VOLUME 30 NUMBER 2 April 2024

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases

cfDNA ULP-WGS for prognosis in HCC

Linvencorvir phase 2 trial for HBV
Signature gene set for discrimination of MASLD progression
Incidence of adverse events associated with NAFLD
JCAD in cholestatic fibrosis
Prognosis of MASLD

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0064
Clinical and Molecular Hepatology 2024;30:269-271

Letter to the Editor

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

Yun-Fan Liaw

Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan

Keywords: End-of-therapy; Quantitative HBsAg; HBV DNA

Dear Editor,

The multicenter cohort study conducted by 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 following the cessation of nucleos(t)ide analogue (Nuc). The study also showed that only 3.5% of 203 patients experienced bilirubin elevation >2 mg/dL, and all fully recovered after retreatment, hence confirmed that discontinuing Nuc in HBV-suppressed patients is reasonably safe. However, there are several major points that require clarification and/or further discussion.

Multivariable analysis showed that the time-varying HBcrAg level was a significant factor for subsequent CR. However, Figure 5 presents a seemingly contradictory observation, depicting a cumulative CR incidence that remains comparable among patients with different HBcrAg kinetics. It suggests the necessity for a precise definition of "time-varying HBcrAg level" to reconcile this controversy. Their findings that there is no discernible difference in CR rate among patients with different patterns of HBcrAg changes over time contradicts their implication that dynamic serum HBcrAg measurement would be informative/helpful for off-Nuc monitoring.

Multivariable analysis also showed that the 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 levels did not exhibit such associations. Together with the controversial results of HBcrAg in point 1, highly sensitive assays for HBsAg (HBsAg-HQ) and HBcrAg (iTACT-HBcrAg) could potentially exert an impact on the study results.

The results from the multivariable analysis have confirmed the findings of an earlier head-to-head comparison, demonstrating 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 out of 54) in patients with qHBsAg $<10^2$ IU/mL, which was nearly half of the 39.8% (39 out of 98) observed 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

Corresponding author : Yun-Fan Liaw
Liver Research Unit, Chang Gung Memorial Hospital, 199, Tung Hwa North Road, Taipei, 105, Taiwan
Tel: +886-3-3281200 ext. 8120, Fax: +886-3-3282824, E-mail: liveryfl@gmail.com
https://orcid.org/0000-0003-0664-9372

Editor: Han Ah Lee, Chung-Ang University College of Medicine, Korea

Received : Jan. 24, 2024 / **Revised :** Jan. 29, 2024 / **Accepted :** Jan. 31, 2024

CR following Nuc cessation. The present study could further engage in a head-to-head comparison to assess the predictive ability of different EOT qHBsAg and HBcrAg levels for off-Nuc CR. Furthermore, in contrast to the 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 post-Nuc cessation.[3,4] It would be more informative if the cumulative incidence over time was compared among patients with different EOT qHBsAg levels.

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 sufficiently long to yield the cumulative incidence of HBsAg loss in this cohort, particularly among those who remained un-retreated, to test the predictive ability of HBcrAg for HBsAg loss.

Univariable analysis showed a hazard ratio (HR) of 1.36 (95% CI 1.15–1.61) for time-varying HBV DNA levels. 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 to provide an adjusted HR. Furthermore, it has been shown that off-Nuc HBV DNA levels >2,000 IU/mL during off-Nuc follow-up may predict subsequent CR.[7] This factor should be considered or compared in the analysis. Additionally, the Asian-Pacific stopping rule recommended HBV DNA assay every 3 months in the first year, and more frequent monitoring for CR if virologic relapse (>2,000 IU/mL) was detected.[8] As such, it appears HBcrAg may not play a complimentary role during off-Nuc follow-up.

In conclusion, EOT qHBsAg $<10^2$ IU/mL is a superior predictor for CR compared to HBcrAg $<10^3$ U/mL, at least in the first year post-Nuc cessation. Their findings do not support the conclusion that the dynamic HBcrAg measurement after Nuc cessation was more accurate than the dynamic HBsAg levels in the prediction of CR. 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 warranted. Finally, cost is an important concern in clinical practice. In our hospital, the cost of a qHBsAg assays is less expensive than that of HBcrAg assays and only less than 25% of the cost of HBV DNA assays.[10] Unless the clinical utility of HBcrAg has a significant advantage over qHBsAg, it appears more advisable to utilize qHBsAg during and/or after antiviral therapy.

Acknowledgements

The author has been supported by grants from Chang Gung Medical Research Fund (CMRPG1N0111) and the Prosperous Foundation, Taipei, Taiwan.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Tsai YN, Wu JL, Tseng CH, Chen TH, Wu YL, Chen CC, et al. Hepatitis B core-related antigen dynamics and risk of subsequent clinical relapses after nucleos(t)ide analog cessation. Clin Mol Hepatol 2024;30:98-108.
2. Huang PY, Wang JH, Hung CH, Lu SN, Hu TH, Chen CH. The role of hepatitis B virus core-related antigen in predicting hepatitis B virus relapse after cessation of entecavir in hepatitis B e antigen-negative patients. J Viral Hepat 2021;28:1141-1149.
3. Chen CH, Hu TH, Wang JH, Lai HC, Hung CH, Lu SN, et al. Comparison of HBsAg changes between HBeAg-negative patients who discontinued or maintained entecavir therapy. Hepatol Int 2020;14:317-325.
4. Jeng WJ, Chien RN, Chen YC, Lin CL, Wu CY, Liu YC, et al. Hepatocellular carcinoma reduced, HBsAg loss increased, and survival improved after finite therapy in hepatitis B patients with cirrhosis. Hepatology 2024;79:690-703.
5. Berg T, Lampertico P. The times they are a-changing - A refined proposal for finite HBV nucleos(t)ide analogue therapy. J Hepatol 2021;75:474-480.
6. Liaw YF, Chien RN. Finite nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B: From an "option" to an "active recommendation". Kaohsiung J Med Sci 2022;38:295-301.
7. Hall SAL, Burns GS, Anagnostou D, Vogrin S, Sundararajan V, Ratnam D, et al. Stopping nucleot(s)ide analogues in non-cirrhotic HBeAg-negative chronic hepatitis B patients: HBsAg loss at 96 weeks is associated with low baseline HBsAg levels.

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

https://doi.org/10.3350/cmh.2024.0064

Aliment Pharmacol Ther 2022;56:310-320.
8. Liaw YF, Kao JH, Piratvisuth T, Chan HL, Chien RN, Liu CJ, et al. Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2012 update. Hepatol Int 2012;6:531-561.
9. Mak LY, Wong D, Kuchta A, Hilfiker M, Hamilton A, Chow N, et al. Hepatitis B virus pre-genomic RNA and hepatitis B core-related antigen reductions at week 4 predict favourable hepatitis B surface antigen response upon long-term nucleos(t)ide analogue in chronic hepatitis B. Clin Mol Hepatol 2023;29:146-162.
10. Liaw YF. Clinical utility of HBV surface antigen quantification in HBV e antigen-negative chronic HBV infection. Nat Rev Gastroenterol Hepatol 2019;16:631-641.