



Efficacy of 24-week Administration of Tenofovir Disoproxil Fumarate in the Management of Naïve Chronic Hepatitis B

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Abstract

Edited by: Slavica Hristomanova-Mitkovska
Citation: Darmadi D, Siregar GA. Efficacy of 24-week Administration of Tenofovir Disoproxil Fumarate in the Management of Naïve Chronic Hepatitis B. Open Access Maced J Med Sci. 2020 Oct 21; 8(B):1005-1009. <https://doi.org/10.3889/oamjms.2020.5424>
Keywords: Chronic hepatitis B; Efficacy; HBeAg; HBV DNA; Tenofovir disoproxil fumarate
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Received: 06-Sep-2020
Revised: 10-Oct-2020
Accepted: 11-Oct-2020
Copyright: © 2020 Darmadi Darmadi, Gontar Alamsyah Siregar
Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist.
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BACKGROUND: Chronic hepatitis B (CHB) is becoming a common liver abnormality worldwide. Thus, a series of good management is needed to prevent the progression and complications of hepatitis B infection. Tenofovir disoproxil fumarate (TDF) is one of the drugs of choice that's used for CHB management.

AIM: Limited studies were found regarding the efficacy of tenofovir in dealing with CHB. Hence, the aim of this study is to determine the efficacy of TDF administration for 24 weeks in subjects with naïve CHB in Medan, Indonesia.

METHODS: Retrospective study was conducted in Haji Adam Malik Hospital Medan, Indonesia, between January and December 2019. Subjects were CHB patients aged 18 years or older and were treated TDF for 24 weeks. Demographic, clinical, and CHB disease progression parameters (serum alanine aminotransferase [ALT], hepatitis B envelope antigen [HBeAg], and hepatitis B virus deoxyribonucleic acid [HBV DNA]) data were obtained.

RESULTS: One hundred and twenty subjects were obtained and divided into 2 groups: HBeAg positive and HBeAg negative. Mean age of subjects was 46.5 ± 10.36 years in HBeAg positive group and 48.6 ± 10.67 years HBeAg negative group, with predominant males' subjects in both groups (58.3% vs. 61.7%, respectively). Serum ALT normalization and undetectable serum HBV DNA were observed in more than 70% and 65% of subjects in both groups, respectively (both $p < 0.001$). Serum HBeAg loss was achieved in 10.8% subjects ($p < 0.001$). No subject showed serum HbsAg loss.

CONCLUSION: Our results are consonant with current clinical guidelines and other evidence literature. For both HBeAg-positive and HBeAg-negative populations, TDF administration for 24 weeks has good efficacy in naïve CHB patients.

Introduction

Hepatitis B virus, also known as HBV, is a double-stranded deoxyribonucleic acid (DNA) virus from the hepadnavirus family that causes acute and chronic liver infections in human [1]. From the epidemiological perspective, the highest prevalence of CHB is reported in Africa and Asia [2]. According to Baseline Health Research, the prevalence of Hepatitis B in Indonesia increased from 0.2% in 2013 to 0.4% in 2018 [3]. Although the coverage for early detection and immunization for hepatitis B has always reached the target until 2017 [4], Indonesia is still categorized as a moderate-to-highly endemic region for HBV infection [5]. The majority cases of Hepatitis B can progress to chronic liver disease, with the chronicity depends on the time exposure to hepatitis B virus (HBV) [6]. If left untreated, the disease can lead to fatal complications, including cirrhosis, liver failure, and hepatocellular carcinoma [6], [7], [8]. In fact, after 5 years of suffering from CHB, the risk of developing hepatocellular carcinoma increases up to 17% in Eastern countries

compared to 10% in western countries. The 5-year survival rate for patients with decompensated liver cirrhosis due to HBV is 17–35% [9]. Thus, a series of good management is needed to prevent the progression and complications of Hepatitis B infection.

