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Original Research Article

Is tenofovir disoproxil nephrotoxic in all patients? side effects of tenofovir and entecavir on kidney

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ABSTRACT

Background: Hepatit B virus (HBV) is one of the main causes of liver related morbidity and mortality in worldwide. This condition is also a significant healthcare problem in Turkey. Entecavir (ETV) and tenofovir (TDF) are potent nucleos(t)ide analogues (NAs) recommended for the treatment of chronic HBV (CHB) infection. The aim of the study was to determine the association of NAs and nephrotoxicity in our CHB cohort.
Methods: Between the January 2011-February 2021, there were 294 patients treated with TDF (N=194) and ETV (N=100). Glomerular filtration rate (GFR) was calculated by the modification of diet in renal disease (MDRD) method. Kidney function tests were assessed at baseline and follow-up visits.
Results: There were 294 patients in the total group. The mean follow-up period was 66±18 months. Age and sex distributions and baseline assessments including liver function tests, creatinine, GFR, HBV DNA values and pathology scores (HAI and fibrosis) were similar between TDF (N=194) and ETV (N=100) groups. Creatinin and GFR assessed at the last visit were 0.81±0.01 g/dl and 102.94±19.78 ml/min for TDF and 0.81±0.013 g/dl and 104.65±19.05 ml/min for ETV. These values were not significant between the both treatment groups. In terms of nephrotoxicity, none of the patients had significant changes in terms of creatinine and GFR that may require dose adjustment.
Conclusions: We showed that the use of both drugs led to a decrease in GFR that was not clinically important in chronic hepatitis B patients with normal baseline renal tests and without co-morbidity.

Keywords: Entecavir, Tenofovir, GFR, Chronic hepatitis B

INTRODUCTION

Hepatitis B virus is a DNA virus which globally affects an average of 250 million people and causes the death of an average of 600 thousand patients with HBV annually.[1,2] Although HBV is an global problem, increased access to vaccines reduces the incidence of hepatitis B.[3] HBV-related comorbidities are common causes of hospitalization. The primary purpose in the treatment of HBV infection is to obtain the seroconversion from HBsAg to anti-HBs and prevent the complications such as cirrhosis and hepatocellular carcinom (HCC).[4,5]

Entecavir (ETV) and tenofovir (TDF), which are nucleoside analogues, are widely used today.[6-8] And in tenofovir group, there are tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF). TAF is less nephrotoxic than its predecessor prodrug, TDF.[9]

The aim of the study was to evaluate nephrologic side effects of nucleoside analogues such as entecavir and

tenofovir disoproxil fumarate in the long-term in patients with chronic HBV.

What's already known about this topic?

ETV and TDF are potent nucleos(t)ide analogues (NAs) recommended for the treatment of chronic HBV infection. TDF might be nephrotoxic and should be followed regularly in terms of nephrotoxicity.

What does this article add?

In this study, there were no difference between entecavir and tenofovir in terms of nephrotoxicity in our region where HBV infection is prevalent in the young population.

METHODS

Our study was designed as a reprospective cohort study in the gastroenterology service of Dicle University. The ethics committee of Dicle University approved it on 18 May 2018 with the decision numbered 167.

Two-hundred-ninthy-four patients with HBV treated with NAs between January 2011-February 2021 in Dicle University were retrospectively included.

To be eligible, patients needed to be treatment-naive and exposed to NA for at least 12 months. Patients were required to have at least 24 months of follow-up and serum creatinine measurements before and during anti-viral therapy (at least one measurement during follow-up).

Exclusion criteria were as follows: age under 18 years; acute kidney disease or chronic kidney disease; decompansated cirrhosis and HCC or history of liver transplantation; treated with both entecavir and tenofovir; other liver diseases such as HCV, HDV, autoimmune hepatitis, alcoholic liver disease.

