Oral antiviral therapy reduces the risk of hepatocellular carcinoma in persons with chronic hepatitis B infection: combining evidence and common sense

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According to a recent global systemic review, in 2010 about 248 million persons in the general population worldwide were chronically infected with hepatitis B virus (HBV), with the highest HBsAg prevalence rates being in Africa (8.83 %) and the Western Pacific region (5.26 %) [1]. Universal HBV vaccination programs in newborns have led a remarkable decline in HBsAg prevalence among young age groups in many countries such as China [2], but the huge number of persons with chronic HBV infection, if left untreated, will still cause an enormous disease burden associated with cirrhosis and hepatocellular carcinoma (HCC) in the next decades [3].

Long-term prospective cohort studies have shown that the serum level of HBV DNA is a key driver for disease progression from CHB to cirrhosis and HCC [4]. A Korean retrospective cohort study demonstrated that compensated cirrhosis patients, even with low viral load, were still at increased risk for HCC [5]. Pivotal clinical trials and real-life studies have shown that nucleoside or nucleotide analogs (NAs) have excellent efficacy in suppressing HBV DNA and improving liver biochemical tests. Furthermore, long-term therapy with NAs, especially entecavir (ETV) or

tenofovir disoproxil fumarate (TDF), improves fibrosis or even early stage of cirrhosis as well as necroinflammation [6, 7]. More importantly, NA therapy improves clinical outcomes such as liver function reserve as measured by Child-Pugh or MELD scores, implicating that NAs could not only prevent compensated cirrhosis from decompensation but also reverse from decompensation to compensation (so-called recompensation) [8]. Therefore, antiviral therapy with highly potent and low resistance NAs such as ETV and TDF is recommended by major international guidelines including those recently released by WHO [9].

However, whether NA therapy could reduce the risk of HCC development is still an issue for discussion. A widely cited double-blind, randomized, placebo-controlled trial reported by Liaw et al. demonstrated that, in patients with advanced fibrosis or early cirrhosis, treatment with lamivudine could reduce the HCC if cases found within the first year were excluded from both groups, but the emergence of drug resistance compromised the benefit [10]. Clinical cohort studies from other centers in Hong Kong and Taiwan also showed a consistent trend of reduced incidence of HCC in patients treated with NAs [11, 12]. Furthermore, a population-based study carried out in Taiwan suggested that, compared with the pre-antiviral era, the incidence and mortality of HCC in the general population were decreasing with the increasing coverage rate of antiviral therapy for HBV and HCV, as shown in databases of medical insurance [13]. In addition, authors from US and Canada have also reported that NA treatment reduced the incidence of HCC in patients with CHB [14, 15].

In this issue of *Hepatology International*, Watanabe and coworkers [16] report that, in a retrospective cohort of 249 patients with CHB, 5 years after starting ETV treatment, liver functional reserve improved (prothrombin activity increased from 85.9 ± 17.4 to 97.0 ± 16.9 %, $p < 0.001$,

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and albumin level increased from 4.0 ± 0.5 to 4.3 ± 0.3 mg/dL, $p < 0.001$) and the incidence of HCC was only 1.8 %. On multivariate analysis, older age and low platelet count were significant independent contributing factors for HCC incidence. Therefore, the authors of that paper conclude that long-term treatment with ETV improved hepatic functional reserve and decreased the incidence of HCC. This result confirmed the findings of another study from Japan that HCC incidence in patients treated with NAs was much lower than untreated historical controls [17].

However, reports from European countries have shown less optimistic results. For example, Arends et al. reported that, in 744 CHB patients (42 % Caucasian, and 22 % cirrhosis) treated with ETV from 11 European referral centers within the VIRGIL Network, the 5-year cumulative incidence rates of HCC were 2.1 and 10.9 % for non-cirrhotic and cirrhotic patients, respectively [18]. They concluded that the cumulative incidence of HCC is low in patients treated with ETV, but that ETV does not eliminate the risk of HCC. This discrepancy may partly be explained by the different patients profiles between reports from European and Asian centers. Indeed, a large Greek nationwide study indicated that the HCC risk remains increased at least for the first 5 years after starting ETV therapy in HBeAg-negative CHB patients with cirrhosis, particularly in those of older age [19]. An Italian multi-center study also showed that virological response does not appear to significantly reduce the overall incidence of HCC, and that cirrhosis and age ≥ 60 years are the stronger risk factors for HCC in genotype D HBeAg-negative patients [20]. In addition, it would not be surprising that NA therapy could not eliminate the HCC risk because HBV DNA is not the only factor to determine HCC development, where host and environmental factors also play important roles [21].

