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Review

Impact of HCV protease-inhibitor-based triple therapy for chronic HCV genotype 1 infection

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Boceprevir and telaprevir are the first HCV protease inhibitors to be approved for the treatment of chronic hepatitis C genotype 1 infection. These drugs must be used in combination with pegylated interferon plus ribavirin (P/R) to maximize efficacy and prevent the emergence of resistance-associated variants (RAVs). In randomized, placebo-controlled international studies in treatment-naive and previously treated HCV patients, treatment with either boceprevir- or telaprevir-based triple therapy regimens significantly increased sustained virological response rates compared with placebo plus P/R.

Protease inhibitors have the potential, not only to significantly increase cure rates among patients with genotype 1 infection, but also to reduce the duration of treatment for patients who have an extended rapid virological response. Boceprevir is associated with an increased incidence of anaemia and dysgeusia and telaprevir is associated with an increased incidence of rash and anaemia. The emergence of RAVs was associated with an increased risk of virological failure in clinical studies. Although these new drugs bring significant promise, it remains unclear if all genotype 1 patients will need triple therapy. Here, we review some of the complexities uncovered and controversies highlighted by the introduction of HCV protease inhibitors.

Introduction

For the last decade the combination of pegylated interferon (PEG-IFN) plus ribavirin (RBV; P/R) has been the standard of care for chronic hepatitis C [1]. This combination has historically produced an overall cure rate of approximately 50% in previously untreated patients and is less effective in individuals with advanced fibrosis, African heritage, HIV–HCV-coinfection and those patients who have not responded to previous IFN-based therapy [1]. In addition, this combination is not well-tolerated or particularly effective in patients with compensated cirrhosis or portal hypertension [2], or in those patients with decompensated liver disease and in liver transplant recipients [1].

There has, therefore, been an urgent need to develop more effective therapy for chronic hepatitis C. The recent approval of the first direct-acting antiviral agents (DAAs) has ushered in a new era of therapy for chronic hepatitis C. Boceprevir and telaprevir are linear inhibitors of the HCV NS3/4A protease, an enzyme that plays a pivotal role in post-translational processing of the viral polyprotein. In patients with chronic hepatitis C, protease inhibitors produce rapid and profound reductions in serum HCV-RNA levels when administered as monotherapy, but such responses are short-lived because of a low barrier to resistance [3,4]. Thus, boceprevir and telaprevir are not expected to replace P/R, but rather must be used in a triple combination regimen with these two agents in order to maximize efficacy and prevent the emergence of resistance-associated variants (RAVs) and virological failure [5].

In particular, RBV remains an essential component of combination regimens for chronic hepatitis C. An early phase clinical trial that compared telaprevir plus PEG-IFN-α2a (40 KD) with telaprevir plus PEG-IFN-α2a and RBV demonstrated convincingly that relapse rates were considerably higher in patients receiving the dual therapy regimen [6]. The development of IFN-free regimens is an important objective that may well be attained in the near future [7–9]. Ongoing trials will determine whether RBV prevents relapse and/or increases sustained virological response (SVR) rates when used as a component in all-oral IFN-free regimens.

The purpose of this review is to evaluate the efficacy and safety of protease-inhibitor-based triple therapy, as demonstrated in large Phase III clinical trials. Available data show convincingly that protease-inhibitor-based regimens have the potential to significantly increase overall cure rates in genotype 1 patients, primarily by decreasing the rate of relapse, and to shorten the required duration of therapy for many of these individuals. Realization of these benefits will, however, require clinicians and patients to cope with a number of challenges. For example, protease inhibitors will likely increase the cost of treatment for patients with chronic hepatitis C. This will increase the financial burden on patients in countries such as the USA, where many individuals with chronic hepatitis C do not have health insurance [10], and on governments in countries such as Austria [11] and Taiwan [12], where there are comprehensive and universal healthcare programmes.

Efficacy

The efficacy and safety of boceprevir- and telaprevir-based triple therapy has been evaluated in international, randomized, Phase III studies in HCV genotype 1 patients including treatment-naive individuals [13–15] and individuals with a previous unsuccessful outcome after treatment with P/R (Figure 1). All studies recruited adults with chronic hepatitis C and compensated liver disease, and excluded individuals with HIV–HCV-coinfection and major comorbidities. The key features of these trials are shown in Table 1 and the baseline characteristics are presented in Table 2.

Treatment-naive HCV genotype 1 patients

Boceprevir

In the SPRINT-2 trial, boceprevir or matching placebo was not introduced until the end of a 4-week lead-in phase during which all patients received PEG-IFN-α2b (12 KD) plus RBV (Figure 1A). This 4-week lead-in was adopted in the boceprevir pivotal trials in an effort to ensure that both PEG-IFN-α and RBV had reached or approached steady-state pharmacokinetics and to allow an initial period of viral suppression prior to the addition of the protease inhibitor. There are also several other potential benefits of the lead-in strategy: it allows assessment of IFN sensitivity; it was hypothesised that it may reduce the risk of viral resistance to the protease inhibitors; it provides an opportunity to assess patient tolerance of IFN-based therapy; and it theoretically identifies patients with a rapid virological response (RVR) [16], which may then eliminate the need for a protease inhibitor, an aspect of considerable importance for areas of the world that are economically challenged with bearing the cost of a protease inhibitor.

In the SPRINT-2 trial, overall SVR rates were consistently and significantly higher in patients treated with boceprevir than placebo (63–68% versus 38%; $P<0.001$) and in both the non-Black and Black cohorts (Figure 2A) [13].

In non-Black patients, SVR rates were consistently high among patients who were HCV-RNA-negative at the end of the 4-week P/R lead-in period (range 89–96%), among those who were HCV-RNA-negative at week 8 (86–91%) and among those who were HCV-RNA-negative between weeks 8 and 24 (93–97%) with no statistically significant differences across the three treatment groups in any of these strata; however, the proportion of patients in the P/R control group who were HCV-RNA-negative at treatment week 8 (18%) and between weeks 8 and 24 (13%) was considerably lower than in either of the boceprevir treatment groups (59–60% were HCV-RNA-negative at week 8 and 46–47% had an extended rapid virological response [eRVR]) [13].

SVR rates were lower among individuals who were HCV-RNA-positive at the end of the 4-week P/R lead-in period, but were consistently and significantly higher in boceprevir recipients compared with the P/R control group (68–69% versus 36%; $P<0.001$) [13].

Similar trends were apparent in Black patients although few patients overall were HCV-RNA-negative at week 4 (3/159) or week 8 (44/159) or between weeks 8 and 24 (37/159) [13].

The trial enrolled a small proportion of patients with Metavir stage 3 or 4 fibrosis. Among those in the non-Black cohort, SVR rates were numerically higher among boceprevir recipients (50% versus 39% in the P/R control group). A similar trend was apparent in the Black cohort, although the patient numbers were even smaller [13].

