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Observation of Glomerular Filtration Change in Chronic Hepatitis B Patients Using Tenofovir Disoproxil Fumarate

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Abstract

Introduction: This study was conducted to assess kidney function tests in outpatient individuals with a diagnosis of chronic hepatitis B who were receiving treatment with Tenofovir Disoproxil Fumarate (TDF).

Materials and Methods: Our study included patients who presented to the Infectious Diseases Polyclinic at Gazi State Hospital with a diagnosis of chronic hepatitis B (CHB) and were treated with Tenofovir Disoproxil Fumarate (TDF). The hospital data, available retrospectively since 2013, allowed us to examine patient follow-ups up to that year. As a result, we were able to analyze a maximum follow-up period of nine years. The study encompassed individuals over 18 years of age whose data were complete and who were regularly monitored in the outpatient clinic.

Results: Among the subjects, 69% (n: 69) were male, and 31% (n: 31) were female. Significant reductions in glomerular filtration rates (GFR) were observed in the 4th and 6th years compared to GFR measurements before initiating TDF treatment . Furthermore, creatinine values at the 4th and 6th years were significantly lower compared to the pre-treatment values . No modifications were made to the patients' treatment during the follow-up period.

Conclusion: Our findings reveal differences in GFR and creatinine values similar to those observed in most studies involving patients using TDF. It is evident that TDF can lead to renal impairment. Thus, it is essential to closely monitor patients and make necessary treatment adjustments when indicated. In cases of renal insufficiency, alternative treatment options should be considered at the initiation of therapy. This approach can contribute to the prevention of nephrotoxicity.

Keywords: Chronic hepatitis B; tenofovir disoproxil fumarate; nephrotoxicity.

Introduction

Several antiviral agents are available, with Tenofovir Disoproxil Fumarate (TDF) being one of them. Extensive experience has been gained in its usage for the treatment of chronic hepatitis B (1,2). Despite its favorable safety profile, renal toxicity is a potential concern with TDF, as it is excreted through glomerular filtration and active tubular transport. Various studies have observed a decline in glomerular filtration rate in patients using TDF, and improvements in renal function were detected with dose reduction and/or medication adjustment. In rare cases, TDF treatment has been associated with Fanconi syndrome (3). In light of these findings, it has been recommended to assess the risk of renal toxicity both before and after initiating TDF treatment, along with periodic monitoring of renal function. Moreover, it is advisable to weigh the potential benefits of treatment against the risks, particularly in patients with existing kidney issues or those at risk. Furthermore, it has been recommended to calculate the glomerular filtration rate (GFR) periodically and adjust the dosage regularly in such patients (4). In our study, we conducted an assessment of kidney function tests in outpatient individuals receiving TDF.

Materials and Methods

Choice of patients: Our study included patients who presented at the Infectious Diseases Outpatient Clinic of our hospital with a diagnosis of chronic hepatitis B and were being treated with Tenofovir Disoproxil Fumarate (TDF). We conducted a retrospective analysis of hospital data, which had been available since 2013, enabling us to examine patient follow-ups up to that year, thus allowing for a maximum follow-up

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period of nine years. Inclusion criteria encompassed patients over the age of 18, who were consistently adhering to their treatment regimen, and whose follow-up data were complete and accessible. Patients using nephrotoxic medications, those diagnosed with chronic or acute kidney failure (irrespective of diagnosis), individuals with a calculated glomerular filtration rate (GFR) of 60 or below, as recommended by KDIGO (KIDNEY DISEASES IMPROVING GLOBAL OUTCOMES), and/or a creatinine value of 1.2 mg/dL or higher, as suggested by the Turkish Society of Nephrology, were excluded from the study. Patients with comorbid conditions such as diabetes mellitus, hypertension, and liver cirrhosis were also excluded. A total of one hundred patients who met our study's protocol criteria were enrolled and subjected to statistical analysis. This study was conducted in accordance with the revised version of the Declaration of Helsinki.

