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The Efficacy of Tenofovir in Chronic Hepatitis B Patients.

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Abstract

Background: Aim: To evaluate the long-term treatment outcomes of tenofovir therapy in patients in a tertiary care setting. **Subjects and Methods:** We performed a retrospective analysis of treatment outcomes among treatment-naïve patients receiving a minimum 3 month tenofovir therapy in Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh. Patients were excluded in the setting of HIV, hepatitis C or hepatitis D co-infection, pregnancy and uncontrolled HCC or were less than 18 years of age. We considered virological and biochemical response, as well as safety outcomes. Virological response was determined by measurement of hepatitis B virus (HBV) DNA using sensitive assays; biochemical response was determined via serum liver function tests; histological response was determined from fibroscan; safety analysis focused on renal function and bone mineral density. The primary efficacy endpoint was complete virological suppression over time, defined by HBV DNA < 20 IU/mL. Secondary efficacy endpoints included rates of biochemical response, and HB e antigen (HBeAg)/HB surface antigen loss and seroconversion over time. **Results:** 100 patients were identified who fulfilled the enrolment criteria. Median follow-up was 24 month (range 6- 36). Mean age was 46 (24-72) years, 64 patients (70%) were male and 36 (36%) were females. All patients were treatment-naïve. Majority of the patients (70%) were HBeAg-negative. Overall, complete virological suppression was achieved in 86% of the patients with a median time to suppression of 6 months. Rates of complete virological suppression were 70% at 12 months, (57/82), 85% at 24 months, (42/50), and 100% at 36 months, (30/30). Partial virological response (HBV DNA 20-2000 IU/mL) was achieved in 97% of the patients. ALT normalization was achieved in 80% of the patients. Multivariate analysis showed a significant relationship between virological suppression at end of follow-up and baseline HBV DNA level (OR = 0.897, 95%CI: 0.833-0.967, P = 0.0047) and HBeAg positive status (OR = 0.373, 95%CI: 0.183-0.762, P = 0.0077). Three cases of virological breakthrough occurred in the setting of probable non-compliance. Tenofovir therapy was well tolerated. **Conclusion:** Tenofovir is an efficacious, safe and well-tolerated. Our data are similar to the reported experience from various other studies.

Keywords: Tenofovir, Hepatitis B virus, Virological suppression, chronic hepatitis B.

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Introduction

Hepatitis B virus infection is a global health problem and it is estimated by the World Health Organization (WHO), that approximately one third of the world population has been infected with HBV with serological evidence of past or present infection. Of the approximately 2 billion people who have been infected worldwide, more than 350 million (5 -7 % of the world's population) suffer from chronic hepatitis B infection. Approximately 15 – 40 % of the patients infected with HBV will develop life threatening liver consequences (including cirrhosis, liver failure and hepatocellular carcinoma) resulting in 600,000 to 1.2 million deaths per year due to HBV.

India has over 50 million HBV carriers and accounts for 10–15 % of the entire pool of HBV carriers of the world. Of the 25 million infants born every year in India, it is estimated that that over 1 million run the life time risk of developing chronic HBV infection. Every year over 100,000 Indians die due to illness related to HBV infection.

There are varying reports of overall rate of HbsAg positivity in India ranging between 2 – 4.7%.[1,2] Pockets of higher endemicity are found in tribal areas where the high burden is maintained through intracaste marriages, tribal customs, illiteracy and poor exposure to health care resources. Spread of HBV infection in many South Asian countries is attributed to unsafe blood supply, reuse of contaminated syringes, lack of maternal screening to prevent perinatal transmission and delay in introduction of hepatitis B vaccine.[3] The predominant mode of transmission is horizontal rather than vertical in India. The exact mode of horizontal transmission remains undefined, but it may be due to contact of non-intact skin or mucous membranes with tears, saliva or blood containing HBV-infected secretions or through sharing of toothbrushes. The age of acquisition of HBV is an important determinant of outcome.[4]

Until now it has been difficult to completely eradicate HBV

because of its integration to host genome as co-valently close circular DNA (cccDNA).[5] The latter serves as the transcriptional template for host RNA polymerase II, an enzyme that produces a series of sub-genomic transcripts.

