Boceprevir and Treatment of Chronic Hepatitis C

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KEYWORDS

• Boceprevir • Peginterferon • Ribavirin • Hepatitis C

KEY POINTS

- The addition of boceprevir to peginterferon and ribavirin has improved sustained response rates markedly.
- Boceprevir is effective in treatment naïve, relapsers, partial responders, and null responders. Those with advanced fibrosis require 44 weeks of boceprevir therapy after a 4-week peg/ribavirin lead-in.
- The main side effect with boceprevir is anemia, and ribavirin dose reduction is an effective strategy.
- In those who are poorly peg/ribavirin responsive, an additional stopping rule of $<10^3$ HCV RNA reduction at Week 8 seems to help minimize the likelihood of reducing resistance-associated variants.
- Additional data in special populations, including HIV/Hepatitis C coinfected, those with cirrhosis, and those with Hepatitis C recurrence after orthotopic liver transplant are required to assess the efficacy of boceprevir in these populations.

In May 2011, the direct acting antiviral therapies boceprevir and telaprevir, both NS3/NS4 protease inhibitors, were approved for the treatment of genotype I Hepatitis C in combination with peginterferon and ribavirin (PR). Boceprevir when added with PR, significantly improved sustained response (SVR) rates in the treatment of genotype I treatment-naïve patients and those who had failed previous therapy. This approval was based on 2 large registration trials. The Sprint 2 trial examined the efficacy of boceprevir in treatment-naïve patients, whereas the Respond 2 trial examined the efficacy of boceprevir therapy in partial responders and relapsers to previous PR therapy. This review examines the current treatment paradigm of boceprevir-based treatment

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of chronic hepatitis C, examining treatment paradigms, predictors of response, futility rules, as well as preliminary results from studies examining boceprevir efficacy in additional populations.

The current treatment recommendations for boceprevir in combination with peginterferon and ribavirin are derived from the large Phase 3 Sprint 2 and Respond 2 studies. In the Sprint 2 study, a total of 938 nonblack and 159 black patients were treated with peginterferon alfa-2b and ribavirin (PR) or boceprevir plus peginterferon and ribavirin in a response-guided paradigm for a fixed duration of 44 weeks.[1] The control group received the previous standard of care PR for 48 weeks (Group 1). Group 2 received boceprevir plus PR for 24 weeks in a response-guided paradigm in combination with boceprevir after a 4-week lead-in of PR, with those with having detectable HCV RNA levels between Week 8 and 24 receiving an additional 20 weeks of PR for a total of 48 weeks. The third group received fixed duration boceprevir for 44 weeks with peginterferon and ribavirin after a 4-week PR lead-in. In the nonblack cohort, boceprevir in the response-guided arm led to an overall SVR rate of 67%, which was virtually identical to the 68% SVR rate seen in the group with fixed duration boceprevir with peginterferon and ribavirin treatment. Both were statistically higher than the PR control group of 40%. In the black cohort, which had the same study design, the SVR rate in both the fixed and response-guided paradigm arms were superior to PR control (53% and 42% vs 23% respectively), although numerically higher SVR rates were seen with fixed duration boceprevir 44 weeks with peginterferon and ribavirin in this cohort. Moreover, the 4-week PR lead-in viral decline was an important tool in predicting the SVR rate, with those having a greater than 1 log reduction of the SVR rate experiencing an 82% overall SVR rate with boceprevir addition, regardless of response-guided or fixed duration boceprevir treatment. In the black cohort, SVR rates were also higher, with greater than 1 log decline from baseline during the 4 weeks of peginterferon and ribavirin treatment at 67% and 61%, respectively. After the Food and Drug Administration review, boceprevir was approved for a response-guided paradigm in noncirrhotic individuals and those who had greater than 1 log reduction during the 4-week peg/ribavirin lead-in. These individuals could receive a 4-week peg/ribavirin lead-in, followed by 24 weeks of peginterferon and ribavirin with boceprevir in those who are at Treatment Week 8 to 24 undetectable, truncation of therapy at 28 weeks is appropriate. Those with detectable virus at Week 8 and who clear virus by Week 24 receive 32 weeks of boceprevir and PR and then a 12-week tail of PR. In the PR poorly responsive individuals (those with <1 log reduction during the lead-in) and those with cirrhosis, 44 weeks of boceprevir with PR is provided. Treatment week futility rules were set as HCV RNA level greater than 100 IU/mL at Week 12 or Week 24 detectable levels of HCV RNA, during which all therapy should be discontinued because SVR will not occur, to minimize the development of resistance-associated variants (RAVs).

With the use of boceprevir for genotype 1 hepatitis C, all subjects receive a 4-week PR lead-in. The 4-week peg/ribavirin lead-in initially was examined in the Sprint 1 study, in which it was hypothesized that steady state levels of peginterferon and ribavirin achieved after 4 weeks would minimize the development of RAVs and improve SVR rates.[2] No statistically significant difference in SVR rates were noted in the Sprint 1 study between lead-in and non–lead-in groups, although the 4-week peg/ribavirin lead-in provided prognostic information about the opportunity to achieve SVR. At present, the lead-in should be used as a tool that allows the assessment of the patient's ability to tolerate the backbone PR before the addition of a direct-acting antiviral therapy.

In those who have failed peginterferon and ribavirin treatment, the treatment paradigm is based on the large Respond 2 study.[3] Patients again were randomized into 3 groups. Treatment Group 1 was the control group and received 48 weeks of PR.