Review of boceprevir and telaprevir for the treatment of chronic hepatitis C

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OBJECTIVE: To summarize and evaluate the published literature pertaining to boceprevir and telaprevir, and to provide clinicians with suggestions for use in patients with chronic hepatitis C infection.
METHODS: A standardized search strategy was performed using the MEDLINE, EMBASE, Google Scholar and International Pharmaceuticals Abstracts databases using the search terms "boceprevir", "telaprevir", "boceprevir and hepatitis C" and "telaprevir and hepatitis C". A manual search of references was performed to identify articles missed by the electronic search. Studies were included in the review if they assessed either boceprevir or telaprevir in comparison with standard of care in chronic hepatitis C patients.
RESULTS: The studies identified assessed boceprevir and telaprevir in genotype-1 hepatitis C patients. In both treatment-naive and treatment-experienced patients, sustained virological response rates were achieved more often with boceprevir or telaprevir in combination with pegylated interferon and ribavirin compared with pegylated interferon and ribavirin alone. Both medications were well tolerated, with anemia presenting as the most treatment-limiting adverse effect.
CONCLUSIONS: Boceprevir and telaprevir will revolutionize the management of hepatitis C genotype 1 patients and will most likely decrease the burden of end-stage disease worldwide. However, current clinical limitations include establishing appropriate and cost-effective treatment durations, and use in special populations such as transplant patients and patients coinfected with HIV. Future research will need to clarify these clinical obstacles to clearly define the role of these agents in hepatitis C management.

Key Words: *Boceprevir; Hepatitis C; Protease inhibitors; Telaprevir; Viral hepatitis*

L'analyse du bocéprévir et du télaprévir pour le traitement de l'hépatite C chronique

OBJECTIF : Résumer et évaluer les publications relatives au bocéprévir et au télaprévir et fournir aux cliniciens des suggestions utiles auprès des patients atteints d'une infection chronique par l'hépatite C.
MÉTHODOLOGIE : Les chercheurs ont utilisé une stratégie de recherche standardisée dans les bases de données MEDLINE, EMBASE, Google Scholar et International Pharmaceuticals Abstracts, au moyen des termes de recherche *boceprevir, telaprevir* et *hepatitis C*. Ils ont procédé à une recherche manuelle des références afin de repérer les articles omis par la recherche électronique. Ils ont inclus les études dans l'analyse lorsqu'elles évaluaient soit le bocéprévir, soit le télaprévir par rapport aux normes de soins chez les patients atteints d'hépatite C chronique.
RÉSULTATS : Les études retenues évaluaient le bocéprévir et le télaprévir chez des patients atteints d'hépatite C de génotype 1. Tant chez les patients naïfs au traitement que chez ceux qui en avaient déjà subi, on parvenait plus souvent à des taux de réponse virologique soutenue grâce au bocéprévir ou au télaprévir associé à de l'interféron pégylé et à de la ribavirin equ'associé seulement à de l'interféron pégylé ou de la ribavirine. Les deux médicaments étaient bien tolérés, l'anémie représentant l'effet indésirable le plus limitatif du traitement.
CONCLUSIONS : Le bocéprévir et le télaprévir révolutionneront la prise en charge des patients atteints d'hépatite C de génotype 1 et réduiront tout probablement le fardeau de la maladie en phase terminale de par le monde. Cependant, les limites cliniques actuelles incluent la détermination de la durée pertinente et rentable des traitements et leur utilisation dans des populations ayant des besoins particuliers, telles que les patients greffés ou co-infectés par le VIH. Les futures recherches devront préciser ces obstacles cliniques afin de définir clairement le rôle de ces agents dans la prise en charge de l'hépatite C.

Hepatitis C is a global health burden. Although exact estimates are unknown, millions of people worldwide are infected with the hepatitis C virus (HCV). Fifteen per cent to 30% of patients infected with chronic HCV will develop cirrhosis, often leading to transplantation or death (1). Furthermore, hepatitis C is associated with a 1% to 4% annual risk of developing hepatocellular carcinoma (2). These complications are associated with enormous burdens to health care systems worldwide, and the negative consequences of the disease create high levels of physical and emotional stress for patients, families and caregivers.

