Maximizing Opportunities and Avoiding Mistakes in Triple Therapy for Hepatitis C Virus

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Abstract

Recently developed drugs and innovative strategies for the treatment of chronic infection with genotype 1 hepatitis C virus (HCV) have become the standard of care. The protease inhibitors telaprevir (Incivek) and boceprevir (Victrelis) are the first direct-acting antiviral (DAA) agents approved, and many more are being developed. These drugs substantially increased rates of sustained virologic response in treatment-naïve and -experienced patients, in conjunction with peginterferon and ribavirin (triple therapy), in phase 3 trials. The efficacy of triple therapy depends on appropriate selection of patients, although the population of patients that receive triple therapy could be expanded as the risk/benefit ratio improves. Attention to details that reflect the standard of care, such as appropriate dosing, anticipation of adverse effects, and strict adherence to stopping rules, will insure the success of these drugs and lead the way for new combination therapies.

Keywords

Hepatitis C; Boceprevir; Telaprevir; Safety; Triple Therapy

In 2011, great advances were made in the treatment of chronic infection with genotype 1 hepatitis C virus (HCV). Gastroenterologists and hepatologists now treat these patients with the immunomodulator peginterferon (PEG-IFN) and ribavirin (RBV), combined with directacting antiviral (DAA) agents. Telaprevir (Incivek; Vertex Pharmaceuticals, Inc, Cambridge, MA) and boceprevir (Victrelis; Merck & Co, Inc, Whitehouse Station, NJ) are nonstructural serine (NS3/4) protease inhibitors and the first DAAs approved for use in the United States and European Union, although many others are in the pipeline. The combination of DAAs, PEG-IFN, and RBV (triple therapy) substantially increases the rate of sustained virologic response (SVR) in treatment-naïve and –experienced patients.

Boceprevir and telaprevir stop HCV replication by inhibiting the NS3/4 protease, which is required for processing of the HCV polyprotein. These agents mimic the carboxy-terminal

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end of the NS3 protease and thereby interfere with formation of the HCV polyprotein, which blocks HCV replication.[1] Although protease inhibitors are potent antiviral agents, they must be given in combination with PEG-IFN and RBV to prevent the rapid selection of resistant variants.[2–4] Studies have shown that removal of RBV from the treatment regimen compromises efficacy, increasing the rate of virologic breakthrough.[5] Optimizing the rates of SVR to these drugs requires strategies to promote appropriate use and to avoid misuse of these drugs.

Triple Therapy Increases Rates of SVR for All Populations

Five distinct phase 3 trials have been performed with boceprevir and telaprevir (Table 1). For treatment-naïve patients, the serine protease inhibitor therapy-2 (SPRINT-2)[6] trial examined the effects of PEG-IFN α-2b, RBV, and boceprevir, whereas the A new direction in HCV care: astudy of treatment naïve hepatitis c patient with telaprevir (ADVANCE)[7] and illustrating the effects of combinatherapy with telaprevir (ILLUMINATE)[8] studies investigated the effects of PEG-IFN α-2a, RBV, and telaprevir. Treatment-experienced patients were included in retreatment with HCV serine protease inhibitor boceprevir and pegIntron/rebetol-2 (RESPOND-2) study,[9] in which they received boceprevir, and in the retreatment of patients with telaprevir based regimen to optimize outcomes (REALIZE) study,[10] in which they received telaprevir. Each trial reported improved efficacy compared with the standard of care (SOC) and demonstrated the opportunity to increase rates of curing HCV infection and shortening the duration of therapy for selected patients.

SPRINT-2 included separate cohorts of black and non-black patients and had a 4-week lead-in phase, in which patients were given PEG-IFN α-2b and RBV before triple therapy was initiated with boceprevir. Patients were randomly assigned to groups given either the SOC (48 weeks of PEG-IFN α-2b and RBV), boceprevir for 44 weeks with a fixed duration of PEG-IFN α-2b and RBV, or response-guided therapy (RGT), in which they received 24 weeks of boceprevir in a total treatment duration of 28 weeks. Patients who received RGT and had an undetectable level of HCV RNA at weeks 8 and 24 received no further therapy. If HCV RNA was detected, they received PEG-IFN α-2b and RBV, plus a placebo, for an additional 20 weeks (total treatment duration of 48 weeks). In the non-black patients cohort, patients in the fixed duration treatment group had an SVR rate of 68%, comparable with those who received RGT (67%), whereas the SVR rate in the control arm was only 40%. The rates of SVR following treatment with boceprevir were lower in the black than in the non-black patients cohort; there was a numerical but not statistically significant difference between the groups that received RGT and those that received 48 weeks of treatment, possibly because of the small number of patients in the black patients cohort (Table 1).

