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Editorial

Enhancing off-nucleos(t)ide analogue outcome predictions in chronic hepatitis B with time-varying hepatitis B core-related antigen

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Nucleos(t)ide analogue (NA) therapy stands as the cornerstone in the treatment of chronic hepatitis B (CHB), and its cessation is considered safe only upon achieving seroclearance of hepatitis B surface antigen (HBsAg).[1] Yet, this milestone is rarely reached during long-term NA therapy.[2] Premature discontinuation of NA treatment is associated with virological relapse, with approximately half of patients experiencing hepatitis flare or hepatic decompensation.[3,4] The current challenge lies in identifying patients who are suitable for cessation of NA treatment before HBsAg seroclearance through the utilization of various viral and host markers. Previous studies have indicated that lower serum levels of viral protein at the end of treatment (EOT), as indicated by HBsAg and hepatitis B core-related antigen (HBcrAg), are associated with a reduced risk of clinical relapse.[5,6] HBcrAg serves as a surrogate marker for intrahepatic covalently closed circular DNA transcriptional activity.[7] In untreated CHB patients, the kinetics of serum HBcrAg have been shown to correlate with various clinical outcomes, including HBsAg seroclearance and the development of adverse events such as hepatitis B e antigen (HBeAg)-negative hepatitis and liver cancer.[8-10] However, it remains unclear how the time-varying HBcrAg levels post-NA cessation could be utilized to predict clinical relapse. In this study, Tsai et al.[11] enrolled 203 HBeAg-negative CHB patients who discontinued tenofovir or entecavir therapy. Clinical relapse was defined as serum alanine aminotransferase levels exceeding 2 times the upper limit of normal, along with serum hepatitis B virus (HBV) DNA levels surpassing 2,000 IU/mL. Viral markers, including HBsAg, HBcrAg, and HBV DNA, were assessed at the EOT, one year post-NA cessation, and two years post-NA cessation, respectively. They adopted time-varying levels based on the most recent measurements to predict the subsequent development of clinical relapse.

In the univariable analysis, HBcrAg and HBsAg levels at EOT,

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as well as the time-varying levels of HBcrAg, HBsAg, and HBV DNA, were all associated with the development of clinical relapse. In the multivariable analysis, only the time-varying HBcrAg levels, but not time-varying HBsAg and HBV DNA levels, remained an independent risk factor for clinical relapse (adjusted hazard ratio [HR] 1.53 per log U/mL; 95% confidence interval [CI], 1.12–2.08). Low post-treatment HBcrAg levels below 1,000 U/mL were associated with a decreased risk of clinical relapse (adjusted HR of 0.41; 95% CI, 0.21–0.81). Interestingly, they found that dynamic levels of HBcrAg, rather than the pattern of post-treatment changes in HBcrAg, were useful in predicting subsequent clinical relapse. In summary, this study is the first to show that not only the levels at EOT but also the kinetic levels of HBcrAg predict the risk of clinical relapse, which may help optimize clinical management.

While this study is the first to show that the kinetic levels of HBcrAg predict clinical relapse post-NA treatment cessation, there are still some unaddressed issues. For instance, the area under the receiver operating characteristic (ROC) curve for HBcrAg levels at EOT in predicting clinical relapse is only 0.61 (95% CI, 0.53–0.69). Moreover, approximately 50% of patients had HBcrAg levels below the quantification range (<1,000 U/mL). The introduction of a novel high-sensitivity assay for HBcrAg (iTACT-HBcrAg), which is approximately 10 times more sensitive, holds promise for enhancing risk prediction of clinical relapse compared to conventional assays.[12]

Another crucial consideration impacting clinical practice is whether routine HBV DNA measurement should be replaced by HBcrAg measurement post-NA cessation. Previous studies have highlighted the predictive value of dynamic HBV DNA monitoring for subsequent clinical relapse.[13,14] However, further research is needed to determine if dynamic HBcrAg monitoring offers additional clinical benefits beyond HBV DNA quantification.

In summary, this study underscores the importance of time-varying HBcrAg levels post-NA cessation in predicting the risk of clinical relapse. Nevertheless, more extensive data are required to elucidate how to integrate various viral markers at different time points to identify patients suitable for safe cessation of antiviral treatment and to design a comprehensive monitoring schedule aimed at initiating early antiviral treatment to prevent severe hepatic flares.

Authors' contribution

Guarantor of the article: Tai-Chung Tseng; Concept: Chen-Te Huang, Tai-Chung Tseng; Manuscript drafting: Chen-Te Huang; Manuscript edition and final approval: Chen-Te Huang, Tai-Chung Tseng.

Conflicts of Interest

T-C. T. has served on speaker's bureaus for Fujirebio, Bristol-Myers Squibb, and Gilead Sciences and received grant support from Gilead Sciences.

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Abbreviations:

NA, nucleos(t)ide analogue; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; EOT, end of treatment; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HR, hazard ratio; CI, confidence interval; and ROC, receiver operating characteristic

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