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Efficacy and safety of tenofovir disoproxil fumarate in Chinese patients with chronic hepatitis B virus infection

A 2-year prospective study

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Abstract

To date, a small number of studies concerning the effects and safety of tenofovir disoproxil fumarate (TDF) in Chinese individuals were conducted. In this study, we aimed to assess the antiviral effects and nephrotoxicity of TDF in Chinese patients with chronic hepatitis B virus (HBV) infection.

Patients with chronic HBV infection were prospectively recruited and TDF treatment was given for 96 weeks. HBV serologic markers, HBV DNA, creatinine and phosphorus were collected.

Fifty-seven treatment-naïve and 48 treatment-experienced patients were recruited. Irrespective of the prior treatment history, more than 95% of patients achieved virological response during 96 weeks treatment with TDF. Estimated glomerular filtration rate (eGFR) significantly declined in the first year of treatment in patients with chronic hepatitis B or younger age (<65 years old) (both $P < .05$), while that was not achieved in patients with liver cirrhosis or older age (≥65 years old) (both $P > .05$). For patients who were treatment-naïve or treated previously with adefovir dipivoxil, eGFR declined at the 48th week; however, eGFR was partially recovered at the 96th week. Furthermore, multivariable analysis showed that basal eGFR <90 mL/min/1.73 m^2 ($P = .001$; odds ratio: 4.821; 95% confidence interval: 1.904–12.206) is the only independent risk factor for eGFR <90 mL/min/1.73 m^2 at the 96th week.

TDF has potent antiviral effect in both treatment-naïve and treatment-experienced patients.

Abbreviations: ADV = adefovir dipivoxil, ALT = alanine transaminase, eGFR = estimated glomerular filtration rate, ETV = entecavir, HBeAg = hepatitis B e antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LAM = lamivudine, LC = liver cirrhosis, LDT = telbivudine, NA = nucleot(s)ide, TDF = tenofovir disoproxil fumarate.

Keywords: drug resistance, hepatitis B virus, real-world, tenofovir

1. Introduction

According to the statistics, more than 240 million individuals have been chronically infected with hepatitis B virus (HBV) worldwide, and those are at high risk of developing liver cirrhosis (LC) or hepatocellular carcinoma (HCC).[1] HBV resistance to nucleos(t)ide analogs (NAs), resulting from the wide use of lamivudine (LAM) and adefovir dipivoxil (ADV) in the last decade, has become a health problem in China.[2,3]

Tenofovir disoproxil fumarate (TDF), possessing potent and sustainable antiviral efficacy, has been reported to be efficacious and safe for patients with multidrug-resistant HBV infection as a rescue therapy.[4,5,6] Long-term TDF therapy may lead to regression of liver fibrosis, and also reduce the risk of HCC in patients with and without LC.[7,8] Due to the potent effect and high barrier to resistance, TDF is recommended to treatment-naïve and treatment-experienced patients.[9]

However, nephrotoxicity of TDF remains a controversial concern. A study showed that estimated glomerular filtration rate (eGFR) did not remarkably change during 3 years TDF treatment irrespective of prior treatment history.[10] Trinh et al reported that TDF was not associated with higher risk of renal dysfunction among patients with normal baseline eGFR, while renal function deteriorated significantly in patients with baseline renal impairment.[11] Nevertheless, 2 recent studies showed that patients receiving TDF treatment-experienced higher rate of eGFR loss compared with those receiving entecavir (ETV),[12] and TDF could be an independent risk factor associated with renal dysfunction.[13] Regarding wide-spread use of TDF in patients with prior ADV therapy,

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nephrotoxicity of TDF should be monitored during long-term follow-up.

To date, a limited number of real-world studies concerning the effects and safety of TDF in Chinese patients were conducted.[14,15] In the present study, we aimed to evaluate the antiviral effects and nephrotoxicity of TDF in Chinese patients with chronic HBV infection.

