







## Investigation of Efficacy and Safety in Chronic Hepatitis B Patients Receiving Tenofovir Alafenamide Treatment

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### ABSTRACT

**Objective:** The objective of this study was to evaluate the long-term efficacy and safety in chronic hepatitis B (CHB) patients who were treated with Tenofovir Alafenamide (TAF) for at least one year.

**Materials and Methods:** A total of 133 patients diagnosed with CHB and treated with TAF between June 2018 and June 2022 were screened. Biochemical, serological, and molecular data, patient complaints, and physical examination findings were scanned. These collected data were reviewed retrospectively to investigate their relationship with TAF.

**Results:** In this study, 78 patients were included. The median (minimum-maximum) age of the patients was 56.5 (24–84) years, and 52.6% of them were male. Of the patients, 74.4% were treatment-experienced and 85.9% were hepatitis B e antigen (HBeAg) negative. Virological response rates at the 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months were 88.5%, 81.3%, and 100%, respectively. Biochemical response rates at the 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months were 72.7%, 90.9%, and 90.9%, respectively. Anti-HBe seroconversion with HBeAg loss occurred in two (18.2%) patients. Hepatitis B surface antigen (HBsAg) loss was detected in only one (1.3%) patient. In 39.7% of the patients, a total of 44 symptoms or findings that could be associated with drug adverse events were found. The three most common adverse events were weight gain (11.5%), weight loss (8.9%), and pruritus (8.9%). Treatment was discontinued in one patient (1.3%) due to the detection of hyperlipidemia.

**Conclusion:** TAF is an effective and safe treatment option for CHB, controlling the disease and preventing complications. Further studies are needed, especially to investigate the metabolic effects of TAF.

**Keywords:** Hepatitis B, tenofovir alafenamide, long-term, efficacy, safety.



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### INTRODUCTION

Hepatitis B virus (HBV) is the main cause of chronic viral hepatitis. Approximately 296 million people worldwide live with chronic hepatitis B (CHB), which causes over 800,000 deaths annually due to associated complications.<sup>1</sup> Türkiye is among the countries with intermediate endemicity. According to a recent study, the hepatitis B surface antigen (HBsAg) positivity rate was determined to be 4%.<sup>2,3</sup>



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Tenofovir alafenamide (TAF) is a nucleotide reverse transcriptase inhibitor and a tenofovir prodrug like tenofovir disoproxil fumarate (TDF).<sup>4</sup> In non-inferiority studies comparing TAF and TDF, TAF treatment offers greater bone and renal safety while maintaining efficacy comparable to TDF.<sup>5,6</sup> Worsening of the lipid profile of patients was observed after switching from TDF to TAF in some studies.<sup>7,8</sup> Body weight gain was also noted in treatment-experienced CHB patients after switching to TAF.<sup>9</sup>

In our country, TAF is a relatively new treatment regimen that has been used in the treatment of CHB. This study aimed to evaluate the efficacy and safety of CHB patients treated with TAF for at least one year.

## MATERIALS AND METHODS

Patients diagnosed with CHB and treated with TAF in the Infectious Diseases and Clinical Microbiology Outpatient Clinic at Erciyes University Faculty of Medicine between June 1, 2018 and June 1, 2022 were included in this retrospective study. The medical records of the patients were obtained from hospital information records and medical files.

Patients over 18 years of age, treated with TAF for at least one year, treatment-naïve or experienced, non-cirrhotic patients were included in this study. Patients who did not attend their follow-ups regularly, died, and were co-infected with hepatitis C virus (HCV), human immunodeficiency virus (HIV), and hepatitis D virus (HDV) were excluded from the study.

Age, gender, comorbid diseases, adverse events, treatment experience, treatments used in treatment-experienced patients, biochemical, serological, and molecular parameters were all recorded. Patient complaints and physical examination findings were reviewed retrospectively in line with the anamnesis that was questioned and recorded during outpatient follow-ups at regular intervals. These collected data were evaluated, and their relationship with the use of TAF was investigated.

