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Triple Therapy with the New Hepatitis C Protease Inhibitors: Challenges and Strategies

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Hepatitis C virus (HCV) infection is the leading cause of chronic liver disease and death from liver disease in the United States. While spontaneous resolution of the infection is possible, about 55-85% of those infected with the virus develop chronic hepatitis C and many of those who have the disease are unaware until they develop the complications of cirrhosis or hepatocellular carcinoma (HCC) many years later. HCV is classified into 6 major genotypes, with genotype 1 being the most common in the US. [1] Genotype 1 HCV infection is also considered one of the most difficult to treat, with successful clearance of virus only achieved in 50% of treated patients.

Treatment for HCV has evolved over the last several decades. Until recently, the combination of peginterferon and ribavirin (PR) was considered the standard of care (SOC).[1,2] Because clinical trials are not long enough to provide evidence on long-term clinical outcomes, HCV effectiveness is measured by sustained virologic response (SVR). This endpoint is used to evaluate HCV outcomes as it is associated with reductions in mortality, liver failure, and cancer.[3,4] Overall, rates of SVR in those with genotype 1 with PR are approximately 40-50%. However, certain patient populations are less responsive to therapy and have much lower rates of SVR. In May 2011, two direct acting antiviral (DAA) agents, boceprevir (BOC) and telaprevir (TVR) were approved by the FDA for genotype-1 HCV in combination with PR.[5,6] Both agents have shown improved virologic outcomes in treatment-naïve and treatment-experienced patients with genotype 1 HCV compared to PR alone. Although these drugs are an important advancement in the treatment of hepatitis C, BOC and TVR are associated with a myriad of toxic side effects, potential drug-drug interactions, complex dosing regimens, potential for HCV resistance, and add a significant cost to current treatments. This article will review the efficacy and safety data for the protease inhibitors as well as review potential challenges associated with their use.

Table 1: Definitions of Virologic Parameters

Sustained Virologic Response (SVR)	Absence of detectable HCV RNA 24 weeks after therapy is complete
Extended Rapid Virologic Response (eRVR)	Undetectable HCV RNA at treatment week 4 and 12
Late Responders	Detectable HCV RNA at treatment week 8, but undetectable at week 24
Partial Responders	Reduction of 2 $\log_{10}$ or more in HCV RNA after 12 weeks of therapy but HCV RNA is detectable
Prior Relapsers	Undetectable HCVRNA at the end of treatment, with a detectable HCV RNA level during the follow- up period
Null Responders	Reduction of less than 2 $\log_{10}$ in HCV RNA after 12 weeks of therapy

Boceprevir

The SPRINT-2 study was a randomized, double-blind, phase 3 trial that compared triple therapy with BOC to PR in two treatment-naïve cohorts, one black and one non-black, with a primary endpoint of SVR.[7,8] All patients received PR during a four week lead-in period. Then patients were randomized to 1) PR + placebo for 44 weeks, 2) PR + BOC for 44 weeks (fixed duration therapy or FDT), or 3) PR + BOC given for 24-44 weeks based on viral load (response guided therapy or RGT).[7,8] In the RGT group, if HCV RNA levels were undetectable from week eight through week 24 (early responders), treatment was completed. Late responders received an additional 20 weeks of PR and ended treatment at week 48. Overall, SVR rates were significantly higher in the groups receiving BOC than those in the PR control group (63% RGT and 66% FDT vs. 38%, p<0.001) with better rates observed in the non-black cohort compared to the black cohort (14% of total patients).[9] These findings indicated that a total treatment duration of 28 weeks would be sufficient for early responders, while 48 weeks of therapy (4 weeks of lead-in, 24 weeks of triple therapy, and 20 weeks of PR alone) would be preferred for late responders. However, the FDA recommended 4 weeks of lead-in, 32 weeks of triple therapy, and 12 weeks of PR for late responders based on a reanalysis of the SVR rates of Groups 2 and 3 and a subgroup analysis of early and late responders.[8]