All included patients had at least 2 follow-up creatinine measurements. Baseline laboratory measurements were determined before the initiation of ETV or TDF treatment. All measurements after treatment initiation were considered follow-up data.

Demographic data, urea, creatinine, ALT, AST, GGT, ALP, total bilirubin, total protein, albumin leves and serologic markers of hepatitis (B, C and Delta), HBV DNA levels, HAI and fibrosis score were obtained from the Medical record system (PROBEL) of our hospital.

Cirrhosis was determined by the presence of clinical, radiologic, endoscopic, and laboratory evidence of cirrhosis or portal hypertension (i.e.; nodular contour on imaging, thrombocytopenia with platelets <120.000/µl, splenomegaly, and presence of varices) or symptoms of clinical hepatic decompensation (ascites, hepatic encephalopathy, jaundice, and variceal hemorrhage).

The presence of hypertension or diabetes mellitus were confirmed though medical chart review.

Statistical analysis

The normal distrubition assumption of the data was tested with the Kolmogorov-Smirnov test. Normally distributed descriptive statistics of continous variables were shown with mean and standard deviation (SD) values. Non-normally distributed data were shown as median and lower-upper bound. Yates Chi-square test with correction were used in the analysis of cross tables. Student's t test was used to compare the normally distributed data of the tenofovir and entecavir groups, and the Mann Whitney U test was used to compare the data that did not show a normal distribution. Paired sample test was used for the evaluation of repeated measures. Hypotheses are two-sided and $p<0.05$ was considered statistically significant. Statistical analyzes were performed using SPSS 18.0 for Windows (SPSS Inc., Chicago, IL, USA) package program.

RESULTS

In this study, 294 patients with chronic hepatitis B were included. There were 195 male (66.3%) and 99 (33.7%) female patients. Mean age of patients was 32.9±11.1 years. 66% of patients (N=194) were treated with tenofovir and 32% of patients (N=100) were treated with entecavir. There were no significant difference between the both groups in terms of mean age and gender ($p>0.05$). Mean follow-up of patients were 66±18 months (TDF: 66.8±18.7 months, ETV: 65.9±18,3 months ($p=0.706$).

In the tenofovir and entecavir groups, there were 9 (4.6%) and 2 (2%) patients with hypertension, 15 (7.7%) and 5 (5%) patients with DM respectively (Table 1). There was no statistically significance for both disease ($p>0.05$).

HBV DNA levels before treatment were 5.8±77 log IU/ml and 6.2±78 log IU/ml for ETV and TDF groups subsequently. There were statistically no difference between the two group in terms of initial HBV DNA levels ($p=0.681$).

Creatinine and GFR levels in tenofovir group before treatment were 0.78±0.12 mg/dl, 106.4±18.2 ml/min and following treatment 0.81±0.13 mg/dl and 102.9+19.7 ml/min respectively. In group treated with entecavir, creatinine and GFR levels before treatment were 0.78±0.13 mg/dl and 110.085±22.104 ml/min and following treatment mg/dl, 0.81±0.13 mg/dl and 104.651±19.046 ml/min respectively (Figure 1 and 2).

Changes in creatinine and GFR levels before and after treatment was statistically found significant in tenofovir group (p score<0.05 for creatinine and GFR levels). Changes in creatinine, GFR levels were also statistically significant in entecavir group (p score<0.05). But most significantly, there were no significant difference between

the two groups in terms of changes in creatinine and GFR levels (p score=0.936 for creatinine, p score=0.48 for GFR).

Table 1: Baseline demographic characteristics and laboratory values of both groups.

