Protease inhibitors for the treatment of chronic hepatitis C genotype-1 infection: the new standard of care

Brian L Pearlman

For the past decade, the standard treatment for chronic hepatitis C infection has been pegylated-interferon plus ribavirin. With US Food and Drug Administration approval of boceprevir and telaprevir—two protease inhibitors—the standard-of-care treatment for genotype-1 infection, the main genotype worldwide, is now peginterferon plus ribavirin and a protease inhibitor. Rates of sustained virological response or cure with triple combination treatment have improved substantially, both in patients who have had previous treatment and in those who have not. Improvements have been most substantial in populations regarded as difficult to treat, such as individuals with cirrhosis. However, despite improved response rates, protease inhibitors have incremental toxic effects, high costs, increased pill burden, and many drug interactions. Moreover, because new antiviral drugs directly inhibit hepatitis C virus, viral resistance has become an important issue, essentially precluding use of protease inhibitor monotherapy, and potentially restricting future treatment options for patients who consequently do not achieve sustained virological response. Protease inhibitors are the first of many antiviral medications that will probably be combined in future interferon-free regimens.

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Introduction

Hepatitis C virus is a leading cause of liver failure and hepatocellular carcinoma[1] and infects about 3% of the population worldwide.[2] Treatment with pegylated interferon and ribavirin cures only about 45% of patients with hepatitis C genotype-1, the main strain in Europe and the USA.[3]

The virus is a single-stranded linear RNA virus with a genome encoding a polyprotein of about 3000 aminoacids. Cellular and viral proteases cleave this large polyprotein into several structural and non-structural polypeptides that assist in viral replication within hepatocytes. A crucial cleavage step involves the serine protease NS3-NS4A, a protein composed of the N-terminus of the NS3 protein and a small NS4A protein cofactor.[4] Polyprotein cleavage is not the only function of NS3-NS4A. The protease subverts its host's innate immune response by preventing the phosphorylation, and thus activation, of interferon regulatory factor 3, a key antiviral signalling molecule. This factor induces expression of interferon β, which leads to the expression of many interferon-stimulated genes, thus producing an antiviral state in infected and surrounding cells.[5] NS3-4A also reduces the intrahepatic production of interferon γ, which might impair the hepatic inflammatory response and contribute to viral persistence.[6] Hence, inhibition of NS3-4A might block viral replication and potentially restore suppressed interferon pathways. Small peptides derived from the cleavage products of NS3A can competitively inhibit this enzyme.[7] Peptidomimetic molecules with specific activity against NS3-NS4A have subsequently been formulated.

In 2011, the US Food and Drug Administration (FDA) and European Medicines Agency approved the first two linear protease inhibitors, boceprevir and telaprevir. Although these approvals mark an important advance in treatment of hepatitis C, the drugs have many limitations and additional toxic effects beyond those of pegylated interferon and ribavirin, with which they must be combined.

Clinical trials

Boceprevir

The SPRINT-2 study[8] was a randomised, double-blind, phase 3 trial that compared safety and efficacy of combination treatment with pegylated interferon alfa plus ribavirin (the previous standard of care) with or without boceprevir (800 mg three times a day with food) in groups of previously untreated black and non-black patients with genotype-1 hepatitis C (figure 1 and table 1). Patients were randomly assigned to one of three groups: group one (control group), group two (response-guided treatment), or group three (fixed-duration treatment). The primary endpoint was sustained virological response defined by undetectable hepatitis C RNA at week 24 after treatment (lower limit of detection 9 IU/mL). For both races, patients in the boceprevir group had significantly higher rates of sustained virological response than did those in the pegylated interferon plus ribavirin control group (table 1). For black patients, rates of sustained virological response were 23% in group one, 42% (p=0·04) in group two, and 53% (p=0·004) in group three versus 40%, 67% (p<0·001), and 68% (p<0·001), respectively, for non-black patients.

Findings from this trial resulted in response-guided treatment recommendations in the product label for boceprevir. Patients in the fixed-duration group (48 weeks of treatment) and the response-guided group (28 weeks of treatment) who were so-called early responders, defined by undetectable virus between week 8 and week 24, had similar rates of sustained virological response (96% *vs* 97%). However, late responders (detectable serum hepatitis C RNA at week 8, but undetectable at week 24) had lower rates of sustained virological response with response-guided treatment than did those who received the full treatment course (66% *vs* 75%; p=0·16).[12] The final 20 weeks of response-guided treatment contained pegylated interferon plus ribavirin and

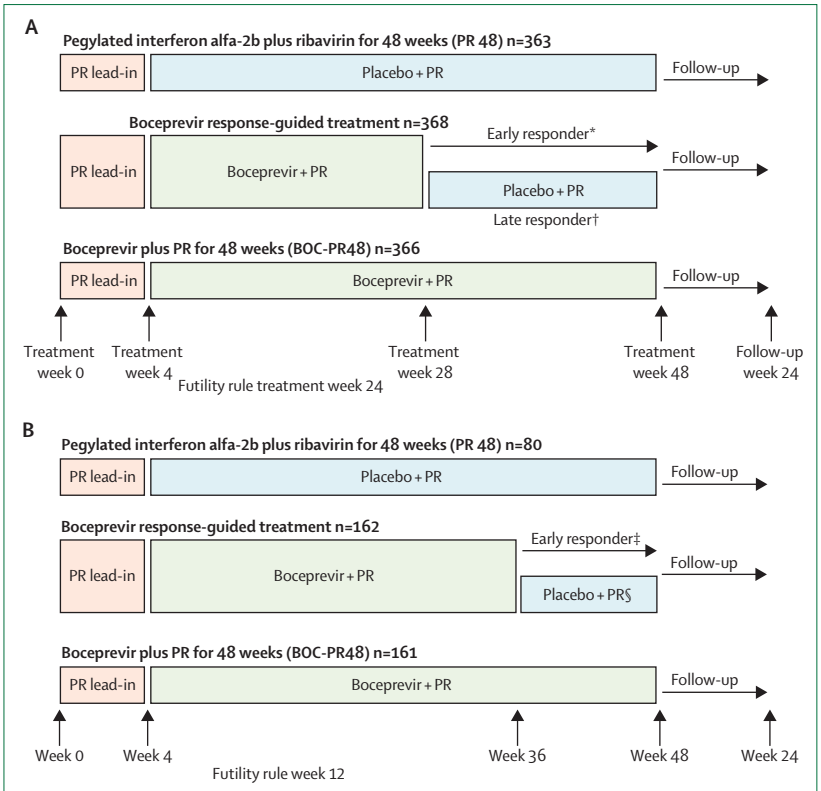

Figure 1: **Phase 3 trials of boceprevir in patients with hepatitis C genotype-1 infection**
(A) SPRINT-2 trial[8] in previously untreated patients. (B) RESPOND-2 trial[9] for previously treated patients; patients were partial responders and relapsers, and null-responders. PR=pegylated interferon alfa-2b 1·5 μg/kg per week plus weight-based ribavirin 600–1400 mg per day. BOC=boceprevir 800 mg every 8 h. *Hepatitis C RNA treatment weeks 8–24 undetectable. †Hepatitis C RNA treatment week 8 detectable, treatment week 24 undetectable. ‡Hepatitis C RNA treatment weeks 8–12 undetectable. §Hepatitis C RNA treatment week 8 detectable, treatment week 12 undetectable.