Until August 2011, the commercially available treatment options for HCV infection were limited to interferon (IFN)-based therapies and ribavirin for all genotypes. The primary end point of therapy, the sustained virological response (SVR), defined as HCV RNA undetectablity six months post-therapy, is well-recognized to be essentially a clinical cure; a definitive study reported a 99.1% durability of the SVR in 1343 patients over a mean of approximately four years (3). Clinical cure with combination pegylated IFN (pegIFN) and ribavirin therapy is possible, with 40% to 50% of genotype 1-infected patients and 70% to 80% of genotypes 2/3-infected patients experiencing this benefit, with the remainder either achieving no response or experiencing relapse (4,5). For patients who do not achieve clinical cure, reported success rates with retreatment with a second course of pegIFN and ribavirin are reasonable (68% to 77%); however, for relapsed patients (those who had initially responded), success rates are dismal (17%) for initial nonresponders (6). It is, therefore, important that new therapies be developed and become publically accessible to increase the rates of treatment success in this heavily burdened population.

Two new oral agents (boceprevir [Victrelis, Merck Canada] and telaprevir [Incivek, Vertex Pharmaceuticals Ltd, Canada]) have been developed and received approval from Health Canada in August 2011, and will soon be entering clinical practice. Both agents are inhibitors of the HCV NS3/4A protease and inhibit viral replication in HCV-infected host cells, and are specific for genotype 1. These agents are the first to be approved among the many other protease and polymerase inhibitors currently undergoing clinical trials (7). The

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incorporation of these agents into clinical practice will forever change HCV management. By using these medications appropriately, clinicians will maximize treatment success and minimize patient harm. As with all new medications, however, it is important for clinicians to be aware of associated efficacy, toxicity and clinical controversies. The objective of the present review is to summarize and evaluate the published literature pertaining to boceprevir and telaprevir, and to provide clinicians with suggestions for use in patients with chronic hepatitis C infection.

METHODS

A standardized search strategy was performed using the MEDLINE (to September 2011), EMBASE (to September 2011), Google, Google Scholar and the International Pharmaceutical Abstracts (to September 2011) databases using the search terms "boceprevir", "telaprevir", "boceprevir and hepatitis C" and "telaprevir and hepatitis C". Clinical studies that assessed boceprevir and telaprevir in treatment-naive and treatment-experienced patients were identified, as were studies that assessed pharmacology and pharmacokinetics. Finally, a manual search of the reference lists of identified articles was performed to capture relevant articles missed by the electronic search.

Studies were included in the review if they assessed either boceprevir or telaprevir in comparison with standard of care (SOC) in chronic hepatitis C patients. All HCV genotypes and patient populations were included. Also included were conference proceedings when no published studies were available for analysis.

RESULTS

Pharmacology

Both boceprevir and telaprevir are NS3/4A protease inhibitors. The NS3 protease is an enzyme that catalyzes the post-transcriptional processing of proteins important for viral replication. NS4A is a cofactor that works with NS3 to expedite this process. Boceprevir and telaprevir directly inhibit this enzyme/cofactor complex and, therefore, reduce viral replication (8). Inhibiting NS3 may also restore virally suppressed IFN pathways that are important for initiating endogenous antiviral mechanisms (9).

Pharmacokinetics

Boceprevir is absorbed following oral administration with a median T_{max} of 2 h. Steady state is achieved after approximately 1 day of three times a day dosing. Food enhances absorption by up to 60% at a dosing regimen of 800 mg three times daily. The mean apparent volume of distribution is 772 L and it is not highly protein bound. Boceprevir is primarily metabolized by the aldoketoreductase-mediated pathway to inactive metabolites. It is also a substrate of CYP3A and is an inhibitor of this enzyme. It has a mean plasma half-life of 3.4 h and is minimally eliminated in the urine (10).

Telaprevir is administered orally and is a substrate of the efflux transporter p-glycoprotein. Food increases absorption and it is recommended to be taken with food to maximize this benefit. It is minimally bound to plasma proteins and has an approximate apparent volume of distribution of 252 L. It is extensively metabolized through multiple hepatic pathways including hydrolysis, reduction and oxidative metabolism by CYP3A. It also acts a strong inhibitor of the CYP3A4 enzyme. It is primarily eliminated in the feces and has an average steady-state plasma half-life of 8 h to 11 h (11).