Characters	TDF group N (%)	ETV group N (%)	P value
Sex, (F/M)	67/127	32/68	0.664
Age (years)	33.6±11.1	31.6±11	0.146
Follow-up (months)	66.8±18.7	65.9±18.3	0.706
Diabettes mellitus	15 (7.7)	2 (2)	<0.05
Hypertension	9 (4.6)	5 (5)	<0.05
HAI score	6.15±1.92	6.11±1.72	0.845
Fibrosis score	2.33±0.95	2.31±0.84	0.861
HBV DNA (log IU/ml)	5.8±7.7	6.2±7.8	0.681
Urea (mg/dl)	28.1±7.5	26±7.4	0.22
Creatinine (µmol/l)	0.78±0.12	0.78±0.13	0.836
GFR (ml/min)	106±18	110±22	0.138
AST (U/l)	41±20	42±20	0.650
ALT (U/l)	66±39	69±39	0.543
GGT (U/l)	29±22	29±29	0.881
ALP (U/l)	89±45	87±40	0.684
Total bilirubin (mg/dl)	0.8±0.7	0.7±0.3	0.335
Total protein (g/dl)	7.6±9.7	7.5±0.5	0.730
Albumin (g/dl)	4.1±0.4	4±0.4	0.168

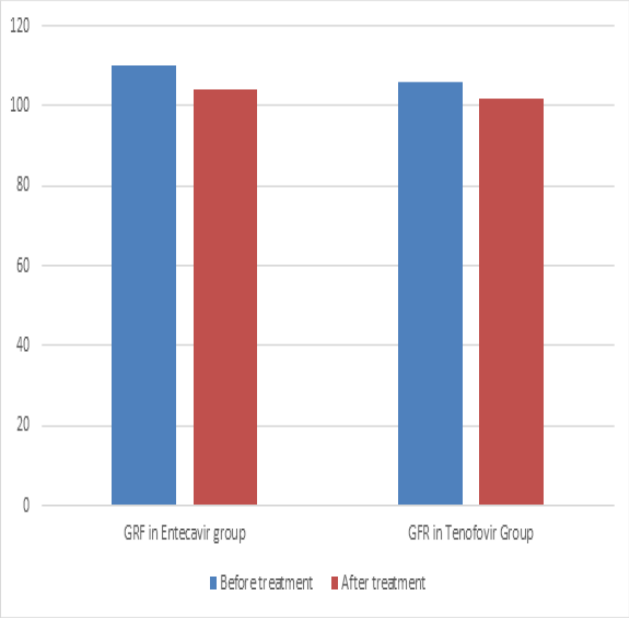

Figure 1: GFR levels before and after treatment in tenofovir and entecavir groups (p score=0.48).

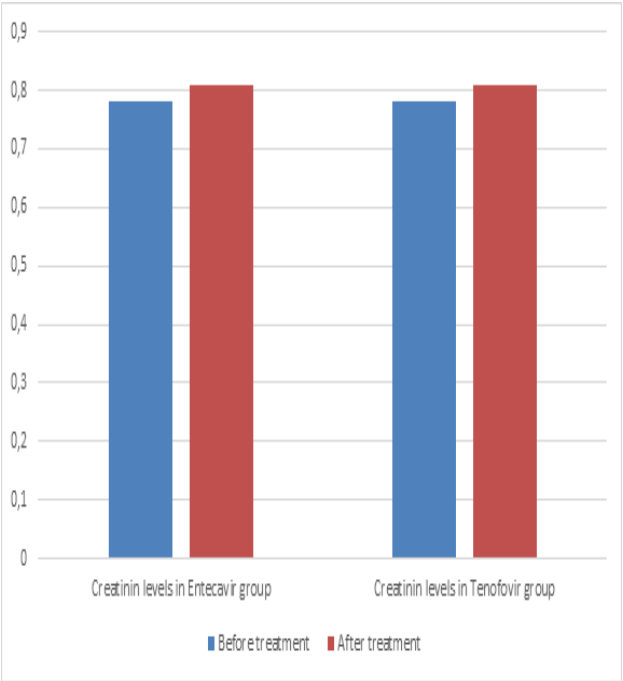

Figure 2: Creatinine levels before and after treatment in tenofovir and entecavir groups (p score=0.936).