Of note is the methodological issue in designing this kind of clinical study. Retrospective non-controlled design is a big concern of the current study [16]. Without controls, the conclusion is less convincing because other confounding factors might cause the decreased incidence of HCC development. However, practical issues should also be taken into consideration. In fact, since its efficacy and safety have been proven, NA therapy has become a standard of care in patients with CHB, especially in those with advanced fibrosis or cirrhosis. Obviously, ethnical concerns made the randomized controlled trials less feasible. Therefore, later investigations on this topic usually adopted a cohort study design, with untreated or different treatment arm(s) as historical or external control group(s). The imbalance of known confounding factors across different

arms can be minimized by special statistical techniques such as propensity score matching (PSM) analysis [11, 17]. However, this would need much bigger sample sizes in order to have a large enough number of patients left after PSM. Another approach is to compare the observed incidence of HCC in the treated cohort with that projected in untreated cohorts by prediction models such as CU-HCC, GAG-HCC or REACH-B [18]. This should also be carried out cautiously because the application of the models is conditional, for example, other hosts (such as ethnic groups) and viral factors (such as genotype and HBeAg status) which should be taken into consideration. For example, a European study did show that HCC prediction models derived from Asian populations had a poorer performance in Caucasian patients [18]. Medical insurance database analysis would offer the chance of population-based study but the correct linkage of personal data and the appropriate management of missing data would also pose technical challenges.

To properly design, conduct and interpret clinical studies addressing the effect of NA therapy on HCC development, careful selection of study population is of paramount importance. Common sense tells us that, if a study includes more patients with non-cirrhotic CHB or even in immune tolerance phase, the incidence of HCC would be very low, and therefore a very large number of patients and a long duration of follow-up would be required to see differences in HCC incidence. On the other hand, if more patients were of older age and with cirrhosis, the incidence of HCC will remain high for several years after starting the therapy, and again a much larger number of patients and a longer duration of follow-up would be required. In this context, patients with advanced fibrosis or early cirrhosis would be the population who needs treatment urgently and in whom the clinical benefit could be easily observed.

By combining the common sense and the available evidence, we should understand that NA therapy reduces but does not eliminate the risk of HCC development in cirrhotic patients [22], therefore, on-treatment monitoring for HCC is still needed, since HCC could occur even after the HBsAg loss [23]. We hope further well-designed, carefully conducted clinical or population-based studies will provide stronger evidence to clarify this issue.

Finally we need to understand that the prevention of HCC is only one of the goals of HBV DNA suppression. Therefore, antiviral therapy with NAs should be initiated in patients with active CHB, compensated or even with decompensated cirrhosis, to prevent or even to reverse liver fibrosis, cirrhosis, and decompensation, as well as to reduce the risk of HCC.

