Long-Term Renal Safety Between Patients With Chronic Hepatitis B Receiving Tenofovir vs. Entecavir Therapy: A Multicenter Study

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Abstract

Background

Renal safety is a critical issue in chronic hepatitis B (CHB) patients receiving long-term entecavir (ETV) or tenofovir disofuroxil fumarate (TDF) therapy. We investigated their effects on estimated glomerular filtration rate (eGFR).

Methods

Treatment-naïve CHB patients receiving ETV or TDF for ≥ 1 year were recruited. The eGFR was assessed using the Chronic Kidney Disease Epidemiology Collaboration equation. We calculated average annual percent change (AAPC) in eGFR using Joinpoint regression.

Results

At beginning of observation, ETV group had unfavorable conditions than TDF group: lower eGFR and higher FIB-4 and APRI than TDF group (all $P < 0.001$). After 6 years antiviral therapy, the mean eGFR in ETV group ($n = 1,793$) was maintained (96.0 at first year to 95.6 mL/min/1.73 m² at sixth year; AAPC -0.09%; $P = 0.322$), whereas that in TDF group ($n = 1,240$) significantly decreased annually (101.9 at first year to 96.9 mL/min/1.73 m² at sixth year; AAPC -0.88%; $P < 0.001$). Notably, in TDF group, even patients without diabetes (AAPC -0.80%; $P = 0.001$) or hypertension (AAPC -0.87%; $P = 0.001$) experienced significant decrease in eGFR. Expectably, accompanying diabetes (AAPC -1.59%; $p = 0.011$) or hypertension (AAPC -1.00%; $p = 0.002$) tended to accelerate eGFR decrease. TDF treatment (odds ratio 1.66, $P < 0.001$), along with eGFR < 60 mL/min/1.73 m², serum albumin < 3.5 mg/dL, and hypertension, were independently associated with ongoing renal dysfunction, defined as a negative slope of the mean eGFR change.

Conclusions

Compared to ETV, long-term TDF treatment induced slow, but progressive renal dysfunction. Although the annual eGFR change by TDF was small, careful monitoring is necessary, especially in patients requiring life-long therapy.

Introduction

Chronic hepatitis B virus (HBV) infection is a major public health problem affecting approximately 257 million people worldwide [1]. Patients with high serum HBV-DNA levels are more likely to develop liver cirrhosis, hepatic decompensation, and hepatocellular carcinoma (HCC) [2, 3]. Thus, suppression of HB-DNA through antiviral therapy (AVT) using oral nucleos[t]ide analogues (NUCs) has become the major

basis for treatment of HBV infection [4–8]. Currently, two prominent oral NUCs with high antiviral efficacy and minimal resistance, entecavir (ETV) and tenofovir disoproxil fumarate (TDF), are recommended in the initial treatment of CHB according to the clinical guidelines [4–6]. Since oral NUCs can effectively suppress HBV replication, but not eradicate intra-hepatic virus itself, their use should be life-long in most patients. Therefore, along with the issue of antiviral efficacy, the long-term safety of oral NUCs has become a concern.

Of their potential adverse effects, renal safety is the most important given that the medications are known to be excreted by renal filtration. Furthermore, chronic kidney disease is more often associated with patients with CHB than with non-CHB controls [9]. For instance, CHB patients with cirrhosis are more likely to develop renal insufficiency, including acute kidney injury or hepatorenal syndrome, due to reduced renal blood flow and hemodynamic disturbances [10]. Furthermore, renal tubular dysfunction and Fanconi syndrome have been associated with TDF therapy for a decade [11–13]. Subsequently, several studies have reported the comparative analyses of renal function between patients receiving ETV and TDF; however, these studies had small sample sizes [14, 15] and short follow-up periods [16, 17]. Moreover, in most previous studies, renal dysfunction was defined at a cross-sectional level, that is, only a decrease in the estimated glomerular filtration rate (eGFR) at one or two time points [13, 18].

