VOLUME 30 NUMBER 2 April 2024

pISSN 2287-2728
eISSN 2387-285X

CLINICAL and MOLECULAR HEPATOLOGY

The forum for latest knowledge of hepatobiliary diseases

cfDNA ULP-WGS for prognosis in HCC

Linvencorvir phase 2 trial for HBV
Signature gene set for discrimination of MASLD progression
Incidence of adverse events associated with NAFLD
JCAD in cholestatic fibrosis
Prognosis of MASLD

KASL

pISSN 2287-2728
eISSN 2287-285X

CLINICAL and MOLECULAR HEPATOLOGY

https://doi.org/10.3350/cmh.2024.0115
Clinical and Molecular Hepatology 2024;30:144-146

Editorial

Cardiovascular risk of tenofovir disoproxil fumarate or tenofovir alafenamide in patients with chronic hepatitis B: More questions than an answer

Pin-Nan Cheng[1] and Ming-Lung Yu[2,3]

[1]Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital; College of Medicine and Center for Liquid Biopsy and Cohort Research, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]School of Medicine and Doctoral Program of Clinical and Experimental Medicine, College of Medicine and Center of Excellence for Metabolic Associated Fatty Liver, National Sun Yat-sen University, Kaohsiung, Taiwan

Keywords: TDF; TAF; HBV; SDG 3; Good health and well-being

See Article on https://doi.org/10.3350/cmh.2023.0328

Hepatitis B virus (HBV) infection has been associated with lower cardiometabolic risks and even a protective factor for major adverse cardiovascular events (MACE) when compared with hepatitis C virus infected patients or controls.[1-3] Antiviral treatment also provides a lower risk of MACE than those without antiviral treatment in patients with chronic hepatitis B.[4] As the lipid-lowering effect has been unexpectedly and uniquely observed in patients treated with tenofovir disoproxil fumarate (TDF) but not in those treated with tenofovir alafenamide (TAF), their impact on long-term MACE has been raised. A recent retrospective study from Korea by Hong et al. investigated the risk of MACE in patients with chronic hepatitis B (CHB) treated by TDF or TAF. After propensity score matching to control confounding factors, a comparable risk of long-term MACE between TDF- and TAF-treated patients was observed despite different lipid profiles between the two groups.[5] This study provides important information to some degree to answer the uncertain association of TDF or TAF with cardiovascular outcomes. However, unresolved issues remain and need to be investigated.

In Hong's study, significantly lower lipid profiles were observed in TDF-treated patients rather than in TAF-treated patients,[5] which was consistent with a previous study that showed TDF reduced lipid profiles in HBV patients, when compared to TAF.[6] A Recent study further demonstrated that the lipid profiles greatly increased in HBV patients switching from TDF to TAF, but not in patients switching from entecavir to TAF.[7] Meanwhile, the presence of metabolic traits, including gain of body weight, worsening of insulin resistance, and

Corresponding author : Ming-Lung Yu
Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, 100 Tzyou Road, Kaohsiung City 807, Taiwan
Tel: +886-7-312-1101 ext. 7475, Fax: +886-7-312-3955, E-mail: fish6069@gmail.com
https://orcid.org/0000-0001-8145-1900

Editor: Han Ah Lee, Chung-Ang University College of Medicine, Korea

Received : Feb. 14, 2024 / **Revised :** Feb. 16, 2024 / **Accepted :** Feb. 16, 2024

a trend towards increased atherosclerotic cardiovascular disease scores, may possibly predispose to cardiovascular diseases in TDF-switch patients. These results indicated that TDF and TAF may exert effects on metabolic risk factors other than lipid profiles. In contrast to the lipid-lowering effects of TDF, TAF monotherapy could greatly increase lipid profiles when compared with entecavir monotherapy.[8] In patients with human immunodeficiency virus infection, the TAF-containing regimen did show an increase in lipids compared to the non-TAF-containing regimen.[9] The two phase 3 studies also showed progressively increased low-density lipoprotein and triglycerides, but decreased high-density lipoprotein during 5-year TAF treatment for CHB patients.[10] These results may imply that TAF alone may induce changes in lipid profiles, increasing the risk of MACE. Therefore, the investigations on mechanisms of lipid changes associated with TDF or TAF treatment are important not only to clarify the mechanisms of changes in lipid profiles but also to understand the detailed changes in lipid components that are beneficial or harmful to the occurrence of MACE. From these points of view, more studies addressing the association between TDF/TAF and MACE are needed.

