Boceprevir: a novel nonstructural 3 (NS3) protease inhibitor for the treatment of chronic hepatitis C infection

Paul Y. Kwo

Ther Adv Gastroenterol

[2012] 5(3) 179–188

DOI: 10.1177/
1756283X11436317

© The Author(s), 2012.
Reprints and permissions:
[http://www.sagepub.co.uk/
journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: Chronic hepatitis C infection is a leading cause of morbidity and mortality worldwide, with hepatitis C related cirrhosis being the most common indication for transplant and a major cause for the increase in hepatocellular carcinoma worldwide. Treatment for hepatitis C has consisted of nonspecific immunomodulatory therapies that stimulate the immune system and inhibit hepatitis C replication. Pegylated (peg-)interferon and ribavirin have been the standard of care with an overall sustained response rate of 40–50% in patients with genotype 1 infection, and 80% in genotype 2 or 3. Recently, direct-acting antiviral agents, including boceprevir, have demonstrated improved sustained response rates in patients with genotype 1 infection when given in combination with interferon and ribavirin. Boceprevir is a structurally novel hepatitis C virus (HCV) nonstructural 3 (NS3) protease inhibitor that has demonstrated robust antiviral activity in HCV replicons. Clinically, in phase II and III trials, boceprevir 800 mg three times daily with peginterferon and ribavirin has led to improved sustained response rates in genotype 1 infection treatment-naïve patients, relapsers, partial responders, and null responders. Phase II data have demonstrated that ribavirin is essential for optimal boceprevir response. Moreover, phase II data have suggested that a 4-week peginterferon or ribavirin lead-in strategy may reduce relapse rates and provide crucial on-treatment data for treatment response with boceprevir addition. Side effects of boceprevir when added to peginterferon and ribavirin are similar to peginterferon and ribavirin, though higher rates of anemia have been noted, with an incremental increase in erythropoietin use. The addition of boceprevir represents a major advance in patients with genotype 1 infection who are treatment naïve.

Keywords: hepatitis C, interferon, ribavirin, boceprevir, direct acting antiviral, resistance

Introduction

Chronic hepatitis C affects approximately 170 million people worldwide [National Institutes of Health, 2002; Alter, 2007; McHutchison and Bacon, 2005]. It is the most common blood-borne infection in many parts of the world and is a major cause of chronic liver disease, which if left untreated, may progress to cirrhosis with or without hepatocellular carcinoma. Hepatitis C remains the most common indication for liver transplantation worldwide, with over 500,000 deaths annually due to complications of hepatitis C [Davis *et al.* 2010; El-Serag and Rudolph, 2007]

Therapy of hepatitis C

Until this year, the therapy for hepatitis C has consisted of nonspecific treatments that stimulate

the immune system and interfere in a nonspecific manner with hepatitis C viral replication [Hoofnagle and Seeff, 2006]. The standard of care for all genotypes of hepatitis C is pegylated (peg-)interferon and ribavirin for 24 weeks (genotypes 2 and 3) or 48 weeks (genotype 1), which results in overall sustained response rates of approximately 50% [Lauer and Walker, 2001b]. Other groups have lower sustained response rates due to poor interferon responsiveness. Sustained response rates for black patients are substantially lower, with two studies demonstrating sustained response rates of 19–28% in black patients and lower sustained response rates also seen in patients of Hispanic origin [Conjeevaram *et al.* 2006; Muir *et al.* 2004; Rodriguez-Torres *et al.* 2009]. In patients who achieve sustained response, long-term benefits may be seen, including a reduction

Correspondence to:
Paul Y. Kwo, MD
Professor of Medicine,
Medical Director,
Liver Transplantation
Gastroenterology/
Hepatology Division,
Indiana University
School of Medicine,
975 W. Walnut, IB 327,
Indianapolis, IN 46202-
5121, USA
pkwo@iupui.edu

Figure 1. Sites for direct-acting antiviral agents. UTR, untranslated region.

Figure 2. Boceprevir bound to NS3 active site 520 Da ketoamide.

in inflammation, improvement in liver fibrosis and better quality of life [Poynard *et al.* 2000]. Most recently, the concept of response-guided therapy through the use of viral kinetics has allowed for tailoring of duration of therapy in genotype 1 and genotypes 2 and 3 [Diago *et al.* 2010; Ferenci *et al.* 2010; Shiffman *et al.* 2007].