References

- Schweitzer A, Horn J, Mikolajczyk RT, Krause G, Ott JJ. Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013. *Lancet* 2015; pii:S0140-6736 (15)61412-X.
- Yang S-g, Wang B, Chen P, C-b Yu, Deng M, Yao J, et al. Effectiveness of HBV vaccination in infants and prediction of hbv prevalence trend under new vaccination plan: findings of a large-scale investigation. *PLoS One*. 2012;7(10):e47808.
- El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. *Gastroenterology*. 2012;142(6):1264–73.
- Iloeje UH, Yang HI, Chen CJ. Natural history of chronic hepatitis B: what exactly has REVEAL revealed? *Liver Int*. 2012;32(9):1333–41.
- 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(3):694–701.
- Chang TT, Liaw YF, Wu SS, Schiff E, Han KH, Lai CL, 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(3):886–93.
- Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, Jacobson IM, 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(9865):468–75.
- Peng CY, Chien RN, Liaw YF. Hepatitis B virus-related decompensated liver cirrhosis: benefits of antiviral therapy. *J Hepatol*. 2012;57(2):442–50.
- WHO. Guidelines for the prevention, care and treatment of persons with chronic hepatitis infection (Internet). 2015; Available from: <http://www.who.int/hiv/pub/hepatitis/hepatitis-b-guide-lines/en/>.
- Liaw YF, Sung JJ, Chow WC, Farrell G, Lee CZ, Yuen H, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004;351(15):1521–31.
- Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. *Hepatology*. 2013;58(5):1537–47.
- Wu CY, Lin JT, Ho HJ, Su CW, Lee TY, Wang SY, et al. Association of nucleos(t)ide analogue therapy with reduced risk of hepatocellular carcinoma in patients with chronic hepatitis B: a nationwide cohort study. *Gastroenterology*. 2014;147(1):143–51.
- Chiang CJ, Yang YW, Chen JD, You SL, Yang HI, Lee MH, et al. Significant reduction in end-stage liver diseases burden through the national viral hepatitis therapy program in Taiwan. *Hepatology*. 2015;61(4):1154–62.
- Gordon SC, Lamerato LE, Rupp LB, Li J, Holmberg SD, Moorman AC, et al. Antiviral therapy for chronic hepatitis B virus infection and development of hepatocellular carcinoma in a US population. *Clin Gastroenterol Hepatol*. 2014;12(5):885–93.
- Coffin CS, Rezaeeaval M, Pang JX, Alcantara L, Klein P, Burak KW, Myers RP. The incidence of hepatocellular carcinoma is reduced in patients with chronic hepatitis B on long-term nucleos(t)ide analogue therapy. *Aliment Pharmacol Ther*. 2014;40(11–12):1262–9.
- Watanabe T, Tokumoto Y, Joko K, Michitaka K, Mashiba T, Hiraoka A, et al. Effects of long-term entecavir treatment on the incidence of hepatocellular carcinoma in chronic hepatitis B patients. *Hepatol Int* 2015; (**in press**).
- Hosaka T, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013;58(1):98–107.
- Arends P, Sonneveld MJ, Zoutendijk R, Carey I, Brown A, Fasano M, et al. Entecavir treatment does not eliminate the risk of hepatocellular carcinoma in chronic hepatitis B: limited role for risk scores in Caucasians. *Gut*. 2015;64(8):1289–95.
- Papatheodoridis GV, Manolakopoulos S, Touloumi G, Nikolopoulos G, Raptopoulou-Gigi M, Gogos C, et al. Hepatocellular carcinoma risk in HBeAg-negative chronic hepatitis B patients with or without cirrhosis treated with entecavir: HepNet.Greece cohort. *J Viral Hepat*. 2015;22(2):120–7.
- Pellicelli AM, Vignally P, Messina V, Izzi A, Mazzoni E, Barlattani A, et al. Long term nucleotide and nucleoside analogs treatment in chronic hepatitis B HBeAg negative genotype D patients and risk for hepatocellular carcinoma. *Ann Hepatol*. 2014;13(4):376–85.
- Song IH, Kim SM, Choo YK. Risk prediction of hepatitis B virus-related hepatocellular carcinoma in the era of antiviral therapy. *World J Gastroenterol*. 2013;19(47):8867–72.
- Aghemo A, Lampertico P, Colombo M. Assessing long-term treatment efficacy in chronic hepatitis B and C: between evidence and common sense. *J Hepatol*. 2012;57(6):1326–35.
- Kim GA, Lee HC, Kim MJ, Ha Y, Park EJ, An J, Lee D, Shim JH, Kim KM, Lim YS. Incidence of hepatocellular carcinoma after HBsAg seroclearance in chronic hepatitis B patients: a need for surveillance. *J Hepatol*. 2015;62(5):1092–9.