Effectiveness and Safety of Tenofovir Disoproxil Fumarate in Patients Treated for Hepatitis B in the National University Hospital of Cotonou

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Abstract

Introduction: Viral hepatitis B (VHB) is a serious and global public health issue, particularly in sub-Saharan Africa where it is endemic. The objective of this work was to evaluate the effectiveness and safety of tenofovir disoproxil fumarate (TDF) in the treatment of chronic VHB in Cotonou. **Methods**: This was a descriptive cross-sectional study with a retrospective collection of data from January 1st, 2015 to December 31st, 2016 (24 months) and prospective from May to August 2017 (4 months). Chronic VHB patients treated with TDF for at least 6 months were included. The non-detectability of HBV DNA and the normalization of aminotransferases defined the virological and biochemical responses, respectively. The evaluation of the treatment response on liver fibrosis was done by using APRI score. Renal impairment was assessed by a reduction in glomerular filtration rate according to MDRD (Modifications of the Diet in Renal Disease) formula below 90 mL/min/1.73 m^2. **Results**: In all, 42 patients treated with TDF were included. The average age was 46.7 ± 13.8 years. The study population was predominantly male with a sex ratio of 2.5. Among the 42 patients treated with TDF for an average of 60 weeks (24 to 96 weeks), 36 patients (85.7%) had a virological response; 21 patients (50%) had a biochemical response. Virologic response was 70% at week 24 (W24), 92.6% at W48, 87.5% at W72 and 100% at W96 without significant difference between W24 and W48; between W48 and W72 then between W72 and W96. There was a regression of fibrosis and cirrhosis but not significantly. Renal involvement occurred in 3 out of 19 cases (15.8%) including a

case of chronic end stage renal failure and 2 cases of mild chronic renal failure. **Conclusion:** The treatment with TDF is effective and globally safe in our patients with chronic viral hepatitis B in Cotonou.

Keywords

1. Introduction

Viral hepatitis B (VHB) is a serious and global public health issue problem. More than 2 billion people worldwide have past or current signs of hepatitis B virus (HBV) infection and 257 million people were chronically infected with the virus in 2015 [1]. Sub-Saharan Africa is an area of high endemicity of VHB with prevalences above 8%. In Benin, the national prevalence of VHB is estimated to 9.9% according to a survey in 2013 among new blood donors [2]. It is therefore necessary to set up a strategy for the therapeutic management of chronic VHB in our country, which is strongly affected by this endemic disease. Based on international recommendations, antiviral therapy should be offered to subjects with at least moderately active chronic VHB prior to the potential complications of cirrhosis and hepatocellular carcinoma. Except pegylated interferon, several antiviral drugs are used for the treatment of this disease. The first is lamivudine, followed by adefovir and entecavir. Tenofovir Disoproxil Fumarate (TDF) is the newest drug in the treatment of hepatitis B. It is highly effective and safe. Studies worldwide, particularly in the United States of America, Asia (Japan, Korea, China and Turkey) and Europe (France and Germany) have shown high efficacy and good tolerance of TDF in treatment of chronic VHB [3] [4] [5] [6]. Generic forms of TDF are marketed in Benin since 2015. Treatment is either provided free of charge to the patient through a government grant (mostly for public servants) or purchased by the patient himself. To our knowledge, very few studies have been conducted on the efficacy and safety of TDF in Africa. The objectives of this study were to evaluate the efficacy and safety of TDF in Cotonou.

2. Patients and Methods

The study was carried out in the Department of Gastroenterology and hepatology of the National University Hospital "Hubert Koutoukou Maga" of Cotonou. It was a descriptive and cross-sectional study with a retrospective collection of data from January 1st, 2015 to December 31st, 2016 (24 months). It was also prospective from May to August 2017 (4 months). The study population consisted of all patients treated with TDF for VHB in our department. Were Included, subjects who met the following criteria: to be over the age of 15, to have chronic VHB, being on TDF for at least 6 months at baseline; have in his medical file the values of the viral load, aminotransferases and an assessment of liver fi-

