ORIGINAL ARTICLE

Renal function in patients with chronic hepatitis B during antiviral therapy

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ABSTRACT

Aim To analyse the impact of the length of antiviral therapy with tenofovir disoproxil fumarate (TDF) on the renal function in patients with chronic hepatitis B (CHB).

Methods A cross-sectional study included 75 patients with CHB treated with tenofovir, who had a normal renal function at the beginning of the treatment. Renal function was determined based on glomerular filtration rate (eGFR) value using the Modification of Diet in Renal Disease formula (MDRD). Measurement of serum creatinine concentration and urinary protein excretion were performed using standard laboratory analyses. Viral load quantification (HBV-DNA) was determined by polymerase chain reaction (PCR). The degree of liver fibrosis was determined using fibrosis-4 (FIB-4) and aspartate transaminase to platelet ratio index (APRI) fibrosis score.

Results Out of 75 CHB patients, 37 were on antiviral treatment for up to 2 years (group 1) and 38 patients on antiviral treatment longer than two years (group 2). Mean age of patients was not significantly different between the groups (p=0.076), nor was the gender distribution. There was no statistically significant difference between the mean values of the eGFR in the two groups (91.89±9.24 vs. 88.42±7.84 mL/min/1.73m^2; p=0.42), as well as between the mean values of serum creatinine (p=0.360) and 24-hour urine protein excretion (p=0.380). There was no statistically significant correlation between renal parameters and viral load, APRI and FIB-4 fibrosis score.

Conclusion Results of our study did not show significant changes in the measured parameters of renal function in group 1 and group 2 of patients, regardless of the length of antiviral treatment, indicating a good renal safety profile of TDF.

Key words: kidney, liver, tenofovir

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INTRODUCTION

Chronic hepatitis B (CHB) represents a significant public health problem and it is one of the most common causes of the cirrhosis and primary liver cancer (1).

Tenofovir diproxil fumarate (TDF) (tenofovir) is one of the first-line antiviral agents against chronic hepatitis B (2). It presents bioavailable prodrug of tenofovir, which is a potent nucleotide analogue reverse transcriptase inhibitor with activity against hepatitis B virus and human immunodeficiency virus (HIV) (3,4).Tenofoviris is eliminated by glomerular filtration, with 20-30% being actively transported into the renal proximal tubule cells (5).

Some studies showed no or very low prevalence of consequential renal disease during antiviral treatment (6,7). However, a few studies have shown opposite results and signs of renal toxicity during antiviral therapy, manifesting as a decline in estimated glomerular filtration rate (eGFR) (8), as well as proximal renal tubular dysfunction leading to treatment discontinuation (9-11). Mocroft et al. confirmed in people with normal renal function an increased annual incidence of chronic kidney disease for up to 6 years of exposure to TDF (12).

The prevalence of chronic kidney disease is increasing all over the world and represents an important public health problem that carries numerous adverse consequences for patients and high healthcare costs (13). In addition to the conventional risk factors for chronic kidney disease in the general population, CHB may be an additional cause of chronic kidney disease, as well as the adverse effects of some drugs on kidney function, especially those used long-term in antiviral therapy (14). Based on previous research, it is not entirely clear whether drugs used to treat chronic hepatitis B virus infection cause significant damage to kidney function (15).

Examining the safety profile of tenofovir in patients with chronic hepatitis B is of great clinical importance for daily practice, considering the fact that already there are patients on therapy for over 6 years, and that number will increase every year, because of long-term therapy in 98% patients. Research on this problem has not been carried out in Bosnia and Herzegovina (B&H) so far. The nephrotoxicity of tenofovir disoproxil fumarate (TDF) in chronic hepatitis B (CHB) patients without chronic kidney disease (CKD) remains controversial (8-10).

Since tenofovir therapy in patients with CHB infection is often lifelong, it is important to examine possible alterations of renal function depending on the duration of antiviral treatment. The aim of this study was to evaluate the relationship between the renal function in patients with CHB infection on short-term (for up to two years) and long-term (more than two years) treatment with tenofovir therapy.