The established common risk factors for MACE include hypertension, diabetes, obesity, hyperlipidemia, tobacco smoking, a sedentary lifestyle, and a lack of adequate physical activities.[11] As expected, Hong's study showed that active smoking and a history of cardiovascular events were the two independent factors associated with an increased risk of MACE. As the HBV infection has been known not to be a risk factor for MACE, the association between long-term TDF/TAF treatment and changes in lipid profiles may influence or add impacts on cardiovascular risk for certain degree, if any, but not serve as one of the major determinants. For long-term outcomes in CHB patients, liver-related complications remain the main causes of morbidity and mortality. In addition to chronic viral hepatitis, metabolic derangements also contribute to the progression of liver diseases. Traditional risk factors for developing MACE still play a central and important role. Furthermore, HBV infection has been reported to be inversely associated with hepatic steatosis.[12] As MACE and metabolic dysfunction-associated fatty disease (MAFLD) share common risk factors, cardiovascular disease is the leading cause of mortality in patients with MAFLD.[13] Patients with simultaneous CHB and MAFLD tend to have accelerated progression of liver disease, exhibit more liver-related complications, and have a higher death rate than patients with CHB alone or MAFLD alone.[14] In Hong's study, the prevalence of HBV patients with the diagnosis of fatty liver was much lower than the reported prevalence in the general population of Korea (15.4% vs. 32.9%).[15] The impact of MAFLD on MACE may be underestimated; hence, the effect of TDF/TAF on MACE is supposed to be further minimized in CHB patients. In this aspect, risk factors for MACE may play a more dominant role. Moreover, Hong's study conducted a retrospective design with chart review in one medical hospital, which may introduce selection bias and confounding factors. The cohort effect due to the late introduction of TAF to the market might also contribute to the imbalance in the proportion of patients taking lipid-lowering agents and the misinterpretation of the effect on MACE between the TAF- and TDF-treated groups.

There are several issues that need to be further clarified. First, long-term use of TDF/TAF is always required for the majority of CHB patients. Safety concerns should be taken into account. Unclear mechanisms of TDF/TAF make the impact of lipid changes on MACE uncertain. At present, whether the lipid profiles related to TDF/TAF are truly "benefit" or "bad" for MACE remains to be resolved. Second, the risk of MAFLD in CHB patients warrants stratification of MACE risk according to the grade of cardiometabolic risk factors. In the current era, metabolic derangements contribute to diseases of different organs and have become an important determinant of outcome measurements. Evaluation of MACE risk in the presence of cardiometabolic risk factors is warranted in the long-term care of CHB patients under antiviral therapy.

Authors' contribution

PN Cheng drafted the manuscript. ML Yu reviewed and finalized the manuscript.

Acknowledgement

Prof ML Yu receives research grant from the "Center of Excellence for Metabolic Associated Fatty Liver Disease, Nation-

Abbreviations:

HBV, hepatitis B virus; MACE, major adverse cardiovascular events; TDF, tenofovir disoproxil fumarate; TAF, tenofovir alafenamide; CHB, chronic hepatitis B; MAFLD, metabolic dysfunction-associated fatty disease

al Sun Yat-sen University, Kaohsiung" from The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

Conflicts of Interest

The authors have no conflicts to disclose.