brosis (liver biopsy puncture, Fibrotest-Actitest and/or the APRI score) at the initiation of TDF. Patients with primary liver cancers (before treatment) and patients who refused to participate in the study were not included. Each patient was made an observation file. Patients with chronic VHB and on TDF but lost during follow-up were excluded from this study. The quantification of the HBV-DNA was carried out by real-time PCR (Roche Cobas Taq Man, sensitivity threshold 10 UIn/mL, Cerba Pasteur Paris). The virological response (VR) was defined by the non-detectability of HBV DNA (below 10 IU/mL). Quarterly control of aminotransferases was done during treatment and at 6 months post-treatment. The biochemical response (BR) was defined as a standardized alanine aminotransferase (ALT) level (less than 40 IU/ml). An abdominal ultrasound was performed every six months in case of cirrhosis and annually in the absence of cirrhosis. The evaluation of the response on liver fibrosis was done using the APRI score (Aspartate aminotransferases to Patelet Ratio Index). APRI = (**AST/40**)/(Platelet (*G/l*)) × 100. An APRI score greater than 1.5 showed clinically significant fibrosis and an APRI score greater than 2 indicated cirrhosis. A response on fibrosis or cirrhosis resulted in a decrease in APRI score under treatment. A half-yearly dosage of alphafoetoprotein (AFP) was done in addition to ultrasound for screening for hepatocellular carcinoma. Renal impairment was assessed by a reduction in glomerular filtration rate (MDRD) below 90 mL/min/1.73 m^2. Paraclinical examinations were supported by the patients themselves. Data were collected on a questionnaire including sociodemographic, clinical, paraclinical and progressive characteristics during physical examination of patients and from included patient records. Data entry and statistical analysis were done using the Epi Data 3.5.1 and SPSS version 23 software. The qualitative variables were compared using the Chi square test and the quantitative variables using the test of Student. A value $p < 0.05$ was considered significant.

3. Results

3.1. Demographic and Clinical Characteristics of the Study Population

A total of 42 patients treated with TDF were included. The mean age was 46.7 ± 13.8 years. The most represented age group was 50 to 60 years old. The extremes were 18 and 74 years old. The study population was predominantly male (30 men, 71.4%), with a sex ratio of 2.5. The majority of patients in our study were married (35 out of 42 or 83.3%). Clinically, the main physical sign was hepatomegaly (6 out of 42 cases). Patient characteristics and clinics are presented in Table 1. The main patients' paraclinical characteristics were as follows: in relation to liver function 14 of 39 patients had hepatic cytolysis with ALT levels greater than 2 normal, 14 of 41 patients had prothrombin time (PT) < 70%. HBeAg was negative in 36 cases (85.7%). The viral load was greater than 20000 IU/ml in 64.3% and less than 2000 IU/ml in 21.4%. It is between 2000 and 20,000 IU/ml in 14.3%. The abdominal ultrasound performed at the initiation of

Table 1. Sociodemographic and Clinical Characteristics of Patients.

	Population size (%)
Average age in years (extreme)	46.7 ± 13.8 (18 - 74)
Men	30 (71.4)
History of cirrhosis	10 (23.8)
Alcohol intake	18 (42.8)
Obesity or overweight	20 (47.6)
Diabetes mellitus	3 (7.3)
HCV	1 (2.4)
Jaundice	1 (2.4)
Portal hypertension	2 (4.8)
Hepatomegaly	6 (14.3)
Splenomegaly	2 (4.8)

treatment was normal in 29 cases (69%). The main ultrasound abnormalities were: signs of cirrhosis in 5 cases (11.9%) and hepatic steatosis in 4 cases (9.5%). In the relation to evaluation of liver fibrosis before treatment, hepatic biopsy was performed in 3 cases (7.3%), Fibroscan in one case and APRI alone in 6 cases (14.3%). In our study, Fibrotest® was the most used test, in 78% (32 cases). Fibrosis was greater than or equal to F2 according to Fibrotest in 21 cases (65.6%) and cirrhosis (F4) in 10 cases.

3.2. Effectiveness of TDF

During the study period, 42 patients out of a total of 150 treated with TDF for chronic hepatitis B were included. The average duration was 60 weeks, ranging from 24 weeks (6 months) to 96 weeks (2 years).

