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Correspondence

Optimizing off-treatment outcome predictions: The potential of time-varying HBcrAg and the need for more research

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Dear Editor,

We sincerely appreciate the editorial by Drs. Huang and Tseng,[1] commenting on our recent study published in *Clinical and Molecular Hepatology*[2] regarding the role of time-varying hepatitis B core-related antigen (HBcrAg) in predicting clinical relapse (CR) for chronic hepatitis B (CHB) patients who discontinued tenofovir or entecavir. We agree that nucleos(t)ide analogue (NA) cessation is generally safe with hepatitis B surface antigen (HBsAg) seroclearance,[3] which is the only treatment endpoint widely acceptable across guidelines.[4,5] Unfortunately, it rarely occurs during long-term NA therapy.[6] Treatment discontinuation without first achieving HBsAg seroclearance invariably leads to recurrence of viremia and could precipitate hepatitis flare and even life-threatening acute on chronic liver failure.[7] The strategy of finite NA therapy, therefore, cannot be practiced without thorough consideration of the conceivable benefits and potential risks for an individual patient.

Substantial research efforts have been devoted to identify suitable candidates for finite NA therapy. Nevertheless, most predictors reported in the literature were host factors or viral biomarkers at or prior to treatment cessation.[3] Little is known about the risk assessment during the posttreatment monitoring. The risk could vary over time and the assessment may need to change accordingly to inform clinical management.

Our study demonstrated for the first time that serum HBcrAg levels as a time-varying predictor was more accurate than a fixed value in stratifying the risks of CR. This finding was further affirmed by multiple variable analyses adjusted for the serum level of HBsAg measured at treatment cessation, which was a validated biomarker associated with CR risks. Accordingly, our data suggest the most recent HBcrAg level is more predictive than a previous measurement to guide posttreatment monitoring. For the convenience of clinical application, the cutoff may be set at 1,000 U/mL to

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stratify distinct risks of CR.

Serum HBcrAg can only come from the covalently closed circular DNA (cccDNA) of HBV, in contrast to HBsAg which may also be produced via transcription of fragments of viral DNA integrated to host genome, particularly in the setting of long-term NA therapy.[8] This feature distinguishes the two circulatory viral markers with great implications for clinical utility. A growing body of literature has shown the potential of applying HBcrAg measurement in clinical practice as it may help predict HBeAg seroconversion, durability of NA therapy response, as well as the occurrence and recurrence of hepatocellular carcinoma.[9,10] In fact, prior studies including our own work, have shown that serum HBcrAg level at treatment cessation was useful to predict off-therapy relapses.[11-13] Our current study further expanded the potential utility of this biomarker, suggesting that serum HBcrAg not only be measured at treatment cessation but also during posttreatment follow-up.

As the editorialists point out, however, the commercial assay employed in the current study was not a sensitive one and unable to quantify serum HBcrAg levels below 1,000 U/mL. The current assay might fail to detect subtle fluctuations of serum HBcrAg after NA cessation. Consequently, it is not possible to appreciate the variability among HBcrAg levels lower than the detection limit and evaluate how it might correlate with clinical outcomes. This limitation could substantially compromise the usefulness of this biomarker particularly when more than half the patients in our study cohort had a serum HBcrAg level unquantifiable by the present assay. Although it is reasonable to classify patients with a HBcrAg level below 1,000 U/mL into a low-risk group, whether they can be more precisely risk stratified was unclear. Therefore, we agree with the editorialists that further research using more sensitive assay, such as the iTACT-HBcrAg,[14] is needed to harness the full potential of HBcrAg measurement in clinical application.

We also concur with the editorialist's insightful comment highlighting the importance of frequent HBV DNA measurement in the posttreatment monitoring. According to the updated Asian Pacific Association for the Study of the Liver (APASL) guidance, serum HBV DNA should be measured monthly for the initial 3 months after NA cessation, followed by bi-monthly or tri-monthly measurement, if viremia remains undetected.[15] This intensive early monitoring aims to promptly identify emerging viral breakthrough and early forecasts imminent hepatitis flares or even severe acute exacerbations.

We did not propose to replace HBV DNA by HBcrAg in the management of patients who stopped NA therapy. In our opinion, these two biomarkers play different yet complementary roles during the posttreatment monitoring. Nevertheless, we acknowledge that it was beyond the scope of the present study to investigate how the various predictors can be combined to optimize posttreatment monitoring of patients discontinuing NA therapy. More research is clearly warranted.

In summary, our study demonstrated the clinical relevance of measuring serum HBcrAg during the follow-up of patients who stop NA therapy, and found that the most recent level was more accurate than a previous measurement to predict CR. Although the commercial assay lacks the sensitivity to detect nuances of serum HBcrAg below the lower limit of detection ranges, a HBcrAg level below 1,000 U/mL may still serve as a clinically useful cutoff for predicting CR. A more sensitive assays with a broader range of detection may improve the clinical utility of HBcrAg and refine the risk assessment based on its dynamic measurement. Finally, it remains largely unknown how to incorporate various risk predictor for optimizing posttreatment monitoring. Our novel findings should call for further studies.

Authors' contribution

Manuscript drafting: Ying-Nan Tsai, Yao-Chun Hsu. Manuscript edition and final approval: all authors.

Conflicts of Interest

Ying-Nan Tsai reported no conflicts of interest. Jia-Ling Wu reported no conflicts of interest. Yao-Chun Hsu has received research grants from Gilead Sciences, lecture fees from Abbvie, Bristol-Myers Squibb, Gilead Sciences, and Novartis, and has served as an advisory committee member for Gilead Sciences.

Abbreviations:

CHB, chronic hepatitis B; CR, clinical relapse; EOT, end of treatment; HBcrAg, hepatitis B core-related antigen; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analogue

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