Research Article

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HBV prophylaxis with TAF in immunosuppressive therapy

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Efficacy and tolerability of tenofovir alafenamide fumarate prophylaxis in HBV-infected individuals receiving chemo/immunosuppressive therapy

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Abstract

Background and Aim: This study aimed to determine the efficacy and safety of tenofovir alafenamide fumarate (TAF) prophylaxis in hepatitis B virus (HBV)-infected or HBV-experienced individuals with benign and malignant diseases receiving chemo/immunosuppressive or biological modifier therapy.

Materials and Methods: This is a multicenter, observational study in which data from 13 centers were reviewed and entered into a standardized electronic case report form.

Results: A total of 158 individuals who received TAF prophylaxis were included in the analysis. Before starting the prophylaxis, 51 individuals were hepatitis B surface antigen positive, while 107 were HBV-experienced. Thirty patients had detectable HBV DNA levels. Twelve of them had abnormal serum alanine aminotransferase levels. Forty patients were switched to TAF. Solid tumors (34%) were the most common primary disease types. The median follow-up period was 17.2 months. From baseline to the end of the follow-up period, none of the patients had clinical, biochemical, or serological evidence of HBV reactivation under TAF prophylaxis. The virological response rate was 87%. HBV suppression was well maintained after switching in the 40 patients who were switched to TAF treatment. All patients maintained their chemo/immunosuppressive therapy without interruption. TAF prophylaxis was well tolerated. No drug discontinuation due to adverse effects was observed. No HBV-related morbidity or mortality was observed during the TAF prophylaxis. No significant differences were found in the glomerular filtration rate change or hypophosphatemia during TAF prophylaxis, but the serum triglyceride levels were significantly increased (p=0.019).

Conclusion: TAF prophylaxis is effective, safe, and tolerable in preventing chemo/immunosuppressive or biological modifier-induced HBV reactivation in HBV-infected or HBV-experienced individuals.

Keywords: Chemotherapy; efficacy; HBV infection; immunosuppressive therapy; prophylaxis; safety; tenofovir alafenamide fumarate.

Introduction

Hepatitis B virus (HBV) infection is a global public health problem affecting approximately 300 million people worldwide, with 1.5 million new infections each year.[1] A significant proportion of these individuals develop chronic hepatitis, cirrhosis, and hepatocellular carcinoma, which are associated with an increased risk of liver-related morbidity and mortality.[2] In 2019, HBV resulted in an estimated 820,000 deaths.[1] Despite a successful HBV vaccination program and efforts to reduce transmission and prevention in Turkiye, HBV infection remains a major public health problem, especially in the adult population. In 2009, an epidemiologic study determined that hepatitis B surface antigen (HBsAg) positivity was around 4% and that hepatitis B core antibody (anti-HBc) positivity was 31% in Turkiye.[3]

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HBV reactivation (HBVr) is a well-recognized complication of chemo/immunosuppressive and biological modifier therapies in HBV-infected or HBV-experienced individuals.[4] HBVr is characterized by the emergence of HBV particles in patients with previously resolved HBV or an increase in HBV viremia in patients with previously chronic HBV infection.[5] Reactivation can occur spontaneously, but it is generally triggered by immunosuppressive therapy. HBVr is a serious event that can result in hepatic decompensation, acute liver failure, and death.[6] Several risk factors, such as host factors (male gender, older age, severity of liver disease), virological factors (HBV DNA levels), primary disease (lymphoma, stem cell transplantation), and type and degree of an immunosuppressive agent, are associated with HBVr.[6,7] There is a rapid expansion of new immunosuppressive agents, such as monoclonal antibodies, immune checkpoint inhibitors, and tyrosine-kinase inhibitors, which are used in the treatment of various autoimmune, dermatologic, and rheumatologic diseases and many cancers. It has been demonstrated that a risk gradient of immunosuppressive drugs could affect HBVr.[8] Thus, these drugs have been categorized into low-, moderate-, and high-risk groups based on their estimates of HBVr.

