Correlation Between HBsAg Quantitation and HBV DNA in HBeAg-Negative HBV/D Patients

Hepatitis B virus (HBV) is a major worldwide health problem infecting about 2 billion people and causing chronic hepatitis in up to 400 million.\[1,2\] Undesirable outcomes of chronic HBV infection include hepatic decompensation, cirrhosis, and hepatocellular carcinoma, which cause great morbidity and mortality.\[3\] Significant medical advances in antiviral therapies and vaccination programs have led to drastic improvements in outcomes, but the worldwide disease burden remains high.\[4,5\] Chronic hepatitis B is defined by a positive hepatitis B surface antigen (HBsAg) for ≥6 months. There are four phases of HBV infection: An immune tolerant phase with a high HBV DNA, a normal alanine aminotransferase (ALT), and minimal liver inflammation; an immune active phase with diminishing HBV DNA, rising ALT, and evidence of hepatitis; an inactive carrier state with marked reduction in HBV DNA, normalization of ALT, and minimal liver inflammation or fibrosis; and a reactivation phase with increasing ALT, HBV DNA, and progression of liver disease.\[2\]

In the Middle East, HBV is of intermediate-to-high prevalence, commonly genotype D, and usually lacking hepatitis B envelope antigen (HBeAg).\[6\] The hepatitis B genotype D (HBV/D) may lead to later HBeAg seroconversion, a greater rate of progression to chronic liver disease, lower response rates to interferon-alpha, and variable response rates to nucleos(t) ide analogs.\[7\] A diagnosis of HBV is made by the utility of various serological Markers, such as HBsAg, hepatitis B core antigen, HBeAg, hepatitis B surface antigen antibody, hepatitis B core antigen antibody, hepatitis B envelope antigen antibody, and HBV DNA. The quantification of HBV DNA provides a marker of active HBV replication, monitors response to antiviral therapy, and identifies the development of resistance. However, HBV DNA monitoring does not come without its limitations, such as cost, standardization, sensitivity, absolute cutoff levels, and being labor intensive.\[8\] Multiple studies in various clinical scenarios have attempted to determine if HBsAg quantitation correlates with HBV DNA and can be used as a marker of disease activity and response to treatment. The results have been conflicting and studies on this correlation in a Middle Eastern population have been limited.\[9-16\]

The study by Alghamdi et al., in this issue of the Journal, is a cross-sectional study that attempted to study the correlation between HBsAg quantitation and HBV DNA in treatment-naïve patients with HBeAg-negative HBV/D in a Saudi Arabian population to determine if the HBsAg quantitation can be used as a reliable predictor of HBV DNA level.\[17\] A total of 106 patients were recruited of whom 78 were inactive carriers (IC) and 28 had chronic active hepatitis (AH). The definitions were based on European Association for the Study of the Liver (EASL) guidelines with IC patients having a persistently normal ALT (<65 IU/L) and low HBV DNA (<2000 IU/mL), whereas AH patients had a persistently or intermittently increased ALT (>65 IU/L) and a high HBV DNA (>20,000 IU/mL).\[18\] The median log10 HBsAg titer was significantly lower in the IC group compared with that of the AH group at 3.09 versus 3.68 (P < 0.001). There was a significant positive correlation between HBsAg and HBV DNA levels in the whole cohort, AH, and IC groups (r = 0.402, P < 0.001; r = 0.383, P < 0.05; r = 0.309, P < 0.01, respectively). The suggested cutoff of HBsAg titer to determine between the IC and AH groups was 3.79 log10 IU/mL (sensitivity 67.9%, specificity 66.4%, P < 0.05). The authors concluded that serum HBsAg titers correlate well with HBV DNA in treatment-naïve HBeAg-negative HBV/D patients, and support the use of HBsAg levels in clinical practice as a predictor of serum HBV DNA levels.

This study had several drawbacks that should be mentioned. A small number of patients were included, especially in the AH group, which may have limited the statistical significance obtained. The authors also used the EASL definitions for the IC and AH hepatitis patients without serial measurements. Viral fluctuation is common among chronic HBeAg-negative HBV-infected patients and there is a possibility of misclassification. It would have been better to correlate disease activity with a better standard, such as baseline liver biopsies. This would also have determined if any patients had underlying cirrhosis. HBV DNA and not transcriptionally active covalently closed circular (ccc) HBV
DNA were measured, which may be a more appropriate correlator of HBsAg. Serial HBsAg and HBV DNA measurements were not performed, which could confirm reproducibility in individual patients seen in this study. In the results section, the author suggested a cutoff value of HBsAg titer that differentiates between the two groups of 3.46 log10 IU/mL (sensitivity 67.9%, specificity 66.4%, \( P < 0.05 \)). However, Brunetto et al. showed that HBsAg was accurate and reliable for distinguishing IC from AC with a specificity of 90.2% and a positive predictive value of 75.4%. This poor specificity and sensitivity make the reliability of this cutoff questionable. This could be due to the sample size or the study design.

It should be noted that quantitation of HBsAg, as a correlation of HBV DNA, should not replace the role of HBV DNA. It is a rough estimate and not a gold standard, but it can definitely have a role in correlating disease especially in stable patients after an initial HBV DNA is performed to save expenses and minimize the cumbersome nature of HBV DNA testing. Despite the limitations of this study, Alghamdi et al., provide useful information on the correlation between HBsAg and HBV DNA in HBV/D in a Middle Eastern population. Future studies will have to address the reproducibility of the correlation in a larger patient population over time with liver biopsies also taken to correlate inflammation, a correlation with cccDNA, and if the correlation still exists in patients on various forms of antiviral therapy and in cirrhotic patients.

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