Editorial

Immune tolerant HBV and HCC: time to revise our tolerance levels for therapy?

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The immune tolerant (IT) phase, the first phase of chronic hepatitis B virus (HBV) infection, has historically been perceived as a benign period in the natural history of this disease. Perinatal infection leads to a prolonged IT phase, with transition to immune clearance with seroconversion to anti-HBe in the second to third decade, whereas immediate progression to immune clearance usually occurs in newly infected children and adults (1). Since HBV is a non-cytopathic virus and hepatic damage stems from host immune activity, the IT moniker was derived from early studies demonstrating an inverse correlation between circulating HBV DNA and histologic damage (2). The IT phase is characterized by positive hepatitis B e-antigen (HBeAg), high viremia (typically $>10^7$–10^8 IU/mL), and normal alanine aminotransferase (ALT) activity, but the hallmark is no/minimal necroinflammatory activity and no fibrosis on liver histology (3). Recent studies have challenged the traditional view that the host immune system "tolerates" the virus, as both innate and B-cells responses have been found to be quite active during IT phase, with trained immunity seen in HBV-infected newborns (4,5). Reflecting this new understanding of the hepatitis B immunopathogenesis, alternative terms have been proposed for the IT phase, including "high replicative, low inflammatory" (6) and "non-inflammatory HBeAg positive" (7) phase.

In the absence of curative therapies, the primary objective of HBV therapy remains the prevention of cirrhosis and hepatocellular carcinoma (HCC). The strong positive correlation between HCC risk and HBV DNA levels, independent of ALT and fibrosis stage, identified in the REVEAL-HBV cohort study has fostered consideration of antiviral suppressive therapy across a broader spectrum of HBV-infected. However, since the REVEAL-HBV cohort was 85% HBeAg-negative with median age of 45 years, the number of IT adults included in the cohort was low (8,9). Thus, there remains an important knowledge gap—what is the risk of HCC in adults in the IT phase and can we identify a subgroup of adult IT patients who warrant consideration of HBV suppression for HCC prevention? Kim *et al.* attempt to address this question in their recent *Gut* article (10). Using a large retrospective cohort of Korean genotype C patients, they compared incidence of HCC, liver transplantation and mortality over 10 years between 413 IT patients and 1,497 IA patients treated with oral HBV therapy. IT phase was defined as HBeAg-positive, HBV DNA level ≥20,000 IU/mL, and normal ALT (<19 U/L in females and <30 U/L in males) for one year. Patients who transitioned to IA phase [ALT ≥2× upper limit of normal (ULN)] or started on therapy within one year were excluded. The principal finding of their study was a substantially increased risk of HCC (HR 2.5; 95% CI: 1.5–4.2) and death or transplantation (HR 3.4; 95% CI: 1.9–6.2) in IT patients as compared to treated IA patients in adjusted models.

On the surface, these findings are quite concerning. However, the question is whether this was an IT cohort at baseline and for the duration of the study. There are several considerations that suggest this may not be the case. Firstly, 26% had HBV DNA levels $<10^7$ IU/mL,

(lower than expected for IT patients), 25% with platelet count <167×10^9/L (suggesting more advanced fibrosis) and the median age of the IT patients (38 years) was older than typically seen in IT phase, although studies have shown genotype C patients tend to seroconvert much later (11). Restricting analysis to patients that better fit the IT phenotype, i.e., age <40 with HBV DNA >10^7 or 10^8 and absence of significant fibrosis would have been informative. Second, the baseline characteristics of IT patients who developed HCC warrant a comment. Of those with available liver samples and HCC, 70% had F3-4 fibrosis. A prior high-quality prospective study with paired biopsies showed minimal fibrosis progression in IT patients with persistently normal ALT over 5 years (12). We would argue that if advanced fibrosis is found in an IT patient, high viremia alone is not the only factor; rather, either misclassification occurred, or accumulation of risk with age or additional co-factors such as alcohol, fatty liver or aflatoxin exposure contributed to HCC risk. Since fibrosis assessments were not performed in this study, a subset of patients in the IT group could have had significant fibrosis at baseline, although results were consistent on additional matched analyses that should adjust for fibrosis severity. Most importantly, the transition to MA or IA disease should lead to initiation of antiviral therapy and whether this was systematically undertaken in all IA patients is unclear. Per the reimbursement criteria in Korea, treatment was only started if ALT ≥80 IU/mL. Thus, while patients were censored when treatment was initiated, an unknown number of patients with MA or IA disease remained in the IT cohort. Considering these points, it is difficult to conclude that adults in the IT phase are a high-risk group for HCC.

What this study does highlight is the need for careful evaluation of adults with an IT profile, particularly those over the age of 40 years and those with lower HBV DNA levels (<10^7 IU/mL) or mildly elevated ALT levels. Serial monitoring and staging of inflammation/fibrosis in HBV patients with an IT serologic profile is crucial to assess for transition and need for antiviral therapy. Guidelines recommend routine assessment for significant fibrosis in HBeAg-positive patients with ALT > ULN but <2× ULN on follow-up (7,13). Growing availability of non-invasive testing such as transient elastography allows for more efficient, accessible and repeated measurements. A potential shortcoming of non-invasive testing is the inability to distinguish fibrosis from moderate-to-severe necroinflammation as both would warrant consideration of therapy in an IT population. A lower necroinflammatory threshold to treat, in addition, may be considered in older patients with reduced capacity for hepatic regeneration (14). As a fully infected liver yields 10^9–10^{10} IU/mL of virus in serum, a declining level of HBV DNA (<10^8 IU/mL) may reflect hepatocyte injury or clonal expansion of virus-resistant hepatocytes. This interesting hypothesis leads to the suggestion that HBV DNA levels, especially if <10^7–10^8 IU/mL, may be a marker of transition to a more inflammatory phase, even if ALT levels are not elevated (15). While more natural history studies are needed, the study by Kim *et al.* serves to remind us of the dynamic nature of chronic hepatitis B and the importance of comprehensive follow-up.

Given the safety of currently approved therapies, one might argue that treatment should be given to all adults with the IT profile, citing the strong correlation between HBV DNA levels and risk of HCC. Concerns for viral integration and clonal hepatocyte repopulation among persons with higher quantities of circulating virus also have been raised (16). Further research in the IT population is needed to clarify this issue. On the other hand, reasons to hold off on antiviral therapy in children and adults with the IT profile include low rates of response (as defined by HBeAg and HBsAg loss) (17,18), cost of long-term therapy, and a lack of established benefit in preventing HCC.

Looking to the future, additional biomarkers to ascertain adults in the IT phase who are at risk for HCC would be highly desirable. In the meantime, a rigorous definition of IT phase in HBV patients is needed in clinical research and in guiding clinical practice. Failure to recognize when an adult in the IT phase is transitioning to a more inflammatory phase is a missed opportunity to prevent future liver complications. In essence, we must no longer simply "tolerate" the adult in the IT phase, but rather actively manage risk factors that promote fibrosis and HCC, such as alcohol use or fatty liver, and serially track changes in the IT profile that signal phase transition to more active disease and the need to initiate antiviral therapy.

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