Efficacy

Previously, the SOC for treating chronic HCV infection was the combination of pegIFN and ribavirin (1). There are two pegIFN alternatives available: alpha-2a and alpha-2b. Both agents are similarly effective for treating chronic hepatitis C infection (12). The overall goal of treatment is the achievement of an SVR. This response is defined as an undetectable HCV RNA level six months after the completion of treatment. Patients who achieve this marker are highly unlikely to relapse and can be considered 'clinically cured'. While it is possible to achieve this outcome with SOC, only approximately 40% to 50% of patients infected with genotype 1 HCV are successful (4,5,12).

Boceprevir

Phase 1 and phase 2 trials established the efficacy and optimal dosing of boceprevir in combination with pegIFN and ribavirin for both treatment-naive and treatment-experienced patients (13,14). Interestingly, the use of a four-week lead-in phase with SOC before initiating boceprevir achieved greater response rates in treatment-naive patients in the Serine Protease Inhibitor Therapy 1 (SPRINT-1) trial (14). The lead-in phase theoretically decreases rates of resistance by initiating the protease inhibitor at lower viral loads. From a practical, cost-effective perspective, this strategy may guide response-guided treatment decisions by identifying those who respond early to pegIFN and ribavirin treatment, and have a strong likelihood of achieving SVR without boceprevir. Patients who are HCV undetectable at week 4 of pegIFN and ribavirin treatment (ie, rapid virological response) are well recognized to have an excellent likelihood (89%) of achieving an SVR with only 24 weeks of antiviral therapy (15,16). It should be strongly noted, however, that such a strategy awaits further clinical study. Subsequent phase 3 trials were designed to include lead-in phases and used a dose of boceprevir 800 mg three times daily with food. Early studies also provided support for response-guided boceprevir, pegIFN and ribavirin treatment. That is, determining duration of therapy by assessing rapid and early virological responses (defined as achieving reductions/undetectable viral loads at weeks 4 and 12, respectively). As discussed below, phase 3 trials included arms that assessed treatment responses when therapy was guided using this principle, and all used pegIFN α-2b as the pegIFN in the SOC arm.

A summary of phase 3 studies is presented in Table 1. The SPRINT-2 trial assessed boceprevir in treatment-naive genotype-1-infected patients (17). All patients were given pegIFN and ribavirin during a four-week lead-in phase. Following the lead-in phase, patients began treatment in one of three previously randomized groups. The control group received placebo in addition to pegIFN and ribavirin for 44 weeks after the lead-in period, for a total treatment duration of 48 weeks. The response-guided treatment group received boceprevir in addition to pegIFN and ribavirin for weeks 4 through 28. Individuals in this group, who had detectable virus at any point between weeks 8 through 24, received a course of pegIFN and ribavirin and placebo for an additional 20 weeks (total of 48 weeks), and those with undetectable virus at weeks 8 to 24 discontinued treatment at week 28. The treatment group received boceprevir in addition to pegIFN and ribavirin for 44 weeks, giving a total treatment period of 48 weeks. Patients were analyzed based on race (African descent and non-African descent) to compare treatment responses between racial cohorts.

The results significantly favoured treatment with boceprevir. Approximately 40% of patients in the control group achieved an SVR, compared with responses of 67% to 68% in the response-guided group and treatment group for patients of non-African descent. For the cohort of African descent, SVR was achieved in 23% of control patients, while the boceprevir-treated groups achieved response rates of 42% and 53%. An interesting finding of this study was the similar response rates between the response-guided treatment group and the non-response-guided treatment group, meaning that response-guided treatment should be considered for patients responding early to boceprevir, resulting in a shorter treatment duration. Predictors of achieving an SVR were similar between the treatment groups. These include a milder fibrosis score compared with cirrhotic or precirrhotic patients, or ≥ 1 $\log_{10}$ IU/mL decrease in the HCV RNA level at the end of the four-week lead-in phase, and viral load in patients with a viral load $\leq$400,000 IU/mL performing less well than those with a viral load >400,000 IU/mL (17).