Assessment of data: Demographic data (age, sex) of all patients, creatinine and GFR values measured every year before and after treatment were recorded. If there is more than one outpatient application in a year, the highest value of that year is taken. GFR was calculated with the Modification of Diet in Renal Disease (MDRD) equation recommended for routine clinical use, in line with the recommendations of the Turkish Society of Nephrology.

Results

A total of 69 individuals (79%) in the study were male, while 31 individuals (31%) were female. The mean age of the participants was 51.67±12.29, with the age range spanning from 23 to 79 years (Table 1).

Table 1: Findings Related to Demographic Variables

		N	%
Gender	Male	69	69.0
	Female	31	31.0
Age	Min.-Max.	23-79	
	$\bar{X}$ ±SD	51.67±12.29	

The analysis revealed no statistically significant difference between the glomerular filtration rate values before treatment and the mean values at 1, 2, 3, 5, 7, and 8 years ($p>0.05$). However, there was a statistically significant difference between the glomerular filtration rate before treatment and at the 4th year ($p<0.05$). The pre-treatment values (101.24±21.34) were higher than the Year 4 values (96.83±20.15) (Table 2).Similarly, a statistically significant difference was observed between the pre-treatment values and the values obtained at the 6th year ($p<0.05$), with the pre-treatment values (92.98±19.50) being higher than the 6th-year values (Table 2). Significant differences were found between pre-treatment creatinine values and values obtained at 1, 2, 3, 4, 5, 7, and 8 years ($p<0.05$). The pre-treatment values (0.83±0.17) were lower than the 4th-year values (0.85±0.18) (Table 3). Additionally, significant differences were identified between pre-treatment creatinine values and values obtained at 6 years ($p<0.05$), with the pre-treatment values (0.83±0.17) being lower than the 6th-year values (0.87±0.18) (Table 3). There was also a statistically significant difference between pre-treatment creatinine values

Table 2: Findings Related to Comparison of GFH Change in Pre-Treatment and Post-Treatment Years

	$\bar{X}$ ±SD	$\bar{X}$ ±SD	t	p
GFR Before-GFR 1 Year	101.24±21.34	102.03±24.37	0.19	0.85
GFR Before -GFR 2 Year	101.24±21.35	99.74±25.08	0.48	0.63
GFR Before -GFR 3 Year	101.24±21.36	100.96±22.12	-0.30	0.76
GFR Before -GFR 4 Year	101.24±21.37	96.83±20.15	2.39	0.02
GFR Before -GFR 5 Year	101.24±21.38	98.59±24.95	-0.30	0.76
GFR Before -GFR 6 Year	101.24±21.39	92.98±19.50	2.77	0.01
GFR Before -GFR 7 Year	101.24±21.40	91.47±22.01	0.99	0.33
GFR Before -GFR 8 Year	101.24±21.41	92.95±22.25	1.29	0.21
GFRBefore-GFR AVE*.Year	101.24±21.42	99.00±20.00	1.59	0.11

***GFR:** Glomerular Filtration Rate ***AVE:**Average

Table 3: Findings Concerning the Comparison of Creatine Pretreatment Values with Changes by Years

	$\bar{X}$ ±SD	$\bar{X}$ ±SD	t	p
Cr Before-Cr 1 Year	0.83±0.17	0.83±0.18	-0.57	0.57
Cr Before-Cr 2 Year	0.83±0.18	0.85±0.19	-1.17	0.25
Cr Before-Cr 3 Year	0.83±0.19	0.83±0.18	0.16	0.87
Cr Before-Cr 4 Year	0.83±0.20	0.85±0.18	-2.19	0.03
Cr Before-Cr 5 Year	0.83±0.21	0.85±0.19	0.07	0.95
Cr Before-Cr 6 Year	0.83±0.22	0.87±0.18	-2.22	0.03
Cr Before-Cr 7 Year	0.83±0.23	0.87±0.20	-1.45	0.16
Cr Before-Cr 8 Year	0.83±0.24	0.92±0.18	-0.96	0.35
Cr Before-CrAVE. Year	0.83±0.25	0.85±0.17	-2.01	0.04