2. Methods

2.1. Study population and data collection

Patients with chronic HBV infection (non-LC and LC), who initiated the first prescription of TDF between January 2016 and May 2017, were prospectively recruited. Non-LC was defined as chronic necroinflammatory liver disease caused by HBV infection, without LC.[16] LC was defined based on the ultrasound or histopathological test.[17] Patients with immunodeficiency diseases, autoimmune diseases, co-infection with other hepatitis viruses, alcoholic liver disease or cancer, were excluded. Treatment-experienced patients were defined as patients with NA monotherapy or combination therapy for at least 1 year (Table 1), and were directly switched to TDF due to persistent viremia. Demographic and laboratory data, including age, sex, alanine transaminase (ALT), aspartate aminotransferase, total bilirubin, albumin, cholesterol, glucose, creatinine, phosphorus, HBV serologic markers, HBV DNA, were collected at baseline, 4th, 24th, 48th, and 96th weeks.

The study was approved by the Ethics Committee of our Hospital, and the written informed consents were obtained from all the patients as well.

2.2. Virologic response (VR), HBV serological response and renal toxicity

The efficacy endpoints included the VR and hepatitis B e antigen (HBeAg)/anti-HBe seroconversion at 96th week. The VR was defined as achieving an undetectable serum HBV DNA level (lower limit of detection, 20 IU/mL; Cobas Taqman HBV test Roche AG, Basel, Switzerland). HBeAg/anti-HBe seroconversion was defined as undetectable HBeAg combined with positive anti-HBe (Murex Abbott, Chicago, IL). The secondary endpoint was nephrotoxicity, which was defined as a confirmed elevation in serum creatinine of 0.5 mg/dL, or a decline in eGFR of ≥25% from baseline during TDF treatment.[18] In addition, eGFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration equation.[13]

2.3. Statistical analysis

All data were analyzed by using SPSS 17.0 software (SPSS Inc, Chicago, IL). Continuous variables were presented as mean ± standard deviation, and were compared using student *t* test or 1-way analysis of variance test followed by post hoc least significant difference test. Categorical variables were expressed as frequencies, and analyzed by the Chi-square test. Independent predictors for eGFR ≤ 90 mL/min/m^2 were analyzed using univariate and multivariate logistic regression analyses. A 2-sided *P*-value $< .05$ was considered statistically significant.

3. Results

3.1. Baseline characteristics of patients

A total of 116 patents including 71 HBeAg positive and 45 HBeAg negative patients, were recruited. Of these, 11 patients

Table 1

Characteristics of patients at baseline.

Variables	CHB (n = 72)	LC (n = 33)	*t* or χ^2-value	*P*-value
Age, yr	38.22 ± 10.99	53.18 ± 10.52	−6.560	<.001
Male, n (%)	53 (73.61%)	28 (84.85%)	1.621	.316
ALT, U/L	182.74 ± 219.95	93.24 ± 211.77	1.958	.053
Creatinine, μmol/L	78.00 ± 15.90	80.35 ± 17.03	−0.0686	.494
eGFR (mL/min/1.73 m^2)	101.96 ± 17.67	93.62 ± 18.11	2.224	.028
Serum phosphorus	1.07 ± 0.25	0.98 ± 0.19	1.828	.071
eGFR categories, n (%)				
<60	0 (0%)	1 (3.03%)	2.203	.314
60–89	22 (30.56%)	12 (36.36%)	0.349	.654
>89	50 (69.44%)	20 (60.61%)	0.795	.382
HBeAg (+), n (%)	53 (73.61%)	13 (39.39%)	11.348	.001
HBV DNA, Log_{10}IU/mL	5.85 ± 2.05	3.79 ± 1.76	4.991	<.001
Prior treatment regimen, n (%)				
Treatment-naïve	47 (65.28%)	10 (30.30)	11.154	.001
LAM	3 (4.17%)	5 (15.15%)	3.879	.105
ADV	3 (4.17%)	3 (9.09%)	1.018	.376
LDT	2 (2.78%)	0 (0%)	0.934	.468
ETV	9 (12.50%)	2 (6.06%)	1.000	.496
LAM + ADV	2 (2.78%)	2 (6.06%)	0.666	.588
LDT + ADV	0 (0%)	1 (3.03%)	2.203	.314
ETV + ADV	6 (8.33%)	10 (30.30%)	8.456	.007
Hypertension	3 (4.17%)	3 (9.09%)	1.018	.376
Diabetes mellitus	1 (1.39%)	4 (12.12%)	5.747	.033

Comparison was conducted by a Student *t* test method (means ± standard deviation) for continuous variables, and Chi-square test for categorical values.