Prior to discussing new therapies for hepatitis C, it is important to have a basic understanding of the hepatitis C viral lifecycle. The hepatitis C virus (HCV) is a single-stranded RNA molecule that is approximately 9600 nucleotides in length [Lauer and Walker, 2001a]. Viral protein synthesis is mediated by an internal ribosome entry site that binds directly to ribosomes. RNA is translated into a polyprotein of 3000 amino acids that is proteolytically cleaved into four structural and six nonstructural (NS) proteins (Figure 1) [Bartenschlager and Lohmann, 2000; Bartenschlager, 2002]. The structural proteins are used to assemble new viral particles and the NS proteins support viral RNA replication. The NS3/4A is a serine protease (NS3) and cofactor (NS 4A) that catalyzes the post-translational processing of NS proteins from the polyprotein, which is important for viral replication. The NS3 protease cleaves NS4A–NS4B, NS4B–NS5A and NS5A–NS5B junctions. The products released go on to form a replicative complex responsible for forming viral RNA. Thus, NS3/4A provides an ideal target for antiviral therapy.

HCV replicons have provided an important tool in the investigation of the serine protease as a potential target for anti-HCV therapies. Prior to HCV replicons, *in vitro* HCV replication models had been difficult to establish. In 1999, Lohmann and colleagues described a reliable method of HCV replication with subgenomic HCV RNA in a hepatoma cell line [Lohmann *et al.* 1999]. Based on the finding that in other viral replication models, structural proteins are not required for RNA replication, the HCV RNA genome was modified. Structural proteins were replaced with a selectable marker; in this case, a gene encoding neomycin phosphotransferase (NPT), which inactivates the cytotoxic drug G418. The hepatoma cells were then transfected with the subgenomic RNA replicon and placed in a medium containing G418. Only cells in which the replicon amplified sufficiently were able to produce NPT and confer G418 resistance. The surviving cells were isolated to form colonies of cell clones that carry stable replicating HCV replicons. This technique has allowed evaluation of therapeutic agents that inhibit viral replication and characterization of resistant mutants [Bartenschlager, 2002].

Boceprevir early clinical results

Boceprevir is a structurally novel ketoamide HCV NS3 linear protease inhibitor that forms a covalent and reversible bond to the NS3 protease active site (Figure 2). *In vitro* studies have demonstrated

robust antiviral activity in an HCV replicon model, with treatment of HCV replicons resulting in a 2 log₁₀ reduction of HCV RNA level at 72 h and 4 log₁₀ reduction by day 15 [Malcolm *et al.* 2006]. In these preliminary studies, boceprevir demonstrated no toxic effects. The addition of interferon appeared to be additive, rather than synergistic, and these promising preliminary data were used as the foundation to design clinical trials for boceprevir.

Phase I studies: boceprevir monotherapy

The initial phase I trial evaluated the safety, tolerability, and efficacy of the NS3 protease inhibitor, boceprevir, at doses ranging from 100 to 400 mg daily in a genotype 1 population whose condition had not responded to interferon and ribavirin. In this European trial, 26 patients with genotype 1a or 1b infection without early virologic response were randomized to a three-way crossover study with boceprevir at doses of 200 or 400 mg three times a day for 1 week, peginterferon α 2b, 1.5 μ g/kg weekly for 2 weeks, and a combination of peginterferon and boceprevir [Sarrazin *et al.* 2007]. At least 2 weeks between treatments was mandated for washout of therapy. The combination of peginterferon and boceprevir gave the greatest viral reductions which were additive. The HCV RNA reductions ranged from 2.28 logs in the group receiving boceprevir 200 mg three times a day to a maximum of 2.7 logs in the group receiving boceprevir 400 mg three times a day. Pharmacokinetic data did not reveal significant interaction between peginterferon and boceprevir with area under the curve (AUC) for each drug comparable to AUC results noted with monotherapy for either drug.

With the preliminary data from the phase I studies, a phase II dose-finding study, RESPOND-1 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol), was initiated with multiple goals. The first goal was to ascertain the optimal boceprevir dose to maximize sustained response while minimizing toxicity. The second goal was to determine whether ribavirin would be required in combination with peginterferon α 2b and boceprevir in the treatment of null responders. Finally, this study sought to determine the optimal duration of boceprevir in the treatment of a null responder population. In this phase II study, 357 null responders who failed to achieve early virologic response (<2 log₁₀ reduction), or failed to clear the virus after 12 weeks of

