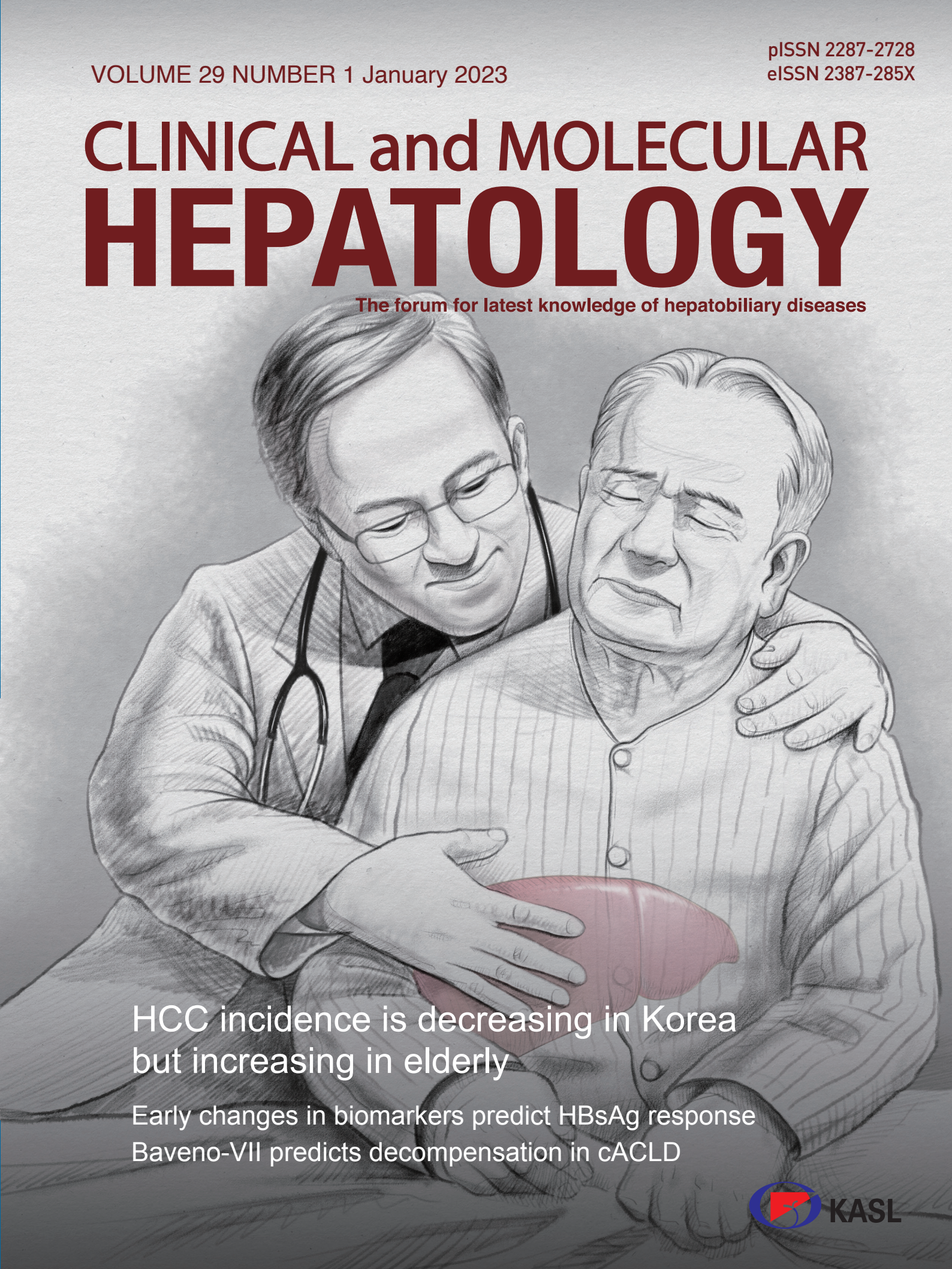
VOLUME 29 NUMBER 1 January 2023

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases



HCC incidence is decreasing in Korea but increasing in elderly

Early changes in biomarkers predict HBsAg response

Baveno-VII predicts decompensation in cACLD

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2022.0410
Clinical and Molecular Hepatology 2023;29:191-193

