Pharmasset's Two-Drug Non-Interferon Combo Packs Quick Hep C Punch

April 5, 2011 By Tim Horn

A combination of two experimental once-a-day drugs active against the hepatitis C virus (HCV) is showing excellent potential, without the addition of standard pegylated interferon and ribavirin (IFN/RBV), according to results from a small clinical trial reported Saturday, April 2, at the 46th annual meeting of the European Association for the Study of the Liver (EASL) in Berlin. The drugs, Pharmasset's PSI-7977 and PSI-938, reduced viral loads to undetectable levels after just 14 days in 15 of 16 patients included in the study.

PSI-7977 and PSI-938 are direct-acting antivirals (DAAs) that specifically target HCV proteins. They work differently from standard therapy's pegylated interferon and ribavirin, drugs that boost the immune system's ability to clear the virus. Most DAAs in development today—including protease inhibitors, NS5A inhibitors and nucleoside analogues—are being studied in combination with IFN/RBV to maximize efficacy, though there is considerable interest in studying DAAs in the absence of toxicity-prone IFN and RBV.

Leaked results from a small clinical trial testing PSI-7977 and PSI-938 made headlines before their official presentation by Erik Lawitz, MD, of Alamo Medical Research in El Paso, Texas, and his colleagues at EASL.

The study enrolled 40 patients—all of whom had genotype 1 and none of whom had cirrhosis or previous HCV treatment—and randomized them to one of four dosing groups. The first group received PSI-938 alone for 14 days. A second group started with seven days of PSI-938 treatment and then added PSI-7977 for additional seven days. A third group started with seven days of PSI-7977 and then received both drugs for another week. The fourth group received both drugs for 14 days. A fifth group, consisting of eight patients who received a placebo, was included as well.

PSI-938 was dosed at 300 milligrams (mg) once a day; PSI-7977 was dosed at 400 mg once daily.

After 14 days of treatment, four of the eight patients who received PSI-938 alone had undetectable viral loads. All of the eight patients who started treatment with PSI-938 and then added PSI-7977 had undetectable viral loads after 14 days. In those who used both drugs for the 14-day period, or started with PSI-7977 and then added PSI-938, seven of eight patients in each group had undetectable viral loads after 14 days.

What is not yet clear, based on the data reported thus far, is whether the encouraging 14-day results using these DAAs without IFN/RBV will translate into rapid virologic responses (RVRs) and early virologic responses (EVRs)—undetectable HCV viral loads at four weeks and 12 weeks, respectively—which are widely considered to be predictors of sustained virologic responses: Viral cures once treatment is stopped.

Lawitz reported that all regimens were well tolerated, with no serious side effects and no patients discontinuing treatment because of adverse events. Mild adverse events were noted in some patients, including headache in two patients, fatigue in one patient, chest pain in one patient and dizziness in one patient.

Though nearly half of the patients entered the study with elevated liver enzymes (ALTs), they normalized in all patients after 14 days of treatment.

Additional studies of PSI-938 and PSI-7977, used alone, together and in combination with IFN/RBV, are anticipated. On March 30, Pharmasset announced one such study, the Phase IIb ATOMIC trial, testing PSI-7977 in combination with IFN/RBV.

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