Bulevirtide Is a Safe and Effective Treatment for Hepatitis D

The drug, which blocks entry of HBV into liver cells, also prevents HDV replication.

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The entry inhibitor bulevirtide led to a reduction in hepatitis delta virus (HDV) viral load and improved liver enzyme levels both in a clinical trial and in real-world studies in France and Austria, according to findings presented at the 2021 AASLD Liver Meeting. Several other studies presented at the conference shed more light on hepatitis D prevalence and outcomes.

Hepatitis delta is a defective virus that can only replicate in the presence of hepatitis B virus (HBV). Over time, chronic hepatitis B can lead to severe liver disease, and people with both HBV and HDV typically experience more aggressive disease progression and develop complications at a younger age than those with HBV alone. Studies presented at the conference showed that people who carry both viruses were more likely to progress to decompensated cirrhosis, develop liver cancer or need a liver transplant.

How Common is Hepatitis D?

Experts estimate that some 15 million people are living with hepatitis D worldwide. The American Association for the Study of Liver Diseases recommends that people who test positive for hepatitis B surface antigen (HBsAg) and have additional risk factors should be screened for hepatitis delta. This includes people who inject drugs, men who have sex with men, people with HIV coinfection and immigrants from areas with high HDV prevalence. But HDV testing is inconsistent, and the disease is not routinely reported to health authorities, so it is uncertain how many people may be living with hepatitis D in the United States.

At the Liver Meeting, Robert Gish, MD, of the Hepatitis B Foundation, and colleagues reported that the HDV prevalence was 11% among people diagnosed with HBV in a large insurance claims database.

In another study, Ilona Argirion, PhD, MPH, of the National Cancer Institute, and colleagues looked at HDV prevalence among nearly 5,000 participants in the Women's Interagency HIV Study (WIHS). About three quarters were HIV positive, 19% had chronic hepatitis C virus (HCV), 35% tested positive for HBV antibodies, meaning they were previously exposed to the virus, and 32% tested HBsAg positive, meaning they had active HBV infection.

Among the women who tested positive for HBV antibodies, 1% also had HDV antibodies, rising to 22% among those who tested HBsAg positive. On average, women with HDV were older, and they were more likely to have joined the WIHS cohort in later years. HDV prevalence did not differ by age, race/ethnicity, HIV status or injection drug use. Interestingly, among the HBV antibody positive women, those with resolved HCV infection and those who never had hepatitis C were over three times more likely to have HDV than those with chronic HCV.

HDV Treatment

While there is currently no approved treatment for hepatitis D in the United States, the Food and Drug Administration is currently considering Gilead Sciences' bulevirtide. The drug, marketed as Hepcludex (formerly known as Myrcludex), was approved in Europe in July 2020.

Bulevirtide blocks surface receptors that HBV uses to enter liver cells. This interferes with the hepatitis B lifecycle and thereby also prevents HDV replication.

At the 2019 EASL International Liver Congress, Heiner Wedemeyer, MD, of Hannover Medical School in Germany, reported findings from a study of bulevirtide plus pegylated interferon alpha-2a (Pegasys). HDV viral load fell steeply during treatment, and half of participants taking the combination had undetectable HDV RNA at the end of the 48-week treatment period. What's more, 27% experienced HBsAg loss and 20% achieved seroconversion—considered a functional cure.

Results from an extension phase of the study, presented at the 2019 Liver Meeting, 87% of people who receive a higher dose of bulevirtide plus pegylated interferon and 40% of those treated with a lower dose of bulevirtide plus the HBV antiviral Viread (tenofovir disoproxil fumarate) achieved an undetectable HDV viral load but, disappointingly, only one experienced HBsAg loss.

At the 2021 International Liver Congress, Wedemeyer presented interim results from the Phase III MYR301 trial (NCT03852719), in which 150 adults with chronic hepatitis D—nearly half of whom already had cirrhosis—were randomly assigned to receive either immediate treatment with 2 milligrams or 10 mg of bulevirtide once daily or else delayed treatment.

After 24 weeks, 55% of people in the 2 mg bulevirtide group and 68% in the 10 mg group either reached an undetectable HDV viral load or experienced at least a 2-log decrease in HDV RNA from baseline, compared with just 4% in the delayed treatment arm. About one third in the immediate treatment group reached a combined endpoint of undetectable HDV and ALT liver enzyme normalization.

Bulevirtide was safe and well tolerated. No serious adverse events were reported, and no one discontinued treatment for this reason. Bulevirtide blocks a bile salt transporter, and asymptomatic bile salt increases were common, but no one experienced symptomatic elevation.

At this year's Liver Meeting, Lena Allweiss, PhD, of University Medical Center Hamburg-Eppendorf, presented updated results showing that after 48 weeks of treatment, HDV RNA levels in the liver strongly declined in a subgroup of 66 people who underwent paired liver biopsies; 33% in the 2 mg

bulevirtide arm and 52% in the 10 mg arm reached undetectable HDV RNA. HDV antigen levels and the number of HDV antigen positive liver cells also declined. People in both groups had a similar decline in expression of inflammatory genes.

“Changes in host genome expression correlated with HDV infection levels,” the researchers concluded. “This indicates that therapeutic reduction of HDV infection also diminishes liver inflammation.”

What’s more, Maria Buti, MD, PhD, of Hospital Universitario Valle Hebron in Barcelona, and colleagues found that study participants treated with bulevirtide reported greater improvement in health-related quality of life than those in the delayed treatment group, including general health, pain, vitality, mental health, social functioning and hepatitis-specific limitations and health distress.

Real-Word Studies

These promising clinical trial findings were confirmed in the first real-world studies of bulevirtide since the European approval.

Victor De Ledinghen, MD, PhD, of Bordeaux University Hospital, and colleagues looked at outcomes from the French early access program. The analysis included 145 patients with chronic HBV and HDV who either had advanced fibrosis or compensated cirrhosis or moderate fibrosis and elevated ALT levels. They were treated with 2 mg bulevirtide once daily, either alone (77 patients) or with pegylated interferon (68 patients), for at least one year. Nearly 80% were also using antivirals to treat hepatitis B.

Among people treated with bulevirtide alone, mean serum HDV RNA viral load declined by -3.64 log at 12 months. Among those treated with bulevirtide plus pegylated interferon, the corresponding reduction was -5.56 log. People treated with bulevirtide alone were much less likely to reach an undetectable HDV viral load than those who added pegylated interferon (39% vs 85%). However, those on monotherapy were more likely to achieve a normal ALT level (49% vs 36%).

In another analysis, Teresa Binter, MD, of the Medical University of Vienna, and colleagues assessed 17 patients who received bulevirtide, first through a compassionate use program and then through the Austrian health insurance system. Fifteen received 2 mg bulevirtide once daily, but two used a 10 mg dose. Most were also taking antivirals for hepatitis B and had been unsuccessfully treated with pegylated interferon.

About 80% of patients saw at least a 2-log reduction in HDV RNA, and about 90% experienced ALT normalization at 48 weeks. Four people achieved HDV viral suppression for at least six months while on treatment. One person without cirrhosis who started on the 10 mg dose maintained an undetectable viral load for 20 weeks after stopping treatment. Another who received a 2 mg dose for about a year maintained an undetectable viral load for six months, experienced viral rebound four weeks after stopping treatment and restarted bulevirtide. Four non-responders added pegylated interferon, which resulted in steep drops in HDV RNA.

“To eradicate HDV, long-term treatment is needed,” the investigators concluded, suggesting that an individualized approach is needed.

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