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Evaluation of clinical characteristics and treatment patterns of patients infected with hepatitis B

Ayşin Kılınç Toker, Azade Kanat, Ayşe Turunç Özdemir, Esma Eryılmaz Eren, Duygu Çerçioğlu Özdemir, Deniz Kamalak Güzel, Tuğba Tok, Zehra Beştepe Dursun, Musa Göksu, İlhami Çelik

Department of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital, Kayseri, Turkiye

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ABSTRACT

Aims: Chronic hepatitis B virus (CHB) infection causes chronic liver disease, cirrhosis, and hepatocellular carcinoma. Our study aimed to evaluate the effects of newly initiated tenofovir alafenamide fumarate (TAF) on clinical parameters in naïve and treatment-experienced patients with CHB.

Methods: This retrospective, single-center observational study was performed in the Department of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital. Demographic and clinical characteristics of the cases were obtained from the outpatient clinic follow-up files. The change over time in the clinical data of all patients at the beginning, 3rd, 6th, and 12th months of TAF treatment was evaluated using One-Way Analysis of Variance in Repeated Measures (ANOVA) and Friedman Analysis of Variance in Repeated Measures, according to their compliance with normal distribution.

Results: The mean age of the patients was 56.5±12.2 years, and 59 (57.8%) were male. 70.6% of the patients had at least one additional disease, and the most common additional diseases were hypertension (29.4%) and Diabetes mellitus (23.5%). Of the 102 patients who started TAF treatment, 81 (79.4%) were treatment-experienced, and 21 (20.6%) were treatment-naïve patients. The reasons for switching to TAF treatment were osteoporosis (44.1%), the need for a more potent agent (34.3%), and low GFR (13.7). While the detectable HBV DNA rate was 38.2% at the beginning of treatment, this rate was 2.9% at the 12th month ($p<0.001$). While there was a statistically significant change in ALT, abnormal ALT, and detectable HBV DNA rates from all four follow-up periods within 12 months after the start of TAF treatment (p values <0.001), there was no significant change in AST ($p=0.081$). While the GFR level did not change statistically significantly during the follow-up period ($p=0.381$), the phosphorus level changed statistically significantly (p-value<0.001).

Conclusion: In our study, a significant improvement in detectable HBV DNA, ALT level, and phosphorus level was observed in both naive and treatment-experienced patients with the initiation of TAF.

Keywords: Chronic hepatitis B, tenofovir alafenamide fumarate, alanine transaminase, phosphorus

INTRODUCTION

According to the World Health Organization report, it was reported that approximately 296 million people were living with chronic hepatitis B (CHB) infection worldwide in 2019, and there were 1.5 million new infections every year.1 Chronic hepatitis B virus infection is the leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma.2

The main goals of HBV treatment are to stop disease progression and prevent disease-related complications by suppressing hepatitis B virus (HBV) DNA replication.3 Since complete elimination of the virus is impossible, treatment is usually lifelong. Nucleoside/nucleotide analogs approved to date for the treatment of HBV in humans include lamivudine (LAM), adefovir dipivoxil (ADV), entecavir (ETV), telbivudine (LdT), tenofovir disoproxil fumarate (TDF), and tenofovir alafenamide (TAF).4

Drugs with high barriers against the development of antiviral resistance in HBV treatment are ETV, TDF, and TAF. These are drugs with high treatment success that effectively suppress HBV-DNA in the majority of patients. TDF is converted to tenofovir by hydrolysis and then phosphorylated to tenofovir diphosphate by cellular enzymes.5 Side effects associated with TDF include lactic acidosis, severe hepatomegaly with steatosis, osteoporosis, and nephropathy. As the CHB population ages, more patients will likely develop bone loss.6-8

Corresponding Author: Murat Oğuz ÖZİLHAN, murat_ozilhan@hotmail.com

TAF is the last licensed treatment option for HBV treatment in our country and in the world. Our country's reimbursement scope included it with the Health Implementation Communiqué dated June 2020. First, it is approved for use in patients whose use of TDF is limited due to osteoporosis and nephropathy. However, it can be used today in all CHB patients requiring treatment.9

This study aimed to evaluate the effect of TAF on some clinical parameters, GFR, and phosphorus levels in patients with CHB.