HBVr can be prevented when at-risk individuals are identified through screening and started on antiviral prophylaxis if indicated. Antiviral prophylaxis with potent nucleos(t)ide analogs (NUCs) is strongly recommended for HBV-infected patients or HBV-experienced individuals who are considered high risk for HBVr undergoing chemo/immunosuppressive and biological modifier therapies.[8] Previous studies have shown that antiviral prophylaxis is associated with an 87% relative risk reduction of HBVr and an 84% relative risk reduction of HBV-associated hepatitis flares.[9] Lamivudine (LAM), entecavir (ETV), and tenofovir disoproxil fumarate (TDF) may have potential use in the prevention of HBVr in patients undergoing chemo/immunosuppressive therapy. As high long-term antiviral efficacy leading to undetectable HBV DNA levels is necessary, clinical guidelines recommend the use of potent NUCs with high genetic barriers, such as ETV or TDF, over LAM prophylaxis against HBVr in such patients.[9,10] More recent antiviral agents, such as tenofovir alafenamide fumarate (TAF), which is a prodrug proven to be non-inferior to TDF by providing a more stable plasma concentration of tenofovir, have also been proposed to have some beneficial aspects, such as less drug exposure to bone and kidneys.[11] Little data have been gathered on the efficacy and tolerability of TAF prophylaxis in HBV-infected patients undergoing chemo/immunosuppressive and biological modifier therapies. Thus, the aim of the study was to determine the efficacy and tolerability of TAF prophylaxis in HBV-infected or HBV-experienced individuals undergoing chemo/immunosuppressive and biological modifier therapies.

Materials and Methods

Patients

Between January 2019 and June 2021, a total of 326 HBV-infected or HBV-experienced patients who were candidates for chemo/immunosuppressive and/or biological modifier therapies were enrolled in this investigation. TAF was administered at a dose of 25 mg/day at the initiation of chemo/immunosuppressive therapy. A specific electronic case report form (CRF) was designed for data collection and recording. Each center entered the relevant data into the CRF. This study was approved by the Ankara University Ethics Committee of the Ankara Medical School (12.06.2020/09.2020.698), and written informed consent was waived due to the retrospective nature of the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

The laboratory investigations conducted included serum alanine aminotransferase (ALT), aspartate aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, bilirubin, creatinine, fasting glucose levels, lipid profile, and prothrombin time. Complete blood cell counts were obtained using the local central laboratory of each unit. HBsAg, anti-HBs antibody, HBeAg, anti-HBe antibody, anti-HBc IgM and IgG antibodies, and anti-delta antibody were performed. HBV DNA levels were measured using the Roche COBAS TaqMan assay (lower limit of quantitation of 20 IU/mL).

Definitions

HBVr was defined as the presence of abnormal serum ALT levels (>1.3-fold increase above the upper limit of normal), detection of HBV DNA in individuals with previously undetectable HBV DNA levels, a ≥2 log increase in HBV DNA level from baseline, or sero-reversion of HBsAg in HBsAg-negative individuals.

Hypophosphatemia was defined as a serum phosphate level of less than 2.5 mg/dL.

The primary endpoint of the study was to determine the incidence of HBVr and hepatitis flare during TAF prophylaxis. The secondary endpoint was to determine the tolerability and adverse effects of TAF in such patients.

Safety

Safety and tolerability analyses were assessed during TAF prophylaxis. Adverse events (AEs), serious AEs, laboratory abnormalities, drug discontinuation due to AEs, and deaths were evaluated. Serum creatinine level and estimated glomerular filtration rates (eGFR) were evaluated. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula.

Follow-up

All patients were seen at three- or six-month intervals in the outpatient clinic after antiviral prophylaxis was started. A physical examination was performed, and vital signs and patient compliance were assessed. Blood was drawn to determine metabolic, biochemical, and serological parameters. HBsAg and HBeAg loss and seroconversion were monitored.

