

## Treatment of Chronic Hepatitis B with Tenofovir

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### Abstract

**Background:** Tenofovir is among the first-line treatments for chronic hepatitis B (CHB) virus infection. We evaluated the efficacy of Tenofovir in the treatment of Iranian adult patients with CHB.

**Methods:** In a retrospective study, we evaluated 154 HBsAg positive patients referred to Sadoughi hospital in Yazd-Iran for treatment during 2009-2014. Forty-five patients were naive and 109 patients were treated previously with lamivudine or interferon. HBs Ag, HBeAg, HBeAb and quantitative HBV- DNA PCR were measured. The patients with HBV DNA >10,000 copy per ml in precore mutant and HBV DNA >100,000 copy per ml in wild type and ALT >two times of normal value were included. Tenofovir disoproxil fumarate 300 mg was administered and continued for three years. Data were analyzed using SPSS19.

**Results:** We enrolled 154 (109 males 45 female) patients. Mean age of patients was 41± 8 years (18-58 year old). Forty-five of them were naive and the rest had previously experienced treatment. In this study, 113 of patients were of wild type and 41 patients were precore mutant variant. In wild type patients, 25 ones were naive and in precore mutant subtype, 20 patients were naive.

HBsAg disappeared in 5 patients (3.2 percent). Forty one of 45 patients in the naive group (91 percent) and 96 of 109 patients in the previously treated group (88 percent) were cured. AST and ALT levels decreased in over 80 percent of patients and means of AST and ALT levels showed more decrease in naive and precore mutant subgroups. Serum AST and ALT and HBV DNA were higher in the wild type group than in the precore mutant group. Seroconversion occurred in 69 out of 113 patients at the end of the study.

**Conclusion:** Treatment response rate to Tenofovir in Iranian patients with CHB was high. Tenofovir could be recommended as the first-line therapy of chronic HBV infection in Iran.

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### Introduction

Chronic Hepatitis B is a major health problem in the world and it is estimated that over 400 million ones are chronically

infected with HBV with a changing epidemiology due to several factors including vaccination policies and migration (1, 2). In Iran, over 30 percent of population had stigmata of

previous HBV in blood. The prevalence of HBV infection in the general population of Iran was 2.9% (95% CI: 2.5% - 3.4%) before 2010 and 1.3% (95% CI: 0.9% - 1.7%) after 2010 (3, 4). The majority of them will not experience complication but 15% to 40% of them will have sequelae of cirrhosis and complication and ultimately hepatocellular carcinoma. The level of virus (HBV DNA) is an important factor that is strongly related to the progression of HCC, cirrhosis and other sequelae of diseases. Higher levels of HBV DNA are associated with an increased risk of hepatocellular carcinoma (HCC) and cirrhosis (5).

The management of chronic HBV infection is complex and depends upon multiple factors including clinical variables (e.g., the presence or absence of liver inflammation and/or cirrhosis), the patient's immunologic response to infection (e.g., hepatitis B e antigen status), virology factors (e.g., the HBV viral load and genotype), and risk factors for disease progression (e.g., age >40 years and family history of hepatocellular carcinoma) (6).

Responses can be divided into biochemical, serological, virological and histological. All responses can be estimated at several time points during and after the treatment. The definitions of virological responses vary according to the timing (on or after therapy) and type of therapy. Two different types of drugs can be used in the treatment of CHB: conventional or pegylated interferon alpha (IFN or PEG-IFN) and nucleoside/nucleotide analogues referred to collectively as NAs in this document (7).