PATIENTS AND METHODS

Patients and study design

This cross-sectional observational study was performed at the Gastroenterology and Hepatology Clinic, Clinical Centre of the University of Sarajevo, from January 2020 to December 2021. The study included 75 patients with mean age 51.76±10.38 years suffering from CHB. Out of 75 patients, there were 37 patients with CHB on antiviral treatment up to 2 years (average length of treatment 1.8 years, group 1) and 38 patients with CHB on antiviral treatment longer than two years (average 4.3 years, group 2). They did not have renal insufficiency at the beginning of the antiviral treatment. According to the official guidelines for the treatment of chronic hepatitis B, tenofovir was administered at a dose of one tablet of 245 mg per day (16). The exclusion criteria were: hepatitis C virus coinfection, autoimmune liver disease, hepatocellular carcinoma, diabetes mellitus, heart failure, and glomerular filtration rate (GFR) below 60 mL/min/1.73m^2. All patients provided a written informed consent. The study protocol was approved by the Ethics Committee of the University Clinical Centre Sarajevo, and was performed in accordance with the Helsinki Declaration.

Methods

Patient history, including demographic data and family history, were collected from all patients. Renal function was assessed based on estimated glomerular filtration rate (eGFR). Glomerular filtration rate is the rate in millilitres per minute at which substances in plasma are filtered thro-

ugh the glomeruli. Calculation and evaluation of eGFR value were performed using the Modification of Diet in Renal Disease formula (MDRD) according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines (17):

GFR (mL/min/1.73 m^2) = 175 × (serum creatinine in µmol/L)$^{-1.154}$ × (age)$^{-0.203}$ ×0.742 (for women) x 1.212 (for African Americans). The normal GFR in adults is in the range 90-120 mL/min/1.73m^2.

Serum creatinine concentration (reference values 45 – 115 µmol/L) was measured using the kinetic Jaffe reaction on the DimensionR clinical chemistry system (Siemens, Germany), where creatinine produces quantitatively an orange colour with picric acid in alkaline medium. Determination of protein in urine was performed by spectrometric method on the Dimension Xpand Plus (Siemens, Germany) at the Department of Clinical Biochemistry with Immunology, Clinical Centre of the University of Sarajevo. Excretion of protein in the urine of more than 200 mg in 24-hour represented proteinuria.

HBV DNA test by real-time polymerase chain reaction (RT-PCR) in serum of patients with chronic HBV infection was used for quantitation of viral load and monitoring the effects of chronic hepatitis B treatment (18). Non-invasive scores, APRI (aspartate transaminase to platelet ratio index) and FIB-4 (Fibrosis-4 score), which include four parameters- age, platelet count, transaminase levels aspartate aminotransferase (AST) and alanine aminotraferase (ALT), were used for the assessment of liver fibrosis (19,20). FIB-4 score >3.25 and APRI score >1.5 represent significant predictors of liver fibrosis. APRI score was calculated using the following formula: APRI = [(AST level/ULN)/platelet count (10^9/L)] × 100. The FIB-4 score was determined using the formula: FIB-4 = [age × AST/platelet count (10^9/L) × √ALT].

Statistical analysis

Kolmogorov-Smirnov test was used to evaluate the normal distribution of continuous variables. Data are expressed as mean±SD for normally distributed variables. Quantitative variables were compared by Student's t-test. The relationship between the variables is determined using Spearman rank correlation. The $p<0.05$ was considered as statistically significant.

RESULTS

The average age of CHB patients on antiviral treatment up to 2 years (group 1) was 51.54±10.56 years, while in the group on antiviral treatment for more than two years (group 2) it was 52.94±10.20 years (p=0.076). There was also no difference between the groups in the representation of patients by male (p=0.929) and by female gender (p=0.908), although males were more numerous than women in both groups of patients. The highest number of HBV DNA PCR positive patients was found in group 1, comparing to the group 2 (p=0.020). Liver fibrosis according to APRI and FIB-4 score was mild to moderate, but statistically significantly higher in patients from group 1 compared to group 2 (p=0.001 and p=0.006, respectively) (Table 1).

