INVITED EDITORIAL

Editorial: serum HBV RNA biphasic decline in patients with HBeAg-positive chronic hepatitis B treated with nucleos(t)ide analogues

Serum hepatitis B virus (HBV) RNA is a potentially valuable biomarker for treatment and prognosis of chronic HBV infection.[1-3] Serum HBV RNA, the direct downstream product of intrahepatic covalently closed circular DNA (cccDNA), could better reflect the transcription activity of cccDNA than serum HBV DNA. Positive serum HBV RNA signified the presence of transcriptionally active cccDNA in patients.[4] In recent years, studies have demonstrated that serum HBV RNA was used to predict the treatment efficacy of nucleos(t)ide analogues (NAs) and pegylated interferon.[5-7] More importantly, serum HBV RNA at the end of NA therapy has been reported to be associated with post-treatment clinical relapse.[8] Hence, achieving undetectable serum HBV RNA might be a novel and promising surrogate endpoint for chronic hepatitis B (CHB) patients receiving NA therapy. However, many aspects of this viral marker need further study. The mechanisms underlying the decline in serum HBV RNA during NA therapy are not yet fully understood.

The retrospective study by Liu et al[9] is the first comprehensive analysis that characterised the kinetics of serum HBV RNA in a prospective multicentre clinical trial. The investigators found that undetectable serum HBV RNA always occurred after serum HBV DNA became undetectable. The decline of serum HBV RNA during long-term NA therapy was biphasic. Rapid virological response (RVR) was independently associated with a rapid decline in serum HBV RNA in these two phases. Patients with RVR had greater decline in serum HBV RNA by 0.281 (95% confidence interval [CI], 0.211-0.351, $P < 0.0001$) $\log_{10}$ copies/mL per month than those without.

Patients with RVR needed a median of 29.95 months (interquartile range [IQR]: 21.78-36.49) to achieve undetectable serum HBV RNA after NA initiation, which was significantly shorter than those without RVR (62.98 months, IQR: 46.37-98.77). The estimated time to achieve undetectable serum HBV RNA and to identify its influencing factors could be useful to inform particular patient groups about their expected treatment duration. More potent NAs should be used to achieve RVR, an important predictor for serum HBV RNA decline, thereby shortening the treatment duration of achieving undetectable serum HBV RNA. Furthermore, serum HBV RNA should also be incorporated in the evaluation of the efficacy of novel antiviral agents under development.

Several caveats warrant attention when interpreting the studies that depict the serum HBV RNA and RVR. First, host and viral factors are associated with serum HBV RNA levels among patients needing treatment.[10] Second, there is no standardised assay for HBV RNA quantitation. Third, the definition of RVR is not yet universally agreed. RVR was defined arbitrarily as achieving undetectable serum HBV DNA within 9 months in the study. Finally, the estimated time to achieve undetectable serum HBV RNA was obtained from generalised estimating equations. Therefore, developing an accurate and standardised protocol for serum HBV RNA is urgently needed. This should be validated in further clinical studies on expected treatment duration to achieve these promising stopping criteria obtained by undetectable serum HBV RNA.

LINKED CONTENT

This article is linked to Liu et al papers. To view these articles, visit https://doi.org/10.1111/apt.15890 and https://doi.org/10.1111/apt.15993

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