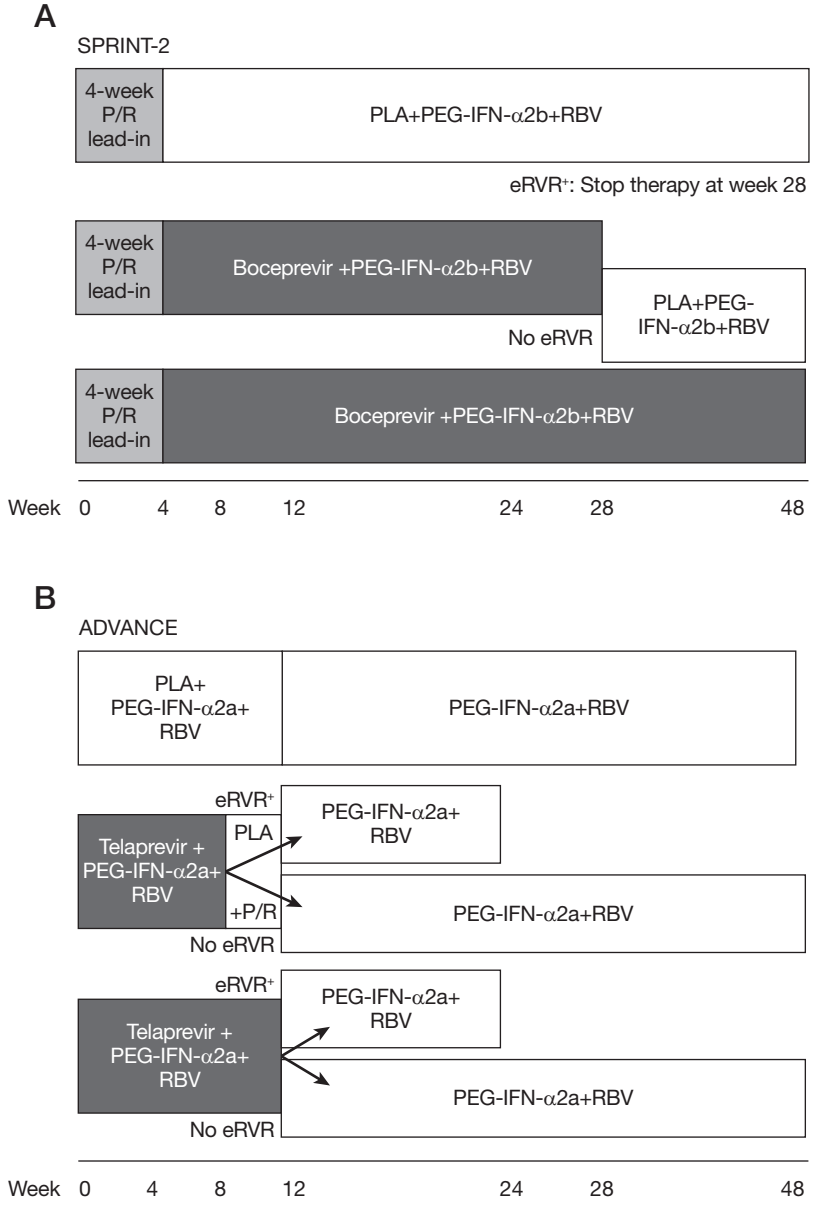
The two boceprevir treatment strategies, response-guided therapy (RGT; based on HCV-RNA levels between weeks 8 and 24, or a full 48-week course of triple therapy) produced similar SVR rates in the non-Black cohort (67% and 68%, respectively). In contrast, SVR rates were numerically higher in Black patients randomized to the full 48-week course of treatment (65%) than to the RGT strategy (50%). This suggests that further study is required to determine whether RGT-based triple therapy with boceprevir is suitable for treatment-naive Black patients, and if so, what criteria can be used to identify suitable candidates [13].

Telaprevir

In the ADVANCE trial (Figure 1B), overall SVR rates were significantly higher in patients enrolled in the two telaprevir treatment groups (75% in the 12-week group and 69% in the 8-week group, as against 44% in the P/R control group; $P<0.001$; Figure 2B) [14].

SVR rates were higher in patients who received 12 weeks (75%) compared with 8 weeks (69%) of telaprevir. Furthermore, across subgroups, SVR rates were higher among patients who received 12 weeks of telaprevir compared with 8 weeks, including those with an extended RVR (89% versus 83%), those infected with HCV genotype 1a (71% versus 66%) or 1b (79% versus 74%), in Black patients (62% versus 58%), in

Figure 1. Study design of randomized, international, Phase III trials of protease-inhibitor-based triple therapy in patients with HCV genotype 1 chronic hepatitis C



Taken from [13] and [18] with permission of the copyright owner Massachusetts Medical Society. White represents pegylated interferon (PEG-IFN) plus ribavirin (RBV; P/R). Dark grey represents triple therapy with P/R plus boceprevir or telaprevir. Light grey represents 4-week lead-in. Boceprevir was given at a dosage of 800 mg three times daily and telaprevir was given at a dosage of 750 mg three times daily. PEG-IFN-α2b (12 KD) was given at a dosage of 1.5 μg/kg once weekly plus RBV 600–1,400 mg/day. PEG-IFN-α2a (40 KD) was given at a dosage of 180 μg once weekly plus RBV 1,000–1,200 mg/day. **(A)** SPRINT-2 (boceprevir) in treatment-naive patients. **(B)** ADVANCE (telaprevir) in treatment-naive patients. **(C)** ILLUMINATE (telaprevir) in treatment-naive patients. **(D)** RESPOND-2 (boceprevir) in previously treated patients. **(E)** REALIZE (telaprevir) in previously treated patients. eRVR, extended rapid virological response. eRVR was defined as undetectable HCV RNA (<9.3 IU/ml, limit of detection of Cobas TaqMan assay [Roche, Basel, Switzerland]); PLA, placebo; +, positive.

