



Original Article

Clinical impact of the early alanine aminotransferase flare during tenofovir monotherapy in treatment-naïve patients with chronic hepatitis B

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Background/Aims: Little is known about the effect of early flares on response during first-line tenofovir disoproxil fumarate (TDF) treatment for chronic hepatitis B (CHB). The aim of this study was to investigate the incidence and outcome of early alanine aminotransferase (ALT) flare in treatment-naïve patients with CHB during long-term TDF monotherapy.

Methods: One hundred eighty-one treatment-naïve CHB patients were treated with a 300-mg once-daily dose of TDF for more than 12 weeks. Virological markers of hepatitis B virus (HBV) and biochemical data were measured at baseline and every 4-12 weeks during the therapy. The proportion of patients with undetectable HBV DNA level (< 100 copies/mL) was noted.

Results: The median age was 48.3 years and 122 patients (67.4%) were men. Hepatitis B envelope antigen (HBeAg) was positive in 101 patients (55.8%). No patient had cirrhosis. The median follow-up duration was 45 weeks (12-155 weeks). ALT flare (>5 × upper limit of the normal range) occurred in seven patients (3%) without viral breakthrough within the first 8 weeks after the start of TDF monotherapy. Among them, six patients were HBeAg-positive and one patient was HBeAg-negative. All cases of early ALT flares resolved within 4 weeks and virologic response was observed in all patients without interruption or discontinuation of treatment.

Conclusions: Continuous TDF monotherapy was effective and safe in treatment-naïve patients with CHB who experienced early ALT flares followed by a decrease in HBV DNA level. (*Clin Mol Hepatol* 2017;23:154-159)

Keywords: Tenofovir; Chronic hepatitis B

INTRODUCTION

It is estimated that approximately 350 million people are chronically infected with hepatitis B worldwide¹ and more than 780,000 people die each year due to complications of hepatitis B.² The

goal of treatment for chronic hepatitis B (CHB) is sustained suppression of hepatitis B virus (HBV) replication, to decrease morbidity and mortality related to CHB.³

Currently, the following three drugs are approved as first-line therapeutic options for CHB: entecavir (ETV), tenofovir disoproxil

Abbreviations:

ALT, alanine aminotransferase; CHB, chronic hepatitis B; ETV, entecavir; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; SD, standard deviation; TDF, tenofovir disoproxil fumarate

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fumarate (TDF), and pegylated interferon α -2a.⁴⁻⁸ The Interferons are not recommended for use in patients with decompensation or immunosuppression as they may have treatment-limiting side effects.⁵ Even though some adverse events including mild renal impairment⁹ (particularly with TDF¹⁰) or lactic acidosis with ETV¹¹ in patients with decompensated liver disease and high MELD scores (model for end-stage liver disease) (≥ 22) have been reported, both oral antiviral agents showed favorable safety profiles over 5 years.^{7,8}

Chronic HBV infection is a dynamic state of interactions between HBV and immune cells. Therefore, alanine aminotransferase (ALT) flare, defined as abrupt rise of ALT levels more than 5 or 10 times upper limit of normal may occur spontaneously or during antiviral therapy.¹² Oral antiviral therapy related ALT flare may occur in up to 3-10% of patients, being higher in hepatitis B envelope antigen (HBeAg)-positive patients and lower in those receiving more potent antiviral agents, such as ETV or TDF.^{4,5,12-19} Few studies have been performed on early ALT flares in patients undergoing long-term TDF therapy. The aim of this study was to investigate the incidence and outcome of early alanine aminotransferase (ALT) flare in treatment-naïve patients with CHB during long-term TDF monotherapy.

PATIENTS AND METHODS

Patients

One hundred eighty one treatment-naïve CHB patients were consecutively included from Konkuk University Chungju Hospital and Korea University Anam Hospital in South Korea between January 2013 and December 2016. The inclusion criteria were as follows: hepatitis B surface antigen (HBsAg) present in serum for more than 12 weeks, serum HBV DNA level greater than 2,000 IU/ml, and serum ALT level greater than twice the upper normal limit. Exclusion criteria included co-infection with hepatitis C, hepatitis D, and human immunodeficiency virus and the use of an antiviral agent with activity against HBV before enrolment. The clinical diagnosis of cirrhosis was based on imaging findings (abdominal computed tomography or magnetic resonance imaging) and compatible clinical features (esophageal varices or thrombocytopenia).

