Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1179106
J Health Sci Med 2022; 5(6): 1688-1692

Evaluation of the safety and antiviral efficacy of the tenofovir alafenamide fumarate molecule in immunosuppressed patients

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Cite this article as: Durak S, Coşar AM. Evaluation of the safety and antiviral efficacy of the tenofovir alafenamide fumarate molecule in immunosuppressed patients. J Health Sci Med 2022; 5(6): 1688-1692.

ABSTRACT

Aim: Patients with chronic or prior hepatitis B virus (HBV) infection may experience HBV reactivation during immunosuppressive therapy. The objective of this study was to evaluate the safety and antiviral efficacy of tenofovir alafenamide fumarate (TAF) for prophylaxis of HBV reactivation in patients on immunosuppressive therapy.

Material and Method: This study included patients who were started on immunosuppressive treatment due to hematologic/solid malignancy, autoimmune disease, or inflammatory disease and were treated with TAF for at least six months due to HBsAg and/or total anti-HBc positivity at Karadeniz Technical University Farabi Hospital between January 2018 and February 2021. Electronic medical records were retrospectively reviewed and the adverse event profile was analyzed.

Results: Of the 94 patients enrolled in the study, 70.2% (n=66) were male. The mean age of the patients was 60.37±14.56 years. The reasons for initiation of immunosuppressive drug treatment were hematologic malignancies in 48.9% (n=46), solid tumors in 27.7% (n=26), and other causes (autoimmune/inflammatory) in 23.4% (n=22). There was no statistically significant difference in creatinine, phosphorus, glucose, and LDL profile between baseline and 6-12 months of TAF treatment (p=0.861, p=0.136, p=0.323, p=0.304, respectively). All patients in whom HBV DNA was detectable at baseline became negative at the last follow-up visit. None of the patients developed HBV reactivation and there was no need to discontinue antiviral/immunosuppressive treatment due to side effects.

Conclusion: TAF is a safe and effective short-term option to prevent HBV reactivation in patients receiving immunosuppressive therapy.

Keywords: Hepatitis B, chronic hepatitis B, reactivation, tenofovir alafenamide, chemotherapy, immunosuppression

INTRODUCTION

The Hepatitis B virus (HBV) is a DNA virus that can cause acute/chronic hepatitis, liver failure, liver cancer (HCC), and even death. It has infected more than 2 billion people worldwide, about 400 million of whom have a chronic disease (1,2). Our country is one of the endemic regions at intermediate risk for HBV infection. According to the TURHEP study, the positivity rate for hepatitis B virus surface antigen (HBsAg) was 4% and the positivity rate for hepatitis B core protein antibody (anti-HBc total) was 31% (3).

HBV reactivation may develop in patients with chronic or previous hepatitis B infection during immunosuppressive treatment. Reactivation is characterized by the sudden relapse or elevation of HBV DNA in a patient with previously inactive or disappeared HBV infection. Especially in patients who receive rituximab-based chemotherapy and undergo bone marrow/stem cell transplantation, the reactivation rate can be up to 88% (4-6).

Depending on the efficacy of immunosuppressants and overall HBs-Ag and/or anti-HBc total positivity, the risk of HBV reactivation is classified as high risk (> 10%), intermediate risk (1%-10%), and low risk (< 1%) (7).

The molecules entekavir and tenofovir are oral antiviral drugs recommended as the first-line treatment for HBV due to their high efficacy (8). Tenofovir has two different molecules: tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF). It is known that long-term use of TDF may cause a decrease in bone

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Received: 23.09.2022 **Accepted:** 15.10.2022

mineral density and renal toxicity (9). For these reasons, switching from TDF to TAF or entecavir is recommended in patients who receive long-term antiviral treatment (10,11), and treatment with TAF is recommended in immunosuppressive patients at high risk for bone and renal side effects (12).

The objective of this study was to evaluate the short-term safety and antiviral efficacy of the TAF molecule in immunosuppressed patients.