Figure 1. Continued

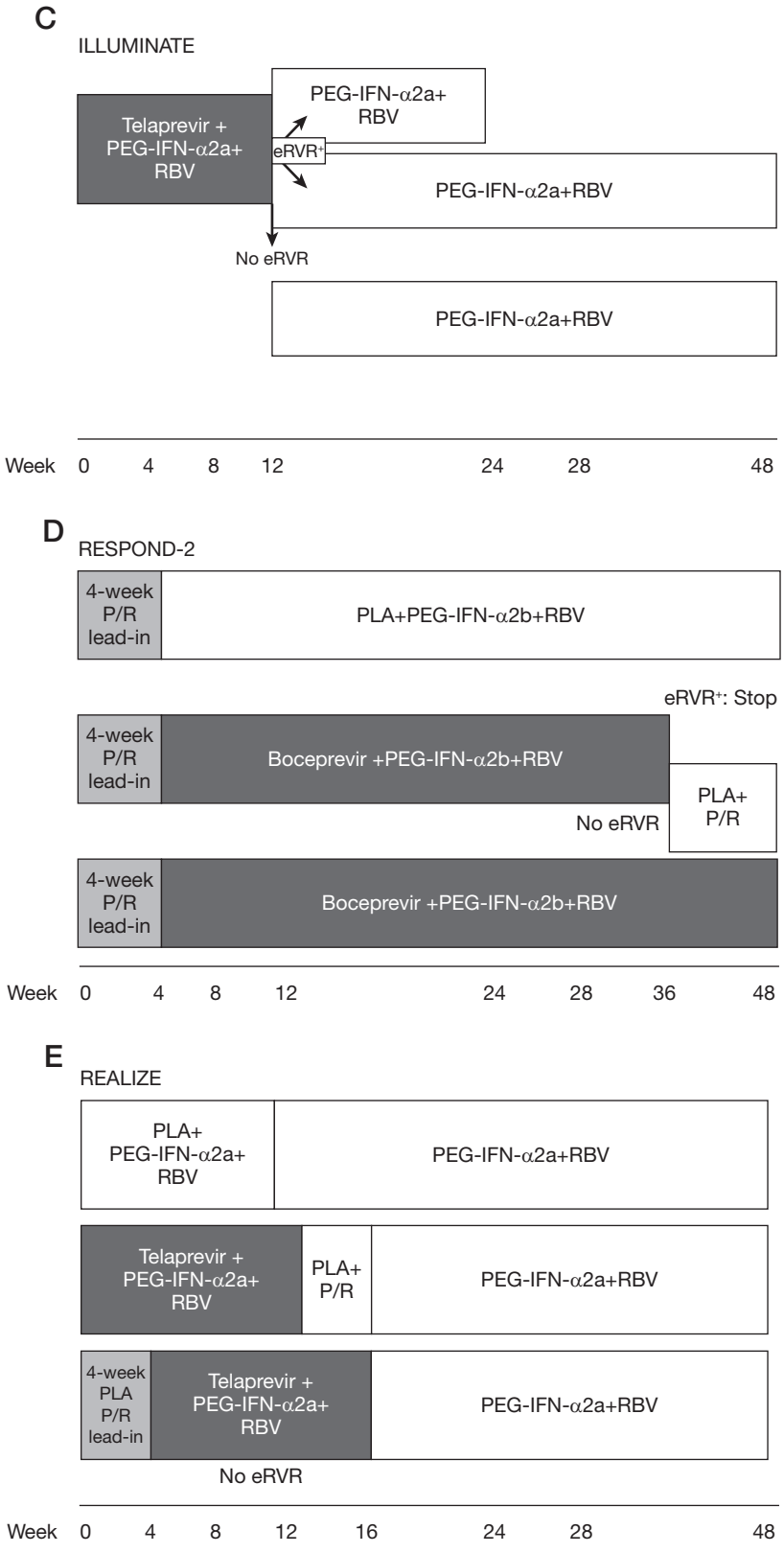


Table 1. Comparative features of randomized, international, placebo-controlled, Phase III studies of boceprevir and telaprevir

	Treatment-naive patients			Previously treated patients	
Feature	SPRINT-2, boceprevir	ADVANCE, telaprevir	ILLUMINATE, telaprevir	RESPOND-2, boceprevir	REALIZE, telaprevir
Reference	Poordad *et al.* [13]	Jacobson *et al.* [14]	Sherman *et al.* [15]	Bacon *et al.* [18]	Zeuzem *et al.* [20]
Evaluated 4-week P/R lead in	Yes	No	No	Yes	Yes
PEG-IFN-α product (weekly dose)	2b (1.5 μg/kg)	2a (180 μg)	2a (180 μg)	2b (1.5 μg/kg)	2a (180 μg)
RBV dose, mg/day	600–1,400	1,000/1,200	1,000/1,200	600–1,400	1,000/1,200
Duration of triple therapy	24 or 44 weeks after lead in	8 or 12 weeks followed by P/R for 12–40 weeks	12 weeks followed by P/R for 12–36 weeks	32 or 44 weeks	12 weeks with or without lead-in
Total duration of therapy in protease inhibitor treatment groups, weeks	28 or 48	24 or 48	24 or 48	36 or 48	48
Duration of treatment in P/R control, weeks	48	48	NA	48	48
Duration of untreated follow-up, weeks	24	24	24	24	24
Extended RVR definition	Undetectable HCV RNA from week 8 to 24	Undetectable HCV RNA at weeks 4 and 12	Undetectable HCV RNA at weeks 4 and 12	Undetectable HCV RNA from week 8 to 24	NA
Sustained virological response definition	Undetectable HCV RNA in serum (<10 IU/ml) at end of untreated follow-up	Undetectable HCV RNA in serum (<10 IU/ml) at end of untreated follow-up	Undetectable HCV RNA in serum (<10 IU/ml) at end of untreated follow-up	Undetectable HCV RNA in serum (<10 IU/ml) at end of untreated follow-up	Undetectable HCV RNA in serum (<10 IU/ml) at end of untreated follow-up

NA, not applicable; P/R, pegylated interferon (PEG-IFN) plus ribavirin (RBV); RVR, rapid virological response.

patients with a high baseline viral load (74% versus 66%) and in those with bridging fibrosis or cirrhosis (62% versus 53%) [14].

A second Phase III, randomized, non-inferiority trial (ILLUMINATE, *N*=540) in treatment-naive patients compared a total treatment duration of 24 and 48 weeks in patients with an eRVR (undetectable HCV RNA at weeks 4 and 12) who had completed 20 weeks of treatment (Figure 1C). All patients enrolled in the trial received telaprevir plus P/R for 12 weeks, after which P/R was continued through to completion of the assigned treatment duration. Final SVR rates in patients randomized to 24 (*n*=162) or 48 (*n*=160) weeks were 92% and 88%, respectively, and the difference of 4.5% (95% CI 2.1–11.1%) fell within the pre-specified non-inferiority margin of -10.5% (Figure 2C) [15]. The overall SVR rate in the trial was 72% (including 118 patients who did not achieve an eRVR and were assigned to 48 weeks of treatment, and 100 patients who did not complete therapy) [15].

Although telaprevir was evaluated exclusively in combination with PEG-IFN-α2a (40 KD) in Phase III studies, it is approved for use with both commercially available PEG-IFN. In an earlier Phase II trial, 161 treatment-naive genotype 1 patients were randomized to 12 weeks of treatment with telaprevir at a dosage of 750 mg every 8 h or 1,125 mg every 12 h, and to treatment with either PEG-IFN-α2a (40 KD) plus RBV or PEG-IFN-α2b (12 KD) plus RBV (that is, there were four treatment groups) [17]. Patients with undetectable HCV RNA between weeks 4 and 20 stopped all treatment at week 24; all others were assigned to complete a total duration of 48 weeks of treatment. Overall, 74% of patients randomized to the PEG-IFN-α2a (40 KD) treatment groups were eligible for the abbreviated treatment (compared to 62% of those randomized to PEG-IFN-α2b [12 KD]). Final SVR rates ranged from 81% to 85% across the four treatment groups with no statistically significant between-group differences [17].

