Immune-tolerant Chronic Hepatitis B Infection—Is the Liver Really Tolerating?

To the Editor,

The Indian National Association for Study of the Liver (INASL) constantly provides Indian consensus guidelines to manage various diseases affecting the liver. The INASL recently published its guidelines to manage patients with Hepatitis B Virus (HBV) infection in your esteemed journal and I would like to congratulate the authors on their commendable work.¹

I would however want to draw the attention of the INASL hepatitis B task force to certain critical points relating to Immune-tolerant (IT) chronic HBV infection phase which would likely influence updating the HBV infection guidelines in the ensuing time and plan future studies in this area.

(i) The INASL guidelines recommend that patients in IT phase should not be treated if aged <30 years and the algorithm provided clearly mentions that patients in the IT phase with

Figure 1 Proposed algorithm to evaluate and manage patients with HBeAg positive chronic HBV infection.

high HBV DNA and persistently normal Alanine Aminotransferase (ALT) levels are not candidates for antiviral therapy. In a key study done by Park et al.² the authors noted that 28% of patients who were Hepatitis B e Antigen (HBeAg) positive having normal ALT and HBV DNA $>2 \times 10^4$ IU/ml had significant histology on liver biopsy. In another pivotal study from India by Kumar et al.³ the authors demonstrated that 40% of patients with HBeAg positivity with normal ALT levels had significant fibrosis on histology. The authors also noted that HBV DNA levels were a poor surrogate to predict underlying fibrosis in this subset of patients.

- (ii) More unnerving data has recently been published by Kim et al.⁴ The authors performed a historical cohort study on 413 patients in IT phase of HBV infection and compared them with 1497 patients in the Immune-active (IA) phase receiving antiviral therapy. The authors noted that the 10-year estimated cumulative incidence of Hepatocellular Carcinoma (HCC) (12.7% vs. 6.1%) and death/liver transplantation (9.7% vs. 3.4%) was significantly higher in patients in IT phase when compared to those in IA phase.

This opens up views to very pertinent questions. (A) Is the liver really tolerating IT phase of HBV infection well in all subset of patients? (B) Can slow ongoing underlying fibrosis be contributing in part to the development of HCC in these patients? (C) Can initiation of antivirals prevent these adverse outcomes in this subset of patients? Future studies looking at liver histology on larger number of patients in IT phase of HBV infection would be needed to conclusively answer these questions.

I hence suggest that non-invasive assessment of liver fibrosis should be done in all patients with HBV infection in IT phase by modalities like transient elastography (where available) or aspartate Aminotransferase to Platelet Ratio Index (APRI). With suggestion of significant fibrosis by either of these tests, a liver biopsy and histologic evaluation should be done and in the subset of patients where significant fibrosis ($\geq F2$) or moderate to severe

necroinflammation is documented, initiation of antiviral therapy is to be strongly considered (Figure 1).

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