Telaprevir Improves Viral Cure Rates After Previous Treatment Failure

March 31, 2011 By Tim Horn

People living with hepatitis C virus (HCV) whose earlier treatment was unsuccessful are more likely to achieve a sustained virologic response (SVR) upon being retreated with the experimental protease inhibitor telaprevir combined with pegylated interferon and ribavirin, compared with those taking pegylated interferon and ribavirin (IFN/RBV) alone. This is the conclusion of the Phase III REALIZE study, the final results of which were reported Thursday, March 31, at the 46th annual meeting of the European Association for the Study of the Liver (EASL) in Berlin.

REALIZE is the only Phase III study completed to date designed to evaluate the efficacy of a direct-acting treatment on all major subgroups of people with genotype 1 HCV whose earlier treatment was unsuccessful, including those who relapsed, those who achieved a partial response and those who had almost no response, known as a null response.

The study also evaluated whether SVRs or viral cures—defined as an undetectable HCV viral load six months after completed treatment—could be further improved by delaying the start of telaprevir by four weeks, during which time patients received four weeks of IFN/RBV, compared with a simultaneous start. The REALIZE data, reported by Stefan Zeuzem, MD, of Johann Wolfgang Goethe University Medical Center in Frankfurt and his colleagues, showed no clinical benefit to this lead-in for people treated with telaprevir-based combination therapy.

In this study, 663 patients were randomized to two telaprevir-based treatment groups—one group received telaprevir plus IFN/RBV arms from the start (simultaneous group); the other group received IFN/RBV alone for four weeks before adding telaprevir (lead-in group)—or a control arm of 48 weeks of IFN/RBV. Telaprevir was used for a total of 12 weeks, whereas IFN/RBV was continued in all groups for 48 weeks.

Prior relapsers were defined as individuals whose HCV was undetectable after completing at least 42 weeks of treatment but whose virus became detectable during follow-up. Prior partial responders were individuals who saw their HCV viral loads decreased by at least 2 logs after 12 weeks of treatment but never went undetectable. Prior null responders were defined as people who didn't see their HCV viral loads fall by at least 2 logs.

Forty-eight percent of patients overall had advanced liver fibrosis or cirrhosis—scarring of the liver—and 89 percent of patients overall had high HCV viral loads—in excess of 800,000

copies—before retreatment.

Among those in the simultaneous start group, 83 percent of prior relapsers, 59 percent of prior partial responders and 29 percent of null responders achieved SVRs, compared with 24 percent, 15 percent and 5 percent, respectively, of those who received IFN/RBV alone.

SVRs among those in the lead-in group were 88 percent among prior relapsers, 54 percent among prior partial responders and 33 percent among prior null responders—viral cure rates that didn't differ significantly when compared with those in the simultaneous start group.

Unfortunately, viral cure rates were low among prior null responders with cirrhosis, which was documented in 14 percent of those treated with telaprevir and IFN/RBV, compared with 10 percent of those treated with IFN/RBV alone. Among prior partial responders with cirrhosis, SVRs were documented in 34 and 20 percent, respectively. And in prior relapsers with cirrhosis, 84 percent and 13 percent, respectively, achieved SVRs.

The most common side effects in REALIZE —much like those documented in other telaprevir/IFN/RBV studies—were fatigue, itching, nausea, headache, rash, anemia, flu-like symptoms, insomnia and diarrhea. Rash and anemia occurred more frequently in the telaprevir-based treatment groups compared with the control group.

More than 90 percent of rash was mild to moderate and primarily managed with the use of topical corticosteroids and/or antihistamines. Anemia was primarily managed by reducing the dose of ribavirin.

In conclusion, Zeuzem noted that telaprevir, combined with IFN/RBV, demonstrated superior efficacy compared with IFN/RVN alone in all prior treatment failure populations, including null- and partial-responders. "A lead-in did not have a significant impact on SVR rates," his group added. "The safety profile of [telaprevir, IFN and RBV] in prior treatment-failure patients was consistent with that observed in treatment naïve patients."

The FDA has scheduled its Antiviral Drugs Advisory Committee to discuss the Vertex Pharmaceuticals' petition to approve the drug on April 28, 2011. The new drug application (NDA) submitted by Vertex includes data from three pivotal studies—ADVANCE, ILLUMINATE and REALIZE—which evaluated telaprevir in combination with pegylated-interferon and ribavirin in people with hepatitis C who were new to treatment as well as those who did not achieve a viral cure after treatment with currently available treatments.

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