Treatment-experienced patients

Studies of telaprevir and boceprevir in previously treated individuals were designed to evaluate the drugs in patients with well-characterized virological responses to previous P/R treatment (Table 2).

Boceprevir

In the RESPOND-2 trial, SVR rates were significantly higher in patients randomized to boceprevir than to placebo overall (59–66% versus 21% in the P/R control group), in previous relapsers (61–67% versus 22%),

Table 2. Comparative features of randomized international placebo-controlled Phase III studies of boceprevir and telaprevir

	Treatment-naive patients			Previously treated patients	
Characteristic	SPRINT-2, boceprevir	ADVANCE, telaprevir,	ILLUMINATE, telaprevir	RESPOND-2, boceprevir	REALIZE, telaprevir
Reference	Poordad *et al.* [13]	Jacobson *et al.* [14]	Sherman *et al.* [15]	Bacon *et al.* [18]	Zeuzem *et al.* [20]
Number of patients randomized	1,097 (938 non-Black, 159 Black)	1,088	540 treated (322 with an eRVR randomized at week 12 to complete 24 or 48 weeks treatment)	403	663
Mean age, years	49	49 (median)	51 (median)	53	51
Male gender, %	60	58	60	67	69
Race					
White, %	82	88	79	85	93
Black, %	15	9	14	12	5
Other, %	3	3	7	2	2
Patients with bridging fibrosis/cirrhosis F3/F4, %	9	21	–	21	48
Patients with F3, %	–	15	16	8	22
Patients with F4, %	–	6	11	13	26
Patients with HCV RNA >800,000 IU/ml, %	85	77	82	88	88
HCV subtype					
1a, %	64	58	72	59	45
1b, %	33	41	28	40	45
Unknown, %	3	1	<1	1	10
Previous HCV RNA response to P/R					
Undetectable with relapse during follow-up	–	–	–	64	53
Detectable with ≥2-log drop	–	–	–	36	19
Detectable with <2-log drop	–	–	–	0	28

eRVR, extended rapid virological response; P/R, pegylated interferon plus ribavirin.

and in patients with a previous non-response (40–52% versus 7%; Figure 2D) [18]. SVR rates were consistently higher in patients randomized to a full 48-week course of boceprevir-based triple therapy than to the variable 36- or 48-week RGT regimen; however, the difference between the two groups was not statistically significant in any stratum [18].

The difference between the two boceprevir groups was apparently driven by an imbalance in the virological response rate among the subgroup of cirrhotic patients during the first 8 weeks of the trial, at which point 18% of such patients in the RGT group had undetectable HCV RNA compared with 73% of such individuals in the 48-week group. Among patients without cirrhosis the virological response rates at week 8 were almost identical (49–50%). The reason for the imbalance in patients with cirrhosis is unclear.

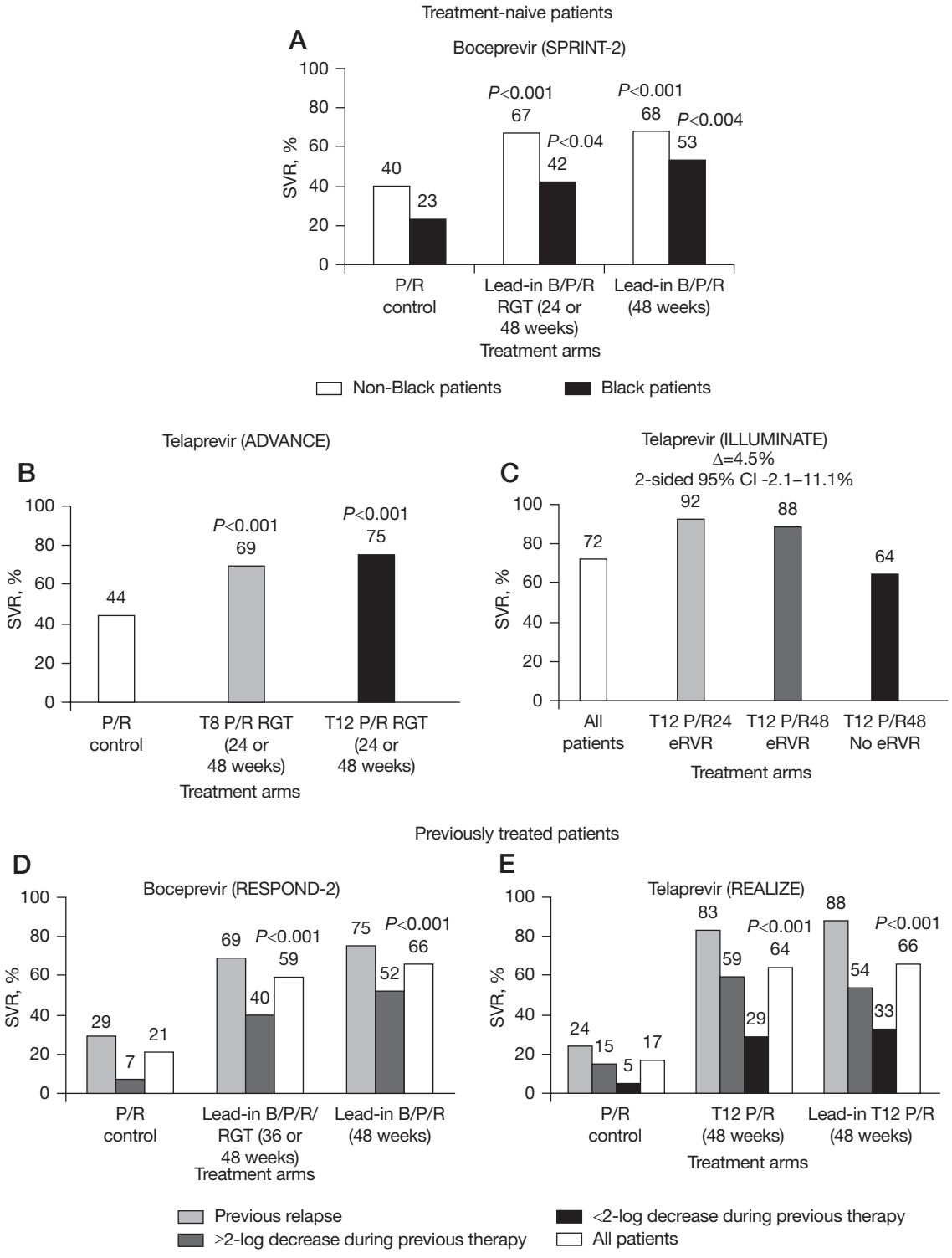
The magnitude of the change in HCV-RNA level at the end of the 4-week lead-in phase was predictive of SVR. SVR rates were higher in patients who had at least a 1-$\log_{10}$ decrease in HCV RNA by week 4 (73–79% in the two boceprevir treatment groups versus 25% with placebo) and were lower in patients who had less than a 1-$\log_{10}$ decrease at this time point (33–34% versus 0%) [18].