Statistical Analysis

Means and standard deviations, medians, ranges and interquartile ranges, and frequencies and percentages were used in descriptive statistics. For categorical variables, differences between groups were assessed using the chi-squared test or Fisher's exact test as appropriate. GLMMs (Generalized Linear Mixed Models) were conducted for comparisons versus baseline values. R vers. 2.15.3 software (R Core Team, 2013) was used for data analyses. P-values of less than 0.05 were considered statistically significant.

Results

A total of 158 HBV-infected or HBV-experienced individuals with benign and malignant diseases who received TAF prophylaxis were included in the analysis. The remaining 168 patients who were lost to follow-up (n=78), followed short term (<6 months) (n=63), or died (n=27) due to primary disease were excluded (Fig. 1). The mean age

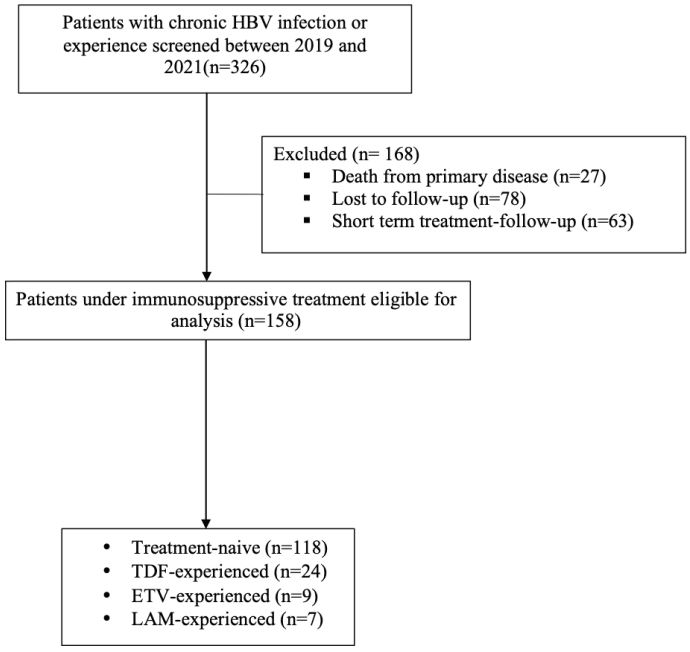


Figure 1. Study flow chart.

ETV: Entecavir; HBV: Hepatitis B virus; LAM: Lamivudine; TDF: Tenofovir disoproxil fumarate.

was 59.5±12.2 years, and the gender distribution was predominantly male (52.5%). Before starting TAF prophylaxis, 51 individuals (32.3%) were HBsAg-positive, while the remaining 107 individuals (67.7%) were HBV-experienced (anti-HBs positivity and anti-HBc IgG positivity). Thirty patients had a detectable HBV DNA level: 27 were HBsAg-positive, and the remaining three were only anti-HBc IgG-positive as occult hepatitis B infection. Twelve of these 30 patients had abnormal serum ALT levels (>40 U/L). Overall, only eight patients (8/158, 5%) were HBeAg-positive. Before TAF prophylaxis, 118 patients were treatment-naive. Forty patients were initially treated with TDF (n=24), ETV (n=9), or LAM (n=7) and were switched to TAF due to older age (>60 years), renal dysfunction, or osteoporosis. The characteristics of the patients are summarized in Table 1.

Solid tumors (33.5%) were the most common primary disease types, followed by rheumatologic/autoimmune diseases (32.9%) and myeloproliferative diseases (32.2%). Overall, 48% of the patients received cytotoxic chemotherapy, 17% received B-cell–depleting therapy, 13% received anti-TNF therapy, 8% received glucocorticoid therapy, and 12% received biological modifier therapies (imatinib, revlimid, ocrelizumab, bevacizumab, or ibrutinib). The characteristics of the primary diseases and chemo/immunosuppressive and/or biological modifier therapies are presented in Table 1. The median follow-up period was 17.2 months (range, 9.4–25 months).