Correspondence

Correspondence on Editorial regarding "HBV pgRNA and HBcrAg reductions at week 4 predict favourable HBsAg response upon long-term nucleos(t)ide analogue in CHB"

Lung-Yi Mak[1,2], Wai-Kay Seto[1,2], and Man-Fung Yuen[1,2]

[1]Department of Medicine and [2]State Key Laboratory of Liver Research, The University of Hong Kong, Hong Kong

Keywords: Biomarkers; Treatment outcome

Dear Editor,

We sincerely appreciate the editorial piece from Liang et al.[1] reviewing our recent paper on the role of early on-treatment decline in viral biomarkers in predicting favourable hepatitis surface antigen (HBsAg) response in chronic hepatitis B (CHB) infection, published in *Clinical and Molecular Hepatology*.[2] We agree with Liang and co-authors on the potential use of hepatitis B core-related antigen (HBcrAg) and hepatitis B virus (HBV) pre-genomic RNA (pgRNA) in multiple facets of management in the clinical context of CHB infection. Our study provided serum-liver correlations in the magnitude of decline in viral biomarkers upon nucleos(t)die analogue (NA) treatment–those with ≥1 log decline in covalently closed circular DNA (cccDNA) at week 48 had more significant reductions in serum pgRNA and HBcrAg at multiple timepoints of assessment. This further strengthens the proposition for these serum viral biomarkers to be used as surrogates for cccDNA activity.

The findings of our study suggest that subjects without early biomarker response (defined as week 4 pgRNA decline ≥5.32 log copies/mL for hepatitis B envelope antigen (HBeAg)-positive subjects, or week 4 HBcrAg decline ≥2.05 log U/mL for HBeAg-negative subjects) had a low likelihood of achieving favourably low levels of quantitative HBsAg (qHBsAg) (<100 IU/mL) or HBsAg seroclearance, and they should be prioritized for clinical trials while maintaining the NA therapy. As most current trials only consider qHBsAg and/or HBV DNA when screening patients for enrolment eligibility, HBcrAg and pgRNA would provide additional layer of information to identify patients who are most in need for new treatment approaches.[3] HBsAg seroclearance plus HBV DNA undetectability >6 months after treatment cessation is the primary endpoint for phase III trials in the functional cure program of CHB. Notably, the benchmark of ≥30% patients achieving this endpoint[4] has not been met by any of the currently developing novel compounds, despite initial promising results in qHBsAg knockdown by RNA interference-based therapy.[5,6] This has engendered discussions about the practicability of such stringent treatment endpoint.[7] Taking a step

Corresponding author : **Man-Fung Yuen**
Department of Medicine, The University of Hong Kong, Pokfulam Road, Hong Kong
Tel: +852-22553984, Fax: +852-28162863, E-mail: mfyuen@hku.hk
https://orcid.org/0000-0001-7985-7725

Editor: Seung Up Kim, Yonsei University College of Medicine, Korea

Received : Nov. 17, 2022 / **Accepted :** Nov. 18, 2022

back, a 'looser' endpoint of achieving serum qHBsAg <10 IU/mL or <100 IU/mL (HBsAg cut-off levels still subjected to debate) by novel compounds might be more feasible, as such endpoint implies that a patient with CHB had a lower risk of off-therapy virological relapse and can potentially employ the 'stop-to-cure' approach to induce functional cure.[8]

The potential of serum HBcrAg and HBV RNA should not be limited to the context of novel compound development, but may also be applicable to consideration of NA withdrawal in those fulfilling criteria.[9] The timing of biomarker assessment relative to NA therapy is an interesting point to consider. Our study looked at the early (as early as 4 weeks) on-treatment viral biomarker profiles instead of end-of-treatment (EOT) levels. The role of EOT pgRNA and/or HBcrAg in off therapy virological control have been investigated in multiple trials.[10,11] Instead of having to wait for reaching EOT (≥3 years, which is the minimum consolidation period for NA in HBeAg-negative patients),[12] early on-treatment profile of these biomarkers would provide valuable insights to identify patients potentially suitable for this treatment approach.

