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Editorial

New biomarkers of hepatitis B virus (HBV) infection: HBV RNA and HBV core-related antigen, new kids on the block?

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Through long-term treatment with nucleos(t)ide analogues (NUC), the prevention of disease progression to end-stage liver disease and reduction in the risk of hepatocellular carcinoma (HCC) is achievable in most patients with chronic hepatitis B (CHB). However, functional cure (hepatitis B surface antigen [HBsAg] seroclearance) is very rarely achievable even with long-term NUC treatment, and the optimal timing of treatment initiation and discontinuation remains debatable.

With recent advances in molecular analysis, several new biomarkers of the hepatitis B virus (HBV) have been identified, including quantification of HBsAg (qHBsAg), HBV RNA, and HBV core-related antigen (HBcrAg).[1,2] Integration of these biomarkers with the conventional ones, such as the hepatitis B e antigen (HBeAg) test and HBV DNA quantitation, may improve our understanding of the natural history of CHB and its response to antiviral therapy. All of qHBsAg, HBV RNA, and HBcrAg have been proposed as surrogate markers of HBV covalently closed circular DNA (cccDNA) activity. Studies have shown the potential utility of these novel biomarkers in a range of clinical settings, such as monitoring response to anti-viral therapy, predicting relapse after treatment cessation or estimating the risk of HCC.[3,4] However, HBsAg may be produced from both cccDNA and integrated viral genomes and its correlation with intrahepatic cccDNA is particularly weak in the HBeAg-negative patients. Therefore, attention has shifted to other serum biomarkers such as HBV RNA and core re-lated antigen.

In this issue of Mak et al.,[5] a new role of HBV pre-genomic (pg) RNA and HBcrAg in predicting favourable HBsAg response (FHR; <100 IU/mL or HBsAg seroclearance) during median 17 years of NUC treatment. For HBeAg-positive patients, serum HBV pgRNA decline at week 4 was significantly greater for patients with FHR compared to non-FHR patients (5.49 vs. 4.32 log copies/mL, respectively). For HBeAg-negative patients, instead of increase in serum HBcrAg from baseline in non-FHR patients, FHR patients had median reduction in HBcrAg at week 4 (increment of 1.75 vs. reduction of 2.98 log U/mL). This may have a significance as a new study that

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showed the usefulness of HBV pgRNA and HBcrAg in predicting FHR during NUC treatment. However, its clinical implication is limited because this study cannot address whether early biomarker response can help to predict successful off-NA virological control. Nonetheless, the results of this study could be used as companion diagnostic tests in the clinical trials to develop new novel drugs to induce CHB functional cure.

It is noteworthy that the HBV RNA and HBcrAg were significantly lower in all time points among HBeAg-negative patients compared to HBeAg-positive patients, a finding that is consistent with previous reports. This is especially true for HBcrAg due to the poor detectability in HBeAg-negative patients because HBeAg is part of HBcrAg (which consists of HBcAg, HBeAg and p22cr). Therefore, the analyses were performed in HBeAg-positive and HBeAg-negative patients separately.

Overall, the use of novel biomarkers for HBV infection carries enormous potential, and it is possible that new biomarker-based models, used in combination with traditional ones, will become an integral part of our daily practice in near future as well as in the development of new drugs. The addition of HBV RNA and HBcrAg to our armamentarium as new biomarkers should be embraced and will be beneficial in our efforts to eliminate HBV. However, before using these biomarkers, the assays for these biomarkers should be standardized with their improvement in the detection sensitivity and also availability.

Conflicts of Interest

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Abbreviations:

cccDNA, covalently closed circular DNA; CHB, chronic hepatitis B; FHR, favourable HBsAg response; HBcrAg, HBV core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NUC, nucleos(t)ide analogues; pg, pre-genomic; qHBsAg, quantification of HBsAg