ADV = adefovir dipivoxil, ALT = alanine aminotransferase, eGFR = estimated glomerular filtration rate, ETV = entecavir, GPR = gamma-glutamyl transpeptidase-to-platelet ratio, HBeAg = hepatitis B e antigen, LAM = lamivudine, LDT = telbivudine, NA = nucleot (s)ide.

were lost to follow-up in the first year, and were; therefore, excluded from the analysis. Until the last follow-up visit on November 16, 2018, 57 treatment-naïve and 48 treatment-experienced patients had taken TDF monotherapy at least for 96 weeks. Seventy-two patients were diagnosed with non-LC, and the rest with LC.

The baseline characteristics of patients are shown in Table 1. The available data can be downloaded from Supplementary Materials, http://links.lww.com/MD/D296. Positive HBeAg was more common ($\chi^2=11.348$, $P=.001$) and HBV DNA levels ($t=0.991$, $P<.001$) were higher in the non-LC group than those in LC group. More patients in the non-LC group were treatment-naïve compared with those in the LC group ($\chi^2=11.154$, $P=.001$), and more patients had previously received ADV therapy in the LC group ($\chi^2=15.195$, $P<.001$). For the comorbidities, the proportions of patients with hypertension were compared between non-LC and LC groups ($\chi^2=1.018$, $P=.376$), while more patients were diagnosed with diabetes in the LC group ($\chi^2=5.747$, $P=.033$).

Moreover, eGFR at baseline was significantly lower in patients with LC than that in patients with non-LC ($t=2.224$, $P=.028$). No significant difference was found in baseline creatinine and serum phosphorus between the 2 groups ($t=-0.686$ and 1.828, $P=.494$ and .071, respectively).

There was no significant difference in baseline creatinine, eGFR, and phosphorus between patients with prior ADV therapy and treatment-naïve patients ($t=-1.073$, 1.674 and 0.950, $P=.286$, .097, and .344, respectively). Besides, 5 patients with diabetes and 6 patients with hypertension had no significant difference in baseline creatinine, eGFR, and phosphorus compared with patients without comorbidities. Baseline eGFR of older patients (age ≥65 years old) was lower than that of younger patients (age <65 years old) ($t=-2.118$, $P=.037$), while there was no significant difference in baseline creatinine and phosphorus between these 2 groups ($t=1.480$ and 0.799, $P=.142$ and .426, respectively).

3.2. Virologic, biochemical, and serologic responses

As shown in Figure 1A, patients who achieved VR were comparable between non-LC and LC groups at the 48th and 96th weeks ($\chi^2=0.011$ and 1.779, $P=.616$ and .232, respectively). Irrespective of the treatment-experienced history, >95% of patients achieved VR by 96 weeks (Fig. 1B). One treatment-naïve patient with high HBV DNA levels (8.33 lg IU/mL) at baseline, had detectable HBV DNA levels (252 IU/mL) at the 96th week. Moreover, 1 patient with telbivudine-resistance history and 1 patient with ETV-resistance history had persistent low levels of HBV DNA (549 IU/mL and 145 IU/mL, respectively) combined with normal ALT.

Of the 66 patients who were HBeAg positive at baseline, 14 (21.21%) patients lost HBeAg, and 2 (3.03%) patients achieved HBeAg/anti-HBe seroconversion at the 96th week of TDF treatment. In addition, 1 patient in HBeAg(+) non-LC group achieved HBeAg/anti-HBe seroconversion at the 48th week and lost HBsAg at the 96th week.