In this multicenter study, we aimed to investigate the long-term effects of ETV and TDF on renal function in a large-scale study population by assessing the serial changes in renal function in the long-term.

Methods

Patients

Treatment-naïve CHB patients who received AVT with either daily 0.5 mg ETV (ETV group) or 300 mg TDF (TDF group) as the first-line regimen between 2007 and 2018 in the Division of Gastroenterology and Hepatology at three academic teaching hospitals in the Republic of Korea (Yonsei University Severance Hospital, Kyungpook National University Hospital, and Cha Bundang Medical Center), were screened for eligibility. The exclusion criteria were as follows: (1) age <19 years, (2) history of HCC at enrollment, (3) decompensated cirrhosis at enrollment, (4) AVT for less than 12 months, (5) co-infection with human immunodeficiency virus (HIV) or other hepatitis viruses, (6) history of organ transplantation, and (7) HCC occurrence within 6 months of enrollment (**Supplementary Figure 1**).

The reimbursement criteria for ETV and TDF in the Republic of Korea are identical (**Supplementary Table 1**). If histologic information was not available, cirrhosis was clinically defined according to the following criteria: (1) platelet count <150,000/μL and ultrasonographic findings suggestive of compensated cirrhosis, including a blunted, nodular liver surface accompanied by splenomegaly (>12 cm); or (2) clinical signs of portal hypertension, such as gastroesophageal varices.

The study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of each institute. Informed consent was waived because of the

retrospective nature of the study.

Clinical evaluation and follow-up

During follow-up, patients underwent routine laboratory tests, including serum creatinine and HBV-DNA levels as well as other viral markers that were monitored at 3–6-month intervals. Patients were screened for HCC and cirrhotic complications every 6 months using ultrasonography and serum alpha-fetoprotein levels [19-22].

Each patient's renal function was monitored every 3–6 months. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI): $eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$ [23]. Renal insufficiency was defined as an eGFR <60 mL/min, as calculated by the CKD-EPI equation.

Abbreviations / Units

eGFR (estimated glomerular filtration rate) = mL/min/1.73 m²

S_{Cr} (standardized serum creatinine) = mg/dL

κ = 0.7 (females) or 0.9 (males)

α = -0.329 (females) or -0.411 (males)

min = indicates the minimum of S_{Cr}/κ or 1

max = indicates the maximum of S_{Cr}/κ or 1

Statistical analysis

Data are presented as mean ± standard deviation, or number (%) as appropriate. Differences among continuous and categorical variables were compared using Student's *t*-test and chi-squared test, respectively. To evaluate the change in eGFR during the 6 years of observation, we used the Joinpoint regression method to calculate the average annual percent change (AAPC) in eGFR, odds ratio (ORs), and 95% confidence interval (CI). Logistic regression analysis was performed to investigate the predictors of ongoing renal dysfunction; ORs and 95% CIs were also calculated. Subsequently, a multivariate regression analysis was performed to assess the independent association between the univariate predictors and ongoing renal dysfunction.

All statistical analyses were conducted using SAS software (v9.4; SAS Institute, Cary, NC, USA) and R (v3.6.0, <http://cran.r-project.org/>). Two-sided p-values <0.05 were considered to indicate statistical significance.

Results

Baseline characteristics

A total of 3,033 patients with CHB who were treated with daily ETV (0.5 mg) or TDF (300 mg) as the first-line antiviral regimen for at least 1 year were analyzed. Table 1 describes the clinical characteristics of these patients at the first year of AVT. The mean age of the cohort was 48.8 years, and men were predominant (63.8%). Liver cirrhosis was noted in 852 (28.1%) patients, with mean APRI and FIB-4 scores of 0.63, and 2.38, respectively. The mean creatinine and eGFR calculated using the CKD-EPI equation were 0.9 mg/dL, and 92.8 mL/min/1.73 m², respectively.