HBV is the cause of chronic liver disease in 5% of adults. Patients with liver cirrhosis due to HBV infection may experience decompensation at a rate of 2%–5% annually.[6] More than 600000 people worldwide die from liver cirrhosis or complications of cirrhosis every year. The 5 year survival rate for patients with decompensated liver cirrhosis due to HBV is 17%–35%.[5,7]

The treatment of HBV infection aims to suppress HBV DNA replication, decrease necroinflammation, prevent progressive fibrosis, HCC, and finally to eradicate HBV.[8-10] Until now, it has been difficult to eliminate HBV because of its integration in the host genome as covalently close - genomic transcripts.[5]

The goal of treatment for CHB is to improve survival by preventing disease progression to cirrhosis, liver failure and HCC.[11] This can be achieved by long-term suppression of hepatitis B virus (HBV) DNA levels.[12-15] In long-term follow-up, sustained virological suppression has been associated with histological improvement and regression of cirrhosis, as well as reduced risk of hepatic decompensation and HCC.[11,16-18]

Surrogate endpoints used in clinical trials include rates of biochemical [serum alanine aminotransferase (ALT) < upper limit of normal (ULN)], virological (undetectable HBV DNA level), serological [HB e antigen (HBeAg)/HB surface antigen (HBsAg) loss ± seroconversion] and histological (improvements in necro-inflammatory grade and fibrosis stage) response.[18]

Table 1: Surrogate End Points on Treatment for Chronic Hepatitis B.

Category	Surrogate end points	Clinical significance
Biochemical	Normalization of ALT/AST	Not specific to CHB.
Virological	HBV DNA supression	Poor durability of treatment
Histological	Improvement in liver inflammation and or fibrosis	Clinically more relevant Fibrosis slow to change Durability of treatment?
Serological	HBeAg loss+ /development of AntiHBe HBsAg loss+/development of anti-HBs	Predicts favourable outcome if maintained off therapy. Excellent prognosis. Relatively rare event with currently available therapies.

Current therapies approved for CHB include peginterferon-alpha, lamivudine (LMV), adefovir (ADV), telbivudine, entecavir (ETV) and tenofovir (TDF).

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). Genotypic resistance to TDF has not been described. TDF is effective for the treatment of both treatment-naïve and treatment-experienced patients. TDF has a reported good safety profile. Reversible renal toxicity has been reported in < 2% of patients in various studies.[19] Decreased bone mineral density has been reported in HIV-infected patients treated with TDF, but the effect in HBV-mono-infected patients remains unclear.[20-21]

Subjects and Methods

Data Collection

A total of 100 patients were identified. Data was collected retrospectively from the clinical database of the patients presenting in indoor and outpatient units of Teerthanker Mahaveer medical college and Research Centre between 1st August 2015 to 1 August 2018.Median duration of follow was 24 months (6-36months).

Inclusion criteria

- Patients receiving 300 mg tenofovir daily for HBV mono-infection.
- Treatment-naïve.
- Age > 18 years.
- Non-cirrhotic patients were required to demonstrate documented chronic liver injury and confirmed via liver function tests or fibroscan.
- Appropriate HBV DNA levels for starting treatment according to HBeAg status.
  - ❖In HBeAg positive patients HBV DNA > 20000 IU/mL;
  - ❖In HBeAg negative patients HBV DNA > 2000 IU/mL).
- Patients with cirrhosis were required to demonstrate detectable HBV DNA levels.

Exclusion Criteria

Patients were excluded in the setting of HIV, hepatitis C or hepatitis D co-infection, pregnancy and uncontrolled HCC.

HBV DNA assay

HBV DNA levels were measured using the Cobas Taqman assay (LLD = 20 IU/mL, Roche Molecular Systems, Pleasanton, CA, United States).

Definitions of Response

Complete virological suppression/ response was defined as plasma HBV DNA level < 20 IU/mL. Partial virological suppression/ response was defined as plasma HBV DNA level of ≥ 20 IU/mL and < 2000 IU/mL. Virological breakthrough (VBT) was defined as an increase in viral load > 1 log10 from nadir, or by a detectable HBV DNA level on two serial measures in a patient who had previously achieved an undetectable HBV DNA level. Biochemical response was defined as the normalisation of serum ALT to < 45 IU/L. Serological response was defined as the loss of detectable HBeAg and/or HBsAg from serum (HBeAg/HBsAg loss) ± the development of antibodies against these antigens (HBeAg/HBsAg seroconversion).

Clinical Endpoints

The primary efficacy endpoint was complete virological suppression/response over time, defined by HBV DNA < 20 IU/mL. Secondary efficacy endpoints included rates of biochemical response, and HBeAg/HBsAg loss and seroconversion over time. We also measured rates of virological breakthrough and the occurrence of clinical

events including hepatic decompensation and HCC. The assessment of safety was specifically focused on renal function and, where available, bone mineral density.

Statistical Analysis

All statistical analysis was made using Statistical Package for the Social Sciences 16.0 (SPSS software, SPSS Inc, Chicago, Illinois, USA). Statistical significance was set at a p-value of less than 0.05.