***Cr:** Creatine ***AVE:** Average

Table 4: The Relationship Between Glomerular Filtration Rate and Average Creatine Values and Age

		Age
Glomerular Filtration Rate	r	-0.40
	p	0.00
Creatine Year Average	r	0.21
	p	0.04

and the mean values at 8 years ($p<0.05$), with pre-treatment values (0.83±0.17) being lower than the mean values at 8 years (0.85±0.17) (Table 3).Furthermore, a statistically significant moderate negative correlation was observed between the mean glomerular filtration rates over 8 years and age (r:-0.40, $p<0.05$) (Table 4). On the other hand, there was a statistically significant low positive correlation between the mean creatinine values over 8 years and age (r:0.21, $p<0.05$) (Table 4). It's important to note that there were no changes in the treatment regimens of the patients throughout the follow-up period.

Ethical consent: In our study, written consent was obtained from all participants, adhering to the principles outlined in the Declaration of Helsinki. Ethics committee approval was secured from the Ondokuz Mayıs University(OMÜ) Faculty of Medicine Clinical Research Ethics Committee, as evidenced by their decision dated June 27, 2022, and designated as 2022/322.

Statictical analysis: The SPSS (Statistical Package for the Social Sciences) version 22 for Windows was utilized to store and analyze all data on the computer. Prior to conducting data analysis, assumptions required for statistical tests were examined to determine whether parametric or nonparametric tests were suitable. Normality of data distribution was assessed using the Kolmogorov-Smirnov plot, as well as other indicators of normal distribution, including kurtosis and skewness values and the histogram plot. For comparing two related groups, the paired sample t-test was employed. To explore the relationship between variables, Pearson correlation analysis was conducted. A significance level of 0.05 was utilized as the threshold for determining the statistical significance of the obtained values.

Discussion

Tenofovir disoproxil fumarate is a potent antiviral agent, with most of its side effects manifesting in the form of adverse effects on bone mineral density and kidney function. Nephrotoxicity can manifest through various means, including a reduced glomerular filtration rate (GFR), nephrotic syndrome, and electrolyte imbalances caused by glomerular and tubular damage. Drug-induced nephrotoxicity refers to any kidney damage directly or indirectly attributed to drug use. Chronic renal failure can progress slowly, with patients often displaying no symptoms until their GFR drops below 30 mL/min/1.73 m2. Up to a GFR of less than 60 mL/min/1.73 m2, serum creatinine values may remain within normal limits, potentially leading to the oversight of nephrotoxicity. Since monitoring patients primarily relies on observing creatinine increases, this issue can be addressed (5,6). In a multicenter retrospective study involving 200 chronic hepatitis B patients in our country who were treated with TDF, these patients were monitored for 48 weeks, and no significant alterations were observed in GFR and creatinine levels. Similarly, another study included 294 patients monitored for 24 weeks, and