Table 1. Basic characteristics of patients

Variable	Group 1 (n =37)	Group 2 (n = 38)	p
Age (mean±SD)	51.54±10.56	52.94±10.20	0.076
Male (N/%)	23/ 62.1%	24/ 63.1%	0.929
Female (No/%)	14/ 37.8%	14/ 36.8%	0.908
Serum creatinine (µmol/L) (mean±SD)	76.27±8.69	78.18±9.26	0.360
eGFR (ml/min/1.73m^2) (mean±SD)	91.89±9.24	88.42±7.84	0.420
24h proteinuria (g/d) (mean±SD)	0.12±0.06	0.13±0.06	0.380
HBV DNA PCR (+) (No/%)	9/24.3%	2 / 5.3%	0.020
APRI score (mean±SD)	0.75±0.44	0.39±0.25	0.001
FIB-4 score (mean±SD)	1.84±0.72	1.28±0.71	0.006

eGFR-estimated glomerular filtration rate; HBV DNAPCR, hepatitis B virus deoxyribonucleic acid polymerase chain reaction; APRI score, aspartate aminotransferase to platelet ratio index; FIB-4 score, fibrosis 4 score

The eGFR value was slightly lower in patients on a longer period of tenofovir therapy (group 2), but there was no statistically significant difference between the mean values of the eGFR in the two groups of patients (91.89±9.24 vs. 88.42±7.84; p=0.42) (Figure 1).

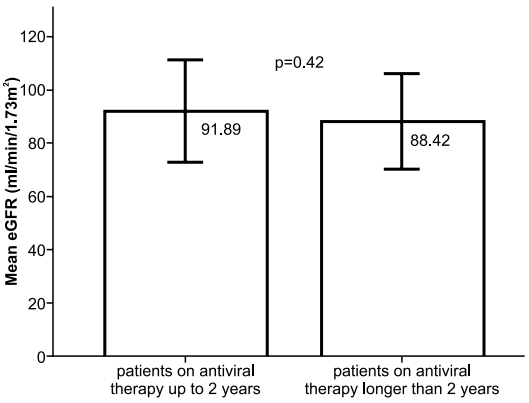

Figure 1. Mean estimated glomerular filtration rate (eGFR) in patients with chronic hepatitis B

No statistically significant difference was found between the mean serum creatinine values of both groups of patients (76.27±8.69 vs. 78.18±9.26 μmol/L, p=0.360). Serum creatinine values in both groups of patients were within the reference limits for a healthy adult population (Figure 2).

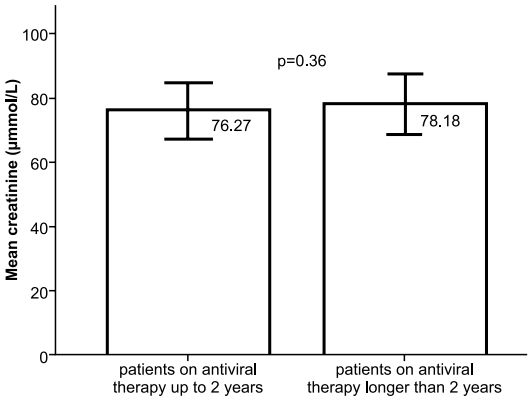

Figure 2. Mean serum creatinine values in patients with chronic hepatitis B

The mean value of 24-hour proteinuria was not significantly different between these two patient groups (0.12±0.06 vs. 0.13±0.06 g/d; p=0.380). Urine analysis showed that patients in both groups had proteinuria within physiological limits (Figure 3).

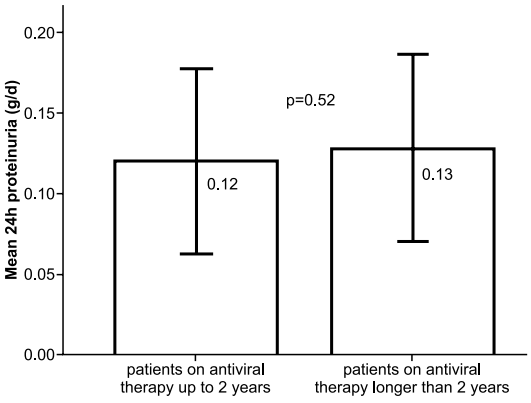

Figure 3. Mean 24-hour (h) proteinuria in patients with chronic hepatitis B

Although the data analysis showed a higher percentage of HBV DNA PCR positive patients in group 1 and statistically significant differences in the percentage of HBV DNA PCR positive patients between the two groups of patients (24.3% vs. 5.3%; p=0.020), as well as in liver fibrosis scores, no statistically significant correlation was confirmed between renal parameters, viral load and liver fibrosis score values in any group of patients (Table 2).