At the 96th week of TDF treatment, only 3 patients had ALT elevation. Among them, 2 patients suffered from non-alcoholic fatty liver disease, and another patient developed HCC during TDF treatment, and received transcatheter arterial chemo-embolization therapy. Moreover, the HBV DNA level was undetectable in the 3 patients.

3.3. Nephrotoxicity of TDF in patients with LC

Although basal eGFR in patients with LC was lower than that in patients with non-LC, no significant difference was found in creatinine, eGFR, and phosphorus at the 48th or 96th week between the 2 groups. Data obtained from this study showed that eGFR declined significantly in the first year of treatment in patients with non-LC ($P<.001$), while that was not observed in the patients with LC ($P=.311$). However, no patient had an eGFR lower than 60 mL/min/1.73 m^2 or discontinued due to an adverse side-effect. Unexpectedly, eGFR was partially recovered at the 96th week for both groups (Fig. 2).

3.4. Nephrotoxicity of TDF in older patients (≥65 years old)

In 87 younger patients (age <65 years old), there was a significant decline in eGFR at the 48th and 96th weeks, while the serum creatinine declined ($P=.009$), and eGFR significantly increased ($P=.028$) at the 96th week compared with those at 48th week

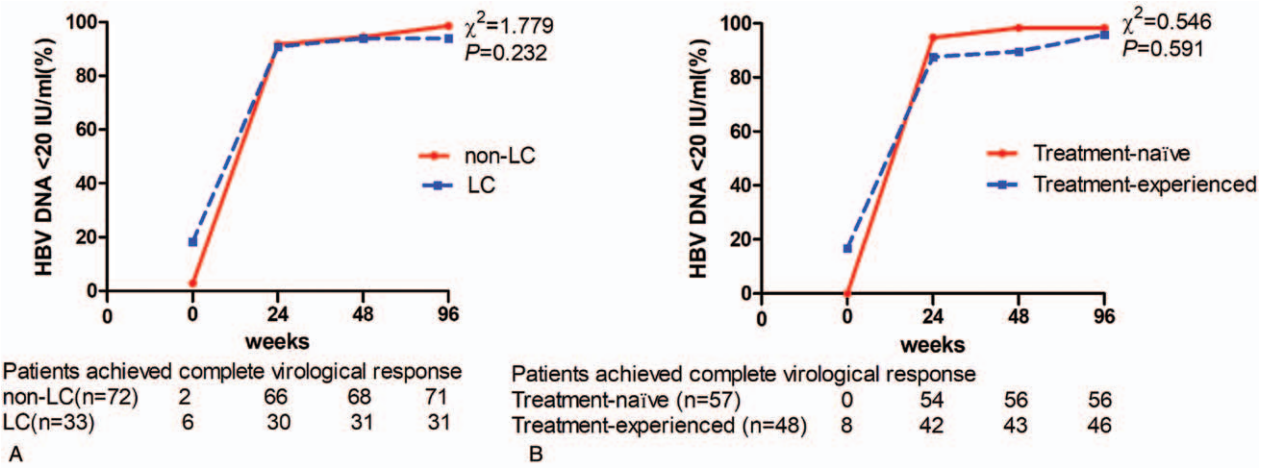

Figure 1. Virologic responses in patients with non-LC and LC (A), treatment-naïve and treatment-experienced history (B). LC = liver cirrhosis, NA = nucleot(s)ide.

