Research Article

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Tenofovir Disoproxil Fumarate in the Management of Chronic Hepatitis B Infection in Children

Çocuklarda Kronik Hepatit B Enfeksiyonunda Tenofovir Disoproksil Fumarat Tedavisi

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ABSTRACT

Objectives: The aim of this study was to present real-world data regarding the efficacy and safety of tenofovir disoproxil fumarate (TDF) in pediatric patients with chronic hepatitis B (CHB).

Materials and Methods: In this observational retrospective cohort study, medical records of 10 children with CHB receiving TDF were reviewed.

Results: All patients were positive for hepatitis B e antigen (HBeAg) at baseline. HBV-DNA <400 copies/mL was achieved in 70% of the patients, while 20% had undetectable levels of HBV-DNA at last visit. The median HBV-DNA at baseline was approximately 8 $\log_{10}$ copies/mL and decrease in HBV-DNA levels after 3 months, 12 months and at last visit was approximately 3.2 $\log_{10}$ copies/mL, 5.2 $\log_{10}$ copies/mL and 6.1 $\log_{10}$ copies/mL, respectively. All but 1 had (n=9, 90%) elevated transaminases at baseline and serum alanine aminotransferase (ALT) levels were normalized in an average of 10.1 (3.7; 5-16) months in 7 patients. Three nucleos(t)ide-naïve patients (30%) experienced HBeAg loss and seroconversion in 12 to 18 months. There were no observed serious adverse events. Renal function was maintained well through follow-up in all patients.

Conclusion: Tenofovir monotherapy is effective in terms of virologic and biochemical responses in pediatric patients with CHB. Tenofovir has a favorable safety profile.

Keywords: Antiviral, chronic hepatitis B infection, nucleos(t)ide analog, tenofovir disoproxil fumarate

ÖZ

Amaç: Bu çalışmanın amacı, pediatrik kronik hepatit B (KHB) tedavisinde tenofovir disoproksil fumaratın (TDF) etkinliği ve güvenliği ile ilgili verileri sunmaktır.

Gereç ve Yöntemler: Bu gözlemsel retrospektif kohort çalışmasında, TDF tedavisi alan KHB enfeksiyonu olan 10 çocuğun tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Tedavi başlangıcında tüm hastalarda hepatit B e antijen (HBeAg) pozitifti. Son poliklinik kontrolünde, hastaların %70'inde HBV-DNA <400 kopya/mL olarak saptanırken, %20'sinde HBV-DNA negatifti. Başlangıçtaki ortanca HBV-DNA değeri yaklaşık 8 $\log_{10}$ kopya/mL idi ve 3. ay, 12. ay ve son kontrolde HBV-DNA değerlerinde sırasıyla yaklaşık 3,2 log10 kopya/mL, 5,2 $\log_{10}$ kopya/mL ve 6,1 $\log_{10}$ kopya/mL düşüş saptandı. Tedavi başlangıcında biri hariç tüm hastaların (n=9, %90) serum alanin aminotransferaz (ALT) seviyeleri yüksekti ve 7 hastada ortalama 10,1 (3,7; 5-16) ayda ALT seviyesi normale döndü. Daha önce hiç nükleoz(t)it analoğu almayan 3 hastada (%30), 12 ila 18 ayda HBeAg kayboldu ve serokonversiyon görüldü. Hastaların hiçbirinde ciddi yan etki gözlemlenmedi. Hastaların takipleri boyunca böbrek fonksiyonları normal sınırlarda seyretti.

Sonuç: Tenofovir monoterapisi, KHB enfeksiyonu olan pediatrik hastalarda virolojik ve biyokimyasal tedavi hedeflerine ulaşmak açısından etkilidir. Çocuklarda tenofovir tedavisi güvenlidir.