therapy and who demonstrated an 80% compliance with medicines and duration, were enrolled. These null responders were treated with peginterferon α 2b and boceprevir in ascending doses (100, 200, 400, 800 mg three times daily) or with peginterferon α 2b, boceprevir 400 mg three times a day and ribavirin [Schiff *et al.* 2008]. The control arm received peginterferon α 2b plus ribavirin. An interim analysis by the Data Safety Monitoring Board led to a protocol amendment in that all patients who responded (who have $<10,000$ IU/ml on their original randomized therapy) were assigned to receive open-label peginterferon α 2b, weight-based ribavirin, and boceprevir 800 mg three times a day for 24 weeks. The sustained response rates were low in this study; however, the results establish several important concepts that have been carried forward in the treatment of hepatitis C with NS3 protease inhibitors. For the treatment of null responders (and all patients with genotype 1 infection as later determined), ribavirin is required for optimal response. The study also determined an optimal boceprevir dose of 800 mg three times daily, a dose that no patient initially received. With boceprevir in null responders, a more rapid clearance of HCV RNA and longer duration of therapy with undetectable HCV RNA levels also predicted sustained response. Finally, null responders who initially received peginterferon α 2b and ribavirin without boceprevir (control arm) with interferon responsiveness (1–2 log₁₀ reduction at week 13) were more likely to go on to a sustained response with boceprevir addition, regardless of the dose.

These preliminary results led to a design of a phase II clinical trial, the HCV Serine Protease Inhibitor Therapy I (SPRINT I) study, evaluating boceprevir in combination with peginterferon α 2b and ribavirin in genotype 1 treatment-naïve patients [Kwo *et al.* 2010]. There were two parts to this multiarm study, which enrolled patients with genotype 1 infection. In the first part, patients received peginterferon α 2b, weight-based ribavirin, and boceprevir therapy 800 mg three times a day for 28 (PRB28) or 48 weeks (PRB48), or a lead-in strategy with 4 weeks of peginterferon α 2b and ribavirin, followed by boceprevir 800 mg three times a day with peginterferon and ribavirin for 24 weeks (PR4/PRB24) or 44 weeks (PR4/PRB44), and these therapies were compared with peginterferon α 2b and ribavirin for 48 weeks. A second part explored a low-dose ribavirin arm due to an anemia signal with boceprevir, in which

Table 1. Effect of treatment duration on sustained virologic response.

	P/R control, 48 weeks <i>N</i> = 104	P/R/B, 28 weeks <i>N</i> = 107	P/R, 4 weeks → P/R/B, 24 weeks <i>N</i> = 103	P/R/B, 48 weeks <i>N</i> = 103	P/R, 4 weeks → P/R/B, 44 weeks <i>N</i> = 103	P/R/B, 48 weeks <i>N</i> = 16	P/low-dose R/B, 48 weeks <i>N</i> = 59
Gender							
Men (%)	67	59	50	61	56	56	69
Race							
White (%)	80	80	83	84	83	75	73
Black (%)	15	17	15	14	15	25	27
Mean age (years)	48.3	46.4	47.7	46.7	47.6	50.3	48.7
Mean weight (kg)	83.4	83.4	79.9	80	78.4	81.4	88.5
HCV subtype (%)							
1a	51	63	51	53	58	44	66
1b	40	28	36	35	34	44	31
1 (no subtype)	9	9	13	12	8	13	3
Viral load mean (log ₁₀ IU/ml)	6.53	6.64	6.53	6.54	6.53	6.43	6.47
HCV RNA > 600,000 IU/ml (%)	90	92	87	91	90	81	83
Cirrhosis (%)	8	7	7	9	6	0	7

B, boceprevir; HCV, hepatitis C virus; P, pegylated interferon α 2b; R, ribavirin.

patients were randomized to receive peginterferon α 2b, boceprevir 800 mg three times a day, and ribavirin 400–1000 mg, and this was compared with triple therapy with full-dose ribavirin (800–1400 mg) with peginterferon α 2b, and boceprevir.

The rationale for the potential benefit of the lead-in strategy with 4 weeks of peginterferon α 2b and ribavirin was based on allowing peginterferon α 2b and ribavirin to reach steady-state concentrations by week 4. This meant that boceprevir could be added when the backbone drug levels were optimized and the patient's immune system fully activated. It was hoped that this approach would minimize the time on functional monotherapy, given the relatively low barrier to resistance seen with the linear NS3 protease inhibitors, and reduce the development of drug resistance and breakthrough. In this multicenter international trial, 100 patients were enrolled in each arm in part 1 and stratified according to the presence of cirrhosis (6–9% per arm) and African American race (14–17% per arm). Demographic data from the SPRINT I study are shown in Table 1.