The following parameters were retrospectively scanned at the beginning of the treatment and during follow-ups (3<sup>rd</sup>, 6<sup>th</sup>, 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months): hemoglobin, leukocyte, platelet, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase, direct bilirubin, total bilirubin, blood urea nitrogen (BUN), creatinine, albumin, total protein, alpha-fetoprotein (AFP), serum calcium, serum potassium, and serum sodium levels.

Serological imaging for hepatitis B was performed by the third-generation enzyme immunoassay (EIA) method HBsAg, HBeAg, hepatitis B surface antibody (anti-HBs), hepatitis B core antibody (anti-HBc), hepatitis B e antibody (anti-HBe), hepatitis C antibody (anti-HCV); Cobas; Roche, USA). HBV DNA level was measured by real-time polymerase chain

## KEY MESSAGES

- Our study's evaluation of virological and biochemical response rates demonstrated high success rates for tenofovir alafenamide (TAF). According to the results of our study, TAF has proven to be an effective option for managing chronic hepatitis B (CHB), controlling the progression of the disease and preventing complications. The results of our study regarding adverse events and overall safety suggest that TAF is a safe treatment option. However, further research is necessary to explore the metabolic effects associated with TAF treatment.

reaction (RT-PCR) method (Abbott RealTime HBV; Abbott Laboratories, Germany).

### Definition of Terms Used in the Study

Patients with HBV DNA levels less than 10 IU/ml were considered undetectable/negative for HBV DNA. Undetectable serum HBV DNA during therapy was considered a virological response.<sup>10</sup>

The decrease in serum ALT level to the normal range (<40 U/L) was considered a biochemical response.<sup>11</sup>

The serological response is defined as HBeAg loss and seroconversion to anti-HBe in patients with HBeAg-positive chronic HBV infection, and HBsAg loss and seroconversion to anti-HBs for all patients.<sup>10,11</sup>

### Statistical Analyses

Data were analyzed using the SPSS 25.0 software package (license: Z125-3301-14). Descriptive statistics are presented as means with standard deviations. The Friedman test was used to examine measurements at different times, and the Durbin-Conover test was applied to assess differences in measurements. The McNemar test was performed to determine whether HBV DNA levels differed at various times. P-values less than 0.05 were considered statistically significant in the study.

This study was approved by the Non-Invasive Clinical Research Ethics Committee of Erciyes (date: May 25, 2022; number: 2022/416).

## RESULTS

A total of 133 patients underwent screening. Fifty-three patients who did not meet the study requirements were excluded. The records of eighty patients were reviewed, and it was determined that the treatments of two patients were stopped within the first month due to adverse events. Data from 78 patients were analyzed in the study (Fig. 1).

**Table 1.** Demographic data, treatment experience, predisposing diseases, and previously used treatments of the patients

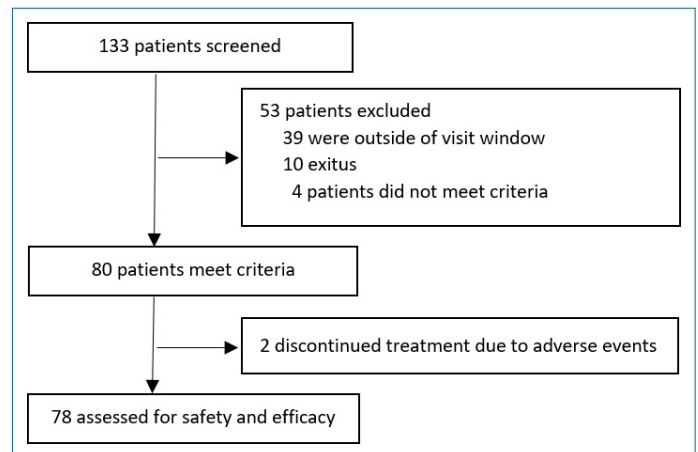
	n
Median age (range)	56.5 (24–84)
Sex	
Female	37
Male	41
Treatment experience	
Naive	20
Experienced	58
Predisposing diseases*	
Hypertension	23
Diabetes mellitus	10
Coronary artery disease	6
Chronic kidney disease	3
Chronic obstructive pulmonary disease/asthma	5
Malignancy	8
Other	18
Previously used treatments*	
Tenofovir disoproxil fumarate	42
Entecavir	14
Lamivudine	10
Adefovir	2
Telbivudine	1
Interferon	2

\*: Multiple choices can be selected for each patient.