placebo, compared with the fixed-duration treatment, which was triple therapy (pegylated interferon plus ribavirin with boceprevir) in the same period.

The RESPOND-2 trial[10] was a randomised, double-blind, phase 3 trial that enrolled 403 patients with genotype-1 infection, in whom pegylated interferon plus ribavirin had previously been ineffective. 64–65% of enrolled patients had relapsed after previous hepatitis C treatment and 36% had had a partial response; no previous null-responders were enrolled (figure 1 and appendix). Overall efficacy rates were significantly higher ($p<0·001$) in the two boceprevir groups than in the control group (table 1). As expected, rates of sustained virological response were better in patients with previous relapse than in those with prior partial response (figure 2).

See Online for appendix

Telaprevir

The ADVANCE trial[10] was a randomised, double-blind, placebo-controlled phase 3 study assessing the efficacy of telaprevir combined with peginterferon alfa-2a plus ribavirin. 1088 previously untreated patients with chronic hepatitis C genotype-1 were randomly assigned (1:1:1) to one of three groups: placebo with peginterferon alfa-2a plus ribavirin for 12 weeks followed by peginterferon alfa-2a plus ribavirin for 36 weeks (control group), and two telaprevir groups with telaprevir 750 mg three times a day for 8 or 12 weeks, and peginterferon alfa-2a plus ribavirin for 24 or 48 weeks (figure 3 and table 1). The assay for measurement of viral load had a lower limit of detection of 25 IU/mL. The primary endpoint was sustained virological response. 58% of patients in the telaprevir groups were eligible for shortened (24 weeks) treatment duration, because they achieved extended rapid virological response, defined by undetectable hepatitis C RNA at treatment week 4 and week 12. These patients had higher rates of sustained virological response than did those who were not eligible for 24 weeks of treatment (83–97% *vs* 39–54%); thus, the likelihood of sustained virological response was determined by the rate of the viral RNA decline.

The ILLUMINATE trial[13]—a randomised, open-label, phase 3 non-inferiority trial of previously untreated patients—strongly supported shortening of treatment duration for patients who achieved extended rapid virological response. Patients with an extended rapid virological response after 12 weeks of triple therapy with telaprevir and peginterferon plus ribavirin were randomly assigned (1:1) after week 20 to receive dual treatment with peginterferon plus ribavirin for another 4 weeks or 28 weeks (figure 3). The overall rate of sustained virological response was 72%. 92% of patients in the 24 week group and 88% in the 48 week group had sustained virological response (absolute difference 4%; 95% CI –2 to 11), which confirmed non-inferiority. As in ADVANCE,[10] the likelihood of sustained virological response was determined by rate of viral decline: patients who did not achieve extended rapid virological response, but continued treatment to week 48, had a rate of response of only 64%.

The randomised, phase 3 REALIZE trial[11] assessed the addition of telaprevir to peginterferon alfa-2a plus ribavirin in patients with genotype-1 hepatitis C in whom previous treatment with peginterferon alfa-2a plus ribavirin had been ineffective. Unlike the RESPOND-2 trial,[9] REALIZE included patients who were null-responders to previous treatment (figure 3). Overall, rates of sustained virological response were significantly higher in the two telaprevir groups than in the control group ($p<0·0001$). Rates of response were highest in patients with previous relapse, followed by those with a partial response, and the lowest rates of response were in those with previous null-response (figure 2).

The effect of fibrosis in REALIZE was crucial. Patients with cirrhosis who were previous null-responders had only a 14% chance of achieving sustained virological response; whereas, null-responders with mild fibrosis scores (F0–F2) had response rates of 41%, and even previously null-responders bridging fibrosis (F3) had rates of 42%. Moreover, cirrhosis was not always

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	Number of patients treated	Protease inhibitor studied	Patients with bridging fibrosis or cirrhosis on biopsy	Number of black patients	Overall efficacy; sustained virological response*	Relapse rates*	Serious adverse events*
SPRINT-2[8]	1097	Boceprevir	34 (9%)	52 (14%)	63–66% *vs* 38%; p<0·001	9% *vs* 22%	11–12% *vs* 9%
RESPOND-2[9]	403	Boceprevir	78 (19%)	49 (12%)	59–66% *vs* 21%; p<0·001	12–15% *vs* 32%	10–14% *vs* 5%
ADVANCE[10]	1088	Telaprevir	231 (21%)	94 (9%)	69–75% *vs* 44%; p<0·001	9% *vs* 28%	9% *vs* 7%
REALIZE[11]	662	Telaprevir	316 (48%)	30 (5%)	64–66% *vs* 17%; p<0·001	7% *vs* 5%	12% *vs* 5%

Data are n (%) unless otherwise indicated. *Treatment *vs* control groups.