MATERIAL AND METHOD

The study was conducted with the permission of Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (Date: 24.11.2021, Decision No: 24237859-850). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Since this was a retrospective study, informed consent was not obtained from the patients.

Study Design

This study included patients over 18 years of age who initiated immunosuppressive treatment for hematologic/solid malignancy, autoimmune disease, or inflammatory disease, were found to be HBs-Ag or anti-HBc total positive, started TAF treatment, and had at least six months of treatment and follow-up between January 2018 and February 2021 at Karadeniz Technical University Farabi Hospital (**Figure 1**).

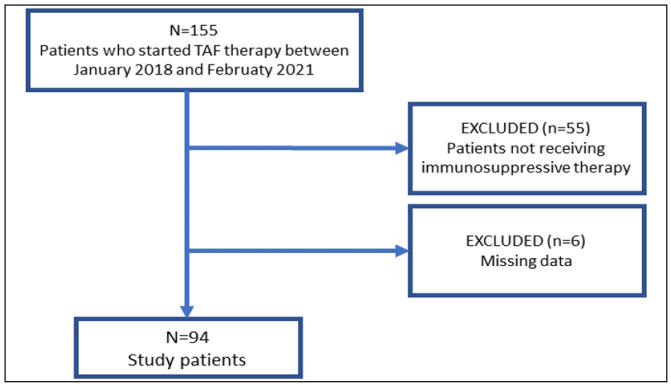

Figure 1. Flow chart of the patients included in the study

Age, sex, body mass index (BMI) (kg/m²), chronic diseases, reason for immunosuppressive treatment, HBV seroprofile (HBs Ag, anti-HBs, HBe, anti-HBe, HBV DNA), creatinine (mg/dL), phosphorus (mg/dL), Data for lipid profile (low density lipoprotein (LDL) (mg/dL), triglycerides (mg/dL), high density lipoprotein (HDL) (mg/dL)) were obtained retrospectively from the hospital electronic data archive. For laboratory tests, baseline values and final values at 6-12 months were recorded. HBV DNA was analyzed by PCR and reported in units of IU/mL.

HBV reactivation was defined as a positive HBV DNA level, a positive HBV DNA level when Hbs-Ag was negative, or a ≥1 log10 increase in baseline HBV DNA level.

Based on immunosuppressive treatment and HBV serology, HBV reactivation risk has been classified as high (> 10%), intermediate (1-10%), and low risk (< 1%) according to the recommendations of the Asian Pacific Association for the Study of Liver (APASL) (7).

Statistical Analysis

The SPSS Windows version 22 program was used for statistical tests. Continuous variables were analyzed by the histogram or Q-Q plot in terms of normal distribution and Shapiro-Wilk or Kolmogorov-Smirnov tests depending on the number of variables. We presented normally distributed continuous variables throughout the study as mean±standard deviation, and the t-test for independent variables was used to compare the two groups. Other continuous variables were presented as median (minimum-maximum), and the nonparametric Mann-Whitney U test was used to compare the groups. We presented categorical variables as frequencies and percentages and used the Pearson chi-square test or Fischer's exact probability test to compare the groups. Tests with a p-value of 0.05 or less at the 95 percent confidence interval were considered statistically significant.

RESULTS

The study included 94 patients. 70.2% (n=66) were male and 29.8% (n=28) were female. The mean age of the patients was 60.37±14.56 years. There was no significant difference between men and women in terms of age (p=0.606). Patients' mean BMI was 26.83±5.74 and no significant difference was found between men and women in terms of BMI (p=0.372) (**Table 1**).

Table 1. Demographic characteristics of the patients

Variable		p
Male / Female, n (%)	66 (70.2) / 28 (29.8)	
Age, mean±SD	60.37±14.56	0.606
Male	59.86±14.99	
Female	61.57±13.65	
BMI, mean±SD	26.83±5.74	0.372
Male	26.42±5.61	
Female	27.80±6.06	

*BMI: Body Mass Index

The comorbidities of the patients were as follows: Hypertension in 40.4% of patients (n=38), diabetes mellitus in 23.4% (n=22), chronic renal failure in 19.1% (n=18), coronary artery disease in 10.6% (n=10), osteoporosis in 7.4% (n=7).

