Entry Inhibitor Could Potentially Cure Hepatitis B and D

Bulevirtide plus pegylated interferon shows promise for hard-to-treat coinfection.

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Bulevirtide, formerly known as Myrcludex B, in combination with pegylated interferon, suppressed hepatitis delta virus (HDV) and led to a functional cure of hepatitis B virus (HBV) in some people living with HBV/HDV dual infection, according to a presentation at the 2019 International Liver Congress in Vienna.

HBV is difficult to treat in part because it produces cccDNA (covalently closed circular DNA), a genetic blueprint of the virus that can lie dormant in liver cells and evade both the immune system and standard therapy. Nucleoside/nucleotide antivirals such as Viread (tenofovir disiproxil fumarate), Vemlidy (tenofovir alafenamide) and Baraclude (entecavir) can suppress HBV replication long term during treatment, but they don't eliminate the virus and usually do not lead to a cure, as indicated by hepatitis B surface antigen (HBsAg) loss and seroconversion.

Hepatitis delta is a defective virus that can only replicate in the presence of HBV. Over years or decades, chronic hepatitis B can lead to advanced liver disease including cirrhosis, liver cancer and end-stage liver failure. Liver disease is more aggressive and progresses faster in people with HBV/HDV coinfection than in those with HBV alone. There is currently no approved therapy for HDV, though it is sometimes treated with pegylated interferon.

Bulevirtide is an experimental entry inhibitor that binds to the same receptor HBV uses to enter liver cells, thereby both interfering with the lifecycle of HBV and preventing HDV replication.

Heiner Wedemeyer, MD, of Essen University Hospital in Germany presented findings from a Phase IIb study of the safety and efficacy of bulevirtide plus Pegasys (pegylated interferon-alfa-2a).

At last year's Liver Congress, Wedemeyer reported results from a study of bulevirtide in combination with Viread. Although bulevirtide suppressed HBV and HDV replication during treatment, it usually did not lead to a cure.

This year's study included 60 people with HBV/HDV coinfection. They were randomly assigned to receive pegylated interferon alone, 2 milligrams of bulevirtide alone, 2 mg of bulevirtide plus Pegasys or 5 mg of bulevirtide plus Pegasys. Pegasys was given as a once-weekly injection and

bulevirtide was given as a daily injection. All participants were treated for 48 weeks with a 24-week follow-up period after completing therapy.

HDV viral load fell steeply during treatment in the two combination therapy groups and modestly in the two single-drug, or monotherapy, groups, Wedemeyer reported. After stopping treatment, HDV RNA levels rebounded back to near the baseline level in the two monotherapy groups, and rose to about half the initial level in the 5 mg combination group. However, HDV viral load remained suppressed in the 2 mg combination group.

Nine of 15 people (60%) taking the 2 mg bulevirtide combination and six of 15 (40%) taking the 5 mg combination achieved undetectable HDV RNA by the end of treatment at week 48, compared with just two people (13%) in each monotherapy group. At 72 weeks, eight (53%) and four (27%) people in the 2 mg and 5 mg combination arms still had suppressed HDV, while no one in the monotherapy groups had sustained viral suppression.

In addition, six of 15 people in the 2 mg combination group and two of 15 in the 5 mg combination group had greater than a 1-log decline or reached undetectable HBsAg levels by week 72. Looking at both combination arms together, 27% experienced HBsAg loss and 20% achieved seroconversion—considered to be a functional cure. In contrast, no one taking either bulevirtide or pegylated interferon alone achieved HBsAg loss or seroconversion.

Just over a third of people (37%) taking the two combination regimens and 67% of those taking bulevirtide alone experienced ALT liver enzyme normalization at 48 weeks. But while ALT normalization was sustained in the combination arms, levels rose again after stopping treatment in the bulevirtide monotherapy group.

Treatment was generally safe and well tolerated. No serious adverse events were observed during treatment and there were no discontinuations due to bulevirtide-related side effects, Wedemeyer reported. Bulevirtide-related adverse events were generally mild; most side effects were attributable to pegylated interferon, which is known to be difficult to tolerate. Bile salts increased during treatment but returned to normal soon after stopping therapy.

“The results of this trial suggest that bulevirtide is a promising treatment for chronic HDV infection, and that the combination of bulevirtide and [pegylated interferon] has the potential to cure HBV/HDV coinfection in some patients,” Wedemeyer said.

He noted that this is the largest clinical trial and the best results ever seen for HDV. Given that virus levels rebounded after stopping therapy, he added that longer treatment durations will be explored in Phase III trials.

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