Journal of Research in Pharmacy Practice

Original Article

Tenofovir in treatment of Iranian patients with chronic hepatitis B virus infection: An open-label case series

Behrooz Ataei[1], Mahsa Khodadoostan[2], Babk Pouria[3], Peyman Adibi[2]

[1]Infectious Diseases and Tropical Medicine Research Center, Isfahan University of Medical Sciences, Isfahan, Iran

[2]Department of Gastroenterology and Hepatology, Isfahan University of Medical Sciences, Isfahan, Iran

[3]Department of Internal Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Received: February 2016
Accepted: April 2016

Corresponding author:
Dr. Mahsa Khodadoostan,
E-mail: mkhodadoostan@yahoo.com

ABSTRACT

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

Methods: Forty treatment-native patients with CHB but without concurrent hepatitis C or human immunodeficiency virus infections were treated with Tenobiovir(™) 300 mg/day. The hepatitis B virus (HBV) DNA load, hepatitis B e antigen (HBe Ag), anti-hepatitis B e antibody (HBe Ab), liver enzymes, and creatinine were measured before and at least 3 months after the treatment.

Findings: The mean age of patients was 38.1 ± 12.4 years and 65% of them were male. Seventeen (42.5%) patients were HBe Ag-positive and 15 (37.5%) patients had alanine aminotransferase (ALT) of two times above the normal. The HBV DNA load was significantly decreased after the treatment ($P < 0.001$). Twenty-seven (67.5%) patients had viral load of ≤2000 IU/ml and 22 (55%) patients had undetectable HBV DNA level after the treatment. Among positive HBe Ag patients, the HBe Ag became negative in 15 (88.2%) patients after the treatment and HBe Ab became positive in 3 (17.6%) patients. Liver enzymes' levels were significantly decreased after the treatment ($P < 0.05$) and ALT transaminase level became normalized in 86.7% (13 out of 15) of cases with baseline levels twice the normal.

Conclusion: Treatment response rate to Tenofovir in Iranian patients with CHB was high. The virological and serological response rate and safety of Tenofovir in our population was comparable to other populations. Considering availability and costs, Tenobiovir(™) could be recommended as the first-line therapy of chronic HBV infection in Iran.

Keywords: Chronic hepatitis B; Tenofovir; therapy

INTRODUCTION

Infection with the hepatitis B virus (HBV) is a worldwide health problem with significant burden and mortality rate.[1] According to recent data, about 240 million persons are estimated to be suffering from chronic HBV infection and being carriers of the virus all over the word.[2] In Iran, about 1% of the general population has positive hepatitis B surface antigen (HBs Ag) according to the recent data from studies conducted in different regions of the country.[3-5]

Current guidelines recommend treatment for patients with chronic active HBV as evident by abnormal liver enzymes' levels and high viral load with or without

Access this article online

Website: www.jrpp.net

DOI: 10.4103/2279-042X.185714

How to cite this article: Ataei B, Khodadoostan M, Pouria B, Adibi P. Tenofovir in treatment of Iranian patients with chronic hepatitis B virus infection: An open-label case series. J Res Pharm Pract 2016;5:166-70.

positive hepatitis B e antigen (HBe Ag). The goals of treatments are consistent suppression of the virus replication and prevention of progression of the disease to cirrhosis, liver failure, and hepatocellular carcinoma. In patients with positive HBe Ag, the goal is to rich a negative HBe Ag status and HBe Ag seroconversion and in those with already negative HBe Ag, the goal is consistent suppression of the virus replication.[6-8]

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.[9] However, there are a number of limitations associated with each of the approved drugs including high costs,[10] drug resistance,[11] or adverse effects.[12] Nucleotide analogs have potent antiviral activity as well as very low rates of drug resistance and side effects.[11] Tenofovir disoproxil fumarate is a nucleotide analog reverse transcriptase and HBV DNA polymerase inhibitor. It is one of the most potent and first-line oral antiviral agents for HBe Ag-positive as well as HBe Ag-negative patients. Treatment with this drug reduces HBV DNA levels to undetectable or nearly undetectable levels in most treated patients within weeks or months of initiating therapy.[13]

Tenofovir is currently produced in our country under the commercial name of Tenobiovir(™) (Bakhtar BioShimi Co., Kermanshah, Iran). There is no data on the efficacy and safety of this drug in our country. Because the prevalence of HBV genotypes varies geographically and the genotypes may correlate with clinical course and response to treatments,[14] it is worthwhile to evaluate treatment response to Tenofovir in various populations. Accordingly, this open-label case series was conducted to evaluate the effectiveness and safety of Tenofovir in treatment of Iranian patients with chronic HBV infection.