Study Population

A total of 100 patients were identified .The majority of patients were male 70% and had HBeAg negative disease 70%.

Table 2: Baseline Demographics.

Baseline demographics	Total population (n = 100)/ Treatment naïve (n = 100)
Age (yr)	
Mean (IQR)	46 (36-54)
Gender n (%)	
Male	64
Female	36
Duration of therapy (mo)	
Median (IQR)	24 (6-36)
HBe antigen status n(%)	
HBeAg positive	30
HBeAg negative	70
Treatment history n(%)	
Naïve	100
HBV DNA load (IU/mL) n (%)	
< 20	13
20-2000	24
2000-100000	13
> 100000	50
Median (IQR)	1.8 × 105 (302-1.6 × 107)
ALT (U/L) n (%)	
0-20	11
20-40	28
40-400	57
> 400	4
Median (IQR)	30 (22-41.8)
Serum creatinine (mg/dl)	
Median (IQR)	1.2 (0.7- 1.4)
Fibroscan score n (%)	
F0	15
F1	42
F2	20
F3	8
F4	15

Results

Table 3: Virological suppression at on treatment time points (n=100)

Follow-up(month)	0	6	12	18	24	30	36
Patient with viral load n(%)	100	92	82	63	50	33	30
Virological suppression n (%)	25 (25%)	56 (51%)	58 (70%)	50 (80%)	40 (80.4%)	29 (87%)	27 (90%)

"Patients with viral load'' refers to refers to number of patients at each time of points who had an HBV DNA load. " Virological suppression'' refers to the number of patients with HBV DNA <20 IU /ml.

Virological Outcomes-

Virological response to TDF detailed in [Table 3]. Overall, complete virological suppression was achieved in 86 patients with a median time to suppression of 6 months. Rates of complete virological suppression were 70% at 12 months, (57/82), 85% at 24 months, (42/50), and 100% at 36 months, (30/30). While a total of 8 patients failed to maintain complete virological suppression, only three patients experienced virological breakthrough. This may be associated with poor compliance. Partial virological suppression was achieved in 97% of the patients. (HBV DNA 20- 2000 IU/ml).

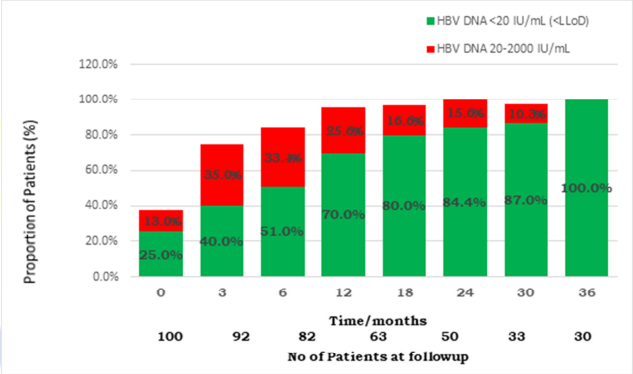

Figure 1: Complete virological suppression and partial virological suppression at on treatment time points. The proportion of patients who achieved complete virological suppression (HBV DNA<20 IU/ML) or partial virological suppression (HBV DNA 20-2000 IU/ML) while on tenofovir therapy. The number of patients followed up at each time points is recorded below the time axis.

Predictors of Virological Outcome

Cox proportional hazard analysis was carried out on viraemic patients with baseline HBV DNA, HBeAg status, Age and baseline ALT. Multivariate analysis showed a significant relationship between virological suppression the at end of follow up and baseline HBV DNA and HBeAg status.

Table 4: Cox regression model of predictors of end of follow-up virological suppression

Covariates	Multivariables Hazard ratio (95%CI)	p value
Baseline HBV DNA (log10 IU/ml)	0.998(0.833- 0.967)	0.0047
HBeAg status (HBeAg pos vs neg)	0.483(0.183- 0.762)	0.0077
AGE (yr)	1 .029(0.992 – 1.044)	0.1760
ALT (log10IU/ml)	1 .098 (0.816- 1.465)	0.5505

Biochemical Outcomes

Mean ALT at baseline was 136 ± 342 and 34 ± 14 U /ml. At the end of follow up with a median change of -102 ± 340

U/ml. Baseline serum ALT levels were within the normal range in 46 % of the patients. By the end of treatment 86% of the patients were within normal range. Of the 56 patients who were above the ULN at the baseline 44 (80%) achieved normalization of ALT by the end of treatment.

Clinical Outcomes

No case of hepatic decompensation were noted during the course of treatment.3 cases of HCC were diagnosed within 12 months of starting tenofovir treatment. All of them were in F4 stage of fibrosacan at the stage of treatment.