The study protocol was approved by the institutional review board and was conducted in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Study design

One hundred eighty one treatment-naïve patients received 300 mg TDF once daily for more than 12 weeks from January 2013 and onwards. All patients were monitored at the baseline and every 4-12 weeks during antiviral therapy. Before enrollment, the patients were assessed clinically according to medical history, physical examination, electrocardiography, HBeAg status and serum HBV DNA level. The patients were followed every 4-12 weeks during antiviral therapy for clinical assessment of tolerability, physical examination, and assessment of blood chemistry and HBV status. The serum HBV DNA levels were measured using the CFX96 Touch™ Real-Time PCR Detection System (Bio-Rad, Hercules, CA, USA), which has a lower limit of detection of 20 IU/mL. ALT flares were defined as an abrupt elevation of serum ALT to $> 5 \times$ ULN or ≥ 3 -fold increase in ALT, whichever was higher.^{12,20} The virological response was defined as a decrease in the serum HBV DNA to a level undetectable by PCR assay; the loss or seroconversion of HBeAg in patients who were initially HBeAg-positive; and a decrease in the serum ALT level to the normal range. Virological breakthrough was defined as an increase in serum HBV DNA level of more than 1 log₁₀ (10-fold) above the nadir after achieving virological response during treatment.

Statistical analysis

HBV DNA levels were logarithmically transformed for analysis. Continuous variables were expressed as the mean \pm standard deviation (SD), and categorical variables were shown as absolute and relative frequencies. The chi-square test was used to analyze the categorical variables, such as gender and liver cirrhosis. Continuous variables, such as age, serum HBV DNA level, and serum ALT level, were analyzed using the Mann-Whitney *U*-test. The *P*-values less than 0.05 were considered statistically significant. SPSS version 21.0 was also used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

RESULTS

Patients

The baseline characteristics of the patients are summarized in Table 1. One hundred eighty one were included between January 2013 and December 2016. All patients were treatment naïve and

Table 1. Baseline characteristics of the patients enrolled in the study

Characteristics	Total (n=181)	Early ALT flare (-) (n=174)	Early ALT flare (+) (n=7)	P-value
Sex(male, n [%])	122 (67.4)	118 (67.8)	4 (57.1)	0.684
Median age, year (range)	48.3 (20.4-71.0)	48.1 (20.4-71.0)	53.0 (26.0-65.0)	0.924
Cirrhosis (n, %)	0 (0)	0 (0)	0 (0)	
HBeAg-positive (n, %)	101 (55.8)	95 (54.5)	6 (85.7)	0.135
Median duration of treatment (weeks, range)	45 (12-155)	44 (12-155)	64 (27-114)	0.101
Mean serum HBV DNA level (log ₁₀ IU/mL)	6.42 ± 1.60	6.36 ± 1.69	7.67 ± 1.28	0.017
Mean serum ALT (IU/L)	197.48 ± 281.25	193.43 ± 280.78	298.14 ± 295.52	0.045
Mean serum total bilirubin level (mg/dL)	1.57 ± 2.32	1.60 ± 2.36	0.8 ± 0.24	0.199
Mean serum albumin level (g/dL)	3.89 ± 0.61	3.89 ± 0.62	3.84 ± 0.51	0.689

Values are mean ± SD (range) unless otherwise indicated.

ALT, alanine aminotransferase; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus.

Table 2. Virological responses during tenofovir therapy in treatment-naïve patients with chronic hepatitis B

Response	48 weeks		96 week	
	Early ALT flare (-) (n=174)	Early ALT flare (+) (n=7)	Early ALT flare (-) (n=174)	Early ALT flare (+) (n=7)
Undetectable HBV DNA level (n, %)				
HBeAg-positive	42/48 (88.8)	6/6 (100)	15/15 (100)	4/4 (100)
HBeAg-negative	12/12 (100)	1/1 (100)	8/8 (100)	NA
HBeAg seroconversion (n, %)	16/48 (33.3)	3/6 (50)	6/15 (40.0)	2/4 (50)

Values are presented as n (%).

ALT, alanine aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B envelope antigen; NA, not available.

received 300 mg of TDF once daily for more than 12 weeks. At baseline, the median age of the subjects was 48.3 years, 122 (67.4%) were men. HBeAg was positive in 101 patients (55.8%). No patient had cirrhosis. The median follow-up duration was 45 weeks (12–155 weeks). The baseline serum HBV DNA and ALT levels were 6.42 ± 1.60 log₁₀ IU/mL and 197.48 ± 281.25 IU/mL, respectively.