The ADVANCE and ILLUMINATE studies investigated triple therapy with a combination of telaprevir, PEG-IFN α-2a, and RBV (Table 1). Patients in the ADVANCE trial were randomly assigned to groups given 12 weeks of triple therapy, 8 weeks of triple therapy, or the SOC. Patients who received triple therapy continued PEG-IFN α-2a and RBV for a minimum duration of 24 weeks, whereas therapy was stopped for patients with extended rapid virologic responses (eRVRs; undetectable levels of HCV RNA at weeks 4 and 12). All others continued to receive PEG-IFN and RBV through week 48. Patients treated with 12 weeks or 8 weeks of telaprevir had significantly higher rates of SVR (75% and 69%, respectively) than the SOC group (44%).[7]

The ILLUMINATE study was designed to confirm that shortened treatment duration, based on response-guided principles, was not inferior to fixed treatment duration for patients who achieved eRVRs. All patients were initially treated with triple therapy that included telaprevir. Those achieving eRVRs were randomly assigned to groups that were given 12 or

36 additional weeks of PEG-IFN and RBV (total treatment duration of 24 weeks or 48 weeks). Among patients who achieved an eRVR (65%), the rates of SVR were similar after 24 or 48 weeks of therapy (92% and 88%, respectively). Therapy can therefore be shortened for a substantial number of patients, without compromising efficacy.[8]

Triple therapy substantially improves outcomes for patients previously treated with only PEG-IFN and RBV. The RESPOND-2 trial focused on treatment-experienced patients, who were given triple therapy with boceprevir (Table 1). This trial included prior partial responders (patients with a 2$_{log}$ decline in HCV RNA by week 12 of treatment with PEG-IFN and RBV, but with detectable levels of HCV RNA throughout the course of treatment) and relapsers (patients with undetectable levels of HCV RNA during therapy but did not attain an SVR). Patients who did not have a 2$_{log}$ reduction in HCV RNA (prior null responders) were excluded. As with all boceprevir studies, RESPOND-2 included a 4-week lead-in phase of PEG-IFN and RBV therapy, followed by triple therapy for a fixed duration of 44 weeks (total treatment duration of 48 weeks). The study included a group that received RGT, in which patients with undetectable levels of HCV RNA at weeks 8 and 24 continued triple therapy for only 32 weeks (total treatment duration of 36 weeks). Prior partial responders had SVR rates of 52% for those who received 48 weeks of therapy, 40% for those who received RGT, and 7% in the SOC arm. As anticipated, prior relapsers had substantially greater rates of SVR than the partial responders (75%, 69%, and 29% for the 3 treatment regimens, respectively).[9]

The study of telaprevir in treatment-experienced patients (REALIZE) included prior null responders, partial responders, and relapsers. Participants were treated with the SOC or a fixed duration of triple therapy (12 weeks), followed by PEG-IFN and RBV through week 48. One group received a 4-week lead-in with PEG-IFN and RBV before triple therapy. However, because no difference in response was observed (lead-in vs no lead-in), results from these telaprevir-treated groups were combined. The rates of SVR in the SOC and triple therapy groups, respectively, were 5% and 31% among prior null responders, 15% and 57% among prior partial responders, and 24% and 86% among prior relapsers (Table 1).[10]

The phase 3 programs for boceprevir and telaprevir have provided many important insights into the opportunities and limitations of triple therapy for diverse populations.

- Treatment-naïve and -experienced patients benefit from triple therapy.

- Half to two-thirds of treatment-naïve patients given boceprevir and telaprevir can have reduced duration of treatment, without compromising efficacy.

- Among treatment-experienced patients, prior relapsers have the best response, whereas less than one-third of prior null responders have an SVR.

- Certain populations, such as patients with advanced fibrosis or cirrhosis, have lower rates of SVR even when using triple therapy—response-guided regimens are not recommended.

- Telaprevir and boceprevir have adverse effects that pose challenges for patients and providers.

Initiating Triple Therapy

Patients with HCV genotype 1 infections are potential candidates for triple therapy regimens that include boceprevir or telaprevir provided they have no contraindications to PEG-IFN and RBV, which remain the backbone of therapy. When determining which of these patients should receive therapy, health care professionals can consider treating a broader population of patients (eg, those with milder disease, stage 0–1 fibrosis) that might have had treatment

delayed in the past. Now that rates of SVR approach 70% among treatment-naïve patients, and a shorter duration of therapy is possible for most, the risk/benefit ratio could lead to earlier treatment of many patients.

However, concerns about adverse events from PEG-IFN–based regimens remain a deterrent for some patients and providers. Additionally, many patients might ask whether they truly need triple therapy. Patients with the CC polymorphism of *interleukin 28b (IL28B)*, associated with increased response to therapy, should achieve rates of SVR on dual therapy comparable with those of triple therapy, although no randomized clinical trials have been performed to test this assertion.[11] Furthermore, the superior SVR rates of patients with the CC polymorphism reflect 48-week regimens of dual therapy; these same patients are likely to have a shortened duration of therapy if they take 3 drugs. Boceprevir and telaprevir have shown activity against other HCV genotypes, although the clinical data are too limited for recommendation of their routine use in patients with HCV non-1 genotype infections. [12–14] Once the decision has been made to begin triple therapy, clinicians should emphasize the importance of proper administration of the drugs to maximize the chance for an SVR and to minimize viral resistance to these and future DAAs.