- Virological response (VR)

42 patients among the 150 patients treated with TDF had achieved viral load (quantification of HBV DNA) during treatment. Among these, 36 patients (85.7%) had a VR for an average of 60 weeks (24 to 96 weeks). Ten patients had achieved control viral load after 24 weeks (6 months) of treatment. Among these 10 patients, 7 patients had undetectable HBV DNA, that to say 70% of the VR at 24 weeks of treatment. 27 patients had achieved control viral load after 48 weeks (12 months) of treatment. Among these 27 patients, 25 patients had undetectable HBV DNA, that to say a VR of 92.2% at 48 weeks of treatment. 8 patients had achieved control viral load after 72 weeks (18 months) of treatment. Among these 8 patients, 7 patients had undetectable HBV DNA, that to say a VR of 87.5% at 72 weeks of treatment. VR was 100% (2 out of 2) after 96 weeks (24 months) of treatment. Comparative statistical analysis of these different virological responses showed that there was no significant difference between VR at W24 and at W48 (p = 0.074); between VR at W48 and W72 (p = 0.074) and between VR at W72 and W96 (p = 0.0598). These results of VR are specified in Table 2.

Table 2. Distribution of patients by duration of treatment and virological response.

Duration of treatment in weeks	Population size	Undetectable HBV DNA (%)
24	10	7 (70)
48	27	25 (92.6)
72	8	7 (87.5)
96	2	2 (100)

- Biochemical response (BR)

Among a total of 42 patients who were ALT-controlled during treatment, the normalization of ALT was obtained in 21 cases, that to say a BR of 50% over an average of 60 weeks, from 24 to 96 weeks. Ten patients had performed the ALT assay after 24 weeks (6 months) of treatment. Among these 10 patients, 6 patients had achieved normalization of ALTs, that to say a BR equal to 60% at 24 weeks of treatment. Twenty-two patients had ALT controls after 48 weeks (12 months) of treatment. Among these 22 patients, 10 patients had ALAT normalization, that to say a BR equal to 45.5% at 48 weeks of treatment. After 72 weeks (18 months) of treatment, the BR was 50% (4 out of 8 cases). This BR was 50% (one in two cases) after 96 weeks (24 months) of treatment. Comparative statistical analysis of these different biochemical responses showed that there was no significant difference between BR at W24 and at W48 (p = 0.0447), between BR at W48 and at W72 (p = 0.827) and between BR at W72 and at W96 (p = 1).

- Response on liver fibrosis

APRI score had been used to evaluate liver fibrosis during treatment. After an average duration of 60 weeks of treatment, with extremes of 24 and 96 weeks, there was a clinically significant fibrosis regression (APRI score between 1.5 and 2) from 2 cases/31 to 1 case/31. Cirrhosis (APRI > 2 score) initially present in 6 patients was no longer detected in any patient during treatment. But the difference is not statistically significant (p = 0.156). Figure 1 illustrates these results.

3.3. TDF Safety

Renal function was normal (GFR ≥ 90 mL/min/1.73m²) in 19 patients at initiation of treatment. Of these 19 patients with a normal initial GFR, 3 out of 19 cases (15.8%) had developed chronic renal failure at W48 treatment. Chronic renal failure was mild in 2 cases and terminal in one case. We did not notice any cases of hypophosphoremia and glycosuria. Proteinuria was demonstrated in 4 out of 36 cases (11.1%) after an average of 60 weeks. The combination of hypophosphoremia, glycosuria and proteinuria (Fanconi syndrome) were not noticed in our study.

4. Discussion

This work has some limitations. It was a partially retrospective study with missing data in the files. Thus, the APRI score could be calculated before and after treatment only in 31 patients (Figure 1). The second limitation is the use of the
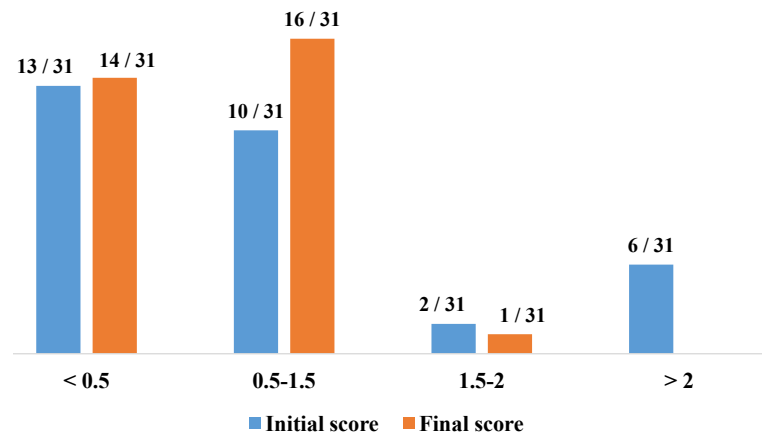
Figure 1. Distribution of patients according to the regression of fibrosis from the APRI score.

