pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2020.0084
Clinical and Molecular Hepatology 2020;26:315-317

Editorial

Low-level viremia in patients undergoing antiviral therapy: Does it indicate time for a change?

Jung Hee Kim[1] and Dong Hyun Sinn[2]

[1]Division of Gastroenterology, Department of Internal Medicine, Hallym University Dongtan Sacred Heart Hospital, Dongtan; [2]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Keywords: Hepatitis B; Medication adherance; Hepatocellular carcinoma; Liver cirrhosis

See Article on Page 364

The goal of chronic hepatitis B (CHB) treatment is to decrease liver disease-related mortality by preventing fibrosis progression and development of hepatocellular carcinoma (HCC).[1] Serum hepatitis B virus (HBV) DNA testing provides a direct measure of the level of viral replication and is a strong predictor of disease progression and long-term outcomes in CHB.[2,3] Nucleos(t)ide analogs (NAs) are available to effectively inhibit HBV replication.[1] When serum HBV DNA levels decrease to undetectable levels in a real-time polymerase chain reaction assay by NAs use, it is defined as a virologic response (VR).[4]

VR can be achieved in most patients undergoing therapy with potent NAs. However, some patients show persistent or intermittent episodes of detectable, but low levels of serum HBV DNA (<2,000 IU/mL), referred to as low-level viremia (LLV) or suboptimal VR.[5] When using low genetic barrier NAs such as lamivudine, LLV signals emerging resistance and virologic breakthrough, and continued use can lead to treatment failure.[6] Hence, detecting LLV indicated a time for a change: switch from low genetic barrier NAs to high genetic barrier NAs.[6] The situation is different when using high genetic barrier NAs, such as entecavir and tenofovir. Continued use of high genetic barrier NAs in patients with LLV can further induce VR with very low risk of resistance and virologic breakthrough.[7] Thus, it is unclear whether LLV in patients under high genetic barrier NAs means a time for a change as in patients under low genetic barrier NAs. In this issue, Lee et al.[8] analyzed the association between LLV and long-term outcomes in 894 patients with CHB who were treated with entecavir, a high genetic barrier NA, to address this issue.

The goal of NA treatment is to achieve persistent undetectable serum HBV DNA levels, known as maintained virologic response (MVR).[1] However, virologic tools used to measure HBV DNA have improved over the past years. MVR that would have been previously defined using old assays could now be classified as LLV with the use of more sensitive assays. Patients reaching LLV, rather than having undetectable HBV DNA levels, may be sufficient for improving patient prognosis.[9] The study by Lee et al.[8] supports that continued treatment with high genetic barrier NAs is suffi-

Abbreviations:

CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LLV, low-level viremia; MVR, maintained virologic response; NAs, nucleos(t)ide analogs; VR, virologic response

Corresponding author : Dong Hyun Sinn
Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
Tel: +82-2-3410-3409, Fax: +82-2-3410-6983
E-mail: dh.sinn@samsung.com
https://orcid.org/0000-0002-7126-5554

Editor: Tai-Chung Tseng, National Taiwan University Hospital, Taiwan

Received : Apr. 24, 2020 / **Revised :** May 29, 2020 / **Accepted :** May 31, 2020

Copyright © 2020 by Korean Association for the Study of the Liver
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

cient in adherent patients with LLV. In this study, LLV was associated with HCC in the entire cohort, indicating that LLV is an alarming sign of poor prognosis. However, there was no association between LLV and poor prognosis when the analysis was limited to 617 adherent patients. Thus, poor prognosis in patients with LLV was mostly driven by poor adherence. Hence, the study suggested that LLV means time to check adherence but is not a time for a change in treatment when using a high genetic barrier NA. This study provides evidences on how to manage patients with LLV when using high genetic barrier NA.