Hematologic malignancies ranked first among causes of immunosuppressive drug treatment with a rate of 48.9% (n=46). Immunosuppressive drug treatment was initiated for solid tumors in 27.7% of patients (n=26) and for other reasons (autoimmune/inflammatory diseases) in 23.4% of patients (**Figure 2**).

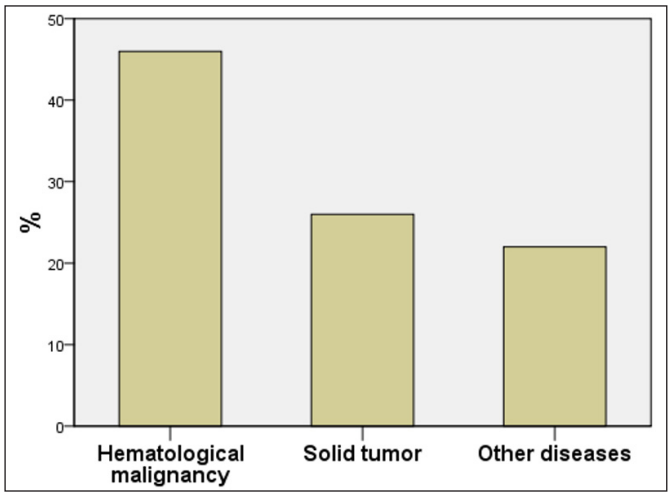

Figure 2. Reasons for initiating immunosuppressive drug treatment

When patients' hepatitis B seroprofiles were analyzed, 24.5% (n=23) were HBs-Ag positive, 75.5% (n=71) were HBs-Ag negative and anti-Hbc total positive.

6.4% (n=6) of patients received antiviral treatment before TAF treatment (one patient with lamivudine, two patients with entecavir, and the remaining three patients with tenofovir disoproxil fumarate). TAF treatment was initiated in two patients because of hypophosphatemia, in one patient because of a GFR <of 60 ml/min/1.73 m², in one patient due to the use of drugs affecting bone mineral density, and in two patients due to the preference of the physician.

Regarding HBV reactivation, 33% (n=31) of patients were at low risk, 42.6% (n=40) were at intermediate risk, and 24.5% (n=23) were at high risk.

When we analyzed serum creatinine (p=0.861), phosphorus (p=0.136), glucose (p=0.323), total cholesterol, LDL, HDL, and triglyceride levels at baseline and after 6-12 months of TAF treatment, no statistically significant difference was found (p>0.05) (**Table 2**).

Table 2. Patients' baseline and most recent laboratory values at follow-up

Variable, mean±SD	Baseline	Most recent	p
Glucose, n=47	120.59±46.76	115.98±42.3	0.323
Creatinine, n=59	0.93±0.43	0.87±0.28	0.861
Phosphorus, n=45	3.49±0.83	3.31±0.71	0.136
Total cholesterol, n=11	215.36±51.21	237.64±81.59	0.262
LDL, n=11	138.82±45.28	156.73±64.22	0.304
HDL, n=12	57.92±29	51.5±15.4	0.402
Triglycerides, n=12	149.42±68.14	196.33±152.293	0.363

*LDL: Low dansity lipoprotein, HDL: High dansity protein

All 17 patients with measurable HBV DNA values before treatment had negative HBV DNA values during follow-up after 6-12 months of TAF treatment. No patient developed hepatitis B reactivation.

Regarding the side effect profile, no patient had to discontinue antiviral treatment.

DISCUSSION

Our country is among the intermediate-risk regions in terms of HBV (3). HBV reactivation is a common complication in patients receiving immunosuppressive therapy and can be prevented by appropriate screening and treatment options (13).

The risk of HBV reactivation is classified into three groups based on HBV serology and immunosuppressive treatment received. HBV reactivation risk is classified as high risk if it is more than 10%, intermediate risk if it is between 1-10%, and low risk if it is <1% (7).