An additional randomized trial compared the combination of boceprevir, PEG-IFN-α2a (40 KD) and RBV for 48 weeks with a standard 48-week P/R regimen in 201 patients who had not responded to previous treatment with PEG-IFN-α2b (12 KD) plus RBV [19]. Boceprevir was started after a 4-week P/R lead-in and was continued to complete a total of 48 weeks of treatment. The definitions of relapse and non-response were identical to those used in RESPOND-2 (Table 1). Final SVR rates in the boceprevir and P/R control groups were 64% and 21% overall (P<0.0001), 70% and 28% in previous relapsers and 47% and 5% in previous non-responders. These results are similar to those obtained in RESPOND-2, and demonstrate that the efficacy of boceprevir is consistent regardless of which type of PEG-IFN it is combined with.

Telaprevir

Among patients enrolled in the REALIZE trial, approximately half (53%) of the patients were previous

Figure 2. SVR rates in randomized international placebo-controlled Phase III trials of protease-inhibitor-based triple therapy regimens in patients with HCV genotype 1 chronic hepatitis C



The sustained virological response (SVR) rates in **(A)** SPRINT-2, **(B)** ADVANCE, **(C)** ILLUMINATE, **(D)** RESPOND-2 and **(E)** REALIZE are shown. Lead-in refers to a 4-week period during which pegylated interferon plus ribavirin (P/R) was administered before initiation of the protease inhibitor. *P*-values are for comparisons with the P/R control group. B, boceprevir; eRVR, extended rapid virological response; P/R24, treatment with P/R for total of 24 weeks; P/R48, treatment with P/R for total of 48 weeks; RGT, response-guided therapy; T8, treatment with telaprevir for 8 weeks; T12, treatment with telaprevir for 12 weeks.

relapsers, 19% had a previous partial response and 28% were previous non-responders to P/R (Table 2) [20]. SVR rates were significantly higher in both telaprevir regimens compared with the P/R control group overall (64–66% versus 17%), and in previous relapsers (83–88% versus 24%), partial responders (54–59% versus 15%), and non-responders (29–33% versus 5%; Figure 2E) [20]. Among patients with bridging fibrosis or cirrhosis and a prior non-response, the SVR rate was 28%. Thus, while protease inhibitors overall have advanced HCV therapy, there still remains a major challenge with the much-in-need-of-therapy population of patients with cirrhosis and a demonstrated lack of IFN sensitivity.

The 4-week lead-in P/R phase did not produce significantly higher SVR rates compared with the group that started telaprevir therapy concurrently with P/R. SVR rates in the group with the week 1 start were numerically lower among patients with a previous relapse (83% versus 88% in the lead-in group) and non-response (29% versus 33%), but were identical in those with a previous partial response (41%) [20].

Maximizing efficacy in everyday clinical practice

The introduction of protease inhibitors into clinical practice has the potential to significantly increase cure rates for HCV genotype 1 patients, and also to shorten the duration of therapy for many treatment-naive patients. Importantly, this includes patients who have not responded to previous treatment with P/R, a large group of patients in whom retreatment with P/R is not particularly effective.

Whether increased cure rates with protease inhibitors are associated with an increase in the number of patients seeking treatment will be influenced by a number of factors, including the efficacy and safety profile of other DAAs currently in clinical development, including innovative IFN-free regimens. However, the increase in efficacy seen with regimens containing telaprevir or boceprevir will likely increase to some degree the number of patients seeking treatment and this may place a strain on clinic resources. In turn, this may limit resources available to treat those infected with HCV genotypes 2 to 6, for whom P/R remains the standard of care. Encouraging general practitioners to participate in the treatment of patients infected with 'easy-to-treat' genotypes may be one way to reduce the increased burden on specialists. This approach has been shown to be very effective where care was delivered by general practitioners who received guidance from specialists [21].

The treatment algorithm for genotype 1 patients is now much more complex than it was during the P/R era. Not only do the dosages, treatment schedules and duration of treatment differ markedly for the two available protease inhibitors, but also the need for a lead-in phase, the definition of eRVR and the stopping rules for futility also differ. For example, boceprevir treatment was stopped in clinical trials if HCV RNA was detectable at week 24 of triple combination therapy [13]. In contrast, treatment with telaprevir was stopped if the HCV-RNA level was greater than 1,000 IU/ml at week 4 (dual P/R therapy was continued in these individuals), and all treatment (telaprevir plus P/R) was stopped if the drop in HCV RNA was less than 2-$\log_{10}$ at week 12 or if HCV RNA was detectable at any time between weeks 24 and 40 [14].

Measurement of HCV RNA at week 4 of treatment and at week 8 (if boceprevir is chosen) or week 12 (if telaprevir is chosen) is now mandatory. Adequate laboratory infrastructure and rapid turnaround time will be required to ensure the new treatment algorithms can be implemented effectively. Patient education and adherence are more important than ever.

The lead-in phase is particularly important because it is included in the label for boceprevir but not for telaprevir. We speculate that some clinicians will be tempted to use a lead-in phase with telaprevir as well. Such a strategy would allow clinicians to identify those individuals (that is, with an RVR) who are most likely to achieve a cure with P/R alone, and would drive down the viral load and theoretically reduce the likelihood of resistance in those who do start a protease inhibitor at week 4. However, it should be noted that evidence of a reduction in resistance through use of a lead-in phase is currently lacking.

The improvement in SVR rates with triple therapy is largely attributable to a substantial reduction in relapse rates (for example, to approximately 9% from approximately 20–30% with P/R) but also due to enhanced initial virological control and improved end-of-treatment responses; however, achievement of an RVR remains a very important milestone during treatment, regardless of whether a patient is receiving triple therapy or P/R. An important consideration is whether patients with an RVR after a 4-week lead-in phase even require treatment with a protease inhibitor. Analyses of large data sets of patients treated with P/R have shown that, although there is wide variation in the rate of RVR across populations (Table 3), up to 90% of patients with an RVR achieve an SVR, including those who are treated for just 24 weeks [22–24]. Indeed RVR is the best predictor of SVR after P/R therapy [25]. Thus, it can be argued that the addition of a protease inhibitor is unlikely to increase the probability of a cure, but exposes the patient to a higher probability of adverse events, albeit with potentially a reduced overall treatment duration. Further shortening of the duration of triple therapy with telaprevir may be possible, but only if supported by data from large, well-designed studies. Preliminary data from the PROVE-2 trial suggested

Table 3. Frequency of RVR and SVR in patients with an RVR in large, randomized studies of pegylated interferon-α plus ribavirin in treatment-naive patients with HCV genotype 1 infection

