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LETTER TO THE EDITOR

Letter: serum HBV RNA and HBcrAg may help to evaluate safely stopping nucleot(s)ide analogues in patients with HBeAg-negative chronic hepatitis B and without cirrhosis

Editors,

We read with interest the prospective multi-centre study by Hall *et al* evaluating the clinical outcomes after stopping nucleot(s)ide analogues (NAs) in non-cirrhotic HBeAg-negative chronic hepatitis B.[1] The authors found that virological reactivation was very common after stopping NAs, whereas hepatitis B surface antigen (HBsAg) loss was rare. As the suggestion that HBeAg-negative patients can stop NAs is actually mentioned in the hepatitis B management guidelines of the APASL and Chinese Medical Association,[2,3] the findings of this study are of potential interest to clinicians and patients.

We have analysed the virological relapse (VR) and biochemical relapse after stopping NAs in 28 HBeAg-negative non-cirrhotic patients who had achieved undetectable hepatitis B virus (HBV) DNA and then at least 18 months of intensive treatment. Among these, 42.9% had positive HBV DNA (≥100 IU/ml) and 42.9% had elevated alanine aminotransferase (ALT; 30 U/L for male and 19 U/L for female) 1 year after stopping NAs (Figure 1). Our findings suggest that most HBeAg-negative patients will not safely achieve stopping of NAs.

In the study by Hall *et al*,[1] the rates of biochemical (serum ALT <2× ULN) and virological remission at week 96 (HBV DNA <2000 IU/ml) were also reported. Based on such a threshold criterion, we further analysed the biochemical and virological remissions of our patients, which suggested 78.5% biochemical remission and 57.1% virological remission one year after stopping NAs. Despite such a loose criterion of disease remission, a considerable number of patients still could not safely stop NAs.

Hall *et al*[1] found very low HBsAg levels at baseline to predict HBsAg loss and disease remission. However, extremely low HBsAg levels were very rare. In our patients, serum HBsAg levels <10 IU/ml at the end of therapy (EOT) was not observed. Additionally, there was no difference in distribution of serum HBsAg between patients with and without VR. Therefore,

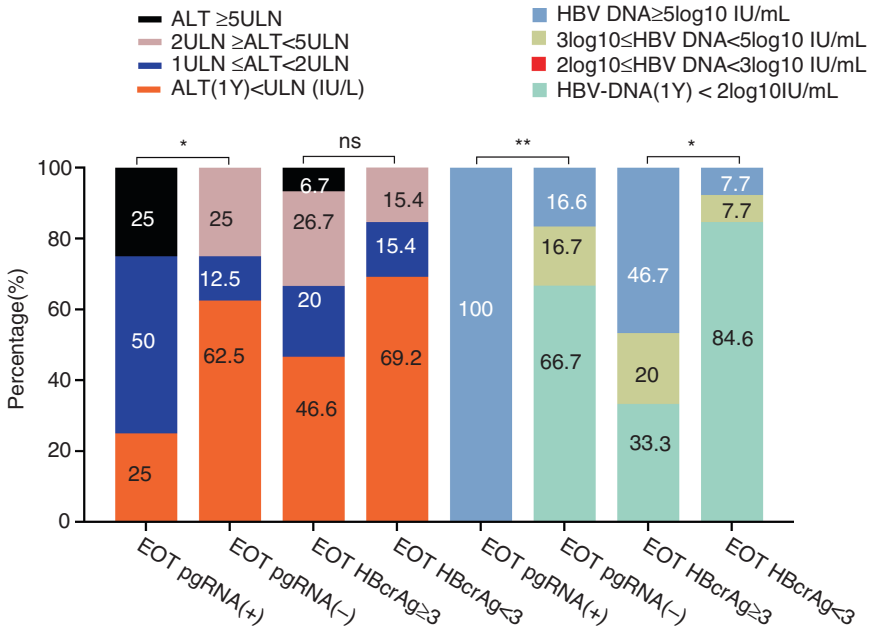

FIGURE 1 Serum hepatitis B virus (HBV) DNA and alanine aminotransferase (ALT) distribution at 1 year after stopping nucleot(s)ide analogues (NAs) according to serum HBV RNA and hepatitis B core-related antigen (HBcrAg) at the (EOT) end of treatment. *< 0.05, **< 0.01.

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it seems impractical to predict disease remission using EOT HBsAg level.

Serum HBV RNA and hepatitis B core-related antigen (HBcrAg) were reported to be surrogate markers of intrahepatic covalently closed-circular DNA.[4] Thus, these indicators are considered to be helpful in predicting VR risk after stopping NAs. Although there was no significant difference in the distribution of EOT HBcrAg between patients with and without relapse, there was a significant difference in HBV RNA, and patients with EOT-positive HBV RNA all had VR. Importantly, the lower HBcrAg and undetectable HBV RNA were both significantly related to lower HBV DNA level at year 1 of stopping NAs; EOT-undetectable HBV RNA was also related to lower ALT levels (Figure 1).

Our observations, together with the findings of Hall *et al*, showed that VR and biochemical relapse are challenges for most non-cirrhotic HBeAg-negative patients who have not achieved HBsAg seroclearance. However, if new biomarkers such as serum HBcrAg and HBV RNA are measured, these patients may be able to safely stop NAs.

AUTHOR CONTRIBUTIONS

Meng-Lan Wang: Writing – original draft (equal); writing – review and editing (equal). **Fa-Da Wang:** Writing – original draft (equal); writing – review and editing (equal). **En-Qiang Chen:** Data curation (equal); investigation (equal); project administration (equal); resources (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal).

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Not applicable.

CONFLICT OF INTEREST

E-QC served as a speaker and as a consultant for Gilead.

LINKED CONTENT

This article is linked to Hall et al papers. To view these articles, visit https://doi.org/10.1111/apt.16968

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