Editorial

How long will it take to eliminate HCC risk in patients with chronic hepatitis B patients with potent antivirals?

Terry Cheuk-Fung Yip[1,2], **Grace Lai-Hung Wong**[1,2,3]

[1]Institute of Digestive Disease, [2]Department of Medicine and Therapeutics, [3]State Key Laboratory of Digestive Disease, The Chinese University of Hong Kong, Hong Kong, China

Correspondence to: Grace Lai-Hung Wong, MD. Department of Medicine and Therapeutics, 9/F Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, Hong Kong, China. Email: wonglaihung@cuhk.edu.hk.

Comment on: Papatheodoridis GV, Idilman R, Dalekos GN, *et al*. The risk of hepatocellular carcinoma is decreasing after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017. [Epub ahead of print].

Received: 15 August 2017; Accepted: 27 August 2017; Published: 18 September 2017.

doi: 10.21037/amj.2017.08.28

View this article at: http://dx.doi.org/10.21037/amj.2017.08.28

Entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are currently the first-line oral antiviral agents for patients with chronic hepatitis B (CHB). They have high potency on viral suppression, a high genetic barrier to drug resistance mutations (1), and a good safety profile in long-term use (2-5). Thus, long-term therapy with ETV/TDF provides maintained viral suppression in CHB patients, improves liver histology, prevents fibrosis progression, liver-related complications and mortality (3,4,6,7). Despite a better clinical course, the risk of hepatocellular carcinoma (HCC) persists in CHB patients undergoing a long-term treatment (8,9). Currently, little data with large sample size and long follow-up duration are available on assessing the change in HCC incidence following long-term treatment and the corresponding risk factors on subsequent HCC development. The million-dollar question would be—if HCC can be eliminated one day if a CHB patient has been taking ETV/TDF for long enough.

In a recent publication, Papatheodoridis *et al.* evaluated the HCC incidence and the risk factors associated with HCC development after the first 5 years of ETV/TDF therapy in Caucasians CHB patients, and compared the HCC incidence during and after the first 5 years of therapy (10). They performed a multicenter prospective cohort study on 1,951 Caucasians CHB adults with at least one year of ETV and/or TDF treatment, which showed an annual incidence rate of HCC of 1.22% within the first 5 years and 0.73% after the first 5 years of therapy. This is probably the first prospective cohort study with respectably large sample size and long follow-up duration for evaluation of the change of annual incidence rate of HCC in the long run, and the risk factors of HCC beyond year 5 of ETV/TDF treatment in Caucasians CHB patients. The study also examined the effect of parameters at baseline and after 5 years of treatment separately on the risk of subsequent HCC development, which provided useful information on the change in risk factors of HCC under virological remission in long-term antiviral therapy.

Liver cirrhosis has long been demonstrated as a major risk factor of HCC. This is reflected in the findings by the consistently higher risk of HCC in patients with lower platelet counts at baseline and after year 5, as well as a liver stiffness ≥12 kPa at year 5 after adjustment of age. An increased HCC risk was also observed in baseline cirrhotic patients with persistently lower platelet counts at year 5. Moreover, Papatheodoridis *et al.* showed that the annual HCC incidence rate of CHB patients with compensated cirrhosis at baseline decreased substantially from 3.22% to 1.57% after long-term ETV/TDF therapy, whereas remained comparable among non-cirrhotic patients (0.49% *vs.* 0.47%). This may imply regression of cirrhosis in patients under long-term antiviral treatment. Previous studies have shown that antiviral treatment may contribute to the regression of fibrosis and cirrhosis over time (11,12). This also echoes with the findings that the risk of HCC tended to be lower in patients with baseline cirrhosis who had liver stiffness <12 kPa at year 5. Since liver fibrosis takes years to decades to form and also years to regress (13), this study provides useful information on the effect of change in liver fibrosis in the long run.

Liver stiffness measurement has been shown to be an important parameter to assess liver fibrosis and predict prognosis (14). Liver stiffness measurement by transient elastography has been widely validated as a non-invasive method for the assessment of liver fibrosis. Different algorithms combining liver stiffness and serum markers have also been proposed to improve the diagnostic accuracy of transient elastography on diagnosing advanced fibrosis (15,16). The findings of this study by Papatheodoridis *et al.* further supported the incorporation of longitudinal assessment of liver stiffness in CHB patients under long-term antiviral treatment, as reflected by the elevated risk of HCC in patients with liver stiffness ≥12 kPa at year 5.