The Retreatment with HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol 2 (RESPOND-2) trial was a phase 3 study assessing boceprevir in genotype 1 patients who had failed previous treatment with pegIFN and ribavirin (18). This study enrolled both relapsers (ie, patients who were HCV RNA undetectable at the end of therapy but relapsed subsequently, and nonresponders [patients who did not achieve an end-of-treatment response]). The nonresponders enrolled

TABLE 1
Summary of phase 3 studies of boceprevir and telaprevir

Trial (reference)	Population	Mean age, years	Groups	Primary outcome	Patients achieving SVR, %
Boceprevir					
SPRINT-2 (17)	Treatment naive cHCV-1 Nonblack cohort: n=938; black cohort: n=159	49.3	Control: Peginterferon α-2b 1.5 µg/kg subcutaneously once weekly + ribavirin 600–1400 mg orally per day (SOC) for 48 weeks RGT: SOC × 4 weeks, then SOC + boceprevir 800 mg three times daily × 24 weeks. If virus was undetectable throughout weeks 8–24, treatment stopped at 28 weeks. If detectable during weeks 8–24, SOC + placebo x 20 weeks (total duration of 48 weeks) TG: SOC × 4 weeks, then SOC + boceprevir 800 mg three times daily × 44 weeks	SVR	Nonblack cohort: Control: 40; RGT: 67; TG: 68 Black cohort: Control: 23; RGT: 42; TG: 53 Combined black and nonblack cohorts: Control: 38; RGT: 63; TG: 66
RESPOND-2 (18)	Retreatment of cHCV-1 previous nonresponders or relapsers, n=403	52.7	Control: Peginterferon α-2b 1.5 µg/kg subcutaneously once weekly + ribavirin 600–1400 mg orally per day for 48 weeks RGT: SOC × 4 weeks, then SOC + boceprevir 800 mg three times daily × 32 weeks. If virus was undetectable at weeks 8 and 12, treatment stopped at 36 weeks. If detectable at weeks 8 and 12, SOC + placebo x 12 additional weeks (total duration of 48 weeks) TG: SOC × 4 weeks, then SOC + boceprevir 800 mg three times daily × 44 weeks	SVR	Control: 21 RGT: 59 TG: 66
Telaprevir					
ADVANCE (26)	Treatment naive cHVC-1, n=1088	49 (median)	Control: Peginterferon α-2a 180 µg subcutaneously once weekly + ribavirin 1000–1200 mg orally per day (SOC) for 48 weeks RGT: Group 1: SOC + telaprevir 750 mg three times daily × 8 weeks, then placebo + SOC × 4 weeks, then SOC alone × 12 weeks if RNA undetectable at weeks 4 and 12. If detectable at either week 4 or 12, SOC alone for 36 additional weeks Group 2: SOC + telaprevir 750 mg three times daily × 12 weeks and then SOC alone × 12 weeks if RNA undetectable at weeks 4 and 12. If detectable at either week 4 or 12, SOC given alone for 36 additional weeks	SVR	Control: 44 Group 1: 69 Group 2: 75
REALIZE (27)	Retreatment of cHCV-1 previous nonresponders or relapsers	51	Control: Placebo + peginterferon α-2a 180 µg subcutaneously once weekly + ribavirin 1000–1200 mg orally per day (SOC) for 48 weeks Non-lead-in: Telaprevir 750 mg three times daily + SOC × 12 weeks, then placebo + SOC × 4 weeks, then SOC alone × 32 weeks Lead-in: Placebo + SOC × 4 weeks, then telaprevir 750 mg three times daily + SOC × 12 weeks, then SOC alone × 32 weeks	SVR	Control: 15 Non-lead-in: 64 Lead-in: 66