Table 1
Clinical characteristics of patients at 1 year of AVT (n=3,033)

Variables	All	ETV (n=1,793)	TDF (n=1,240)	P value
Age (years)	48.8 ± 11.6	48.7 ± 11.4	48.9 ± 11.8	0.735
Male gender	1,936 (63.8)	1,134 (63.2)	802 (64.7)	0.442
Body mass index (kg/m ²)	23.7 ± 3.7	23.8 ± 4.3	23.6 ± 2.8	0.185
Diabetes mellitus	247 (8.1)	159 (8.9)	88 (7.1)	0.091
Hypertension	271 (8.9)	174 (9.7)	97 (7.8)	0.080
Liver cirrhosis	852 (28.1)	509 (28.4)	343 (27.7)	0.681
HBeAg positivity	1,501 (49.5)	891 (59.4)	610 (40.6)	0.796
HBV-DNA (log ₁₀ IU/ml)	5.8 ± 6.0	5.4 ± 5.9	5.9 ± 5.8	0.890
AST (IU/L)	30 ± 30	31 ± 36	29 ± 17	0.038
ALT (IU/L)	30 ± 24	29 ± 27	29 ± 17	0.394
Albumin (g/dL)	4.3 ± 0.5	4.3 ± 0.5	4.3 ± 0.5	0.647
Total bilirubin (g/dl)	0.9 ± 0.8	0.9 ± 0.9	0.8 ± 0.5	0.003
Gamma-glutamyl transpeptidase (IU/L)	77 ± 99	79 ± 100	66 ± 96	0.027
Platelet count (×10 ⁹ /L)	165 ± 79	160 ± 86	171 ± 69	<0.001
Prothrombin time (INR)	1.65 ± 0.79	1.0 ± 0.2	0.9 ± 0.2	0.320
Serum Na (mmol/L)	141 ± 3	140 ± 3	141 ± 3	0.322
Creatinine (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.8 ± 0.2	<0.001
eGFR by CKD-EPI equation (ml/min/1.73 m ²)	98.4 ± 20.9	96.0 ± 20.3	101.9 ± 21.3	<0.001
FIB-4 index	2.38 ± 2.28	2.57 ± 2.74	2.10 ± 1.80	<0.001
APRI score	0.63 ± 1.26	0.70 ± 1.38	0.54 ± 0.47	<0.001
Variables are expressed as mean ± standard deviation or no. (%).				
Abbreviations: AVT, antiviral therapy; ETV, entecavir; TDF, tenofovir disoproxil fumarate; HBeAg; hepatitis B e antigen; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation				

At the beginning of the observation period, patients in the ETV group (n=1,793) had significantly unfavorable conditions (higher aspartate aminotransferase level, serum creatinine level, FIB-4 score, and APRI score) than patients in the TDF group (n=1,240) (all $P < 0.05$) (Table 1). In particular, patients in the ETV group had lower eGFRs (mean, 96.0 vs. 101.9 mL/min/1.73 m², $P < 0.001$) than those in the TDF group.

Changes in renal function during AVT among the entire cohort

For the entire cohort (n=3,033), eGFR was measured annually for 6 years after the commencement of AVT (Figure 1). The mean eGFR reduced progressively with statistical significance during 444,673 person-years of follow-up; 98.9, 98.3, 98.0, 97.9, 97.2, and 96.2 mL/min/1.73 m² at 1, 2, 3, 4, 5, and 6 years, respectively. The AAPC in eGFR was -0.49% (95% CI; -0.61 to -0.37, $P < 0.001$), showing a trend of significant decrease in the mean eGFR during the 6 year-observation period.