The RESPOND-2 trial evaluated BOC in patients previously treated with PR who were partial responders or relapsers, while patients who were null responders (<2 $\log_{10}$ decline at treatment week 12 and no SVR) were excluded.[10] Patients in the RESPOND-2 trial received four weeks lead-in treatment with PR, and then were randomized to similar groups as in SPRINT-2 for 32 to 44 weeks. SVR rates were also significantly higher in the two BOC groups compared to SOC (59-66% vs. 21%; p<0001).[9,10] Additionally, prior relapsers achieved higher SVR rates than prior partial responders in all three arms (29%-75% vs. 21%-66%). [10] Based on the results of RESPOND-2, patients who are prior partial responders or relapsers with dual therapy should be considered candidates for re-treatment with triple therapy. In addition to these trials, a smaller, open-label study (SPRINT-1) has also been published.[11]

Telaprevir

The FDA reviewed six phase 2 studies and three phase 3 studies supporting the effectiveness of TVR.[12–16] The ADVANCE trial evaluated the efficacy of TVR in combination with PR in treatment-naïve patients.[17] Patients were randomized to 1) TVR + PR for 12 weeks (T12PR) then PR for 12 or 36 weeks based on viral response, 2) TVR + PR for eight weeks (T8PR), followed by PR + placebo for four weeks then PR for 12 or 36 weeks based on viral response, or 3) PR + placebo for 12 weeks followed by PR for 36 weeks (SOC). Patients in the TVR groups were eligible for a shorter duration of dual therapy (24 weeks) if an early rapid virological response (eRVR) was achieved (defined by undetectable HCV between weeks four and 12). SVR rates were 75%, 69%, and 44% for T12PR, T8PR, and SOC, respectively (p<0.001).[12,17] Patients achieving eRVR had higher rates of SVR than those who did not. Of note, too few Hispanic and black patients were included in the trial to assess response in these populations.[17] This trial established that triple therapy including TVR for 12 weeks followed by response guided PR of 12 to 36 additional weeks is superior to SOC in treatment-naïve patients.

The ILLUMINATE trial was a supportive, open-label, non-inferiority trial, evaluating the efficacy of TVR with PR in treatment-naïve patients who had achieved eRVR after 12 weeks of triple therapy, followed by PR.[18] Patients who had an eRVR were randomized at week 20 to receive either four or 28 additional weeks of PR (24 weeks total of PR; T12PR24 or 48 weeks total of PR; T12PR48, respectively). SVR was achieved in 92% of patients in the T12PR24 arm and 88% in the T12PR48 arm, meeting the pre-defined non-inferiority margin of -10.5%, confirming that 24 total weeks of PR is sufficient in TVR treated patients achieving an eRVR.[18].

The REALIZE trial evaluated the efficacy of TVR in previously treated patients who were partial responders, relapsers, or null responders as well as the effects of a four week lead-in of PR therapy.[19] Overall SVR rates were 64-66% in the TVR groups compared to 17% in the control group (p<0.001)[9], and treatment outcomes were similar with or without lead-in therapy.[12,19] Similar to RESPOND-2, prior relapsers achieved the highest SVR (83-88% TVR and 24% PR) while previous null responders achieved the lowest rate of SVR (29-33% TVR groups vs. 5% SOC). Additionally, null responders experienced higher rates of anti-viral resistance.[12,19] Since less than one-third of null responders in the REALIZE study achieved SVR, the decision to re-treat these patients should be individualized, taking into consideration the risk of anti-viral resistance, serious side effects, and high cost of therapy.

Safety and Side Effect Management

In addition to the adverse events already associated with standard PR therapy, serious adverse events were consistently more frequent with triple therapy compared to PR, making adherence an even greater challenge.

In BOC trials, the most common adverse event that occurred more than placebo was anemia, occurring in 49% of BOC containing regimens compared to 29% of PR patients.[8] In the BOC clinical trials, anemia was managed with ribavirin (RBV) dose reduction and/or erythropoietin stimulating agents (ESA), and 43% received ESA to manage the anemia. Rates of SVR were 74%, 78%, and 71% for patients whose anemia was managed with ESA, RBV dose reduction, and both, suggesting similar rates of SVR between management strategies.[20]