METHODS

This retrospective, single-center observational study was performed in the Department of Infectious Diseases and Clinical Microbiology, Kayseri City Hospital. The study was approved by the Kayseri City Hospital Clinical Researches Ethics Committee (Date: 28.11.2023, Decision No: 953). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

CHB patients aged 18 years and over who started TAF treatment with appropriate indications between January 2020 and October 2023 at the infectious diseases and clinical microbiology outpatient clinic of Kayseri City Hospital were retrospectively examined. Demographic and clinical characteristics of the cases were obtained from the outpatient clinic follow-up files. The criteria for conversion to TAF were determined as follows: 1. Hypophosphatemia; serum phosphorus level <2.5 mg/dl, 2. osteoporosis; T score on BMD <-2.5, 3. low GFR; creatinine clearance <60 ml/min and 4. detectable HBV DNA; HBV DNA level > 20 IU/ml. Elevated alanine aminotransferase (ALT) was defined according to AASLD criteria (>35 U/L in men, >25 U/L in women).10 Liver fibrosis staging and histological activity index (HAI) scores were evaluated using the Modified Ishak Scoring System.11

Statistical Analysis

Categorical data were presented as frequency distributions and percentages, and continuous variables were presented as mean (± standard deviation) and median (minimum and maximum). The chi-square test was used to compare categorical data. The normal distribution of continuous variables was evaluated with the Kolmogorov-Smirnov test. Normally distributed glomerular filtration rate (GFR) and serum phosphate level were compared using the Paired-Samples T-test. AST, ALT, and normalized ALT that did not show normal distribution were compared using the non-parametric Wilcoxon test. Repeated measurements of normally distributed glomerular filtration rate (eGFR) and phosphate level were evaluated using "one-way analysis of variance in repeated measurements (ANOVA)." Mauchly's test of sphericity was used to test the ANOVA assumption of sphericity. In Mauchly's sphericity test, when p <0.05, the sphericity assumption was considered not fulfilled, and the epsilon value was checked. When the epsilon value was less than 0.75, the "Greenhouse-Geisser" value was used, and when it was more significant, the "Huynh-Feldt" value was used. The data were then evaluated at the 0.05 significance level using the Bonferroni correction. AST, ALT, and normalized ALT values that did not show normal distribution were assessed using "friedman analysis of variance in repeated measurements." In the data with a difference according to the friedman test, the "Wilcoxon paired two sample test" was used to find out which data caused the difference.

RESULTS

The average age of the patients was 56.5±12.2 years, and 59 (57.8%) were male. 70.6% of the patients had at least one comorbidity, and the most common comorbidities were hypertension (29.4%) and Diabetes mellitus (23.5%). Of the 102 patients who started TAF treatment, 81 (79.4%) were treatment-experienced, and 21 (20.6%) were treatment-naïve patients. The reasons for switching to TAF treatment were osteoporosis (44.1%), the need for a more potent agent (34.3%), and low GFR (13.7). The patient's baseline characteristics are presented in **Table 1**.

The change in HBV DNA detection over time in all patients at the beginning, 3, 6, and 12 months of TAF treatment is presented in **Figure 1**. While the detectable HBV DNA rate was 38.2% at the beginning of treatment, this rate was 2.9% at the 12th month (p<0.001).