Changes in renal function according to antiviral regimen

We computed the eGFR at each time point according to treatment with either ETV or TDF (Figure 2 and Table 2). During the 6-year observation period after the commencement of AVT, the mean eGFR was maintained in the ETV group at 96.0 mL/min/1.73 m² in the first year and 95.6 mL/min/1.73 m² in the sixth year ($P > 0.05$). In contrast, the mean eGFR significantly reduced in the TDF group from 101.9 mL/min/1.73 m² after the first of AVT to 96.9 mL/min/1.73 m² after 6 years ($P < 0.001$). In the ETV group, the mean eGFR was similarly maintained with an AAPC in eGFR of -0.09% (95% CI, -0.25 to -0.08; $P = 0.322$). In contrast, among the TDF group, the mean eGFR decreased significantly every year with an AAPC of -0.88% (95% CI, -1.05 to -0.71; $P < 0.001$).

Table 2
Changes in eGFR in chronic hepatitis B patients treated with ETV or TDF (n=3,033)

Antiviral regimen	Time after starting AVT	eGFR (ml/min/1.73 m ²)	95% CI
ETV (n=1,793)	1 year	96.0 ± 20.3	(94.8, 97.2)
	2 years	96.3 ± 19.9	(95.1-97.5)
	3 years	96.7 ± 20.9	(95.5-97.9)
	4 years	96.5 ± 19.9	(95.3-97.7)
	5 years	96.1 ± 19.9	(94.9-97.3)
	6 years	95.6 ± 19.7	(94.3-96.8)
TDF (n=1,240)	1 year	101.9 ± 21.3	(99.3-104.4)
	2 years	100.3 ± 21.7	(97.6-102.9)
	3 years	99.4 ± 22.0	(96.7-102.1)
	4 years	99.4 ± 21.5	(96.8-102.0)
	5 years	98.3 ± 21.0	(95.6-100.9)
	6 years	96.9 ± 19.1	(94.2-99.6)
Variables are expressed as mean ± standard deviation.			
Abbreviations: eGFR, estimated glomerular filtration rate; ETV, entecavir; TDF, tenofovir disoproxil fumarate; CI, confidence interval			

Changes in renal function according to comorbidities

In the ETV group, there was no decrease in the eGFR of patients without diabetes mellitus (AAPC of eGFR, -0.01%; 95% CI, -0.23 to 0.22; $P=0.959$) or hypertension (AAPC of eGFR, 0.01%; 95% CI, -0.19, 0.21; $P=0.901$). However, when diabetes mellitus or hypertension was present, a significant decrease in eGFR was observed; AAPC in eGFR was -0.84% (95% CI, -0.98 to -0.70; $P<0.001$) in patients with diabetes, and -1.01% (95% CI, -1.38 to -0.63; $P=0.01$) in those with hypertension.

In contrast, among the TDF group, there was a significant decrease in eGFR even in patients without diabetes mellitus or hypertension, with an AAPC of -0.80% (95% CI -0.99 to -0.62; $P=0.002$), and 0.87% (95% CI -1.07 to -0.67; $P=0.001$), respectively. If either diabetes or hypertension was present, the decline in eGFR showed a trend toward more accelerated patterns; an AAPC of -1.59% (95% CI, -2.29 to -0.89; $P=0.011$) and -1.00% (95% CI, -1.29 to -0.70; $P=0.002$) in patients with diabetes and hypertension, respectively.

Predictors of ongoing renal dysfunction

During the 6-year observation period after the commencement of AVT, a total of 681 (22.4%) patients developed ongoing renal dysfunction, which was defined as a negative slope of the mean change in eGFR during AVT. **Table 3** shows the comparison of the characteristics of patients with and without ongoing renal dysfunction. The group with ongoing renal dysfunction had older patients, a higher proportion of those with diabetes mellitus, hypertension, and liver cirrhosis, who received treatment with TDF (all $p < 0.05$), and had lower serum albumin and eGFR at 1 year of AVT, compared to those without.

