



Incidence of Side Effects During Tenofovir Alafenamide Monotherapy in Patients with Chronic Hepatitis B

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Objective: Tenofovir alafenamide (TAF) is a new prodrug of tenofovir that is widely used in chronic hepatitis B (CHB) patients, and its side effects have rarely been reported. We aimed to evaluate the incidence of side effects of TAF in CHB patients.

Methods: We conducted a cross-sectional study that enrolled CHB patients who initiated TAF treatment at West China Hospital from January 2018 to January 2021, and investigated the incidence of side effects by questionnaire. The questionnaire included basic patient characteristics, symptoms, the time of side effects, etc.

Results: A total of 256 eligible patients with a median age of 39 (33, 47) years participated in this study. After 94 (65, 131.5) weeks of TAF treatment, 32% (82/256) of patients experienced side effects, some patients experienced multiple symptoms. The time to side effects was 4 (1, 12) weeks and the degree was mild, the occurrence of side effects had no significant effect on antiviral efficacy ($P > 0.05$). The incidence of skin system side effects was the highest, accounting for 29.3% (75/256) of patients, with alopecia (21.1%) as the main symptom. Systemic and musculoskeletal adverse effects occurred in 27% (69/256) of patients. Gastrointestinal side effects accounted for 18.8% (48/256) of patients, and the main symptom was abdominal distension (12.1%). In addition, 9% (23/256) of patients experienced neurological side effects, 8.6% (22/256) of patients experienced laboratory abnormalities, and 4% (10/256) of patients experienced bone impairment.

Conclusion: CHB patients treated with TAF had a higher incidence of side effects. Fortunately, these side effects were mild and did not affect the antiviral efficacy.

Keywords: Tenofovir alafenamide; Chronic hepatitis B; Side effects; Incidence; Symptom.

Introduction

The World Health Organization estimates that approximately 296 million people worldwide are chronically infected with the hepatitis B virus (HBV) in 2019. Despite the existence of effective antiviral drugs and vaccines, nearly one million people die each year from HBV-related end-stage liver disease and its complications^[1-3]. At present, there are no drugs that can eliminate HBV from hepatocytes, but effective suppression of viral replication can prevent and delay the progression of chronic hepatitis B (CHB) to end-stage liver diseases, such as cirrhosis and hepatocellular carcinoma^[4,5]. Therefore, suppressing HBV replication is the most important means of managing CHB patients.

According to the Clinical Practice Guidelines on the management of HBV infection, there are two main treatment options for chronic hepatitis B (CHB) patients: treatment with a nucleos(t)ide analogues (NAs) with a high barrier to resistance, such as Entecavir (ETV), Tenofovir disoproxil fumarate (TDF) and the recently approved Tenofovir alafenamide (TAF), or with interfer-

ons (IFNs)^[6,7]. Due to the indications, usage, and side effects of IFNs, NAs are commonly used oral drugs in clinical practice. Although TDF and ETV usually have the advantages of high tolerability and strong antiviral efficacy and have been the primary agents for the treatment of CHB in the past decade, some patients have experienced side effects during long-term use, such as bone and kidney toxicity of TDF, drug resistance and low-level viremia (LLV) of ETV^[8-10].

TAF is a new prodrug of tenofovir. Compared with TDF, TAF has higher plasma stability and hepatic targeting. Low doses of TAF can exert similar antiviral efficacy as TDF, thus reducing systemic exposure to TFV and decreasing the risk of bone and renal impairment. Numerous clinical studies have demonstrated that bone and renal safety have improved in TDF-experienced CHB patients after switching to TAF treatment^[11,12], so TAF has become the most preferred antiviral agent for CHB patients and Human Immunodeficiency Virus (HIV) patients. Although it is generally agreed that TAF has high safety profile, there are still case reports of adverse events, such as renal impairment in HIV patients^[13-15]. The side effects of TAF on CHB patients are rarely reported. This study aimed to investigate the incidence of side effects in CHB patients who received TAF treatment.

Materials and Methods

Patients

This is an observational cross-sectional study. The study subjects

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were chronic hepatitis B patients over 18 years old who started TAF treatment in West China Hospital from January 2018 to January 2021. Exclusion criteria were as follows. (1) Co-infection with hepatitis C virus and other hepatitis viruses or HIV. (2) Patients on long-term medications other than anti-HBV drugs. (3) Combination of other chronic liver diseases, such as alcoholic and autoimmune liver diseases. (4) Patients with chronic diseases, such as chronic kidney disease, heart disease, digestive system diseases, etc. (5) Complicated pregnancy or suffering from uncontrollable malignancy. (6) Patients with incomplete questionnaire information.