During and after the administration of chemo/immunosuppressive and/or biological modifier therapies, none of the patients had clinical, biochemical, or serological evidence of HBVr during TAF prophylaxis. From baseline to the end of the follow-up period, the virological response rate was 87%. Serum ALT levels were significantly improved in patients with abnormal ALT levels from baseline to the end of the follow-up period (p=0.04). HBV suppression was well maintained after switching in the 40 patients who were switched to TAF treatment.

Table 1. Baseline characteristics of patients who received TAF prophylaxis for HBV reactivation

	Whole cohort (n=158)
Age, years, median (min–max)	59.6 (23–85)
Male sex, n (%)	83 (53)
Hypertension, n (%)	62 (41)
Diabetes mellitus, n (%)	37 (24)
Chronic renal failure, n (%)	28 (19)
Osteoporosis, n (%)	27 (32)
Diagnoses requiring IS therapy, n (%)	
Solid malignancies	53 (34)
Rheumatologic/autoimmune	52 (33)
Myeloproliferative disease	51 (32)
Stem cell transplantation	2 (1)
IS treatment type, n (%)	
Cytotoxic chemotherapy	77 (48)
B cell suppressing therapies	27 (17)
Anti-TNF	21 (13)
Glucocorticoids	13 (8)
Others	20 (12)
Previous nucleoside/nucleotide use (%)	
Treatment naive	118 (75)
Tenofovir disoproxil fumarate	24 (15)
Entecavir	9 (6)
Lamivudine	7 (4)
Initial HBV status, n (%)	
HBs-Ag positive	51 (32)
Anti-HBc positive	107 (68)
HBe-Ag positive	8 (5)
Detectable HBV-DNA	27
Follow-up period, months	17.2±7.8
Exitus from underlying disease, n (%)	27 (17)

IS: Immunosuppressive; TNF: Tumor-necrosis factor; HBV: Hepatitis B virus.

Safety

TAF prophylaxis was well tolerated. Headache, nausea, and fatigue were the most common adverse effects. No drug discontinuation was observed due to adverse effects. No HBV-related morbidity or mortality was observed. All patients maintained their chemo/immunosuppressive therapy without interruption. No significant clinical side effects or serious AEs were reported during TAF prophylaxis

Changes in laboratory values during the follow-up period in treatment-naive and TDF-experienced patients are presented in Table 2 and Table 3. In the treatment-naive group, the mean eGFR change

Table 2. Changes in laboratory values of patients who received TAF prophylaxis **(treatment-naive)**

Treatment-naive (n=118	Baseline (mean±SD)	6-months (mean±SD)	12-months (mean±SD)	18-months (mean±SD)	24-months (mean±SD)	p value (pairwise comparisons vs baseline)			
						6-mon.	12-mon.	18-mon.	24-mon.
Fasting glucose (mg/dL)	110.7±37.1	117.6±37.7	122.9±61.6	112.4±38.1	103.0±22.5	0.095	0.033*	0.147	0.693
Total cholesterol (mg/dL)	200.5±55.1	199.5±50.0	222.3±50.1	236.8±100.0	252.3±92.0	0.322	0.290	0.484	0.187
Triglycerides (mg/dL)	147.5±90.1	179.3±111.7	165.17±106.72	168.9±95.5	168.7±77.7	0.050	0.506	0.083	0.019*
HDL (mg/dL)	46.2±14.5	45.6±11.5	53.1±16.3	54.6±20.9	60.1±21.7	0.755	0.165	0.754	0.244
LDL (mg/dL)	125.8±43.8	119.5±35.3	146.6±39.8	149.3±90.7	140.5±91.3	0.788	0.318	0.502	0.877
eGFR (mL/min)	83.2±26.5	84.2±23.7	82.7±26.1	84.1±27.8	91.5±27.3	0.423	0.906	0.126	0.936
Blood phosphate (mg/dL)	3.5±0.8	3.4±0.7	3.3±0.6	3.4±0.6	3.3±0.6	0.061	0.015*	0.069	0.150

eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation; Mon: Months; *: Indicates p-values <0.05.