In all treatment arms, the addition of boceprevir improved sustained virologic response (SVR)

rates (Figure 3). In the 28-week treatment arms, SVR rates were 56% for the PR4/PRB24 lead-in arm and 54% with triple therapy (PRB28). Extending boceprevir therapy for 44 weeks (PR4/PRB44) improved the SVR rate to 75% in the peginterferon α 2b and ribavirin lead-in arm with 44 weeks of peginterferon α 2b, ribavirin, and boceprevir and 67% in the triple therapy arm with peginterferon α 2b, ribavirin, and boceprevir (PRB48) all given for 48 weeks. In addition, improved SVR rates were seen in difficult-to-treat patients. Up to 53% of black patients achieved sustained response with the addition of boceprevir. This number represents a substantial improvement over the 21–23% SVR rate that has been reported for 48 weeks of peginterferon α 2b and ribavirin [Muir *et al.* 2004; Conjeevaram *et al.* 2006]. Moreover, patients with cirrhosis also demonstrated substantial improvement in SVR rates, with rates as high as 67% reported. In part 2 of the study, low-dose ribavirin was shown to be associated with reduced SVR rates with high rates of breakthrough and relapse.

Achieving rapid virologic response (RVR) with the addition of boceprevir could also predict sustained response. Compared with the control

Figure 3. Sustained virologic response rates for the SPRINT I trial.

^aRoche COBAS TaqMan LLD <15 IU/ml; ^b $p = 0.013$; ^c $p = 0.005$; ^d $p < 0.0001$; ^e $p < 0.0001$ compared with P/R control; ^fone late relapser after follow-up week 24, not included in SVR.

B, boceprevir; HCV, hepatitis C virus; P, pegylated interferon $\alpha 2b$; R, ribavirin; SVR, sustained virologic response; wk, week.

Table 2. Effect of treatment duration on sustained virologic response.

Time to first PCR-negative HCV RNA*	P/R control, 48 weeks	P/R, 4 weeks → P/R/B, 24 weeks	P/R, 4 weeks → P/R/B, 44 weeks
	% (n/N)	% (n/N)	% (n/N)
≤4 weeks	100 (8/8)	82 (54/66)	94 (62/66)
>4 to ≤12 weeks	83 (24/29)	21 (4/19)	79 (15/19)
>12 weeks	30 (7/23)	0 (0/1)	0 (0/1)

*Time after pegylated-interferon $\alpha 2b$ plus ribavirin in control arm; time after boceprevir dosing in treatment arms.
B, boceprevir; HCV, hepatitis C virus; P, pegylated interferon $\alpha 2b$; R, ribavirin.

group of peginterferon $\alpha 2b$ and ribavirin, substantially more patients in the boceprevir treatment groups achieved RVR (week 4 of boceprevir addition), and this predicted high rates of sustained response with shorter duration of therapy. In the SPRINT I study, RVR and complete early virologic response (cEVR) were defined by the week of boceprevir therapy; therefore, the week 4 RVR and cEVR were at weeks 8 and 16 of total therapy with peginterferon $\alpha 2b$ and ribavirin. RVR rates were observed in 60% of the PR4/PRB24 arm, 39% in the triple therapy PRB28 arm, and 8% in the PR48 control arm. Similar rates were seen in the 48-week treatment arms, with an RVR rate of 64% in the PR4/PRB44 arm, and 37% in the PRB48 arm. Regardless of the treatment arm, achieving RVR predicted sustained response, with 82% of the PR4/PRB24 arm achieving SVR and 74% of the PRB28 RVR patients achieving SVR. In the PR4/PRB44 treatment arm, 94% of patients achieved an RVR at

week 4 of boceprevir, and 84% of patients in the PRB48 arm achieved sustained response. Achieving cEVR (undetectable HCV RNA at week 12 of boceprevir) also predicted sustained response. Moreover, patients who cleared the virus between weeks 4 and 12 of boceprevir therapy (late responders) were more likely to go on to achieve sustained response in the lead-in arms if they received a total of 48 weeks of therapy (Table 2). Indeed, approximately two-thirds of patients achieved undetectable HCV RNA (RVR at week 4 of boceprevir). An additional 19 patients in both lead-in arms cleared the virus between weeks 4 and 12, and in those who received extended therapy for 48 weeks, 15 of 19 went on to achieve sustained response. These results suggest that a response-guided paradigm may be appropriate for boceprevir, with those clearing the virus early requiring just 28 weeks of therapy and those who are late responders benefiting from an extension of therapy.

Figure 4. Relapse for all treatment arms in the SPRINT I trial.

^a $p = 0.0079$; ^b $p = 0.0002$ compared with P/R control.

B, boceprevir; P, pegylated interferon $\alpha 2b$; pt, patient; R, ribavirin; RVR, rapid virologic response; wk, week.