This study was conducted in accordance with the 1975 Declaration of Helsinki. The study protocol was approved by the West China Hospital Ethics Committee, and informed consent was obtained from each patient.

Procedures

Obtain the patient's phone number through the hospital's medical record, and then contact the patient and send an electronic questionnaire to obtain the patient's clinical data (Electronic questionnaires will be sent to patients every six months after the start of TAF treatment to collect patient information, with follow up periods ending in June 2022). The questionnaire content included basic patient information, bad habits, duration of used TAF, previous medication history, comorbidity, time of side effects, symptoms, severity, etc. The severity of side effects was ranked from 1 to 5 (1 = Extremely mild, 2 = mild, 3 = moderate but tolerable, 4 = very serious and unbearable, 5 = extremely serious).

Statistical issue

Continuous numerical variables are expressed as the mean $\pm$ SD or median (interquartile range), and categorical variables are expressed as ratios. For categorical variables, the χ^2 test or Fisher's exact test was used to compare differences. For continuous variables, t-tests, or non-parametric tests were used as appropriate.

Statistical analyses were performed using IBM SPSS software version 26.0 and GraphPad Prism 8.0 software.

Results

Patient characteristics

After screening, a total of 256 eligible patients were enrolled in this study with a median age of 39 (33, 47) years, including 154 males (Fig. 1). Of these patients, 9.4% (24/256) had bad habits, including smoking, drinking, and staying up late. Before receiving TAF treatment, 80.1% (205/256) of the patients experienced a history of NAs, and 5.1% (13/256) used IFN. After 94 (65, 131.5) weeks of TAF treatment, 32% (82/256) of patients experienced side effects, which occurred at 4 (1, 12) weeks, but the severity was mild (Table 1). The occurrence of side effects had no significant effect on antiviral efficacy (80/82 vs 170/174, $P > 0.05$). Gender, height, weight, bad habits, and previous medication history did not affect the occurrence of side effects ($P > 0.05$), but the patients with side effects were younger ($P < 0.05$), the basic characteristics and follow-up data of patients treated with TAF are presented in Table 1 and Table 2. The symptoms of side effects were manifested as discomfort in the digestive, neurological, dermatological, and musculoskeletal systems, including headache, dizziness, fatigue, abdominal distension, etc (Fig. 2).

Gastrointestinal adverse effects

A total of 18.8% (48/256) patients experienced gastrointestinal adverse effects, and some patients had more than one symptom (Fig. 3A). Among them, 5.5% (14/256) patients had diarrhea, 2.7% (7/256) patients had nausea, 3.1% (8/248) patients had abdominal pain, 3.1% (8/248) patients had constipation, 12.1% (31/256) patients had abdominal distension, and 3.9% (10/248) patients had anorexia. In phase III clinical trial of TAF, the incidence of nausea, dyspepsia, and diarrhea exceeded 5%, but abdominal distension was not mentioned^[8].

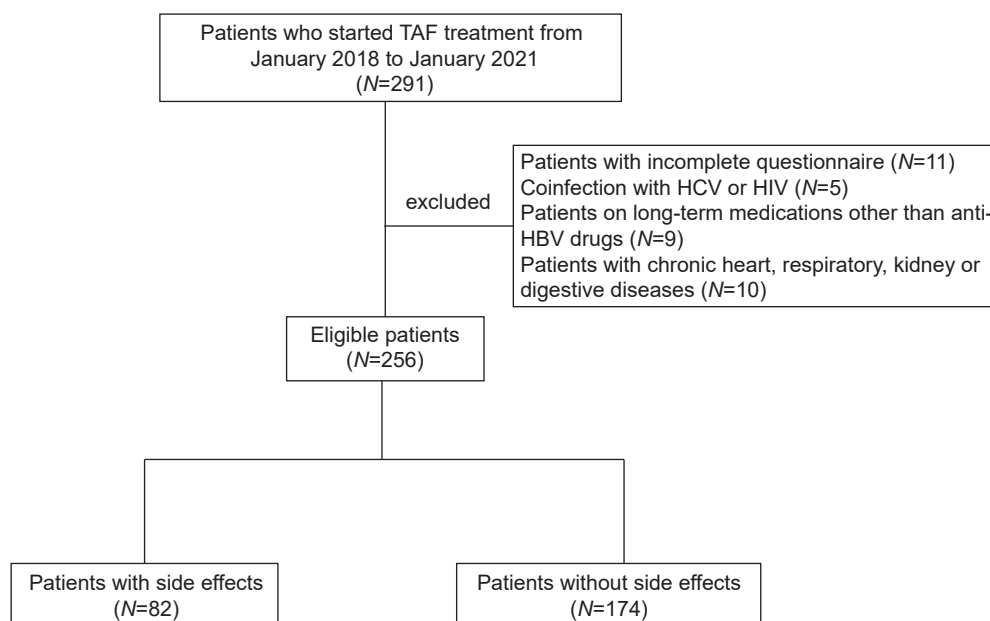


Fig. 1. The patient screening and enrollment flow chart.