Telaprevir is manufactured as a 375-mg tablet that is dosed as 2 pills, 3 times a day, 7–9 hours apart, with food; boceprevir is prepared as 200-mg capsules and dosed as 4 capsules (800 mg), 3 times a day, 7–9 hours apart, with food (Table 2). Boceprevir and telaprevir must be administered only in combination with PEG-IFN and RBV to minimize and prevent viral resistance.[15] If the protease inhibitors are given as monotherapy, viral resistance will develop within several days to 2 weeks and severely compromise the efficacy of these and other drugs in this class. The importance of adherence to all the drugs in the triple therapy regimen must be fully explained, and potential barriers to adherence should be addressed with each patient before therapy begins.

Evaluating Drug Interactions

Before treating patients with protease inhibitors, clinicians must review all the medications used by their patients to avoid potentially harmful drug interactions. Boceprevir and telaprevir are each metabolized via the cytochrome p450 pathway, along with many other common medications.[16,17] These drugs also inhibit and/or serve as substrates for p-glycoprotein.[17] Administration of boceprevir and telaprevir could therefore alter plasma concentrations of the other drugs that are metabolized by this pathway (or those drugs could alter the concentrations of boceprevir and telaprevir) affecting efficacy or increasing toxicities.[16,17]

For this reason, there are a number of drugs that are contraindicated for use with boceprevir and telaprevir (Table 3). Certain drugs could be given at reduced doses to patients who are taking protease inhibitors or used with careful monitoring of therapeutic dose and efficacy. Systemic hormonal therapies might not be as effective in women who take these protease inhibitors: 2 additional methods of birth control, such as barrier contraception and an intrauterine device, should be used in women of child-bearing age.[16,17] Boceprevir and telaprevir could also affect metabolism of cholesterol-lowering agents (statins) and antidepressant medications such as escitalopram. Users of statins might take a break from therapy while taking a protease inhibitor: once the triple therapy phase is complete, patients can safely resume use of these drugs. Levels of escitalopram can decrease during telaprevir therapy, so the dose of escitalopram might have to be modified to maintain its therapeutic effects. The product information brochures for boceprevir and telaprevir provide guidance about drug interactions, and many on-line resources (such as www.hcvadvocate. org and

www.hep-druginteractions.org, among others) are available to assist clinicians with management.

Monitoring Levels of HCV RNA and Adherence to Treatment Algorithms

The telaprevir treatment algorithm for treatment-naïve patients and prior relapsers is shown in Figure 1*A*. These patients could be eligible for RGT with telaprevir. Patients begin taking PEG-IFN, RBV, and telaprevir (750 mg, 3 times a day, 7–9 hours apart) concurrently. The importance of the dosing interval for telaprevir should be emphasized to patients. The 7–9 hour window is important for drug pharmokinetics and for timing with meals. Telaprevir absorption is increased by 237% when taken with a standard-fat meal (~500 calories, 20 g fat), compared with no food. It should be administered within 30 minutes of a meal or snack that has at least 20 g of fat.[16]

Levels of HCV RNA should be checked 4 and 12 weeks after therapy begins to determine whether patients are eligible for RGT. Those who have an undetectable level of virus at weeks 4 and 12 (an eRVR) can be considered for 24 weeks of total therapy and only need an additional 12 weeks of treatment with PEG-IFN and RBV. Without an eRVR, an additional 36 weeks of PEG-IFN and RBV are recommended for a total of 48 weeks of therapy. A shortened duration of treatment is not recommended for prior partial and null responders: these patients should complete 12 weeks of treatment with PEG-IFN, RBV, and telaprevir, and then receive 36 more weeks of PEG-IFN and RBV, for a total of 48 weeks of therapy (Figure 1).[16]

In contrast to telaprevir, combination therapy with boceprevir begins with a 4-week lead-in phase of only PEG-IFN and RBV. Boceprevir is added at week 4, and triple therapy is continued through at least week 28. The drug is taken at the same interval (3 times a day, 7–9 hours apart), and plasma levels are increased by 65% when the drug is taken with food compared with a fasting state. Bioavailability, however, does not vary with type of meal (high fat or low fat).[17] Patients who are treatment naïve and have undetectable levels of HCV RNA at weeks 8 and 24 qualify for RGT, and treatment can be stopped at week 28. Those patients with detectable levels of HCV RNA at week 8 but undetectable levels at week 24 should continue to take all 3 drugs through week 36 and then continue to take PEG-IFN and RBV through week 48 (Figure 1*B*).