The addition of boceprevir after the 4-week lead-in period also demonstrated that SVR could be predicted by the degree of peginterferon $\alpha 2b$ /ribavirin responsiveness achieved during the initial 4 weeks of therapy. If a reduction of more than $1.5 \log_{10}$ was achieved during the lead-in period, high rates of SVR were achieved with boceprevir addition regardless of treatment duration. However, even patients whose condition responded poorly to peginterferon $\alpha 2b$ /ribavirin with less than $1 \log_{10}$ reduction at week 4 of the lead-in period could achieve SVR with boceprevir addition. A total treatment duration of 48 weeks led to better SVR rates (55%) than the 28-week treatment duration (28%) in these patients. Thus the lead-in period may be used to assess the degree of peginterferon $\alpha 2b$ /ribavirin responsiveness and could help predict SVR with boceprevir addition.

The relapse rates in the 28-week treatment arms were comparable and the presence of RVR markedly reduced relapse rates (Figure 4). In the 48-week treatment arms, a lower relapse rate was noted in the peginterferon $\alpha 2b$ /ribavirin lead-in arm, although it was not statistically superior to the non-lead-in arm. Similarly, a modest reduction in viral breakthrough in the lead-in arms was noted compared with the no-lead-in arm, though this did not reach statistical significance.

The most common side effects of boceprevir were anemia, nausea, vomiting, and dysgeusia, and treatment discontinuation rates were higher in the boceprevir groups compared with the standard

therapy groups (26–40% versus 15%). The majority of hemoglobin reductions were grade 1 and 2 according to the World Health Organization criteria, and no increase in skin or subcutaneous disorders was noted. Treatment discontinuation for anemia was rare in all boceprevir-containing arms. A recent study suggested that anemia may represent a surrogate marker of ribavirin exposure in patients with genotype 1 infection, with higher rates of anemia correlating with sustained response [Sulkowski *et al.* 2010]. In the SPRINT I study, in which erythropoietin was used to manage anemia at the investigator's discretion, the development of anemia and erythropoietin use were associated with improved SVR rates (Figure 5). A large trial is currently under way and will explore the role of erythropoietin α administration versus ribavirin dose reduction as an anemia management strategy in patients receiving peginterferon $\alpha 2b$, ribavirin, and boceprevir.

Phase III studies

The two large phase III trials of boceprevir, SPRINT II for patients who are treatment naïve, and RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2, NCT00708500) for those whose condition has not responded, have been fully enrolled. SPRINT II enrolled over 1000 patients and will test a peginterferon $\alpha 2b$ /ribavirin response-guided therapy paradigm with peginterferon $\alpha 2b$ /ribavirin lead-in period and 44 weeks of boceprevir to peginterferon $\alpha 2b$ /ribavirin control. In the

Figure 5. Sustained virologic response rates and development of anemia are shown for the lead-in arms of the SPRINT I trial.

^aOne patient in each group missing in-treatment hemoglobin values.

B, boceprevir; Epo, erythropoietin; HCV, hepatitis C virus; Hgb, hemoglobin; P, pegylated interferon α 2b; R, ribavirin; SVR, sustained virologic response; wk, week.

response-guided paradigm, patients receive 24 weeks of peginterferon α 2b, ribavirin, and boceprevir after a 4-week lead-in period, followed by a peginterferon α 2b tail without boceprevir in slow responders who do not clear the virus at week 8 and week 24 of treatment. The final results have been reported and the addition of boceprevir was found to lead to an overall SVR rate of 63–66% [Poordad *et al.* 2011b]. In this study, two cohorts were predefined as non-black and black. The SVR rate in the non-black cohort was 67% in the response-guided therapy arm *versus* 68% in the 44-week boceprevir fixed-duration arm. These rates were both significantly higher than the peginterferon α 2b/ribavirin control SVR rate of 40%. In the black cohort, the response-guided arm achieved an SVR rate of 42% *versus* 53% in the 44-week boceprevir arm, with a rate of 23% achieved in the peginterferon α 2b/ribavirin control arm. The US Food and Drug Administration approved a response-guided paradigm with boceprevir, and if HCV RNA levels are undetected at weeks 8 and 24, patients may be treated for 28 weeks. If HCV RNA is detected at week 8 and undetected at week 24, then patients should receive peginterferon α 2b/ribavirin with boceprevir for 36 weeks followed by a 12-week peginterferon α 2b/ribavirin tail for a total of 48 weeks of therapy. Patients with cirrhosis and whose condition responds poorly to peginterferon α 2b/ribavirin ($<1 \log_{10}$ reduction after lead-in

period) should receive peginterferon α 2b/ribavirin for 4 weeks, followed by 44 weeks of peginterferon α 2b/ribavirin and boceprevir.

