Immunotolerant Chronic Hepatitis B Infection: When Do I Treat?

To the Editor, We would like to address two issues pertaining to recent article and letter to editor in your esteemed journal. First, Indian National Association for Study of the Liver (INASL) recommendation¹ of “maybe” treat HBeAg positive patients aged >30 years with normal ALT (Alanine Aminotransferase) needs further refinement in selecting cases who would benefit from treatment and also, is not backed by convincing evidence from prospective studies. Secondly, Satsangi² suggested evaluation with non-invasive tests in “all” IT (Immunotolerant) phase patients, which might lead to unwarranted investigation in this context since they have wide age distribution, especially in endemic countries.

Most of studies from which data has been extrapolated to extend treatment age in HBeAg positive normal ALT patients has biases in selection of cases, age of patients considered to be IT, HBV DNA levels and long term follow up. The only data favouring treatment in these cases came in 2010 from west, where age of HBeAg seroconversion (<30 vs 31–40 vs >40 years) correlated with complications, and showed that HBeAg seroconversion during age <30 years is associated with significantly lower risk of complications compared to age of seroconversion >40 years.³ Age of seroconversion between 31 and 40 years had increased risk of cirrhosis compared to <30 years. But, upto 57% patients had an age at entry into the study

Table 1 Studies Determining Role of Treatment in HBeAg Positive Chronic Hepatitis B Patients.

Articles	Results of the study pertaining to HBeAg positive patients	Drawbacks in the study
Kim et al., ⁷ Gut 2017	Untreated IT-phase patients with CHBV had higher risks of HCC and death/transplantation than treated IA-phase patients. Unnecessary deaths could be prevented through earlier antiviral intervention in select IT-phase patients.	Mean age of IT phase patients was 38 ± 11 vs 40 ± 11 years in IA phase with inclusion of the very few treated IT-phase patients. Also, serum HBV DNA levels overlapped extensively and showed no significant difference between the IT and IA groups. Authors suggested to consider IT patients in study group as ‘preactive phase’ or ‘immune-active phase in remission’ in subsequent response to letter to editor.
Kumar et al., ⁸ Gastroenterology 2008	Upto 40% of HBeAg positive and 13% of HBeAg negative CHBV with persistently normal ALT had fibrosis stage ≥2.	Out of 603 HBeAg positive patients in the study, only 12.1% had persistently normal ALT and among them, fibrosis grade F <2 was seen in 60.3%. The results of the study was criticized for a potential selection bias and the quality of follow-up was suboptimal.
Park et al., ⁹ J Viral Hepat 2008	Age and ALT levels were predictors of fibrosis.	Median age in this study was 39 years (range 18–68) and persistently normal ALT was seen in only 27.8% (analyses of ALT levels were based on measurements taken at the time of liver biopsy; selection bias cannot be excluded).
Wong et al., ¹⁰ Clin Gastroenterol Hepatol 2009	Risk of advanced liver fibrosis increased in HBeAg-positive patients older than 35 years of age with an ALT level greater than 0.5–1 times ULN (Upper Limit of Normal).	ULN of ALT was taken as 58 in the study and analysis done with gender specific ALT showed significance only with ALT of more than 2 times.

Abbreviations: IT: Immunotolerant; IA: Immuneactive; CHBV: Chronic Hepatitis B Virus Infection; ALT: Alanine Aminotransferase; ULN: Upper Limit of Normal.

Figure 1 Algorithm to evaluate and manage patients with Immunotolerant chronic HBV infection.

Abbreviations: APRI: Aspartate Aminotransferase to Platelet Ratio Index; LSM: Liver Stiffness Measurement; FIB-4: Fibrosis-4; HCC: Hepatocellular Carcinoma.

between 31 and 40 years (considering intermittent flares that would have happened prior to inclusion into study) and also age at entry was excluded in the meta-analysis. However, other studies have not reproduced similar results and had methodological flaws in defining IT cases (Table 1). Chronic HBV infection has a dynamic natural course; duration of interaction between host immunity and virus varies in each phase of infection, and the key to determine true IT is meticulous, longterm follow-up. In Asian countries, most of HBV infection is acquired during perinatally/early childhood and presence of IT phase even at age of more than 30 years logically indicate prolonged infectious state, which may predispose to complications. However, evidence to support that treatment would reduce development of these complications is still questionable.

There is an important concern of resistance if we treat all patients in IT phase at an early age. Only less than 5% show HBeAg seroconversion⁴ and so, antivirals will be continued with no definite end point to stop. Data on their resistance profile is limited to less than a decade and would lead to therapeutic misadventure if drug resistant strains develops. The unknown benefit of preventing

future complications and the risk of resistance to few available drugs, cost burden and compliance on longterm should be weighed. Consideration of treatment at 30 years maybe too early and it is prudent to begin “evaluation” at the age of 30 years and start treatment when they are more likely effective. So, we suggest to begin evaluation with non-invasive/invasive methods to assess fibrosis in HBeAg positive patients between 30 and 40 years and to consider treatment if they show significant fibrosis and, to definitely consider treatment in patients above 40 years^{5,6} (Algorithm 1).

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