Serological Outcomes

HBeAg loss / Seroconversion:

Among 30 HBeAg- positive at baseline 6 (17%) underwent HBeAg loss and Seroconversion. Median time to Seroconversion was 12months.

HBsAg Loss /Seroconversion

No patient underwent HBsAg loss or seroconversion during the entire duration of study.

Treatment Discontinuation and Safety

Treatment had to be discontinued in 2 patients due to rise in serum creatinine levels. Creatinine returned to normal on switching the patients to entecavir .Bone mineral density was not performed routinely and was done in minority of the patients. None of them had their base line BMD available for comparision.

Discussion

Treatment with nucleos (t)ide analogs in chronic hepatitis B infection rapidly suppresses viral load, decreases occurrence of liver cirrhosis, increases seroconversion of HBeAg with minimal side effects, and length of survival.[22-26] The main disadvantages of treatment with nucleos (t)ide analogs are the risks of developing resistance to prolonged therapy, indefinite /prolonged duration of treatment, and less increase in HBeAg and HBsAg seroconversion, particularly in patients who are HBeAg-negative.

Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir that inhibits the activity of viral HBV DNA polymerase, while terminating viral DNA chain elongation and stopping viral genome replication, having a high genetic barrier to resistance. It is eliminated without changing the glomerular filtration and tubular secretion.[27]

The efficacy of TDF therapy in our cohort largely reflects various clinical trial experiences and studies. A daily dose of 300 mg of TDF was found to achieve at least partial virological suppression in 97% of patients and complete virological suppression in 86% of patients, demonstrating robust efficacy. Complete virological suppression was sustained by 94% of patients over time. Virological breakthrough was only observed in only 3 patients with possible poor compliance. The clinical variables that were independently associated with time to suppression were high HBV DNA level at baseline, and HBeAg seropositivity. HBeAg seroconversion was achieved in 17% (6 patients) of HBeAg positive patients, with median duration of follow-up of 24 mo. No patient underwent HBsAg loss and seroconversion during the entire duration of therapy. The efficacy data are therefore broadly consistent with the results in various trials and studies.[28-30]

In a study by Hyo Jun Ahn and et al,[31] CVR in TDF-based therapy at week 96 was achieved in 84.6% of all patients. HBeAg negative status and HBV DNA levels were confirmed as independent predicting factors for CVR in a multivariate analysis, consistent with previous studies. Specifically, in NA-naïve patients, CVR was achieved in 91.5% of patients at week 96. According to HBeAg status, CVR was achieved in 85.2% of HBeAg (+) and 95.5% of HBeAg (-) CHB patients at week 96. The rate of CVR in NA-naïve patients in our cohort is comparable to that of previous studies.[32-33]

Our findings are also in keeping with "real life" international studies. Pol et al,[34] reviewed safety and efficacy data from two real-life cohorts in the United Kingdom and Europe. The cohorts had a combined sample size of 362 NA-naïve patients with a median follow-up of 9-28 mo. Virological suppression was achieved in 80%-89% of patients with breakthrough identified in 2% of patients, without any corresponding resistance mutations. HBeAg seroconversion occurred in 7%-18% of patients and HBsAg loss occurred in 2% of the European cohort. Eighty-seven percent of patients achieved ALT normalization by 30 wk. Pan et al,[35] analyzed the real-life safety and efficacy of TDF in 90 Asian-American patients over 48 wk. Virological suppression was achieved in 82% of patients. 12% of patients underwent HBeAg seroconversion and 66% of patients showed ALT normalization by the end of follow-up. No resistance to TDF was detected and the treatment was considered well-tolerated with few related adverse events.

In our study therapy had to be discontinued in 2 patients due to concerns about rising serum creatinine level. Bone mineral density findings in few patients could not be attributed to TDF therapy as none of the patients had their BMD measured before study. And on the top of that chronic liver disease itself is a risk factor for osteoporosis. Still monitoring of BMD during TDF therapy could be recommended.

Conclusion

Our experience shows TDF to be an effective and safe therapy for patients with CHB. Rates of complete virological suppression were very high. Elevated baseline HBV DNA level and HBeAg-positive disease were associated with slower time to suppression, and most patients achieved complete virological suppression with continued therapy. Tenofovir was generally well tolerated. However the effectiveness of tenofovir in the seroconversion of HBeAg and HBsAg were not satisfactory. So the drug we hope to be the cure for HBV must not only have higher HBV suppression and ALT normalization potential but also higher HBeAg and HBsAg seroconversion rates.

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