Table 1: **Placebo-controlled phase 3 trials of boceprevir and telaprevir**

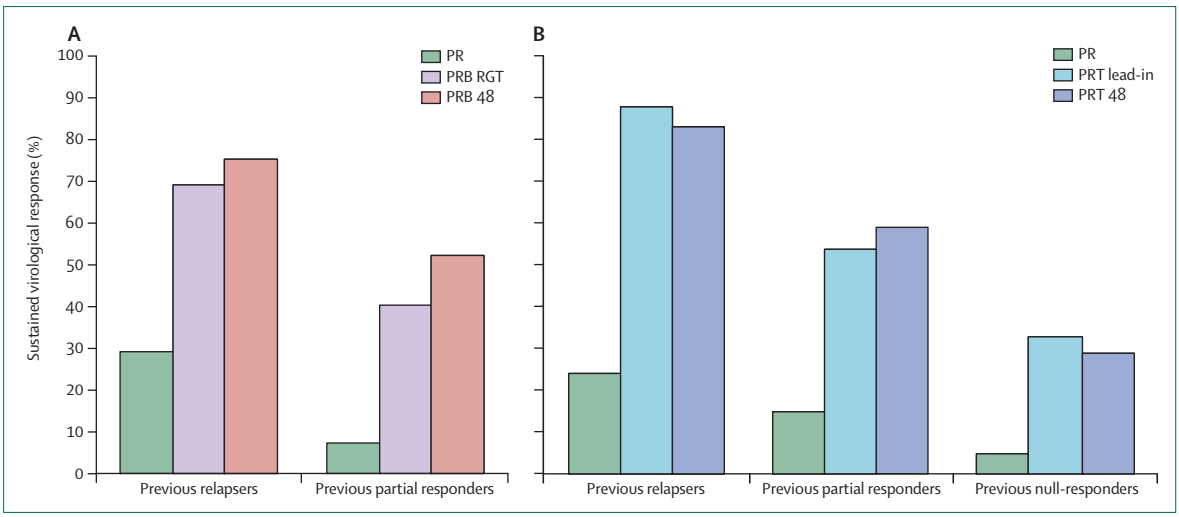

Figure 2: **Rates of sustained virological response for previously treated patients in the RESPOND-2 trial[9] and REALIZE[11] trials**
(A) RESPOND-2, p<0·001 for study *vs* control groups. (B) REALIZE, p<0·001 for study *vs* control groups. PR=pegylated interferon and ribavirin control groups. PRB RGT=pegylated interferon, ribavirin, and boceprevir, response-guided treatment. PRB 48=pegylated interferon, ribavirin, and boceprevir fixed duration 48 weeks. PRT lead-in=4 weeks of pegylated interferon and ribavirin followed by pegylated interferon, ribavirin, and telaprevir. PRT 48=pegylated interferon, ribavirin, and telaprevir fixed duration 48 weeks' treatment.

associated with poor response. Patients with cirrhosis who had previously relapsed achieved sustained virological response 86% of the time.[14] Both previous response and fibrosis severity are important considerations when deciding whether to retreat previously treated patients with triple therapy.

Limitations of clinical trials

Telaprevir and boceprevir are indicated only in patients with compensated cirrhosis in the Child Pugh class A. Although findings from the ADVANCE trial[10] showed that rates of sustained virological response were much higher when patients with cirrhosis were treated with a protease inhibitor than with peginterferon plus ribavirin, especially in previously untreated patients (telaprevir 62% *vs* control 33%), few of these patients were studied and the rates were still lower than in those with milder disease (62% for patients with cirrhosis *vs* 81% for those with minimal or no fibrosis).

A general limitation of the phase 3 discussed trials was that few black (African American) patients enrolled (table 1). Black patients have lower rates of sustained virological response than do non-black patients, especially with peginterferon plus ribavirin treatment, and should have represented a greater percentage of patients than they did. In the REALIZE trial,[11] only 3–4% of patients enrolled were African American. Even in SPRINT-2,[8] despite a separate analysis, the black cohort was only 14% of patients studied.

A limitation of RESPOND-2 was the exclusion of patients with classic null-response to previous treatment (defined as less than a 2 $\log_{10}$ decline in virus after 12 weeks of treatment), because they have the lowest rates of sustained virological response among non-responsive patients when retreated with triple therapy. Despite this exclusion, the FDA has still approved boceprevir for use in patients with previous null-response to pegylated interferon plus ribavirin on the basis of interim results from the PROVIDE study.[15] In this study, patients with previous null-response in the control groups of phase 3 trials RESPOND-2 and SPRINT-2, and in one additional phase 2 study[16] received a 4 week

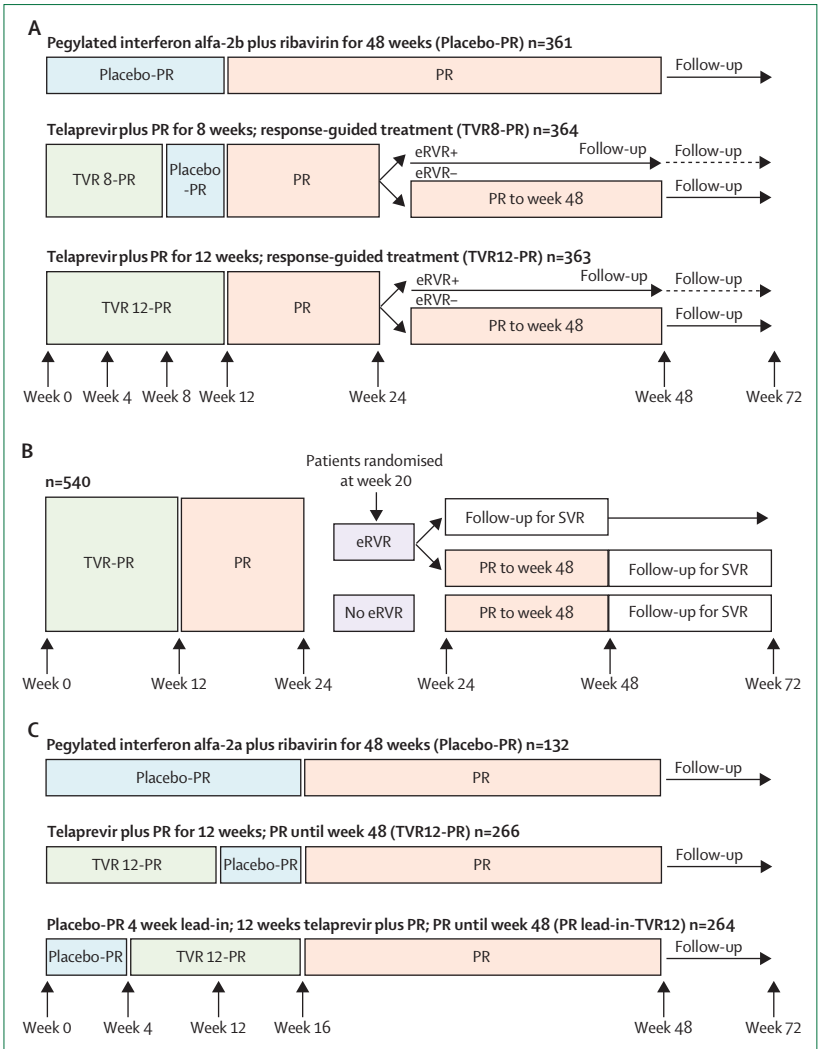

Figure 3: **Phase 3 trials of telaprevir in patients with hepatitis C genotype 1 infection**
(A) ADVANCE trial[10] in previously untreated patients. (B) ILLUMINATE trial[13] of response-guided treatment for previously untreated patients. (C) REALIZE trial[11] of previously treated patients, included those with partial response, relapse, and non-responders. PR=pegylated interferon alfa-2a 180 μg per week plus weight-based ribavirin 1000–1200 mg per day. TVR=telaprevir 750 mg every 8 h. eRVR=extended rapid virological response, undetectable hepatitis C virus RNA at weeks 4 and 12. SVR=sustained virological response.