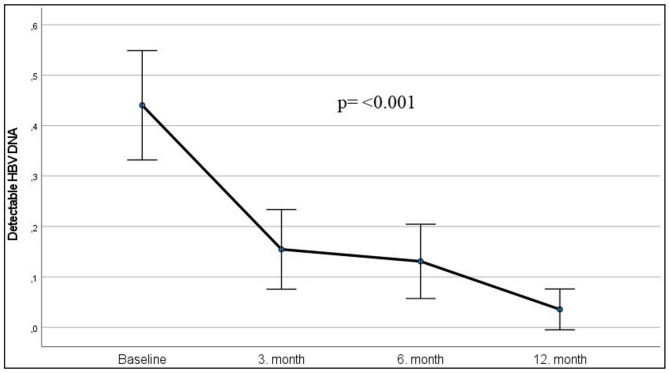

Figure 1. The changes in detectable HBV DNA over time

The change graph in the patients' AST, ALT, eGFR, and phosphorus levels at the beginning of TAF treatment and the 3rd, 6th, and 12th months is presented in **Figure 2**. While there was a statistically significant change in ALT, abnormal ALT, and detectable HBV DNA rates obtained from all four follow-up periods within 12 months after the start of TAF treatment (p values<0.001), there was no significant change in AST value (p=0.081) (**Table 2**). ALT level, abnormal ALT, and detectable HBV DNA rates decreased significantly during the follow-up period.

Table 1. Baseline characteristics of the patients (n=102)

Characteristics	n (%)
Age, years, (mean± Std)	56.5±12.2
Male mean	59 (57.8)
Comorbidities	72 (70.6)
Diabetes	24 (23.5)
Hypertension	30 (29.4)
COPD	10 (9.8)
Cardiovascular disease	9 (8.8)
CKD	5 (4.9)
Cirrhosis	5 (4.9)
Malignancy	13 (12.7)
Transplant patient	7 (6.9)
Rheumatological disease	19 (18.6)
Previous treatment	
Naïve	21 (20.6)
Tenofovir disoproxil fumarate	59 (57.8)
Entecavir	32 (31.4)
Lamivudine	22 (21.6)
Tenofovir disoproxil fumarate+entecavir	6 (5.9)
Causes for the initiation of TAF treatment	
Proteinuria	10 (9.8)
Osteoporosis	45 (44.1)
Phosphorus level <2.5, mg/dl	2 (2)
eGFR <60, ml/min/1.73 m²	14 (13.7)
Switching to a more potent drug	35 (34.3)
Detectable HBV DNA	39 (38.2)
Prevalence of high ALT	27 (26.5)
HAI (mean± Std)	6.3±2.2
Fibrozis (stage) (mean±Std)	2.8±1.3
White blood cell count (10^3/mm³) (mean±Std)	7±1.9
Thrombocyte (10^3/mm³) (mean±Std)	234.7±71.5
eGFR (mL/min/ 1.73 m²) (mean±Std)	88.9±24.1
Phosphorus (mg/dl) (mean±Std)	3.2±0.68
Hemoglobin (mg/dl) (median, IQR)	14.9 (13.5-15.9)
AST (U/L) (median, IQR)	21 (17-28)
ALT (U/L) (median, IQR)	18 (15-30.5)

COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, HAI: Histological activity index, eGFR: Estimated glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, IQR: Interquartile ranges, Detectable HBV DNA: HBV DNA level >20 IU/ml, High ALT was defined according to AASLD criteria (>35 U/L in men, >25 U/L in women)

Table 2. Change in the AST, ALT values, and abnormal ALT level according to AASLD criteria

Factors (n)	Baseline, median (IQR)	3rd month, median (IQR)	6th month, median (IQR)	12th month, median (IQR)	Friedman Test p-value	Wilcoxon analysis p-value
AST (U/L)	21 (17-28)	21 (17-29)	20 (17-26.5)	20 (16-23)	0.081	
ALT (U/L)	21.5 (16-48)	22 (16-44.5)	19 (14-26.2)	18 (14.7-22)	<0.001	
				Baseline vs	3rd month	0.443
					6th month	0.004
					12th month	<0.001
				3rd month vs	6th month	0.002
					12th month	<0.001
				6th month vs	12th month	0.005
Prevalence of abnormal ALT (n, %)	27 (26.5)	27 (26.5)	11 (10.8)	6 (5.9)	<0.001	
				Baseline vs	3rd month	0.346
					6th month	0.008
					12th month	<0.001
				3rd month vs	6th month	<0.001
					12th month	<0.001
				6th month vs	12th month	0.059
Detectable HBV DNA (n, %)	39 (38.2)	13 (12.7)	11 (10.8)	3 (2.9)	<0.001	
				Baseline vs	3rd month	<0.001
					6th month	<0.001
					12th month	<0.001
				3rd month vs	6th month	0.317
					12th month	0.002
				6th month vs	12th month	0.005

AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, AASLD: American Association for the Study of Liver Diseases, IQR: Interquartile range

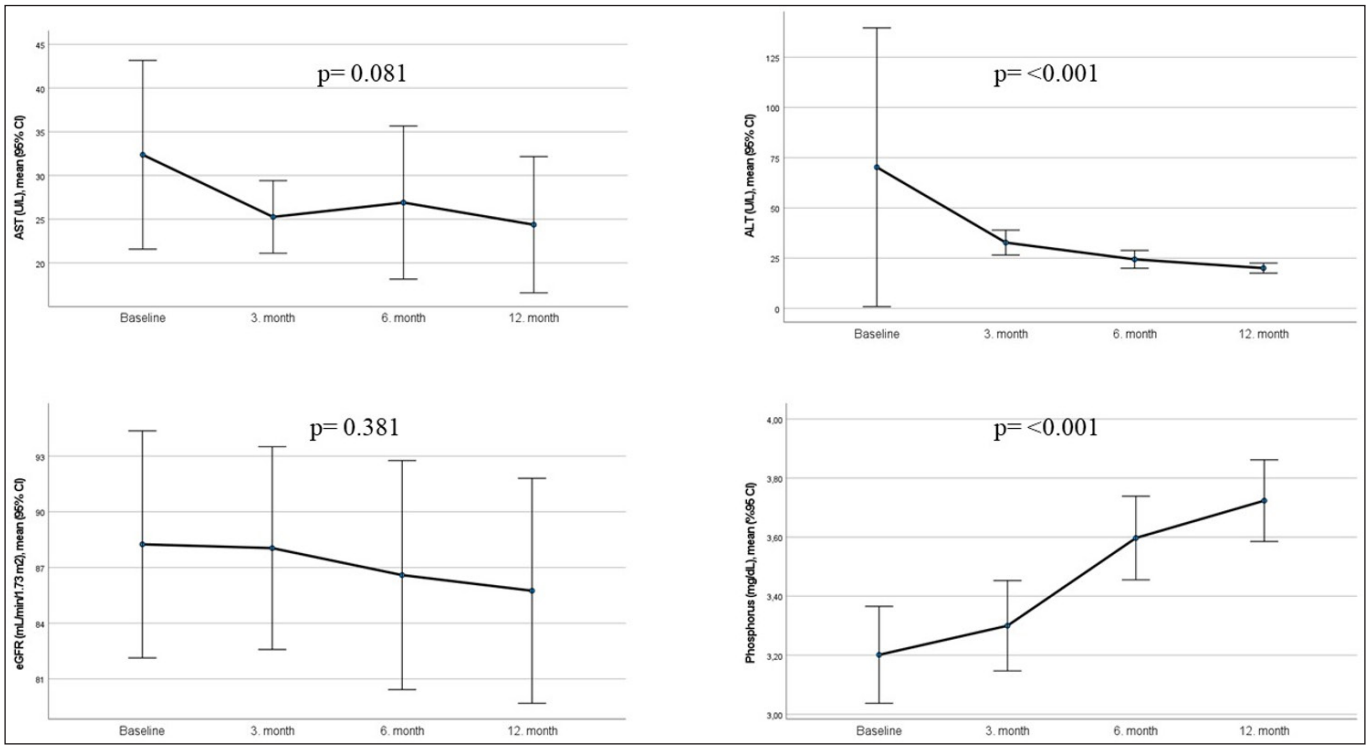

Figure 2. The changes in AST, ALT, eGFR, and phosphorus levels over time

When eGFR and phosphorus data obtained from all four follow-up periods within 12 months after switching to TAF treatment were examined, while the eGFR level did not change statistically significantly during the follow-up period (p=0.381), the phosphorus level changed statistically significantly (p-value<0.001). After starting TAF treatment, the phosphorus level increased statistically significantly (**Table 3**).