ADVANCE A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C; cHCV-1 Chronic hepatitis C virus genotype 1; REALIZE A Randomized, Double-blind, Placebo-controlled, Phase III Trial of 2 Regimens of Telaprevir (With and Without Delayed Start) Combined With Pegylated Interferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Subjects With Chronic, Genotype 1, Hepatitis C Infection Who Failed Prior Standard Treatment RESPOND Retreatment with HCV Serine Protease Inhibitor Boceprevir and Pegintron/Rebetol; RGT Response-guided treatment; SOC Standard of care; SPRINT Serine Protease Inhibitor Therapy; SVR Sustained virological response; TG Treatment group

all demonstrated a 2 $\log_{10}$ decrease in HCV RNA at week 12 of their original pegIFN and ribavirin therapy but were HCV RNA detectable throughout therapy (ie, defined as partial responders). Similar to SPRINT-2, patients underwent a four-week lead-in period in which they received pegIFN and ribavirin. At four weeks, patients started treatment in one of three previously randomized groups. The control group received pegIFN and ribavirin in addition to placebo for 44 weeks, giving 48 weeks of total treatment. The response-guided treatment group received boceprevir in addition to pegIFN and ribavirin for 32 weeks (total treatment period of 36 weeks). Those with undetectable HCV RNA at weeks 8 and 12 discontinued therapy at 36 weeks. Those who had detectable HCV RNA at week 8 but undetectable at week 12 continued with placebo in addition to pegIFN and ribavirin for an additional 12 weeks, giving a total treatment duration of 48 weeks. The treatment group received boceprevir in addition to pegIFN and ribavirin for 44 weeks, giving a total treatment duration of 48 weeks.

Results, again, significantly favoured the use of boceprevir in this difficult-to-treat population. When assessing all previously treated patients, the control group achieved an SVR rate of 21%, which was expected based on previous studies with pegIFN and ribavirin in treatment-resistant patients. The response-guided treatment group and non-response-guided treatment group achieved SVR responses of 59% and 66%, respectively. Previous relapse patients showed greater response rates in all groups compared with previous nonresponders (29%, 69% and 75%, versus 7%, 40% and 52% in control, response-guided and non-response-guided groups, respectively. Although more patients in the non-response-guided treatment group achieved an SVR compared with the response-guided treatment group, this was not statistically significant. Five factors associated with achieving an SVR were: assignment to a boceprevir group; previous relapse versus nonresponse; low viral load at baseline; absence of cirrhosis; and >1 $\log_{10}$ IU/mL decrease in HCV RNA levels at week 4 (18).

Telaprevir

Phase 1 and phase 2 trials established efficacy in a daily dosage regimen of 750 mg three times a day of telaprevir in both treatment-naive and treatment-experienced patients (19-25). Because pegIFN and ribavirin are associated with many dose- and duration-limiting adverse events, phase 2 trials assessed whether telaprevir could be combined with pegIFN alone without coadministration of ribavirin. The Protease Inhibition for Viral Evaluation 2 (PROVE-2) trial found that lower rates of SVR were achieved when ribavirin was excluded from treatment regimens, 36% in the telapravir, pegIFN 12-week arm compared with 60% in the telaprevir, pegIFN and ribavirin 12-week arm (25). Therefore, all phase 3 trials assessed the use of telaprevir in combination with both pegIFN α-2a and ribavirin.

A summary of phase 3 studies is presented in Table 1. A Phase 3 Study of 2 Dose Regimens of Telaprevir in Combination With Peginterferon Alfa-2a (Pegasys®) and Ribavirin (Copegus®) in Treatment-Naïve Subjects with Genotype 1 Chronic Hepatitis C (ADVANCE) was a phase 3 study that assessed telaprevir in treatment-naive, chronic genotype 1 hepatitis C-infected patients (26). Patients were randomly assigned to one of three groups. The control group received pegIFN and ribavirin plus placebo for 12 weeks, followed by pegIFN and ribavirin alone for 36 additional weeks (total treatment duration of 48 weeks). Group 1 was a response-guided treatment group that received telaprevir plus pegIFN and ribavirin for eight weeks, followed by four weeks of placebo plus pegIFN and ribavirin; group 2 was a response-guided treatment group that received telaprevir plus pegIFN and ribavirin for 12 weeks. Individuals in groups 1 and 2 who achieved undetectable HCV RNA levels at weeks 4 and 12 received 12 additional weeks with pegIFN and ribavirin, for a total treatment duration of 24 weeks. Those who had detectable HCV RNA levels at either week 4 or 12 received 36 additional weeks with pegIFN and ribavirin, for a total treatment duration of 48 weeks.