pegylated interferon plus ribavirin lead-in followed by 44 weeks of triple therapy with boceprevir. The end-of-treatment response of 39% was roughly comparable to that of 44% among patients with less than 1 $\log_{10}$ decrement in hepatitis C RNA at week 4 in the groups receiving boceprevir in the phase 3 trials. Furthermore, a decline in viral load of less than 1 $\log_{10}$ at 4 weeks of pegylated interferon plus ribavirin correlates with the definition of classic null-response.[17]

The complexity and disparate designs of phase 3 clinical trials hampers comparison of protease inhibitors without a head-to-head study. The American Association for the Study of Liver Disease guidelines provide further information about the trials.[18]

FDA-approved dosing

The recommended regimen for boceprevir in previously untreated patients is triple therapy with a 4 week lead-in with pegylated interferon plus ribavirin, followed by the addition of boceprevir (figure 4 and table 2).[19] Patients who are difficult to treat, including any with cirrhosis or previous null-responders, should receive the maximum duration of protease inhibitor—ie, 4 week lead-in followed by 44 weeks of triple therapy. Furthermore, 48 weeks of treatment (44 weeks of triple therapy) should be considered for previously untreated patients who respond poorly to interferon in the lead-in period (<1 $\log_{10}$ decline in hepatitis C RNA from baseline). None of these groups qualify for response-guided treatment, and treatment time should not be shortened, irrespective of virological response. For patients with cirrhosis, fewer in the response-guided treatment group (41%) had sustained virological response than in the fixed dosing group (52%). Response rates were particularly disparate in patients who had received previous treatment (response-guided treatment 14 [44%] of 32 patients *vs* full-treatment course 21 [68%] of 31 patients); however, these numbers were small and did not differ significantly.

According to the boceprevir package label,[19] all treatment should be stopped if the serum hepatitis C RNA is either 100 IU/mL or more at 12 weeks, or detectable (at any level) at week 24. Not only was the likelihood of sustained virological response extremely low for patients with insufficient viral suppression in the phase 3 trials, but also, patients with serum virus concentrations greater than these thresholds had an increased chance of having drug-resistant variants.

No lead-in phase is needed for regimens containing telaprevir, and all patients begin triple therapy from day 1 of treatment with peginterferon plus ribavirin and telaprevir for 12 weeks. The US FDA-approved regimen for telaprevir allows for response-guided treatment if a patient is either previously untreated or had had a past relapse to pegylated interferon plus ribavirin (previous partial responders are not candidates for shortened treatment duration with telaprevir; figure 4, table 2).[20]

According to the telaprevir package label, when either previously untreated or therapy-experienced patients are treated, pegylated interferon, ribavirin, and telaprevir should all be discontinued if the serum concentration of hepatitis C RNA is 1000 IU/mL or more at treatment week 4 or week 12, or detectable (at any level) at week 24.[20] These futility rules are based on findings from the phase 3 trials in which patients with serum concentrations of hepatitis C RNA greater than these thresholds had extremely low chances of achieving sustained virological response. The FDA recommends 1000 IU/mL, rather than 100 IU/mL, as the stopping threshold for telaprevir, because in the ADVANCE, ILLUMINATE, and REALIZE trials, five of 19 untreated, and one of seven previously treated patients achieved sustained virological responses

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after having concentrations of 100–1000 IU/mL of serum hepatitis C RNA at week 4 of treatment.[21]

Response-guided treatment for patients who had previously relapsed was not prospectively assessed in the REALIZE trial. The FDA based this recommendation on supportive data from two phase-2 trials of telaprevir, in which 52 patients who had previously relapsed after pegylated interferon plus ribavirin, achieved a sustained virological response rate of 94% when treated with 12 weeks of triple therapy containing telaprevir, followed by 12 weeks of peginterferon plus ribavirin alone.[22,23]

Approved dosing for both boceprevir and telaprevir (table 2) is three times a day (7–9 h apart). Boceprevir is taken as 800 mg (four capsules) and telaprevir as 750 mg (two capsules). Although a phase 2 study[24] showed non-inferiority for a regimen of telaprevir 1125 mg twice a day, the study was small and enrolled patients who were easy to treat. The larger ongoing phase 3 OPTIMIZE trial[25] is likely to confirm the non-inferiority question. Both telaprevir and boceprevir should be taken with food, but telaprevir needs a meal or a snack containing at least 20 g of fat (systemic exposure to telaprevir is increased by 237% when taken with a standard fat meal compared with exposure when fasting).[20] Frequent assessment with complete blood counts are needed with telaprevir and boceprevir, as is pregnancy testing every month for women of childbearing age, which is the same as assessment for pegylated interferon plus ribavirin. Because both drugs must be combined with ribavirin, a known teratogen, patients and their sexual partners must continue to use two effective contraceptive methods during treatment, and up to 6 months after treatment cessation.