However, the study design was an observational cohort study with inherent limitations. Lee et al.[8] provide excellent discussion on the potential limitations and implications of their findings. In addition, some points need to be further discussed. LLV usually refers to a subgroup of patients that exhibit persistent or intermittent episodes of detectable, but low serum HBV DNA levels (<2,000 IU/mL) without virologic breakthrough. However, patients with virologic breakthrough were included in this study. Out of the 240 patients with LLV, 56 (23.3%) switched to tenofovir and were censored when entecavir treatment was switched to tenofovir. In contrast to findings from Lee et al.,[8] some studies suggest that changing instead of continuing with the current treatment may be better approach. In an analysis of 239 patients with paired liver biopsy, LLV was more frequently observed for patients with fibrosis progression (50%) than in patients with fibrosis regression (19%) or indeterminate fibrosis (26%) (P=0.015), suggesting that LLV may still promote fibrosis progression.[10] In our previous study, we observed a higher risk of HCC in cirrhotic patients with LLV than with MVR.[5] In a randomized trial conducted in Korea, patients with CHB with detectable HBV DNA (>60 IU/mL) treated with 0.5 mg of entecavir for >12 months showed higher VR (HBV DNA <20 IU/mL) after switched to tenofovir (55%) than in patients that continued with entecavir (20%, P=0.022).[11]

Therefore, here is the question: Is LLV during high genetic barrier NA therapy a meaningful sign to change therapy? In this study, Lee et al.[8] showed similar risks of liver-related death, transplantation, HCC, and hepatic decompensation between MVR and LLV groups in good adherent patients. However, the ultimate question is whether a change in therapy (switch to another NA or adding an additional NA) can decrease the risk of liver-related mortality or HCC among patients showing LLV. To our knowledge, no information is available on whether changing NA therapy can decrease the risk of liver-related mortality or HCC compared to continuing same treatment. In the recently revised guidelines of the Korean Association for the Study of the Liver, either continued treatment or switching to another NA has been suggested as a treatment option.[1] The findings from Lee et al.[8] provide another clue for the answer, yet, are imperfect to direct one approach. Until more robust data are available, the decision to continue, switch, or add another NA should be made based on available evidence, precise follow-up, and careful assessment of risks and benefits.

Authors' contribution

Manuscript writing: Jung Hee Kim and Dong Hyun Sinn
Final approval of manuscript: Jung Hee Kim and Dong Hyun Sinn

Conflicts of Interest

The authors have no conflicts of interests to disclose.

REFERENCES

1. Korean Association for the Study of the Liver (KASL). KASL clinical practice guidelines for management of chronic hepatitis B. Clin Mol Hepatol 2019;25:93-159.
2. Chen CJ, Yang HI, Su J, Jen CL, You SL, Lu SN, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
3. Iloeje UH, Yang HI, Su J, Jen CL, You SL, Chen CJ, et al. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology 2006;130:678-686.
4. Mommeja-Marin H, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. Hepatology 2003;37:1309-1319.
5. Kim JH, Sinn DH, Kang W, Gwak GY, Paik YH, Choi MS, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. Hepatology 2017;66:335-343.
6. Korean Association for the Study of the Liver. KASL clinical practice guidelines: management of chronic hepatitis B. Clin Mol Hepatol 2012;18:109-162.
7. Zoutendijk R, Reijnders JG, Brown A, Zoulim F, Mutimer D, Deterding K, et al. Entecavir treatment for chronic hepatitis B: adaptation is not needed for the majority of naïve patients with a partial virological response. Hepatology 2011;54:443-451.
8. Lee SB, Jeong J, Park JH, Jung SW, Jeong ID, Bang SJ, et al. Low-level viremia and cirrhotic complications in patients with chronic hepatitis B according to adherence to entecavir. Clin Mol Hepatol 2020;26:364-375.
9. Terrault N. Is low level viremia acceptable during antiviral therapy of patients with HBV infection and decompensated cirrhosis? Clin Gastroenterol Hepatol 2018;16:1876-1878.

10. Sun Y, Wu X, Zhou J, Meng T, Wang B, Chen S, et al. Persistent low level of hepatitis b virus promotes fibrosis progression during therapy. Clin Gastroenterol Hepatol. 2020 Mar 6. doi: 10.1016/j.cgh.2020.03.001.

11. Yim HJ, Kim IH, Suh SJ, Jung YK, Kim JH, Seo YS, et al. Switching to tenofovir vs continuing entecavir for hepatitis B virus with partial virologic response to entecavir: a randomized controlled trial. J Viral Hepat 2018;25:1321-1330.