There are many different treatment options available. Treatments that are used in CHB management are peginterferon-alpha, lamivudine (LMV), adefovir (ADV), telbivudine, entecavir (ETV), and tenofovir (TDF) [7]. Several parameters are used to monitor CHB progression such as serum alanine aminotransferase (ALT) level, HBV DNA level, antigens specific to HBV, and histopathological examination [1], [7], [10], [11]. Viral suppression, ALT normalization, absence of viral resistance, HBeAg loss, HBsAg seroconversion, and liver histology improvement are the short-term goals regarding with CHB infection [1]. Furthermore, the long-term aims of management of CHB are to improve survival rate and to prevent complications [2], [9], [10]. Moreover, the treatment for this condition may need to be lifelong, thus the drugs used must be both efficacious and safe [11].

TDF is one of the nucleotide analogue drug that is used as the first-line treatment of CHB [8], [12], [13], [14].

This pharmacological agent is recommended for naive CHB patients but can also be administered to patients with previous treatment failure [8], [9]. Many literatures stated that TDF has good efficacy and safety. However, several adverse events have been reported such as renal toxicity and bone demineralization [6], [7], [15]. Other disadvantages of nucleotide analogs in treating CHB are indefinite duration of treatment, risk of developing resistance, and less HBeAg and HBsAg conversions [9], [15]. Only one single-centered study was found that has discussed the efficacy and side effects of tenofovir in Indonesia [16,17,18]. Moreover, Indonesia is a country with a diversity of cultures, religions, and races so that the research on the efficacy of TDF against CHB infection regarding that heterogeneity is in need. Unfortunately, limited studies were found regarding the efficacy of tenofovir in dealing with CHB in Indonesia. Our study aimed to determine the efficacy of 24-week TDF treatment in naive CHB subjects in Medan, Indonesia.

Methods

A retrospective study was conducted in Haji Adam Malik Hospital Medan, Indonesia between January and December 2019. The inclusion criteria were patients aged 18 years or older, who were diagnosed with CHB. Patients were excluded if they had underlying liver damage other than CHB such as liver cirrhosis, hepatocellular carcinoma, co-infection with others hepatitis virus, renal disease, autoimmune disease, and immunodeficiency disease. Consecutive sampling method was used for this study and subjects should have received 300 mg of TDF daily for a minimum 24 weeks. Moreover, subjects were divided into 2 groups based on the HBeAg positivity. Demographic and clinical characteristics were gathered from each subject's medical record along with CHB disease progression parameters (serum ALT, HBV DNA level, HBeAg, and HBsAg) after 24 weeks of TDF treatment. Data analysis was conducted using McNemar's test for the categorical dependent variable, for instance, seroconversion of HBeAg. Continuous variables (serum ALT, HBV DNA level) were presented as mean \pm standard deviation and were compared using the paired t-test. $p < 0.05$ was considered statistically significant. This study was approved by the Health Research Ethical Committee, Medical School, Universitas Sumatera Utara.

Results

A total of 120 subjects were enrolled in this study and almost equally divided into two groups based on the HBeAg positivity. In this study, male subjects

were mostly found in HBeAg positive (58.3%) and HBeAg negative (61.7%) groups. Mean age and body mass index of subjects were higher in HBeAg negative compared to HBeAg positive group. On the other hand, serum ALT and HBV DNA levels were higher in subjects in the HBeAg positive group (Table 1).

Table 1: Baseline characteristics of the subjects

Characteristics	HBeAg positive (n = 52)	HBeAg negative (n = 68)
Mean age, years	46.5 \pm 10.36	48.6 \pm 10.67
Sex, n (%)		
Male	70 (58.3%)	74 (61.7%)
Female	50 (41.7%)	46 (38.3%)
Mean body mass index, kg/m ²	22.2 \pm 3.22	23.3 \pm 2.98
Family history of hepatitis B, n (%)	89 (74.2%)	86 (71.7%)
Mean serum ALT (*), IU/L	128.1 \pm 96.75	112.4 \pm 89.31
Mean HBV DNA (**), log ₁₀ IU/mL	7.06 \pm 1.24	6.21 \pm 1.32
Family history of hepatitis B, n (%)	89 (74.2%)	86 (71.7%)

*ALT: Alanine aminotransferase, **HBV DNA: Hepatitis B virus deoxyribonucleic acid

Administration of TDF for 24 weeks showed good efficacy both in HBeAg negative and positive groups. In point of fact, serum ALT normalization was achieved in 71.7% subjects with HBeAg positive ($p < 0.001$) and in 75% subjects with HBeAg negative ($p < 0.001$). A similar proportion was observed in subjects with undetectable serum HBV DNA in both groups. The decline of serum HBV DNA was lower in HBeAg positive group (6.08 log₁₀ IU/mL; $p < 0.001$) in compared with those in HBeAg negative group (5.02 log₁₀ IU/mL; $p < 0.001$). HBeAg loss was achieved by 10.8% of subjects with HBeAg positive ($p < 0.001$) although no subjects in this study showed HBsAg loss (Table 2).