DISCUSSION

The best predictor of HBV infection treatment response is the course of HBV DNA. Achieving undetectable HBV DNA directly correlates with positive clinical outcomes.[12] In our study, the rate of detectable HBV DNA in CHB patients at 12 months was 2.9%. A high virological response was achieved in 97.1% of patients. This effective antiviral treatment can be explained by the longer plasma half-life of TAF and its more effective concentration in hepatocytes.[12]

The EASL (European Association for the Study of the Liver) 2017 clinical practice guideline on managing hepatitis B virus infection identified ALT normalization as another endpoint of long-term suppression of viral replication in treating HBV infection.[13] In our study, consistent with the literature, it was observed that median ALT values decreased significantly with the initiation of TAF. Abnormal ALT rates, according to AASLD criteria, also decreased significantly. However, it has been stated in the literature that ALT normalization may be affected by various factors such as being overweight, having low albumin, being young, and having a high cholesterol level.[12,14]

Tenofovir disoproxil fumarate has adverse effects on renal function and bone mineral density. It is known that there is a decrease in bone density and kidney function with TDF. In addition to risk factors such as age and baseline renal function, urinary excretion of low molecular weight proteins, phosphate, uric

Table 3. Change in the eGFR and phosphorus levels

Factors (n)	Baseline, mean± SD	3rd month, mean± SD	6th month, mean± SD	12th month, mean± SD	ANOVA Test p-value	p-value*
eGFR (mL/min/1.73 m²)	88.25±24.5	88±21.9	86.6±24.7	85.8±24.3	0.381	
Phosphorus (mg/dl)	3.2±0.67	3.3±0.63	3.6±0.58	3.7±0.6	<0.001	
				Baseline vs	3rd month	0.194
					6th month	<0.001
					12th month	<0.001
				3rd month vs	6th month	<0.001
					12th month	<0.001
				6th month vs	12th month	0.215

eGFR: glomerular filtration rate, *: Adjustment for multiple comparisons: Bonferroni.

acid, and glucose increases with TDF. In extensive studies, the use of TDF has been identified as one of the main risk factors associated with chronic kidney disease. Hyperphosphaturia secondary to tubular dysfunction can lead to progressive bone loss. Bone loss due to changes in phosphate metabolism can be rapidly resolved by TDF discontinuing.[15] The information provided suggests that there are studies in the literature demonstrating no significant association between the use of TDF and a higher degree of kidney damage in patients with HBV compared to other nucleoside and nucleotide reverse transcriptase inhibitors. Specifically, it has been shown that TDF is not associated with a worsening of kidney function during short or medium-term follow-up periods in patients without significant renal failure.[16,17] In our study, we observed no significant change in GFR values during the follow-up period, and we attribute this to the fact that the initial and follow-up GFR levels in the patients of our study were nearly normal overall. Furthermore, our study is consistent with the literature in showing a significant increase in phosphate levels at 3, 6, and 12 months after the initiation of tenofovir alafenamide (TAF) treatment.[18,19]

Limitations

Our study had some limitations. The most important limitation of this study is that it is a retrospective study. Additionally, our study included a small number of patients. Since there were deficiencies in the necessary follow-up of patients for osteoporosis/osteopenia, sufficient information could not be obtained about the effects of TAF on bone tissue. Another limitation of our study was that data regarding the measurements of the patients' lipid profiles during the follow-up period were missing. For this reason, the changes in the patients' lipid profiles over time could not be investigated. There was no significant change in GFR level in our study. We think longer-term follow-up data is needed for the change in GFR to be meaningful.

CONCLUSION

In our study, a significant improvement in detectable HBV DNA, ALT level, and phosphorus level was observed in both naïve and treatment-experienced patients with the initiation of TAF. In addition, a positive but not statistically significant change was observed in AST and GFR. TAF, whose reliability in terms of bone and kidney is supported by various studies, is a promising treatment option for side effects that may occur in patients using TDF.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Kayseri City Hospital Clinical Researches Ethics Committee (Date: 28.11.2023, Decision No: 953).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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