Bulevirtide Plus Pegylated Interferon Can Maintain Undetectable Hepatitis D

People who used the combination regimen were more likely to still have an undetectable HDV load a year after stopping treatment.

June 7, 2024 By Liz Highleyman

About half of people treated with a higher dose of the antiviral bulevirtide (Hepcludex) plus pegylated interferon had a sustained undetectable hepatitis delta virus (HDV) viral load one year after completing treatment, according to study results presented Thursday at the European Association of the Study of the Liver's EASL Congress 2024 and published in The New England Journal of Medicine.

"HDV is the most severe form of viral hepatitis," Tarik Asselah, MD, PhD, of Université de Paris-Cité, said in a news release. "These new data support the potential for bulevirtide as a finite treatment option, demonstrating that almost half of people treated with bulevirtide 10 mg in combination with pegylated interferon remained undetectable for HDV RNA one year after treatment cessation. These long-term data are the highest posttreatment response rates ever reported for HDV."

Hepatitis delta is a defective virus that can replicate only in the presence of hepatitis B virus (HBV). It is estimated that around 5% of people with HBV—or around 12 million people worldwide—also have HDV, but accurate numbers are hard to come by due to limited testing.

Over time, chronic hepatitis B can lead to severe liver disease, and people with hepatitis B and D coinfection typically have more aggressive disease progression than those with HBV alone. People with both viruses tend to progress to cirrhosis at a younger age, and they are more likely to develop liver cancer or need a liver transplant.

Bulevirtide, from Gilead Sciences, is a first-in-class entry inhibitor that blocks surface receptors that HBV and HDV use to enter liver cells. By interfering with the hepatitis B life cycle, the drug also prevents HDV replication. The European Medicines Agency approved bulevirtide—sold as Hepcludex—in 2020. The U.S. Food and Drug Administration declined to do so in 2022, citing manufacturing and delivery concerns, but may reconsider its decision this year.

Asselah and colleagues evaluated the safety and efficacy of bulevirtide plus pegylated interferon alfa-2a (Pegasys) as a treatment for hepatitis D. In a prior Phase III clinical trial, bulevirtide alone

led to HDV suppression in a majority of patients and normalization of ALT liver enzymes in about half. Pegylated interferon is sometimes used off-label for HDV, but the combination has not been extensively studied, Asselah noted. In particular, the researchers wanted to determine whether the combination could be used as finite rather than continuous treatment.

The Phase IIb MYR204 trial (NCT03852433) included 175 adults with HBV and HDV coinfection and modestly elevated ALT. Most were white men, the average age was 41 years and about a third had cirrhosis. People with decompensated cirrhosis or very low platelet counts were excluded. About half had previously tried pegylated interferon, but they could not have taken it within the past six months. They were allowed to use concomitant nucleoside/nucleotide antivirals for hepatitis B—such as tenofovir (Viread or Vemlidy) or entecavir (Baraclude)—and nearly half did so.

The participants in this open-label study were randomly assigned to receive one of the following regimens:

- Pegylated interferon alone given as a once-weekly injection for 48 weeks (24 patients)
- 2 mg of bulevirtide—the dose approved in Europe—given as a daily injection plus once-weekly pegylated interferon for 48 weeks, followed by bulevirtide alone for 48 more weeks (50 patients)
- 10 mg of bulevirtide once-daily plus once-weekly pegylated interferon for 48 weeks, followed by bulevirtide alone for 48 more weeks (50 patients)
- 10 mg of bulevirtide once daily as monotherapy for 96 weeks (50 patients).

The primary study endpoint was undetectable HDV RNA viral load at 24 weeks after the end of treatment, and the primary comparison was between the group that received 10 mg bulevirtide plus peginterferon or those who used 10 mg bulevirtide alone.

At 24 weeks after completing treatment, 17% of participants in the pegylated interferon monotherapy group, 32% and 46% in the two combination groups and 12% in the bulevirtide monotherapy group still had undetectable HDV RNA. For the primary comparison, the 34% difference was statistically significant. At 48 weeks posttreatment, the respective response rates were not much different: 25%, 26%, 46% and 12%, respectively.

The researchers noted that the 70% end-of-treatment response rate in the 10 mg bulevirtide plus pegylated interferon group was higher than that seen in prior trials of pegylated interferon with or without tenofovir (33% to 48%) and bulevirtide alone (20% to 36%).

About three quarters of people in the 10 mg bulevirtide plus pegylated interferon group experienced ALT normalization—more than any other group—but this fell to about half 48 weeks

later. However, only a few patients with sustained undetectable HDV RNA experienced hepatitis B surface antigen (HBsAg) loss, which is considered a functional cure.

Treatment was generally safe, but side effects were common, especially in the groups that received pegylated interferon. The most frequent adverse events were low white blood cell counts (leukopenia and neutropenia) and low platelet counts (thrombocytopenia). The most common side effects attributable to bulevirtide were injection site reactions and asymptomatic bile acid elevation. Most adverse events related to bulevirtide were mild to moderate, and none were considered serious. Despite daily injections, few people discontinued treatment early. As expected, some people experienced worsening liver inflammation after stopping bulevirtide.

“Our results indicate that a regimen of finite duration for chronic hepatitis D led to a sustained undetectable HDV RNA response, as measured by a highly sensitive HDV RNA assay, beyond 24 weeks after the end of treatment,” the researchers concluded. “This response appeared to be maintained from 24 to 48 weeks after the end of treatment—a finding that supports the concept that sustained undetectable HDV RNA for at least one year after treatment is possible in patients with chronic hepatitis D who have been treated with a finite duration of therapy of at least 96 weeks, including 48 weeks of peginterferon alfa-2a therapy.”

The most effective regimen in this trial involves a two-year course of therapy with daily injections, and still only about half of treated patients achieved sustained HDV suppression after completing treatment.

“Ultimately, therapy that has an acceptable safety profile and that is easily administered will be needed to ensure that HDV therapies can be broadly applied to achieve a cure for persons with HDV infection,” Norah Terrault, MD, MPH, of the University of Southern California, wrote in an accompanying editorial.

The trajectory of treatment for HIV and hepatitis C shows how therapy can evolve to become more effective, better tolerated and more convenient. Hepatitis C treatment also used to involve a year of pegylated interferon, with a sustained response rate of around 50%. Today, more than 90% can be cured with well-tolerated oral direct-acting antiviral therapy taken for just eight to 12 weeks.

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