The phase III RESPOND-2 trial also evaluated a response-guided therapy arm. The trial compared a peginterferon α 2b/ribavirin lead-in period and 32 weeks of peginterferon α 2b, ribavirin, and boceprevir, followed by a 12-week peginterferon α 2b/ribavirin tail, depending on viral response, with a 4-week peginterferon α 2b/ribavirin lead-in period and 44 weeks of peginterferon α 2b/ribavirin, and boceprevir in relapsers and partial responders to peginterferon α 2b/ribavirin. The results have been published and show that the addition of boceprevir markedly improved SVR rates in relapsers and nonresponders. Relapsers achieved an SVR rate of approximately 75%, and partial responders achieved an SVR of approximately 52% with 44 weeks of peginterferon α 2b, ribavirin, and boceprevir. Again, lower SVR rates were noted in patients whose condition poorly responded to peginterferon α 2b/ribavirin. In this study, null responders were not prospectively enrolled; however, a recent report of the PROVIDE study suggested that SVR rates with peginterferon α 2b, ribavirin, and boceprevir are comparable to SVR rates seen with the addition of telaprevir to peginterferon α 2b/ribavirin in null responders [Vierling *et al.* 2011]. The phase III trials allowed a retrospective analysis of the role of the

interleukin (IL)-28B polymorphism in patients receiving boceprevir. The recently identified IL-28 polymorphism helps predict responsiveness to pretreatment with peginterferon α 2b and ribavirin. Patients with the IL-28 CC genotype have the greatest likelihood of achieving sustained response (70–80%) with peginterferon α 2b and ribavirin, and IL-28B is the strongest pretreatment predictor of SVR in patients receiving peginterferon α 2b/ribavirin for genotype 1 infection [Thompson *et al.* 2010]. The retrospective analyses from the SPRINT II and RESPOND-2 studies suggest that patients with the IL-28 CC genotype 1 are highly likely to be treated for just 6 months with boceprevir. Interestingly, when the 4-week viral decline is analyzed, the 4-week viral load decline is a more potent predictor of SVR than IL-28B with boceprevir-based therapy [Poordad *et al.* 2011a]

Viral resistance to boceprevir

As we enter the era of direct-acting antiviral agents, clinicians will need to monitor patients for the development of resistance-associated variants when SVR is not achieved. The addition of direct-acting antiviral agents, such as boceprevir, can select for drug-resistant mutations. The early phase II RESPOND-1 study used a suboptimal dose of boceprevir without ribavirin, and high rates of viral breakthrough due to resistance-associated variants were noted. The low-dose ribavirin arm in part 2 of the SPRINT I study was associated with high rates of viral breakthrough, suggesting that full-dose ribavirin is also required for optimal response to peginterferon α 2b and ribavirin. With ideally dosed boceprevir (800 mg three times a day), peginterferon α 2b, and ribavirin and optimal response, there is viral suppression of wild-type strains with the replication of resistance-associated variants likely inhibited by the backbone of peginterferon α 2b and ribavirin. In the SPRINT I study, population sequencing of the NS3 domain demonstrated that the major mutations noted were V36M, T54S, and R155K, with minor mutations noted of T54A, V55A, R155T, A156S, V158I, and V170A. It is likely that a greater frequency of drug-resistant mutations were generated in the low-dose ribavirin arms, in which high rates of relapse and breakthrough lower sustained response rates were observed. Additional studies with final sequencing are still ongoing and the long-term clinical significance of these resistant mutations is being assessed in follow-up trials. Optimal doses of ribavirin with full-dose boceprevir is the best strategy to minimize

resistance, in combination with peginterferon α 2b. In the future, combinations of direct-acting antiviral therapies may provide the ideal treatment strategy to prevent the emergence of viral resistance as has been demonstrated in an *in vitro* study [Flint *et al.* 2009].

Conclusions

The standard therapy for HCV genotype 1 achieves SVR in approximately 50% of patients. The addition of direct-acting antiviral agents, such as boceprevir, peginterferon α 2b, and ribavirin will improve SVR rates and shorten treatment duration in patients with genotype 1 infection. Boceprevir is not approved for use in genotype 2 and 3 infection. *In vitro* and *in vivo* data have demonstrated that boceprevir has potent viral suppression, and early phase II trials have shown that the optimal boceprevir dose is 800 mg three times a day. The SPRINT I trial results have established several important findings. First, the addition of boceprevir, regardless of treatment strategy, improves SVR rates. A lead-in strategy may reduce relapse and prevent breakthrough, though the arms were not large enough to demonstrate statistical superiority. Peginterferon α 2b/ribavirin responsiveness appears to be important in achieving SVR when boceprevir is added. In the 28-week and 48-week treatment arms, SVR rates were substantially improved, and in the 48-week treatment arms there was a near doubling of the rate – 75% *versus* the peginterferon α 2b/ribavirin control SVR of 38%. Finally, response rates in African American patients with cirrhosis whose condition typically responds poorly to peginterferon α 2b/ribavirin therapy were also substantially higher. These results were confirmed in the phase III SPRINT-2 and RESPOND-2 trials. Boceprevir added to peginterferon α 2b/ribavirin improved SVR rates in patients who were treatment naïve and in those whose condition did not respond. Furthermore, boceprevir has been approved for the treatment of genotype 1 hepatitis C in the USA.

