TMC435, Peg-Interferon and Ribavirin Combo Boosts Cure Rates for Hep C Genotype 1

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Adding Janssen Therapeutics' TMC435, a once-daily experimental hepatitis C virus (HCV) protease inhibitor, to pegylated interferon and ribavirin brought cure rates to over 80 percent among first-time treatment takers with genotype 1 HCV infection. These results from PILLAR, an international Phase II trial, were reported Monday, November 7, at the 62nd annual meeting of the American Association for the Study of Liver Diseases (AASLD) in San Francisco.

Michael Fried, MD, of the University of North Carolina Liver Center at Chapel Hill and his colleagues compared different doses and durations of TMC435-based treatment, using response-guided therapy (RGT). For people with HCV viral loads below 25 international units per milliliter (IU/mL) after four weeks of treatment, therapy was shortened to 24 weeks if hepatitis C subsequently remained undetectable at weeks 12, 16 and 20; otherwise, treatment was given for 48 weeks.

According to Fried's report, the overall cure rate among PILLAR participants treated with 150 milligrams (mg) of TMC435 once daily—the dose being explored in Phase III trials—plus pegylated interferon/ribavirin ranged from 81 percent to 86 percent, and a majority (79 percent to 86 percent) were treated for only 24 weeks. Among people eligible for shorter treatment, sustained virologic response (SVR)—or viral cure rates—topped 90 percent, ranging from 93 percent to 96 percent. In the placebo group, in which participants were treated with 48 weeks of pegylated interferon and ribavirin, 65 percent were cured.

Overall, 20 people who received pegylated interferon/ribavirin plus 150 mg TMC435 for either 12 or 24 weeks were not cured. Viral breakthrough—which generally happened before week 12—was reported in 7.8 percent of people in the TMC435 12 week group and 2.5 percent of people in the TMC435 24 week group. Relapse rates were similar in both groups, being 8.7 percent among the 12-week group, and 8 percent among the 24-week group.

Resistance to TMC435 was found in everyone who experienced viral breakthrough, and most people who relapsed. In the placebo arm, viral breakthrough was reported among 5.2 percent of study participants, and 17.7 percent relapsed after treatment completion.

Almost all of the PILLAR participants were white and in their late 40s, and the majority had a

hepatitis C viral load greater than 800,000 IU/mL.

Characteristics usually linked to treatment response, such as IL28B CC genotype, were not evenly distributed across study groups. For example, 40 percent of those who took 150 mg of TMC435 for 12 weeks had a CC genotype, which is linked to a higher likelihood of cure with pegylated interferon and ribavirin, whereas only 25 percent had the CC genotype in the 24-week 150 mg group. Thus, comparisons between the two groups are difficult to analyze.

Fried noted, however, that TMC435 improved cure rates among people with the harder-to-treat IL28B genotypes: CT and TT. Among those who took pegylated interferon/ribavirin alone, 50 percent of people with the CT or TT genotype were cured, compared with 78 percent of those with IL28B CT or TT in the 150 mg dosing groups.

Cure rates in the 150 mg dosing groups did not differ according to viral subtype, with 82 percent of people with HCV genotype 1a and 84 percent of people with HCV genotype 1b experiencing SVRs.

“Once-daily TMC435 was well tolerated,” Fried noted, with “…no increase in the incidence of adverse events or treatment discontinuations due to adverse events between TMC435 and placebo groups.” Overall, he reported, serious side effects were reported in 6.5 percent of people treated with TMC435 versus 13 percent of the placebo group. The only side effect linked with TMC435 was an increase in bilirubin, which returned to normal levels after TMC435 was stopped.

“Once-daily TMC435 with PegIFN/RBV was more effective than PegIFN/RBV alone,” Fried concluded, adding that “triple therapy with TMC435 reduced the impact of unfavorable IL28B genotypes on virologic response.”

A pair of Phase III trials, QUEST-1 and QUEST-2, are studying 150 mg of TMC435 or placebo once daily for 12 weeks, plus 24 to 48 weeks of pegylated interferon and ribavirin in first-time treatment takers with HCV genotype 1. The PROMISE study is looking at the same strategy for people with HCV genotype 1 who relapsed after completing treatment.