Table 3. Comparison of patients with and without ongoing renal dysfunction

Variables	Preserved renal function (n=2,352)	Ongoing renal dysfunction (n=681)	P-value
Age (years)	47.2 ± 10.9	48.7 ± 11.2	0.019
Male gender	1,505 (64.0)	456 (37.0)	0.312
Body mass index (kg/m ²)	23.7 ± 3.1	23.6 ± 2.7	0.693
Diabetes mellitus	186 (7.9)	81(11.9)	0.030
Hypertension	186 (7.9)	88 (12.9)	0.007
Liver cirrhosis	611 (26.0)	219 (32.2)	0.026
HBeAg positivity	1,220 (51.9)	317 (46.5)	0.082
HBV- DNA (log ₁₀ IU/ml)	5.2 ± 6.7	5.1 ± 4.2	0.890
AST (IU/L)	30 ± 24	30 ± 18	0.866
ALT (IU/L)	32 ± 40	30 ± 23	0.566
Serum albumin (g/dL)	4.4 ± 0.4	4.3 ± 0.4	<0.001
Total bilirubin (g/dl)	0.9 ± 0.4	0.8 ± 0.7	0.060
Gamma-glutamyl transpeptidase (IU/L)	79 ± 95	77 ± 90	0.320
Platelet count (×10 ⁹ /L)	166 ± 75	165 ± 70	0.741
Prothrombin time (INR)	1.0 ± 0.2	0.9 ± 0.2	0.017
Serum Na (mmol/L)	140 ± 3	141 ± 3	0.411
Creatinine (mg/dL)	0.9 ± 0.2	0.8 ± 0.2	<0.001
eGFR by CKD-EPI (ml/min/1.73 m ²)	100.0 ± 18.9	92.6 ±17.5	<0.001
TDF (vs. ETV)	2,116 (9.1)	154 (22.6)	<0.001

Variables are expressed as mean ± standard deviation or no. (%).

Abbreviations: HBeAg; hepatitis B e antigen; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration equation; TDF, tenofovir disoproxil fumarate; ETV, entecavir

On univariate analysis, significant factors associated with ongoing renal dysfunction were age >60 years (OR 1.557, 95% CI 1.169-2.075; p=0.002), hypertension (OR 2.667, 95% CI 1.931-3.684; p<0.001), diabetes mellitus (OR 1.861, 95% CI 1.292-2.681; p<0.001), eGFR < 60mL/min/1.73 m² at 1 year of AVT (OR 1.963,

95% CI 1.285-2.996; $p=0.002$), serum albumin <3.5 mg/dL at 1 year of AVT (OR 2.128, 95% CI 1.453-3.117; $p<0.001$), and treatment with TDF (OR 1.572, 95% CI 1.242-1.989; $p<0.001$). Subsequently, these univariate predictors were entered into the multivariate logistic regression model, showing that treatment with TDF (adjusted OR [aOR], 1.656; 95% CI 1.303–2.107; $P<0.001$; Table 4) proved to be an independent risk factor, along with hypertension (aOR 2.356, 95% CI 1.664-3.334; $P<0.001$), eGFR <60 mL/min/1.73 m² at 1 year of AVT (aOR 1.823, 95% CI 1.179-2.821; $P=0.001$), and serum albumin at 1 year of AVT (aOR 2.023, 95% CI 1.370-2.988; $P<0.001$).

Table 4. Risk factors of ongoing renal dysfunction

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	<i>P</i> value	Adjusted OR (95% CI)	<i>P</i> value
Male	1.140 (0.896-1.450)	0.285		
Age > 60 years	1.557 (1.169-2.075)	0.002	1.249 (0.925-1.688)	0.147
Hypertension	2.667 (1.931-3.684)	<0.001	2.356 (1.664-3.334)	<0.001
Diabetes mellitus	1.861 (1.292-2.681)	0.001	1.387 (0.934-2.059)	0.105
Liver cirrhosis	1.286 (0.999-1.654)	0.051		
eGFR <60 mL/min/1.73m ² at 1 year of AVT	1.963 (1.285-2.996)	0.002	1.823 (1.179-2.821)	0.007
Albumin <3.5 mg/dL at 1 year of AVT	2.128 (1.453-3.117)	<0.001	2.023 (1.370-2.988)	<0.001
TDF (vs. ETV)	1.572 (1.242-1.989)	<0.001	1.656 (1.303-2.107)	<0.001

