HEPATOLOGY

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

EDITORIALS | HEPATOLOGY, VOL. 66, NO. 2, 2017

Low-Level Viremia in Hepatitis B Patients on Antiviral Treatment: Can We Ignore It?

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In the landmark REVEAL study on the natural history of patients infected with hepatitis B virus (HBV), an association between baseline HBV DNA levels and the risk of cirrhosis and hepatocellular carcinoma (HCC) was established.[1] With the goal of antiviral treatment being to decrease the morbidity and mortality associated with chronic hepatitis B (CHB), the first-line antiviral agents recommended for treating CHB patients by the American Association for the Study of Liver Diseases (AASLD) include pegylated interferon, entecavir, and tenofovir.[2] With their easy tolerability and efficacy in suppressing viral replication associated with high genetic barrier to resistance, many patients with HBV worldwide were treated with either oral agent, often achieving reversal of cirrhosis and reduced incidence of HCC.[3,4]

One question posed in the recently updated AASLD guidelines for management of CHB was whether there would be a role for adding a second antiviral agent with persistent low-level viremia (LLV; <2000 IU/mL) while on entecavir or tenofovir. The guidelines suggest that such CHB patients with LLV continue monotherapy.[2] This approach was demonstrated in a European cohort study in which long-term entecavir monotherapy led to a virologic response in the vast majority of treatment-naïve patients, including those with a partial virologic response after 48 weeks of treatment.[5] In this issue of HEPATOLOGY, a large retrospective study by Kim and Sinn et al. indicates that among patients on antiviral therapy, LLV, defined as persistent or intermittent episodes of HBV DNA greater than the lower detection limit of 12 IU/mL but <2000 IU/mL, was associated with a higher risk of developing HCC when compared with those who maintained virologic response (MVR) with persistently undetectable HBV DNA levels.[6] Previously treatment-naïve 875 patients were treated with entecavir for at least 1 year. During a median follow-up of 4.5 years, 85 patients (9.7%) developed HCC. Overall, the development of HCC was more frequent in patients with LLV than MVR (14.3% versus 7.5% at 5 years, $P = 0.016$). On multivariate analysis, LLV was an independent risk factor associated with HCC development (HR = 1.98, $P = 0.002$). However, although patients who have cirrhosis with LLV had a higher risk of developing HCC than those with cirrhosis and MVR, among patients without cirrhosis there was no statistically significant difference in the risk of HCC occurrence between patients with LLV and those with MVR, possibly due to a lower risk of HCC in that population than in patients with cirrhosis. Achieving MVR even in noncirrhotic patients may still be important, but we would need a study with a much larger sample size and/or a longer follow-up to show such impact, including stratified analysis by age and sex that may be helpful in accounting for the effect of those strong covariates. Thus, at least for CHB patients with cirrhosis, presence of LLV while on entecavir or tenofovir may not be ignored with a higher risk of developing HCC than those with MVR.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; CHB, chronic hepatitis B; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LLV, low-level viremia; MVR, maintained virologic response.

Received March 1, 2017; accepted April 19, 2017.

View this article online at wileyonlinelibrary.com.
DOI 10.1002/hep.29235

Potential conflict of interest: Dr. Min advises and has received grants from Bristol-Myers Squibb and Gilead.

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Whether or when a compliant CHB patient with LLV on treatment with entecavir or tenofovir should add another agent is not clear.[2,7] Entecavir or tenofovir fails to achieve HBV DNA undetectability after 48 weeks in 10% and 30% in HBeAg-negative and HBeAg-positive patients, respectively.[2] In light of the Kim and Sinn et al. study, we should consider a potential alternative strategy, at least in patients with cirrhosis. There is no prospective, well-designed study in answering what is the best strategy among the three options in compliant patients with LLV on entecavir or tenofovir—whether to continue the initial agent, switch to the other agent or add the second agent. It will be difficult to design a study to determine the optimal timing of the alternative strategy while trying to correlate it with the risk of HCC development. Undoubtedly, any strategy to manage such patients who have cirrhosis with LLV on treatment should be optimally evaluated in a scientifically rigorous study. One may opt to narrow a focus of any potential study using a specific antiviral agent in a cirrhotic population and wait for viral response to plateau before implementing a predefined alternative strategy. However, as is the case for the above hypothetical study in the noncirrhotic population, the number of patients and time required to arrive at a meaningful answer would still be immensely prohibitive for such study to be performed. Thus, one has to rely upon indirect evidence, as has been the case for answering most challenging issues in management of CHB patients.[7] For example, in trying to ascertain whether to treat CHB patients with compensated cirrhosis and LLV (<2000 IU/mL) with an antiviral agent, Lok et al. did not find any comparative studies to guide their decision but found one specific study (performed by the same group as the authors of the Kim and Sinn et al. article) examining the benefit of antiviral therapy in CHB patients with compensated cirrhosis and LLV with reduced incidence of HCC in the treated group.[7,8] Despite the presence of confounding factors such as differences in the characteristics between the treated and untreated groups in that retrospective study and absence of other randomized controlled trials, the AASLD guidelines recommend that such patients with compensated cirrhosis and LLV should be treated with antiviral therapy to reduce the risk of decompensation.[2]