Table 1. Basic characteristics of patients.

Variable	Total (n = 256)	Patients with side effects (n = 82)	Patients without side effects (n = 174)	P value
Sex, male/female, n%	154(60.2)/102(39.8)	52(63.4)/30(36.6)	102(58.6)/72(41.4)	0.496
Age, Y	39(33,47)	37(30,45)	41(34,48.5)	0.004
Height, cm	165(159,170)	166(160,171)	165(158,170)	0.153
Weight, Kg	62(55,70)	63.5(55,70)	61.5(54,69.5)	0.282
Bad hobbies, yes/no, n%	24(9.4)/232(90.6)	8(9.8)/74(90.2)	16(9.2)/158(90.8)	0.525
Smoking	18(7)/238(93)	6(7.3)/76(92.7)	12(6.9)/162(93.1)	0.544
Drinking	8(3.1)/248(96.9)	2(2.4)/80(97.6)	6(3.4)/168(96.6)	0.499
Stay up late	56(21.9)/200(78.1)	17(20.7)/65(79.3)	39(22.4)/135(77.6)	0.872
NAs history, yes/no, n%	205(80.1)/51(19.9)	61(74.4)/21(25.6)	144(82.8)/30(17.2)	0.132
LAM	34(13.3)/222(86.7)	7(8.5)/75(91.5)	27(15.5)/147(84.5)	0.167
ADV	55(21.5)/201(78.5)	18(22)/64(78)	37(21.3)/137(78.7)	0.511
LdT	18(7)/238(93)	5(6.1)/77(93.9)	13(7.5)/161(92.5)	0.798
ETV	103(40.2)/153(59.8)	33(40.2)/49(59.8)	70(40.2)/104(59.8)	0.552
TDF	122(47.7)/134(52.3)	42(51.2)/40(48.8)	80(46)/94(54)	0.503
IFN history, yes/no, n%	13(5.1)/243(94.9)	5(6.1)/77(93.9)	8(4.6)/166(95.4)	0.407
TAF, week	94(65,131.5)	92(67.8,132.5)	94(65,130.5)	0.883
HBV-DNA> 20 IU/L, yes/no, n%	6(2.3)/250(97.7)	2(2.4)/80(97.6)	4(2.3)/170(97.7)	0.945
Side effects, week		4(1,12)		
Severity, 1/2/3/4/5, n%		29.3/61/9.7/0/0		

Data are presented as n (%), median (first-third quartile). TDF: tenofovir disoproxil fumarate, TAF: tenofovir alafenamide, ETV: entecavir, LAM: lamivudine, ADV: adefovir dipivoxil, LdT: telbivudine, IFN: interferon, HBV: hepatitis B virus. Severity of side effects, 1 = extremely mild, 2 = mild, 3 = moderate but tolerable, 4 = very serious and unbearable, 5 = extremely serious.

Table 2. Follow-up data of patients.

	Beginning time	End of follow-up time	P value
Weight, Kg	62 (55, 70)	62.7 (55.3, 70.6)	0.000
ALT, IU/L	23 (21, 27.8)	31 (25, 36)	0.000
TG, mmol/L	1.34 (1.25, 1.45)	1.4 (1.28, 1.52)	0.000
TC, mmol/ L	3.8 (3.3, 4.3)	4.1 (3.6, 4.4)	0.0002
LDL, mmol/L	1.56 (1.32, 2.34)	2.21 (1.45, 2.34)	0.000
eGFR, mL/min/m ²	102.5 (97.6, 108.6)	99.9 (99.5, 105.3)	0.000
Serum phosphorus, mmol/L	1.12 (0.99, 1.23)	1.11 (1, 1.23)	0.0006

Data are presented as median (first-third quartile). ALT: alanine aminotransferase, TG: triglycerides, TC: total cholesterol, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate.

