Interferon-Free Alisporivir Treatment Showing Promise in Genotype 2/3 Trial

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Alisporivir, a once-daily drug being developed by Novartis at the forefront of a new class of hepatitis C virus (HCV) compounds known as cyclophilin inhibitors, is showing promise as a component of interferon-free therapy for people with genotype 2 or 3 HCV infection, according to new results from a Phase II study reported in San Francisco at the 62nd annual meeting of the American Association for the Study of Liver Diseases.

Nearly half of all study volunteers using the drug in combination with ribavirin, but without interferon, have undetectable HCV levels after six weeks of treatment, reported Jean-Michel Pawlotsky, MD, of the University of East Paris and his colleagues. In addition, roughly a third of the genotype 2/3 patients in the study had undetectable HCV levels at the six-week mark of therapy with alisporivir alone—use of the drug without either pegylated interferon or ribavirin.

Also known as DEB025, alisporivir works by inhibiting a cellular protein called cyclophilin known to play a role in the reproduction of HCV. The drug is similar to—and actually synthesized from—cyclosporin A, a compound used to suppress the immune system during organ transplants to prevent the body from rejecting the organ. Alisporivir does not, however, suppress the immune system. And because alisporivir targets a cellular protein used by all types of HCV, it may prove to be an effective option against a broad range of HCV genotypes and less susceptible to drug resistance.

The clinical trial reported by Pawlotsky's team has enrolled about 340 previously untreated people living with genotype 2 or 3 HCV infection. Five groups are being compared in the study. Two groups are receiving alisporivir—either 600 milligrams (mg) or 800 mg once daily—plus ribavirin (400 mg twice daily). A third group is receiving alisporivir (600 mg once daily) plus once-weekly pegylated interferon. A fourth group is receiving standard therapy: pegylated interferon plus twice-daily ribavirin. A fifth group is receiving 1,000 mg alisporivir monotherapy.

Only interim data—all participants in the study remain on treatment—were reported by Pawlotsky's group. Final results—rates of sustained virologic responses (SVR)s, or viral cures—will be available once therapy is discontinued and study volunteers have been off treatment for 24 weeks.

Six weeks into treatment, 49 percent of those receiving alisporivir plus ribavirin have undetectable

HCV levels. In addition, 97 percent of those who had undetectable viral loads at six weeks in the alisporivir/ribavirin groups and had been followed for at least 12 weeks of treatment maintained HCV viral loads below the level of detection.

Also encouraging, 32 percent of those receiving alisporivir alone also have viral loads below the level of detection after six weeks of treatment.

Response rates are thus far similar in the two alisporivir/ribavirin treatment groups—51 percent of those in the 600 mg group had undetectable viral loads at six weeks, compared with 48 percent of those in the 800 mg group. Interim response rates are also similar among those with genotype 2 versus genotype 3 HCV.

Of note, participants receiving alisporivir/ribavirin or alisporivir monotherapy who have detectable HCV levels after four weeks of treatment are receiving add-on pegylated interferon (or pegylated interferon/ribavirin) therapy from week six onward. For those who have met these criteria, as little as two weeks of add-on treatment reduced HCV viral loads to undetectable in more than 85 percent.

Thus far, there has been a low incidence of serious side effects, with rates of adverse events comparable between the treatment groups. A low number of people experienced an increase in bilirubin, a pigment found in the liver, which can cause yellowing of the skin, nails and eyes. Increased bilirubin can also be a sign of liver damage. However, according to Pawlotsky, the bilirubin increases seen in patients receiving alisporivir have not been associated with any other signs of liver damage.

A Phase III study of alisporivir evaluating its safety and effectiveness, when combined with pegylated interferon and ribavirin, for people with hard-to-treat genotype 1 HCV infection is currently under way. Preliminary Phase II data involving this population of patients were reported earlier this year in Berlin at the 46th Annual Meeting of the European Association for the Study of the Liver.

Other studies are being conducted as well, including Phase II evaluations involving people with genotype 1 HCV who tried and failed earlier treatment.