One cautionary note is that we cannot extrapolate Kim and Sinn et al.'s findings to treatment-naïve HBV patients without cirrhosis who are considered to be in the inactive phase, demonstrated by either intermittently or persistently detectable HBV DNA levels but always <2000 IU/mL and normal alanine aminotransferase values. The REVEAL study showed that CHB patients having LLV (between 60 and 2000 IU/mL) at baseline are not at a higher risk of developing HCC than those whose baseline viral levels are below the lower limit of quantitation.[1] Unlike patients on antiviral treatment in the Kim and Sinn et al. study, most patients with LLV in the inactive phase of CHB have minimal evidence of liver injury. In the 2016 AASLD annual meeting, a large retrospective cohort study compared the risk of developing HCC between patients with CHB who achieved virologic response with antiviral therapy and patients in the inactive CHB phase (HBV DNA <2000 IU/mL) after adjusting for fibrosis status.[9] Clinical outcomes were comparable between CHB patients with virologic response using oral antiviral therapy and those in the inactive phase of CHB when adjusted for fibrotic burden. Moreover, it is reassuring that among noncirrhotic patients on antiviral therapy in the Kim and Sinn et al. study, there was no significant difference in the risk of developing HCC between CHB patients with LLV and those with MVR.

However, half of the patients in the Kim and Sinn et al. study had cirrhosis at baseline, and most patients with HBV and HCC have cirrhosis.[10] In addition, having undetectable viral level rather than a loss of HBsAg was associated with a lower risk of HCC.[11] Even those CHB patients who ultimately achieve "functional cure" with loss of HBsAg, albeit an uncommon occurrence with or without antiviral therapy, remain at risk for HCC development.[11] With cirrhosis as the major risk factor of HCC development, and in light of the Kim and Sinn et al. study's findings, we may no longer be able to ignore the significance of LLV in patients with compensated cirrhosis who are already on antiviral therapy. However, in considering how to convert those being treated from LLV to MVR camp, without well-designed comparative studies available we would have to make a decision based on indirect evidence, incorporating data from observational studies, individual patient preference, and available resources.[7] Fortunately, the good news is that with currently available effective antiviral agents that are associated with high genetic barrier to resistance, the number of HBV-related patients who have cirrhosis with LLV on treatment will account for a small portion of CHB patients in clinical practice. However, we are once again reminded that in managing CHB patients, we should remain vigilant in continuing regular HCC surveillance indefinitely, regardless of

whether undetectable HBV DNA levels and/or even loss of HBsAg have been achieved, particularly in patients with cirrhosis.

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REFERENCES

1) Chen C-J, Yang H-I, Su J, Jen C-L, You S-L, Lu S-N, et al, for the REVEAL-HBV Study group. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA 2006;295:65-73.
2) Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH. American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. HEPATOLOGY 2016;63:261-283.
3) Chang TT, Lai CL, Kew Yoon S, Lee SS, Coelho HS, Carrilho FJ, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. HEPATOLOGY 2010;51:422-430.
4) Ahn J, Lim JK, Lee HM, Lok AS, Nguyen M, Pan CQ, et al. Lower observed hepatocellular carcinoma incidence in chronic hepatitis B patients treated with entecavir: results of the ENUMERATE Study. Am J Gastroenterol 2016;111:1297-1304.
5) Zoutendijk R, Reijnders JGP, 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 virologic response. HEPATOLOGY 2011;54:443-451.
6) **Kim JH, Sinn DH**, Kang W, Gwak G-Y, Paik Y-H, Choi MS, et al. Low-level viremia and the increased risk of hepatocellular carcinoma in patients receiving entecavir treatment. HEPATOLOGY 2017;66:335-343.
7) Lok ASF, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, et al. Antiviral therapy for chronic hepatitis B viral infection in adults: a systematic review and meta-analysis. HEPATOLOGY 2016;63:284-306.
8) Sinn DH, Lee J, Goo J, Kim K, Gwak GY, Paik YH, et al. Hepatocellular carcinoma risk in chronic hepatitis B virus-infected compensated cirrhosis patients with low viral load. HEPATOLOGY 2015;62:694-701.
9) Kim HS, Kim BK, Kim SU, Park JY, Kim DY, Ahn SH, et al. Clinical outcomes were comparable between chronic hepatitis B patients with virological response using oral antiviral therapy and inactive carriers when adjusting for fibrotic burden. HEPATOLOGY 2016;64(Suppl. S1):38A.
10) Yang JD, Kim WR, Coelho R, Mettler TA, Benson JT, Sanderson SO, et al. Cirrhosis is present in most patients with hepatitis B and hepatocellular carcinoma. Clin Gastroenterol Hepatol 2011;9:64-70.
11) Nathanson MH, Terrault N. Hepatitis B surface antigen loss: not all that we hoped it would be. HEPATOLOGY 2016;64:328-329.

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