Treatment duration	Region or country	Study	*N*	RVR, *n* (%)	SVR in patients with an RVR, *n* (%)
Total treatment duration of 48 weeks					
	International	Ferenci *et al.* [22][a]	569	90 (16)	79 (88)
	International	Jensen *et al.* [23][b]	271	55 (20)	(91)
	Europe	Buti *et al.* [44]	1,428	224 (16)	Not reported
	France	Bronowicki *et al.* [45]	173	44 (25)	33 (75)
	Germany	Berg *et al.* [46]	230	51 (22)	43 (84)
	Spain	Sánchez-Tapias *et al.* [47]	371	80 (22)	23 (66)
	USA	McHutchison *et al.* [48]	2,054	239 (12)	206 (84)
Total treatment duration of 24 weeks					
	International	Jensen *et al.* [23][b]	216	51 (24)	(89)
	Europe	Zeuzem *et al.* [24][c]	235	110 (47)	98 (89)
	Austria	Ferenci *et al.* [49]	450	120 (27)	89 (79)
	Italy	Mangia *et al.* [50]	459	123 (27)	95 (77)
	Taiwan	Yu *et al.* [51]	200	87 (44)	40 (89)
	Taiwan	Liu *et al.* [52]	308	201 (65)	79 (76)
Total treatment duration of 24 to 30 weeks					
	Germany	Sarrazin *et al.* [53]	398	48 (12)	42 (88)

In these studies HCV RNA assays with different sensitivities were used, thus rapid virological response (RVR) rates are not directly comparable. [a]Subanalysis of data from the trial by Fried *et al.* [54]. [b]Subanalysis of data from the trial by Hadziyannis *et al.* [55]. [c]Patients with low viral load (<600,000 IU/ml). SVR, sustained virological response.

that there was no significant difference in SVR rates between patients who were treated for 12 weeks with telaprevir-based triple therapy (60%) and those who received triple therapy for 12 weeks and then P/R for 12 weeks (69%) [6]. Further study is therefore warranted. In geographic regions where high RVR rates are common and where the cost of protease inhibitors is prohibitive, it might be reasonable to treat patients with an RVR with P/R and reserve triple therapy for patients who do not achieve an RVR after a 4-week lead-in.

It is clear, however, that triple therapy has a substantial advantage over P/R in patients without an RVR and in individuals who have not responded to a previous course of P/R. As shown in clinical trials, triple therapy is particularly effective in these subsets of patients [18,20]. Since most trials restricted the inclusion of patients with cirrhosis, there is limited experience with triple therapy in this patient group. Moreover, telaprevir-based triple therapy produced an SVR rate of approximately 10% in previous null responders with cirrhosis. Similarly, P/R is less effective in patients with cirrhosis (Metavir F4), especially if portal hypertension is present [2]. However, these individuals have the greatest need for effective therapy and for many of these individuals treatment is a matter of 'now or never'. Controversies that remain to be resolved include whether abbreviated treatment could be used in previous relapsers who achieve an extended RVR, and the optimal treatment duration for patients with cirrhosis and for Black patients.

Impact of *IL28B* polymorphisms on response to protease inhibitors

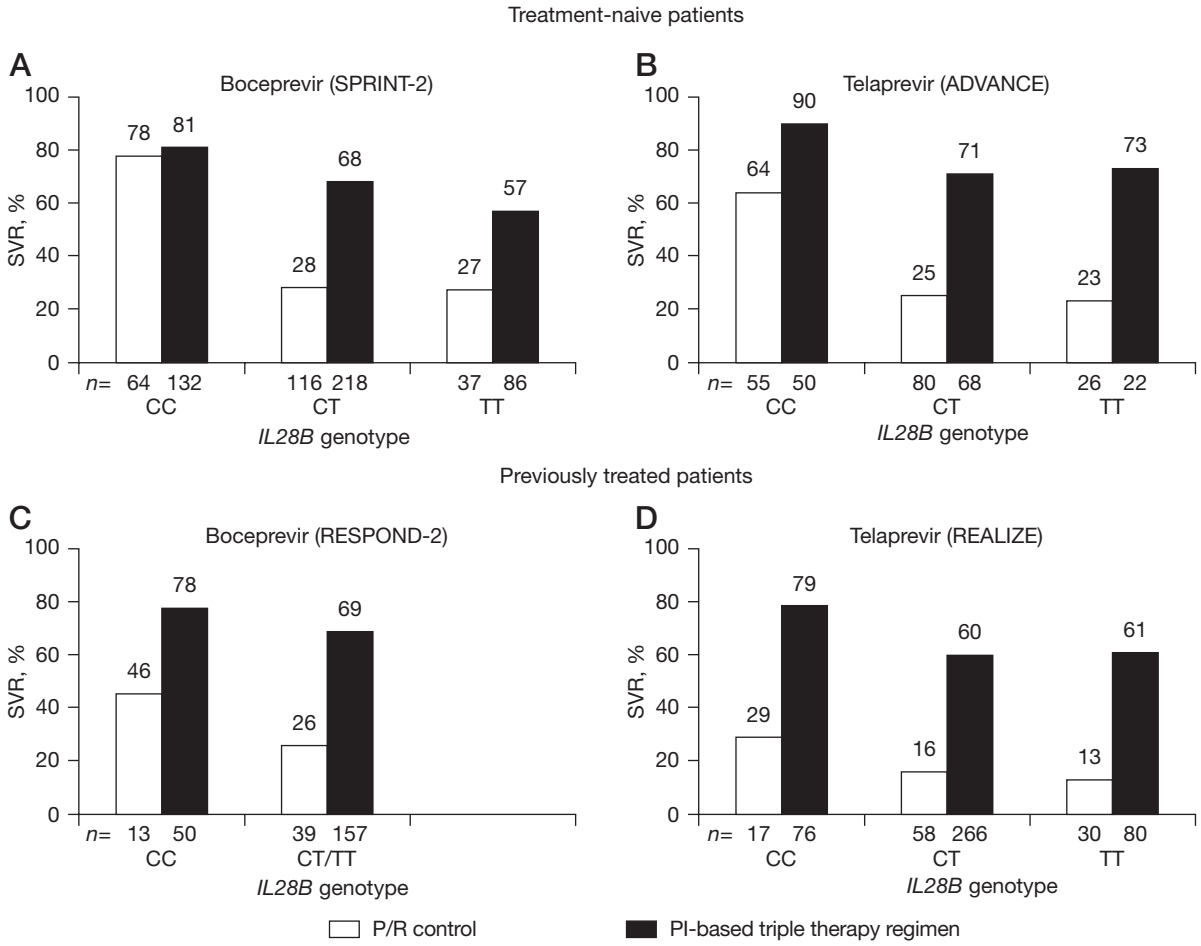
A genetic polymorphism on chromosome 19, rs12979860, in the promoter region for the *IL28B* gene is the strongest pretreatment predictor of outcome following treatment with P/R [26]. Patients with the CC genotype have the highest probability of achieving an SVR, and individuals who carry a T allele (C/T or T/T) have significantly lower SVR rates. Differences in gene frequencies in ethnic groups are thought to largely explain the well-established racial differences in SVR rates between Black and non-Black patients [26]. The significance of *IL28B* polymorphism was not understood when Phase III trials of protease inhibitors were designed; hence patients were not stratified by *IL28B* genotype at baseline. However, a subset of patients in each trial consented to be genotyped, and the results provide preliminary insight into the impact of host genotype on treatment outcome in patients treated with protease-inhibitor-containing triple therapy regimens (Figure 3) [27,28].

