Low-Level Hepatitis B Viral Load Raises Liver Cancer Risk

Low but detectable HBV DNA during antiviral therapy is associated with detrimental long-term outcomes.

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Having even a low level of hepatitis B virus (HBV) while on treatment with Baraclude (entecavir) increases the risk of liver cancer, according to a recent report in Hepatology. These findings suggest that low-level viral load is not harmless, but the best approach for managing it remains unclear.

Over years or decades, chronic HBV infection can lead to serious liver disease, including cirrhosis and hepatocellular carcinoma (HCC), a type of primary liver cancer.

The nucleoside/nucleotide analog antivirals Baraclude and Viread (tenofovir disoproxil fumarate), which are the current recommended first-line medications for hepatitis B, can suppress HBV replication over the long term, but they seldom lead to a cure. Effective antiviral therapy can slow, halt or even partially reverse liver disease progression, but people with hep B remain at risk for liver cancer, especially if they have developed cirrhosis.

However, the implications of persistent or recurring low-level virus while on antiviral therapy are not well understood. It is not clear whether people with low but detectable viral load while on a single potent antiviral should switch therapy or add another drug.

To address this question, Jung Hee Kim, MD, of Sungkyunkwan University School of Medicine in Seoul, and colleagues did a study of previously untreated people with hepatitis B who started Baraclude monotherapy (taken alone).

This retrospective analysis included 875 chronic hepatitis B patients. Two thirds were men, and the mean age was 48 years. About half had cirrhosis when they started Baraclude.

The researchers compared the HCC risk of patients who maintained virological response, defined as persistently undetectable HBV DNA, and those who experienced persistent or intermittent episodes of detectable but low-level viral load not exceeding 2,000 international units per milliliter.

Most people (97.1 percent) achieved a complete virological response after starting Baraclude,

defined as HBV DNA below 12 IU/mL. More than half of these (58.6 percent) maintained viral suppression during follow-up, but the rest sometimes had low-level detectable virus. People with high pretreatment viral load and those who were hepatitis B “e” antigen (HBeAg) positive were less likely to maintain viral suppression.

Overall, 85 people (9.7 percent) were newly diagnosed with HCC over a median follow-up period of nearly five years. People with low-level viral load developed liver cancer nearly twice as often as those who maintained viral suppression (14.3 percent vs. 7.5 percent at five years, respectively).

The difference in HCC risk was even greater when looking only at patients with liver cirrhosis (23.4 percent vs. 10.3 percent, respectively). However, the difference in HCC incidence rates (4.0 percent vs. 6.9 percent, respectively) was no longer statistically significant among people without cirrhosis, meaning it could have occurred by chance.

Based on these findings, the study authors concluded that low-level HBV levels are “not benign.”

As low-level virus is associated with a worse clinical outcome, these findings suggest that “active management that can further induce [maintained virological response] should be pursued” for people with low-level HBV DNA while on potent nucleoside/nucleotide analogs, especially for those with cirrhosis, according to the authors.

However, they acknowledge that studies of switching treatment for patients with low-level virus have produced conflicting results. Some studies support staying on the same antiviral monotherapy while others favor changing to a different high-potency antiviral or adding a new potent drug to existing therapy.

“More data that can guide clinical practice are needed,” they wrote. “Until such data are available, clinicians must evaluate adherence for patients with [low-level virus]. If adherence is not a concern, providers should discuss the risks and benefits of each treatment strategy (add-on, switching and continuing monotherapy) in everyday practice, and the treatment decisions should be individualized.”

In addition, people with hepatitis B should continue to undergo liver cancer screening.

In an accompanying editorial, Albert Min, MD, of the Icahn School of Medicine at Mount Sinai, wrote: “[W]e are once again reminded that in managing chronic hepatitis B patients, we should remain vigilant in continuing regular HCC surveillance indefinitely, regardless of whether undetectable HBV DNA levels and/or even loss of HBsAg have been achieved, particularly in patients with cirrhosis.”

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