Anahtar Kelimeler: Antiviral, kronik hepatit B enfeksiyonu, nükleoz(t)id analoğu, tenofovir disoproksil fumarat

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Introduction

Hepatitis B infection is caused by the hepatitis B virus (HBV) and can be either acute or chronic. It is estimated that worldwide, 240 million are chronically infected by HBV (1). Chronic hepatitis B (CHB) - defined as persistence of hepatitis B surface antigen (HBsAg) for six months or more - in pediatric patients is a major health problem due to high overall prevalence of the disease globally despite the advances in prevention, diagnosis, and management strategies (2). Chronic HBV infection during childhood has been considered to follow a rather benign course as they are generally in the immune-tolerant phase and the majority of children will not require antiviral therapy. However, early identification and monitoring of children at risk for progression of liver disease remains important due to the risk of developing cirrhosis or hepatocellular carcinoma before adulthood in asymptomatic carriers is non-negligible with the risk of 3-5% and 0.01-0.03%, respectively (3).

Lack of appropriate clinical trials and delay in licensing of new drugs in children are some most important issues regarding the management of pediatric CHB. The therapeutic options for pediatric CHB comprises of five drugs: interferon-alpha (INF-α), lamivudine (LMV), entecavir, adefovir, and tenofovir (4). Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir with an excellent safety profile. Tenofovir was approved by the US Food and Drug Administration for the treatment of CHB infection in adolescents ≥12 years in March 2010 and in children 2 to <12 years of age weighing ≥10 kilograms in November 2018. The European Medicines Agency has also approved tenofovir for pediatric populations.

Data regarding TDF treatment in children with CHB is promising but limited. Results from a previous clinical trial in adolescents have indicated that tenofovir is an effective and safe treatment option in adolescents older than 12 years old with no observed resistance (5). The results of a phase 3 clinical trial for evaluation of efficacy and safety profiles of TDF in children aged 2 to 12 years with chronic HBV infection revealed higher rates of HBV-DNA suppression and alanine aminotransferase normalization compared to placebo with no resistance at week 48 (6). Recently, TDF monotherapy was reported to be superior to LMV monotherapy in terms of antiviral efficacy in nucleos(t)ide-naïve children and adolescents with CHB (7).

The aim of the present study was to present real-world data regarding the efficacy and safety of tenofovir treatment in pediatric CHB patients.

Materials and Methods

Study Design and Patients

This was an observational retrospective cohort study. All available medical records from 10 CHB patients who were treated with tenofovir at our institution between 2012 and 2018 were retrospectively reviewed. The study was approved by the Non-interventional Ethics Committee of the hospital and conducted in accordance with the principles of the Declaration of Helsinki (approval number: GO 18/575-16, date: 21/06/2018).

The inclusion criteria were as follows: patients <18 years at the time of treatment initiation who were put on tenofovir treatment as a first line therapy or switched from another nucleos(t)ide analog (NA) due to persistent viremia despite adequate treatment for a minimum of 24 weeks before switching to tenofovir, continuation of tenofovir treatment at least 12 months, having available clinical, laboratory and histopathologic data, pretreatment HBV-DNA level >10^4 copies/mL, pre-treatment alanine aminotransferase (ALT) levels more than two times the upper limit of the normal value persisting for >6 months or >3 months without HBV-DNA decrease, pathology revealed histological activity index ≥ grade 4 and/or fibrosis ≥ stage 2 according to the Ishak score or regardless of the ALT level fibrosis ≥ stage 2 according to the Ishak score. Patients with a history of any concurrent liver disease, patients with concomitant hepatitis C infection and immunocompromised patients were excluded. TDF dosage was determined according to the body weight of the patients as recommended by the manufacturer and relevant guidelines. All of the patients in the study were >35 kg in weight and received oral TDF 300 mg once daily.