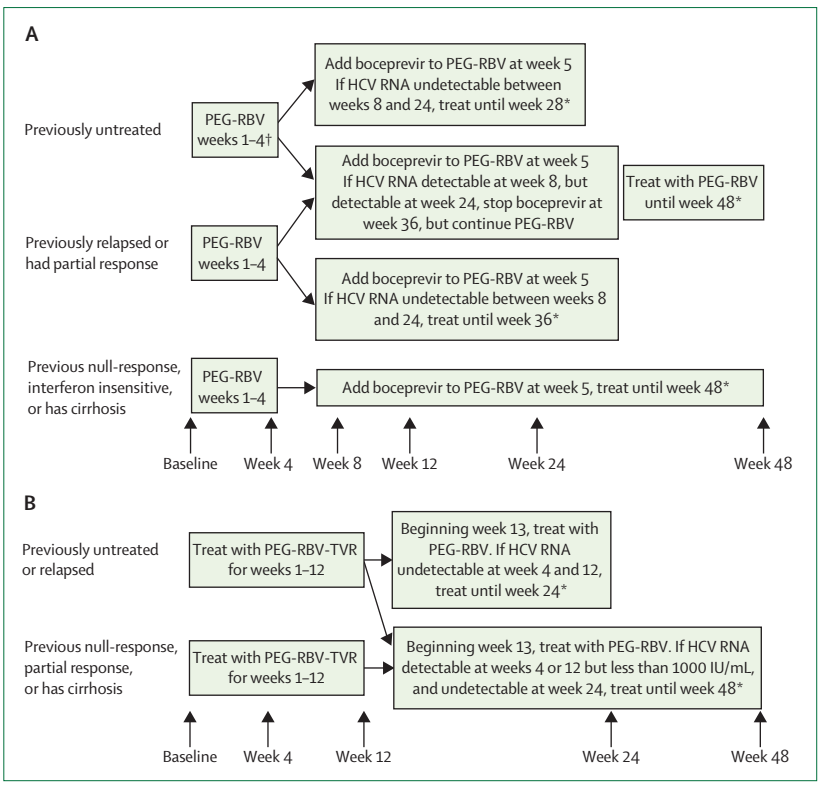

Figure 4: **Dosing regimens**
Vertical arrows show the weeks at which hepatitis HCV RNA should be checked with an assay with a lower limit of detection of ≤10–15 IU/mL. Check HCV RNA at end of therapy, and, if undetectable, recheck 24 weeks later for sustained virological response. (A) For boceprevir, if HCV RNA ≥100 IU/mL at week 12 or detectable at week 24, treatment should be discontinued. (B) For teleprevir, if HCV RNA ≥1000 IU/mL at week 4 or 12, or detectable at week 24, treatment should be discontinued. PEG-RBV=pegylated interferon plus ribavirin. TVR=telaprevir. *Check HCV RNA at end of treatment, and, if undetectable, recheck 24 weeks later for sustained virologic response. †Consider not adding protease inhibitor for patients with no cirrhosis and low viral loads who have undetectable serum virus at end of lead-in; total treatment duration 24 weeks.

Importance of the lead-in phase

The lead-in phase of pegylated interferon plus ribavirin with no protease inhibitor was intended to minimise resistance and treatment failure by reducing viral replication before addition of the third molecule. In the phase 2 SPRINT-1 trial[16] with separate groups for boceprevir, with or without a lead-in phase, the rate of viral breakthrough was slightly lower with lead-in than without it (4% *vs* 9%; p=0·057). Because no control group without a lead-in phase was used in SPRINT-2, findings could not confirm the significance of this phase; however, the predictive value of the virological response was high during lead-in. In all treatment groups of non-black patients, those with a decline of 1 $\log_{10}$ of more in hepatitis C RNA had higher rates of sustained virological response than did those without it (82% *vs* 29–39%; p<0·0001). Thus, a patient's interferon responsiveness or sensitivity is crucial to successful treatment outcome, despite the addition of a protease inhibitor.

In the REALIZE trial,[11] rate of sustained virological response did not differ between the group with the lead-in phase (66%) compared with that without (64%). However, a lead-in period might still be useful with telaprevir for previous non-responders. Preliminary data[14] from an analysis of the REALIZE trial showed that patients with no previous response and decline in hepatitis C RNA of less than 1 $\log_{10}$ from baseline (59%) had only a 15% chance of achieving sustained virological response with triple therapy compared with those with at least a decline of 1 $\log_{10}$ from baseline who achieve a response 54% of the time. Thus, a lead-in period might help clinicians make a better decision about treatment cessation than when no lead-in is used, particularly in patients who respond poorly to interferon treatment, previous null-responders, and those with mild fibrosis scores. In previous non-responders with mild liver disease who achieve less than a $\log_{10}$ decline in virus at week 4, treatment can potentially be stopped while awaiting more effective treatment.

By contrast, a rapid virological response—an undetectable concentration of hepatitis C RNA after the lead-in phase of pegylated interferon plus ribavirin—has excellent positive predictive value for success. Patients with genotype-1 infection who achieve this outcome have an 88% chance of sustained virological response.[26]

	Boceprevir	Telaprevir
Dosing	Three times a day	Three times a day
Number of tablets per dose	Four 200 mg tablets	Two 375 mg tablets
Food requirement	Yes	Yes*
Major side-effects	Anaemia, dysgeusia	Anaemia, rash, pruritus, anorectal complaints
Lead-in recommended	Yes	No
Response-guided treatment (treatment duration)	Previously untreated patients (28 weeks); previous relapsers (36 weeks); previous partial responders (36weeks)†	Previously untreated patients (24 weeks); previous relapsers (24 weeks)†
Treatment duration	28–48 weeks	24–48 weeks
Futility points	Weeks 12 and 24	Weeks 4, 12, and 24
Cost	$US1100 per week (44 weeks maximum)	$US4100 per week (12 weeks maximum)
Product advantages	Fewer side-effects; less expensive; does not need a fatty meal	Less complex treatment dosing regimen; shorter duration of triple therapy

*Needs a meal or a snack with at least 20 g of fat. †Patients must not have cirrhosis.

Table 2: **Comparison of boceprevir and telaprevir**

Patients with genotype-1 infection, no cirrhosis, a low baseline viral load (<600 000 IU/mL), and a rapid virological response can be treated with pegylated-interferon plus ribavirin with a shortened treatment duration of 24 weeks, according to European Guidelines.[27] For these patients, addition of a protease inhibitor might not be beneficial because of increased cost and side-effects, despite similar effectiveness. In an ongoing trial, we have randomised patients with genotype-1 infection and low viral loads who achieve rapid virological response, to either 24 weeks of pegylated interferon plus ribavirin, or to a further 24 weeks of triple therapy with the addition of boceprevir. Interim results are expected by November, 2012.

Safety and adverse effects

Because boceprevir and teleprevir must be combined with pegylated-interferon plus ribavirin, which are usually accompanied by adverse effects, toxic effects associated with these protease inhibitors will be in addition to those of the previous standard of care. If patients have absolute contraindications for either pegylated-interferon or ribavirin, they are not candidates for protease inhibitors. Dose of protease inhibitors should crucially not be lowered, because this reduction could engender treatment failure via resistance.