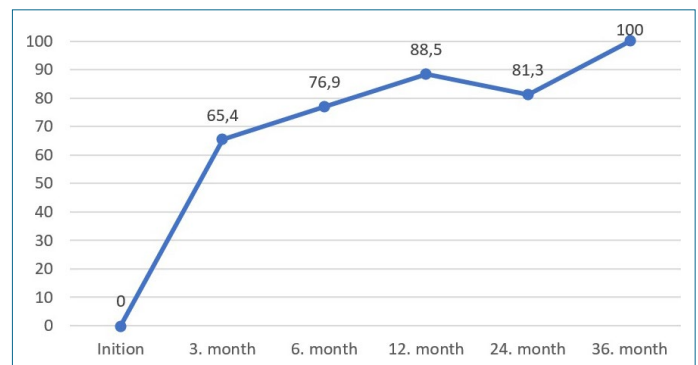
In this study, 78 patients were included. The demographic data, treatment experience, predisposing diseases, and previously used treatments are detailed in Table 1.

The number of patients with detectable viremia (HBV DNA level >10 IU/ml) at the beginning of TAF treatment was 26 (33.3%) (Appendix 1). Virological response rates at the 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months were 88.5%, 81.3%, and 100%, respectively (Fig. 2). It was observed that the virological response was faster in the HBeAg-negative patient group (Fig. 3). Among treatment-experienced patients (n=58), the rates of negative HBV DNA levels (<10 IU/ml) at the 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months were 98.3%, 97.2%, and 100%, respectively.

There were 11 (14.1%) patients with an ALT level above 40 U/L at the beginning of TAF treatment. Biochemical response rates at the 12<sup>th</sup>, 24<sup>th</sup>, and 36<sup>th</sup> months were 72.7%, 90.9%, and 90.9%, respectively (Fig. 4).



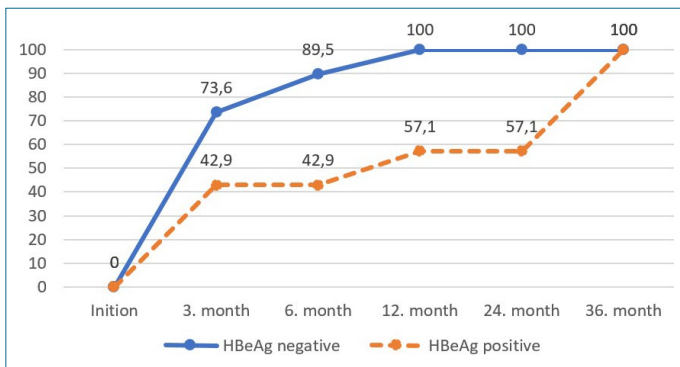
**Figure 1.** Flowchart illustrating the inclusion of patients in the study.



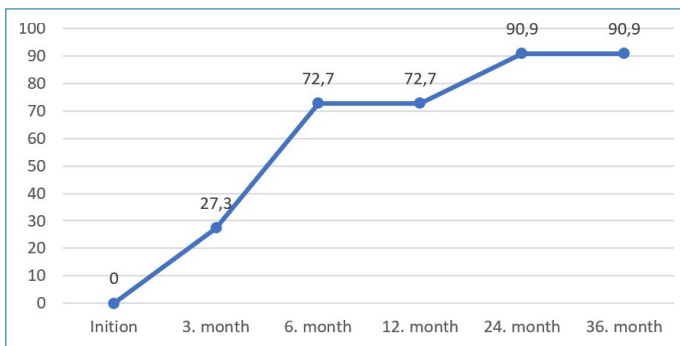
**Figure 2.** Virological response rates of patients over time (%).