Clinical data including age at diagnosis, follow up duration to initiation of first treatment, follow up duration to initiation of tenofovir treatment, treatment indication, previous treatment history, type, duration and outcome of previous treatments, reason for switching from another nucleoside analog to tenofovir were recorded. Hemogram, transaminases, liver and kidney function tests, hepatitis B e antigen (HBeAg) and antibody to hepatitis B e antigen (anti-HBe) status, HBV genotype, HBV-DNA, serum alpha-fetoprotein level and hepatobiliary ultrasonography findings were recorded. Liver biopsy was performed prior to initiation of antiviral treatment in all subjects and histologic grading and staging were done with Ishak score by an experienced pathologist. All patients were positive for HBsAg and HBeAg at baseline. Serologic (HBeAg loss and seroconversion to anti-HBe for HBeAg-positive patients), virologic (complete response if HBV-DNA level is undetectable) and biochemical (normalization of ALT levels) responses were evaluated on the follow up of every patient. Any side effect related to tenofovir treatment was noted.

Statistical Analysis

All data were summarized in a descriptive fashion. No statistical testing was performed. Data were presented using descriptive statistics [mean with standard deviation (SD) or median with range for continuous variables, and n (%) for categorical values].

Results

Patient Characteristics

A total of 10 patients treated with tenofovir in our center were enrolled in the study. The demographic and baseline characteristics of the patients are summarized in Table 1. Half of the patients were nucleos(t)ide-naïve before tenofovir treatment and four of them received TDF as the first line CHB therapy. The mean (SD; range) time from the first HBV treatment to initiation of TDF treatment in patients with prior treatment history (n=6, 60%) was 36.6 (19.2;

Table 1. Patient demographics and baseline characteristics	
n (male/female)	10 (7/3)
Age at diagnosis, years, mean ± SD (range)	5.9±3.8 (0.8-13)
Age at the time of first HBV treatment, years, mean ± SD (range)	12.8±3.5 (4.8-16.6)
Age at the time of TDF treatment, years, mean ± SD (range)	14.8±2 (10.4-17.8)
Prior treatment, n (%)	6 (60%)
INF-α (5 M units/m^2)	1
LMV	3
INF-α (5-8 M units/m^2) followed by LMV	2
Baseline HBV-DNA, $\log_{10}$ copies/mL, median (range)	8 (4.3-9.7)
Baseline ALT, U/L, mean ± SD (range)	110.6±58.5 (20-232)
Normal ALT at baseline, n (%)	1 (10%)
Liver biopsy before TDF treatment, n (%)	9 (90%)
Time to normalization of ALT after TDF treatment, months, mean ± SD (range)	10.1±3.7 (5-16)

HBV: Hepatitis B virus, TDF: Tenofovir disoproxil fumarate, LMV: Lamivudine, ALT: Alanine aminotransferase, INF-α: Interferon-alpha; SD: Standard deviation

12-68) months. The mean TDF treatment duration at the time of data collection was 34 (5.6; 24-42) months. All but one had (n=9, 90%) elevated ALT levels at baseline. Hepatobiliary ultrasonography findings were normal in all patients except minimal hepatomegaly which was detected in three patients. Serum alfa-fetoprotein levels were in the normal range in all patients throughout the study period.

Efficacy

Complete virologic response which is defined by undetectable levels of HB-DNA was achieved by only 10% (n=1) of the patients at the end of the first year. When the primary end point of previous TDF trial in adolescents with CHB was used, HBV-DNA <400 copies/mL was achieved by 40% (n=4) of patients by the first year. Among all patients with a mean TDF treatment duration of 34 (5.6; 24-42) months, complete virologic response and HBV-DNA <400 copies/mL were achieved by 20% and 70% of patients at the time of the data collection, respectively. HBV-DNA levels were dramatically decreased with TDF treatment (Figure 1). The median HBV-DNA at baseline was approximately 8 $\log_{10}$ copies/mL in the study group. Decrease in median HBV-DNA after three months, 12 months and at last visit was approximately 3.2 $\log_{10}$ copies/mL, 5.2 $\log_{10}$ copies/mL and 6.1 $\log_{10}$ copies/mL, respectively.