Virological and biochemical responses

Serum HBV DNA was undetectable in 88.8% and 100% of the patients at weeks 48 and 96, respectively (Table 2). Serum ALT level was normalized in all patients at both weeks 48 and 96. HBeAg seroconversion was observed in 35.1% in patients at week 48 and 42.1% at week 96, respectively. No patients experienced HBeAg loss or seroconversion during TDF monotherapy. ALT flare (>5 × upper limit of the normal range) occurred in seven patients (3%) without viral breakthrough within the first 8 weeks after the start of TDF monotherapy. Among them, six patients were

HBeAg-positive and one patient was HBeAg-negative. In six HBeAg-positive patients, four showed HBeAg seroconversion and virologic response during the antiviral therapy but two patients showed ALT flares without HBeAg loss or seroconversion within the first 4 weeks after the start of TDF monotherapy (Fig. 1). One patient had an increase in serum ALT level from 325 U/L at baseline to 1,258 U/L at week 4 and another patient had an increase in serum ALT level from 113 U/L at baseline to 996 U/L at week 2. Such early on-treatment ALT flares occurred in concomitant with a reduction in serum HBV DNA levels by >2 log₁₀ IU/mL within 4 weeks. Early ALT flares resolved within 4 weeks and all patients showed virologic response without interruption or discontinuation of treatment. Baseline characteristics such as age, sex, initial HBeAg status, initial ALT levels, and initial HBV DNA levels were not associated with the development of an early ALT flare (Table 3).

Safety

Patients underwent routine check-ups every 4-12 weeks during

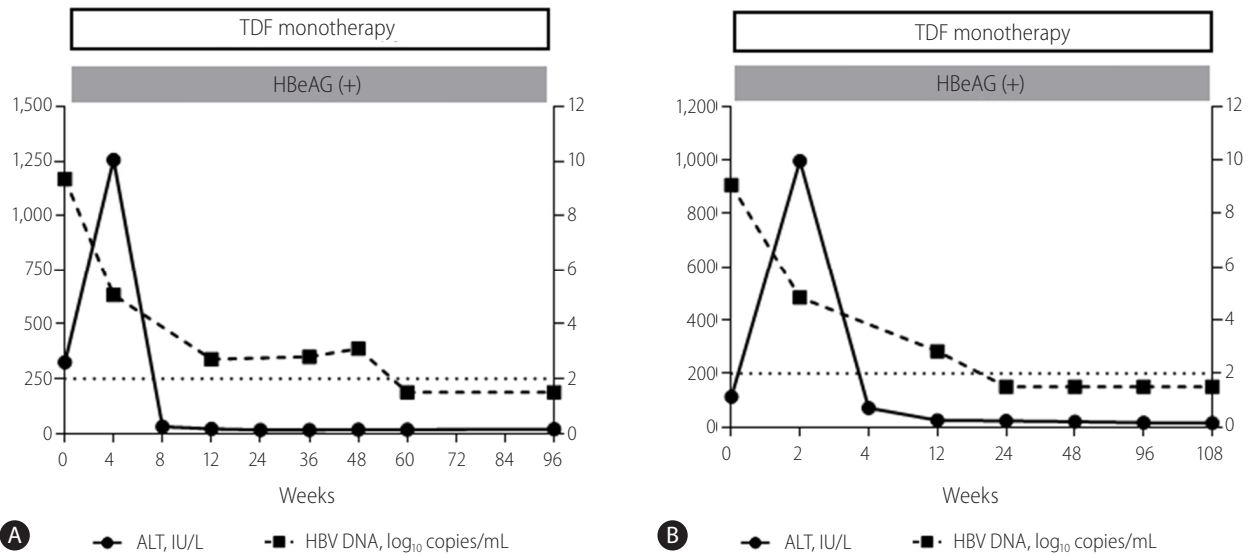


Figure 1. Clinical courses of two hepatitis B e antigen (HBeAg) positive patients with one episode of hepatitis flare. (A) A 26-year-old male patient (B) A 28-year-old female patient. ALT, alanine aminotransferase; TDF, tenofovir disoproxil fumarate; HBV, hepatitis B virus.

