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Nucleos(t)ide Analog Therapy of Chronic Hepatitis B and Liver Cancer Risk Reduction: Better Nucleotides than Nucleosides?

Choi J, Kim HJ, Lee J, et al. Risk of hepatocellular carcinoma in patients treated with entecavir vs tenofovir for chronic hepatitis B: a Korean nationwide cohort study. JAMA Oncol 2019;5:30–36.

Globally, 240 million people are chronically infected with the hepatitis B virus (HBV) and every year almost 800,000 of them succumb from fatal HBV-related complications, including hepatocellular carcinoma (HCC) (Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599). Although this worrisome scenario has driven the World Health Organization (WHO) along with other health authorities to enforce a campaign for expanding recognition and treatment of HBV with the understanding of eliminating viral hepatitis by 2030, encouraging news come from modelling studies of viral hepatitis epidemiology that have highlighted the benefits conferred by widespread articulated interventions of sanitation, one above all the mass vaccination against HBV of newborns that contributed substantially to shrink the burden of HBV by >30% over the past decades (Draft global health sector strategies; available: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf) As a matter of fact, strategies of interruption of mother-to-child transmission of HBV with vaccination are in place in most WHO countries and, in the years to come, they are expected to further downsize HBV transmission among the general population while standing as the only pragmatic approach to prevent mortality from the hepatitis delta virus that is a severe untreatable infection that is co-transmitted with HBV (J Hepatol 2017;67:370–398).

Mitigating against all this good news, however, is the recent report from the WHO pinpointing the very limited number of patients chronically infected with HBV (<10%) who have currently been identified and linked to care with specific antivirals, the other approach shown to decrease mortality from end-stage HBV infection (Draft global health sector strategies; available: http://apps.who.int/gb/ebwha/pdf_files/WHA69/A69_32-en.pdf). This point is not trivial because prolonged suppression of HBV with nucleos(t)ide analogs (NA) has been shown to temper progression of HBV infection to fatal complications including HCC, whose prevention, however, is not absolute (approximately 50%) and can only be maximized when antiviral therapy is started before the development of cirrhosis (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599). Unfortunately, the causal relationship between HBV suppression and HCC risk reduction took a long time to emerge owing to the long period of time during which largely imperfect treatment modalities, such as interferon and first- and second-wave Nas, were available to treat HBV that caused studies to be flawed by referral biases, high rates of treatment failures, and ultimately by a suboptimal percent suppression of HBV (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599). This is no longer the case, with the advent of the third-wave nucleotide analog tenofovir disoproxil fumarate (TDF) and the nucleoside analog entecavir (ETV), whose records of safety and antiviral efficacy are undisputedly almost absolute, whereas the incidence and mortality of HCC could be prevented in >85% of patients who received NAs for years (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599; Hepatology 2015;61:1154–1162). Given the differences in patient access (ETV is discouraged in lamivudine-experienced patients), market distribution and the site of HBV polymerase targeted by the 2 NAs, nonrandomized studies have been done to compare the HCC risk reduction associated to these 2 Nas, however, without reaching a conclusive demonstration of one being superior to the other one (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599). Common to both NAs is, in fact, a failure to clear the nuclei of infected hepatocytes from HBV DNA sequences integrated into chromosomes and from free viral covalently closed circular DNA, 2 events known to contribute the neoplastic transformation of the liver in patients chronically infected with HBV (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599).

The nationwide historical population cohort study in Korea by Choi et al tried to provide an answer to this debate by interrogating the national health insurance database involving >24,000 treatment-naive adults with both compensated and decompensated chronic hepatitis B who started treatment with either TDF or ETV between 2012 and 2014 (JAMA Oncol 2019;5:30–36). In all patients, the starting point of therapy was a serum alanine aminotransferase of >80 IU/L, but there was a disparity in the duration of follow-up between groups because TDF was approved later than ETV. Not mentioned was how many patients had undergone surveillance for HCC with imaging studies performed at 6-month intervals as recommended by the Asian Pacific Association for the Study of the Liver (APASL). Because the population study could not capture such covariates of prognostic relevance as serum HBV DNA and aminotransferase level, the impact of multiple predictors of treatment outcome was investigated in a separate validation cohort of 2701 patients who were similarly treated in a tertiary referral center. With the primary endpoint of HCC incidence and the secondary endpoints of all-cause mortality and liver transplantation, the study revealed that at the population level the annual incidence of HCC was significantly lower in the TDF group than in the ETV group, the percent person-years being 0.64 vs 1.06, however without significant differences in risk reduction of mortality and liver transplantation rates. After matching patients by a propensity score, the differences in HCC risk between TDF and ETV remained appreciable in both the population and hospital cohorts, whereas in the latter patients TDF and ETV seemed to be equally effective in decreasing all-cause mortality and liver transplantation. Intriguingly enough, the TDF group of the validation study showed stronger anti-HCC activity to associated with higher rates of virologic responses at year 1 of therapy (85.2% vs 78.7%; $P < .001$) and fewer patients requiring a switch from one to another NA or add on treatment with other NAs (0.2% vs 11.7%; $P < .001$). In this study, however, virologic response to NAs did not emerge as an independent modulator of HCC risk and regrettably how many patients were under surveillance for HCC in accordance with APASL recommendations is not mentioned.

