Letter regarding: Hepatitis B core-related antigen dynamics and risk of subsequent clinical relapses after nucleos(t)ide analog cessation

Prediction of clinical relapses after nucleos(t)ide analog cessation: HBcrAg vs qHBsAg

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List of abbreviations

CR: clinical relapse; EOT: end-of-therapy; HBcrAg: hepatitis B core-related antigen; HR: hazard ratio; Nuc: nucleos(t)ide analogue; qHBsAg: quantitative HBsAg
To the Editor:

The multicenter cohort study of Tsai et al [1] showed that hepatitis B core-related antigen (HBcrAg) <10^3 U/mL was significantly associated with lower clinical relapse (CR) and that time-varying HBcrAg level was a risk factor for subsequent CR after nucleos(t)ide analogue (Nuc) cessation. The study also showed that only 3.5% of 203 patients encountered bilirubin elevation >2mg/dl and all recovered fully after retreatment, hence confirmed that Nuc cessation in HBV-suppressed patients is reasonably safe. However, there are several major points that require clarification and/or further discussion.

1. Multivariable analysis showed that time-varying HBcrAg level was a significant factor for subsequent CR. However, Figure 5 showed that the cumulative CR incidence was similar between patients with different HBcrAg kinetics. These results seem contradictory. Perhaps a clear definition of “time-varying HBcrAg level” is needed to solve this controversy. Their findings of no difference in CR rate between patients with different patterns of HBcrAg changes over time do not support their implication that dynamic measurement of serum HBcrAg would be informative/helpful for off-Nuc monitoring.

2. Multivariable analysis also showed that end-of-therapy (EOT) quantitative HBsAg (qHBsAg) level was a significant factor associated with the risk of CR, whereas EOT HBcrAg and time-varying HBsAg level were not. Together with the controversial results of HBcrAg in point 1, highly sensitive assay for HBsAg (HBsAg-HQ) and HBcrAg (iTACT-HBcrAg) could impact the study results.

3. The results of the multivariable analysis have confirmed the findings of an earlier head-to-head comparison that HBcrAg was not a predictive factor for off-Nuc CR [2]. Recalculation of their reported data, including Supplementary Figure 3, showed that the
1-year CR rate was 22.2% (12 of 54) in patients with qHBsAg <10^2 IU/mL which was nearly 2-times lower than 39.8% (39 of 98) in those with HBcrAg <10^3 U/mL. These findings suggest that qHBsAg <10^2 IU/mL is more predictive than HBcrAg <10^3 U/mL for 1-year CR after cessation of Nuc. The results of the current study can further conduct a head-to-head comparison of the predictive value of different EOT qHBsAg and HBcrAg for off-Nuc CR. Furthermore, unlike the finding of minimal fluctuation of HBcrAg during off-Nuc follow-up, qHBsAg decline was reported to be significantly accelerating from -0.095 \log{10} IU/mL per year during Nuc therapy to -0.116 \log{10} IU/mL per year after cessation of Nuc [3,4]. It would be more informative if the cumulative incidence over time was compared between patients with different EOT qHBsAg levels.

4. HBsAg loss, a hallmark of functional cure, is the main justification for the strategy of finite Nuc therapy [5,6]. The duration of follow-up (16.7-67.1 months) of this study is long enough to provide the cumulative incidence of HBsAg loss of this cohort, especially those who remained un-retreated, to test the predictive role of HBcrAg for HBsAg loss.

5. Univariable analysis showed a hazard ratio (HR) of 1.36 (95% CI 1.15-1.61) for time-varying HBV DNA level. The HR is almost identical to 1.36 (95% CI 1.14-1.63) for the time-varying HBcrAg level. This should be included in the multivariable analysis and provide an adjusted HR. In addition, it has been shown that off-Nuc HBV DNA levels >2000 IU/mL during off-Nuc follow-up may predict subsequent CR [7]. This factor should be considered or compared. In addition, the Asian-Pacific stopping rule recommended HBV DNA assay 3 monthly in the first year, but monitored more frequently for CR if virologic relapse (>2000 IU/mL) was detected [8]. As such, HBcrAg has no complimentary role during off-Nuc follow-up.

In conclusion, EOT qHBsAg <10^2 IU/mL is better than HBcrAg <10^3 U/mL as a
predictor for CR, at least in the first year after cessation of Nuc. Their conclusion that the dynamic HBcrAg measurement after Nuc cessation was more accurate than the dynamic HBsAg level in the prediction of CR was not supported by their findings. Further studies on the role of HBcrAg in patients with low EOT qHBsAg levels or in combination with other biomarkers, such as HBV-RNA [9], are needed. Finally, cost is an important concern in clinical practice. The cost of a qHBsAg assay is less expensive than that of HBcrAg assay and only <25% of the HBV DNA assay, at least in our hospital [10]. Unless the clinical utility of HBcrAg has a marked and worthy advantage over qHBsAg, it seems better to make good use of qHBsAg during and/or after antiviral therapy.
References:


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