Virologic Breakthrough

Virologic breakthrough, which was defined as an increase in the HBV-DNA level more than 10-fold of patient's HBV-DNA nadir observed during therapy was detected in two patients. The reason for virologic breakthrough was poor adherence to treatment in both patients. After restoration of treatment compliance, rapid decline in patients' HBV-DNA levels was achieved.

Alanine Aminotransferase and Liver Histology

Baseline serum ALT levels were more than two times the upper limit of normal in 90% of patients. A significant decline in ALT levels parallel to the decline in viral load was observed in the study group (Figure 1). The mean ALT levels after six months and at last visit were 40.5 (30.5; 18-122) U/L and 32.4 (21.3; 16-72) U/L, respectively. Serum ALT levels were normalized in seven of the nine patients (78%) with initial hypertransaminasemia in an average of 10.1 (3.7; 5-16) months (Figure 2). Two patients who had mildly elevated transaminases at last follow-up were the ones experiencing virologic breakthrough due to treatment incompliance. The indication of CHB treatment in the only patient with normal ALT was moderate inflammation and fibrosis (histological activity index: 11, fibrosis stage: 3) on liver histology. Eight of nine patients with liver biopsy had only mild inflammation and fibrosis (histological activity index: 1-6, fibrosis stage: 0-2).

Serology

None of the patients experienced HBsAg loss during follow-up. On the other hand, three patients (30%) experienced HBeAg loss and seroconversion in 12 to 18 months after initiation of TDF treatment. All three patients were nucleos(t)ide-naïve with one of the patients had a prior INF exposure.

Safety

There were no observed serious adverse events in any of the patients that could lead to interruption of treatment. One patient experienced transient dizziness and fatigue. Cardiovascular and neurologic evaluation of the patient was normal and her symptoms were resolved without any further intervention.

Serum creatinine and electrolytes were normal in all patients at baseline and during follow-up. Nephrological pathologies were the most common co-morbidities in the study group. Hematuria due to Nutcracker syndrome (n=1), nephrolithiasis (n=1), postural proteinuria (n=1) and nephrotic syndrome due to membranous glomerulopathy (n=1) were baseline pathologies accompanying CHB in four patients (40%). Renal function was maintained well through follow-up in these children.

Discussion

The goal of anti-HBV therapy in children is to improve long-term survival and quality of life by preventing disease progression and its complications. After the approval of NAs with higher efficacy and genotypic barrier to resistance including entecavir and tenofovir, first-line treatment recommendations for adolescents have been changed. Tenofovir DF (for patients older than 12 years of age) or entecavir (for patients >16 years old) are suggested as best therapy

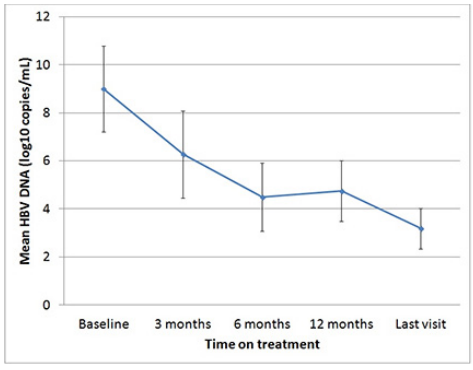

Figure 1. Mean ± standart deviation $\log_{10}$ HBV-DNA (copies/mL) throughout patient follow-up
HBV: Hepatitis B virus

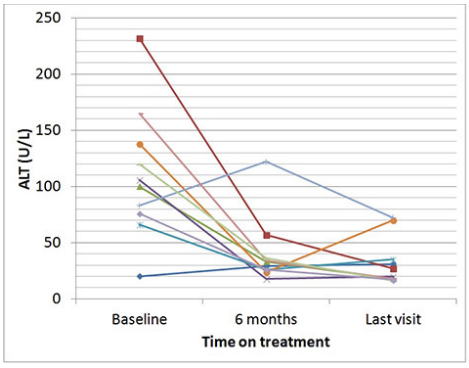

Figure 2. ALT levels of each study patient throughout follow-up
ALT: Alanine aminotransferase

options with strong recommendation and high quality of evidence by European Society of Pediatric Gastroenterology, Hepatology, and Nutrition clinical practice guideline published in 2013 (8). However, data regarding the use of TDF in pediatric CHB patients is limited.