Table 3. Changes in laboratory values of patients who received TAF prophylaxis **(TDF experienced)**

TDF-experienced (n=24	Baseline (mean±SD)	6-months (mean±SD)	12-months (mean±SD)	18-months (mean±SD)	24-months (mean±SD)	p value (pairwise comparisons vs baseline)			
						6-mon.	12-mon.	18-mon.	24-mon.
Fasting glucose (mg/dL	93.81±13.07	122.89±41.79	105±37.09	107.5±46.48	91.67±17.36	0.039*	0.244	0.263	0.920
Total cholesterol (mg/dL)	203±48.85	199.5±50.2	183.33±29.74	208±0	216.5±12.02	0.998	0.996	0.867	0.652
Triglycerides (mg/dL)	141.44±75.16	142.64±39.55	116.33±30.24	156±0	141.5±20.51	0.976	0.829	0.582	0.999
HDL (mg/dL)	47.63±17.9	46.5±10.33	63.33±22.05	69±0	62.5±9.19	0.758	0.270	0.477	0.377
LDL (mg/dL)	122.67±38.16	124.49±36.84	105±20.66	136±0	139±4.24	0.329	0.998	0.496	0.795
eGFR (mL/min)	82.68±23.68	83.97±23.13	83.89±23.39	78.59±30.48	100.7±12	0.571	0.314	0.361	0.138
Blood phosphate (mg/dL)	3.34±0.77	3.51±0.71	3.02±0.63	3.31±0.97	3.08±0.71	0.436	0.405	0.947	0.636

eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; SD: Standard deviation; Mon: Months; *: Indicates p-values <0.05.

from baseline to the end of the follow-up period during TAF prophylaxis was generally stable (82.9 mL/min to 91.5 mL/min). Serum phosphorus levels remained stable in 87% of the patients, temporarily decreased in 8.5%, and decreased in 4.6% during TAF prophylaxis. At baseline, hypophosphatemia (<2.5 mg/dL) was found in seven patients. At the end of the follow-up period, hypophosphatemia improved in six of these seven patients. No differences were found in the eGFR change and hypophosphatemia in the follow-up of patients with TDF experience.

Serum triglyceride (TG) levels were significantly increased from baseline to the end of the follow-up period in antiviral treatment-naive patients (p=0.019). Serum fasting glucose levels increased at 48 weeks (p=0.033) but improved at 96 weeks in these patients. However, serum fasting low-density lipoprotein cholesterol (LDL) levels were slightly increased (mean from 125.8±43.8 mg/dL to 140.5±91.3 mg/dL, p=0.877) (Table 3). Serum fasting glucose levels and lipid profiles did not significantly change in the follow-up of patients with TDF experience.

Overall, 27 patients died because of progression of primary diseases.

Discussion

This is the first multicenter observational study with a large sample to determine the efficacy and tolerability of TAF prophylaxis in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies. No HBVr or HBV-related morbidity or mortality was observed during TAF prophylaxis. TAF prophylaxis also enabled patients treated with these agents to complete their treatment protocol without interruption because of HBVr. Two single-center studies have recently reported that TAF prophylaxis is effective against HBV infection in HBV-infected patients undergo-

ing chemotherapy.[12,13] This result indicates that TAF prophylaxis in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies prevents chemo/immunosuppressive therapy–induced HBVr.

Current HBV clinical practice guidelines recommend ETV, TDF, and TAF as the first-line treatment options in patients with chronic hepatitis B (CHB).[14,15] Real-world studies have shown that TAF is effective and tolerable without the emergence of drug resistance in patients with CHB.[16–18] Therefore, TAF should be preferable to TDF or ETV in patients of older age (>60 years), with renal dysfunction, bone disease (osteopenia/osteoporosis), or prior NUC experience.[14,15,19] TAF does not require renal dose adjustment in patients with chronic kidney disease (CKD) and is not affected by food digestion.[20] Taking advantage of these benefits, TAF has been widely used in patients with CHB in clinical practice. However, limited data report the efficacy and tolerability of TAF prophylaxis in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies in preventing chemo/immunosuppressive therapy–induced HBVr. The present study shows that TAF treatment has a high virological response rate, comparable with a previous study demonstrating a virological response rate of 96% more than one year after starting TAF prophylaxis.[13] Notably, all patients who switched from other NUC treatments to TAF had a comparably high virological response rate after switching.