DISCUSSION

Oral NAs are effective and well tolerated agents in the treatment of HBV. So far, a significant number of chronic hepatitis B around the world have been treated with oral NAs and there has been good data on the safety of these agents.[10] New current guidelines recommend use of antivirals with high efficacy and less resistance as first-line agents in the treatment of chronic hepatitis B infection.[6-8] Side effects of NAs on renal function are an important issue that should be shed on light. Because even HBV infection itself could increase the risk of impairment in renal function.[11] With the use of NAs, nephrotoxicity is mostly caused by damage in proximal tubules and may present with increased creatinine levels, proteinuria, diabetes insipidus, hypophosphatemia or more severe, fanconi syndrome.[12] Given that information, primary purpose in the treatment of chronic hepatitis B is to obtain the seroconversion, prevent the complication caused by HBV infection and keep the side effects minimal during treatment. Tenofovir is one of the most potent oral NAs. It has still being questioned however potential renal toxicity caused by tenofovir especially in the treatment of HIV and HBV.[13] Therefore, tenofovir alafenamide has been developed to improve renal safety.[14]

In our study, patients with HBV treated with entecavir or tenofovir at least for 24 months were retrospectively followed, Decrease in GFR was observed in both groups. However, these GFR changes did not require dose adjustment or change of drugs, and these changes were not found to be statistically significant. Most important risk factor for renal disease in patients treated with NAs are diseases such as DM, coinfection with HIV,

decompansated cirrhosis, uncontrolled hypertension and solid organ transplantation.[17] In our region where vertical transmission (mother-to-child) rates are high, the relatively young age of patients could be explanation of less renal side effects, in connection with the low rate of nephrotoxicity risk factors mentioned above.

In a meta-analysis conducted by Yang et al which evaluated the renal safety of entecavir and tenofovir in patients with HBV infection, showed that both agents could be associated with decreased renal function. However, they found that the various risk factors such as existing kidney disease and comorbities were also associated with reductions in kidney function during tenofovir or entecavir treatment.[13,15] This meta-analysis also revealed that there was a decrease in GFR depending on time in the tenofovir groups, whereas it showed increase and decrease in the entecavir group. In our study, there was decrease in both groups. There was no statistically difference between the two groups in terms of decrease rate of GFR. This is mostly related to the absence of pre-treatment kidney disease and lower comorbidity rates in our study compared to the meta-analysis.

In an another study conducted by Wu et al, which evaluated treatment of 419 treatment-naive patients in terms of long-term efficacy and safety retrospectively, tenofovir and DM were found to be independent risk factor for acute kidney injury. In this study, patients treated with tenofovir had more comorbidities compared to our study (7.7% and 10.4% DM; 4.6% and 24% HT; 0% and 27% cirrhosis in our study and this study respectively). And mean age of patients in this study were higher than patients in our study (32±11 years in our study and 47±12 years). These both factors may be among the possible reasons that could explain the less adverse renal side effect of the tenofovir in our study. According to Wu et al ETV and TDF have the similar efficacy in the treatment of naive-patients to NAs. Nevertheless tenofovir has higher incidence for acute kidney injury compared to entecavir.[16]

Most important limitations of our study was to be single-center and retrospective. And absence of telbivudin and adefovir groups due to absence of patient, absence of phosphor levels, which is important cause of renal toxicity, low rate of comorbid diseases, exclusion of patients with cirrhosis and kidney disease are another limiting factors. However, it offers important results in terms of showing the effect of long-term renal toxicity and presenting real-life data.

CONCLUSION

Tenofovir is a safe and effective agent in patients who have initially normal renal function, who do not have comorbidities for renal disease and who do not develop cirrhosis, in terms of renal safety. Although GFR changes that may require dose modification, especially in young patients without comorbidities, are not observed during NAs treatment, regular renal function monitoring will be beneficial in all patients.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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