Prior partial responders and relapsers are also given a 4-week lead-in phase with PEG-IFN and RBV and then start taking boceprevir at week 4. Levels of HCV RNA are measured at weeks 8 and 24. Patients who have undetectable levels of HCV RNA at both time points should continue triple therapy through week 36, and then all drugs may be stopped. For those who have detectable HCV RNA at week 8 but not week 24, triple therapy should be continued through week 36 followed by PEGIFN and RBV through week 48 (Figure 1).[17]

HCV has a rapid but imperfect replication process, so quasispecies and resistant variants exist in treatment-naïve patients[18] and are selected for in patients with suboptimal responses to therapy. Commercial tests for resistant variants are available but are not generally recommended because results will not alter decisions about current therapy. If triple therapy does not work, this must be recognized at an early stage to minimize development of resistant variants. Guidelines for discontinuing therapy should be followed (Figure 1). Patients treated with telaprevir who have a viral load >1000 IU/mL at week 4 should stop taking all 3 drugs. At week 12 (when telaprevir is finished), a viral load >1000 IU/mL also mandates cessation of PEG-IFN and RBV treatment. Futility of boceprevir-based triple therapy is defined as a level of HCV RNA   100 IU/mL at week 12 or any detectable HCV RNA at week 24. If either of these conditions are met, treatment should be stopped (Figure

1).[17] Detection of virus at week 24 also indicates treatment failure, and PEG-IFN and RBV therapy should be stopped.[16]

Strict adherence to the treatment guidelines is essential for optimal outcome, so patients should be advised to use pill boxes, timers, and premade meals and snacks. Patients also benefit from an educational session before therapy begins to address these issues. Regular clinic visits are required to manage adverse events and monitor adherence.

Response-Guided Treatment Based on Level of HCV RNA

Assays for HCV RNA vary in their lower limit of quantification (LLQ; the lowest level of virus for which quantification is considered accurate) and in the actual limit of detection (LOD; the lowest level at which the presence of analyte in a sample of HCV RNA can be detected in serum or plasma).[19] A post hoc analysis by the US Food and Drug Administration found that rates of SVR were reduced by approximately 20% when therapy was shortened for patients with levels of HCV RNA below the LLQ but above the LOD (indicating a low level of residual viremia).[20,21]

In trials of protease inhibitors, HCV RNA was measured using Roche COBAS Taqman Test v.2 with the high pure system. The LLQ for this test is 25 IU/mL, and the LOD was 9.3 IU/mL.[16,17] A patient with a value between these levels might be reported as having HCV RNA that is less than 25 IU/mL but detectable. This finding indicates that the virus is still present and should not be considered undetectable[16,17] for the purpose of applying RGT of shortened duration. Clinicians and laboratory managers should ensure that the characteristics of their HCV RNA assay meet or exceed those of assays used in the clinical trials and report the results in a manner most useful to clinicians, who make treatment decisions based on this information.

Identification and Management of Adverse Events

Anticipating the adverse effects of telaprevir and boceprevir, informing patients about their risk, and being prepared to manage them is important for safe and successful outcomes from triple therapy. Adverse events from PEG-IFN and RBV therapy are well established and still account for most adverse effects associated with triple therapy.[16,17] However, certain adverse effects can be exacerbated, and new adverse events can occur with these regimens (Table 4). In the phase 3 trials for telaprevir, some of the most significant adverse effects were rash (56%), anemia (36%), and anorectal complaints (29% in aggregate).[7,8,10,16] The most significant adverse effects in the phase 3 trials of boceprevir were anemia (45%–50%) and dysgeusia (35%–44%).[6,9,17]

Anemia

Anemia is an adverse effect of telaprevir- and boceprevir- based triple therapy (Supplementary Table 1). The severity of anemia reported in clinical trials was additive to that expected from RBV. Hemoglobin levels decreased approximately 1 g more than with PEG-IFN and RBV but returned to expected levels once telaprevir or boceprevir were discontinued. In trials of telaprevir, anemia was managed by reducing the dose of only RBV, whereas, in trials of boceprevir, erythropoietic growth factors were given to 43% of participants compared with 24% of the patients receiving only PEG-IFN and RBV.[6,9,17] Among patients given either drug, anemia was initially managed by regular monitoring (every 2 weeks) and reducing the dose of RBV. In practice, the dose of RBV should be lowered when hemoglobin decreases by 1.5 g/dL within a 2-week period[22] to pre-empt severe anemia and discontinuation of RBV. Fortunately, SVR rates are not reduced when the dose of RBV is reduced.[23] Patients with severe (persistently 10 g/dL), symptomatic, or

progressive anemia, despite a reduced dose of RBV, can be given growth factors such as epoeitin-α. It is important to note that doses of protease inhibitors cannot be reduced: they are used in an all or none manner. If the anemia becomes severe enough to require cessation of RBV, telaprevir must be stopped as well.[16] Additionally, if IFN-related adverse effects prompt its discontinuation, all drugs must be stopped.

Rash

Management of a telaprevir-associated rash begins with an assessment of its severity. Mild rashes are localized or have a limited distribution and appear with or without pruritus. Patients with these adverse effects can be given an oral antihistamine and a topical corticosteroid, if necessary. Importantly, all drugs for treatment of HCV should be continued. Moderate rashes are diffuse and can have some peeling skin, pruritus, or involvement of mucous membranes, without ulceration. These rashes should also be treated with oral antihistamines and topical corticosteroids. All HCV therapies can be continued with close observation. It is a challenge to differentiate mild-moderate rashes caused by telaprevir from those caused by RBV.