APRI score as a method of assessing fibrosis, instead of more indicated method such as fibroscan or liver biopsy puncture.

The VR was 85.7% (36 out of 42) for all of our patients, with an average treatment duration of 60 weeks, with extremes of 24 and 96 weeks. This VR rate is consistent with the data from the literature. In the study of Bulent B *et al.* [7] in Turkey in 2012, the VR ranged from 67% to 94% over a period of 6 months to 52 months. 70% (7 out of 10) of the patients had a VR at the 24th week of treatment. This rate is higher than that found in Brazil in 2015 by Camila V *et al.* [8] 62.3%. Calvin QP *et al.* [9] in the United States in 2014 also reported a lower score than we found. In their study, VR was 61%. By contrast, Dan H *et al.* [10] in China in 2015 found a much higher rate (82.14%). But it should be noted that the 28 patients included in their study had been treated first with lamivudine. This could explain this higher rate. In our series, 92.6% (25/27) of patients had responded to treatment at week 48 with undetectable HBV DNA. This rate is identical with that found by Marcellin *et al.* [3] (2016 in Clichy, France) which was 92%. In contrast, Sang K *et al.* [11] in 2014, in a study conducted in Korea on 136 patients had found 71% VR in 48 weeks of treatment. This result is significantly lower than ours. Nevertheless, several studies had revealed response rates a little higher than ours after 48 weeks. Thus, Calvin QP *et al.* [12] in their 2015 US study of 512 patients including 217 Asian patients and 299 non-Asian patients found 96% and 97%, respectively, in Asian and non-Asian patients as the VR rate after 48 weeks of treatment. In our study, 87.5% (7 of 8 cases) responded to treatment at week 72. In the study of Jae H *et al.* [6] (2014) in Korea on 151 patients at this treatment duration, the VR rate was 69.3%. This result is inferior to ours. But we must take into account the small size of our sample at 72 weeks of treatment. Viral load was undetectable in both patients (100% of VR) at the 96th week of treatment. In the Hyo J *et al.* [13] study, the rate was 84.6% after two years of treatment. Our result therefore seems a little better with the reserve of the small size of our sample. There was no statistically significant difference in VR between the 24th and 48th week (p = 0.074) between week 48 and

week 72 (p = 0.074) and between week 72 and week 96 (p = 0, 5982). After the virological response, the other criterion for therapeutic efficacy is BR. The BR was 50% (21 out of 42) for all of our patients over a period of six months to two years. Sombie R *et al.* [14] in Burkina Faso in 2015 reported a rate of 87% over a period of 1 to 9 years of treatment. This result is superior to ours. This difference could be explained by the longer duration of treatment during their study. Also, the presence of other causes of liver disease found in our study seems to justify the low rate of BR. Indeed, 42.9% of patients would consume alcohol (consumption weaned since the initiation of treatment). The association of diabetes (7.3%), overweight and obesity (47.61%) was also noted. Liver steatosis (control of a metabolic cause of elevation of aminotransferases) was objectified on ultrasound in 9.5% (4 of 42) cases.

