First Hepatitis D Treatment Approved in Europe

Hepcludex, formerly known as Myrcludex B, suppressed hepatitis B and hepatitis D virus replication in clinical trials.

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The European Medicines Agency—the European Union's counterpart to the U.S. Food and Drug Administration (FDA)—has approved the first drug for the treatment of hepatitis D, or hepatitis delta, which can accompany and worsen the complications of hepatitis B.

The new drug, Hepcludex (bulevirtide), suppressed hepatitis D virus (HDV) and hepatitis B virus (HBV) replication and was well tolerated in Phase II clinical trials. It was granted conditional marketing authorization, equivalent to the FDA's accelerated approval, and larger studies are underway.

"Today's approval marks a great achievement for patients suffering from the most severe form of viral hepatitis without any specific treatment option until today," Stephan Urban, PhD, of the University of Heidelberg, one of the inventors of Hepcludex, said in a press release from the German company MYR Pharmaceuticals, which is developing the treatment in collaboration with the university and the German Center for Infection Research.

Hepcludex has not yet been approved in the United States. However, it has received a breakthrough therapy designation from the FDA, intended to speed up development and approval of therapies that address an unmet need for treatment of serious or life-threatening conditions, as well as orphan drug status. The treatment was approved in Russia late last year under the brand name Myrcludex.

HDV is a small, defective virus that can replicate ionly n the presence of HBV. Over years or decades, chronic hepatitis B can lead to fibrosis (scarring of the liver), cirrhosis, liver cancer and liver failure. Coinfection with both HBV and HDV typically leads to more rapid and severe liver disease progression. People who acquire HDV in addition to HBV tend to develop cirrhosis a decade or more earlier than those with HBV alone, and even young people often progress to advanced liver disease.

Although only around 5% of people with HBV also have HDV, coinfection is thought to play a role in about 20% of cases of advanced liver disease and liver cancer in people with hepatitis B,

according to the World Health Organization. Coinfection is more common among people who inject drugs and people who also have hepatitis C or HIV.

Hepatitis B can be prevented with a vaccine, which also prevents hepatitis D. Antivirals such as Viread (tenofovir disoproxil fumarate), Vemlidy (tenofovir alafenamide) and Baraclude (entecavir) can suppress HBV replication during treatment, but they seldom lead to a cure. Until now, no treatments were specifically approved for hepatitis D, although people with HBV and HDV coinfection may be treated with pegylated interferon alpha.

Hepcludex is a first-in-class entry inhibitor that binds to surface receptors HBV uses to enter liver cells. This interferes with the hepatitis B life cycle and thereby also prevents HDV replication. It is administered as a 2 milligram once-daily injection under the skin, either alone or in combination with oral antiviral drugs for hepatitis B.

The treatment was originally developed by scientists at the University of Heidelberg and INSERM in France, a process that has been underway for 25 years. Researchers have presented results from clinical studies of Hepcludex at recent medical conferences.

At the 2018 International Liver Congress, Heiner Wedemeyer, MD, of Essen University Hospital presented findings from a study of Hepcludex plus Viread. After 24 weeks, 55 of the 90 participants (61%) treated with the combination had suppressed HDV viral load, compared with just one of the 28 people (4%) randomized to Viread alone. People treated with the combination were also more likely to experience normalization of ALT liver enzymes. However, the treatment usually did not lead to a cure.

At the 2019 EASL International Liver Congress, Wedemeyer reported findings from a Phase IIb study of Hepcludex plus pegylated interferon alpha-2a (Pegasys) in 60 people with HBV and HDV coinfection. They were randomly assigned to receive pegylated interferon alone, Hepcludex alone or one of two doses of Hepcludex (2 mg or 5 mg once daily) plus pegylated interferon for 48 weeks.

HDV viral load fell steeply during treatment in the combination therapy groups and modestly in the monotherapy groups. Half of the participants in the combination groups had undetectable HDV RNA at week 48, compared with 13% of those who used either drug alone. Six months after completing treatment, 53% in the 2 mg combination group and 27% in the 5 mg combination group still had an undetectable HDV viral load, compared with just one of those treated with Hepcludex alone and none who received pegylated interferon alone. In the two combination groups combined, nearly 40% experienced ALT normalization, 27% achieved hepatitis B surface antigen (HBsAg) loss and 20% experienced hep B antibody seroconversion—considered a functional cure.

At the 2019 AASLD Liver Meeting, Wedemeyer presented interim findings from an extension phase of the study in which 30 participants were randomly assigned to receive a higher 10 mg once-daily dose of Hepcludex plus pegylated interferon or 5 mg twice-daily doses of Hepcludex plus Viread for 48 weeks. In the latter group, Hepcludex was essentially acting as monotherapy, as Viread is

not active against HDV.

At the end of treatment, 87% of those taking 10 mg once-daily Hepcludex plus pegylated interferon had undetectable HDV viral load, compared with 40% in the 5 mg twice-daily Hepcludex plus Viread group. However, only one person in the former group and none in the latter group achieved HBsAg loss, thus failing to replicate the promising functional cure rate seen in the main study. Further data are expected at this year's International Liver Congress later this month.

Treatment with Hepcludex is generally safe and well tolerated, although combining it with pegylated interferon leads to more side effects. The most common side effects of Hepcludex alone are elevated bile salts in the blood and injection site reactions.

A Phase III trial of Hepcludex alone (ClinicalTrials.gov number NCT03852719) and a Phase II study of Hepcludex in combination with pegylated interferon (NCT03852433) for people with HBV and HDV coinfection are currently underway.

As noted in a press release from the German Center for Infection Research, Hepcludex is also effective against HBV, but because hep B antivirals are already approved, it does not meet the criteria for faster approval for this indication.

"In [the] future, it will be very interesting to examine whether a combination of Hepcludex and an immune modulator can also cure HBV patients who are not coinfected with HDV," Urban said.

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