An important clinical question is whether HCC surveillance is necessary after long-term treatment of potent antiviral therapy. The investigators assessed the risk of HCC development by several frequently used HCC risk scores. Their findings showed that patients with low PAGE-B, CU-HCC or GAG-HCC scores at year 5 were of minimal risk of subsequent HCC development (17-19). This might suggest that those patients may not require HCC surveillance if they do not have cirrhosis. Nonetheless, despite validation on frequently used HCC risk scores in ETV-treated cohort (8), none of those scores demonstrated good prediction accuracy and genuine clinical utility for the development of HCC in 5 to 10 years of ETV/TDF therapy, which was reflected by their corresponding modest c-indexes. As most of the ETV/TDF-treated patients would have to be on treatment for years or even decades, if not life-long, adjustment on HCC risk scores to account for the on-treatment response of liver fibrosis and modified natural history of HBV infection under long-term ETV/TDF treatment deserves further investigation to identify patients in high risk of HCC development in the long run (20).

In conclusion, the study by Papatheodoridis *et al.* provides valuable data on the reduced risk of HCC under long-term potent treatment of ETV/TDF beyond 5 years of treatment, and the corresponding factors associated with the reduced yet non-negligible risk of HCC. Future study should be directed towards the adjustment of HCC risk scores under long-term antiviral treatment for better indication on HCC surveillance. Hopefully one day we would be able to tell our CHB patients the time that their HCC risk has been eliminated, finally.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *AME Medical Journal*. The article did not undergo external peer review.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2017.08.28). Dr. Wong reports grants from Gilead Sciences, personal fees from Gilead Sciences, personal fees from Janssen, personal fees from Abbott, personal fees from AbbVie, personal fees from Bristol-Myers Squibb, personal fees from Echosens, personal fees from Roche, outside the submitted work. Dr. Yip reports grants from Gilead Sciences, personal fees from Gilead Sciences, outside the submitted work.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Wong GL, Wong VW, Chan HY, et al. Undetectable HBV DNA at month 12 of entecavir treatment predicts maintained viral suppression and HBeAg-seroconversion in chronic hepatitis B patients at 3 years. Aliment Pharmacol Ther 2012;35:1326-35.
2. Wong GL, Tse YK, Wong VW, et al. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: A cohort study of 53,500 subjects. Hepatology 2015;62:684-93.
3. European Association For The Study Of The Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-85.
4. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology

2016;63:261-83.
5. Wong GL, Tse YK, Yip TC, et al. Long-term use of oral nucleos(t)ide analogues for chronic hepatitis B does not increase cancer risk - a cohort study of 44 494 subjects. Aliment Pharmacol Ther 2017;45:1213-24.
6. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int 2016;10:1-98.
7. Wong GL, Chan HL, Mak CW, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology 2013;58:1537-47.
8. Wong GL, Chan HL, Chan HY, et al. Accuracy of risk scores for patients with chronic hepatitis B receiving entecavir treatment. Gastroenterology 2013;144:933-44.
9. Papatheodoridis GV, Chan HL, Hansen BE, et al. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol 2015;62:956-67.
10. Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma is decreasing after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017. [Epub ahead of print].
11. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology 2010;52:886-93.
12. Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 2013;381:468-75.
13. Wong GL, Chan HL, Yu Z, et al. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B--a prospective cohort study with paired transient elastography examinations. Aliment Pharmacol Ther 2014;39:883-93.
14. Wong GL. Transient elastography: Kill two birds with one stone? World J Hepatol 2013;5:264-74.
15. Chan HL, Wong GL, Choi PC, et al. Alanine aminotransferase-based algorithms of liver stiffness measurement by transient elastography (Fibroscan) for liver fibrosis in chronic hepatitis B. J Viral Hepat 2009;16:36-44.
16. Wong GL, Wong VW, Choi PC, et al. Development of a non-invasive algorithm with transient elastography (Fibroscan) and serum test formula for advanced liver fibrosis in chronic hepatitis B. Aliment Pharmacol Ther 2010;31:1095-103.
17. Wong VW, Chan SL, Mo F, et al. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers. J Clin Oncol 2010;28:1660-5.
18. Papatheodoridis G, Dalekos G, Sypsa V, et al. PAGE-B predicts the risk of developing hepatocellular carcinoma in Caucasians with chronic hepatitis B on 5-year antiviral therapy. J Hepatol 2016;64:800-6.
19. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. J Hepatol 2009;50:80-8.
20. Wong GL, Chan HL, Wong CK, et al. Liver stiffness-based optimization of hepatocellular carcinoma risk score in patients with chronic hepatitis B. J Hepatol 2014;60:339-45.

doi: 10.21037/amj.2017.08.28
Cite this article as: Yip TC, Wong GL. How long will it take to eliminate HCC risk in patients with chronic hepatitis B patients with potent antivirals? AME Med J 2017;2:141.