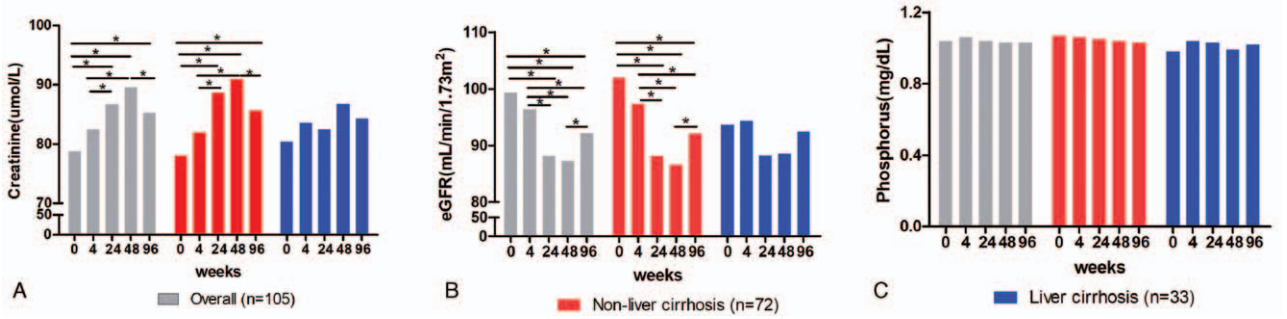

Figure 2. Dynamic changes of creatinine, eGFR, and phosphorus in patients with chronic hepatitis B and liver cirrhosis, $^{*}P < .05$. eGFR = estimated glomerular filtration rate.

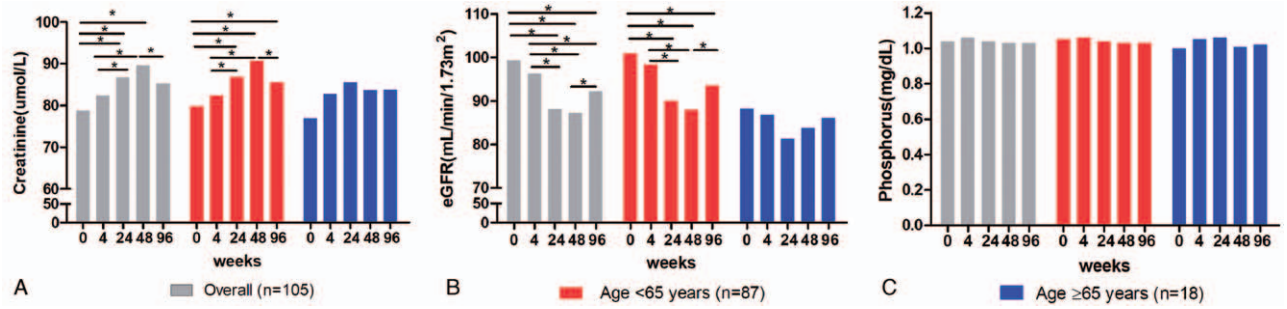

Figure 3. Dynamic changes of creatinine, eGFR, and phosphorus in patients <65 and ≥65 years old, $^{*}P < .05$. eGFR = estimated glomerular filtration rate.

(Fig. 3). Apart from patients who were <65 years old, 18 older patients (age ≥65 years old) had no significant changes in serum creatinine, phosphorus, as well as eGFR during 96 weeks of follow-up (all $P > .05$).

3.5. Nephrotoxicity of TDF in patients with prior ADV therapy

In 27 patients with prior ADV therapy, serum creatinine increased ($P = .039$), while eGFR declined ($P = .033$) at the 48th week (Fig. 4). Then, the serum creatinine declined and eGFR increased at the 96th week, and there was no significant difference in creatinine and eGFR between 96th week and baseline ($P = .215$ and .319, respectively). Similar to patients with prior ADV therapy, creatinine in 78 patients without prior ADV therapy significantly increased and eGFR decreased at the 48th week compared with baseline (both $P < .001$). Although creatinine declined ($P = .055$) and eGFR increased ($P = .082$) at the 96th week from 48th week, the creatinine level was higher and eGFR level was lower at 96th week compared with baseline ($P = .006$ and .005, respectively).

3.6. Nephrotoxicity of TDF in patients with diabetes and hypertension

In the 5 patients with diabetes and 6 patients with hypertension, no significant difference was found in creatinine, eGFR or phosphorus during the 96 weeks of follow-up.