In pooled phase 3 trials[19] of boceprevir treatment (n=1548), the most common adverse events with a frequency of 5% and greater than those with placebo (listed in order of occurrence) were anaemia, nausea, dysgeusia (altered sense of taste), chills, neutropenia, and vomiting. In SPRINT-2,[8] serious adverse events occurred in 11–12% of patients in the boceprevir groups versus 9% of those in the control groups, compared with 10–14% versus 5%, respectively, in RESPOND-2.[9]

In SPRINT-2,[8] boceprevir was associated with a significantly higher incidence of anaemia than was the control regimen (49% *vs* 29%; p<0·001); similar findings were shown in RESPOND-2 (43–46% *vs* 20%; p<0·001). In patients receiving boceprevir, haemoglobin concentrations were less than 8·5 g/dL in 6% of those who had had no previous treatment and 10% in those who had, versus 1–3% of those in the control groups.[9] In both trials, 41–46% of patients receiving boceprevir who became anaemic were given erythropoietin (an off-label drug used for mono-infected patients with hepatitis C) compared with 24% of those in control groups. In the telaprevir trials,[8,9] growth factors were prohibited.

Additional adverse events more common in the boceprevir groups of both phase 3 trials compared with the control groups were neutropenia (absolute neutrophil count 500–750/µL, previously untreated patients 24–25% *vs* 14% control, p<0·001 and previously treated patients 19–20% *vs* 9% control; response-guided treatment group *vs* control group p=0·06, fixed-duration group *vs* control group p=0·03) and dysgeusia (previously untreated patients 37–43% *vs* control 18%, p<0·001; previously treated patients 43–45% *vs* control 11%, p<0·001). Dysgeusia was not a major dose-limiting adverse event in either trial.[8,9]

In pooled phase 3 trials[20] of telaprevir (n=1787), the most common adverse effects with a frequency of 5% and greater than that of placebo (listed in order of occurrence) were rash, fatigue, pruritus, nausea, anaemia, diarrhoea, vomiting, haemorrhoids, anorectal discomfort or pruritus, and dysgeusia. In the ADVANCE trial,[10] treatment discontinuation because of adverse events occurred in 10% of patients in the telaprevir groups versus 7% of those in the control group. In the ILLUMINATE trial,[13] 18% of patients discontinued all study drugs because of serious adverse events, although response-guided treatment resulted in fewer adverse events and treatment discontinuations in those for whom duration of treatment was shortened. In the REALIZE trial,[11] 5% of patients in the telaprevir groups stopped treatment because of adverse events versus 3% in the control group. 29% of patients given telaprevir had anorectal discomfort compared with 7% of those in the

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control groups; however, less than 1% of patients stopped treatment because of anorectal complaints. Anorectal symptoms associated with telaprevir include burning, itching, and haemorrhoids, and rarely lead to treatment cessation. For intolerable symptoms, perianal topical lidocaine or zinc oxide might give partial relief. Although most rashes were mild to moderate in the phase 3 trials of telaprevir, severe rashes occurred in only 6% of patients; telaprevir was stopped in many cases and pegylated-interferon plus ribavirin were continued. Three patients (<1%) developed Stevens-Johnson syndrome and 11 (<1%) developed drug rash with eosinophilia and systemic symptoms.[20] Although the mechanism for rash due to telaprevir is unknown, the histology of most rashes is a spongiotic pattern with lymphocytic perivascular infiltration.[28]

Rash associated with telaprevir typically occurs in the first 8 weeks of treatment, but severe rash can occur anytime during the drug's 12 week dosing period. Strict management rules have been established because of findings from clinical trials. For patients with mild to moderate rash (up to 50% of body surface area), patients should be managed with topical steroids and antihistamines. For those with systemic signs or symptoms associated with a rash, so-called red-flag features, such as mucosal involvement or a rash progressing to 50% or more of body surface area, telaprevir should be stopped and dermatological referral sought. Pegylated-interferon plus ribavirin can be continued if the rash abates within 7–10 days. Rash typically resolves within 7–10 days after telaprevir cessation. Once the drug is withdrawn, it cannot be restarted, and patients need to be reassessed regularly. Although pruritus due to telaprevir is generally present with a rash, it can present in the absence of any other dermatological symptoms. Treatment is similar to that for a rash and rarely warrants treatment discontinuation.

Although anaemia was common in the boceprevir trials, it was also important in the telaprevir trials. With telaprevir, the main mechanism of anaemia in the first 8 weeks of treatment is haemolysis; thereafter, myelosuppression can have an additional role.[28] In a pooled analysis of phase 3 data,[20] 14% of patients in the telaprevir groups, versus 5% of those in the control groups, had haemoglobin nadirs of less than 8·5 g/dL. In the ADVANCE study,[10] rates of anaemia were about two times higher in patients in the telaprevir group than in those in the control groups (37–39% *vs* 19%), and more than two times higher in the SPRINT-2 trial[8] of boceprevir compared with those in the control group (49% *vs* 20%). In the ADVANCE trial, 12% of patients with anaemia who were given telaprevir needed blood transfusions compared with 3% of those with anaemia who were previously untreated and given boceprevir;[29] however, growth factors used in previously untreated patients could have been transfusion sparing.

Anaemia is a common side-effect with either boceprevir or telaprevir. In accord with ribavirin package labelling, for haemoglobin concentrations of less than 10 gm/dL, ribavirin dose should be reduced, and, for those of less than 8·5 gm/dL, it should be stopped and the protease inhibitor discontinued. How providers should treat anaemia is unclear when using these new molecules either to use growth factors (off-label prescribing) or to reduce ribavirin dose. Past experience with pegylated-interferon plus ribavirin showed that changes in ribavirin dose early in treatment had the most substantial effect on relapse rate.[30] A retrospective pooled analysis[31] from the ADVANCE and ILLUMINATE trials showed that reductions in ribavirin dose had no apparent effect on sustained virological response in the groups given telaprevir, but seemed to have a deleterious effect on response in those without it. Preliminary evidence from a prospective trial[32] showed that with boceprevir-associated anaemia, reduction of the ribavirin dosage or addition of a growth factor were reasonable approaches; both methods produced similar rates of sustained virological response.

Drug interactions

Boceprevir and telaprevir are strong inhibitors of cytochrome P450 3A4 (CYP3A4) and potential inhibitors of p-glycoprotein.[19,20] Thus, drugs metabolised mainly by CYP3A4 might have increased exposure when given with either protease inhibitor, thereby prolonging or increasing therapeutic events and toxic effects (appendix).

The most important and commonly prescribed classes of drug that interact with the first-generation protease inhibitors are hormonal contraceptives, statins, dihydropiridine calcium channel blockers, and phosphodiesterase-5 inhibitors. Because serum concentrations can change, systemic hormonal contraceptives can no longer be relied upon to provide contraception during interferon-based treatment that includes boceprevir or telaprevir; thus, only barrier methods and intrauterine devices are recommended.

