Efficacy and safety of Tenofovir Disoproxil Fumarate in Patients with Chronic Hepatitis B with High Baseline Viral Load

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Abstract:

Background: Chronic hepatitis B virus infection is an important cause of morbidity and mortality. Tenofovir disoproxil fumarate was licensed for the treatment of hepatitis B virus infection. So, the current study aimed to Evaluate efficacy and outcome of Tenofovir Disoproxil Fumarate in patients with Chronic Hepatitis B with High Baseline Viral Load.

Patients and methods: One hundred Chronic HBV patients attend Outpatient Clinic of HBV treatment unit, Qena fever hospital, Qena, Egyptwere enrolled in this study and treated with Tenofovir Disoproxil Fumarate (300mg/day) for 24 weeks. Patients categorized into two groups: **Group A:** included 50 chronic HBV patients with Low Viral load < 1 million/ml and Group **B:** included 50 chronic HBV patients with High Viral load ≥ 1 million/ml.virological and biochemical response, as well as safety outcomes were assessed after 24 weeks of treatment.

Results:The mean age of patients was 38.4 years and 33.9 years in Group A and Group B respectively. Number of males was 32 (64%) and 36 (72%) in Group A and Group B respectively. HBeAg was positive in 20 % and 36 % in Group A and Group B respectively. The rates of complete virological suppression were 88% in group A and 72% in group B. All patients achevied normalization of ALT. No severe adverse events were reported during the present study. No elevations in creatinine level were detected.

Conclusion: Tenofovir Disoproxil Fumarate is an efficacious, safe and well-tolerated treatment in an Egyptian patient.

Key Words: Tenofovir, HBV, ALT.

Introduction

Chronic hepatitis B (CHB) is a major health problem worldwide **(Wang, 2009).**CHB is associated with the long-term complications of cirrhosis, liver failure and hepatocellular carcinoma (HCC) in 15%-40% of patients (**MacLachlan and Cowie, 2012).**

Anti-viral therapy, which aims to reduce the HBV DNA levels as much as possible, is

key in the management of CHB **(Marcellin et al., 2009)**.

Nucleos(t)ide analogues (NAs) are commonly used to treat CHB patients. Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are the most potent HBV inhibitors and have a high genetic barrier to resistance **(Marcellin et al., 2009)**.

Tenofovir is a nucleotide analogue (NA) recommended as first-line treatment for CHB. Tenofovir was first developed as an antiviral for the treatment of human immune-deficiency virus (HIV) **(Lovett.,2017).**

Tenofovir was approved in 2008 for the treatment of CHB **(GORDON et al., 2013).**

Aims of the Study:

The aim of the current study was to Evaluate efficacy and outcome of Tenofovir Disoproxil Fumarate in patients with Chronic Hepatitis B With High Baseline Viral Load.

Patients and methods:

This was a prospective cohort study involving 100 Egyptian patients chronically infected with HBV.

Setting: Outpatient Clinic, HBV treatment unit, Qenafever hospital, Qena, Egypt.

Inclusion criteria :-

1. Patients had chronic HBV infection with positive HBV DNA level by PCR, ALT above upper limit of normal.
2. The age range was between 18 and 75 years.

Exclusion criteria :-

1. Patients who are co-infected with HIV or HCV.
2. Patients who <18 or >75 years old.
3. Pregnant female
4. Hepatocellular carcinoma or other extrahepatic malignancy
5. Renal impairment with GFR less than 30 ml / minute
6. Non-compliant patients.

Patients were categorized into:

1. Group I : included 50 CHB patients with Low Viral load <1 million/ml .
2. Group II : included 50 CHB patients with High Viral load ≥ 1 million/ml .

All patients were submitted to clinical examination, laboratory testing, abdominal ultrasonography to assess hepatic echo pattern of the liver, the patency of portal vein, presence of splenomegaly and to exclude hepatocellular carcinoma.

All the patients were subjected to the following laboratory tests:

1. Complete blood count.
2. Liver and kidney function assessment for serum alanine, aspartate aminotransferaseandalfaphetoprotien.
3. Hepatitis markers for hepatitis B and hepatitis C were detected by an enzyme immunoassay (EIA) Cobas e411 (Roche Diagnostic Mannheim-Germany)
4. HBV RNA viral load assessment by quantitative real-time polymerase chain reaction (QT-PCR) assay pre-treatment and at 24 weeks of treatment.

