Telaprevir, Boceprevir Improved HCV Cure Rates

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VITALS

Major Finding: The HCV protease inhibitors telaprevir and boceprevir improve sustained virologic response rates and shorten treatment duration in patients with chronic hepatitis C virus infection.

Data Source: Four phase III clinical trials evaluating the safety and efficacy of the direct-acting antivirals in treatment-naive and treatment-resistant HCV patients.

Disclosures: Dr. Jacobson and Dr. Sherman disclosed relationships with Vertex Pharmaceuticals, which manufactures telaprevir. Dr. Jacobson also has a relationship with Tibotec, which also is involved with the development of telaprevir. Dr. Poordad and Dr. Bacon also disclosed relationships with Merck, which manufactures boceprevir.

BOSTON – The forthcoming availability of the protease inhibitors telaprevir and boceprevir for the treatment of chronic hepatitis C is likely to vastly improve virologic response rates and cut treatment times, but experts warn that such advancements need to be balanced against the "huge potential" for misuse of the agents and the need to manage side effects and monitor for antiviral resistance.

When used in combination with standard therapy of pegylated interferon plus ribavirin-based therapy, both of these investigational drugs improved sustained virologic response rates and reduced treatment duration, compared with standard therapy alone, in four pivotal, phase III trials reported at the meeting.

Telaprevir Boosts Viral Cure Rates

In the ADVANCE trial, a three-arm, double-blind, placebo-controlled study, investigators compared two telaprevir-based regimens with standard therapy in 1,088 treatment-naive patients with chronic genotype 1 hepatitis C virus (HCV) infection, according to lead investigator Dr. Ira M. Jacobson of New York Weill Cornell Medical Center in New York City.

Patients in treatment arms 1 and 2 received 750 mg of telaprevir plus standard therapy for 8 and 12 weeks, respectively, whereas patients in the control group received standard therapy alone, which consisted of 180 mcg/week of pegylated interferon alfa-2a and 1,000-1,200 mg/day of ribavirin.

Patients who achieved extended, rapid virologic response (RVR) – defined as undetectable HCV RNA viral load at treatment weeks 4 and 12 – were treated with standard therapy for an additional 16 and 12 weeks in the 8- and 12-week telaprevir arms, respectively, for a total of 24 weeks, Dr. Jacobson explained. Patients in whom HCV RNA was detectable at either week 4 or 12 received an additional 40 and 36 weeks of therapy, respectively, for a total of 48 weeks, he said.

Compared with 44% of patients in the control group who achieved sustained virologic responses (SVR) 24 weeks after the last treatment, significantly more patients in both telaprevir arms – 69% of the 8-week group and 75% of the 12-week group – met that end point, Dr. Jacobson reported.

The extended RVR rates in the 8- and 12-week groups were 57% and 58%, respectively, compared with 8% in the control arm, he said.

Significantly improved SVRs were also observed in difficult-to-treat subgroups, according to Dr. Jacobson.

"Among black patients, the [SVR] rates were 58% and 62% in the 8- and 12-week treatment arms, and 25% in the control arm, and in cirrhotic patients the respective rates were 53%, 62%, and 33%," he reported.

The phase III, open-label ILLUMINATE trial was designed to determine whether extending the telaprevir and standard therapy regimen from 24 to 48 weeks would be beneficial in treatment-naive, genotype 1 HCV patients who achieved extended RVR. In all, 540 patients were initially treated with the 12-week telaprevir regimen described above. Of the 352 patients who achieved RVR, 322 remained on treatment and were randomized to either a 24-week or 48-week treatment arm.

"The [SVR] rates associated with the 24-week and the 48-week arms were statistically similar, at 92% and 87.5%, respectively," reported Dr. Kenneth E. Sherman of the University of Cincinnati. Analyses of the data based on race and extent of liver damage showed that 88% of black patients who experienced extended RVR achieved SVR in both the 24- and 48-week treatment arms, and 82% and 88% of patients with advanced fibrosis/cirrhosis achieved SVR in the 24-week and 48-week arms, respectively, he said.

The high viral cure rate observed in the study – the overall SVR rate was 72% in an intent-to-treat analysis – "[supports] the role of response-guided therapy with telaprevir-based regimens" in treatment-naive patients," he said.

Boceprevir Benefits Nonresponders

Response-guided, fixed-duration therapy with boceprevir was safe and effective in a cohort of HCV genotype 1 patients who were enrolled in the RESPOND-2 study and who failed standard therapy, reported lead investigator Dr. Bruce R. Bacon of St. Louis University.