In summary, our study demonstrated that the degree of cccDNA silencing is the main determining factor for favourable HBsAg response, and can be reflected by early on-treatment changes in HBcrAg and HBV RNA. Patients without early biomarker response while on NA, as an additional consideration on top of qHBsAg levels, should be prioritized to participate in clinical trials in order to achieve functional cure.

Authors' contribution

LYM: literature review and original drafting; WKS and MFY: critical revision of article.

Conflicts of Interest

LYM serves as advisor for Gilead Sciences. WKS received speaker's fees from AstraZeneca and Mylan, is an advisory board member of CSL Behring, is an advisory board member and received speaker's fees from AbbVie, and is an advisory board member, received speaker's fees and researching funding from Gilead Sciences. MFY serves as advisor/consultant for AbbVie, Assembly Biosciences, Aligos Therapeutics, Arbutus Biopharma, Bristol Myer Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, GlaxoSmithKline, Gilead Sciences, Immunocore, Janssen, Merck Sharp and Dohme, Hoffmann-La Roche and Springbank Pharmaceuticals, Vir Biotechnology and receives grant/research support from Assembly Biosciences, Aligos Therapeutics, Arrowhead Pharmaceuticals, Bristol Myer Squibb, Fujirebio Incorporation, Gilead Sciences, Immunocore, Merck Sharp and Dohme, Hoffmann-La Roche, Springbank Pharmaceuticals and Sysmex Corporation.

REFERENCES

1. Liang LY, Wong VWS, Wong GLH, Yip TCF. Moving toward hepatitis B virus functional cure - the impact of on-treatment kinetics of serum viral markers. Clin Mol Hepatol 2023;29:113-117.
2. 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.
3. Kim SW, Yoon JS, Lee M, Cho Y. Toward a complete cure for chronic hepatitis B: novel therapeutic targets for hepatitis B virus. Clin Mol Hepatol 2022;28:17-30.
4. Cornberg M, Lok AS, Terrault NA, Zoulim F; 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty. Guidance for design and endpoints of clinical trials in chronic hepatitis B - report from the 2019 EASL-AASLD HBV treatment endpoints conference. Hepatology 2020;71:1070-1092.
5. Yuen MF, Locarnini S, Lim TH, Strasser SI, Sievert W, Cheng W, et al. Combination treatments including the small-interfering RNA JNJ-3989 induce rapid and sometimes prolonged viral responses in patients with CHB. J Hepatol 2022;77:1287-1298.
6. Yuen MF, Lim SG, Plesniak R, Tsuji K, Janssen HLA, Pojoga C, et al. Efficacy and safety of bepirovirsen in chronic hepatitis B infection. N Engl J Med 2022;387:1957-1968.
7. Cornberg M, Lok A, Terrault N, Zoulim F, editors. AASLD-EASL HBV Endpoints 2022; 2022 Jun 3-4; Washington, D.C.
8. Berg T, Lampertico P. The times they are a-changing - a refined

Abbreviations:

cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; EOT, end-of-treatment; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B envelope antigen; HBsAg, hepatitis surface antigen; HBV, hepatitis B virus; NA, nucleos(t)die analogue; pgRNA, pre-genomic RNA; qHBsAg, quantitative HBsAg

https://doi.org/10.3350/cmh.2022.0410

proposal for finite HBV nucleos(t)ide analogue therapy. J Hepatol 2021;75:474-480.
9. Inoue T, Tanaka Y. Novel biomarkers for the management of chronic hepatitis B. Clin Mol Hepatol 2020;26:261-279.
10. Fan R, Peng J, Xie Q, Tan D, Xu M, Niu J, et al. Combining hepatitis B virus RNA and hepatitis B core-related antigen: guidance for safely stopping nucleos(t)ide analogues in hepatitis B e antigen-positive patients with chronic hepatitis B. J Infect Dis 2020;222:611-618.
11. Papatheodoridi M, Papachristou E, Moschidis Z, Hadziyannis E, Rigopoulou E, Zachou K, et al. Significance of serum HBV RNA in non-cirrhotic HBeAg-negative chronic hepatitis B patients who discontinue effective antiviral therapy. J Viral Hepat 2022;29:948-957.
12. European Association for the Study of the Liver; European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.