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Letter to the Editor

Letter regarding "Long-term prognosis and the need for histologic assessment of chronic hepatitis B in the serological immune-tolerant phase"

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Dear Editor,

In a recent issue of this journal, Yoo et al.[1] reported a high frequency of significant inflammation and fibrosis in immunotolerant (IT) chronic hepatitis B patients and highlighted the need of liver biopsy for these patients. There are a few points that merit clarification and further discussion.

First, the average age of IT patients was quite high (42.7±12.5 years). The median age of IT patients ranged from 29 to 31 years in 4 previous studies.[2-5] Our earliest study in 1985, when we coined the term of IT, showed that the average age of 64 hepatitis B e antigen (HBeAg)-positive patients with minimal histological changes was 25±5 years.[6] In a later study, the age of 240 HBeAg-positive patients with persistently normal alanine aminotransferase (ALT) was 28±6 years.[7] One possible explanation could be that genotype C hepatitis B virus (HBV) predominates in Korea and that HBeAg seroconversion is significantly delayed in genotype C than genotype B infection (mean age of HBeAg seroconversion: 36.4±8.6 vs. 31.8±7.0 years).[8] In addition, there appears to be a high selection bias, as patient enrollment in this study was based on biopsy which is strongly recommended in elderly patients to exclude significant disease.[9]

Second, there is discordance between ALT and histological activity. It remained unclear why ALT levels were not significantly different between histologic IT and non-IT patients. On the other hand, only 35% of the patients with normal ALT (≤35 U/L for men and ≤25 U/L for women according to American Association for the Study of Liver Diseases [AASLD] 2018 guidelines[9]) were proved to be histologic IT patients. Many of these patients appear to be in the immune active phase with normal ALT at remission rather than truly in the IT phase. Diagnosis of IT in this study requiring at least two ALT measurements >3 months apart appears to be insufficient.

Third, the majority of IT patients demonstrated significant inflammation or fibrosis. Notably, the patients in this study were relatively older, with relatively lower HBV DNA ($\geq 10^6$ IU/mL vs. $\geq 10^7$ IU/mL) and higher ALT (≤60 U/L vs. ≤40 U/L). Two earlier histologic studies including 57 and 40 patients with median age of 29 and 31 years, respectively, HBV DNA >10^7 copy/mL and normal ALT revealed only mild disease in all and no patients had significant fibrosis.[3,5] In another study

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including 40 patients with normal ALT and HBV DNA of 8.14 (4.83–10.96) $\log_{10}$ IU/mL, significant inflammation and fibrosis was noted in 2 and 0 of 17 patients with ALT ≤0.5xupper limit of normal (ULN), and in 7 and 4 of 23 patients with ALT 0.5–1xULN.[4] A large series study from China recruited 202 stringently defined IT patients with HBV DNA ≥10^7 IU/mL and ALT ≤40 U/L, according to European Association for the Study of the Liver (EASL) 2017 guidelines,[10] for at least 2 years. Significant inflammation and fibrosis were extremely rare (2% and 0%) in 97 patients with low-normal ALT (≤30 U/L for men and ≤19 U/L for women), regardless of patient age, but much frequent (39% and 10%) in 105 patients with high-normal ALT (31–40 U/L for men and 20–40 U/L for women). Among the latter, the severity of histological activity correlated with patient age.[11] These data from "genuine IT" suggest that it seems appropriate to use the EASL 2017 guidelines to define IT phase, but for patients over 40 years old, it is better to use low-normal ALT.[12]

Fourth, there was a high incidence of liver-related events in IT patients; cumulative rates at 15-years follow-up were 15% and 45% for histologic IT and non-IT patients, respectively. However, chronic HBV infection is a dynamic process that undergoes transition through various phases of disease activity. Patients should be censored at the time of phase transition, otherwise their results will be misleading.

Finally, the authors suggested to treat IT patients with significant fibrosis. Sixty-seven percent of patients had significant fibrosis, implying the need for systematic histologic evaluation in all. However, liver biopsy is an invasive procedure with potential complication. Recently, antiviral therapy is recommended for IT patients over age of 30[10] or 40[2] without the need of histological assessment. Studies from Korea have shown an extremely low or negligible risk of hepatocellular carcinoma (HCC) in IT patients with HBV DNA ≥10^7 IU/mL,[13] HBV DNA ≥10^6 IU/mL and age <40,[14] and FIB-4 index <1.45.[15] Therefore, it is recommended to use strict clinical criteria to define IT phase, i.e., HBV DNA ≥10^7 IU/mL and ALT ≤40 IU/L every 3 months for at least 1 year. Antiviral treatment can be limited to those over 40 years old only if they have high-normal ALT, significant fibrosis as seen using noninvasive serum fibrosis markers or Fibroscan, or family history of HCC.[12]

In summary, strict clinical criteria are needed to define IT phase of chronic hepatitis B infection to avoid clinical confusion and unnecessary liver biopsy or treatment.

Authors' contributions

CM Chu: Conception and design of the letter; Drafting of the manuscript; Approval of the final version of the manuscript. YF Liaw: Design of the letter; Critical revision of the manuscript; Approval of the final version of the manuscript.

Conflicts of Interest

The authors have no conflicts to disclose.

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Abbreviations:

AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; EASL, European Association for the Study of the Liver; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IT, immune tolerance; ULN, upper limit of normal

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