There were 11 patients who were HBeAg positive at the beginning. Anti-HBe seroconversion with HBeAg loss occurred in two (18.2%) of these patients. HBsAg loss was detected in only one (1.3%) patient. However, anti-HBs seroconversion did not occur in any patient.

A statistically significant decrease in platelet counts was detected in the 24<sup>th</sup> and 36<sup>th</sup> months compared to the baseline and other months (p=0.01). There was a statistically significant increase in gamma-glutamyl transferase (GGT) and direct bilirubin levels in the 36<sup>th</sup> month compared to other months (p=0.01). It was observed that initial alpha-fetoprotein (AFP) levels decreased statistically significantly with TAF treatment compared to other months (p=0.04). In our study, creatinine levels were observed to increase over time. While the average of estimated glomerular filtration rate (e-GFR) measurements was 94 mL/min/1.73m<sup>2</sup> at the beginning, it decreased to 85 mL/min/1.73m<sup>2</sup> in the 36<sup>th</sup> month. However, these changes were not statistically significant (p=0.25) (Appendix 1).



**Figure 3.** Virologic response rates of patients over time, categorized by HBeAg status (%).



**Figure 4.** Biochemical response rates of patients over time (%).

In 39.7% of the patients, a total of 44 symptoms or findings that could be associated with drug adverse events were found. The three most common signs or symptoms that can be associated with adverse events are weight gain (11.5%), weight loss (8.9%), and pruritus (8.9%) (Table 2).

Treatment was discontinued due to the detection of hyperlipidemia in one (1.3%) patient, a 24-year-old treatment-naïve woman. It was decided to discontinue treatment after hyperlipidemia was detected in the first year of TAF treatment.

**DISCUSSION**

The first studies with a large patient population on the efficacy and safety of TAF in CHB patients were non-inferiority studies in which it was compared with TDF. In the results of these studies, TAF was not less effective than TDF in both HBeAg-positive and HBeAg-negative CHB patients. In these studies, the percentage of patients with HBV DNA below 29 IU/mL at the 48<sup>th</sup>, 96<sup>th</sup>, and 144<sup>th</sup> weeks was 94%, 90%, 93% in HBeAg-negative patients, and 64%, 73%, 83% in HBeAg-positive patients, respectively.<sup>5,6,12,13</sup> Since the majority of the patients involved in this study were treatment-experienced, virological response

**Table 2.** Adverse events occurring in patients

	n=78 (%)
Weight gain	9 (11.5)
Weight loss	7 (8.9)
Pruritus	7 (8.9)
Fatigue	6 (7.6)
Abdominal pain	4 (5.1)
Headache	3 (3.8)
Rash	3 (3.8)
Hyperlipidemia	3 (3.8)
Insomnia	2 (2.5)

rates were obtained from a relatively small number of patients (n=26). Nevertheless, the virological response rates of our study are similar to those in studies with a large patient population.

It has been observed that the success rate is over 92% when treatment-experienced patients are switched to TAF.<sup>14,15</sup> Our study’s success rates in this patient group were over 97%. These results show that TAF is an effective option for patients who need to switch treatment due to adverse events or other reasons while currently receiving treatment.

The low platelet, high GGT, and direct bilirubin levels seen in the 36<sup>th</sup> month data of our study were statistically significant. However, no data were found in the literature review and drug label information indicating that TAF could cause thrombocytopenia or cholestasis. The results of our study can be considered as a new finding regarding the possible long-term effects of TAF.

