Combination Therapy Holds Promise for People With Hepatitis D

Lonafarnib and bulevirtide, when used with pegylated interferon, reduced hepatitis delta levels in two studies.

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Combination regimens containing the experimental drugs lonafarnib or bulevirtide reduced hepatitis delta virus (HDV) levels in a majority of participants in a pair of Phase II studies, researchers reported last month in Boston at The Liver Meeting, the annual meeting of the American Association for the Study of Liver Diseases.

HDV is a small, defective virus that can only replicate in the presence of hepatitis B virus (HBV). Over years or decades, chronic hepatitis B can lead to cirrhosis (sever scarring), liver cancer and liver failure. People with both HBV and HDV, known as coinfection, typically experience more rapid and severe disease progression than those with HBV alone.

Antivirals such as Viread (tenofovir disoproxil fumarate or TDF), Vemlidy (tenofovir alafenamide or TAF) and Baraclude (entecavir) can suppress HBV replication indefinitely during treatment, but they usually do not lead to a cure. There is currently no approved treatment for hepatitis D.

The Food and Drug Administration (FDA) recently issued draft guidance to help speed up the development of potential new therapies for hepatitis D. Because it is a serious and life-threatening disease, investigational drugs may be eligible for fast track, breakthrough therapy and priority review designations. No surrogate endpoints have been proven to predict clinical benefit, but the FDA said that undetectable HDV RNA viral load or at least a 2 log10 drop in viral load plus normalization of ALT, a liver enzymes that signals liver inflammation, could be used to support accelerated approval.

Lonafarnib

Christopher Koh, MD, of the National Institute of Diabetes and Digestive and Kidney Diseases, presented findings from a study of the prenylation inhibitor lonafarnib in combination with pegylated interferon lambda. Lonafarnib interferes with the production new HDV virus particles. Pegylated interferon lambda—which was previously studied but never approved for hepatitis C—stimulates immune activity against viral hepatitis with fewer side effects than pegylated interferon alfa.

Previous research showed that lonafarnib reduced HDV viral load in short-term studies, but higher doses caused gastrointestinal side effects. As reported at the 2017 Liver Meeting, administering lonafarnib with the booster drug Norvir (ritonavir) enabled more people to take effective doses with acceptable side effects.

Koh presented results from the LIFT HDV trial, which included 26 participants. A majority (60%) were men and the median age was 40. Just over half were Asian, about a third were white and 15% were Black. They had moderate liver fibrosis.

All participants in this open-label study were treated with 50 milligrams of lonafarnib boosted with 100 mg of Norvir administered orally twice daily, along with 180 micrograms of pegylated interferon lambda administered by subcutaneous (under the skin) injection once weekly for 24 weeks.

At 24 weeks, HDV viral load fell by a mean of 3.18 log10 international units per milliliter. This was a significant decline from the baseline level, meaning the change was probably not attributable to chance. Of the 19 people who completed treatment, all but one (95%) had a greater than 2 log10 decline in HDV RNA and 10 (53%) achieved an undetectable level. People with lower HDV viral load at baseline appeared more likely to reach an undetectable level, Koh said.

Treatment was generally safe but side effects were common. The most frequently reported symptoms were diarrhea (100%), nausea (63%), bloating (63%) and gastroesophageal reflux (63%), but these were usually mild and diminished after a few weeks on treatment. Three people reduced their medication doses and four stopped treatment prematurely.

A Phase III study of boosted lonafarnib without or without pegylated interferon alfa is currently under way (ClinicalTrials.gov number NCT03719313).

Bulevirtide

Heiner Wedemeyer, MD, of Essen University Hospital in Germany, presented the latest results from a study of another combination regimen for people with HBV and HDV coinfection, bulevirtide plus either pegylated interferon alfa or TDF.

Bulevirtide, formerly known as Myrcludex B, is an entry inhibitor that binds to receptors HBV uses to enter liver cells. This interferes with the hepatitis B lifecycle and therefore also prevents HDV replication.

The main MYR203 trial enrolled 60 people who were randomly assigned to receive 2 mg or 5 mg of bulevirtide by injection once daily plus 180 mcg of pegylated interferon alfa once weekly, 2 mg bulevirtide alone or pegylated interferon alfa alone, all for 48 weeks.

As Wedemeyer reported at this year's International Liver Congress, 50% of participants in the two combination arms had undetectable HDV RNA at week 48, compared with 13% of those who used either drug alone. At week 72—six months after completing treatment—40% still had an

undetectable HDV viral load and 40% experienced normalization of ALT enzymes. What's more, 27% achieved hepatitis B surface antigen (HBsAg) loss and 20% experienced HBs antibody seroconversion, considered a functional cure.

At this year's Liver Meeting, Wedemeyer presented interim findings from an extension phase of the study, conducted in Russia, which evaluated 10 mg daily bulevirtide plus weekly pegylated interferon alfa or 5 mg twice-daily bulevirtide plus daily TDF for 48 weeks. Both groups included 15 people. Three quarters were men, almost all were white and the mean age was about 37.

At the end of treatment, 87% of those taking 10 mg daily bulevirtide plus pegylated interferon alfa had undetectable HDV viral load. The 48-week response rate in the 5mg twice-daily bulevirtide plus TDF group was 40%. ALT normalization rates were 27% and 40%, respectively. In the latter group, bulevirtide was essentially acting as monotherapy, as TDF is not active against HDV.

Only one person taking the 10 mg daily bulevirtide plus pegylated interferon alfa regimen, and no one taking the TDF combination, achieved HBsAg loss, failing to replicate the promising functional cure rate seen in the main study. Sustained response rates at 72 weeks are still pending.

Again, treatment was generally safe and well tolerated. Most side effects were due to pegylated interferon. No bulevirtide-related serious adverse events or treatment discontinuations were reported. Injection site reactions were uncommon. Almost everyone saw an asymptomatic increase in bile salts, a known side effect of bulevirtide; in the main study, however, levels returned to normal soon after stopping the drug.

Wedemeyer concluded that 10 mg bulevirtide per day, taken either as one 10 mg injection or two 5 mg shots, "is a safe and promising strategy for maintenance therapy of chronic hepatitis D," and adding pegylated interferon alfa shows "a strong syngerism."

A Phase III trial of bulevirtide alone (ClinicalTrials.gov number NCT03852719) and a Phase II study of bulevirtide in combination with pegylated interferon alfa (ClinicalTrials.gov number NCT03852433) are currently under way.

Click here to read the lonafarnib study abstract.

Click here to read the bulevirtide study abstract.

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