Six of the patients in our study group received first HBV treatment before the age of 12. Five of these patients were non-responders to LMV and switched to TDF in the follow-up. A recent meta-analysis showed that TDF is a more effective rescue therapy than other options in LMV resistant patients (9). Although LMV is not considered to be a first-line treatment for children with CHB due to the low genetic barrier to drug-resistance, it is still the only NA currently approved for younger children. Our center's previous experience with LMV in children with INF refractory CHB showed significant HBV-DNA clearance rate (56.4-64.8%) but ineffective HBeAg seroconversion rates (5.6-12.7%) (10,11). In a large pediatric clinical trial of 52-week LMV treatment for HBeAg-positive children with CHB, mutations associated with drug-resistance was observed in 19% of treated children at 52 weeks (12). In a recent pediatric study comparing TDF with a historical cohort receiving LMV, antiviral resistance was reported 33.3% and 41.7% in the LMV group at 96 and 144 weeks, respectively, while, there was no viral mutation until up to 192 weeks of follow-up in the TDF group (7). High rates of genotypic resistance to older NAs emerged the need for new ones with strong antiviral effects and low resistance rates for the treatment of pediatric CHB. Introduction of TDF and entecavir, being potent NAs with high barrier to resistance, has changed the treatment recommendations in both adults and children (8,13).

A phase 3 placebo-controlled randomized clinical trial, evaluating TDF administered for 72 weeks versus placebo in adolescents aged 12 to 18 years old was published in 2012. Virologic response, defined as HBV-DNA <400 copies/mL, was achieved in 89% of TDF treated adolescent CHB patients at the end of 18 months (0% in placebo group, p<0.001). However, no statistically significant effect on HBeAg clearance was reported in this study (5). Similar results were also reported for children aged 2 to 12 years old (6). Rates of virologic response (77% vs 7%; p<0.001) and ALT normalization (52% vs 18%; p=0.002) were significantly higher in children treated with TDF compared to placebo group, while the rate of HBeAg seroconversion was similar (25% vs 24%) (6). Higher virologic response rates (81.3%, 93.8%, and 100% at 24, 48, and 96 weeks, respectively) were reported recently in TDF treated NA-naïve children (7). Recent adult studies in different CHB populations also reported similar efficacy results in terms of complete virologic response ranging from 62% to 96% (14,15,16,17). However, in our small study group only 70% of the patients achieved HBV DNA <400 copies/mL after an average of three years of treatment with TDF. Although subgroup analyses of TDF treated adolescents with CHB suggested that antiviral efficacy was high regardless of baseline ALT, HBeAg status, age, or prior HBV therapy (5), it can be speculated that some factors including poor compliance, HBV genotype, prior antiviral resistance and HBeAg positivity may be responsible for modest difference in efficacy in our study. In an adult study from Saudi Arabia, a better response to TDF has been reported in HBeAg negative patients when compared to HBeAg positive patients (84.4% vs 21.7%, respectively) (15). All patients in the present study were HBeAg positive at baseline and HBeAg seroconversion was achieved three of the patients. Moreover, the presence of adefovir, but not LMV, resistance was reported to impair TDF efficacy in NA-experienced patients (18). Although none of our patients had a history of adefovir exposure, lack of data regarding genotypic resistance makes any further conclusion impossible about impact of these factors on treatment efficacy in our cohort. Non-adherence to treatment and virologic breakthrough which we documented in two of our patients may be partly responsible for lower complete virologic response rates to TDF treatment in our study group. In adults, nearly 40% of the virologic breakthroughs were found to be correlated with medication non-adherence unrelated to antiviral drug resistance (19).