I. Treatment regimen:
All patients received Tenofovir Disoproxil Fumarate 300 mg daily as mono-therapy for 24 week.

II. Monitoring of efficacy and safety
The primary efficacy endpoint was complete virological suppression at end of 24 weeks of treatment, defined by HBV DNA < 50 IU/mL. Secondary efficacy endpoints included Normalization of ALT. The assessment of safety was specifically focussed on renal function.

III. Statistical analysis:
Data were analyzed using a Statistical Program for Social Science (SPSS) version 18.0. Quantitative data were expressed as mean ± standard deviation (M±SD). Qualitative data were expressed as frequency and percentage No(%).Chi-square test:was used when comparing non-parametric data. A one-way analysis of variance (ANOVA), when comparing more than two means.P-values were considered statistically significant at $P < 0.05$**.**

Results:

Baseline characteristics:

Among Group A, 64% were males (32 patients) , The mean age was 38.4 years , 20 % were HBeAg-positive, all patients were seronegative as regard HCV , all female patints were non-pregnant, regardling sonographic findings 26 patients with normal liver and 24 patients with abnormal echopatern liver.

Among Group B, 72% were males (36 patients) , The mean age was 33.9 years , 36 % were HBeAg-positive, all patients were seronegative as regard HCV , all female patints were non-pregnant, regardling sonographic findings 32 patients with normal liver and 18 patients with abnormal echopattern liver.

Treatment efficacy:

Our study results show that the rates of complete virological suppression were 88% in group A and 72% in group B.As regards the level of serum ALT, the present study showed that treatment with tenofovir for 24 weeks achevied normalization of ALT in all patients .

Regarding to Safety and tolerability of Tenofovir disoproxil fumarate , No severe adverse events were reported during the present study. No elevations in creatinine level were detected.

Table (1): Demographic and Laboratory Data in studied groups :-

Demographic data & Risk factors			Group (A) (N=50)		Group (B) (N=50)	
Age (years)	Mean ±SD Min – Max		38.4 ± 12.1 22-65		33.9 ± 11.9 21-70	
Sex	Male Female		32 18	64% 36%	36 14	72% 28%
Pregnancy	Pregnant Non-pregnant		0 18	0% 100%	0 14	0% 100%
Laboratory data			**Group (A) (N=50)**		**Group (B) (N=50)**	
HBe Ag	Positive Negative		10 40	20% 80%	18 32	36% 64%
HBs Ag	Positive Negative		50 0	100% 0%	50 0	100% 0%
HCV Ab	Positive Negative		0 50	0% 100%	0 50	0% 100%
HIV Ab	Positive Negative		0 50	0% 100%	0 50	0% 100%
PCR	Before treatment	Mean ±SD Min – Max	161928.9± 262832 2450-980000		24504270.8±51486487.3 1152000-170000000	
	After treatment	Above detection limit Below detection limit	6 44	12% 88%	14 36	28% 72%

Table (2). Comparison between ALT (before and after treatment) in two group:

		Before treatment	After treatment	P-value
Group A	Mean ±SD	105.7± 34.8	30.6±6.4	<0.001 S
	Median	117	34	
Group B	Mean ±SD	130.9± 103.4	40.2±28	<0.001 S
	Median	112	34	

Table (3). Comparison between s.creat. (before and after treatment) in two group:

		Before treatment	After treatment	P-value
Group A	Mean ±SD	1.0± 0.12	1.0± 0.12	0.96 NS
	Median	1.0	1.0	
Group B	Mean ±SD	1.01± 0.08	0.93± 0.13	0.03 S
	Median	1.0	1.0	

Discussion:

The findings of this study showed that treatment of chronic HBV patients with Tenofovir disoproxil fumarate for 24 weeks achieved high rates of complete virological suppression (88% in group A and 72% in group B).

The results of current study were supported by**Dogan et al.** in which 29 HBeAg-positive and 36 HBeAg-negative cases received tenofovir treatment (*245 mg/day*). All patients were followed every four weeks for until week 48. Among the HBeAg-negative patients, at week 48, 27 patients (75%) achieved HBV-DNA <400 copies/ml (p=0.89). The baseline HBV-DNA level was 7.5 log10 copies/ml. Among the HBeAg-positive patients, at week 48, 20 patients (69%) achieved HBV-DNA <400 copies/ml. The baseline HBV-DNA level was 7.6 log10 copies/ml. In total, 72.3% of patients who received tenofovir had HBV-DNA suppression to <400 copies/ml . normalized serum ALT levels at weeks 48 was achieved (the mean of ALT was 24 IU/L) **(Dogan et al., 2012).**

