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Editorial

Predictors of response to antiviral treatment for chronic hepatitis B

Chronic hepatitis B virus (HBV) infection is prevalent in many Asian countries, notwithstanding three decades of universal hepatitis B vaccination programs. The invention of nucleos(t)ide analogs (NUCs) was a breakthrough in the treatment of chronic hepatitis B (CHB). However, HBV continues to be a challenging disease to completely eradicate using current treatment agents. According to the treatment guidelines recommended by the American Association for the Study of Liver Diseases, the European Association for the Study of the Liver, and the Asian Pacific Association for the Study of the Liver, NUCs with either entecavir or tenofovir is the first-line treatment of choice for CHB.[1−3] Another treatment option is pegylated interferon (PEG-IFN). For those cases involving hepatitis B e antigen (HBeAg)-positive patients, HBeAg seroconversion is the surrogate end point of treatment; nevertheless, some cases would progress to HBeAg-negative CHB and could experience virological or clinical relapse even after achieving HBeAg seroconversion. In general, the HBeAg seroconversion rate is around 20% by NUCs treatment for 1 year, and an average of 30% after 48 weeks or 52 weeks of PEG-IFN treatment. It is generally understood that stronger host immunity against the virus by presenting a high alanine transaminase (ALT) and lower HBV viral load before the NUCs or PEG-IFN treatment has an elevated chance of achieving HBeAg seroconversion. For HBeAg-negative CHB, another phase of chronic HBV infection requiring antiviral treatment, the treatment end point is hepatitis B surface antigen (HBsAg) loss or HBsAg seroconversion by NUCs treatment. Alternatively, PEG-IFN treatment involves a sustained off-treatment virological response as defined by a serum HBV DNA of <2000 IU/mL at 48 weeks post-treatment as the treatment goal.[2] To achieve HBsAg loss or HBsAg seroconversion, indefinite or long-term NUCs treatment is required. Regarding PEG-IFN treatment, the baseline predictor of virological response is poorly defined for HBeAg-negative CHB. However, a low HBsAg level or a higher chemokine level (CXCL9) at baseline is associated with a higher sustained response by PEG-IFN treatment in patients with HBeAg-negative CHB.[4,5] Recently, on-treatment HBsAg decline has been proposed as a significant on-treatment predictor of virological response or HBsAg loss for HBeAg-positive and HBeAg-negative CHB undergoing PEG-IFN treatment. In addition, a high HBsAg (>20,000 IU/mL) at Week 12 can serve as an early termination rule for PEG-IFN treatment in HBeAg-positive CHB with a high negative predictive value.[6]

In this issue, Huang et al[7] reported the role of on-treatment HBV DNA level to predict HBeAg seroclearance in HBeAg-positive CHB undergoing entecavir treatment. By retrospectively reviewing 135 patients receiving at least 96 weeks of entecavir treatment, they found that a higher incidence of undetectable HBV viral load (<20 IU/mL) at 24th and 48th weeks of treatment was observed in patients achieving HBeAg seroclearance at the 96th week, and concluded that undetectable HBV viral load at Weeks 24 and 48 can predict HBeAg loss in HBeAg-positive CHB patients during entecavir treatment. No other baseline factor, including pretreatment ALT level and HBV viral load, was associated with HBeAg seroclearance in this study. Although the finding can potentially apply to clinical practice, several unresolved issues should be further addressed. First, HBeAg seroclearance is a milestone, but not a standard treatment end point for HBeAg-positive CHB. The study did not answer whether early on-treatment undetectable HBV viral load can still predict future HBeAg seroconversion. Second, early undetectable HBV viral load is common under high-potency NUCs treatment, such as entecavir or tenofovir. Previous data showed that after 1 year of third-generation NUCs treatment, nearly 70% of HBeAg-positive and 90% of HBeAg-negative CHB patients can achieve undetectable HBV viral load.[8] Therefore, caution should be exercised when applying HBV viral load as an on-treatment biomarker in terms of its sensitivity. Based on the data of this study, 28 cases had undetectable HBV viral load at Week 24, and 71 cases had undetectable viral load at Week 48, and 11 (39.3%) and 26 (36.6%) achieved HBeAg seroclearance at the 96th week, respectively. That means the sensitivity to predict HBeAg seroclearance was merely 39.3% for undetectable HBV viral load at Week 24, and 36.6% for undetectable HBV viral load at Week 48. The sensitivity is low for a candidate biomarker. On the contrary, a higher specificity could be expected by applying persistent HBV viremia to predict HBeAg antigenemia. However, this indicator is obviously redundant as it could not be anticipated to achieve HBeAg seroclearance or HBeAg seroconversion without prior

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virological response to NUCs treatment. Third, whether an early undetectable HBV viral load can shorten the treatment course is unclear. Currently, at least 12 months of consolidation treatment after HBeAg seroconversion is recommended for NUCs treatment in HBeAg-positive CHB, although the clinical relapse rate can be as high as 28% to 50% under such recommendation.[9,10] A longer consolidation treatment seems to reduce the risk of virological or clinical relapse.[3] Achieving HBeAg seroclearance or HBeAg seroconversion cannot confer a sustained virological response after NUC is discontinued. In this study, the authors did not demonstrate the long-term outcome after HBeAg seroclearance, including the duration of consolidation and relapse rate, of those HBeAg-positive CHB patients. The predictors of sustained virological response should be a more important clinical issue to be addressed further. Fourth, the conventional factors associated with HBeAg seroconversion (high ALT, low HBV DNA at baseline) were not significant in this study. Different target of the end point, HBeAg seroclearance instead of HBeAg seroconversion, might be part of the cause.

Finally, a functional cure of HBV as defined by HBsAg loss or HBsAg seroconversion is now considered to be an ideal treatment end point for not only HBeAg-negative but also HBeAg-positive CHB. On-treatment quantitative HBsAg (qHBsAg) level, although not analyzed in this study, and the kinetics of its changes during antiviral treatment are promising biomarkers to predict the possibility of HBsAg loss based on current evidence. Further studies to investigate the role qHBsAg to guide the antiviral treatment are anticipated.

Conflicts of interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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