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 nonresponse. 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 $\log_{10}$ 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 nonresponse 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 $\log_{10}$ 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 $\log_{10}$ 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 $\log_{10}$ 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.

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Assessing the Value of Treatments to Increase Height

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The use of growth hormone and estrogen has a long and often controversial history in the manipulation of growth. Pharmacologic interventions to increase growth in short children are increasingly common. We believe that the usefulness of growth-promoting treatments depends on well-designed studies that assess both the effect on height and the functional benefit of height gained.

In this issue of the *Journal*, Ross et al. report the results of a unique, placebo-controlled trial of growth hormone treatment, with or without early low-dose ethinyl estradiol, on adult height in Turner's syndrome, which is characterized by short stature and hypogonadism.[1] This randomized trial began in 1987, and bringing it to fruition is an achievement — particularly given the changes in the regulatory environment that have occurred since the study's inception. Such changes included a review by an expert panel of the ethics and safety of this study and a companion study,[2] subsequent Food and Drug Administration approval of the use of growth hormone for Turner's syndrome in 1996, and changes in recommended practices that made growth hormone treatment routine for patients with Turner's syndrome. The results reported here confirm those of previous, less rigorous studies showing that treatment with growth hormone significantly increased adult height in patients with Turner's syndrome.

The results also suggest a modest but intriguing synergism between growth hormone and low-dose estrogen in promoting growth. Estrogen has been the quintessential growth-suppressive hormone — high-dose estrogen has been used to stifle growth in tall girls — and estrogen is necessary and sufficient to bring about epiphyseal closure. However, the effect of estrogen on growth is biphasic: low doses increase height velocity. Estradiol accounts for the normal female growth spurt during puberty and, when provided at a physiologic dose and at the appropriate age, stimulates the pubertal growth of teenagers with hypogonadism without compromising their height potential. Nevertheless, common practice in the management of Turner's syndrome has been to delay estrogen-replacement therapy until the mid-teens because of the perceived possibility of interfering with growth, despite the potential negative implications of such a delay with respect to bone mineral accrual and age-appropriate psychosocial development.

The data reported by Ross et al. are consistent with the results of a controlled study in which the administration of low-dose estradiol in the 12th year of age that was intended to mimic the very low estradiol levels seen in early puberty did not interfere with the effects of growth hormone in Turner's syndrome and tended to increase growth and to lead to earlier attainment of adult height.[3] In the study by Ross et al., initiation of treatment with growth hormone plus low-dose estradiol at an average age of 9.3 years also tended to increase adult height, by a standard-deviation score of 0.26 points (about 1.7 cm), as compared with growth hormone plus placebo.

The overall effect of growth hormone treatment was a gain of 0.78 points in adult height on the standard-deviation score, as compared with placebo — representing a significant gain of 5.0 cm over the 7-year study period. The mean adult height, even with growth hormone treatment, remained below the normal range, and there was considerable variation in the heights gained. Although greater gains might have been achieved with current, higher-dose growth hormone regimens (e.g., a gain of 7.2 cm [2.8 in.] in one study),[4] with earlier institution of treatment, or both,[5] higher doses of growth hormone have also resulted in variable and, on average, subnormal adult heights.

The impact of these findings on practice and policy will depend not only on their statistical significance but also on whether the observed changes in height translate into clinically meaningful benefit. The ability to increase height