Oral nucleotides like Tenofovir disoproxil fumarate (TDF) and entecavir and other drugs, by suppressing HBV DNA, can prevent this complication (8-11). The Food and Drug Administration has approved seven therapeutic agents for the

treatment of chronic HBV infection including interferons and nucleoside or nucleotide analogs (e.g., lamivudine, Tenofovir). These drugs have been shown to be effective in suppressing HBV replication, decreasing inflammation and fibrosis in the liver, and preventing progression of the disease. However, there are a number of limitations and benefits for each drug especially interferon for its many complications and side effects, lamivudine for emerging resistant strain and adefovir for inducing renal failure. Tenofovir, a nucleotide analogue and potent inhibitor of HBV polymerase, is recommended as one of the first-line agents against CHB worldwide (12). Tenofovir disoproxil fumarate may be better than entecavir (13) and is easily available in low cost in Iran. Few studies about this drug have been done during the recent years in Iran. Also, distribution of HBV genotype is important in selection of specific treatment. In Iran, the most common genotype is D that is resistant to interferon treatment; therefore, nucleosides drug are more suitable. The aim of this study was to evaluate treatment response to Tenofovir in hepatitis B patients in Iran. Virological, serologic, and enzymatic responses were evaluated.

## Material and methods

This retrospective study was done to evaluate treatment response to Tenofovir disoproxil fumarate in hepatitis B patients and includes virologic, serologic, and enzymatic responses. Complete clearance of HBsAg is the main target of treatment. This is the main goal and standard response that shows no recurrences in the future. The study was approved by ethical Committee of Shahid Sadoughi University of Medical Sciences.

We evaluated 154 HBsAg positive patients that referred to Shahid Sadoughi hospital and a private gastroenterology and infection clinic in Yazd-Iran for treatment from 2009-2014. Forty-five patients were naïve and 109 patients were treated previously with lamivudine or interferon. HBs Ag, HBeAg, HBeAb and quantitative HBV- DNA PCR were measured using real time method by chromo 6 DNA engine (Corbet) technique with sensitivity of 10 copies with Copes machine. The patients were included in the study regardless of being HBeAg positive or negative and treatment naïve or experienced, if HBV DNA >10,000 copy per ml in precore mutant and HBV DNA >100,000 copy per ml in wild type and normal ALT more than two times. Tenofovir disoproxil fumarate 300 mg was administered and continued for three years.

Exclusion criteria were co-infection with hepatitis C, D or HIV infection, decompensated liver disease, serum creatinine > 1.5 times of normal limit, serious concurrent medical illnesses and pregnancy or breastfeeding.

Complete virologic response (CVR) was defined as a decrease in serum HBV DNA to levels undetectable by a quantitative polymerase chain reaction (PCR) assay. The lower limit of detection for serum HBV DNA was 10 copies/mL. Primary non-response was defined as a decrease in serum HBV DNA of less than 2 log copies/mL after 6 months of therapy. Virological breakthrough was defined as an increase in HBV DNA of more than 1 log

copies/mL compared to nadir. AST, ALT and HBV DNA were checked in the beginning and end of treatment. The secondary endpoints were ALT normalization (upper limit of the normal range: 34 U/L [female patients] and 40 U/L [male patients]), HBeAg and HBsAg loss or Seroconversion. Liver enzymes measurement and PCR were repeated with one year intervals and urea and creatinine were checked every three month.

Continuous variables with normal distributions are presented as means  $\pm$  standard deviations and categorical data are presented as counts and percentages. Between-group comparisons of continuous or categorical variables were conducted using the t-test, chi-square test and Fisher's exact test. Serum levels of HBV DNA were initially measured in copies/mL and recorded as log transformations. Data were analyzed using SPSS software version 19.0 (SPSS Inc., Chicago, IL, USA).

## Results

We enrolled 154 patients (109 male 45 female). The mean age of patients was  $41 \pm 8$  years (ranged 18-58 year). Forty five of patients were naïve and 109 ones were treatment experienced. In this study, 113 patients were wild type and 41 ones were precore mutant variant. In wild type patients, 25 ones were naïve and in precore mutant subtype group, 20 patients were naïve. Laboratory characteristics of patients have been presented in table 1.