As with the development of other direct-acting antiviral agents, the emergence of resistance to protease inhibitors will be an important consideration. Data suggest that these drug-resistant mutations retain peginterferon α 2b/ribavirin sensitivity. Optimally dosed boceprevir and ribavirin will minimize the development of these resistant strains. Finally, *in vitro* data on boceprevir and a polymerase inhibitor, and recently published data

suggest that a combination of protease and polymerase inhibitors may be a successful strategy to reduce the risk of viral development of resistance. In addition, a combination of multiple direct-acting antiviral agents will be an emerging strategy to improve SVR rates and limit the emergence of resistance [Flint *et al.* 2009; Gane *et al.* 2010]. Moving forward, the addition of boceprevir to peginterferon α 2b and ribavirin represents an important advance in the treatment of patients with genotype 1 hepatitis C.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Paul Kwo, MD has disclosed that he has received consulting fees from Abbott, Anadys, Boehringer-Ingelheim, Bristol Myers Squibb, Gilead, Johnson and Johnson, Merck, Novartis, Vertex; he also received fees for Non-CME/CE services directly from Bristol Myers Squibb, Gilead, Merck, Roche and Vertex; and contracted research funding from Abbott, Anadys, Bayer, Bristol Myers Squibb, Conatus, Glaxo Smith Kline, Gilead, Merck, Novartis, Roche, and Vertex.

References

- Alter, M.J. (2007) Epidemiology of hepatitis C virus infection. *World J Gastroenterol* 13: 2436–2441.
- Bartenschlager, R. (2002) Hepatitis C virus replicons: potential role for drug development. *Nat Rev Drug Discov* 1: 911–916.
- Bartenschlager, R. and Lohmann, V. (2000) Replication of hepatitis C virus. *J Gen Virol* 81: 1631–1648.
- Conjeevaram, H.S., Fried, M.W., Jeffers, L.J., Terrault, N.A., Wiley-Lucas, T.E., Afdhal, N. *et al.* (2006) Peginterferon and ribavirin treatment in African American and Caucasian American patients with hepatitis C genotype 1. *Gastroenterology* 131: 470–477.
- Davis, G.L., Alter, M.J., El-Serag, H., Poynard, T. and Jennings, L.W. (2010) Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* 138: 513–521.
- Diago, M., Shiffman, M.L., Bronowicki, J.P., Zeuzem, S., Rodriguez-Torres, M., Pappas, S.C. *et al.* (2010) Identifying hepatitis C virus genotype 2/3 patients who can receive a 16-week abbreviated course of peginterferon alfa-2a (40KD) plus ribavirin. *Hepatology* 51: 1897–1903.
- El-Serag, H.B. and Rudolph, K.L. (2007) Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 132: 2557–2576.
- Ferenci, P., Laferl, H., Scherzer, T.M., Maieron, A., Hofer, H., Stauber, R. *et al.* (2010) Peginterferon alfa-2a/ribavirin for 48 or 72 weeks in hepatitis C genotypes 1 and 4 patients with slow virologic response. *Gastroenterology* 138: 503–512.
- Flint, M., Mullen, S., Deatly, A.M., Chen, W., Miller, L.Z., Ralston, R. *et al.* (2009) Selection and characterization of hepatitis C virus replicons dually resistant to the polymerase and protease inhibitors HCV-796 and boceprevir (SCH 503034). *Antimicrob Agents Chemother* 53: 401–411.
- Gane, E.J., Roberts, S.K., Stedman, C.A., Angus, P.W., Ritchie, B., Elston, R. *et al.* (2010) Oral combination therapy with a nucleoside polymerase inhibitor (RG7128) and danoprevir for chronic hepatitis C genotype 1 infection (INFORM-1): a randomised, double-blind, placebo-controlled, dose-escalation trial. *Lancet* 376: 1467–1475.
- Hoofnagle, J.H. and Seeff, L.B. (2006) Peginterferon and ribavirin for chronic hepatitis C [see comment]. *N Engl J Med* 355: 2444–2451.
- Kwo, P.Y., Lawitz, E.J., McCone, J., Schiff, E.R., Vierling, J.M., Pound, D. *et al.* (2010) Efficacy of boceprevir, an NS3 protease inhibitor, in combination with peginterferon alfa-2b and ribavirin in treatment-naïve patients with genotype 1 hepatitis C infection (SPRINT-1): an open-label, randomised, multicentre phase 2 trial. *Lancet* 376: 705–716.
- Lauer, G. and Walker, B. (2001a) Hepatitis C virus infection. *N Engl J Med* 345: 41–52.
- Lauer, G.M. and Walker, B.D. (2001b) Hepatitis C virus infection. *N Engl J Med* 345: 41–52.
- Lohmann, V., Körner, F., Koch, J.O., Herian, U., Theilmann, L. and Bartenschlager, R. (1999) Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 285: 110–113.
- Malcolm, B.A., Liu, R., Lahser, F., Agrawal, S., Belanger, B., Butkiewicz, N. *et al.* (2006) SCH 503034, a mechanism-based inhibitor of hepatitis C virus NS3 protease, suppresses polyprotein maturation and enhances the antiviral activity of alpha interferon in replicon cells. *Antimicrob Agents Chemother* 50: 1013–1020.
- McHutchison, J.G. and Bacon, B.R. (2005) Chronic hepatitis C: an age wave of disease burden. *Am J Manag Care* 11 (10 Suppl.): S286–S295; quiz S307–S311.