Importance of ribavirin

Because haemolytic anaemia is a major side-effect of ribavirin, initial hopes were that this drug could be eliminated from any treatment regimen containing a protease inhibitor. Unfortunately, rates of sustained virological response are lower in groups treated with pegylated-interferon and a protease inhibitor, than in people given pegylated interferon and ribavirin. For example, in the PROVE3 phase 2 trial[22] of telaprevir for previously treated patients, the triple-therapy group had a rate of sustained virological response of 53% compared with 24% in those given pegylated-interferon alfa and telaprevir, half that of those given pegylated-interferon plus ribavirin.[3] In another phase 2 trial[33] of telaprevir, 60% of patients achieved sustained virological response in a triple-therapy group; however, those in a double-therapy group without ribavirin had a rate of only 36%.

Genotypes and subgenotypes

Although telaprevir was active in patients with genotype-2 infection in a phase 2 study,[34] and has shown activity against genotype-6 in vitro,[35] both telaprevir and boceprevir have poor antiviral activity against genotype-3 virus.[36] With no findings from large clinical trials to support the use of telaprevir or boceprevir in patients with infections other than genotype-1, both molecules should be prescribed only for genotype-1 infection.

Subtypes of genotype-1 have different susceptibility to protease inhibitors. In the REALIZE trial,[11] 37% of previous null-responders with genotype-1b infection achieved sustained virological response compared with 27% of those with genotype-1a; among those with previous partial responses 68% with genotype 1b and 47% with genotype 1a achieved sustained virological response. The most probable reason for disparity in rates of response between subtypes is the genetic barrier to the development of protease inhibitor resistance. Genotype-1b virus has a higher barrier to resistance than does genotype-1a, because it needs two nucleotide substitutions at position 155 in its protease to confer resistance to telaprevir or boceprevir; whereas, genotype-1a needs one substitution in the same position to become resistant.[37,38]

Special groups

Providers might be tempted to begin regimens containing a protease inhibitor in patients with hepatitis C who could benefit from improved cure rates, such as liver transplant recipients, patients with decompensated cirrhosis, young (aged <18 years) or old (>65 years) patients, or those who are renally impaired; no available safety or efficacy data support this decision, thus, providers should avoid this practice. Nonetheless, promising interim results are available from a study[39] of patients with genotype-1 infection who also had HIV treated with triple therapy, including telaprevir. 12 weeks after treatment was completed, 74% of previously untreated patients with co-infection had undetectable hepatitis C RNA when treated with a telaprevir-based regimen, compared with 45% of patients treated with pegylated-interferon plus ribavirin and placebo. Tolerability was comparable to that of telaprevir treatment in patients with hepatitis C mono-infection.

Interleukin-28B polymorphism

rs12979860, a single-nucleotide polymorphism near the interleukin-28B gene, which encodes interferon-λ3, has been associated with responsiveness to treatment with pegylated-interferon plus ribavirin.[40–42] The interleukin-28B genotype test is commercially available (Laboratory Corporation of America, Burlington, NC, USA). The CC genotype predicts interferon responsiveness, whereas the non-CC genotypes TT and TC predict poor interferon response.[40,43] The interleukin-28B polymorphism could explain at least half the disparity between treatment responses in white and black patients given pegylated interferon plus ribavirin.[40] In both the previously untreated and the treated groups of the ADVANCE and REALIZE trials of telaprevir, rates of sustained virological response were increased for all interleukin-28B genotypes in patients receiving telaprevir.[44,45] Unlike in the telaprevir trials, in the SPRINT-2 trial, patients with the CC genotype had similarly high rates of sustained virological response in all groups, including the control group (80–82% *vs* 78%); however, in the patients with non-CC genotypes, rates were significantly higher (data not shown) in the groups given boceprevir than in the control group (55–71% *vs* 27–28%).[46] Overall, the predictive value of the interleukin-28B genotype for sustained virological response has been attenuated by the introduction of the protease inhibitors, and measurement of interferon responsiveness is improved with the 4 week lead-in period, as is standard with boceprevier regimens. The best use of the interleukin-28B test might be to predict treatment duration, because about 90% of patients with the CC genotype will qualify for a shortened duration of treatment.[46]

Resistance

Because the RNA-dependent RNA polymerase of hepatitis C is prone to error, and the rate of virion production is high (up to 10^{13} particles per day),[47] the emergence of resistant variants is frequent. Investigators have estimated that every possible viral variant is produced daily in an infected patient.[48,49] Naturally occurring dominant mutations resistant to the hepatitis C protease inhibitors are present even in previously untreated patients with genotype-1 infection.[50,51] Patients infected with genotype 1a have a higher prevalence (8·6%) of resistance mutations than do those with genotype 1b (1·4%).[50] Despite harbouring baseline resistance mutations, many patients still achieve sustained virological response, because baseline resistance does not correlate with treatment response.[19,20] Phenotypic resistance profiles have no known correlates, and baseline resistance testing has no clinical indication as per current guidelines.[25]

Because of the shallow substrate binding pocket of NS3, even minute structural changes can promote resistance.[52] Monotherapy with protease inhibitors selects for resistance mutations rapidly.[53–55] Several resistant mutations in the NS3 protein have been identified, including Val36Met, Thr54Ala, Arg155Lys, Ala156Ser, Ala156Thr, and Val170Ala (boceprevier only). With ongoing monotherapy with telaprevir, single mutations increase and are eventually replaced by double resistant mutations; compared with single-mutation variants, double mutations confer very high-level resistance to telaprevir (eg, Val36 and Arg155 >50 times compared with Val36 alone less than eight times relative to wild-type).[56] Although the Ala156Ser mutation confers the highest resistance to boceprevir and telaprevir, it renders the virus substantially less fit than wild-type virus.[57]

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In phase 1 studies,[49,53,56] monotherapy with boceprevir and telaprevir engendered emergence of resistance mutations, which were reduced when these molecules were combined with pegylated-interferon. Patients treated with telaprevir in the PROVE2 trial[33] with pegylated-interferon and no ribavirin developed more resistant mutations than did those given triple therapy. In the SPRINT-2 trial,[8] previously untreated patients who were interferon sensitive (decline of <1 $\log_{10}$ in hepatitis C RNA at end of lead-in) had more resistant mutations and lower rates of sustained virological response than did those who were interferon sensitive. Moreover, population sequencing has shown that occurrence of high-level resistance is increased when virological failure occurs during the first 12 weeks of triple therapy with telaprevir compared with the development of low-level resistant variants during the subsequent pegylated-interferon plus ribavirin phase of treatment.[18]

Because similar variants are detected in patients treated with either boceprevir or telaprevir, cross-resistance between these drugs is expected; thus, virological failure with triple therapy containing a protease inhibitor is a contraindication for a change from one drug to another. With virological failure and ongoing exposure to protease inhibitors, resistance mutations are more likely to develop than when these inhibitors are not used; consequently, strict stopping rules have been developed to circumvent further resistance.

