Towards HBV functional cure – do we have a crystal ball for that? - Authors' reply

Running head: early biomarker profile and NA therapy

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Dear Editor,

We sincerely appreciate the editorial piece from Liang, Wong, Wong and Yip¹ reviewing our recent paper on the role of early on-treatment decline in viral biomarkers in predicting favourable HBsAg response in chronic hepatitis B 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 chronic hepatitis B (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 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 endpoint⁴ 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 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.

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