Patients randomly assigned to telaprevir achieved significantly greater SVR rates than those receiving pegIFN and ribavirin. Forty-four per cent of patients in the control group, 69% in group 1 and 75% in group 2 achieved an SVR. When comparing groups 1 and 2, more patients experienced virological failure in the eight-week telaprevir group than in the 12-week telaprevir group (10% versus 5%, respectively). Telaprevir treatment was also associated with greater responses in patients of African descent, those with HCV RNA levels >800,000 IU/mL at baseline, and those with bridging fibrosis or cirrhosis compared with pegIFN and ribavirin alone. Viral load did not appear to affect the likelihood of SVR in the telapravir arms (26).

A Randomized, Double-blind, Placebo-controlled, Phase III Trial of 2 Regimens of Telaprevir (With and Without Delayed Start) Combined With Pegylated Interferon Alfa-2a (Pegasys) and Ribavirin (Copegus) in Subjects With Chronic, Genotype 1, Hepatitis C Infection Who Failed Prior Standard Treatment trial (REALIZE) was a phase 3 study that assessed telaprevir for the retreatment of hepatitis C in patients who had previously not responded to pegIFN and ribavirin, or who experienced a relapse (27). Similar to the boceprevir RESPOND study (14), the REALIZE study included patients who had relapsed after previous pegIFN and ribavirin treatment, and nonresponders to previous therapy. A methodological difference, however, was in the nonresponder patients. The REALIZE study accepted patients who both had achieved a 2 $\log_{10}$ decrease at week 12 of therapy but failed to subsequently achieve undetectable HCV RNA (ie, partial responders) and patients who did not achieve a 2 $\log_{10}$ decrease at week 12 (ie, defined as null responders). Patients were randomly assigned to one of three groups. The control group received placebo and pegIFN and ribavirin for 16 weeks, and then continued on pegIFN and ribavirin for an additional 32 weeks. The nonlead-in treatment group received telaprevir and pegIFN and ribavirin for 12 weeks, and then received placebo plus pegIFN and ribavirin for four weeks and then SOC alone for 32 weeks. Pateints in the lead-in treatment group received placebo in addition to pegIFN and ribavirin for four weeks, followed by 12 weeks of telaprevir plus pegIFN and ribavirin, then pegIFN and ribavirin alone for 32 weeks. The purpose of the lead-in phase was to determine whether greater SVR rates were achieved using lead-in periods, similar to what was previously established with boceprevir.

Results were assessed according to the subtype of previous treatment failure. In patients with previous relapse, the addition of telaprevir to pegIFN and ribavirin resulted in achievement of SVR in 83% to 88% of patients compared with 24% in the control group. Similar response rates were achieved regardless of lead-in phase allocation. In previous nonresponders or partial responders, SVR was achieved in 41% of those randomly assigned to either telaprevir group, compared with 9% of those receiving pegIFN and ribavirin alone. Among the nonresponder to previous therapy patients, 54% to 59% of partial responders achieved an SVR, whereas only 29% to 33% of null responders achieved an SVR. In particular, the likelihood of cirrhotic null responders achieving an SVR with telaprevir was very low. Overall, there were also fewer relapses and virological failures documented in the telaprevir groups compared with the pegIFN and ribavirin group (27). It was shown that patients with higher baseline viral loads and a more advanced degree of cirrhosis were more difficult to cure.

Subsequent to the publication of the ADVANCE study (26), the telaprevir product monograph (Incivik Prescription Information, Vertex Pharmaceuticals, www.vrtx.com) stated that the SVR achieved in the ADVANCE study was 79%. The new SVR determination was allowed by the American regulatory authority, the Food and Drug Administration (FDA) based on a re-analysis that reclassifed patients who were known to have achieved an undetectable HCV RNA level post-treatment week 12, but for whom week 24 post-treatment data were unknown, as having achieved a SVR rather than being declared treatment failures as per the original intention-to-treat principle. The FDA also allowed harmonization of HCV RNA assays between the protease inhibitor clinical trials. The ADVANCE study used an HCV assay with a lower limit of detection (<10 IU/mL) to define the post-treatment response, but with the harmonization, the lower limit of quantification (<25 IU/mL) was declared to be the standard for determining undetectability (ie, patients with HCV RNA <25 IU/mL were now defined as 'undetectable', personal communication: Valerie Philippon, Medical Director, Vertex Pharmaceuticals, Cambridge, USA).