In a single-centre real-world cohort study**Lovett et al ,**A total of 92 patients chronically infected with HBV were enrolled. The majority of patients were male (70%) and had HBeAg-negative disease (69%). Fifty-five (60%) were treatment-

naïve. Thirty-seven (40%) patients had been previously treated with NA therapy. 52 (56.5) of them with high viral load, HBV DNA load > 100 X 10^3 IU/mL.The rate of complete virological suppression was 80% at 24 month**(Lovett et al., 2017).**

The results of current study were superior than **Chan et al.** a double-blind study, in which 64 naïve patients with high levels of hepatitis B virus (HBV) DNA were received oral tenofovir disoproxil fumarate (TDF, 300 mg) for 192 weeks. The patients had a mean age of 33 years and were predominantly Asian , 48% of patients were male . Almost all were positive for HBeAg (99%) and were infected predominantly with HBV genotype B and C. Mean baseline HBV DNA level was 8.41 log10 IU/mL. At week 192, 55% of patients (35 of 64) had levels of HBV DNA <69 IU/mL.(**Chan et al.,2014**).

In agreement with our study, **Gordon et al.** demonstrated that CHB patients with high viral load can achieve Virologic responce at similar rates as patients with lower viral loads . A total of 489 hepatitis B e antigen (HBeAg)-negative and HBeAg-positive patients received 240 weeks of TDF 300 mg . 20% had HVL at baseline (HBV DNA >9 log^{10} copies/mL).Median baseline HBV DNA levels were 9.52 log10 copies/ mL in the HVL group and 7.34 log10 in the non-HVL group. The proportion of patients with cirrhosis was comparable, with 18.6% in the HVL group and 25.2% in the non-HVL group (P ¼ 0.148). Distribution of viral genotypes was not significantly different between the HVL and non- HVL groups. By week 240, 98.3% of HVL and 99.2% of non-HVL patients on treatment achieved HBV DNA <400 copies/mL. Both groups had similar rates of histologic regression between baseline and week 240 **(Gordon et al., 2013).**

The results of current study were supported by **Buti et al**. in which 437 patients chronically infected with HBV entered an open-label phase wth Tenofovir Disoproxil Fumarate and remained on study for 7 years .Suppression of HBV DNA levels at both\69 and\29 IU/ mL was observed in nearly all patients (99.3 % for both measures)who remained on study at year 7, including 99.3 % (both measures) of HBeAg-negative patients and 99.4 % (both measures) of HBeAg-positive patients, 80.0 % achieved serum alanine aminotransferase normalization **(Buti et al., 2015).**

Regarding the effect of treatment on liver biochemical profile, the present study showed that treatment with tenofovir for 24 weeks achieved normalization of ALT in all patients .

Theseresults were supported by**Luo et al.**in which 144 nucleos(t)ide-naïve CHB patients who received TDF monotherapy for at least 3 months were retrospectively analyzed. 144 patients were included , of whom 106 were HBeAg-positive and 38 were HBeAg-negative. Overall, 55.6% of the patients (n=80) were male, and 25 patients (17.4%) had cirrhosis. 29 patients with hepatitis B virus (HBV) DNA ≥8 log10 IU/ml. The proportions of patients achieving

normal ALT levels were 72.1% (**Luo et al.2019**).

In a retrospective cohort study Örmeci et al, in which One hundred and sixty-four patients who were diagnosed with chronic hepatitis B infection were enrolled . fifty-three (32.3%) were females and one hundred eleven (67.7%) were males, whose average age was 45.34 years. Eighty-six patients (52.4%) were naïve. ALT levels at baseline were 103.52±126.67 IU. All patients were monitored from 6 to 62 months with an average follow-up time of 30.31±14.33
months. After 6 months of treatment with tenofovir, ALT levels were reduced to normal in 70.2% of patients and remained so until the last visit in 71.3% of the patients **(Örmeci et al,.2015) .**

Regardling to Safety and tolerability of Tenofovir disoproxil fumarate , No severe adverse events were reported during the present study. No elevations in creatinine level were detected.

In agreement with our study, **Shi et al.** demonstrated that treatment with Tenofovir disoproxil fumarate were well tolerated, with no report of serious clinical adverse reactions (**Shi et al., 2016**).

A recent cohort study in Hong Kong **(Wong et al., 2015)** assessing nucleoside analogues (NA) in treating 53500 CHB patients with median follow-up of 4.9 years found that NA do not increase the risk for renal damage .

Conclusion: Tenofovir is an efficacious, safe and well-tolerated treatmentin an Egyptian patients. Our data are similar to the reported experience from registration trials.

Conflict of Interest:

The authors have no conflict of interest related to this publication .

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