

SUPPLEMENTARY METHODS

Study populations and variables

A retrospective cohort was established using nationwide claims registered from 2010 to 2019 in the National Health Insurance Service (NHIS) database of South Korea. A total of 178,937 patients with chronic hepatitis B (CHB) who began antiviral therapy between 2012 and 2014 with entecavir (ETV) or tenofovir disoproxil fumarate (TDF) were initially included from the NHIS database. The exclusion criteria were as follows: (i) combination treatment with both ETV and TDF, (ii) patients younger than 30 years or older than 80 years, (iii) nucleos(t)ide-analogue treatment for less than 72 days within the first 90 days, (iv) co-infection with hepatitis C virus, hepatitis D virus, or human immunodeficiency virus, (v) liver transplantation before the index date, (vi) history of prior antiviral treatment or any malignancy, (vii) detection of malignancy or death within the first 3 months after initiating antivirals, or (viii) change in antiviral regimen within the first 3 months. After applying exclusion criteria, the remaining 53,486 CHB patients constituted the final study cohort (24,287 treated with ETV; 29,199 treated with TDF).

For each subject, we collected the following data: age, sex, socioeconomic status, level of healthcare, coexisting medical conditions (diabetes mellitus, hypertension, cirrhosis, and presence of ascites or varices), Charlson Comorbidity Index (CCI), and type and cumulative defined daily dose (cDDD) of antivirals prescribed. The socioeconomic status of each patient was determined by inferring their income level from their health insurance expenditures. The cDDD was defined according to the Anatomic Therapeutic Chemical classification system and the Defined Daily Dose Index 2023.¹ The type and duration of antiviral therapy were determined using the claims prescription data. All variables were recorded at the time of cohort entry, except for CCI, which was estimated using data from 1 year before cohort entry.

Outcomes

The primary outcome was the development of any extrahepatic malignancy (EHM). EHMs were defined using the diagnosis code for non-liver cancers (ICD-10 codes: C00–C97 except C22 [hepatocellular carcinoma or intrahepatic cholangiocarcinoma]) and cancer-specific insurance claim codes (V193/194). In South Korea, patients with newly diagnosed malignancy should register with the V193/194 codes to receive financial assistance. Since the Korean government provides financial support to patients with both V193/194 and cancer-related ICD-10 codes after thorough clinicopathologic evaluations, the accuracy of cancer diagnosis is enhanced. Secondary outcomes were the overall intrahepatic malignancy and specific development of any of the 10 most prevalent EHMs in South Korea: stomach, colorectal, lung, thyroid, breast, prostate, pancreas, gallbladder and biliary tract, and kidney cancers, as well as non-Hodgkin lymphoma. Development of malignancies other than those under analysis, and death were treated as competing events in each analysis for secondary outcomes.

Sensitivity analyses

To confirm the robustness of our study findings, various sensitivity analyses were performed. To minimize detection bias, the frequency of hospital visits and surveillance were adjusted for in Models 1A and 1B, respectively. Different statistical approaches were applied including a cause-specific proportional hazard model (Model 2A) and inverse probability of treatment weighting (IPTW) to balance the two treatment groups (Model 2B). In Model 3, patients in the NHIS Health Check-Up Database sub-cohort were analyzed using their examination data. Additional analyses were performed in a group in which the window period was not considered (Model 4), as well as in the crude population without balancing (Model 5). In South Korea, TDF was approved in the late 2012; thus, patients who started antiviral treatment between 2013 and 2014 were analyzed separately (Model 6).

SUPPLEMENTARY RESULTS

Sensitivity analyses

The main results of the study were maintained during various sensitivity analyses (Table 3). TDF was associated with a lower risk of EHM after 3 years from the index date in the models adjusted for the frequency of hospital visits (subdistribution hazard ratio [SHR]=0.71, 95% confidence interval [CI]=0.61–0.82, $P<0.01$) and hepatocellular carcinoma surveillance (SHR=0.68, 95% CI=0.59–0.79, $P<0.01$). This finding was reproduced in the cause-specific analysis (SHR=0.69, 95% CI=0.60–0.81, $P<0.01$) and in the study population balanced using IPTW (SHR=0.70, 95% CI=0.61–0.81, $P<0.01$). The superiority of TDF compared to ETV was confirmed in the analysis of the NHIS Health Check-Up Database subcohort (SHR=0.68, 95% CI=0.57–0.83, $P<0.01$). Both the inclusion of events that occurred within 3 months from the index date (SHR=0.71, 95% CI=0.62–0.82, $P<0.01$) and the analysis of the crude population without balancing (SHR=0.70, 95% CI=0.61–0.81, $P<0.01$) did not change the results. Lastly, among patients who started antiviral treatment between 2013 and 2014, TDF was associated a lower risk of EHM than ETV after year 3 (SHR=0.69, 95% CI=0.53–0.90, $P<0.01$).

SUPPLEMENTARY DISCUSSION

Antivirals and the incidence of breast cancer

The incidence of breast cancer was higher in the TDF group within the first 3 years, whereas it was higher in the ETV group after 3 years. A previous study including transgender women showed that the antiviral effects of TDF against human immunodeficiency virus were significantly decreased in subjects who received feminizing hormone therapy with estradiol.^{2,3} This finding may be attributed to enhanced 5'-nucleotidase activity because of high estradiol levels, which in turn lead to reduced formation of the active metabolite of TDF.^{4,5} In this regard, women diagnosed with breast cancer (within 3 years) may have high baseline estradiol levels, which may reduce the antitumor effects of TDF, as well as predispose patients to estrogen-sensitive breast cancer. However, it should be noted that the effects of feminizing hormone therapy on the antiviral efficacy of TDF are still controversial.^{6,7}

SUPPLEMENTARY REFERENCES

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