Editorial

Potent suppression of hepatitis B virus and hepatocellular carcinoma: how long is good enough?

Sudha Kodali, Ashwani K. Singal

Division of gastroenterology and hepatology, University of Alabama at Birmingham, Birmingham, AL, USA

Correspondence to: Ashwani K. Singal, MD, MS, FACG, FAASLD. Division of Gastroenterology and Hepatology, University of Alabama at Birmingham, 808 7th Ave South, BDB 351, Birmingham, AL 35294-0012, USA. Email: ashwanisingal.com@gmail.com.

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Comment on: Papatheodoridis GV, Idilman R, Dalekos GN, *et al.* The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444-53.

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Approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV). The natural history of chronic HBV infection, ranges from an inactive carrier state to progressive chronic hepatitis B (CHB), which may evolve to cirrhosis and hepatocellular carcinoma (HCC) (1,2). HBV-related end stage liver disease is responsible for over 0.5–1 million deaths per year and currently represent 5–10% of cases of liver transplantation (1). Many factors can potentially induce development of HCC in HBV infected patients. These are (I) chronic necroinflammatory activity induced by immune response to the virus, (II) apoptosis of cells with cellular damage resulting in dysplasia of the hepatocytes, and (III) direct oncogenic potential of HBV with integration of its DNA with the host DNA.

Goal of therapy in CHB is to reduce morbidity and mortality associated with the infection, improve the quality of life and survival by slowing progression to cirrhosis and also to reduce risk of HCC (3,4). A randomized controlled trial for the first time showed benefit of antiviral therapy in reducing the risk of HCC. In this study on 651 CHB patients , lamivudine taken orally 100 mg/d for a median duration of 32 months showed an absolute risk reduction of 3.5% compared to placebo with relative risk reduction of about 50%, (7.4% *vs.* 3.9%) (3). Since then, many observational and randomized studies, as well as meta-analyses have shown benefit of antiviral drugs for HBV in reducing the HCC risk (4-6). Male gender, age >45 years, having a first-degree relative with HCC, the presence of cirrhosis, HBVDNA level, HBeAg-positive status in adults, and reversion from anti-HBe to HBeAg status are all known risk factors for HCC (6-8). The mean follow up period was about 2.5–3 years for randomized studies, and about 5 years for the observational studies. Long term data regarding the benefits of antiviral use for greater than 5 years, especially in risk reduction for HCC are lacking (5,9).

The authors Papatheodoridis *et al.*, in a recent issue of *Hepatology* published on a multicenter prospective cohort of chronic HBV with focus on the risk reduction of HCC after 5 years of being treated with antiviral agents in patients with CHB (10). Other goal of this study was to identify factors associated with long-term HCC occurrence after 5 years of antiviral therapy. A total 1,951 adult Caucasian CHB patients enrolled from ten centers in Europe, who did not have HCC at baseline and received ETV/TDF for ≥1 year were studied. Of these, 1,205 (62%) patients without HCC within the first 5 years of therapy were followed for 5–10 (median, 6.8) years. HCC was diagnosed in 101/1,951 (5.2%) patients within the first 5 years and 17/1,205 (1.4%) patients within 5–10 years. The yearly HCC incidence rate was 1.22% within and 0.73% after the first 5 years (P=0.050). The yearly HCC incidence rate did not differ within and after the first 5 years in patients without cirrhosis (0.49% *vs.* 0.47%, P=0.931), but it significantly declined in patients with cirrhosis (3.22% *vs.* 1.57%, P=0.039) (10). These data clearly show a significant reduction in incidence

of HCC in cirrhotics with longer duration of therapy. In a multivariable analysis model, the authors showed that older age, lower platelets at baseline and year 5, and liver stiffness ≥12 kPa at year 5 independently predicted development of HCC beyond 5 years of follow-up. The authors also examined the role of PAGE-B (using platelets, age, and gender) score, which has been developed earlier in another cohort by the same authors (11). Using this score, they showed that none of patients with low PAGE-B score developed HCC in long run. Two of the variables in PAGE-B score of age and platelets were strong predictors in their current study with internal validation on the utility of this score. However, in this specific study, gender did not emerge as a strong predictor in long run.

This study sheds light on a very important and significant issue of risk reduction of HCC in patients with chronic HBV infection with long term therapy with antiviral agents. With the study reported in Caucasians, these data need confirmation in Asian cohort, given that over 75% of the world population with HBV infection resides in Asia (4). However, these findings remain significant and useful in routine practice for managing these patients with high suspicion and rigorous screening in individuals who are over 50 years of age at start of treatment, patients with cirrhosis, and those patients with low platelets and liver stiffness measurement of >12 kPa at year five of treatment. It is also worthy to note that irrespective of duration of antiviral therapy, there remains risk for HCC, and these patients should continue to receive surveillance for HCC. It remains to be seen that how long patients need to be treated to eliminate this risk. Given that these antiviral drugs are not effective in clearing the closed circular DNA from the hepatocytes, results of ongoing clinical trials using newer drugs at different therapeutic targets in the cell cycle of HBV are awaited as a basis for excellent cure and eradication of HBV (4,12), similar to what the medical and scientific community has achieved for patients infected with hepatitis C virus infection.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. 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.
2. Lok AS, McMahon BJ. Chronic hepatitis B. Hepatology 2007;45:507-39.
3. Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med 2004;351:1521-31.
4. Terrault NA, Bzowej NH, Chang KM, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology 2016;63:261-83.
5. Papatheodoridis GV, Lampertico P, Manolakopoulos S, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010;53:348-56.
6. Singal AK, Salameh H, Kuo YF, et al. Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. Aliment Pharmacol Ther 2013;38:98-106.
7. McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009;49:S45-55.
8. Chen CJ, Yang HI, Su J, et al. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
9. Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. Hepatology 2013;58:98-107.
10. Papatheodoridis GV, Idilman R, Dalekos GN, et al. The risk of hepatocellular carcinoma decreases after the first 5 years of entecavir or tenofovir in Caucasians with chronic hepatitis B. Hepatology 2017;66:1444-53.
11. 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.
12. Peters MG, Locarnini S. New Direct-Acting Antiviral Agents and Immunomodulators for Hepatitis B Virus Infection. Gastroenterol Hepatol (N Y) 2017;13:348-56.

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