Comment. The reversal of hepatic inflammation caused by the potent virus suppression induced by TDF and ETV therapy has created the foundation for recommending these NAs as first-line treatment for patients with chronic hepatitis B. In the vast majority of this patient population, in fact, the prolonged administration of either NA has halted the progression to cirrhosis and liver failure while it caused the attenuation—unfortunately not the eradication—of the HCC risk. With all these benefits being framed by excellent safety records, NA therapy of HBV still faces a number of limitations, most notably, the failure of eradicating covalently closed circular DNA and integrated HBVDNA sequences, a fact that accounts for the limited rates of serum hepatitis B surface antigen (HBsAg) clearance while causing the persistence of a residual risk of HCC that has been observed even in the few patients who cleared serum HBsAg after NA therapy (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599). This finding is no surprise; the development of HCC in patients with pharmacologically suppressed HBV seems to be modulated by a number of diverse virus and host risk modifiers. The first include high serum levels of HBVDNA, prolonged persistence of serum hepatitis B e antigen (HBeAg), the genotype C of HBV, and the subgenotype A1 in noncirrhotic Africans and F1b in Alaskans (and above all, failure to clear serum HBsAg) (J Hepatol 2017;67:370–398). Interacting with these virus-related predictors of HCC are some patient features, including advancing age, male gender, diseases related to the metabolic syndrome, and cirrhosis, that alone or in combination with such environmental risk factors as alcohol, tobacco smoking, and dietary aflatoxin have clearly been associated with an increased risk of HCC in HBV-infected individuals.

Although such a heterogeneous predisposition to liver cancer among HBV-infected patients hampers the design of accurate studies of primary prevention of HCC, evidence has accumulated of liver cancer being effectively prevented by the long-term administration of NAs only when suppression of HBV starts before the onset of cirrhosis (J Hepatol 2018;68:1129–1136). All these caveats should therefore be taken into proper account when interpreting the outcome of retrospective studies like the one signed by Dr Choi, who claims TDF to override ETV in the reduction of HCC risk in patients with chronic hepatitis B after the interrogation of the national health insurance database in Korea. Unfortunately, the Korean database provided no clues to identify such relevant predictors of hepatitis severity and response to antiviral therapy as serum HBV DNA levels and aminotransferases, not to speak about the lack of information on whether patients in study had been exposed to drugs like aspirin and statin known to modulate HCC risk at a population level (JAMA Oncol 2018;4:1683–1690; Oncotarget 2016;7:21753–21762). To overcome such study weaknesses, the authors exploited a number of sensitive analyses, which included patients matching by a propensity score, that confirmed the crude analysis of outcomes of the population study. However, when they investigated a validation cohort of patients treated in a referral center who were also matched by a propensity score for all the variables ascertained, they found no differences between TDF and ETV in the prevention of 2 hard endpoints like all-cause mortality and liver transplantation, whereas it was confirmed the superiority of TDF in HCC risk reduction that had already emerged in the population study. Although such a discrepancy between risk reduction of HCC and all-cause mortality is rather surprising considering the overwhelming role of HCC in HBV-related mortality (J Hepatol 2017;67:370–398; Hepatology 2018;67:1560–1599), in a similarly designed study of 2897 patients with chronic hepatitis B done in 4 academic centers in Korea, Kim Su et al reported no differences in the 5-year risk of HCC, death, and transplantation between patients with HBV monoinfection who for the first time had been exposed to TDF or ETV (J Hepatol 2019;71:456–464). It should be acknowledged, however, that the 2 cohort studies in Korea differed in 3 important

aspects: in the multicenter study, only patients with compensated cirrhosis were enrolled and the 2 NA cohorts were unbalanced for the prevalence of cirrhosis (ETV 33.6% vs TDF 29.1%; $P < .009$), a discrepancy that might have led to biased assessment of the 5-year risk of developing HCC, whereas, at variance with the Choi study that included both compensated and decompensated patients, all patients were under surveillance with semiannual examination with abdominal ultrasound examinations and serum alpha-fetoprotein as recommended by the APASL.