no significant changes were detected in creatinine levels and GFR. In contrast to these examples, our study involved an extended follow-up period of up to 8 years, during which we observed a decrease in glomerular filtration rate and an increase in creatinine values in the 4th and 6th years. We speculate that our divergent results may be associated with the older average age of the patients included and the longer follow-up. The lack of significance in the 5th-year follow-up could be attributed to its coinciding with the pandemic period (7,8). Scherzer et al. assessed renal function tests in treatment-naïve HIV-infected patients after TDF use, revealing a 3% reduction in the estimated glomerular filtration rate (defined as >3 mL/min/1.73 m2/year) and a 3% risk of chronic renal failure. They associated it with a 33% increase (9). In a study tracking 273 TDF users for 24 months, significant differences in creatinine and GFR levels over this period were reported. In another study involving 110 chronic hepatitis B patients, a time-dependent increase in serum creatinine levels at baseline, at 3 months, 6 months, and 12 months was noted in TDF users. Unlike our study, these patients were monitored for a more extended duration, and similarly, significant differences were observed in GFR and creatinine levels (10,11). Lopez Centeno et al. conducted a 48-week renal safety study of TDF, similar to our research, and observed a change in glomerular filtration rate. Two patients had to discontinue TDF due to the development of nephrotoxicity (GFR < 60 ml/min), although no statistically significant difference was detected. Furthermore, in a different study involving 56 patients in our country, a decrease in glomerular filtration rate and an increase in creatinine values, while not statistically significant, were still evident, prompting treatment adjustments in three patients. Although our study showed a significant change in GFR and creatinine levels, no treatment alterations were made. This outcome may be attributed to the creatinine change not exceeding the laboratory's defined limit and the non-routine calculation of GFR (12,13). Various studies have unveiled the long-term implications of Tenofovir Disoproxil Fumarate (TDF) use. According to research by Kim et al., employing the REACH-B risk calculator, extended TDF therapy was associated with a reduced incidence of HCC in patients without cirrhosis who met the treatment criteria. In Buti et al.'s study, the largest analysis conducted thus far on CHB patients with sequential liver biopsies, treatment with TDF for up to five years was linked to favorable virologic, serologic, and histologic outcomes, irrespective of baseline cirrhosis status. Meanwhile, Li et al. found in their research that TDF demonstrated unfavorable renal safety even during short-term treatment. Lastly, in Lee et al.'s research, a multicenter, real-world cohort study demonstrated that the long-term use of TDF monotherapy exhibited non-inferior antiviral efficacy compared to TDF-based combination therapy for patients with MDR (14,15,16,17). Yazie et al and Srisopa et al have shown that renal dysfunction is related to the duration of TDF exposure. At the same time, Srisopa et al also found that discontinuation of TDF, especially in cases where eGFR is higher than 60 mL/min/1.73 m², affects renal function and advantageous in terms of healing proximal renal tubulopathy (18,19. Lastly, in Matlosz et al. similarly showed that renal functions in patients using TDF improved significantly within one year after stopping the drug (20).

Study limitations: Given that our study relied on retrospective data extracted from polyclinic records, the information for patients who interrupted their follow-up could only be recorded intermittently. Furthermore, the Covid-19 pandemic induced delays in outpatient clinic visits for numerous patients, particularly during the years 2020-2021. This was due to the fact that the requirement for report renewal, which aimed to reduce hospital admissions and facilitate patient convenience, was not acknowledged until May 2022. Consequently, data for these years had to be recorded incompletely for some patients. Considering these factors, the absence of mTP and creatinine values in patients' urine can also be recognized as a limitation. Furthermore, since our hospital's database was accessible only up to the year 2013, patients whose treatment commenced before that year and who are still under observation were excluded from the study due to our focus on pre-treatment values.

Conclusions

Similar to many other studies in our study, a significant decrease in glomerular filtration values and a significant increase in creatinine values were detected, and creatinine values were found to be hi:gher than the mean creatinine values of 8 years. Tenofovir disoproxil fumarate nephrotoxicity, acute and chronic renal failure and rarely may result in end-stage renal disease, and our study supports the aforementioned situation. In this case, TDF should be replaced with a suitable alternative. Renal function tests are also observed to improve after discontinuation of treatment. For this reason, patients at risk for kidney failure should be followed closely, and if necessary,

different alternatives should be considered at the beginning of treatment. This approach is very important for the prevention of nephrotoxicity.

Ethical consent: Ethics Committee approval was obtained from the OMÜ Clinical Research Ethics Committee of the Faculty of Medicine with the decision numbered 2022/33 on 27.06.2022.

Conflict of interest: Authors for this study there is no conflict of interest.

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