Minimal renal dysfunction has been reported during long-term NUC therapy, but the nephrotoxic potential is higher with TDF treatment than with ETV or TAF.[14] In addition, fluctuations in renal function tests have been frequently described, and a significant proportion of patients may experience acute kidney injury (AKI) and CKD stage migration during chemo/immunosuppressive therapies.[21,22] AKI is associated with increased morbidity and mortality during this therapy. AKI may also lead to interruption of the treatment protocol. Chemotherapeutic agents such as cisplatin, as well as higher baseline serum creatinine, bilirubin levels, and hypoalbuminemia, are independent risk factors for the development of AKI in such individuals. Lee et al.[13] found no significant difference in the incidence of renal events among the ETV, TDF, and TAF groups receiving chemo/immunosuppressive therapy. In the present study, no significant changes were found in the mean eGFR and serum creatinine levels from baseline to the end of the follow-up period during TAF prophylaxis. No major renal-related adverse effects were observed. Serum phosphate levels were stable in most of the patients. It should be noted that hypophosphatemia improved in six of the seven patients during TAF prophylaxis.

According to previous reports, switching from TDF to TAF seems to be associated with body weight gain, cardiovascular risk scores, and altered lipid profiles with higher LDL and TG levels.[23–32] In the present study, prophylactic TAF treatment was shown to be associated with higher fasting glucose levels at 48 weeks and higher TG levels at 98 weeks. However, the clinical importance of these effects is not yet clearly understood.

Our study has several limitations. As described in the Materials and Methods section, this study aimed to collect data on patients who received prophylactic TAF. Unfortunately, there was no control group to compare the virological response rate and safety potency among the groups. TAF has been demonstrated to have a greater extent of reduction in serum HBsAg levels compared with ETV.[17] Several automated assays have been developed to quantify serum HBsAg levels. The Architect HBsAg QT assay (Abbott Diagnostics, Abbott Park, IL, USA) and the Elecsys HBsAg II assay (Roche Diagnostics, Indianapolis, IN, USA) are the most widely used. Standard HBsAg quantification assays were not routinely used in clinical practice in Turkiye. Bone mineral density at the hip and spine decreases during TDF and TAF treatments. However, this study did not include data regarding body weight or bone mineral density during prophylactic TAF treatment.

Conclusion

TAF prophylaxis prevents chemo/immunosuppressive therapy–induced HBVr in HBV-infected or HBV-experienced individuals receiving chemo/immunosuppressive and/or biological modifier therapies. Prophylactic TAF treatment is safe and tolerable in such individuals.

Ethics Committee Approval: The Ankara University Clinical Research Ethics Committee granted approval for this study (date: 12.06.2020, number: 09.2020.698).

Informed Consent: written informed consent was waived due to the retrospective nature of the study.

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

Financial Disclosure: This is an investigator-sponsored Clinical Trial Study investigating the REAL-Life Efficacy and TolerabilitY of Tenofovir Alafenamide Fumarate (TAF) in special groups of Hepatitis B patients (REALITY) which is conducted on behalf of Turkish Association for The Study of Liver (TASL) by the grant of Gilead Sciences, Inc, Foster City CA. (IN-TR-320-5958).

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Author Contributions: Author Contributions: Concept – RI; Design – RI, SY, FD,HG; Supervision – RI, SY, FD, HG; Data Collection and/or Processing – SD, YU, MD, AEY, ZME, SP, HA, ES, EU, YB; Analysis and/or Interpretation – DOE, PG, DA, FD, COD; Literature Search – FD, COE; Writing – FD, COD; Critical Reviews – FD, SD, YU, MD, AEY, ZME, SM, HA, SY, COD, EU, YB, NE, HG, ESK, DD, OS, HS, NT, MA, RI, DOE, PG, DA, KO, MA, SB.

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