Abbreviations: , OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; AVT, antiviral therapy; TDF, tenofovir disoproxil fumarate; ETV, entecavir

Discussion

The most recent guidelines from the European Association for the Study of the Liver (EASL) recommend ETV or tenofovir alafenamide (TAF) over ETV in CHB patients with renal insufficiency or its risk factors [4]. Although there have been several studies reporting no difference in renal function between patients treated with TDF and those treated with ETV during a relatively short observation period [14, 15, 24, 25], TDF has the inherent potential to be nephrotoxic. Because TDF accumulates in the proximal tubule during its excretion through the kidney, it causes nephrotoxicity through direct proximal tubular cell and

mitochondrial damage [26, 27]. In this study, we confirmed that eGFR significantly decreased in the TDF group (AAPC -0.88%, $P < 0.001$) during the 6-year observation period after the commencement of AVT, in contrast to the ETV group wherein the eGFR was maintained (AAPC -0.09%, $P = 0.322$).

Our findings have several strengths. First, we provide robust evidence to support the above EASL guidelines based on real-world data, emphasizing that special attention needs to be paid to serial changes in renal function, especially in the group receiving TDF, given that AVT treatment is usually life-long [16, 17, 28, 29]. Second, compared to previous studies, our study has the advantage of a longer follow-up duration (up to 6 years) and a larger sample size ($n = 3,033$) from three independent academic teaching hospitals in a real-world setting. Furthermore, from a statistical perspective, we focused on annual changes in the eGFR. In fact, in most previous studies, the occurrence of CKD or eGFR reduction by $\geq 20\%$ was adopted as the major study endpoint [16, 24, 30]. However, given that the annual decline in eGFR among the TDF group, although progressive, was not so rapid, the actual number of events fulfilling the occurrence of overt CKD, i.e. $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ or eGFR reduction by $\geq 20\%$ was very small (3.7–6.8% in other studies; 3.7% in our study) [16, 24, 30]. In such circumstances, there may be a statistically significant concern leading to the false negativity of the type II error. For this reason, we focused on the AAPC in eGFR during the long-term AVT, using Joinpoint regression and adopted a negative slope of the mean change in eGFR during the AVT ($n = 681$, 22.4%) as the major clinical endpoint in the logistic regression. To the best of our knowledge, this study is the first to assess AAPC in eGFR during long-term AVT in patients with CHB.

Notably, in contrast to the ETV group, even patients without diabetes mellitus or hypertension in the TDF group showed significantly decreased eGFR, with AAPCs of -0.80% and -0.87%, respectively. As expected, when diabetes mellitus or hypertension was present in the TDF group, the decline in eGFR showed a trend toward more accelerated patterns: an AAPC of -1.59% and -1.00%, respectively. Physicians should monitor patients' renal function more closely, considering that therapy with TDF is almost life-long. Although patients in the ETV group with diabetes mellitus or hypertension may also experience a significant decline in eGFR, this may be due to the natural history of the accompanying comorbidities rather than an ETV-related adverse event. Nevertheless, given that patients with CHB are aging, and their comorbidities (e.g., diabetes, hypertension, and chronic kidney disease) are also increasing [9, 31], the early recognition of individual risk factors and correspondingly careful monitoring are also required.

The TDF-induced eGFR decrease observed in this study occurred consistently every year after the first year of AVT. There are conflicting opinions regarding whether the renal impairment induced by TDF is prominent early since the beginning of AVT [32] or progressive after several years of AVT [13]. Therefore, further research is needed to investigate the timing of the development of TDF-induced renal toxicity, its degree, and annual progress rate. Specifically, a long-term study of up to 10 years or longer is needed to determine whether the eGFR will continue to drop or there will be a quiescent period. This would provide an important clinical insight into whether TDF should be sustained or replaced with safer oral NUCs that is, ETV or TAF at a certain time point.