**Table 1.** Results of laboratory tests of patients

	HBe Ag (85)-	HBe Ag(69) +	P-value
ALT U/L	38.02	35	0.388
AST U/L	33.25	28	0.437
HBV DNA Level, log 10	56.71	35.05	0.037

**Table 2.** HbeAg and HbeAb in naïve and treatment experienced groups in the beginning and end of treatment

Viral Marker	Beginning of treatment		End of treatment		
	Naïve	Treatment experienced	Naïve	Treatment experienced	
HBeAg	-	20 (44.4)	21 (19.3)	37 (82.2)	48(44)
	+	25 (55.6)	88 (80.7)	8 (17.8)	61(56)
HBeAb	-	25 (55.6)	88 (80.7)	8 (17.8)	62(56.9)
	+	20 (44.4)	21 (19.3)	37 (82.2)	47(43.1)

Hepatitis B treatment response can be divided in three groups of virological, serological, and enzymatical responses:

### Virological response

After the treatment, 41 of 45 patients in naïve group (91 percent) and in 96 of 109 ones in the treatment experienced group (88 percent) were cured.

### Serological response

Seroconversion occurred in 43 out of 113 patients at the end of the study (38%). In the wild type subgroup, of 113 HbeAg positive, 44 ones (39%) became negative and 69 cases remained positive cases.

### Enzymatic response

AST and ALT decreased in over 80 percent of patients and means of AST and ALT levels showed more decrease in naïve and precore mutant subgroups.

### Loss of HBsAg in the course of treatment

HBsAg disappeared in five patients (3.2 percent). Only one patient showed elevated creatinine during the study that by modifying the administered dose, creatinine elevation was stopped.

### Discussion

This study on 154 patients demonstrated that TDF is an effective treatment for CHB in both treatment-naïve and

treatment-experienced patients in clinical practice. The goals of antiviral therapy are suppression of HBV DNA, loss of HBeAg (in patients who were initially HBeAg-positive), and loss of HBsAg. A sustained viral response, particularly in those cleared of both HBeAg and HBsAg, is almost invariably accompanied by normalization of serum ALT, a decrease in necroinflammatory activity, and over time, a decrease in fibrosis as well. Antiviral treatment can also reduce the risk of long-term complications of chronic HBV (e.g., liver failure and hepatocellular carcinoma) as well as the transmission of HBV to others. For some patients, immediate antiviral therapy is indicated, whereas for others, treatment may be deferred with careful monitoring. This study was done to evaluate treatment response to Tenofovir fumarate in hepatitis B patients and included virological, serological, and enzymatic responses.

Virological response was not different in the wild type and precore mutant groups. Also, treatment response was similar in naïve and previously treated patients. HBV DNA decreased in all patients, but it was prominent in previously treated and wild type groups. The obtained results are similar to the findings of some previous studies (14,18). But, in a study in Korea, virological response was 80.4 and 84.6 percent after 48 weeks and 96 weeks of treatment respectively. In the mentioned study, previously treated patients respond less than naïve patients (19) and their finding is different with our results.

In two extensive studies in Germany and France, the efficacy and safety of Tenofovir in HBeAg positive and negative and in naïve and treatment experienced patients were evaluated for 12 months and 36 months. In Germany study, After 36 months, HBV DNA < 69 IU/mL was achieved by 91 % of treatment-naïve patients (90 and 92 % in hepatitis B "e" antigen HBeAg-positive and HBeAg-negative, respectively) and 96 % of treatment-experienced patients (93 and 97 %, respectively). Three patients experienced virologic breakthrough, all with reported non-compliance. Overall, 5.7 % HBeAg-positive and 2.2 % HBeAg-negative patients lost hepatitis B surface antigen. Safety data were consistent with the known TDF safety profile; (15). The results of this study are very similar to our results. Also, in the France study, similar to our study, after 12 months, 92 % of the overall cohort achieved virologic response (HBV DNA <69 IU/mL) which was maintained to 36 months (96 %); virologic response was achieved by >90 % of patients irrespective of HBeAg status, age, or prior treatment history (16). Anti-HBe seroconversion or serological response is another outcome in the treatment of CHB infection. It is defined for HBe Ag-positive patients as HBe Ag loss and Seroconversion to anti-HBe after the treatment (12). Seroconversion in our study was 38%. Previous studies have reported anti-HBe Seroconversion rates of 5–21% with nucleotide analogs (1, 17)). In another study in Iran this rate was 17%. But none of the patients achieved Seroconversion during the treatment in (17). In Van Bommel study, 24% of HbeAg positive patients became negative during the treatment (18). In our study, seroconversion was significantly higher, that might be due to the longer duration of treatment.

