

Nucleos(t)ide Analog Therapy of Chronic Hepatitis B and Extrahepatic Cancer Risk: Is tenofovir better than entecavir?

Running title: Tenofovir vs. Entecavir: EHM Risk in CHB

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Yewan Park¹, Dong Hyun Sinn²

¹Department of Internal Medicine, Kyung Hee University Hospital.

²Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine.

Corresponding author: Dong Hyun Sinn

Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea

Tel: +82-2-3410-3409, Fax: +82-2-3410-6983; E-mail: dh.sinn@samsung.com

<https://orcid.org/0000-0002-7126-5554>

Chronic hepatitis B (CHB) is a major global health burden owing to the high mortality and morbidity related to liver cirrhosis and hepatocellular carcinoma (HCC).¹ Many patients with CHB suffer from persistent or intermittent hepatic necroinflammation, leading to cirrhosis, hepatic failure or hepatocellular carcinoma.² Viral replication is strongly associated with the risk of cirrhosis and HCC.³ Currently, many nucleos(t)ide analogs (NA) that can effectively suppress viral replications are available,⁴ and their use can decrease the risk of cirrhosis and HCC.⁵ Among them, entecavir (ETV) and tenofovir disoproxil fumarate (TDF) are cornerstone therapies in managing CHB,³ since both drugs are highly effective in suppressing viral replication with a low risk of drug resistance. Despite similar mechanisms of action and efficacy in suppressing viral replication, these two drugs have certain differences, especially in terms of renal and bone safety.³ In addition, superiority of tenofovir over entecavir in terms of reducing the risk of HCC, has been reported.⁶ Although controversies exist about whether TDF is superior to ETV in preventing the development of HCC,⁷ there is a possibility that these two drugs may differ in their effectiveness at reducing HCC risk.

The health burden from CHB is not only limited to the liver. Studies suggested increased risk of multiple extrahepatic malignancies (EHM) in patients with CHB.⁸⁻¹⁰ This suggests that clinicians should pay attention to the higher risk of EHM in patients with CHB and try to find a ways to decrease this risk. Of note, Lee et al. reported that long-term NA treatment was associated with a lower risk of EHM development among patients with CHB compared to untreated control.¹¹ Although additional studies are required to validate and elucidate the mechanisms, Lee et al. suggested a potential benefit of NA in terms of reducing the risk of EHM.¹¹ In this issue, the same group investigated whether there is any difference between ETV and TDF in terms of EHM risk.¹²

In this study, the authors included a total of 52,275 patients, 27,839 treated with ETV and

24,436 treated with TDF. EHM incidence within the first 3 years did not differ between antivirals (TDF vs. ETV: SHR=1.01, 95% confidence interval [CI]=0.88–1.17, P=0.84). For the specific cancer type, TDF was associated with a higher incidence of breast cancer than ETV (SHR=1.74, 95% CI=1.05–2.89). After year 3, the risk of EHM was significantly lower in the TDF group than in the ETV group (SHR=0.70, 95% CI=0.60–0.81, P<0.01). For the specific cancer type, TDF was associated with a significantly lower risk of stomach cancer (SHR=0.57, 95% CI=0.38–0.86, P=0.01), breast cancer (SHR=0.53, 95% CI=0.33–0.85, P=0.01), and non-Hodgkin lymphoma (SHR=0.34, 95% CI=0.15–0.78, P=0.01) than ETV. Authors suggested that the antitumor effects of TDF might be greater than those of ETV.

The clinical implications of the findings from Hur et al.¹² are substantial for antiviral treatment choice but warrant careful interpretation. While the study suggested better antitumor effects of TDF over ETV, its retrospective design and reliance on an administrative database have several shortcomings. In addition to the authors' discussion,¹² it should be remembered that the indication for TDF or ETV treatment in this cohort was not to decrease risk of EHM. In real-life practice, the well-known renal and bone toxicities associated with TDF might have influenced the antiviral choice as well. Although there are several plausible mechanisms suggesting that TDF might be superior to ETV, the exact mechanism of possible greater antitumor effects of TDF over ETV has not been proven. The best way to see whether superiority exist is through randomized controlled trials; however, conducting randomized trials seems infeasible given the relatively low incidence of EHM, the proven reductions in liver-related events and mortality from NA treatment among those who meet criteria for NA treatment. Hence, before making any conclusions on this issue, additional multinational or multiethnic cohort studies are required. In addition, tenofovir alafenamide and besifovir have been introduced into clinical practice to address the renal and bone toxicities associated with

TDF.³ Tenofovir alafenamide and besifovir are additional first-line treatment options alongside ETV and TDF,³ and there is no information about potential risks and benefits of tenofovir alafenamide and besifovir regarding this issue. So, at this point, should we consider potential differences in antitumor effects between entecavir and tenofovir in reducing the risk of EHM in patients with CHB? It seems that it may be too early for this in clinical practice. However, findings from Hur et al. require attention. In an analysis of the Korean National Health Insurance Service data, mortality related to HCC decreased, whereas mortality related to EHM increased in the antiviral era.¹³ EHM were the leading cause of death among patients with CHB without cirrhosis.¹³ What does this data mean? We may need to pay more attention to EHM risk in patients with CHB, and the study by Hur et al. is a step forward.

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