Editorial

Quantitative HBsAg: Not helpful to evaluate fibrosis in HBeAg-negative chronic hepatitis B patients

Around 257 million people worldwide have chronic hepatitis B virus (HBV) infection, which leads to almost 1 million deaths per year from complications, mainly decompensated cirrhosis and hepatocellular carcinoma. Current treatments for HBV infection include pegylated interferon-alfa (Peg-IFNα) for a limited duration (48 weeks), which is associated with mild efficacy and poor tolerability, or nucleoside analogues (NA), which require lifelong administration and rarely achieve hepatitis B surface antigen (HBsAg) loss.[1]

Fibrosis is the most important prognosis predictor of survival. Therefore, fibrosis evaluation is mandatory and subjects at risk of fibrosis progression may be prioritized for treatment. According to the guidelines, all patients with HBeAg positive or negative chronic hepatitis B, and active disease defined by HBV DNA more than 2000 IU/mL, alanine aminotransferase (ALT) above the upper limit of normal, or at least moderate liver necroinflammation or fibrosis, are candidates for treatment.[2,3] The patients with extrahepatic HBV-related manifestations are also candidates for therapy.[1]

Several new markers have been developed to assess the fibrosis.[4] For instance, the expression of 13 fibrosis-related microRNAs was analyzed in 194 serums and 177 liver biopsies of patients with either chronic hepatitis B (CHB) or chronic hepatitis C (CHC) to develop models to diagnose advanced fibrosis and cirrhosis.[5]

Quantifying HBsAg (qHBsAg) is certainly an important new tool for predicting the severity of disease and response to therapy in CHB.[6,7] Quantifying HBsAg has been proposed as a surrogate marker of cccDNA. In this way, HBsAg measurement helps tailor follow-up and treatment management. To distinguish active from inactive hepatitis B, a qHBsAg of 1000 IU/mL has been suggested as an appropriate cutoff.[8] Prediction of disease reactivation in patients with asymptomatic HBeAg-vee CHB has been proposed using baseline serum measurements of HBsAg and HBV-DNA.[9] Regarding treatment, in a study of 48 patients with HBeAg-ve receiving Peg-IFNα-2a, a decrease of 0.5 and 1 $\log_{10}$ IU/mL of serum HBsAg levels at weeks 12 and 24 of therapy had a 90% negative predicting value and a 89% positive predicting value for week 12 and 97% negative predicting value and a 92% positive predicting value for week 24 sustained response, respectively.[10] This was the first study to suggest early kinetics (week 12) of HBsAg to differentiate sustained responders from non-responders to Peg-IFN.

In an interesting study published in this issue of the Saudi Journal of Gastroenterology, an important question was raised: whether qHBsAg, in HBeAg-ve chronic HBV, could be a non-invasive biomarker of liver inflammation and fibrosis.[11] Untreated chronic adult HBV (HBsAg detection >6 months) HBeAg-ve patients (n = 75) with mean HBV DNA <2000, 2,000–20,000 and >20,000 IU/mL were included. These well-phenotyped patients were the part of a cohort of 366 HBeAg-ve carriers previously reported by the authors.[12] The methodology was adequate: the qHBsAg levels (Abbott ARCHITECT® Assay, Abbott Diagnostics) were measured at baseline as single-point quantification. Furthermore, all specimens were centrally assessed and scored according to the METAVIR system by a hepatopathologist who was blinded to all clinical information.

The mean age of the patients was 39.4 ± 11.4 years and 58 were male (77.3%). ALT levels were normal in 30 (40%) with the median ALT of the overall cohort being 1.2 ULN (IQR 0.6–1.6). The log10 qHBsAg level of the overall cohort was 3.4 ± 0.9 IU/mL. Significant fibrosis (F2-4) was seen in 31 (41.3%) and these patients were more likely to have higher Log10 HBV DNA, elevated ALT and AST, and lower platelets. In patients with HBV DNA >2000 IU/mL, when qHBsAg levels were >1000 IU/mL (n = 56, 74.7%), F2-4 fibrosis was more frequently seen (50.0%) as opposed to those with qHBsAg <1000 IU/mL (7.1%, P = 0.005). However, in one-half of the patients who fulfilled these criteria of HBV DNA >2000 IU/mL and qHBsAg >1000 IU/mL non-significant (F0-1) fibrosis was found.

Finally, the results show that qHBsAg do not distinguish patients with F2-4 fibrosis. Mean levels were similar in patients with significant and non-significant fibrosis,

and in those with levels >1000 IU/mL less than half had significant fibrosis. More than half the patients with non-significant fibrosis were also found to have a qHBsAg level >1000 IU/mL. More importantly, patients with qHBsAg <1000 IU/mL had a presence of significant fibrosis similar to those with levels >1000 IU/mL. The authors concluded that disease stratification is not feasible with qHBsAg levels, with results being in conformity with other studies in patients with HBeAg-ve where higher qHBsAg levels did not identify significant fibrosis.[13,14]

In conclusion, this interesting study demonstrates that the fibrosis evaluation is not precise with qHBsAg levels in patients with HBeAg-ve. Although this study has few limitations: mainly for the less number of patients and with a limited HBV genotype distribution, the results are in agreement with the previous reports. Future studies will have to address the reproducibility of the correlation in larger, patient cohorts of different origins, with a large HBV genotype distribution, and over time with liver biopsies performed to correlate HBsAg quantification, inflammation, fibrosis, cccDNA, and antiviral therapy in patients with CHB.

Finally, what are the clinical implications of HBs quantification? HBs quantification appears to have a better correlation with fibrosis stage in patients with HBe+ve CHB.[7,15] Monitoring serum HBsAg concentrations in patients with HBV infection could provide substantial complementary information to HBV DNA measurements when predicting treatment response, although this is complicated because it has recently been demonstrated that HBsAg could also be produced by integrated HBV-DNA.[16] Recent studies in chimpanzees suggest a dramatic increase of the integration in the HBeAg-ve phase with more than 90% of the mRNAs deriving from integrated HBV-DNA. A significant proportion of HBsAg in patients with HBeAg-ve could derive from integrated HBV sequences. Immune response (reflected by necroinflammation) with mitochondrial antiviral response has also an important role during HBV infection and might interact with HBs production.[17]

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