The pattern of responses in the P/R control group in each study is consistent with what one would expect, with consistently higher overall SVR rates in patients with the CC genotype compared with individuals who have at least one T allele. SVR rates were similar

in treatment-naive patients with a CC genotype who were treated with boceprevir (81%) or placebo (78%) in SPRINT-2 (Figure 3A) [27]. In contrast, SVR rates were consistently higher in telaprevir recipients than in placebo recipients in the ADVANCE trial (Figure 3B) [28]. Within each *IL28B* genotype group, SVR rates were consistently higher in previously treated patients receiving the protease-inhibitor-based triple therapy regimen compared with the P/R control group (Figure 3C and 3D) [27,28]. These results suggest that protease inhibitors overcome the negative influence of an unfavourable host genotype, to some extent. Patients with the favourable *IL28B* genotype are more likely to have an RVR and thus qualify for the shorter duration of therapy [29]. Future studies should stratify patients by host *IL28B* genotype in order to better study this phenomenon [11].

It remains to be determined how a patient's *IL28B* genotype might influence the use of protease inhibitors. At the moment, host genotype has no direct bearing on the use of protease inhibitors, and further research is required to confirm whether host genotype has a significant impact on efficacy. Preliminary data from a trial of TMC435, an investigational protease inhibitor combined with P/R, suggest that a protease inhibitor reduces the impact of *IL28B* genotype on virological response rates in a dose-dependent manner [30]. In SPRINT-2, patients with undetectable HCV RNA at the end of the 4-week lead-in phase had high SVR rates (89–96%) regardless of the regimen they subsequently received [14]. In addition, the limited *IL28B* data from this trial show that patients with CC genotypes also had similar high SVR rates (78–81%) regardless of whether they received the P/R control regimen or a

Figure 3. SVR rates according to host *IL28B* genotype and treatment regimen in HCV genotype 1 patients



Data from [27,28]. **(A)** Both boceprevir treatment groups from SPRINT-2 were pooled [27]. **(B)** Only patients randomized to 12 weeks of telaprevir-based triple therapy were included from the ADVANCE trial [28]. **(C)** Both boceprevir treatment groups from RESPOND-2 were pooled. **(D)** Both telaprevir treatment groups from REALIZE were pooled [28]. Not all patients in each trial were genotyped. PI, protease inhibitor; P/R, pegylated interferon plus ribavirin; SVR, sustained virological response.

boceprevir-based regimen. Thus, it may be preferable for patients with a homozygous CC genotype who have undetectable HCV RNA at the end of the lead-in phase to continue treatment for a total of 24 weeks with P/R and not initiate treatment with a protease inhibitor. Their chance of achieving a cure would be unchanged; they would not be exposed to the potential adverse effects of the protease inhibitor, and would not acquire resistance mutations that could impair their ability to respond to future treatment with DAAs in the event that treatment with P/R is unsuccessful.

Adverse effects

All patients who receive triple therapy are subject to the adverse event burden imposed by P/R, in addition to that of the protease inhibitor; thus, when compared with the P/R control group, protease-inhibitor-based triple therapy increases the burden of adverse events. The introduction of protease inhibitors will thus require additional clinical resources to educate patients about adverse events before treatment begins, to monitor patients during treatment and to treat patients who present with adverse events.

Treatment with boceprevir in Phase III trials was associated with a significantly higher incidence of anaemia and dysgeusia compared with placebo, both in treatment-naive and previously treated patients [13,18], and with a higher incidence of rash and dry skin in previously treated patients [18].

Across both trials the incidence of anaemia (reported as an adverse event) ranged from 45% to 50% compared with 20% to 30% of placebo recipients [27]. In addition, more boceprevir recipients had a haemoglobin level <10 mg/dl (49% versus 25–29% of placebo recipients) and <8.5 mg/dl (6–10% versus 1–3%) [27]. This occurred despite more widespread use of erythropoietin (43% versus 24% of placebo recipients), a higher rate of blood transfusions (3% versus <1%) and a higher rate of dose modifications of any drug (26% versus 13%) among boceprevir recipients [27]. Use of erythropoietin, blood transfusions and dose modifications was effective in mitigating the effects of boceprevir as indicated by the low rate of treatment discontinuations for anaemia in both groups (1%).

A pooled analysis of safety data from Phase III trials showed that telaprevir was associated with a higher incidence of rash (56% versus 34% with placebo), pruritus (47% versus 28% with placebo), nausea (39% versus 28% with placebo), anaemia (36% versus 17% with placebo), diarrhoea (26% versus 17% with placebo) and anorectal discomfort (11% versus 3%) [28].

The onset of rash was most common during the first 4 weeks of treatment with telaprevir, and 6% of telaprevir recipients discontinued the drug because of rash. Most cases of rash were mild to moderate in severity and did not progress. Severe rash occurred in 4% of telaprevir recipients; cases of drug rash with eosinophilia and symptomatic symptoms (DRESS) and Stevens–Johnson syndrome were reported in <1% of patients [28].

The incidence of haemoglobin level <10 mg/dl (36% versus 17% of placebo recipients) and <8.5 mg/dl (14% versus 5%) was higher among telaprevir recipients; however, anaemia was managed only by RBV dosage reductions – erythropoietin use was not permitted [28]. Among telaprevir recipients, SVR and relapse rates were similar in patients with and without anaemia, and in those with and without RBV dose reductions [31]. Conversely, significantly higher SVR rates were observed for treatment-naive and previously treated patients who developed anaemia (haemoglobin <10 mg/dl) during boceprevir treatment [32].

Management of adverse events is also now more complex. Clinicians who are accustomed to reducing the dose of PEG-IFN and/or RBV to manage adverse events will have to adjust to the all-or-nothing dosage regimens of the protease inhibitors – dosage adjustments of protease inhibitors are not recommended. Discontinuation of PEG-IFN-α and RBV and continuation of protease inhibitor monotherapy is also not recommended. The dose of RBV can be modified during triple therapy without compromising SVR rates [31], but discontinuation of RBV and continuing PEG-IFN and a protease inhibitor is not recommended. Clinicians prescribing boceprevir will have to anticipate the need for erythropoietin (which has its own adverse event profile) and possibly blood transfusions to manage anaemia. On the other hand, those prescribing telaprevir will have to be prepared to manage the rash that often accompanies treatment and that can be severe. The manufacturer recommends use of oral antihistamines and topical corticosteroids to manage the rash, but discourages the use of oral corticosteroids [28]. Formal protocols for the management of rash will be developed as experience with these agents increases. Regardless of which protease inhibitor clinicians choose, they will have to become adept at identifying potentially harmful drug interactions and how to avert them.