The 403 patients included those in whom prior standard therapy induced no notable decrease in HCV viral load (null responders) or a "not undetectable" decrease in HCV viral load (nonresponders), as well as those in whom prior treatment initially resulted in undetectable HCV RNA, followed by a viral rebound (relapsers), he said.

All the patients underwent a 4-week lead-in phase of standard therapy followed by a random assignment to continue standard therapy alone or in conjunction with 800 mg of boceprevir taken three times daily. The treatment duration for patients in the boceprevir arm with undetectable HCV RNA at study weeks 8 and 12 was 36 weeks, whereas those patients in whom HCV RNA was detectable at study week 8, but undetectable at study week 12, stopped boceprevir at week 36 but continued standard therapy for an additional 12 weeks, for a total treatment duration of 48 weeks, Dr. Bacon said. Patients in the control group were treated for 48 weeks.

The SVR rates at 24 weeks after treatment conclusion were significantly higher in the boceprevir groups, compared with the control group. In the response-guided and fixed-duration boceprevir groups, the SVR rates were 59% and 66%, respectively, compared with 21% in the control patients, he said.

In all study arms, "previous relapsers and previous null responders fared better than prior nonresponders," Dr. Bacon said, noting that the respective SVR rates for previous relapsers, null responders, and nonresponders were 29%, 7%, and 0% in the control group; 69%, 40%, and 33% in the response-guided therapy group; and 75%, 52%, and 34% in the fixed-duration group.

Boceprevir with a standard therapy lead-in strategy was also evaluated in the SPRINT-2 study involving HCV genotype 1 treatment-naive patients, according to Dr. Fred Poordad of Cedars-Sinai Medical Center in Los Angeles.

The trial included 1,097 patients who underwent a similar 4-week standard therapy lead-in strategy as defined above, followed by the addition of placebo for 44 more weeks or by the addition of boceprevir, either for 24 more weeks for patients with undetectable HCV RNA at week 8 or for 24 more weeks plus 20 additional weeks of standard therapy for patients with detectable HCV RNA at week 8, but not at week 24, Dr. Poordad explained. Patients with detectable HCV RNA at week 24 were discontinued for futility, he said.

"In both the response-guided and fixed-treatment arms, boceprevir increased viral cure rates significantly, by approximately 70%," he said. Specifically, the SVR rate was 63% in the 28-week response-guided group, 66% in the 48-week fixed-duration group, and 38% in the 48-week control group, he said.

In a cohort analysis of treatment response for the study's 159 black patients, the relative improvement in SVR rates remained significantly improved in the boceprevir arms, although the differences were not as robust, Dr. Poordad said. In this subgroup, the respective SVR rates in the response-guided therapy, fixed-duration therapy, and control groups were 42%, 53%, and 23%, respectively.

The rationale for using a lead-in strategy "is to help physicians identify patient responsiveness to interferon before adding boceprevir," Dr. Poordad explained. This can provide an early indication of the likelihood of treatment success. ■

VIEW ON THE NEWS

The Potential for Misuse Is 'Huge'

In the next year, "we are going to see the approval of two direct-acting antiviral drugs – telaprevir and boceprevir. We anticipate the widespread use of these drugs in the United States and the European Union, as they've been shown to improve sustained virologic response rates by approximately 75% in treatment-naive patients," Dr. Paul Pockros said at the meeting.

Unfortunately, there is also a "huge potential" for misuse of these drugs, owing to prescribing physicians' poor understanding of the therapeutic populations, inadequate viral-assay testing, poor side-effect management, and lack of monitoring for antiviral resistance, he said.

The designs of the trials on which approval will be based, as well as the resulting treatment regimens, are fairly complex, said Dr. Pockros, "so there will be lots of opportunities to screw things up." For example, he hypothesized, "I am sure that some patients are going to be put on telaprevir for 44 weeks with a 4-week pegylated interferon/ribavirin lead-in [even though the lead-in strategy was evaluated for boceprevir, not telaprevir], and other patients might be put on boceprevir for 12 weeks with no lead-in."

For optimal safety and efficacy, physicians must have a good understanding of the treatment regimens, particularly in special populations, and they must actively and frequently monitor for antiviral resistance. Additionally, physicians should anticipate problems with adherence, which is already an issue for some patients on standard therapy, he said.

The objective should be "to keep our eyes on the ball," said Dr. Pockros. "Our primary goal moving forward with all of the new drugs is going to be eradicating the virus."

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