HBeAg seroconversion rate was reported to be higher in TDF treated adolescents with CHB compared to placebo group (21% vs 15%, respectively) without a statistical significance (5). A higher rate of complete response (HBeAg loss and HBV-DNA <357 IU/mL) with TDF compared to LMV was also reported at week 96, however, again without a statistical significance (41.7% vs 28.6%, p=0.443) (7). The seroconversion rate in our small cohort (30%) was comparable to previous data form children and adults with CHB (5,7,13). HBeAg loss and seroconversion was achieved in three nucleos(t)ide-naïve patients in 12 to 18 months after initiation of TDF treatment.

The current evidence demonstrates that TDF is both a safe and well tolerated choice of treatment in children (20). However, the effect of TDF on renal function and bone mineral density is a major concern in clinical practice. Data regarding the renal safety of

TDF in human immunodeficiency virus-infected children includes conflicting results with some studies reporting significant decline in estimated glomerular filtration rate, increase in serum creatinine, proteinuria and reversible hypophosphatemia (21,22,23) while an excellent renal safety profile has been reported from other cohorts (24,25). All patients in our study cohort were evaluated for renal functions before TDF treatment. Serum creatinine levels were normal at baseline and remained in the normal range during the follow-up period. Two patients had a history of proteinuria before the TDF treatment. Etiologic evaluation of patients revealed postural proteinuria which is a benign condition with excellent prognosis in one patient. The other patient had been diagnosed with HBV-associated membranous glomerulopathy at the age of 10 and on immunosuppressive treatment since then. He was unresponsive to previous treatment with LMV with persistently elevated transaminases and switch of antiviral treatment to TDF was done at the age of 14. Although TDF was reported to cause proteinuria with duration of treatment as an independent predictor (23), no exacerbation of proteinuria and renal impairment related to TDF was observed in both patients. Despite the potential renal toxicity of the drug, TDF treatment in a patient with a history of proteinuria may be used cautiously when there is no other available alternative treatment and close monitoring of renal functions should be provided in the light of present literature. The only TDF trial in children with CHB reported no significant renal complications (5). There were no significant adverse events related to TDF in our study cohort.

Study Limitations

This study was limited by the retrospective design, small number of subjects, lack of bone health assessment and lack of data regarding HBV genotype. However, relatively long-term follow-up period of patients with an average of nearly three years makes the results of this study relevant regarding efficacy, safety and resistance profile of TDF treatment in real life clinical practice.

Conclusion

TDF monotherapy is effective in terms of virologic and biochemical response in pediatric patients with CHB. In the present study, no primary non-response to TDF was observed. Normalization of ALT and at least partial virologic response with ongoing decline in viral load were achieved in all of the patients. TDF has a favorable safety profile even in patients with renal comorbidities including Nephrolithiasis, hematuria and proteinuria and can be used with close follow-up of renal functions in these patients. Although treatment compliance is an important problem in adolescents, tolerability and resistance profile of tenofovir is excellent. However, some important issues about tenofovir treatment including renal toxicity, bone health concerns and very recently reported TDF resistance in CHB patients should be addressed in further pediatric studies.

Ethics

Ethics Committee Approval: This study was approved by the Non-interventional Ethics Committee of the university (approval number: GO 18/575-16, date: 21/06/2018).

Informed Consent: Informed consent was not obtained because of the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: E.G., A.N.K., H.H.G., H.D., İ.N.S.T., Design: E.G., A.N.K., H.H.G., H.D., İ.N.S.T., Data Collection or Processing: E.G., A.N.K., H.H.G., H.D., İ.N.S.T., Analysis or Interpretation: S E.G., A.N.K., H.H.G., H.D., İ.N.S.T., Literature Search: S E.G., A.N.K., H.H.G., H.D., İ.N.S.T., Writing: E.G., H.D., İ.N.S.T., Critical Review: H.D., İ.N.S.T.

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