Although there are differences between guidelines, all guidelines recommend initiating prophylactic antiviral treatment in patients with a high risk of reactivation (7,10,12,14).

The American Association for the Study of Liver Diseases (AASLD), APASL, and the European Association for the Study of the Liver (EASL) recommend prophylactic antiviral therapy for all patients with chronic HBV infection, whereas the American Gastroenterological Association (AGA) recommends it only for high- and intermediate-risk patients. For patients with prior hepatitis B infection, the AASLD, APASL, AGA, and EASL recommend prophylactic antiviral therapy for high-risk patients, whereas initiation of antiviral therapy with follow-up is left to the physician's decision for intermediate-risk patients. In low-risk patients, prophylactic antiviral treatment is not recommended. Antiviral treatment should be initiated if HBV reactivation occurs or is suspected during follow-up (7,10,12,14). In the most recent update, the APASL recommends measurement of liver fibrosis in low-risk patients with chronic HBV infection and intermediate-risk patients with prior hepatitis B and recommends initiation of prophylactic antiviral treatment in patients with advanced fibrosis or cirrhosis (7).

In terms of HBV reactivation risk, 33% (n=31) of patients in our study had low risk and 67% (n=63) had moderate and high risk. Prophylactic antiviral treatment is initiated before immunosuppressive treatment to prevent treatment discontinuation after possible HBV reactivation even in low-risk patients and especially in those with hematologic malignancies, due to the late-acquired results of the HBV DNA test (14 days) in our

center and the possibility of treatment discontinuation during follow-up since patients' primary follow-up of HBV reactivation is performed by the clinic where immunosuppressive treatment is first initiated.

It is recommended to start HBV prophylaxis 1-3 weeks before immunosuppressive treatment or at least at the same time (7,10,15). In 48.9% of our patients (n=46), antiviral prophylaxis was initiated before or with immunosuppressive treatment.

Many guidelines recommend entecavir and tenofovir molecules instead of lamivudine for prophylactic antiviral treatment because of their high efficacy and genetic barriers. Yang et al. (16) showed that the risk of HBV reactivation was lower in patients using entecavir, and Picardi et al. (17) showed that the risk of HBV reactivation was lower in patients using tenofovir disoproxil (TDF) compared with lamivudine.

In the literature, TDF use has been associated with decreased renal function and bone mineral density (18,19). Compared with TDF, TAF may produce effects at lower doses because of its high plasma stability and longer plasma life (20,21). It is recommended to use TAF or entecavir instead of TDF in patients at high risk for bone or renal side effects (10,11,22). In our study, consistent with the literature, there was no worsening of patients' renal functions (creatinine and phosphorus levels) (p=0.861 and p=0.136, respectively).

Although the mechanism is unclear, an association between TDF and a decrease in lipid levels has been reported in several studies (23-25). In a study conducted by Malloon et al. (26) examining the lipid profile of patients who were switched from TDF to TAF, an increase in LDL and triglyceride levels was observed after 9-16 months. In our study, an increase in total cholesterol, LDL and triglyceride levels and a decrease in HDL levels were found in patients whose lipid profile was monitored, but no statistically significant difference was found (p>0.05).

Squillace et al. (27) found an increase in glucose levels in patients who were switched from TDF to TAF, and Li et al. (28) found an increase in glucose levels in patients who were switched from entecavir to TAF. In our study, although there was a decrease in patients with glucose monitoring, it was not statistically significant (p=0.323).

The main limitations of our study are that it was a single center and that some of the patients were followed up for HBV reactivation by the clinic where the immunosuppressive treatment was started. Since there are few studies in the literature that include patients receiving immunosuppressive therapy and using antiviral therapy TAF, multicenter prospective studies are needed.

CONCLUSION

TAF is a safe and effective option for preventing HBV reactivation in patients receiving immunosuppressive therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was conducted with the permission of Karadeniz Technical University Faculty of Medicine Scientific Researches Ethics Committee (Date: 24.11.2021, Decision No: 24237859-850).

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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