pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2023.0044
Clinical and Molecular Hepatology 2023;29:513-515

Correspondance

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

Jeong-Ju Yoo and Sang Gyune Kim

Department of Internal Medicine, Gastroenterology and Hepatology, Soonchunhyang University School of Medicine, Bucheon, Korea

Keywords: Chronic hepatitis B; Immune tolerance; Histology

Dear Editor,

We would like to thank Chu and Liaw[1] for their interest in our paper[2] and for providing valuable insights into the immune tolerant (IT) phase. We acknowledge the potential for selection bias in our study due to the relatively high average age of the patients included. We included all patients with the current IT criteria to highlight the wide range of the IT phase. If limited to patients younger than 30 years of age, four out of 51 patients had advanced fibrosis. Out of those four patients, hepatocellular carcinoma occurred in only one patient with severe fatty liver. Likewise, many IT phase patients who meet the current guidelines' criteria often require treatment in real practice.

There is a general agreement that IT phase patients with significant fibrosis should receive treatment.[3,4] Although our study included a large number of such patients, we do not believe that a liver biopsy is necessary for all IT phase patients. The challenge is to accurately identify those with significant fibrosis without a biopsy. There are many diagnostic tools for non-invasive fibrosis, such as transient elastography (TE) or magnetic resonance elastography, and these can be used as secondary tools for accurate diagnosis of the IT phase and excluding significant liver fibrosis.[5,6]

Although seroconversion can be delayed in genotype C patients (commonly found in South Korea), it is usually accompanied by significant fibrosis in patients over 35 years of age.[7] However, the current IT phase diagnosis guidelines only use serological criteria. Our data showed that serum alanine aminotransferase (ALT) levels alone do not fully reflect the histological activity of IT phase. In the same vein, previous studies[8-10] have found that ALT levels do not indicate the actual inflammation in the liver due to the following reasons: i) ALT elevation is associated with the location of inflammation,[11] and ii) the changes in ALT levels occur faster than the changes in histology.[12] One of the alternatives, as mentioned[1] by

Corresponding author : Sang Gyune Kim
Department of Gastroenterology and Hepatology, Digestive Research Center and Liver Clinic Soonchunhyang University Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea
Tel: +82-32-621-5215, Fax: +82-32-621-6079, E-mail: mcnulty@schmc.ac.kr
https://orcid.org/0000-0001-8694-777X

Editor: Seung Up Kim, Yonsei University College of Medicine, Korea

Received : Feb. 6, 2023 / **Revised :** Feb. 9, 2023 / **Accepted :** Feb. 9, 2023

the authors, is that different standards for normal ALT levels might be applied according to age.

Nevertheless, we completely agree with the authors' view of the IT phase patients, and we also believe that ALT levels should be monitored every 3–6 months to detect transitions from the IT phase to the immune active phase. Although there are many diagnostic tools for fibrosis and steatosis with the recent development of technology, there is no powerful diagnostic tool for inflammation other than a liver biopsy.[13,14] In this case, TE can provide information about inflammation as well as fibrosis, but the measured stiffness value should be used with caution. Our research team has found that the liver stiffness value is related to both histologic inflammation and fibrosis in patients with ALT levels less than 200 U/L.[15]

In conclusion, our study highlights the concern that the current IT phase guidelines may delay treatment for actually non-IT phase patients with hepatitis B. As mentioned by Chu and Liaw[1], we fully support the opinion that the HBV DNA cut-off value in the IT phase should be set very high, similar to the EASL guideline, and that the ALT criteria should be adjusted according to age. We hope that future IT phase guidelines will include age criteria and non-invasive diagnostic technologies for accurate fibrosis and/or inflammation diagnosis.

Authors' contribution

Writing manuscript: Jeong-Ju Yoo and Sang Gyune Kim, Supervision: Sang Gyune Kim.

Acknowledgements

This study was supported by the Soonchunhyang University Research Fund.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Chu CM, Liaw YF. Letter regarding "The long-term prognosis and the need for histologic assessment in chronic hepatitis B in serological immune-tolerant phase". Clin Mol Hepatol 2023;29:510-512.
2. Yoo JJ, Park SY, Moon JE, Lee YR, Lee HA, Lee J, et al. Long-term prognosis and the need for histologic assessment of chronic hepatitis B in the serological immune-tolerant phase. Clin Mol Hepatol 2023;29:482-495.
3. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370-398.
4. Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol 2022;28:276-331. Erratum in: Clin Mol Hepatol 2022;28:940.
5. Hsu C, Caussy C, Imajo K, Chen J, Singh S, Kaulback K, et al. Magnetic resonance vs transient elastography analysis of patients with nonalcoholic fatty liver disease: a systematic review and pooled analysis of individual participants. Clin Gastroenterol Hepatol 2019;17:630-637.e8.
6. Semmler G, Jachs M, Mandorfer M. Non-invasive tests-based risk stratification: Baveno VII and beyond. Clin Mol Hepatol 2023;29:105-109.
7. Chan HL, Hui AY, Wong ML, Tse AM, Hung LC, Wong VW, et al. Genotype C hepatitis B virus infection is associated with an increased risk of hepatocellular carcinoma. Gut 2004;53:1494-1498.
8. Kim HJ, Kim SY, Shin SP, Yang YJ, Bang CS, Baik GH, et al. Immunological measurement of aspartate/alanine aminotransferase in predicting liver fibrosis and inflammation. Korean J Intern Med 2020;35:320-330.
9. Liu J, Wang J, Yan X, Xue R, Zhan J, Jiang S, et al. Presence of liver inflammation in Asian patients with chronic hepatitis B with normal ALT and detectable HBV DNA in absence of liver fibrosis. Hepatol Commun 2022;6:855-866
10. Li X, Xing Y, Zhou D, Xiao H, Zhou Z, Han Z, et al. A non-invasive model for predicting liver inflammation in chronic hepatitis B patients with normal serum alanine aminotransferase levels. Front Med (Lausanne) 2021;8:688091.
11. Goodman ZD. Grading and staging systems for inflammation and fibrosis in chronic liver diseases. J Hepatol 2007;47:598-607.
12. Dhaliwal HK, Hoeroldt BS, Dube AK, McFarlane E, Underwood JC, Karajeh MA, et al. Long-term prognostic significance of persisting histological activity despite biochemical remission in

Abbreviations:

IT, immune tolerant; TE, transient elastography; MRE, magnetic resonance elastography; ALT, alanine aminotransferase

https://doi.org/10.3350/cmh.2023.0044

autoimmune hepatitis. Am J Gastroenterol 2015;110:993-999.
13. Choi EJ, Kim YJ. Liquid biopsy for early detection and therapeutic monitoring of hepatocellular carcinoma. J Liver Cancer 2022;22:103-114.
14. Yoo JJ, Kim SG. The rise of non-invasive tools in the diagnosis of portal hypertension: Validation of the Baveno VII consensus. Clin Mol Hepatol 2023;29:102-104.
15. Yoo JJ, Seo YS, Kim YS, Jeong SW, Jang JY, Suh SJ, et al. The influence of histologic inflammation on the improvement of liver stiffness values over 1 and 3 years. J Clin Med 2019;8:2065.