Severe skin rashes are generalized; involve more than 50% of the body surface; and can present with vesicles, bullae, or ulcerations. For patients with severe rash, telaprevir therapy should be stopped, but treatment with PEG-IFN and RBV can be continued. If the rash does not improve after 7 days, or gets worse, all drugs should be stopped, and a dermatologist can be consulted. Only 5%–7% of patients in clinical trials stopped taking telaprevir because of rash.[7,8,10,16] The dose of telaprevir should not be reduced, and, once stopped, therapy should not be reinitiated. Serious cutaneous adverse reactions, such as Stevens–Johnson syndrome r drug rash with eosinophillia and systemic symptoms, such as fever or edema (also known as *DRESS*), are extremely rare. If suspected, urgent medical evaluation and cessation of all treatment are indicated.[16]

Gastrointestinal Adverse Effects

The anorectal complains associated with telaprevir therapy include hemorrhoids, anal puritis, anorectal discomfort, and anal burning. In trials, most events were mild to moderate in severity, and less than 1% led to discontinuation of telaprevir. These adverse effects can usually be managed with topical corticosteroids or analgesics (eg, lidocaine).[16] Over-the-counter hemorrhoid preparations and antidiarrheal agents can also be used. Anorectal symptoms resolve immediately when patients stop taking telaprevir.

Dysgeusia (altered taste sensations or unpleasant taste in the mouth) was the only gastrointestinal symptom that occurred more often in patients given boceprevir than the SOC. Patients are managed based on their symptoms, but no patients were reported to have significant weight loss from dysgeusia.

Limitations of Triple Therapy Regimens for Certain Populations

Phase 3 trials demonstrated the overall efficacy of triple therapy with telaprevir or boceprevir in patients with chronic hepatitis C. However, certain populations were either underrepresented or not included in these studies, so there is uncertainty in the exact point estimates of response.

African American Patients

African American patients were enrolled in the telaprevir and the boceprevir studies, although not at a rate reflective of the HCV prevalence in the African American population. In the phase 3 trial of boceprevir in treatment-naive patients (SPRINT-2), the groups that

received boceprevir included 107 African American patients, within a separate cohort, and more than 600 non-African American patients.[6] Similarly, only about 9% of the population treated with telaprevir triple therapy in the ADVANCE and ILLUMINATE trials was African American.[7,8] Furthermore, among previously treated patients in the phase 3 trials of boceprevir and telaprevir, only 79 were African American.[9,10] Triple therapy with either protease inhibitor substantially increased rates of SVR in African American patients, compared with only PEG-IFN and RBV, although the rate of SVR was still lower than in white thnicity populations.

Patients With Cirrhosis

In the phase 3 trials of telaprevir and boceprevir, approximately 8%–27% of participants had advanced fibrosis or cirrhosis.[6–10] Because of the small numbers of patients with advanced disease, those with cirrhosis or bridging fibrosis were often analyzed together, limiting the conclusions that could be made about either group. Patients with cirrhosis had significant increases in rates of SVR with the addition of a protease inhibitor to therapy, although this rate was still lower than that of patients with milder fibrosis. Cirrhotic patients treated for a shorter time by response-guided criteria had a numerically lower rate of response than those treated with a longer, fixed-duration regimen.[6,8,9,16,17] These results led to the recommendation that fixed-duration regimens (48 weeks of therapy) are most appropriate for patients with cirrhosis to maximize their potential rate of SVR.[16,17]

For patients with cirrhosis, attaining an SVR can eliminate concerns about post-transplant HCV or even obviate the need for liver transplant. However, there is no safety data on treating patients with advanced liver disease beyond well-compensated disease (Childs–Pugh A), so caution and careful patient selection are important. Triple therapy is not approved for patients who have received liver transplants, and protease inhibitors have significant interactions with drugs such as calcineurin inhibitors. Serum levels of tacrolimus increase approximately 25% to 70% fold with concomitant administration of boceprevir or telaprevir, respectively.[24,25]

Prior Null Responders

Treatment-experienced patients have better responses to triple therapy than to re-treatment with PEGIFN and RBV. However, intrinsic IFN responsiveness directly correlates with SVR in treatment-experienced (and naïve) patients. Response also correlated with *IL28B* genotype, in retrospective analyses, although patients with the polymorphisms associated with lack of response (CT and TT) also had substantial increases in rates of SVR to triple therapy compared with PEG-IFN and RBV alone.[26,27] The main risk of re-treating patients with a low chance of treatment success is creating viral resistant populations, particularly in those with poor interferon responsiveness. The long-term impact of these viral variants on retreatment with second-generation protease inhibitors or even quadruple therapies that may contain a protease inhibitor in the future remains unknown.