Table 2. Correlation between renal parameters, viral load and liver fibrosis scores

Variable	eGFR (mL/min/1.73m²)		Serum creatinine (μmol/L)		24-hours proteinuria (g/24h)	
	rho	p	rho	p	rho	p
HBVDNA PCR	0.065	0.578	-0.030	0.801	-0.094	0.422
APRI score	-0.022	0.850	-0.080	0.497	0.086	0.466
FIB-4 score	-0.131	0.261	0.041	0.727	0.155	0.183

eGFR-estimated glomerular filtration rate; rho -Spearman coefficient of correlation;
APRI score, aspartate aminotransferase to platelet ratio index; FIB-4 score, fibrosis 4 score; HBV DNA PCR, hepatitis B virus deoxyribonucleic acid polymerase chain reaction

DISCUSSION

Results of our study did not show significant changes in the measured parameters of renal function in both groups of patients, regardless of the length of antiviral treatment. Although we found slightly lower value of eGFR in patients on longer period of tenofovir therapy and slightly higher values of average serum creatinine in the two groups of patients, our research has not confirmed a significant difference in eGFR and serum creatinine values in patients with CHB infection on short-term and long-term treatment with tenofovir therapy. CHB patients in both groups had proteinuria within physiological limits.

Our results are in accordance with the results of other studies reporting favourable safety profile and no renal adverse events (21,22). A large cohort study conducted in the United Kingdom from 2005 to 2018 year, which included 206 adult patients divided into two groups - patients treated and not treated with TDF, did not show a significant difference in eGFR and serum creatinine values over time between two groups (23). The same results were reported a few years earlier in the study of Wong et al. (24).

Ascher et al. study observed a decline in the eGFR during the first year of TDF exposure in HIV-infected persons on average by 9.2 mL/min/1.73m², followed by the decrease of 0.62mL/min/1.73m² per year afterwards (25). Although some researches have suggested that this initial decline in eGFR might reflect interference with tubular creatinine secretion rather than an actual decline in eGFR (26), observational studies showed that prolonged exposure to TDF was associated with an increased risk of decreased kidney function (27,28). Risk factors for TDF toxicity appear to be similar in patients treated for HIV or hepatitis B virus (29).

Slight serum creatinine increase was verified in patients with chronic hepatitis B in a few studies, as well as a modest but statistically significant decline in eGFR in five years of treatment with TDF (30,31). Cross-sectional retrospective analysis in eastern China, including 8309 patents with CHB, reported 11.37% patients with chronic kidney disease and 8.33% with proteinuria (32).

Several studies investigated and compared renal adverse effects between tenofovir and entecavir treated patients, and could not confirm significant difference between those groups of patients (33,34). Kim et al. compared the renal function change of 468 patients with hepatitis B virus infection who underwent liver transplantation and who received tenofovir or entecavir for antiviral treatment; they did not confirm that postoperative 1-, 2-, and 3-year eGFR and serum creatinine values showed statistical difference in either group (35).

Some studies have indicated that progression of renal dysfunction was mostly observed in patients who had renal impairment before starting antiviral treatment (36,37). Conflicting results of studies can be attributed to differences in the age of patients, basal value of eGFR and comorbidities such as hypertension and diabetes, as well as the use of diuretics (22,38). In patients with these conditions, greater caution to adverse renal effects and nephrotoxicity is required when administering TDF (39-41). Several studies have reported a higher risk for developing chronic renal disease in the general adult population in any hepatitis B infection status than in the absence of infection (42,43).

In our research, we did not find statistically significant correlation between renal parameters and viral load, APRI and FIB-4 liver fibrosis score regardless of the length of antiviral therapy. The patients in our study were middle-aged, with mild to moderate liver fibrosis according to APRI and FIB-4 scores, and only 14.67% of patients had positive HBV DNA PCR, which indicates good control of the disease with antiviral drugs. Our results can be partly explained by the fact that nephrotoxicity with TDF can be manifested primarily as proximal tubular dysfunction before decreased glomerular filtration rates. This is, at the same time, a limitation of our study, since we did not evaluate markers of tubular dysfunction. Testing of such biomarkers is not routinely used in clinical practice, and eGFR was therefore used to monitor renal function. In addition, the limitations of this study are those generally associated with non-interventional, uncontrolled, observational studies. However, additional studies of adequate size and design could provide more information about the relationship between HBV infection, antiviral treatment, and renal status.

In conclusion, tenofovir disoproxil fumarate does not induce renal dysfunction in CHB patients with different duration of antiviral therapy. Therefore. TDF can be used safely in the treatment of CHB patients with the recommendation of careful monitoring of renal function, especially in those who are older and/or with mildly impaired renal function.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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