An eGFR <60 mL/min/1.73 m² and a low albumin level at 1 year of AVT as well as hypertension were independent predictors of ongoing renal dysfunction in our study. Diabetes mellitus was a significant univariate predictor, but did not prove to be independently associated with ongoing renal dysfunction in the multivariate analysis; this is different from the general hypothesis that diabetes mellitus is a well-known risk factor for progression to CKD. This is most likely due to the multi-collinearity of diabetes with hypertension. Indeed, patients with diabetes mellitus were more likely to have hypertension than those without (31.6% vs. 6.9%; OR, 6.20; 95% CI, 4.57-8.42; *P*<0.001). Consistent with the findings of previous studies, baseline eGFR <60 mL/min/1.73 m² was a poor prognostic factor in our study [24, 32], indicating that more caution is required in such a population during follow-up. In addition, albumin synthesis decreases as a result of liver dysfunction in patients with chronic liver disease, and may lead to decreased effective intravascular blood volume, compensatory activation of the renin-angiotensin system and sympathetic nervous system, sodium and water retention, and finally, reduction in renal perfusion and eGFR [33, 34].

This study has several limitations. First, the retrospective design may have led to an inherent selection bias, which we tried to overcome by recruiting a homogeneous study population with a statistically reliable large sample size and event number, providing a longer follow-up duration, gathering data from multiple centers (three independent teaching hospital)s, and applying optimized statistical approaches. However, additional studies are required to validate this hypothesis. Finally, the analyses of new biomarkers for CHB (e.g., serum quantitative hepatitis B surface antigen, serum hepatitis B core-related antigen, serum HBV-RNA, or specific HBV mutants), and for renal insufficiency (i.e., cystatin C, β 2-microglobulin, or neutrophil gelatinase-associated lipocalin) may provide more precise predictions in the future [13, 35].

In conclusion, compared to the ETV group, the TDF group experienced slow, but progressive renal dysfunction. Although the annual eGFR change was small in the TDF group, careful monitoring of renal function is necessary to allow timely intervention, especially in patients requiring life-long AVT.

Abbreviations

CHB, chronic hepatitis B; AVT, antiviral therapy; ETV, entecavir; TDF, tenofovir disoproxil fumarate; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; NUC, nucleos[t]ide analogue; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; AST, aspartate aminotransferase; ALT, aspartate aminotransferase; UNL, upper normal limit; OR, odds ratio; CI, confidence interval; EASL, the European Association for the Study of the Liver; TAF, tenofovir alafenamide.

Declarations

Data availability: Available on request to corresponding author.

Animal Research (Ethics): Not applicable.

Consent to participant (Ethics): Informed consent was waived because of the retrospective nature of the study.

Consent to Publish (Ethics): Yes

Reproducibility: Yes

Clinical Trials Registration: IRB 2020-06-035

Author contributions

Conception: Beom Kyung Kim and Soo Young Park; study design: Soo Young Park, Young Eun Chon and Beom Kyung Kim; participation in patient management and data collection: Seung Up Kim, Young Eun Chon, Soo Young Park, Jae Seung Lee, Hye Won Lee, Mi Na Kim, Jun Yong Park, Do Young Kim, Sang Hoon Ahn, and Beom Kyung Kim; contribution to the data acquisition, responsibility for writing the paper, and statistical analysis: Han Pyo Hong, Young Eun Chon, Beom Kyung Kim, and Soo Young Park.

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Figures

Figure 1

Changes in estimated glomerular filtration rate (eGFR) during long-term antiviral therapy (AVT) among the entire population

Figure 2

Changes in estimated glomerular filtration rate (eGFR) according to treatment with either entecavir (ETV) or tenofovir disoproxil fumarate (TDF)

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