Studies of telaprevir and boceprevir demonstrated that partial responders had incremental improvement in SVR, although there is a clear drop off in response compared with naïve patients and relapsers.[10] Prior null responders were the least likely to achieve SVR (31%) with telaprevir triple therapy in the REALIZE study. The same relationships were evident in the RESPOND-2 boceprevir study, particularly when the virologic response during the lead-in phase was considered as a surrogate for the exclusion of prior null responders.[9] Prior null responders with cirrhosis pose the greatest challenge for treatment. Subgroup analysis of REALIZE suggests only ~15% SVR in this population, although only a small number of patients with these characteristics were included.[10] The risk of selecting resistant variants to

protease inhibitors may be too great when other drug options may be available in the future, although decisions must be individualized for each patient.

Other Populations

There are limited data for the use of triple therapy in special populations, such as patients with human immunodeficiency virus (HIV) or hepatitis B virus coinfection or those with mental health issues. These populations were either underrepresented or excluded from clinical trials. In deciding whether or not to give a patient triple therapy, clinicians should consider whether the addition of a new drug to the treatment regimen has a greater chance of helping or harming each individual patient. For patients coinfected with HIV and HCV, interactions among drugs must be considered. Interactions between HCV and HIV protease inhibitors are complex, as is management of hepatitis B virus coinfected patients.

Patients with mental health comorbidities might benefit from triple therapy, although there are no data available from this specific population. However, now that SVR rates approach 70% and many patients require only 6 months of IFN exposure, antiviral therapy could be possible for certain patients for whom a favorable benefit to risk profile exists. From a public health perspective, broadening the scope of patients treated for HCV infection, combined with the impact of increasing the rate of SVR, provides an opportunity to reduce the future burden of cirrhosis, hepatocellular carcinoma, and end-stage liver disease.[28,29]

Future Directions and Preventing Resistance to New Drugs

Although there are many promising DAAs in development, it is important to remember that decisions made in practice today could affect the success of future drugs. Current triple therapy combinations will eventually be replaced by IFN-free regimens of protease inhibitors, nucleoside/non nucleoside polymerase inhibitors, NS5A inhibitors, and other classes of drugs.[30]

The effects of lack of response to triple therapy have recently been reviewed.[31] Patients who did not respond to telaprevir or boceprevir carried a dominant strain of protease inhibitor-resistant virus that was present at the time of virus breakthrough or relapse, but the wild-type strain reemerged as the dominant quasispecies many months after therapy.[32–35] The significance of these findings is unclear. The return of a wild-type population of HCV could indicate that patients can be rechallenged at a later date, with a combination of drugs that includes one of the first-generation protease inhibitors as has been shown in a small number of patients re-treated with telaprevir-containing regimens after a brief exposure to the protease inhibitor in clinical trials.[36] However, it is also possible that the resistant quasispecies will emerge again, once selective pressure is applied. If these patients respond poorly to PEG-IFN RBV (especially those with the TT genotype of *IL28B*), viral resistance will continue to be a problem until multitargeted DAAs are available.[31,37]

Summary

The NS3/4 protease inhibitors boceprevir and telaprevir are the first in a pipeline of new therapies that will change treatment of HCV infection. Rates of SVR for patients with genotype 1 HCV infection have increased to ~70%, and one-half to two-thirds of patients will be eligible for a shortened duration of therapy. To take advantage of these developments, clinicians must select appropriate patients for therapy, perhaps even expanding the pool of patients treated, as the risk/benefit ratio for therapy improves. Once a commitment to treatment has been made, appropriate dosing, monitoring for drug interactions, anticipation of adverse effects, and strict adherence to stopping rules will optimize responses to the new standard of care. Attention to these details will insure the

success of these new drugs and preserve the promise of future generations of anti-HCV therapies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Biographies

Abbreviations used in this paper

ADVANCE	a new direction in HCV Care: a study of treatment naïve hepatitis C patient with telaprevir
DAA	direct-acting antiviral
eRVR	extended rapid virologic response
HCV	hepatitis C virus
HIV	human immunodeficiency virus
ILLUMINATE	illustrating the effects of combinatherapy with telaprevir
LLQ	lower limit of quantification
LOD	limit of detection
PEG-IFN	peginterferon
RBV	ribavirin
REALIZE	the retreatment of patients with telaprevir based regimen to optioutcomes
RESPOND-2	retreatment with HCV serine protease inhibitor boceprevir and pegintron/rebetol-2
RGT	response-guided therapy

SOC	standard of care
SPRINT-2	serine protease inhibitor therapy-2
SVR	sustained virologic response