Table 3. Univariate analysis of early ALT flare according to baseline factors

Baseline characteristics	Odd ratio (95% CI)	P-value
Sex (male/female)	0.645 (0.148-2.923)	0.684
Age ($\leq 40 / > 40$)	1.209 (0.243-6.017)	1.000
HBeAg (-/+)	1.050 (0.994-1.109)	0.135
Initial ALT level ($\leq 120 / > 120$ IU/mL)	1.050 (0.984-1.121)	0.132
Initial HBV DNA level ($\leq 7.0 / > 7.0$ log ₁₀ IU/mL)	1.048 (0.983-1.117)	0.142

ALT, alanine aminotransferase; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus.

TDF therapy to identify adverse events and evaluate therapeutic responses. None of the patients who received TDF had a confirmed increase in serum creatinine level (more than 0.5mg/dL increase from baseline level). There were no clinically significant adverse events during the treatment period and none of the patients discontinued treatment.

DISCUSSION

In the present study involving 181 treatment-naïve patients with CHB treated with TDF, the incidence of ALT flare was low (3.0% after 155 weeks of therapy). All the patients with early ALT flares showed a virological response. ALT flare is a well-known phenomenon associated with antiviral treatment for CHB.²¹ According to the previous study, ALT flare was further classified as host-induced, virus-induced, or intermediate based on HBV DNA kinetics

in the 24 weeks preceding the flare.^{21,22} Host-induced flares were characterized by an HBV DNA decline > 1 log IU/mL within 24 weeks preceding the ALT peak.^{21,22} It was considered to be associated with declining viral load that may lead to a restored immune activity.^{21,22} In virus-induced flares, ALT peak was preceded by an HBV DNA increase > 1 log IU/mL within 24 weeks,^{21,22} and it was assumed that the increase of viral load was responsible for the ALT flare.^{21,22} Flares that did not meet one of these criteria were classified as intermediate.²¹

In the present study, early ALT flares occurred in 3.0% of patients during TDF monotherapy of CHB and were concomitant with a reduction in serum HBV DNA levels more than 1 log IU/ml. None of them had hepatic decompensation and the flares resolved within 4 weeks after continuing the antiviral therapy. Therefore, all the patients with early ALT flares during TDF could be categorized as host-induced. Host-induced flares during antiviral treatment may be caused by a restoration of T-cell responsive-

ness that accompanies a reduction in viral proliferation.²³⁻²⁶ Previous studies have suggested that the serological response was observed after host-induced flares, but not after virus-induced flares.^{21,22}

The treatment of CHB with lamivudine has been associated with increases in serum aminotransferase levels 3 to 10 times compared with baseline levels in 10% of patients.²⁷ ALT flares during lamivudine treatment tend to occur within the first 4 to 6 weeks, often after major decline in serum HBV DNA level.²⁸ The incidence of ALT flares with an ALT increase $>5 \times$ ULN were as follows: lamivudine, 17%²⁹; adefovir, 21%¹⁵; ETV, 10%⁴; and TDF, 6%.⁵ All oral antiviral therapies induced low rates of early ALT flare with an ALT increase $>10 \times$ ULN, which may occur in up to 2-10% of patients, being higher in HBeAg-positive patients and lower under therapy with more potent antiviral agents, such as ETV or TDF.^{4,5,12-19,22}

In the previous phase 3 studies, early ALT flares with an ALT increase $>10 \times$ ULN occurred in 3.0% of patients during TDF therapy of CHB, and resolved within 4 to 8 weeks without interruption or discontinuation of antiviral treatment.⁵ Early ALT flares during oral antiviral therapy were not associated with hepatic decompensation and usually occurred in association with a reduction in serum HBV DNA levels within 8 weeks of oral antiviral therapy.^{4,5,12,16} In this real-life cohort of patients undergoing long-term TDF therapy, the risk of early ALT flares was low with an incidence of 3.0%, similar to the result of previous clinical trials.

A recent study suggested that baseline HBeAg-positivity and high HBV DNA levels were associated with flares during long-term ETV therapy.²² In the present study, baseline factors, such as age, sex, initial HBeAg status, and initial serum ALT and HBV DNA levels were not associated with the development of an early ALT flare. The present study was limited by the retrospective design that lacked a prospective study protocol. Further studies for clinical parameters are needed to elucidate the immunology during ALT flares.

In conclusion, the incidence of early ALT flares during TDF monotherapy was low. All of the early ALT flares were host-induced flares, which were associated with good treatment response. Continuous TDF monotherapy was effective and safe in treatment-naïve patients with CHB experienced early ALT flares.

Conflicts of Interest

The authors have no conflicts to disclose.

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