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Probability of HBsAg loss after nucleos(t)ide analogue withdrawal depends on HBV genotype and viral antigen levels

To the Editor:

We read with great interest the study by Sonneveld *et al.* which assessed the role of ethnicity, HBV genotypes, and viral antigen levels in predicting HBsAg loss in patients with chronic hepatitis B (CHB) following nucleos(t)ide analogue (NUC) cessation.[1] We believed that this result provides some interesting insights into future management of NUC discontinuation, but we have some concerns about this paper.

Firstly, apart from HBsAg and hepatitis B core-related antigen (HBcrAg), serum HBV RNA, another promising non-invasive surrogate biomarker of covalently closed circular DNA,[2] was also found to be associated with HBsAg loss after stopping NUC therapy in our previous studies.[3,4] The incidence of HBsAg loss at Year 4 after stopping NUCs in patients with undetectable serum HBV RNA and HBcrAg <4 $\log_{10}$ U/ml was as high as 16.1% (5/31) (Fig. 1). Moreover, patients with undetectable serum HBV RNA at the end of treatment displayed a significantly lower risk of clinical relapse after NUC withdrawal (4-year cumulative relapse rate: 15.3%),[5] which also implies that serum HBV RNA could be used as a predictor for safe and beneficial discontinuation of NUCs. Enlightened by this, we have been conducting a multicenter, randomized controlled study (Bio-Stop Study; NCT04519359) to prospectively assess whether patients with low HBsAg (HBsAg <200 IU/ml) combined with either undetectable serum HBV RNA or HBcrAg <3 $\log_{10}$ U/ml at the end of treatment could safely achieve a higher rate of HBsAg loss after stopping NUC treatment.

Secondly, regarding the association of ethnicity and HBV genotype with HBsAg loss after NUC cessation, previous studies have provided some clues suggesting that patients with CHB from Europe exhibit a higher rate of HBsAg loss following NUC withdrawal than those from Asia (annual rate: 6.33% *vs.* 1.78%).[6,7] In the current study, the pooled analysis of patients from Europe and Asia provided further evidence that non-Asian patients or patients infected with genotype A or D HBV have a higher rate of HBsAg loss than Asian patients infected with genotype B or C HBV. However, it is important to note that some of the results from this retrospective study should be interpreted with caution, especially considering the limited case numbers in some subgroups.[1] Moreover, the underlying mechanisms of different HBsAg loss rates after NUC withdrawal among patients with different ethnicities and HBV genotypes also merit further study, in the hope of facilitating the establishment of different stopping rules for different populations.

Lastly, for the multivariable Cox regression analysis in this study, there was no significant difference in HBsAg loss rates between patients who were HBeAg positive at pretreatment baseline and those who were HBeAg negative (p >0.05). This finding was consistent with that from a recent multicenter, multi-ethnic cohort.[8] Nonetheless, in another earlier report, patients who are HBeAg negative at the start-of-treatment, with a stringently longer treatment consolidation duration, are disposed to achieve a higher rate of HBsAg seroclearance after NUC discontinuation compared to those who are HBeAg positive (annual rate: 4.7% *vs.* 3.0%).[9] Moreover, according to a systematic review, initially HBeAg-negative patients had a numerically higher HBsAg loss rate after NUC discontinuation than those initially HBeAg-positive (7.22% [50/693] *vs.* 4.99% [17/341]).[10] Currently, there is a call for more solid evidence about the relationship between pretreatment HBeAg status and HBsAg loss after NUC cessation. Uncovering the underlying mechanisms will provide new knowledge for us to optimize the future management strategy of different patients who stop NUC therapy.

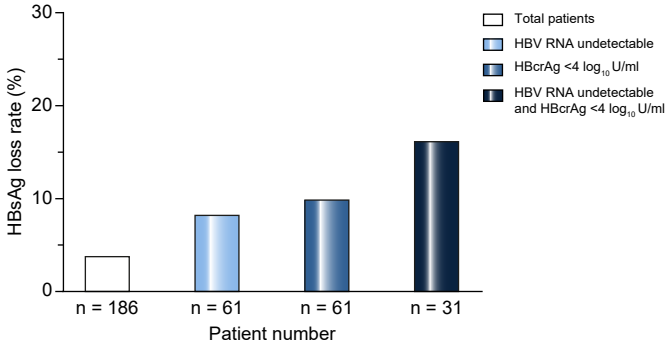

Fig. 1. Rates of HBsAg loss at Year 4 after NUC discontinuation in patients with different serum HBV RNA or HBcrAg levels at the end of treatment. The incidences of HBsAg loss in total patients and those with HBV RNA undetectable, HBcrAg <4 $\log_{10}$ U/ml, as well as HBV RNA undetectable and HBcrAg <4 $\log_{10}$ U/ml were 3.8%, 8.2%, 9.8% and 16.1%, respectively. HBcrAg, hepatitis B core-related antigen; NUC, nucleo(s)tide analogue.

In summary, we concur that the probability of HBsAg loss after NUC withdrawal varies with viral antigen levels and ethnicities. Besides, lower or undetectable serum HBV RNA levels before NUC discontinuation are also associated with higher HBsAg seroclearance and lower relapse rates after stopping therapy. Last but not the least, it might be too early to adjust current guideline recommendations about NUC discontinuation in patients with CHB based on the current inspiring results. Further prospective, randomized, controlled studies with multi-ethnic cohorts and larger sample sizes are warranted.

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Conflicts of interest

JS consults for Guangzhou HEAS BioTech. The other authors declare no conflicts of interest pertaining to this work.

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Authors' contributions

RD contributed to the interpretation of data and drafted the manuscript. RF and JS contributed to the study design and revision for important intellectual concepts. All authors approved the final manuscript prior to submission.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2022.04.022.

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Author names in bold designate shared co-first authorship

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Reply to: "Probability of HBsAg loss after nucleos(t)ide analogue withdrawal depends on HBV genotype and viral antigen levels"

To the Editor:

We would like to thank Sun *et al.* for their interest in our recent article published in the *Journal*.[1,2] In our study, we showed that a combination of HBsAg and hepatitis B core-related antigen (HBcrAg) levels can be used to predict the chance of HBsAg loss after cessation of nucleo(s)tide analogue (NUC) therapy. Despite the high rates of HBsAg loss observed among patients with both low HBsAg and low HBcrAg levels, there remains a major unmet need for other biomarkers to further optimize patient selection as only a limited number of patients have sufficiently low HBsAg and HBcrAg to allow for treatment cessation based on these criteria alone. As suggested by Sun *et al.*, serum levels of HBV RNA may be a promising new tool in this regard,[3] although they are unlikely to be a panacea. In a previous study we have shown that on-treatment kinetics of HBV RNA may differ from those observed for HBsAg and HBcrAg, and that a substantial proportion of patients achieving pronounced HBV RNA declines do not experience a concomitant decrease in viral antigen levels.[4] Interestingly, patients with HBV RNA responses without concomitant viral antigen declines had low rates of sustained response and HBsAg loss, whereas patients achieving combined HBV RNA and viral antigen declines had high rates of favourable outcomes. We therefore feel that combinations of multiple biomarkers that may include different virological (*e.g.* HBV RNA, HBsAg and HBcrAg), but also host markers reflecting the activation of the immune system (*e.g.* anti-HBc and cytokine profiles) will likely be required to identify patients most likely to respond to finite treatment strategies, as highlighted in several recent studies.[3,5–7] Sun *et al.* are to be commended for attempting to validate such a strategy in their ongoing prospective study, and the results of such studies are eagerly awaited by the community.

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