In our study, a worsening of the renal functions of the patients was detected after long-term treatment compared to the beginning. Various studies have shown that TAF treatment has a favorable renal profile compared to TDF. However, it should not be forgotten that TAF is a prodrug of tenofovir and has nephrotoxic potential. A variety of renal adverse events, including acute renal failure, Fanconi syndrome, and proximal tubular nephropathy, have been reported in patients using treatment regimens containing TAF.<sup>16–18</sup> Because the duration of usage is uncertain, just like other nucleoside analogs, patients exposed to TAF for a long time should be closely monitored for renal function.

In various studies, the most commonly reported treatment-emergent adverse events included headache, nasopharyngitis, upper respiratory tract infection, and cough.<sup>5,6,12,13</sup> Another adverse event reported in patients using TAF is changes in the lipid profiles. Studies show an increase in dyslipidemia rates in CHB patients switching from TDF to TAF and recommend

close monitoring of the lipid profile in this patient group.<sup>7,14</sup> In another study that included CHB patients and a non-CHB control group, there was no significant distinction in lipid profiles between the control group and the patient group receiving TAF. However, the patient group that received TDF had a better lipid profile than the other two groups. It was thought that the hyperlipidemia observed in the patient group switching from TDF to TAF may be due to the disappearance of the lipid-lowering effect of TDF.<sup>19</sup>

In our study, the most common symptom or finding that could be associated with adverse events was changes in the body weight of the patients during the treatment process. Many studies have reported an increase in body weight in individuals living with HIV after switching to a TAF-containing regimen.<sup>20–22</sup> However, there are not many studies evaluating body weight in CHB patients receiving TAF treatment. In a study conducted by Yeh et al.,<sup>9</sup> published in 2022, 121 patients who were switched to TAF treatment from other nucleoside analogs (NAs) were followed for at least one year. At the end of the 12<sup>th</sup> month, the average body weight of the patients increased from 66.4±11.8 to 67.8±12.3 kilograms, and this increase was found to be statistically significant. In our study, weight gain was detected in 11.5% of the patients, while 8.9% experienced weight loss. Many different parameters impact body weight. The choice of TAF for CHB treatment should be decided individually for each patient.

No significant HBV DNA elevation was observed in any of our patients during follow-up. For this reason, resistance testing was not performed on any patient. With these results, it is possible to say that drug resistance did not develop in any of our patients under TAF treatment.

This study has some limitations. The study was retrospective and single-centered. Many patients were excluded from the study due to disruptions of their routine outpatient follow-ups caused by the Coronavirus Disease 2019 (COVID-19) pandemic. Lipid profile tests could not be evaluated in most of the patients because they were missing in the initial and early follow-ups. The weight of the patients was not monitored regularly.

## CONCLUSION

When the virological and biochemical response rates of our study were evaluated, TAF was found to have high success rates. According to the results of our study, TAF is an effective treatment option in the treatment of CHB, controlling the disease and preventing complications. Considering the results of our study regarding adverse events and safety, it can be said that TAF is a safe treatment option. However, new studies are needed, especially to investigate the metabolic effects of TAF treatment.

**Ethics Committee Approval:** The Erciyes University Non-Invasive Clinical Research Ethics Committee granted approval for this study (date: 25.05.2022, number: 2022/416).

**Author Contributions:** Concept – HNK, OY, BA, KK, ZT, GKÜ; Design – HNK, OY, BA, KK, ZT, GKÜ; Supervision – HNK, OY, BA, KK, ZT, GKÜ; Resource – HNK, OY; Materials – HNK, OY; Data Collection and/or Processing – HNK, OY; Analysis and/or Interpretation – HNK, OY, BA, KK, ZT, GKÜ; Literature Search – HNK, OY; Writing – HNK; Critical Reviews – HNK, OY, BA, KK, ZT, GKÜ.

**Conflict of Interest:** The authors have no conflict of interest to declare.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Use of AI for Writing Assistance:** Not declared.

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**Peer-review:** Externally peer-reviewed.

