therapy using pegylated-IFNα, RBV and either BOC or TVR. These first-generation

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Executive summary

- The addition of either boceprevir (BOC) or telaprevir to pegylated-IFN and ribavirin significantly improves treatment response rates in patients with genotype 1 hepatitis C virus infection.
- An evaluation of the degree of liver fibrosis, whether by liver biopsy or noninvasive methods, is required to determine the likelihood of response, the duration of therapy and the need for follow-up after sustained virological response (SVR).
- In treatment-naive patients, response-guided therapy allows for shorter treatment duration with no loss in the rate of SVR.
- Response-guided therapy should not be used in patients with cirrhosis (both agents) or those with a <1-log decline during the lead-in phase (BOC).
- In treatment-experienced patients, the prior response to pegylated-IFN and ribavirin is the strongest predictor of response to triple therapy with either agent.
- A lead-in phase may be useful with either agent to help determine the likelihood of SVR in patients with prior null response to pegylated-IFN and ribavirin.
- Prior relapsers can be treated with a response-guided approach to allow for shortening of therapy.
- Both protease inhibitors must be combined with pegylated-IFN (either 2a or 2b) and ribavirin, and must not be given at reduced dosage.
- Established stopping rules for both agents must be followed strictly as viral levels above these thresholds indicate the presence of protease inhibitor-resistant virus and treatment will not be successful.
- The IL-28B genotype may be used to predict the likelihood of response to triple therapy in naive patients, with CC patients having a very high likelihood of being able to shorten treatment with a high rate of SVR. In treatment-experienced populations, the prior treatment response is more predictive of treatment outcome than the IL-28B genotype.
- Telaprevir is associated with rash, anemia and gastrointestinal side effects and BOC is associated with anemia and dysgeusia.
- Both agents have significant drug–drug interactions and all concomitant medications should be reviewed before starting therapy.

DAAs are a major advance and will significantly improve rates of SVR across the spectrum of patients with HCV. Unfortunately, with the new agents come new challenges. The treatment regimens are more complicated and require closer monitoring due to increased side effects and the need for strict compliance. Treatments are less effective in those with poor IFN-responsiveness, particularly previous nonresponders with advanced fibrosis. Whether such patients should consider therapy or wait for the next generation of promising DAAs will have to be an individual decision for patients and physicians. As clinical experience increases, management of the complex regimens and concerning side effects will become more manageable. Until that time, vigilance will be required.

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