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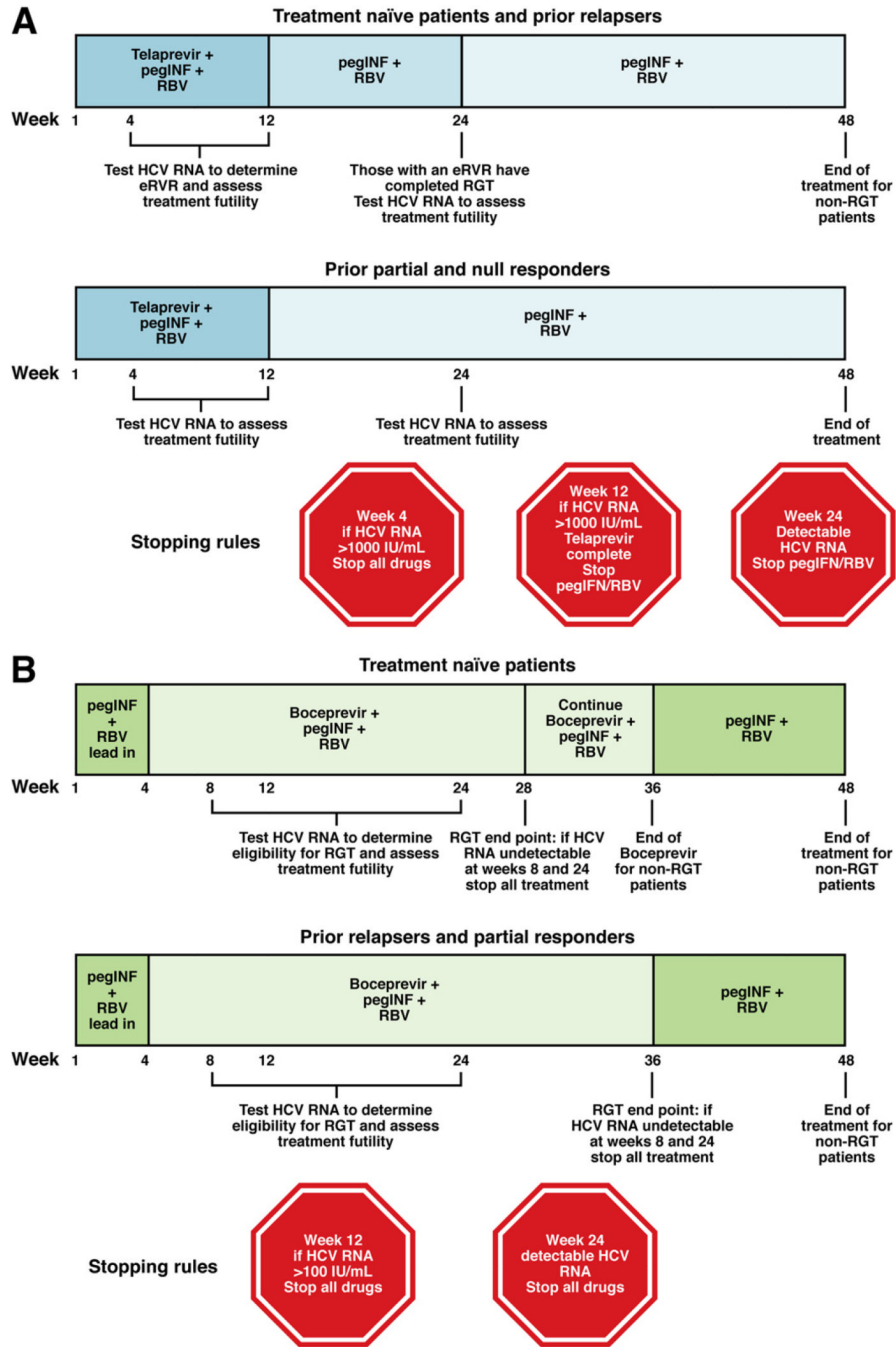
Figure 1.
Duration for telaprevir and boceprevir-based triple therapy, based on previous treatment.

Table 1

Summary of Phase 3 Clinical Trials for Boceprevir and Telaprevir

Study	Drug	Population	Treatment arm(s)	Intervention SVR	SOC SVR	Main findings
SPRINT-2[6]	Boceprevir	Naïve	Black			RGT therapy as effective as 48
			RGT	42%	23%	weeks of therapy for non-black
			48-week therapy	53%		patients
			Non-black			~1/2 of patients eligible for RGT
			RGT	67%	40%	
			48-week therapy	68%		
ADVANCE[7]	Telaprevir	Naïve	T8 (pooled 24- and 48-week total therapy)	69%	44%	12-week telaprevir regimen preferable to 8-week regimen
			T12 (pooled 24- and 48-week total therapy)	75%		
ILLUMINATE[8]	Telaprevir	Naïve	T12 overall	75%	N/A	24-week total therapy for eRVR
			eRVR + 24-week therapy	92%		patients non inferior to 48
			eRVR + 48-week therapy	88%		weeks of therapy
						~2/3 of patients eligible for shorter duration of therapy
RESPOND-2[9]	Boceprevir	Treatment experienced	RGT		Relapsers	Null responders excluded
			Prior relapsers	69%	29%	
			Prior nonresponders	40%		
			48 weeks		Nonresponders	Relapsers had similar outcomes
			Prior relapsers	75%		as naïve population
			Prior nonresponders	52%	7%	
REALIZE[10]	Telaprevir	Treatment experienced	T12 (48-week total therapy)			Relapsers had similar outcomes
			Prior relapsers	86%	24%	as naïve population
			Prior partial responders	57%	15%	
			Prior null responders	31%	5%	

eRVR, extended rapid virologic response; RGT, response guided therapy; SOC, standard of care; SVR, sustained virologic response, T8, 8-week telaprevir arm; T12, 12-week telaprevir arm.