METHODS

This open-label case series was conducted on patients with chronic hepatitis B (CHB) referring to the hepatitis clinic at the Infectious and Tropical Disease Research Center, Isfahan (Iran) between May 2011 and December 2012. Adult patients with positive HBs Ag for at least 6 months, either positive HBe Ag or positive hepatitis B e antibody (HBe Ab), liver enzymes levels two times above normal and HBV DNA >20000 IU/ml or cirrhotic with elevated liver enzymes or high viral load which necessitate treatment according to EASL guideline[8] were consecutively included into the study. All patients were new cases of CHB not being treated prior to the study. Those with concomitant hepatitis C virus or human immunodeficiency virus infections, renal disease, or history of hypersensitivity to anti-viral treatments were excluded from the study. The study was approved by Isfahan University of Medical Sciences and informed consent was obtained from all patients.

Patients were treated with Tenobiovir(™) (Bakhtar BioShimi Co., Kermanshah, Iran) 300 mg/day for 3 consecutive months. Before the treatment, the HBV DNA load was measured with quantitative real-time polymerase chain reaction method (R-Q, Qiegen Co., Germany). The HBe Ag and Ab have been measured with ELISA method (Biorad, USA). Liver enzymes, alanine (ALT) and aspartate (AST) aminotransferases, and alkaline phosphatase (ALP) were measured with enzymatic method (Hitachi 917, Co., Audit, Ireland). The upper limit of the normal range (ULN) for ALT was defined as 19 IU/mL for women and 30 IU/mL for men. Creatinine was checked at the beginning of the study and then monthly.

Virologic response was defined by posttreatment HBV DNA load of ≤60 IU/ml. Anti-HBe seroconversion or serologic response was defined for HBe Ag-positive patients as HBe Ag loss and seroconversion to anti-HBe after the treatment. Normalization of ALT was defined by a decrease of ALT to ≤1.3 of normal laboratory range.[8]

Data were analyzed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Normal distribution of quantitative data was checked with the Kolmogorov–Smirnov Test. Data are reported as mean ± standard deviation or number (%) for continuous and categorical data, respectively. Comparisons between before and after treatment measures were done with the Wilcoxon and McNemar tests for continuous and categorical data, respectively. A two-tailed $P < 0.05$ was considered as statistically significant in all analyses.

RESULTS

Sixty new cases of CHB referring to the hepatitis clinic at the Infectious and Tropical Disease Research Center, Isfahan between May 2011 and December 2012 were selected for the study, which forty of them were finally included in the study. Participants were selected by the census method after they had signed a written informed consent form. Patients included 26 men and 14 women with mean age of 38.1 ± 12.4 years. The HBV DNA level ranged from 356 to 35×10^7 IU/ml and 17 (42.5%) patients were HBe Ag-positive at baseline.

Study outcome variables, before and after the treatment, are presented separately in those with positive and negative HBe Ag in Tables 1 and 2, respectively. The HBV DNA load was significantly decreased after the treatment in both HBe positive and HBe negative patients ($P < 0.001$). A total of 27 (67.5%) patients had posttreatment viral load of ≤2000 IU/ml and 22 (55%) patients had undetectable HBV DNA level after the treatment.

From 17 patients who had positive HBe Ag before the treatment, the HBe Ag became negative in 15 (88.2%) patients after the treatment ($P < 0.001$). Among these patients, HBV DNA level was undetectable in nine (52.9%) patients. One patient with negative HBe Ag before the treatment became HBe Ag-positive after the treatment. In patients who became HBe Ag negative after the treatment, HBe Ab became positive in three (3/17, 17.6%). From 14 patients who had positive HBe Ab before the treatment, it became negative in eight (57.1%) patients after the treatment. However, four patients became HBe Ab positive after the treatment and therefore, no change was observed in the overall frequency of cases with positive HBe Ab after the treatment ($P = 0.388$).

Liver enzymes' levels were significantly decreased after the treatment in both HBe positive and HBe negative patients (all $P < 0.05$). From those who had baseline ALT > ULN U/L ($n = 26$), it became normal in 15 (57.6%) patients after the treatment ($P = 0.001$). However, this change was significant only in those who were HBe Ag-negative before the treatment. Furthermore, change in ALP level was significant only in those who were HBe Ag-negative before the treatment [Table 2].

All patients had stable creatinine during the therapy and renal failure as a side effect of Tenofovir was not seen in any of the patients.

