Core Protein Inhibitor Boosts Antiviral Activity Against Hepatitis B

People who added ABI-H0731 saw greater viral load reductions than those who used nucleoside/nucleotide analogues alone.

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People who used an experimental hepatitis B virus (HBV) core protein inhibitor along with nucleoside/nucleotide analogues saw greater reductions in HBV viral load and residual HBV genetic material, which could lead to a functional cure with longer follow-up, according to a study presented at the 2019 International Liver Congress in Vienna.

The novel treatment was well tolerated, and the rapid, deep declines in HBV DNA and RNA could promote the loss of cccDNA (covalently closed circular DNA), an intermediate form that persists in the nucleus of liver cells and presents a barrier to a cure, said Jay Lalezari, MD, of Quest Clinical Research in San Francisco.

HBV is difficult to treat in part because cccDNA, which carries the genetic blueprint of the virus, can lie dormant in liver cells, evading both the immune system and standard treatment. Over years or decades, chronic HBV infection can lead to liver cirrhosis (scarring), liver cancer and end-stage liver failure requiring a transplant.

Nucleoside/nucleotide antivirals such as Viread (tenofovir disiproxil fumarate), Vemlidy (tenofovir alafenamide) and Baraclude (entecavir) can suppress HBV replication during therapy—indicated by low or undetectable HBV DNA—but they don't completely eliminate the virus, don't prevent formation of cccDNA and usually do not lead to a cure, traditionally indicated by hepatitis B surface antigen (HBsAg) loss.

ABI-H0731, from Assembly Biosciences, is a core protein allosteric modifier (CpAM) that targets the HBV core protein. It interferes with multiples steps of the viral lifecycle, including cccDNA formation.

Lalezari presented interim findings from a pair of Phase IIa studies that evaluated ABI-H0731 in people with chronic hepatitis B and absent to moderate liver fibrosis.

Study 201 included 47 hepatitis B e antigen (HBeAg) positive and 26 HBeAg negative people on nucleoside/nucleotide analogues (mostly Viread or Vemlidy) with suppressed HBV DNA. They were

randomly assigned to add either once-daily oral ABI-H0731 or a placebo.

Study 202 included 25 previously untreated HBeAg positive people with unsuppressed HBV. They were randomized to receive Baraclude plus either ABI-H0731 or a placebo. After 24 weeks, people in both studies could opt to join an ongoing open-label extension study.

In both studies, the ABI-H0731 combination regimen led to faster, steeper and larger declines in HBV viral load starting at week 2. In Study 201, people who added ABI-H0731 had a mean HBV RNA decline of 2.34 log at 12 weeks, compared with 0.05 log in the placebo group. Although most people had not yet reached this time point, the declines at 24 weeks were 2.20 log and 0.15 log, respectively.

In Study 202—those who started treatment with unsuppressed virus—HBV DNA declined by 4.54 log at week 12 and by 5.94 log at week 24 in the combination therapy group, compared with 3.29 log and 3.99 log, respectively, in the Baraclude-only group. Differences in HBV RNA were even greater: a decline of 2.27 log at week 12 and 2.54 log at week 12 in the combination group versus 0.44 log and 0.61 log, respectively, in the Baraclude-only group.

Among Study 201 participants who reached the 24-week time point, sensitive tests to detect low-level HBV DNA showed that residual virus was not eliminated using nucleoside/nucleotide analogues alone, but it fell below the level of detection in five of the six people who added ABI-H0731.

Treatment was generally safe and well tolerated and no serious adverse events, treatment interruptions or treatment-related discontinuations were reported, according to Lalezari.

Eliminating residual HBV DNA will likely be required to prevent new cccDNA formation, and this will be a critical milestone for a cure, Lalezari said. He added that a decrease in cccDNA and declines in HBeAg and and HBsAg are anticipated to follow the elimination of residual virus, and this will be explored in the extension study.

“This interim analysis of two studies supports that ABI-H0731 in combination with [nucleoside/nucleotide analogues] appears to provide rapid, enhanced anti-HBV activity,” Lalezari said in a conference press release. “Although decreases in HBeAg and HBsAg in some individuals have been observed in both studies, it is too early to draw meaningful conclusions about this endpoint. The accelerated decline and significant loss of baseline RNA and DNA viremia suggest that combination therapy with a core inhibitor plus [nucleoside/nucleotide analogues] may enhance loss of cccDNA and viral antigen once residual viremia has been fully cleared.”

Despite these promising findings, Assembly reportedly has decided not to further develop ABI-H0731, but it is working on more potent core protein inhibitors. A Phase Ib dose-finding study of ABI-H2158 is currently underway and ABI-H3733 is expected to enter Phase Ia studies early next year, according to the company.

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