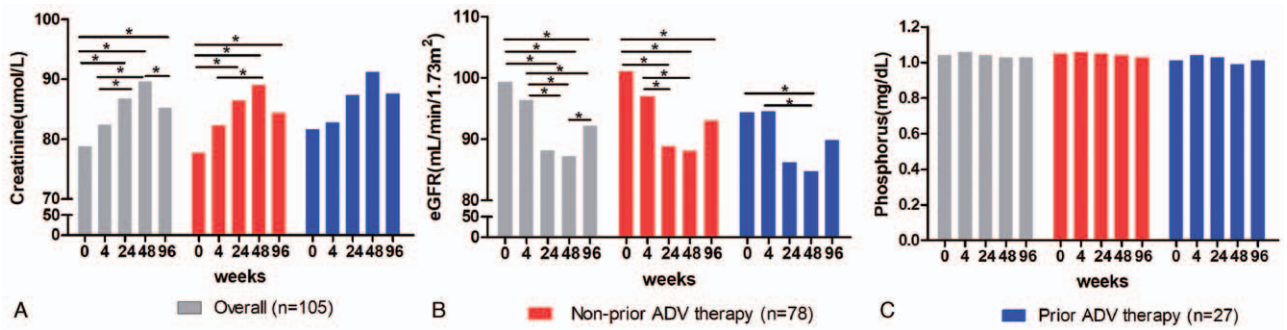

Figure 4. Dynamic changes of creatinine, eGFR, and phosphorus in treatment-naïve patients and patients with prior ADV therapy, $^{*}P < .05$. ADV = adefovir dipivoxil, eGFR = estimated glomerular filtration rate.

Table 2

Risk factors for eGFR < 90 mL/min/1.73 m^2 at the 96th wk.

	Univariate			Multivariate		
Baseline variables	**Odds ratio**	**95% CI**	***P***	**Odds ratio**	**95% CI**	***P***
Age >65 yr old	1.213	0.291–5.058	.791			
Gender	1.336	0.458–3.896	.596			
Liver cirrhosis	1.230	0.397–3.814	.719			
Hypertension	0.335	0.036–3.113	.336			
Diabetes	6.393	0.398–12.717	.190			
Prior ADV therapy	0.719	0.237–2.180	.560			
ALT	0.998	0.993–1.002	.328			
AST	1.002	0.995–1.010	.541			
TBIL	1.035	0.998–1.074	.063			
Albumin	1.036	0.953–1.126	.411			
Cholesterol	1.001	0.994–1.008	.772			
Glucose	1.195	0.660–2.166	.556			
Basal eGFR <90mL/min/1.73 m^2	4.313	1.561–11.914	.005	4.821	1.904–12.206	.001

ADV = adefovir dipivoxil, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = 95% confidence interval, GFR = estimated glomerular filtration rate, TBIL = total bilirubin.

3.7. Risk factors for eGFR <90 mL/min/1.73 m^2 at the 96th week

Among the 105 patients, 32 patients had a basal eGFR <90 mL/min/1.73 m^2. In the 32 patients with a basal eGFR <90 mL/min/1.73 m^2, there were no significant changes in serum creatinine, phosphorus, as well as eGFR during 96 weeks of follow-up (all $P > .05$). In 73 patients with a basal eGFR >90 mL/min/1.73 m^2, there was a significant decline in eGFR at the 48th week ($P < .001$). The eGFR at the 96th week did not increase significantly from 48th week ($P = .105$), and was lower compared with baseline ($P < .001$).

Fifty-two patients had eGFR <90 mL/min/1.73 m^2 at the 96th week, and 7 patients had a decline in eGFR of ≥25% from baseline. Then, we analyzed the risk factors for eGFR <90 mL/min/1.73 m^2 at the 96th week. As presented in Table 2, univariate logistic analysis showed that total bilirubin ($P = .063$) and basal eGFR <90 mL/min/1.73 m^2 ($P = .005$) were associated with eGFR <90 mL/min/1.73 m^2 at the 96th week. Furthermore, multivariable analysis showed that basal eGFR <90 mL/min/1.73 m^2 ($P = .001$; odds ratio: 4.821; 95% confidence interval: 1.904–12.206) was the only independent risk factor for eGFR <90 mL/min/1.73 m^2 at the 96th week.