Systemic and musculoskeletal adverse effects

Systemic and musculoskeletal side effects occurred in 27% (69/256) of patients (Fig. 3B), some patients have multiple symptoms, with 11.3% (29/256) experiencing fatigue, 10.9% (28/256) experiencing weakness, 4.7% (12/256) suffering from lethargy, 6.6% (17/256) having muscle soreness, and 5.9% (15/256) having arthralgia. In addition, 7.9% (20/256) experienced weight changes (weight change more than 3 Kg), 5.9% experienced weight gain, and 2% experienced weight loss.

Nervous system and skin system side effects

The proportion of patients with skin system adverse effects is the

highest, accounting for 29.3% (75/256) of all patients (Fig. 3C), some patients have multiple symptoms, including rash (4.3%), pruritus (5.9%), and alopecia (21.1%). Nervous system adverse effects occurred in 9% (23/256) of patients (Fig. 3C), including dizziness (7.8%) and headache (2.3%). However, in phase 3 clinical trial of TAF, the headache was the most common symptom, accounting for 12% of the total^[8].

Laboratory abnormalities

Of the 256 patients treated with TAF, there was an overall increase in alanine aminotransferase (ALT), triglycerides (TG), total cholesterol (TC), and low-density lipoprotein (LDL), and an

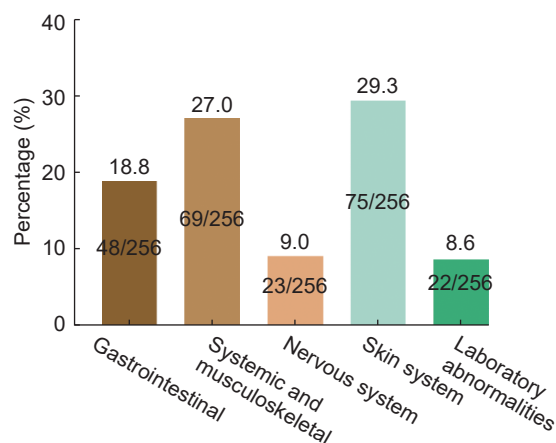


Fig. 2. Incidence of adverse effects in different systems.

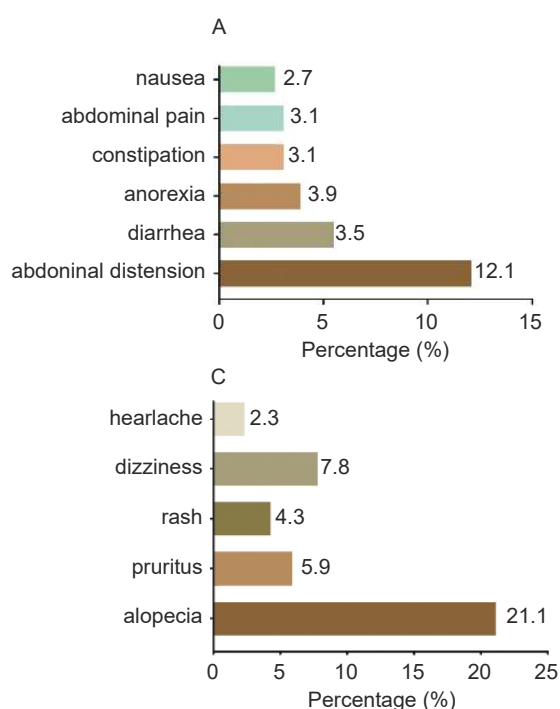


Fig. 3. Incidence of different symptoms.

A. Symptoms and incidence of Gastrointestinal adverse effects.

B. Symptoms and incidence of systemic and musculoskeletal adverse effects.

C. Symptoms and incidence of nervous and skin system adverse effects.

D. Incidence of Laboratory abnormalities.

BMD: bone mineral density, eGFR: estimated glomerular filtration rate, ALT: alanine aminotransferase, LDL: low-density lipoprotein, TC: total cholesterol, TG: triglyceride.

Discussion

To our knowledge, there are few studies have evaluated the incidence of side effects in CHB patients undergoing TAF treatment. TAF has become the preferred antiviral drug in clinical practice due to its antiviral efficacy and safety profile. However, with its extensive clinical application, there are case reports about its side effects, mainly in HIV patients^[13–16]. In phase III clinical trial of TAF, most CHB patients experienced mild-moderate adverse effects after 96 weeks of TAF treatment, such as fatigue and headache, and a small number of patients stopped TAF due to side effects,

but no patients died due to side effects^[8]. In our study, 32% of patients experienced side effects after receiving TAF, and these occurred in the early stage of medication. Fortunately, the severity of side effects was mild, and no patients stopped TAF or died due to adverse effects.