Although the dosing of telaprevir licensed by the FDA and used in the registration trials is 750 mg every 8 h, it is based on the original phase 1 study (19), which was a 14-day monotherapy study. A recent clinical trial (24) reported that a dosing regimen of 1125 mg every 12 h is as efficacious as the standard regimen of three times a day. This study, which reported SVRs of 81% to 85%, also reported no difference in outcome regardless of whether pegIFN α-2a (Pegasys, Hoffman LaRoche, USA) or pegIFN α-2b (Pegatron, Merck Inc, USA) was used in combination with ribavirin. Although this may appear to be a small clinical observation, it should be noted that pegIFN α-2a was used in the phase 2 and phase 3 clinical trials, and the outcome with pegIFN α-2b was not previously known.

Safety of protease inhibitors

Boceprevir-treated patients in the above phase 3 studies were more likely to discontinue therapy compared with the control groups. More patients in the treatment groups experienced anemia (43% to 49% versus 20% to 29%) and this was also associated with greater use of erythropoietin-stimulating agents (ESA) and transfusions (17,18). Anemia treatment was addressed by dose adjustments of ribavirin with or without the use of ESA; dose adjustments of boceprevir were prohibited. Forty-one per cent to 46% of boceprevir patients were given ESA compared with 21% to 24% of controls. Boceprevir was also associated with approximately double the rates of dysgeusia compared with controls. Other adverse effects, including rash, flu-like symptoms, fatigue and nausea, occurred similarly among all study groups.

Telaprevir-treated patients were also more likely to discontinue treatment due to adverse events versus control groups (7% to 11% versus 1%) (26,27). Gastrointestinal disorders (nausea and diarrhea),

rash, pruritus and anemia occurred significantly more frequently in patients in treatment groups compared with controls. Anemia treatment was addressed by dose adjustments of ribavirin and transfusions if required. Dose adjustments of telaprevir and the use of ESA were prohibited. The increase in anemia seen in telaprevir groups was associated with increased transfusion requirements. Other adverse events included flu-like symptoms and fatigue, but these were found at similar rates among all groups.

Drug interactions

Both boceprevir and telaprevir are substrates of CYP3A and also inhibit this enzyme (10,11). Many commonly used medications use and/or affect this metabolic pathway, and the potential for clinically significant drug interactions exists. Commonly used medications that may be affected include HMG CoA reductase inhibitors, antiretrovirals, immunosuppressants and oral contraceptives. Interactions with boceprevir are less likely due to its presence in multiple metabolic pathways, but it is known that the HIV non-nucleoside reverse transcription inhibitor efavirenz decreases C_{min}, and this combination should be avoided (10). There is also less potential for clinically significant drug interactions with oral contraceptives and may be a favoured option in females requiring contraception. The best available evidence suggests that telaprevir increases exposure to tacrolimus (28), cyclosporine (28) and atorvastatin (11), and decreases exposure to darunavir, fosamprenavir and ethinyl estradiol (11). It is, therefore, important to avoid coadministration of these agents and to use back-up contraceptive methods during treatment with telaprevir. Although the use of boceprevir/telaprevir in post-transplant hepatitis C recurrence may be very tempting, given the accelerated natural history of post-transplant HCV recurrence and the fact that HCV is the most common reason for liver transplantation in Canada (29), it should be emphasized that no clinical studies to date have been reported in the post-transplant arena, and these agents are not licensed for use post-transplant. Should clinicians choose to use these drugs off-label post-liver transplant, they should be aware that the half-life of tacrolimus is increased from 40.7 h to 196 h, and cyclosporine's half-life increases from 12 h to 42 h (28). Careful monitoring of tacrolimus/cyclosporine levels will be needed with significant dose reductions before commitment to antiviral therapy. When coadministered with efavirenz, exposure to telaprevir decreases and risk of treatment failure increases (11). Current studies are assessing optimal doses when these two agents are combined.