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**Appendix 1.** Initial and follow-up laboratory data of the patients

	Initial	3 <sup>rd</sup> month	6 <sup>th</sup> month	12 <sup>th</sup> month	24 <sup>th</sup> month	36 <sup>th</sup> month	p	Difference
Detectable HBV DNA (n,%)	26 (100)	9 (34.6)	6 (23.1)	3 (11.5)	3 (11.5)	0 (0)	<b>0.01*</b>	0>3-6>12-24>36
Leukocyte (10 <sup>3</sup> /μL)	8328.85±9492.83	8910.64±14349.53	7939.77±7342.98	7572.66±4628.48	8097.78±11213.43	7836.25±7922.83	0.19	-
Hemoglobin (g/dL)	14.45±1.78	14.32±1.78	14.37±1.84	14.43±1.86	14.49±1.72	14.59±1.36	0.27	-
Platelet (10 <sup>3</sup> /μL)	240205.13±69395.98	244730.77±72884.12	245512.82±68641.69	244628.21±67263.02	237092.59±65499.90	227500±71571.02	<b>0.01*</b>	0-3-6-12>24-36
ALT (U/L)	25.06±18.85	22.05±13.87	20.46±9.94	23.08±25.79	18.87±8.19	17.59±10.94	<b>0.01*</b>	0>3-6-12>24-36
AST (U/L)	23.06±11.36	21.15±7.11	21.08±9.25	21.72±13.11	19.2±6.57	19.69±10.62	<b>0.01*</b>	0>3-6-12>24-36
BUN (mg/dL)	13.87±5.47	14.92±7.52	13.88±5.04	14.43±6.28	13.98±5.85	13.70±5.07	0.19	-
Creatinine (mg/dL)	0.86±0.56	0.92±0.77	0.86±0.56	0.89±0.79	0.96±0.84	0.98±0.73	0.34	-
e-GFR (mL/min/1.73 m <sup>2</sup> )	94.37±20.39	91.87±20.25	94.62±19.45	93.55±20.33	89.67±20.58	85.88±19.50	0.25	-
Total bilirubin (mg/dL)	0.54±0.28	0.51±0.26	0.53±0.27	0.49±0.23	0.54±0.28	0.57±0.39	0.39	-
Direct bilirubin (mg/dL)	0.22±0.09	0.21±0.09	0.22±0.08	0.21±0.07	0.22±0.09	0.24±0.12	<b>0.01*</b>	36>0-3-6-12-24
GGT (U/L)	28.26±65.03	31.37±75.77	32.50±79.09	32.28±63.18	27.19±43.21	44.38±102.26	<b>0.01*</b>	36>0-3-6-12-24
Alkaline phosphatase (U/L)	84.31±60.61	83.81±62.84	82.90±60.46	83.79±48.17	84.87±52.02	85.78±67.52	0.45	-
Albumin (g/dL)	4.59±0.39	4.54±0.36	4.56±0.33	4.52±0.40	4.54±0.34	4.55±0.33	0.56	-
Total protein (g/dL)	7.43±0.52	7.31±0.48	7.35±0.48	7.42±0.49	7.33±0.52	7.34±0.50	0.29	-
Serum sodium (mmol/L)	140.96±2.49	140.29±2.43	140.03±2.46	140.22±1.96	139.96±2.31	140.15±2.54	0.57	-
Serum potassium (mmol/L)	4.47±0.42	4.45±0.30	4.44±0.33	4.48±0.43	4.45±0.42	4.49±0.34	0.48	-
Serum calcium (mg/dL)	9.55±0.42	9.47±0.36	9.49±0.42	9.48±0.42	9.50±0.39	9.50±0.31	0.46	-
AFP (U/mL)	2.11±1.06	1.90±0.92	1.89±0.83	1.85±0.85	1.94±0.93	1.85±0.77	<b>0.04*</b>	0>3-6-12-24-36

Data are Mean±SD, unless otherwise stated. HBV: Hepatitis B virus; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; BUN: Blood urea nitrogen; e-GFR: Estimated glomerular filtration rate; GGT: Gamma-glutamyl transferase; AFP: Alpha-fetoprotein.