Another oral antiviral treatment, but still far away from hepatitis B virus cure

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Keywords: Hepatitis B virus; Besifovir dipivoxil maleate; Hepatitis B surface antigens; Hepatitis B, Chronic

Chronic hepatitis B virus (HBV) infection continues to be a crucial health issue worldwide as more than 200 million individuals are positive for hepatitis B surface antigen (HBsAg). Patients with chronic HBV infection are at an increased risk of developing liver cirrhosis and hepatocellular carcinoma (HCC), resulting in over one million deaths per year. So far, there is no cure for HBV and prolonged suppression of viral replication via inhibiting reverse transcriptase by nucleos(t)ide analogue (NA) treatment is the only way to minimize their liver-related complications and to reduce HCC risk.

Three potent NAs, including tenofovir disoproxil fumarate (TDF), tenofovir alafenamide, and entecavir, are recommended as first-line treatment by clinical practice guidelines. Besifovir dipivoxil maleate (BSV) is a new acyclic nucleotide phosphonate with potent antiviral activity against HBV. In this study, Song et al. explored BSV’s antiviral efficacy and drug safety up to 192 weeks in two groups: 170 patients continuing BSV treatment (BSV-BSV) and 152 patients switching from TDF to BSV after 48 weeks (TDF-BSV). They found more than 90% of virological response rates over 192 weeks in both groups and no drug-resistant mutations to BSV. Bone mineral density and renal function were well preserved in the BSV-BSV group, whereas these initially worsened then recovered after switching therapy in the TDF-BSV group. However, only one participant achieved HBsAg loss in both groups.

Prolonged NA treatment to suppress viral replication is the mainstay treatment strategy in current practice. According to this study, 4-year viral suppression is still far from achieving HBsAg clearance, which is also compatible with other clinical studies using different NA treatments. In addition to the on-going clinical trials aiming at HBsAg clearance, there are several issues that need to be addressed. First, as the goal for prolonged NA treatment is to reduce HCC risk, a precise HCC prediction model in addition to serum HBV DNA and alanine aminotransferase levels is mandatory to decide who should receive early antiviral treatment. For example, around 50% of HBeAg-negative patient without liver cirrhosis are in grey zone for antiviral treatment and...
their prognosis is heterogenous.\textsuperscript{10,12} With a better prediction model integrated with more viral markers,\textsuperscript{13,14} we may be able to identify some of the grey-zone patients who need early antiviral treatment due to the elevated HCC risk.

The second issue is how to predict the residual HCC risk after prolonged antiviral treatment to minimize viral replication. In addition to host factors, including age and sex,\textsuperscript{15} surrogate markers for liver fibrosis have shown their potential to improve the prediction performance of current HCC prediction models.\textsuperscript{16,17} A better HCC prediction model may impact how to perform cost-effective surveillance for HCC.

In summary, although BSV provides us another NA choice to suppress viral replication activity, it is still far from achieving HBsAg clearance. The current unmet need for physicians is to identify the patients with high HCC risk for an early antiviral treatment and to define the residual HCC risk after long-term antiviral treatment, which may impact the HCC surveillance system.

Conflicts of Interest

T-C. T. has served on speaker’s bureaus for Bristol-Myers Squibb and Gilead Sciences and received research grant from Gilead Sciences.

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