4. Discussion

In the present study, we prospectively evaluated the efficacy and safety of TDF in Chinese patients with chronic HBV infection. The data suggested that efficacy of TDF was favorable in both treatment-naïve and treatment-experienced patients. Renal function declined in the first year, while it was partially recovered at the 96th week without TDF withdrawal. In addition, basal eGFR <90 mL/min/1.73 m^2 is the only independent risk factor for eGFR <90 mL/min/1.73 m^2 at the 96th week.

Consistent with Patterson et al's studies, TDF had potent effect in patients with LAM, ADV, or ETV-resistance.[19,20] As mentioned previously,[2,3] drug-resistance has been a clinical challenging problem in China due to the widespread use of low genetic barrier antivirals, thus TDF can be employed in case of multi-drug resistant HBV infection. In the present study, 12 (11.43%) patients had confirmed LAM-resistance, and 11 (10.48%) patients experienced sub-optimal response to ETV, and ETV was not appropriate for these patients. Therefore, we did not take ETV as control in the present study.

Nephrotoxicity has been reported during TDF treatment, especially in patients with lower baseline eGFR or prior ADV therapy.[11,12] Consistent with a previous study performed on Korean individuals,[12,21] data in the present study showed that Chinese patients with lower eGFR at baseline were also susceptible to have eGFR <90 mL/min/1.73 m^2 at the 96th week. Mechanisms of nephrotoxicity in the first 48 weeks may be various, including renal tubular injury, apoptosis, and mitochondrial toxicity.[22] Apart from a previous study,[23] the dynamic renal function showed an unexpected pattern in the present study, and patients with older age (≥65 years old), LC or basal eGFR <90 mL/min/1.73 m^2 experienced milder reduction in eGFR than expected. Multivariable analysis showed that a lower eGFR at baseline was the only independent risk factor for eGFR <90 mL/min/1.73 m^2 at the 96th week. So, there is no evidence that TDF causes a supplementary damage to renal function for these patients. Moreover, the gradual improvement of renal function in the subsequent 48 weeks remains elusive. It is suspected that a compensatory mechanism of renal function may exist after renal injury, and it may be difficult to recover in a short period.

There are some limitations in our study. First, the mechanisms underlying the recovered eGFR at the 96th week were not explored. Secondly, this is not a larger-scale study, thus multicenter real-world studies should be performed to assess its long-term nephrotoxicity.

5. Conclusions

In conclusion, TDF has potent antiviral effect in both treatment-naïve and treatment-experienced patients. Moreover, basal eGFR <90 mL/min/1.73 m^2 is the only independent risk factor for eGFR <90 mL/min/1.73 m^2 at the 96th week.

Author contributions

Conceptualization: Lin Lin.
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References