REFERENCES

1. Shih CI, Wu KT, Hsieh MH, Yang JF, Chen YY, Tsai WL, et al. Severity of fatty liver is highly correlated with the risk of hypertension and diabetes: a cross-sectional and longitudinal cohort study. Hepatol Int 2024;18:138-154.
2. Kuo CS, Chen YT, Hsu CY, Chang CC, Chou RH, Li SY, et al. The impact of chronic hepatitis B infection on major adverse cardiovascular events and all-cause mortality in patients with diabetes: a nationwide population-based study from Taiwan. BMJ Open 2017;7:e016179.
3. Wu VC, Chen TH, Wu M, Cheng CW, Chen SW, Chang CW, et al. Comparison of cardiovascular outcomes and all-cause mortality in patients with chronic hepatitis B and C: A 13-year nationwide population-based study in Asia. Atherosclerosis 2018;269:178-184.
4. Yun B, Oh J, Ahn SH, Yoon JH, Kim BK. Comparable mortality between Asian patients with chronic hepatitis B under long-term antiviral therapy vs matched control: A population-based study. Am J Gastroenterol 2023;118:1001-1009.
5. Hong H, Choi WM, Lee D, Shim JH, Kim KM, Lim YS, et al. Cardiovascular risk in chronic hepatitis B patients treated with tenofovir disoproxil fumarate or tenofovir alafenamide. Clin Mol Hepatol 2024;30:49-63.
6. Jeong J, Shin JW, Jung SW, Park EJ, Park NH. Tenofovir alafenamide treatment may not worsen the lipid profile of chronic hepatitis B patients: A propensity score-matched analysis. Clin Mol Hepatol 2022;28:254-264.
7. Cheng PN, Feng IC, Chen JJ, Kuo HT, Lee PL, Yu ML, et al. Body weight increase and metabolic derangements after tenofovir disoproxil fumarate switch to tenofovir alafenamide in patients with chronic hepatitis B. Aliment Pharmacol Ther 2024;59:230-238.
8. Lai RM, Lin S, Wang MM, Li N, Zhou JH, Lin XY, et al. Tenofovir alafenamide significantly increased serum lipid levels compared with entecavir therapy in chronic hepatitis B virus patients. World J Hepatol 2023;15:964-972.
9. Giacomelli A, Conti F, Pezzati L, Oreni L, Ridolfo AL, Morena V, et al. Impact of switching to TAF/FTC/RPV, TAF/FTC/EVG/cobi and ABC/3TC/DTG on cardiovascular risk and lipid profile in people living with HIV: a retrospective cohort study. BMC Infect Dis 2021;21:595.
10. Chan HLY, Buti M, Lim YS, Agarwal K, Marcellin P, Brunetto M, et al. Long-term treatment with tenofovir alafenamide for chronic hepatitis B results in high rates of viral suppression and favorable renal and bone safety. Am J Gastroenterol 2023;119:486-496.
11. Hajar R. Framingham contribution to cardiovascular disease. Heart Views 2016;17:78-81.
12. Peleg N, Issachar A, Sneh Arbib O, Cohen-Naftaly M, Braun M, Leshno M, et al. Liver steatosis is a strong predictor of mortality and cancer in chronic hepatitis B regardless of viral load. JHEP Rep 2019;1:9-16.
13. Cheng PN, Chen WJ, Hou CJ, Lin CL, Chang ML, Wang CC, et al. Taiwan Association for the Study of the Liver-Taiwan Society of Cardiology Taiwan position statement for the management of metabolic dysfunction- associated fatty liver disease and cardiovascular diseases. Clin Mol Hepatol 2024;30:16-36.
14. Choi HSJ, Brouwer WP, Zanjir WMR, de Man RA, Feld JJ, Hansen BE, et al. Nonalcoholic steatohepatitis is associated with liver-related outcomes and all-cause mortality in chronic hepatitis B. Hepatology 2020;71:539-548.
15. Li J, Zou B, Yeo YH, Feng Y, Xie X, Lee DH, et al. Prevalence, incidence, and outcome of non-alcoholic fatty liver disease in Asia, 1999-2019: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol 2019;4:389-398.