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Letter to the Editor

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Tenofovir over Entecavir on Hepatocellular Carcinoma Prevention: Potential Mechanisms and Suitable Population

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Dear Editor,

We read with great interest the article by Tsai et al. [1] about comparison between tenofovir disoproxil fumarate (TDF) and entecavir (ETV) on their tertiary prevention capabilities for BCLC stage 0/A hepatocellular carcinoma (HCC) in chronic hepatitis B (CHB) patients. Secondary prevention capabilities of nucleos(t)ide analogs (NUCs) for HCC have been extensively investigated, but research concerning tertiary prevention with NUCs remains scarce. This article confirmed the previous finding of Choi et al. [2] that TDF was superior to ETV in preventing HCC recurrence after surgical resection, which could direct NUCs selection for receivers of hepatitis B virus-positive allografts [3]. Tsai et al. [1] further dissected the intergroup differences with competing risks regression and landmark analysis and identified recurrence happening 2 years after surgical resection as the principal contributor to the discrepancies in progression free survival. Such findings are in accord with our common sense that early recurrence after tumor resection is largely determined by the nature of primary HCC [4] and that NUCs are expected to exert tumor preventive effects via viral inhibition and amelioration of hepatitis or cirrhosis, other than direct antitumor response.

The advantage of TDF over ETV in tertiary prevention could possibly be traced back to their virological response in CHB treatment. It has been firmly established that TDF could induce complete viral suppression more efficiently than ETV in HBeAg-positive, NUC-naïve CHB patients [5] and that TDF could induce HBeAg seroconversion in more CHB patients than ETV [6]. The authors displayed that HBeAg positivity was comparable between TDF and ETV groups at baseline, and we wonder whether HBeAg as well as HBeAb positivity changed after postoperative NUC treatment. Other biomarkers, including Mac-2 binding protein glycosylation isomer, might help explain the mechanisms behind differed tertiary preventive effects of TDF and ETV as well [7].

Though ETV and TDF impose a high genetic barrier towards drug resistance, it should not be overlooked that hepatitis B virus might accumulate some mutations in reverse transcriptase and acquire resistance during the long-term treatment of CHB. Considering ETV is widely accepted as the first-line medication and the NUCs' experienced rate was significantly higher in ETV group than in TDF group, the undiscovered resistance might be more prevalent for ETV than for TDF. Such effect could be reflected by the interaction effects of NUCs' experience and types of NUCs, and we suggest the authors to explore the above interaction effects in Cox regression for recurrence and survival.

Whether TDF is more effective than ETV in secondary prevention for HCC in CHB population remains contro-

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versial [8]. The relatively low annual incidence of HCC in the CHB population makes it hard for single cohorts to compare the preventive capabilities of different NUCs, and proper comparison heavily relies on nationwide registration studies or meta-analysis [9]. One meta-analysis reported that the advantage of TDF over ETV in secondary prevention was statistically significant in cirrhotic patients but not in noncirrhotic patients [10], and elastographic reversion of cirrhosis was more frequent in TDF- and ETV-treated patients in a multicenter cohort [11]. The authors have covered some of these points in their discussion section and included cirrhosis in multivariable Cox regression, and we recommend performing cirrhosis-stratified regression on recurrence and survival to provide specific guidance for cirrhotic and noncirrhotic patients, respectively.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yongfa Huang drafted the manuscript, and Huayu Yang and Yilei Mao made critical revisions. All the authors have read and approved the final version of the manuscript, and all the authors fulfill the COPE (Committee on Publication Ethics) requirements for authorship.

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