Table 2: Efficacy of 24-week administration of TDF in CHB subjects

Parameters	HBeAg positive n = 52	p value	HBeAg negative n = 68	p value
Serum ALT (*) normalization, n (%)	86 (71.7%)	$p < 0.001$	90 (75.0%)	$p < 0.001$
HBeAg loss, n (%)	13 (10.8%)	$p < 0.001$	N/A	-
HBsAg loss, n (%)	0 (0.0%)	-	0 (0.0%)	-
Undetectable serum HBV DNA (**), n (%)	81 (67.5%)	$p < 0.001$	83 (69.2%)	$p < 0.001$
Mean decline in serum HBV DNA (**), log ₁₀ IU/mL	-6.08 \pm 1.23	-	-5.02 \pm 1.12	-

*ALT: Alanine aminotransferase, **HBV DNA: Hepatitis B virus deoxyribonucleic acid

Discussion

There are 240–400 million cases of CHB all over the world which is endemic in sub-Saharan Africa and Asia-Pacific region due to the high rate of perinatally and early childhood infection [2], [19], [20], [21]. In the western world, CHB is mainly caused by unhealthy lifestyle such as high-risk sexual behavior and injection drug use [1], [2], [18], [19]. We found that both groups had a male population is more affected than women. This result is not much different from other countries in Asia, such as China, stated that males are more commonly affected by CHB compared

to females [8], [9], [10], [13]. The mean age of HBV positive patients under TDF treatment was 46.5 ± 10.36 years and 48.6 ± 10.67 years in HBeAg positive and HBeAg negative, respectively. According to literature, mean age of patients with CHB ranges from 30.3 to 40.4 years [10]. Other study reported a higher mean which was 51.3 years [16]. Shi *et al.* reported a younger range of age which was 33.7 to 35.1 years [10].

TDF is a nucleotide analogue which acts by inhibiting HBV DNA polymerase reverse transcriptase enzyme, terminating viral DNA chain elongation, and stopping viral genome replication [9], [12], [13], [20]. Initially, TDF is used to treat human immunodeficiency virus (HIV) infection [7]. As stated above, our objective of the study is to examine the efficacy of TDF agent in treating CHB infection. Knowing that TDF is considered highly effective in treating naïve CHB, we chose the naïve CHB patients for being the study population in this research. All of them received TDF monotherapy for 24 weeks and the efficacy of CHB treatment is followed up with serum ALT, HBV DNA levels, and the seroconversion of HBeAg status.

A study conducted by Ormeci *et al.* showed that after a mean follows up of 30.31 months, 86.5% patients with CHB experienced HBV DNA negativity and the other 71.3% had normal alanine aminotransferase level. However, only 19.6% patients showed HBeAg seroconversion in the study [9]. Lovett *et al.* found that TDF might suppress viral load effectively. After administration of the drug for >3 months, virological suppression was increased by time after TDF administration from 71% at 12 months to 96.7% at 36 months after treatment. Indeed, the efficacy was influenced by baseline HBV DNA level and HBeAg positive status. The study also found that efficacy was not different between naïve and previously treated patients. TDF was also well tolerated by the patients in the study [7]. TDF administration for 48 weeks would result in 92.9% virologic response in naïve CHB patients. The rest showed a partial virologic response and it was suggested due to the high level of serum HBV DNA. Continuous treatment with TDF may increase the rate of virologic response [17].

