Editorial

Fluctuating hepatitis B viremia: Full of sound and fury, signifying nothing?

Most of us treasure stability, especially when it comes to a key laboratory value such as hepatitis B viremia in the management of patients with chronic hepatitis B (CHB). Thus, an unstable, fluctuating viral load in such a situation is potentially unsettling, perhaps even full of sound and fury. But what does it really signify?

The management of CHB is complex and the decision to start viral suppression therapy is dependent on clinical factors including HBV DNA levels, liver inflammation, and/or fibrosis. In this issue of the Saudi Journal of Gastroenterology, Sanai *et al.*[1] retrospectively evaluated CHB patients with negative HBe antigen and fluctuating HBV DNA levels (2000 to 20000 IU/mL) vs those without fluctuation (persistently below 2000 IU/mL), comparing their risk of developing of significant hepatic fibrosis. They observed no significant association with HBV DNA levels and liver fibrosis. Interestingly, in the group with fluctuant viremia, F2-F4 fibrosis was lower compared to those without fluctuant viremia (~8% vs 18%). These results were collected from academic centers in the two largest Saudi cities.

The observations made by Sanai *et al.* although largely negative, highlight the complex pathophysiology of CHB infection, the need to factor in the role of host immune responses and the potential for concurrent underlying chronic liver diseases that may have ultimately affected the end-organ liver disease readout of fibrosis. The concept of differential host immune response in driving liver injury is well characterized for early hepatitis B infection. During this early phase of infection, high levels of HBV DNA, indicative of viral replication, are occurring in the setting of normal serum biochemistry and minimal liver fibrosis.[2] The lack of hepatocellular injury in this stage is thought to be in part driven by an attenuated immune response limiting the degree of direct hepatocyte injury. In later stages, which is more representative of the population in the study by Sanai *et al.*, whereby HBe antigen is negative, using a normal ALT to evaluate for the absence of hepatocellular injury may be insufficient for identifying true underlying immune response and hepatocyte injury in the liver environment. One study has highlighted that although rare, in patients with a normal ALT and HBV DNA <20,000 IU/mL, evidence of active liver disease can still be present on histology.[3] Given the invasive nature of liver biopsy, evaluating the effects of fluctuation of HBV DNA on the inflammatory response in the liver environment was understandably not possible in this study. Development of reliable biomarkers identifying patients with active immune response at the liver tissue level beyond what is reflected by ALT levels is needed in CHB. This will allow for better evaluation of overall disease activity in the liver environment. The complex issues in managing CHB, including emerging biomarkers of disease activity/liver damage and the role of the host immune response in CHB have been reviewed elsewhere.[4-6]

Another area of potential interest includes that of the luminal microbiota and its effect on host immune response within the liver. The concept of host microbiota mediating differential immune function has been previously described and well characterized in pre-clinical models.[7,8] Studies have highlighted perturbations in microbial composition in the setting of CHB and its effect on liver injury[9,10] thought to occur via various mechanisms within the gut-liver axis. Avenues include luminal components translocating the gastrointestinal tract and signaling with innate receptors in the hepatic environment, such as lipopolysaccharide-Toll Like Receptor 4, flagellin- Toll Like Receptor 5, and various cell wall components – Toll Like Receptor 2 interactions. The roles of luminal derived metabolites are also of importance and have been discussed elsewhere in the context of different forms of chronic liver diseases.[11-13]

Moreover, in this study the use of a liver stiffness measurement by transient elastography as a non-invasive means of monitoring liver fibrosis reflects real-world management of patients with CHB. The authors minimized inter-observer variability by utilizing single operators at the study centers. The lack of association in fibrosis level change by transient elastography in relation to fluctuant HBV DNA levels may be potentially masked by underlying non-alcoholic steatohepatitis (NASH); a condition that is highly prevalent globally with modeling and epidemiological

data suggesting ~30% of the world's population being affected by the year 2030.[14] NASH and NAFLD are particularly prevalent in the Middle Eastern population.[15] The authors did evaluate the body mass index, presence of diabetes, and dyslipidemia between the HBV fluctuant and non-fluctuant groups and highlighted no significant difference. They also included Controlled Attenuation Parameter score calculated from the transient elastography, which correlates to liver steatosis, and showed no difference between the groups. Although these clinical and noninvasive variables have been previously shown to be associated with NAFLD/NASH, they are not diagnostic of NASH and cannot be used in place of a biopsy to completely rule out the presence of underlying liver inflammation or fibrosis. As such, it is a possibility that HBV DNA fluctuations may drive liver injury but any difference in this observed endpoint was blunted by concurrent NASH. Again, this highlights the need for better biomarkers to reflect immune activity in the setting of CHB.

One of the major conclusions of this study is that apparent viremia fluctuations, especially defined in the authors' manner as any value that crosses the 2000 IU/mL cutoff threshold for 'inactive carriage', are probably clinically insignificant, at least in terms of fibrosis or disease progression. In addition to the above factors, an important methodological/technical note must be emphasized in this regard. That issue is the significance of changes on logarithmic base 10 values. Most human brains cannot easily or intuitively grasp numbers expressed as log-10 values. For example, if hepatitis B DNA levels increase from 2000 to 4000 IU/mL, this absolute doubling may appear quite significant. However, in log-10 terms that is only a modest increase from 3.3 to 3.6. Thus, the results of this study, along with all others that use PCR-based HBV-DNA assays such as the Abbott platform, which is widely used globally, must be carefully considered in view of the natural inherent variability, as this extent of 0.3 log difference is within the accepted coefficient of variability of the assay.[16]

In summary, Sanai *et al.* found no significant difference in fibrosis score on transient elastography in patients with fluctuating HBV DNA levels vs those without fluctuation. Their study highlights the importance of considering both viral and host factors when evaluating end organ outcomes, and suggests that small logarithmic variations in viremia are clinically insignificant.

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