AST and ALT decreased in over 80 percent of patients and means of AST and ALT levels showed more decrease in naïve and precore mutant subgroups. In Peters study, 36 percent of patients treated with Tenofovir had normal ALT after the treatment, and 6 percent of patients showed elevated ALT (14). In the study of Bakhshizadeh et al., ALT was normal in 67 % at the end of treatment and none of the subjects showed elevated level after the treatment (17). In the study of Van Bommel, ALT level became normal after the treatment in 84% of patients and none of them had elevation of this enzyme during the treatment (18), but in Hann et al study, ALT level was not normal after 1 month of treatment (20).

Loss of HBSAg in the course of treatment with nucleotides analogs showed good immune response to HBV and was parallel to decrease of HBV DNA. In this study, 3.2% of patients became HBsAg negative that is similar to 3% reported in Van Bommel study (18). But, in Ceylan B and Bakhshizadeh studies, none of their cases achieved loss of HBsAg. (17, 22). In Germany study, HBsAg loss over the 36-month period was 6.43 % in patients (15). HBsAg loss or seroconversion heralds durable immune control of the cumulative virus, the probability of cure and no recurrence.

Although the achievement of "on-treatment" HBV DNA suppression is an important marker of treatment efficacy for those receiving nucleotides analogues (NA) therapies, an even more desirable treatment outcome is the achievement of HBsAg Seroconversion. The term "functional cure" has been coined to describe patients who achieve HBsAg seroconversion plus persistently undetectable HBV DNA in blood, representing a state of sustained immunologic control. Currently available NA therapy, infrequently, results in

HBsAg loss, especially in patients who are HBeAg negative at the start of treatment.

In the France cohort study, the overall rate of cumulative HBsAg loss in 3 years was 3 %, (16) whereas in the Germany cohort, the 3-year cumulative rate of HBsAg loss was 6 % in HBeAg-positive and 3 % in HBeAg-negative patients (15). These cumulative rates are likely overestimates, as 40–60 % of the treatment-experienced patients in these cohorts started TDF with low or undetectable HBV DNA levels due to prior NA therapy, and this total duration of NA treatment was not accounted for in the cumulative estimates of HBsAg loss. Nonetheless, the overall message from these “real-world” cohorts is that although HBV DNA suppression have been achievable in the vast majority of patients with TDF therapy, HBsAg loss have been a rare event, highlighting the need for new treatment strategies that more frequently result in HBsAg loss. Our study had some limitations. Because many patients with hepatitis b may initially respond very good but resistant strain was developed rapidly. Response to treatment and its

maintenance require longer follow up period such as 5-10 years.

### Conclusion

TDF produced potent suppression of HBV DNA, irrespective of the patient. HBeAg<sup>+</sup> and HBeAg<sup>-</sup>, treatment-naive and treatment-experienced groups had a very robust response to TDF with 89–99 % of patients achieving HBV DNA <69 IU/mL at 3 years.

Treatment with tenofovir caused decrease of HBeAg and significant decrease in HBV DNA level in chronic hepatitis wild type and precore mutant variant and led to loss of HBsAg in 3 percent of patients.

### Conflicts of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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