Intriguingly, there may be a biological plausibility for a stronger activity of TDF over ETV in the risk reduction of HCC; TDF may cause a more profound decline of serum HBsAg levels, a marker of prognostic relevance in HBeAg-negative chronic hepatitis B (Res 2018;48:59–68), while it induces higher serum levels of interferon lambda-3, a cytokine known to strongly antagonize HCC development in mice (Gut 2018;67:362–371). Further, in HBeAg-positive patients, the 48-week percent suppression of HBV DNA is reportedly greater with TDF than with ETV, although a direct comparison between the NAs is not available (Hepatology 2018;67:1560–1599).

More recently, more investigators have been appealed to compare TDF and ETV in terms of risk reduction of HCC, however with discrepant results. Three studies in Korea, the United States, and Europe reported no differences between NAs even after patient matching by a propensity score (J Hepatol 2019;70:e383–e624; J Hepatol 2019;70:e147; G. Papatheodoridis, personal communication). In contrast, in a territory-wide cohort of approximately 29,000 patients from Hong Kong, TDF treatment was associated with a greater risk reduction of HCC than ETV before (adjusted hazard ratio, 0.46; 95% confidence interval, 0.23–0.91; $P = .027$) and after multiple imputation, with and without propensity score weighting (J Hepatol 2019;70:e128).

Cumulatively, all these studies deliver the reassuring message of a robust risk reduction of liver cancer taking place in patients with chronic hepatitis B who experience prolonged virus suppression after NA therapy, but currently they fail to provide convincing evidence that one NA is superior to the other one in determining such clinical benefit.

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Conflicts of interest
The authors have made the following disclosures: Pietro Lampertico is on the speaking bureau/advisory boards for BMS, Roche, Gilead Sciences, GSK, MSD, Abbvie, Janssen, Eiger, and Myr pharma. Massimo Colombo is on the advisory committees for Merck, Roche, Novartis, Bayer, BMS, Gilead Science, Tibotec, Vertex, Janssen Cilag, Lundbeck, GSK, GenSpera, AbbVie, Wasserman, Intercept, and TARGET HCC; and speaks and teaches for Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences, Vertex, Janssen, AbbVie, and Intercept.

Durability and Effectiveness of Cognitive-Behavioral Therapy for Irritable Bowel Syndrome

Everitt HA, Landau S, O'Reilly G, et al. Assessing telephone-delivered cognitive-behavioural therapy (CBT) and web-delivered CBT versus treatment as usual in irritable bowel syndrome (ACTIB): a multicentre randomised trial. Gut 2019;0:1-11.

Lackner JM, Jaccard J, Radziwon CD, et al. Durability and decay of treatment benefit of cognitive behavioral therapy for irritable bowel syndrome: 12-month follow-up. Am J Gastroenterol 2019;114:330-338.

Irritable bowel syndrome (IBS) affects 7%–21% of the world population (Clin Gastroenterol Hepatol 2012;10:712-721), and many patients do not adequately respond to standard medical therapies. Psychological therapies targeting the brain–gut access have demonstrated short-term efficacy for IBS treatment, with numbers needed to treat between 3.5 and 5.5 for cognitive-behavioral therapy (CBT) and gut-directed hypnosis (Am J Gastroenterol 2019;114:21-39). However, $\geq$2 factors may influence the effectiveness of CBT in clinical practice: one includes availability and feasibility, and the second factor is the remaining lack of clarity about CBT's long-term benefit. Everitt et al addressed in an effectiveness trial the role of non–office-based forms of CBT, and Lackner et al addressed the decay over time of CBT treatment effects.

Everitt et al evaluated the effectiveness of non–office-based CBT in 558 patients with refractory IBS recruited from 74 primary care practices and 3 gastroenterology clinics in the UK. Patients were randomized to telephone-delivered CBT (n = 186), web-based CBT (n = 185), or treatment as usual (n = 187). Approximately 70% of enrolled patients completed 12 months of follow-up. The primary outcome, IBS-Symptom Severity Scores (IBS-SSS), reached a clinically significantly decrease of $\geq$50 points in most participants receiving telephone-delivered CBT (99 of 136 [72.8%]) and web-based CBT (82 of 124 [66.1%]) at 12 months compared with 58 of 131 patients (44.3%) in treatment as usual. Work and Social Adjustment Scores were also 3.5 (telephone) and 3.0 (web-based) points lower (ie, better) than treatment as usual (10.8 points) at 12 months ($P \leq .001$ for all comparison groups). The study showed telephone- and web-delivered CBT to be superior to treatment as usual at 12 months.

Lackner et al performed a secondary analysis of the Irritable Bowel Syndrome Outcome Study, which compared 4-session home-based (minimal contact CBT), 10-session clinic-based CBT (standard CBT), or 4 sessions of IBS education. Follow-up occurred at 2 weeks and 3, 6, 9, and 12 months after treatment completion. Treatment response was based on the Clinical Global Impressions Improvement