A meta-analysis showed that TDF had the second-highest HBeAg seroconversion property in patients with CHB. It was only surpassed by telbivudine. This condition was achieved by 52 weeks of treatment. However, HBeAg seroconversion induced by nucleotide analogs is temporary; therefore, it requires long-term treatment [20]. A study from Turkey had shown that no subjects developed resistance toward TDF after 12 months of treatment. In addition, 8.3% subjects had HBeAg seroconversion at 9th month, 80% subjects with positive HBeAg had undetectable HBV DNA, and 91.2% subjects with negative HBeAg had undetectable HBV DNA. At 12th month of treatment, ALT normalization was observed in 80.4% subjects. HBsAg seroconversion was very low in this study (0.85%) [1]. Other study stated that the management of CHB with 96 weeks of TDF

administration had good efficacy in 95% patients. The study involved naïve and previously-treated patients from the Chinese population. Nephrotoxicity had been reported, but it was recovered at 96th week without TDF withdrawal [17].

Those results were similar to the results from our study (Table 2). TDF had good efficacy in managing patients with CHB even with a shorter treatment period. In our study, it showed that more than 70% of the patients achieved ALT normalization, respectively, in HBeAg positive and HBeAg negative population. HBeAg seroconversion was reached in 10.8% population after receiving TDF for 24 weeks. More than 65% subjects had their serum HBV DNA undetected at the 24th week of therapy. However, in our study, serum HBeAg loss rate was low and no subjects showed serum HBsAg loss. The reason for the lower rate of HBeAg loss at the end of 24-week treatment in our study can be explained by the limited number of patients and longer treatment period is expected to improve TDF efficacy in patients with CHB.

In accordance with our study, previous data also showed that HBsAg loss was rarely achieved by administration of TDF alone in patients with CHB. A study done by Ahn *et al.* demonstrated that the combination of TDF and pegylated interferon (PEG-IFN) had significant higher efficacy compared to TDF or PEG-IFN alone. They evaluated the efficacy based on seroconversion of HBsAg and HBeAg [3]. Other study reported that TDF monotherapy had lower virological response compared to TDF-based combination therapy. Longer treatment was associated with higher HBeAg and HBsAg loss or seroconversion [2]. Therefore, combination therapy with drugs from other classes is suggested although longer-duration studies conducted by Liang *et al.* [13] and Chen *et al.* [15] reported that both TDF monotherapy and TDF-based combination therapy possessed good efficacy.

Administration of TDF in patients with CHB who had received other nucleoside analogs previously also showed good efficacy with reference to the serum HBV DNA loss. A total of 93% patients who previously received lamivudine had no HBV DNA detected at 18 months after TDF treatment. A similar condition was observed in 86% of patients who previously received lamivudine and entecavir [8]. Less efficacy of TDF was reported in subjects with human immunodeficiency virus (HIV) and HBV co-infection. In that particular population, TDF-containing regimens administration resulted in 24.9% HBeAg loss, 23.7% HBeAg conversion, 7.3% HBsAg loss, and 5.5% HBsAg conversion. The low rates were due to liver involvement in HIV infection and hepatotoxicity of antiretroviral drugs [14].

Several factors influence the efficacy of CHB treatment. As a long-term, even life-long treatment is usually applied for patients with CHB, patient's compliance is important in achieving disease improvement [6]. Difference in subjects' response

to treatment may be caused by a difference in the genotype of HBV. In Caucasians, for example, the most common genotypes are A and D compared to genotype B and C in the Chinese population [10]. Good efficacy of treatment is affected by HBeAg-negative status, lower baseline HBV DNA level, and lower HBsAg level [2], [19]. In addition, HBV virion is difficult to clear from hepatocytes because of the presence of covalently closed circular DNA in the host's cell nucleus [12], [16].

The strength from our study was that we conducted the research in Medan, which is one of the urban cities in Indonesia with diverse races. On the contrary, this study had several limitations. Its retrospective design prevented us from evaluating subjects' treatment compliance. The evaluation of treatment response did not involve a histopathologic examination. We also did not compare the efficacy of TDF monotherapy and TDF-based combination therapy, the sociodemographic parameters such as age, sex, as well as the efficacy of TDF in naïve and previously treated subjects with CHB. Thus, we recommend future researchers to conduct further analysis on this subject matter. In conclusion, administration of TDF for 24 weeks has good efficacy for patients with CHB.

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