The incidence of systemic and musculoskeletal adverse effects is high in our study, and fatigue is the most common symptom. In addition, the incidence of weight gain is more than 5%, and weight change is a hot clinical issue for patients using NAs, there are many clinical studies on TAF and weight change^[16]. A survey of CHB patients showed that patients lost weight when they

switched their antiviral regimen from TAF to TDF^[17]. Opinions are not uniform about the prognosis of weight gain, a single-center retrospective study from Finland showed that HIV patients who switched their antiviral regimen from TAF to TDF prevented weight gain and reduced the risk of cardiovascular disease^[18]. However, a prospective study from Spain found that although patients with TDF converted to TAF had mild weight gain, it did not affect obesity and metabolic-related clinical events^[19]. Now we need more prospective studies to clarify the impact of weight gain caused by TAF on health.

Laboratory abnormalities are common adverse effects of new drugs. In our study, urinary microglobulin increased in 2% of patients, and blood phosphorus decreased in 2% of patients, indicating that the patient's proximal renal tubule was impaired. In addition, bone mineral density (BMD) decreased in 4% of patients. Previous studies have shown that reduced BMD is associated with hypophosphatasia that results from proximal renal tubular dysfunction^[20,21]. Although the bone and renal safety of TAF is higher than TDF, due to the application time of TAF being short, the long-term safety of bone and renal needs more clinical studies to verify.

Lipid metabolism disorder is another hot issue in TAF use, we know that switching to a TAF-containing regimen was associated with more significant increases in low-density lipoprotein cholesterol LDL-C and TG. A multicenter randomized controlled study showed that after switching antiviral regimens from TDF to TAF, patients' total cholesterol and low-density lipoprotein were significantly increased^[22]. In a study of HIV patients, patients who switched antiviral regimens from TAF to TDF improved plasma lipid profiles and atherosclerotic cardiovascular disease risk scores and prevented weight gain^[18]. However, the results of the study were not consistent. A recent prospective study from Spain showed that in HIV patients after the antiviral regimen was switched from TDF to TAF. However, serum cholesterol and triglyceride increased, and the ratio of total cholesterol to HDL did not change significantly without impacting the incidence of obesity or metabolic-related clinical events^[19]. In addition, a study from South Korea enrolled CHB patients receiving TDF and TAF and normal patients and inactive CHB patients as controls and showed that TAF did not exacerbate lipid metabolism disorders^[23]. Since the current studies are relatively few and time-consuming, more clinical studies and follow-up results are needed to clarify the effect of TAF on lipid metabolism.

In addition, the digestive, skin, and nervous systems have a high incidence of adverse effects, including abdominal distension, diarrhea, headache, dizziness, rash, etc. In some cases, it may affect the patient's medication compliance, so we can try to reduce the incidence of side effects by improving their lifestyle, taking protective drugs, and other methods.

There are some limitations of our study. First, the sample size is relatively small. Second, this is a single-center observational cross-sectional study, and a multicenter prospective study is needed to confirm the results. In addition, this study used a questionnaire survey, and some patients may have incomplete information. Finally, this study lacked other NAs as controls.

Conclusion

In conclusion, as a first-line drug for the treatment of CHB, TAF

has a higher incidence of side effects. Fortunately, these side effects were mild and did not affect the antiviral efficacy. At present, there are relatively few studies on the side effects of TAF, and we need more clinical studies to confirm the results.

Abbreviations

ALT, alanine aminotransferase; BMD, bone mineral density; CHB, chronic hepatitis B; eGFR, estimated glomerular filtration rate; ETV, entecavir; HBV, hepatitis B virus; HIV, human immunodeficiency virus; IFNs, interferons; LDL, low-density lipoprotein; LLV, low-level viremia; NAs, nucleos(t)ide analogues; TAF, tenofovir alafenamide; TC, total cholesterol; TDF, tenofovir disoproxil fumarate; TG, triglycerides; ULN, upper limit of normal.

Ethical approval and consent to participate

This study was conducted in accordance with the 1975 Declaration of Helsinki. The study protocol was approved by the West China Hospital Ethics Committee, and informed consent was obtained from each patient.

Conflict of interest

All authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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We would like to thank the patients who participated, and all the researchers who contributed to this study.

Authors' contributions

EqC contributed to the study concept and design, FdW, JZ, LqL, YjL, YfL were responsible for data acquisition, FdW, YfL were responsible for data analysis and manuscript drafting. All authors approved the final version of the manuscript.

Availability of data and materials

The data supporting the finding of this study are available from the corresponding author upon reasonable request.

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