Most patients in whom triple therapy containing pegylated-interferon plus ribavirin plus a protease inhibitor is ineffective have a dominant resistant virus population, which, at the time of relapse, is resistant to the protease inhibitor proper.[34] In fact, 80–90% of patients with virological failure or relapse after termination of treatment containing protease inhibitor harbour resistant variants, compared with 5–7% in those at baseline.[20,58] These variants are replaced by wild-type virus within weeks to months.[59] Nonetheless, variants resistant to the protease inhibitors remain as minor viral populations replicating at low concentrations. If in the future, patients are rechallenged with protease inhibitors with similar resistance profiles, whether resistant virus will re-emerge is uncertain. Moreover, how these resistant variants might affect future treatment options is unclear.

Selection of patients

Identified patients with hepatitis C should be referred to providers experienced in the use of these new molecules. Unfortunately, many of those infected are not identified or referred for treatment.[60] Primary-care providers must understand that hepatitis C is not only treatable, but is also curable, and cure results in reduced rates of hepatic decompensation events and decrements in liver-related deaths.[60–62] Thus, the improved rates of sustained virological response with these drugs could potentially reduce the substantial disease burden of hepatitis C.[63] Patients with previous null-response to pegylated-interferon plus ribavirin, particularly those with mild liver disease who are interferon insensitive, can benefit from deferral of this first phase of direct-acting antiviral treatment. Previously untreated patients who are interferon insensitive with mild fibrosis scores might also be a group for whom treatment should be deferred. These patients have rates of sustained virological response between 28% and 38% with triple therapy containing boceprevir.[8] New treatment options will be needed with improved effectiveness.

Findings from a preliminary modelling analysis comparing two strategies have provided guidance about how to treat previous null-responders. The first strategy was to treat patients immediately with triple therapies and the second was to withhold treatment until more effective antiviral becomes available. For patients with mild fibrosis and cirrhosis, awaiting better treatment was more reasonable; those with intermediate fibrosis scores would benefit from immediate triple therapy.[64] Patients intolerant of or with substantial contraindications to interferon can benefit from regimens with no interferon, whether approved or in clinical trials, irrespective of fibrosis stage on their baseline liver biopsy.

Cost-effectiveness

The retail cost of boceprevir is US$1100 per week of treatment, and for telaprevir is $4100 per week of treatment (needs only 12 weeks of treatment);[65] however, these costs do not include that of pegylated-interferon plus ribavirin with which the protease inhibitors must be combined. Access to these drugs can be difficult, especially in resource-poor settings. Protease inhibitors are cost effective, and improved cure rates will engender substantial improvements in lifetime clinical outcomes.[66–69]

Future directions

Use of triple combination treatment containing either boceprevir or telaprevir will engender a new population of non-responders in whom this new standard of care did not work. This first regimen will be ineffective in 24–31% of previously untreated patients given triple therapy, as will retreatment with protease inhibitors and pegylated-interferon plus ribavirin in two-thirds of those who had no previous response. Additional treatments are warranted.

In the clinical development pathway for direct-acting antiviral treatment, the next phase of treatment will probably combine pegylated-interferon plus ribavirin with a third molecule that is distinct from the available protease inhibitors. This molecule might have an improved side-effect profile or one with improved dosing schedules compared with those of boceprevir and telaprevir. For example, simeprevir (TMC-435) and BI201335 are both NS3-4A protease inhibitors in phase 3 trials[70,71] that offer once-a-day dosing and possibly improved side-effect profiles compared with presently approved protease inhibitors. Because of common

Search strategy and selection criteria

We identified data from searches of Medline from Jan 1, 1990, to April 30, 2012, with the search terms "HCV," "protease inhibitor," "telaprevir," "boceprevir," and "direct-acting antiviral", and from major clinical meetings. We restricted the search to articles published in English.

resistance mutations, such as Arg155, patients in whom boceprevir and telaprevir are ineffective cannot be switched to these drugs; however, late-generation protease inhibitors, such as MK5172, which is still in phase 2 trials, might be active in the presence of mutations associated with early-generation failure of protease inhibitor—eg, Arg155, Gln80Lys).[72]

Other molecules that might be combined with pegylated-interferon and ribavirin as triple therapy include nucleoside polymerase inhibitors,[73] and NS5a inhibitors.[74] An important treatment goal is to prevent development of resistance by combining of direct-acting antiviral drugs that target distinct components of the hepatitis C life cycle without any cross-resistance; patients who are interferon intolerant or poorly responsive might benefit from treatments that do not include interferon, which can be regarded as the third phase of an overall clinical development programme for direct-acting antiviral drugs. The INFORM trial[75] used 2 week regimens of the nucleoside polymerase inhibitor mericitabine, and a second generation protease inhibitor danopevir, resulting in a substantial decline in serum hepatitis C RNA; however, all patients eventually received pegylated-interferon plus ribavirin. With use of a protease plus a polymerase inhibitor (eg, telaprevir plus MS-0608) for 4 weeks, investigators successfully eradicated hepatitis C from human hepatocyte chimeric mice followed up for 20 weeks after treatment.[76] SOUND-C2[77] —the largest interferon-free trial so far—was a phase 2b open-label study of 362 previously untreated patients with genotype-1 infection given a combination of a protease inhibitor, non-nucleoside polymerase inhibitor, and ribavirin. Preliminary rates of sustained virological response were 83% for genotype-1b infections, and 43% for genotype-1a infections. Other promising interferon-free regimens in human beings are underway.[78,79] To raise an effective barrier to emergence of resistance, and to achieve sustained virological response without interferon, more than two direct-acting antiviral drugs might be needed, especially in patients with genotype 1a.[78,80]

Despite their limitations, the hepatitis C protease inhibitors mark important progress towards achievement of a cure with interferon-free regimens.

Conflicts of interest

I serve on speakers' bureaus for Merck and Vertex pharmaceuticals and do contracted clinical research for Bristol-Myers Squibb, Janssen Pharmaceuticals, and Boehringer-Ingelheim.

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