In the TVR trials, anemia also occurred more frequently than those in the PR group, although ESA use was prohibited. Anemia was managed solely through RBV dose reduction.[12] RBV dose reduction did not appear to be associated with lower rates of SVR in patients. The AASLD Practice Guidelines recommend RBV dose reduction (as low as 600 mg/day) for initial management of anemia and state the benefits and risks of ESAs must be weighed when considering their use.[2]

The most common adverse events in TVR trials were rash, anemia, pruritus, nausea, and diarrhea.[17–19,21] The rash was mild to moderately severe with severe cutaneous reactions reported in <1% of patients receiving TVR.[2] Rash associated with TVR typically occurs in the first eight weeks of treatment but can occur at anytime. Aggressive and early management of this rash is essential. For mild to moderate rash, topical steroids and anti-histamines are suggested. If systemic signs or symptoms develop, it is recommended that TVR be stopped and a referral is made for dermatological treatment.[12,21] In addition to rash, 29% of TVR patients had anorectal discomfort compared to 7% in control groups, however less than 1% of patients stopped treatment as a result.[9,12] For severe symptoms, perianal topical lidocaine or zinc oxide can provide relief. There were no serious dermatologic or anorectal symptoms demonstrated with BOC use.

Challenges and Limitations

In understudied populations where evidence to guide care is lacking, treatment of HCV infection with triple therapy presents some uncertainties. HIV coinfection is present in 17% of patients with HCV and causes a more rapid progression to cirrhosis and suboptimal SVR rates with PR therapy.[9] The DAAs have not yet been studied in this population, and safety concerns exist since BOC and TVR strongly inhibit cytochrome P450 (CYP3A) and have probable drug-drug interactions with antiretrovirals.[2] The DAAs are not recommended in decompensated cirrhosis or in patients with moderate or severe hepatic impairment (Child-Pugh score ≥7). Few cirrhotic patients were included in the studies and those that were experienced lower rates of SVR than those with milder disease. Also, older patients with HCV infections have higher incidence of hepatocellular carcinoma, faster progression to cirrhosis, and lower rates of SVR compared to younger patients. It is possible that DAAs may increase SVR rates in older patients, but tolerability and safety are significant concerns in this vulnerable population.[12,19] In addition, there is insufficient evidence for use in populations who were under represented in studies including: liver transplant patients, patients younger than 18 years of age, older patients >65, those who are renally impaired, black patients, and null-responders. Evidence suggests black patients tend to respond more poorly than non-blacks. However, in both SPRINT-2 and ADVANCE, rates of SVR for black patients were approximately doubled in the triple therapy arms compared to SOC.[7,17]

Who to treat?

Because of the potential development of new agents and the slow progression of HCV, it may be appropriate to defer triple therapy treatment of patients with less severe disease in hopes of new options. Clinical trials have shown that patient characteristics, such as genotype 1, play a role in response to triple therapy. Other considerations in determining the likelihood of response include fibrosis stage and previous treatment experience. Subgroup analyses have shown that response rates in patients with cirrhosis remain relatively low (62% for those with cirrhosis compared to 81% for those with minimal or mild fibrosis), especially in those previously treated with PR. In addition, patients with more severe cirrhosis are more likely to experience associated side effects, and thus have a higher risk of not tolerating treatment.

Treatment-naïve patients without cirrhosis, as well as patients previously treated with PR who were either partial responders without cirrhosis or relapsers can expect relatively high rates of SVR with BOC or TVR based therapy compared to PR alone. For previous null responders, however, the potential benefits of triple therapy may not outweigh the associated risks.[2]

Other considerations when selecting patients for triple therapy include adherence, previous treatment adverse events, and comorbid conditions. The estimated retail costs are $1100 per week of BOC treatment and $4100 per week of TVR treatment.[9,22] Patients with a strong support system, stable living arrangements, and adequate care for concomitant mental health and physical health conditions are most likely to have positive outcomes from treatment with triple therapy. Whereas uncontrolled and/or untreated psychiatric disorders are a contraindication to both PR and triple therapy; when appropriately managed it can represent only a barrier.

In conclusion, despite the limitations and potential safety issues associated with the new DAAs for HCV, when used in the appropriate patient, they have shown tremendous progress in clinical cure of HCV. Treatment and drug choice should be strongly individualized based on patient specific circumstances and tolerance.

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