Table 2

Dosing and Monitoring Rules for Boceprevir and Telaprevir

Drug	Dosing	Duration of protease inhibitor	HCV RNA monitoring	Initial laboratory monitoring
Boceprevir 200-mg capsule	800 mg orally 3 times/d (every 7–9 hs) with food[a]	Treatment naïve: RGT: boceprevir dosed wks 4–28 Non-RGT: boceprevir dosed wks 4–36	Baseline and wks 4, 8, 12, and 24 to assess for RGT and futility	CBC: baseline and wks 4, 6, 8, and 12[c]
	Must be used in conjuction with pegIFN and RBV	Treatment experienced: boceprevir dosed wks 4–36	Assess for SVR 6 mos after therapy is conpleted	Serum electrolytes, creatinine, uric acid, LFTs, TSH: baseline and wks 2, 4, 8, and 12[c]
Telaprevir 375-mg tablet	750 mg orally 3 times/d (every 7–9 hs) with food[b]	All patients: telaprevir dosed wks 0–12 for all treatment regimens	Baseline and wks 4 and 12 to assess for eRVR and futility	CBC, serum electrolytes,creatinine, uric acid, LFTs, TSH: baseline and wks 2, 4, 8, and 12
	Must be used in conjunction with pegIFN and RBV		Assess for SVR 6 mos after therapy is completed	

CBC, complete blood count; eRVR, extended rapid virologic response; LFTs, liver function tests; pegIFN, peginterferon; RBV, ribavirin; RGT, response-guided therapy; TSH, thyroid-stimulating hormone.

[a]Food increases the exposure to boceprevir by 65% compared with fasting state. Bioavailability is similar regardless of type of meal (high fat vs low fat) and may be consumed before or after a meal.17

[b]Telaprevir absorption is increased by 237% when taken with a standard fat meal (~500 calories, 20 g fat) compared with the fasting state. Telaprevir should be administered within 30 minutes of a non-low-fat meal with at least 20 g fat content.16

[c]Monitoring not part of package insert, but recommended by the authors. Laboratory monitoring should be performed at routine intervals throughout therapy and more frequently if clinically indicated.

Table 3

Contraindicated[a] Drugs for Concomitant Use With Boceprevir and Telaprevir

Drug(s)	Class	Contraindicated protease inhibitor	Comments
Potential for increased toxicity of concomitant medication			
Alfuzosin	A1-adrenoreceptor antagonist	Boceprevir and telaprevir	Hypotension or cardiac arrhythmia
Statins	HMG CoA reductase inhibitors	Boceprevir and telaprevir	Myopathy including rhabdomyolysis
Sildenafil[b]	PDE5 inhibitors	Boceprevir and telaprevir	Vision changes, hypotension
Midazolam[c]	Sedatives	Boceprevir and telaprevir	Sedation/respiratory depression (oral formulation)
Pimozide	Neuroleptic	Boceprevir and telaprevir	Cardiac arrhythmias
Dihydroergotamine	Ergot derivitives	Boceprevir and telaprevir	Vasospasm and ischemia
Drosperinone	Oral contraceptive	Boceprevir	Hyperkalemla
Cisapride	Gastrointestinal motility	Boceprevir and telaprevir	Cardiac arrhythmias
Potential for reduced protease inhibitor activity			
Rifampin	Antimycobacterial	Boceprevir and telaprevir	Significant reduction in protease plasma concentration and may lead to viral breakthrough
St. John's Wort	Herbal medication	Boceprevir and telaprevir	
Phenytoin	Anticonvulsants	Boceprevir	

HMG CoA reductase inhibitor, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor; PDE5 inhibitors, phosphodiesterase 5 inhibitors.

NOTE. Please see package inserts for full listing of drug interactions and warnings.

[a] Please see package inserts for full listing of drug interactions and warnings.

[b] When used for pulmonary arterial hypertension. Please see package inserts for warnings and dosing for erectile dysfunction use.

[c] Please see package inserts for warnings and monitoring for intravenous administration.

Table 4

Adverse Events From Boceprevir and Telaprevir vs Standard of Care

Drug	Adverse events[a]	Treatment arm frequency	SOC frequency	Comment
Boceprevir[6,9,15]	Anemia	45%–50%	20%–30%	Erythropoesis-stimulating agents allowed
	Dysgeusia	35%–44%	11%–16%	
Telaprevir[7,8,10,16]	Rash	56%	34%	6% discontinued telaprevir due to rash
	Anemia	36%	17%	
	Anorectal symptoms[a]	29%	7%	

SOC, standard of care; pegIFN, pegylated interferon; RBV, ribavirin.

[a]Anorectal symptoms include hemorrhoids, anorectal discomfort, and anal pruritis.