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Editorial

Assessment of fibrotic burden among chronic hepatitis B virus-infected patients with normal transaminase level

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Given that elevated serum levels of hepatitis B virus (HBV) DNA are associated with an increased risk for liver cirrhosis or hepatocellular carcinoma (HCC),[1] the mainstay of hepatitis B treatment is antiviral therapy (AVT) to suppress viral replication. Currently, commencement of AVT depends on not only serum HBV-DNA level but also serum alanine aminotransferase (ALT) level, hepatitis B e antigen status, and the presence of liver cirrhosis or HCC.[2,3] However, even in cases with normal transaminase levels, patients with high HBV-DNA and histologically proven necro-inflammation or fibrosis (≥F2 grade) may be candidates for AVT, with the goal of minimizing disease progression.

As reported in the most recent issue of *Clinical Molecular and Hepatology*, Cristina et al.[4] found that approximately 14% of subjects with chronic HBV infection and normal transaminase levels had significant liver fibrosis (≥7.9 kPa), as assessed by transient elastography (TE). However, there was concern as to whether patients with well-controlled inflammation may still experience disease progression. In this article, we address several of the above-mentioned concerns.

First, in considering that the enrolled subjects tended to be more obese (mean body mass index 27±5 kg/m^2) compared to previous studies,[5,6] they were more likely to have concomitant liver disease other than chronic HBV infection.[7,8] Obesity is strongly associated with fatty liver disease and metabolic syndrome, both of which can accelerate hepatic fibrosis.[8,9] Steatohepatitis proven on histology may exist even in cases of normal baseline transaminase levels, which suggests that elevated ALT is not predictive of necro-inflammation or fibrosis. The suggestion that patients with altered transaminases are more likely to have a higher fibrotic burden implies that this cohort should include patients with steatohepatitis with, at a minimum, indolent histological activity. Furthermore, increased organ fat can lead to an overestimation of liver stiffness in some patients.[10] Taken together, these findings suggest that combined fatty liver disease with hepatic necro-inflammation, even in the presence of "normal" transaminase levels, may result in a higher proportion of patients with fibrosis in this cohort.

Abbreviations:

ALT, alanine aminotransferase; AVT, antiviral therapy; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IT, immune tolerant; TE, transient elastography

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Second, Cristina et al.[4] defined significant fibrosis as stage ≥ F2 (≥7.9 kPa) using TE. Although the presence of significant fibrosis is considered a hallmark of progressive disease, the diagnostic performance of TE in classifying patients as F2 or higher is relatively limited. Receiver operating characteristic for ≥ F2 was highly variable in a recent meta-analysis, ranging between 68% and 100%.[11] Therefore, TE alone is insufficient in clinical practice, especially in the diagnosis of grades F0–2. Furthermore, it has been suggested that validated biomarker testing (i.e., FibroTest) is superior in differentiating F0 vs. F1 vs. F2.[12]

Lastly, Cristina et al.[4] allocated study participants only when normal transaminase levels were maintained over 3 consecutive tests for 9 months. However, viral phases are subject to change depending on the various interactions between host immunity and viral replication. As such, viral phases are not necessarily sequential,[13] and the duration of 9 months used to define normal transaminase levels might in fact be insufficient. Kim et al.[14] recently demonstrated that untreated immune tolerant (IT) phase patients with normal transaminase levels are also subject to a significant risk for disease progression. This study may be subject to similar criticism, because IT-phase patients were defined through only 1 year of observation. Taken together, these results indicate that patients classified as having well-controlled inflammation at baseline may eventually shift to an immune-active status over an extended clinical course. As such, viral and biochemical status should be continuously tracked during the follow-up.

Although AVT is recommended in patients with significant fibrosis as proven by liver biopsy even in those with normal ALT level,[2,3] it is not always feasible to perform biopsies depending on the presence of fibrosis. Therefore, noninvasive surrogates for liver fibrosis such as TE, shear wave elastography, or magnetic resonance imaging, all of which are more accurate than ultrasound in assessing the overall fibrotic burden, may be required to identify the optimal candidates for AVT among chronic hepatitis B patients with normal transaminase levels.[7,15] As Cristina et al.[4] described, the use of noninvasive imaging surrogates may be necessary to identify chronic HBV patient subgroups where AVT could potentially reduce the risk of disease progression.

In conclusion, the study by Cristina et al.[4] confirm that a thorough assessment of liver fibrosis is required to stratify subgroups of patients with normal transaminase levels, to select optimal candidates for AVT, when histological information is not available.

Authors' contribution

S.U. Kim designed this study. M.Y. Jeon and B.K. Kim wrote the manuscript. All authors contributed to the revision of the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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