

EDITORIALS



A New Era of Hepatitis C Therapy Begins

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A new era of therapy for hepatitis C virus (HCV) infection is dawning with the development of two effective HCV protease inhibitors, boceprevir and telaprevir. In this issue of the *Journal*, the results of two phase 3 trials involving boceprevir, in combination with peginterferon and ribavirin, are presented: the SPRINT-2 (Serine Protease Inhibitor Therapy 2) trial (ClinicalTrials.gov number, NCT00705432), by Poordad and colleagues,¹ and HCV RESPOND-2 (Retreatment with HCV Serine Protease Inhibitor Boceprevir and PegIntron/Rebetol 2; NCT00708500), by Bacon and colleagues.² Both studies focused on patients infected with HCV genotype 1; the SPRINT-2 trial involved those who had not previously received treatment, whereas HCV RESPOND-2 involved those who had previously received treatment.

What are the key background concepts to keep in mind when reading these two important studies? First, boceprevir, a competitive inhibitor of the nonstructural 3 (NS3) protease complex of HCV genotype 1, does not have clinically significant activity against other HCV genotypes.^{3,4} Second, HCV has been shown to rapidly develop resistance when exposed to protease-inhibitor monotherapy, but the addition of interferon reduces the rate of emergence of these resistant variants.⁵ Third, black patients respond less well to antiviral therapy with peginterferon plus ribavirin than do nonblacks, in part because of the decreased prevalence among blacks of an interleukin-28B gene (*IL28B*) polymorphism associated with interferon responsiveness.⁶ Finally, the presence of cirrhosis has a negative impact on response to therapy,⁷ yet it affects a considerable percentage of patients awaiting treatment.

In the SPRINT-2 trial, all patients received peginterferon and ribavirin during a 4-week lead-in

phase before boceprevir (or placebo) was added. There were three treatment groups. The first received a standard regimen of peginterferon and ribavirin for 44 weeks after the lead-in period (control). The second received response-guided triple therapy consisting of boceprevir plus peginterferon-ribavirin for 24 weeks, after which patients with undetectable HCV RNA levels between weeks 8 and 24 after the lead-in period could stop all treatment. The third received fixed-duration triple therapy for 44 weeks after the lead-in period. In both nonblack and black cohorts, the use of boceprevir achieved a substantial and significant increase in the rate of a sustained virologic response. In the combined cohorts of black and nonblack patients, the rate of a sustained virologic response was 38% among controls, 66% among patients receiving 48 weeks of triple therapy, and 63% among patients receiving response-guided triple therapy. Patients with advanced fibrosis represented 7 to 11% of the SPRINT-2 patients and had lower rates of a sustained virologic response than those with less fibrosis. Anemia and dysgeusia were among the most common adverse events associated with boceprevir, occurring in approximately 49% and 40% of boceprevir-treated patients, respectively.

In HCV RESPOND-2, boceprevir was tested in patients with HCV genotype 1 infection who had previously received treatment with peginterferon-ribavirin, with an outcome of relapse or non-response. Importantly, the study excluded patients in whom 12 weeks of the prior therapy resulted in a reduction in the HCV RNA level of less than 2 log₁₀ IU per milliliter. Similar to the SPRINT-2 study, HCV RESPOND-2 included a 4-week lead-in phase and studied both fixed-duration and response-guided therapy. The most important find-

ings from HCV RESPOND-2 are the impressive increase in the rates of a sustained virologic response both in patients who had had a non-response to prior therapy (with rates of 7% in the control group, 40% in the response-guided boceprevir group, and 52% in the fixed-duration boceprevir group) and in patients who had had a relapse after prior therapy (with rates of 29%, 69%, and 75%, respectively). Adverse effects associated with boceprevir treatment included anemia, rash, dry skin, and dysgeusia, yet discontinuation of boceprevir owing to these adverse events occurred in only 8 to 12% of the patients.

The 4-week lead-in period of peginterferon-ribavirin therapy used in the SPRINT-2 trial and HCV RESPOND-2 is a major point of divergence from other studies and appears to have certain key advantages, but also introduces some complexities. In the SPRINT-1 study,⁸ Kwo and colleagues demonstrated that the advantage of having a lead-in phase was modest at best in groups receiving treatment for 24 to 28 weeks (with a rate of sustained virologic response of 56% with a lead-in phase and 54% without it) but was greater in groups receiving 48 weeks of therapy (in which the rates of sustained virologic response were 75% with a lead-in phase vs. 67% without it). However, the advantage of a lead-in period extended beyond the rate of a sustained virologic response: the rate of viral breakthrough during the treatment phase was lower in the group receiving 48 weeks of treatment, which incorporated the lead-in period, than in the other groups.³

In both the SPRINT-2 study and HCV RESPOND-2, the decline in viral load after 4 weeks of lead-in therapy was indicative of the subsequent therapeutic response. Should treatment be discontinued in patients with a decline in the HCV RNA level of less than 1 log₁₀ IU per milliliter at week 4? In the SPRINT-2 study, among the 95 patients in the combined cohort who had a decline in the HCV RNA level of less than 1 log₁₀ IU per milliliter at week 4, the rate of sustained virologic response was 38%, which is actually quite high for this subgroup. However, this success comes at a cost. A total of 38 of 94 patients (40%) showed the development of resistant variants. Clearly, patients with a reduction in the HCV RNA level of 1 log₁₀ IU per milliliter or more should continue therapy, although an argument could be made that those with undetectable levels at week 4 may do just as well by

continuing peginterferon-ribavirin without boceprevir. The lead-in period also makes therapy logistically more complex, since the measurement of the week 4 viral load may take a week or longer to receive from the laboratory.

Anemia was common in both the SPRINT-2 study and HCV RESPOND-2, with more than 40% of patients requiring erythropoietin administration for up to approximately 150 days. In HCV RESPOND-2, more than 8% of patients in the fixed-duration boceprevir group had a reduction in the hemoglobin level to less than 8.0 g per deciliter, and 9% required blood transfusions. This rate of anemia poses concerns. Without erythropoietin, additional reduction in the dose of boceprevir or ribavirin (or both) would be necessary to manage anemia, which might reduce the rate of sustained virologic response.

In summary, HCV protease inhibitors represent a major advance in our ability to treat chronic HCV infection. Future therapy will be more complex, not easier, but the improvement in the rate of sustained virologic response with boceprevir, to nearly 70% in the SPRINT-2 trial and to more than twice the rate in previously treated patients in HCV RESPOND-2, have been eagerly awaited. We will soon embark on a new era of successful HCV therapy.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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