- Muir, A.J., Bornstein, J.D., Killenberg, P.G. and Atlantic Coast Hepatitis Treatment Group (2004) Peginterferon alfa-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-Hispanic whites [see comment]. *N Engl J Med* 350: 2265–2271 [erratum in *N Engl J Med* 2004 351: 1268].
- National Institutes of Health (2002) National Institutes of Health Consensus Development Conference Statement: Management of hepatitis C 2002 (June 10–12, 2002). *Gastroenterology* 123: 2082–2099.
- Poordad, F., Bronowicki, J.P., Gordon, S.C., Zeuzem, S., Jacobson, I.M., Sulkowski, M.S. *et al.* (2011a) IL28B polymorphism predicts virologic response in patients with hepatitis C genotype 1 treated with boceprevir (Boc) combination therapy. *J Hepatol* 54 (Suppl. 1): S6–S6.
- Poordad, F., McCone, J., Jr., Bacon, B.R., Bruno, S., Manns, M.P., Sulkowski, M.S. *et al.* (2011b) Boceprevir for untreated chronic HCV genotype 1 infection. *N Engl J Med* 364: 1195–1206.
- Poynard, T., McHutchison, J., Davis, G.L., Esteban-Mur, R., Goodman, Z., Bedossa, P. *et al.* (2000) Impact of interferon alfa-2b and ribavirin on progression of liver fibrosis in patients with chronic hepatitis C. *Hepatology* 32: 1131–1137.
- Rodriguez-Torres, M., Jeffers, L.J., Sheikh, M.Y., Rossaro, L., Ankoma-Sey, V., Hamzeh, F.M. *et al.* (2009) Peginterferon alfa-2a and ribavirin in Latino and non-Latino whites with hepatitis C. *N Engl J Med* 360: 257–267.
- Sarrazin, C., Rouzier, R., Wagner, F., Forestier, N., Larrey, D., Gupta, S.K. *et al.* (2007) SCH 503034, a novel hepatitis C virus protease inhibitor, plus pegylated interferon alpha-2b for genotype 1 nonresponders. *Gastroenterology* 132: 1270–1278.
- Schiff, E., Poordad, F.F., Jacobson, I.M., Flamm, S.L., Bacon, B.R., Lawitz, E.J. *et al.* (2008) Role of interferon response during RE-Treatment of null responders with boceprevir combination therapy: results of phase II trial. *Gastroenterology* 134: A755.
- Shiffman, M.L., Suter, F., Bacon, B.R., Nelson, D., Harley, H., Sola, R. *et al.* (2007) Peginterferon alfa-2a and ribavirin for 16 or 24 weeks in HCV genotype 2 or 3. *N Engl J Med* 357: 124–134.
- Sulkowski, M.S., Shiffman, M.L., Afdhal, N.H., Reddy, K.R., McCone, J., Lee, W.M. *et al.* (2010) Hepatitis C virus treatment-related anemia is associated with higher sustained virologic response rate. *Gastroenterology* 139: 1602–1611.
- Thompson, A.J., Muir, A.J., Sulkowski, M.S., Ge, D., Fellay, J., Shianna, K.V. *et al.* (2010) Interleukin-28B polymorphism improves viral kinetics and is the strongest pretreatment predictor of sustained virologic response in genotype 1 hepatitis C virus. *Gastroenterology* 139: 120–129.
- Vierling, J., Flamm, S.L., Gordon, S.C., Lawitz, E., Bronowicki, J.P., Davis, M. *et al.* (2011) Efficacy of boceprevir in prior null responders to peginterferon/ribavirin: the PROVIDE study. *Hepatology* 54 (Suppl. 1): 796A.