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Serum HBsAg kinetics in clinical prediction

To the Editor:

We read with great interest the review article "The role of quantitative hepatitis B surface antigen revisited" by Cornberg *et al.* in the *Journal of Hepatology* [1]. Indeed, it is a comprehensive update. However, the role of hepatitis B surface antigen (HBsAg) quantification in the prediction of spontaneous or antiviral therapy related HBsAg seroclearance and relapse after cessation of nucleos(t)ide analog (NUC) therapy was not well addressed. The studies mentioned in the review used an HBsAg level <100 IU/ml as a predictor for remote (6–10 years) HBsAg seroclearance but two studies on short-term prediction of HBsAg seroclearance within 1–3 years were not mentioned. One longitudinal study showed that serum HBsAg level ≤200 IU/ml had a negative predictive value for HBsAg seroclearance of 100% and 92% at 1 and 3 years, respectively, and the positive predictive value increased from 36% at 1 year and 49% at 3 year to 97% and 100%, respectively if combined with a ≥1 $\log_{10}$ IU/ml reduction in the preceding 2 years [2]. Another large case-control study also showed that HBsAg level <200 IU/ml was predictive of HBsAg seroclearance within 3 years and a patient with HBsAg <200 IU/ml and a 0.5 $\log_{10}$ IU/ml HBsAg decline in the next year may predict HBsAg seroclearance in 3 years with a sensitivity of 74% and a specificity of 89.4% [3]. Obviously, prediction of spontaneous HBsAg seroclearance within a much shorter period of 1–3 years is more desirable and useful in daily clinical practice.

Stronger HBsAg decline during NUC therapy associated with higher pretherapy alanine aminotransferase (ALT) was briefly mentioned in the review. Actually, patients with pretherapy ALT over 5× upper limit of normal (ULN) showed greater HBsAg decline not only at an ALT-level dependent manner but also at an alpha-fetoprotein (AFP) level-dependent manner, in which AFP dominated over ALT as a more powerful factor for early "rapid HBsAg decline" [4]. These findings are important because "rapid HBsAg decline" >0.5 $\log_{10}$ IU/ml by month 6 or >1 $\log_{10}$ IU/ml by month 12 of NUC therapy were found to be predictors for HBsAg seroclearance [5], and HBsAg decline ≥75% by week 24 of adefovir/tenofovir therapy was also predictive for HBsAg seroclearance [6]. A most recent study further showed that hepatitis flares (ALT >5× ULN) during pegylated interferon and tenofovir combination therapy in HBeAg positive patients was associated with HBsAg decline >1 $\log_{10}$ by week 12, which was an independent factor for HBsAg loss [7]. More studies on this issue are ongoing.

The issue of stopping NUC therapy in HBeAg-negative patients has attracted more and more attention in recent years. Studies have shown the lower the HBsAg level at the end of NUC therapy, the less chance of clinical relapse [8–10]. HBsAg <100 IU/ml seems to be the best predictive level but no consensus has been reached. This is also applicable in patients with liver cirrhosis who had discontinued NUC therapy, as such patients were included in these studies [8–10].

In conclusion, HBsAg quantification has a wide range of clinical applications. It is anticipated that the role of HBsAg kinetics in the natural course and during antiviral therapy in patients with chronic hepatitis B will remain a hot issue to be explored.

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Conflict of interest

YF Liaw has been involved in clinical trials or served as a global advisory board member of Roche. Wen-Juei Jeng has no relevant conflict of interest.

Authors' contributions

Wen-Juei Jeng: Draft writing; Yun-Fan Liaw: Critical manuscript revision.

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Reply to: "Serum HBsAg kinetics in clinical prediction"

To the Editor:

We agree with W-J Jeng and Y-F Liaw on the pivotal role of spontaneous hepatitis B surface antigen (HBsAg) serum clearance in the clinical history of a hepatitis B virus (HBV) carrier [1] as it is, the hallmark of the control of HBV replication and transition from inactive to occult infection [2]. However, the reported annual rates of HBsAg clearance are highly variable (0.31 to 3.2 × 100 persons/years) because of the heterogeneity of the studied populations [3–6]: mode of infection, age and ethnicity are major factors influencing the HBsAg loss [5–8]. Furthermore, viral features as HBV genotype could play a role as suggested by the lower yearly HBsAg decline in genotype D infected carriers (0.287 and 0.35 $\log_{10}$ IU/ml during 38 months and 9 years median follow-ups, respectively) when compared to genotype B/C infected carriers (0.53 and 0.751 $\log_{10}$ IU/ml during the 5 and 3 years prior serum HBsAg loss, respectively) [9–12]. Finally, different HBsAg kinetics were described according to residual viral replication: a progressive decline till HBsAg clearance was seen in carriers with undetectable HBV DNA at variance with a sharp HBsAg drop about 2 years prior HBsAg clearance in carriers with detectable viremia [8]. Thus, the identification of a universal threshold predictive of short term HBsAg clearance would require the studies of a large cohort of patients infected with different genotypes where all the relevant variables are analyzed: demographic features (age, sex and ethnicity), viral profile (history of HBeAg positivity, HBeAg/anti-HBe seroconversion time, viral load), overall follow-up duration and yearly HBsAg clearance rate. Accordingly, the scoring system developed on the HBeAg negative REVEAL cohort shows that only the combination of several variables (age, BMI, HBsAg and HBV DNA serum levels) can predict with adequate accuracy the probability of HBsAg clearance in the single carrier [8]. On the other hand, acceptable positive predictive value and diagnostic accuracy are achievable only at very low HBsAg levels, as 100 IU/ml proposed by several studies in Asia where genotype B and C HBV are predominant [7,8,13–14]. In fact, when a higher HBsAg threshold (such as 200 IU/ml) is used, HBsAg kinetics have to be added to improve the diagnostic performance [11,12]. This implies the need to monitor HBsAg levels over time. Thus, the use of the latter approach would not modify the current clinical practice since serum HBsAg monitoring would be required anyway to predict and finally to show HBsAg clearance.

W-J Jeng and Y-F Liaw commented also on the issue of HBsAg quantification in the context of nucleos(t)ide analogue (NA) therapy. They discussed their data that HBsAg decline during NA therapy is stronger in patients with higher baseline alanine aminotransferase (ALT; >5× ULN) and higher alfa-fetoprotein (AFP) levels. AFP reflects cell turnover and may be another surrogate for immune responses [15]. The data are in line with our discussion that the immune response but not the mode of action of the NA is important for HBsAg decline [16]. However, the value of baseline parameter (ALT, AFP or IP-10) and on-treatment HBsAg level for the decision when to stop NA treatment is still limited in our view. There are different stop NA approaches in different regions. The Asian Pacific Association for the Study of the Liver (APASL) guideline suggests stopping NA therapy in HBeAg negative patients after treatment for at least 2 years with undetectable HBV DNA documented on three separate occasions, 6 months apart [17]. This is in contrast to the EASL and AASLD guidelines that give a strong recommendation treating all HBeAg negative patients until HBsAg loss [2,18]. Demands for a cut-off to identify patients who should maintain on-treatment or may stop earlier may be different in different regions. As we have discussed in our review, HBsAg levels <100 IU/ml may be a good predictor for maintained HBV DNA suppression after stopping NA therapy [16]. Higher cut-offs of <150 IU/ml [19] or <200 IU/ml [20] have been discussed by other investigators. Other factors such as age [19], previous therapies, kinetics of ALT levels or duration of consolidation therapy could influence the risk of relapse after stopping NA treatment [21]. In our view, the current evidence does not support a strong recommendation for stopping NA therapy at a certain cut-off at this stage. To prevent clinical relapse, we suggested the lower HBsAg cut-off of <100 IU/ml and a consolidation therapy for at least 3 years in our review [16]. However, another strategy to stop NA treatment may be to induce flares and increase HBsAg rates. Hadziyannis *et al.*, have stopped adefovir and observed ALT flares in 76% and subsequently 39% of patients lost HBsAg in the long-term follow-up [22]. Höner zu Siederdissen *et al.* showed 20% HBsAg loss after stopping long-term NA therapy in a small cohort of HBeAg negative patients. Interestingly, not HBsAg levels at stop of therapy but the peak level of HBV DNA and peak ALT during the relapse were the best predictors for later HBsAg decline. The study also showed that IP-10, IL-12, TNF and IL-10 were significantly

induced after stopping NA therapy [23]. As discussed above, the key to achieve HBsAg loss is the modulation of immune responses. An important task is now to analyze which part of the immune response is fundamental for these effects. In conclusion, the topic to stop long-term NA therapy seems to be very interesting but still controversial.

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Authors' contributions

All three authors (M.B., M.C., H.L.Y.C.) contributed to the writing and final approval of the reply letter.

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