[1] Tang LSY, Covert E, Wilson E, et al. Chronic hepatitis B infection: a review. JAMA 2018;319:1802–13.
[2] Zhang HY, Liu LG, Ye CY, et al. Evolution of drug-resistant mutations in HBV genomes in patients with treatment failure during the past seven years (2010–2016). Virus Genes 2018;54:41–7.
[3] Guo X, Wu J, Wei F, et al. Trends in hepatitis B virus resistance to nucleoside/nucleotide analogues in North China from 2009–2016: a retrospective study. Int J Antimicrob Agents 2018;52:201–9.
[4] Lim YS, Lee YS, Gwak GY, et al. Monotherapy with tenofovir disoproxil fumarate for multiple drug-resistant chronic hepatitis B: 3-year trial. Hepatology 2017;66:772–83.
[5] Lim YS, Yoo BC, Byun KS, et al. Tenofovir monotherapy versus tenofovir and entecavir combination therapy in adefovir-resistant chronic hepatitis B patients with multiple drug failure: results of a randomised trial. Gut 2016;65:1042–51.
[6] Yoo EH, Cho HJ. Clinical response to long-term tenofovir monotherapy in Korean chronic hepatitis B patients. Clin Chim Acta 2017;471:308–13.
[7] Nguyen MH, Yang HI, Le A, et al. Reduced incidence of hepatocellular carcinoma in cirrhotic and noncirrhotic patients with chronic hepatitis B treated with tenofovir – a propensity score-matched study. J Infect Dis 2019;219:10–8.
[8] Seto WK, Lo YR, Pawlotsky JM, et al. Chronic hepatitis B virus infection. Lancet 2018;392:2313–24.
[9] Suzuki F, Suzuki Y, Hosaka T, et al. Efficacy of long-term tenofovir-based rescue therapy in patients with chronic hepatitis B refractory to nucleoside/nucleotide analogs. J Gastroenterol 2017;52:641–51.
[10] Marcellin P, Zoulim F, Hezode C, et al. Effectiveness and safety of tenofovir disoproxil fumarate in chronic hepatitis B: a 3-year, prospective, real-world study in France. Dig Dis Sci 2016;61:3072–83.
[11] Trinh S, Le AK, Chang ET, et al. Changes in renal function in patients with chronic HBV infection treated with tenofovir disoproxil fumarate vs entecavir. Clin Gastroenterol Hepatol 2018;17:948–56.e1.
[12] Udompap P, Kim D, Ahmed A, et al. Longitudinal trends in renal function in chronic hepatitis B patients receiving oral antiviral treatment. Aliment Pharmacol Ther 2018;48:1282–9.
[13] Tsai HJ, Chuang YW, Lee SW, et al. Using the chronic kidney disease guidelines to evaluate the renal safety of tenofovir disoproxil fumarate in hepatitis B patients. Aliment Pharmacol Ther 2018;47:1673–81.
[14] Wang HM, Hung CH, Lee CM, et al. Three-year efficacy and safety of tenofovir in nucleos(t)ide analog-naive and nucleos(t)ide analog-experienced chronic hepatitis B patients. J Gastroenterol Hepatol 2016;31:1307–14.
[15] Zhou J, Liu YY, Lian JS, et al. Efficacy and safety of tenofovir disoproxil treatment for chronic hepatitis B patients with genotypic resistance to other nucleoside analogues: a prospective study. Chin Med J (Engl) 2017;130:914–9.
[16] Hou JL, Lai W. The guideline of prevention and treatment for chronic hepatitis B: a 2015 update. Zhonghua Gan Zang Bing Za Zhi 2015;23:888–905.
[17] Nishikawa H, Osaki Y. Liver cirrhosis: evaluation, nutritional status, and prognosis. Mediators Inflamm 2015;2015:872152.
[18] Rodriguez-Novoa S, Garcia-Samaniego J, Prieto M, et al. Altered underlying renal tubular function in patients with chronic hepatitis B receiving nucleos(t)ide analogs in a real-world setting: the MENTE study. J Clin Gastroenterol 2016;50:779–89.
[19] Lim L, Thompson A, Patterson S, et al. Five-year efficacy and safety of tenofovir-based salvage therapy for patients with chronic hepatitis B who previously failed LAM/ADV therapy. Liver Int 2017;37:827–35.
[20] Patterson SJ, George J, Strasser SI, et al. Tenofovir disoproxil fumarate rescue therapy following failure of both lamivudine and adefovir dipivoxil in chronic hepatitis B. Gut 2011;60:247–54.
[21] Min IS, Lee CH, Shin IS, et al. Treatment outcome and renal safety of 3-year tenofovir disoproxil fumarate therapy in chronic hepatitis B patients with preserved glomerular filtration rate. Gut Liver 2018;13:93–103.
[22] Yang YM, Choi EJ. Renal safety of tenofovir and/or entecavir in patients with chronic HBV monoinfection. Ther Clin Risk Manag 2017;13:1273–85.
[23] Jung WJ, Jang JY, Park WY, et al. Effect of tenofovir on renal function in patients with chronic hepatitis B. Medicine (Baltimore) 2018;97:e9756.