DISCUSSION

The addition of protease inhibitors to treatment regimens for chronic HCV will drastically change the face of the disease worldwide. It has been almost 10 years since a new treatment has been approved for HCV. Boceprevir and telaprevir are only the first of many new agents that are likely to be added to treatment regimens within the next few years.

As described above, the phase 3 trials show that both boceprevir and telaprevir are effective for treatment of genotype 1-infected patients. Efficacy is maintained regardless of previous treatment experience or race. Therefore, all patients presenting with genotype 1 infection should be considered for protease inhibitor therapy to maximize the chances of an SVR. Choosing between agents will be clinician-dependent, and should be based on expected adverse reactions, concomitant medications and each patient's medical history. It is important to note that stopping rules were in place for all phase 3 studies reviewed above. In the treatment-naive studies, standard futility rules of <2 $\log_{10}$ drop in HCV RNA levels at week 12 or positive HCV RNA at week 24 resulted in treatment discontinuation. For previously treated patients, both the telaprevir and boceprevir studies discontinued therapy if week 12 HCV RNA was not negative. For patients who fail protease inhibitor therapy, it is currently unknown whether retreatment with the same protease inhibitor, or switching to a different protease inhibitor, would result in treatment success. This question remains to be answered in clinical trials.

Unfortunately, there are no phase 3 trials reporting results from treatment in patients infected with HCV genotypes 2 and 3. According to a phase 2 study (30), these agents may be effective against genotype 2 but appear to have very limited activity against genotype 3. Because pegIFN and ribavirin treatment is associated with a treatment failure rate of approximately 20% to 30% in these populations, it is important for clinical trials to determine the efficacy of new, direct-acting, antiviral agents against genotypes 2 and 3. Because genotypes 2 and 3 are classically easier to treat compared with genotype 1, we suspect that these patients will also benefit from protease inhibitor/polymerase inhibitor therapy, which may increase success rates in these populations. It remains to be seen, however, if the smaller proportional benefit in genotypes 2/3 will be a cost-effective strategy in treatment-naive patients, or whether it would be more cost effective to reserve these treatments for pegIFN and ribavirin treatment failure.

Another point of controversy is treatment duration. It was hoped that regimens including these protease inhibitors would be amenable to shorter treatment durations. This belief has been evaluated in the summarized clinical trials as a treatment-guided response in which duration was determined based on detection of virus at time points between four and 24 weeks depending on the study. It has been shown that similar rates of SVR can be achieved using these strategies and treating for 24 to 36 weeks compared with regimens that maximize traditional treatment durations of 48 weeks (17-18,26,27). While clinicians may be uncomfortable with shorter treatment durations, the best available evidence suggests that it may be safe to do so based on these response markers. We recommend that response-guided treatment be used for patients who are interested in shorter treatment duration and those who experience toxicity from medications.

While these medications are generally well tolerated, the major limiting adverse effect appears to be anemia. Although most cases of anemia did not require intervention, first-line management of anemia in these trials, as is seen in SOC, included dose reductions of ribavirin and transfusions if required. The telaprevir trials prohibited the use of ESA, but some patients in the boceprevir trials initiated erythropoietin therapy. Clinicians need to thoroughly screen patients who are at risk of developing anemia and ensure frequent monitoring while on therapy to minimize disruptions to HCV treatment.

SUMMARY

The present review summarized the available literature with respect to boceprevir and telaprevir, and provides clinicians with insights into associated clinical controversies. The major limitation of the present review is the lack of published data available to evaluate boceprevir and telaprevir in populations other than reasonably healthy genotype 1-infected adults who meet inclusion/exclusion criteria for clinical trials and are extensively monitored by clinical research staff. Whether these excellent outcomes can be replicated in a real-world clinical setting remains to be seen. Moreover, pharmacokinetic studies are mostly limited to manufacturer data or unpublished abstracts and conference proceedings. As more experience is gained with these agents, more literature will become available to assess their role in special populations and concomitant use with interacting medications. Until then, clinicians will need to be vigilant when choosing therapy for patients, with an overall goal of maximizing efficacy and minimizing toxicity.

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