Potential for drug–drug interactions

Both boceprevir and telaprevir undergo cytochrome P450-mediated hepatic metabolism and are strong inhibitors of CYP3A4/5, and thus have the potential to precipitate drug–drug interactions, the results of which are often unpredictable. Few drug–drug interactions have been identified in patients and reported in the literature [33,34]; however, the labelling of both drugs lists a number of drugs that are contraindicated and a number that should be used with caution with both boceprevir and telaprevir

Table 4. RAVs that confer resistance to boceprevir and/or telaprevir that were detected in patients who did not achieve an SVR in Phase III clinical trials of boceprevir and telaprevir

RAV	Boceprevir recipients		Telaprevir recipients	
	Genotype 1a, %	Genotype 1b, %	Genotype 1a, %	Genotype 1b, %
V36A	<1–10	<1–10	–	–
V36A/L	–	–	10	17
V36M	>10	<1–10	49	3
T54A	<1–10	>10	–	–
T54C	–	<1–10	–	–
T54G	–	<1–10	–	–
T54S	>10	>10	–	–
T54A/S	–	–	9	22
V55A	<1–10	>10	–	–
V55I	<1–10	–	–	–
V107I	<1–10	<1–10	–	–
R155K	>10	<1–10	–	–
R155K/T	–	–	56	<1
R155T	<1–10	–	–	–
A156S	<1–10	>10	–	–
A156T	<1–10	<1–10	–	–
A156V	–	<1–10	–	–
A156S/T	–	–	8	12
V158I	<1–10	<1–10	–	–
D168N	<1–10	–	–	–
I/V170A	–	>10	–	–
I/V170T	<1–10	<1–10	–	–
I/V170F	<1–10	–	–	–
M175L	–	<1–10	–	–
V36M+R155K	–	–	40	0

Data from [27,28]. Data represents percentage of patients. RAV, resistance-associated variant; SVR, sustained virological response.

[27,28]. The clinical significance of these potential drug interactions will become more evident once the drugs are in widespread use; however, some of these have immediate implications for clinical practice. For example, boceprevir has been shown to decrease ethinyl estradiol levels in women taking a combination oral contraceptive pill [35]. Prevention of pregnancy is essential because of the teratogenic potential of ribavirin; thus, clinicians will have to ensure that patients are informed of the need for effective contraception, including the use of barrier methods, and the potential for failure of hormonal methods during boceprevir therapy. Telaprevir has been shown to decrease levels of the commonly used antidepressant escitalopram; thus, patients who develop depression during treatment may require higher than expected doses of the drug to achieve an effective antidepressant effect [28]. It remains to be determined whether either of the protease inhibitors affects the efficacy of other commonly used antidepressants. Telaprevir inhibits the metabolism of the immunosuppressants cyclosporine and tacrolimus; thus, further study will be needed to devise dose-adjustment schemes before the drug is studied in transplant recipients [33].

Resistance

Viral resistance is a phenomenon that has not previously had a bearing on the treatment of chronic hepatitis C, but it is an important consideration with the use of DAAs. Because of the high replication rate and the lack of a proofreading function in the HCV protease, RAVs can be produced in the absence of antiviral drug pressure and may be present in patients who have never been treated with a DAA [28,36,37]. Indeed, based on mathematical modelling and ultra-deep pyrosequencing it has been suggested that resistance to HCV protease inhibitors may be present in all patients prior to treatment [38,39].

Protease inhibitors have a low barrier to resistance and there is evidence of extensive cross-resistance between boceprevir and telaprevir. RAVs emerge within days of treatment with telaprevir monotherapy and are associated with virological failure [40]. Similarly, when telaprevir is administered with PEG-IFN alone the rate of virological failure is much greater than when administered in combination with P/R [6]. Thus, triple combination therapy is essential to minimize the development of resistance and to prevent viral breakthrough during treatment. Resistance to protease inhibitors emerges more rapidly in HCV genotype 1a because only one

nucleotide substitution is required to produce an RAV at position R155. In contrast, two nucleotide substitutions are required to produce the same RAV in HCV genotype 1b [41]. This was reflected in higher rates of virological failure in genotype 1a patients treated with telaprevir in Phase III trials [14,28]. Substitutions at position 156 of the NS3/4A confer the highest degree of resistance to telaprevir and boceprevir but have reduced fitness compared with wild-type virus [3]. RAVs detected in patients who did not achieve an SVR in clinical trials of boceprevir and telaprevir are presented in Table 4.

A pooled analysis of data from Phase III trials of telaprevir showed that RAVs were detected in the majority of patients (62%) who did not achieve an SVR [28]. In the REALIZE study, most cases of virological failure (73%) were associated with RAVs with reduced sensitivity to telaprevir [20]. However, resistant variants were no longer detectable at the end of the study (median duration of follow-up 41 months) in the majority of patients (58%) in whom resistance variants had previously been detected. This is consistent with an interim analysis of a long-term follow-up study in patients who were enrolled in clinical studies of telaprevir, in which RAVs were no longer detectable in 89% of patients who failed to achieve an SVR after a median of 22 months of follow-up [42].

RAVs were detected in 15–17% of boceprevir recipients in SPRINT-2. These were more common in patients with a <1-$\log_{10}$ decrease in HCV RNA at week 4 (87/189, 45%) than in patients with a ≥1-$\log_{10}$ decrease in HCV RNA at week 4 (23/463, 5%), which suggests that decreased IFN sensitivity is associated with an increased risk of selecting resistance [13]. Moreover, among patients who did not achieve an SVR in SPRINT-2 or RESPOND-2, the pooled incidence of RAVs was higher in patients who had a <1-log decrease in HCV RNA by week 4 compared with those who had a ≥1-log decrease in HCV RNA by week 4 (68% versus 31%) [27]. Overall, 53% of boceprevir recipients who did not achieve an SVR had resistance mutations detected by population-based sequencing [27].

A long-term follow-up study in 183 patients with virological failure during boceprevir therapy showed that the number of RAVs declined over 2 years, and that wild-type HCV re-emerged at different rates depending on the specific RAV and HCV subtype [43].

Potential impact of protease inhibitors on clinical practice

Hepatologists have not previously had to consider the potential for resistance or cross-resistance when treating patients with chronic hepatitis C. Evaluation of the resistance profile before and during treatment will likely become a standard practice in the near future, especially with the development of commercial assays for clinical use. The use of such assays will likely become routine once drugs from other DAA classes are approved and as all-oral DAA regimens continue to evolve. Prudent use of protease inhibitors will be necessary so as not to limit the future treatment options for patients who do not achieve a cure after triple therapy. Prudent use includes not only careful patient selection on the basis of pretreatment characteristics, but also monitoring and encouraging adherence, because adherence is an important determinant of SVR and poor adherence with a DAA-based regimen may promote resistance.

The introduction of boceprevir and telaprevir marks the beginning of the DAA era. Over the next few years further major developments are likely. Developments in the short term, such as twice-daily dosing of telaprevir, are likely to have a modest impact. Subsequent developments, such as the use of protease inhibitors for individuals with HIV–HCV-coinfection, decompensated liver disease and liver transplants will have a greater impact. The approval of other novel classes of DAAs may usher in the IFN-free treatment era.

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