In the present study, the RB at 24 weeks of treatment was 60%. Soon K *et al.* [15] found a close result equal to 62% in Korea in 2014. Camila V. *et al.* [8] in Brazil in 2015 had found an aminotransferase normalization rate of 53.1% for the same duration treatment among 336 patients. This result is slightly inferior to ours. The small size of our sample seems to justify this difference. After 48 weeks, we observed a BR assessed at 45.5% (10 cases/22). Camila V. *et al.* [8] in 2015 had slightly higher score: 53.1%. This result diverges from that reported by Sukran K *et al.* [16] in 2010 in Turkey. They had shown that TDF was 100% effective in normalizing aminotransferases for 48 weeks of treatment, in their study of 12 patients on TDF after interferon treatment failure. This difference in BR during their study could be explained by the very small size of their sample on the one hand and by the fact that the subjects in their study were initially treated with interferon. However, several studies had proved better BR in the absence of previous treatment including interferon. Thus, Jae H *et al.* [6] reported a high level of normalization of aminotransferases (97.7%) for 48 weeks in 151 patients naive to antiviral treatment. Thus, we can justify this relatively weak biochemical response in the present study by the presence of elevation cofactors of the identified aminotransferases. In fact, 42.8% of our patients would consume alcohol, diabetes was found in 7.3% and overweight and obesity were present in 47.61% of cases. In our study, the BR was 50% (4/8 of the cases) at the 72nd week. This result is much lower than that reported by Mingxing H *et al.* [4] and which was 80%. This difference could be explained by the presence of other causes of liver disease which occurred. BR was 50% of the cases, *i.e.* 1 in 2 of the patients at the 96th week of treatment. In the study by Fatemeh *et al.* [5], the proportion was higher (75%). A similar result was reported by Marcellin P [3] in France, which was 74.6%. There was no statistically significant difference in BR between the 24th and 48th weeks (p = 0.447), between 48th and 72nd week (p = 0.8271) and between the 72nd and 96th weeks (p = 0.1). About the liver fibrosis, in our study, clinically significant fibrosis regression (APRI score between 1.5 and 2) was noted from 6.5% to 3.2% during treatment. Cirrhosis (APRI score >2), present in 19.4% (6 of 31) at the pre-treatment time, was no longer detected in any patient during treatment. But the difference was not statistically signifi-

cant (p = 0.156). Marcellin P *et al.* [3] noted a regression of fibrosis in 51%; 176 out of 348 cases of biopsies performed after 5 years of treatment with TDF. In the study by Calvin QP *et al.* [9], the proportion of patients classified F4 fibrosis after the Fibrotest was reduced from 4% to 1% after 48 weeks of treatment. TDF therefore allows a regression of clinically significant fibrosis and cirrhosis in patients treated for chronic HVB. No cases of hepatocellular carcinoma (HCC) appeared during treatment follow-up. This is probably due to the relatively short duration of follow-up in our study. However, the treatment with TDF decreases the risk of HCC but does not cancel it completely. Grace C *et al.* [17] in Australia in 2016 reported in their study 2 cases of HCC (among 92 patients) after 12 months of treatment but in cirrhotic patients. Jordan J *et al.* [18] in 2013 during a cohort study on the impact of antiviral therapy on fibrosis and cirrhosis noted that the incidence of HCC in treated cirrhotic patients was 2.5% compared with 3.6% in untreated cirrhotic patients.

Renal impairment occurred in 3 among 19 patients (15.8%) at W48 treatment, of whom 1 in 19 (5.3%) of chronic end stage renal failure and 2 out of 19 (10.5%) of mild chronic renal failure. Marcellin *et al.* [3] in 2016 reported that 11% (48 to 440) of patients on TDF for approximately 36 months had a GFR of 60 mL/min/1.73 m^2. In Calvin QP *et al.*'s study [9], however, in the United States, no patient had a GFR < 50 60 mL/min/1.73 m^2 occurred under treatment. 2 in among 19 (10.5%) of the cases in our study had mild chronic renal insufficiency during treatment, with good renal function remaining in 84.2% (16 of 19 cases). This rate seems similar to those of previous studies. Indeed, Sang K *et al.* [11] in Korea also noted that renal function was maintained good in all patients (136) during the period of treatment (48 weeks). We can say that TDF is generally well tolerated in relation to kidney.

5. Conclusion

Overall, treatment with TDF is effective and globally safe in our patients suffering from chronic viral hepatitis B. However, the management of chronic viral hepatitis B in Cotonou still faces difficulties, with occurrence at the high cost of the pre-therapeutic assessment, which limits the accessibility of care to the greatest number. It is therefore important that measures be taken by national health authorities to enable patients with hepatitis B to seek treatment; this will reduce the disease progression to cirrhosis and hepatocellular carcinoma.

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