Interferon-Free Gilead and BMS Combo Shows High Cure Rate Potential

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All-oral treatment with 24 weeks of daclatasvir, Bristol-Myers Squibb's once-daily NS5a inhibitor, and GS-7977, Gilead's once-daily nucleotide polymerase inhibitor—with or without ribavirin—kept hepatitis C virus (HCV) undetectable for four weeks after treatment in 100 percent of people with genotype 1 infection and 91 percent of people with genotype 2 and 3 infection, according to early study results presented Thursday, April 19, and the 47th Meeting of the European Association for the Study of the Liver (EASL) in Barcelona.

In this open-label Phase II trial, reported at EASL by Mark Sulkowski, MD, of Johns Hopkins University School of Medicine and his colleagues, first-time treatment takers without cirrhosis were randomized to receive one of three treatment regimens: GS-7977 alone for seven days with daclatasvir added for an additional 23 weeks, GS-7977 combined with daclatasavir for a full 24-week course, and GS-7977 combined with both daclatasvir and ribavirin. Roughly 15 patients in each group were genotype 1a/1b patients; another 15 were genotype 2/3 patients.

The drugs worked quickly to suppress HCV levels, which were under the limit of quantification in 100 percent of patients by week four, Sulkowski and his colleagues noted.

HCV is considered cured when the virus becomes undetectable during treatment and remains undetectable for 24 weeks after completing therapy, an outcome known as SVR 24. So far, participants in this study have been followed for four weeks after finishing treatment (an outcome called SVR 4). Such results are a strong predictor of high cure rates, but longer follow-up is needed to determine whether relapses occur.

In the genotype 2/3 group, two people who were undetectable at their last study visit were lost to follow-up. One person experienced viral breakthrough during dual therapy, but became undetectable after pegylated interferon and ribavirin were added. A fourth person relapsed four weeks after completing treatment.

In genotype 1 patients, Sulkowski's team noted that neither the IL28B genotype or hepatitis C viral subtype (1a versus 1b) had an impact on SVR 4 outcomes.

In all genotypes, adding ribavirin to the combination did not change response to treatment, but it did add to side effects. According to the study authors, all six cases of anemia documented in the

study occurred in people who were taking the ribavirin-containing regimen.

“Daclatasvir and GS-7977 were generally well-tolerated, based on the available interim 12 week on-treatment data,” noted Sulkowski in his presentation.

Common, mild-to-moderate side effects included fatigue, headache, anxiety, nausea, diarrhea, insomnia and back pain. No moderate-to-severe elevations in liver enzymes or bilirubin levels occurred.

Of the moderate-to-severe serious laboratory abnormalities, six people experienced anemia (all associated with ribavirin use), two people experienced elevated blood glucose, two experienced low phosphorous levels, and one person experienced a low white blood cell count and elevated total cholesterol. None of these led to treatment discontinuation.

Although 10 people experienced serious adverse events during treatment, only three of them were related to treatment—all daclatasvir or GS-7977 overdoses.

There were two study discontinuations: one due to a stroke and one due to fibromyalgia, neither of which was considered treatment-related.

An ongoing trial in people with HCV genotype 1a or 1b is also studying 12 weeks of daclatasvir plus GS-7977, with or without ribavirin, in first-time treatment takers and people who were unsuccessfully treated with pegylated ribavirin plus Incivek or Victrelis.

Sulkowski concluded that “[daclatasvir] and GS-7977 may represent a significant advance in the treatment of HCV; further research is needed to confirm these findings.”

While it is hoped that Gilead and BMS will collaborate on developing a fixed-dose combination tablet containing both daclatasvir and GS-7977, an April 19 New York Times article indicates that the companies have not agreed to collaborate in this regard.

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