Table 1: Study outcome variables before and after treatment in HBe Ag positive patients (*n*=17)

Variable, unit	Before treatment	After treatment	*P*
HBV DNA, IU/ml	$27653\times10^3\pm2030\times10^3$	2998.7±1774.6	<0.001*
HBV DNA ≤2000 IU/ml	-	12 (70.5)	
Undetectable HBV DNA level	-	9 (52.9)	
ALT, U/mL	71.4 (12.4)	43.0 (8.1)	0.012*
ALT >2× ULN	6 (35.3)	2 (11.8)	0.219†
AST, U/mL	46.1 (8.3)	29.6 (4.5)	0.013*
ALP, U/mL	182.6 (8.9)	172.8 (10.2)	0.149*
Positive HBe Ag	17 (100)	3 (17.6)	<0.001†
Positive HBe Ab	4 (23.5)	3 (17.6)	>0.999†

Data are presented as mean±SE, or *n* (%), where applicable. *Wilcoxon test, †McNemar test. SE=Standard error, HBV DNA=Hepatitis B virus DNA, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ALP=Alkaline phosphatase, HBe Ag=Hepatitis B e antigen, HBe Ab=Hepatitis B e antibody, ULN=Upper limit of normal range

Table 2: Study outcome variables before and after treatment in HBe Ag negative patients (*n*=23)

Variable, unit	Before treatment	After treatment	*P*
HBV DNA, IU/ml	$4982\times10^3\pm1853\times10^3$	493.6±201.4	<0.001*
HBV DNA ≤2000 IU/ml	-	15 (65.2)	
Undetectable HBV DNA level	-	13 (56.5)	
ALT, U/mL	130.8 (33.7)	32.7 (3.2)	<0.001*
ALT >2 × ULN	9 (39.1)	0	0.004†
AST, U/mL	71.1 (12.0)	29.2 (2.4)	<0.001*
ALP, U/mL	227.0 (20.0)	189.5 (8.9)	0.021*
Positive HBe Ag	0	1 (4.3)	>0.999†
Positive HBe Ab, *n* (%)	10 (43.4)	7 (30.4)	0.375†

Data are presented as mean±SE, or *n* (%), where applicable. *Wilcoxon test, †McNemar test. SE=Standard error, HBV DNA=Hepatitis B virus DNA, ALT=Alanine aminotransferase, AST=Aspartate aminotransferase, ALP=Alkaline phosphatase, HBe Ag=Hepatitis B e antigen, HBe Ab=Hepatitis B e antibody, ULN=Upper limit of the normal range

DISCUSSION

The aim of this open-label case series was to evaluate the efficacy and safety of Tenofovir in treatment of Iranian patients with chronic HBV infection. Although the ideal outcome of chronic HBV infection treatment is HBs Ag loss, it is infrequently achievable (from 0% to 7%) by current therapies including Tenofovir (3%).[8] However, other outcomes including virologic, serologic, and biochemical responses are satisfactory end points as they have been shown to be associated with improved prognosis.[8] We found viral suppression in approximately 77% of HBe Ag-positive and 87% of HBe Ag-negative patients. Virological response has been defined variously in previous studies by a HBV DNA level <2000 IU/ml after treatment. These studies have reported virological response in 7–19% with interferons,[15-17] 36–92% with nucleoside analogs,[15,18-23] and 13–100% with nucleotide analogs.[24-26] Virological response with Tenofovir is reported from 55%[27] to 100%[22,28-32] by previous studies and our study results is comparable to previous reports in this regard. Furthermore, we found virological remission (undetectable HBV DNA level) in approximately 53% and 57% of HBe Ag-positive and HBe Ag-negative patients, respectively. In this regard, previous studies have reported a virological remission rate of 18–72% after treatment duration of 6–18 months with Tenofovir.[33] Differences among studies in virological response to Tenofovir may be related to differences in patients'

characteristics and more importantly treatment duration which widely ranged among studies.

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 treatment.[8] In our study, anti-HBe seroconversion was happened in 17.6% of HBe Ag-positive patients all of them had undetectable HBV DNA levels. Previous studies have reported anti-HBe seroconversion rates of 5–21% with nucleotide analogs,[24-27] 16–22% with nucleoside analogs,[15,18-23] and 29–32% with interferons.[15-17] The relatively lower rate of anti-HBe seroconversion in our study can be justified by evaluation at shorter treatment duration as the treatment duration significantly affects the anti-HBe seroconversion rates.[8] Durability of serologic response following treatment with Tenofovir is not well studied and requires further evaluation.

Biochemical response defined by normalization of ALT levels is an important outcome in treatment of CHB infection. Previous studies have defined ALT normalization variously by a decrease to 1.25–1.3 times the ULN or to normal range of ALT. In our study, ALT was above 2 × ULN in 37.5% of total patients and became normalized in about 67% and 100% of HBe Ag-positive and HBe Ag-negative patients, respectively, after treatment. Previous studies have reported ALT normalization by various definitions in 32–59% with interferons,[15-17] 41–92% with nucleoside analogues,[15,18-23] and 48–87% with nucleotide analogs.[22,24-27,30] It must be noted that liver enzymes often fluctuates over time, and therefore, a minimum follow-up of at least 1 year posttreatment with repeating measurements at least every 3 months is required to confirm sustained biochemical response.[8]

Our study had some limitations. The study sample was small and limited to a single center and therefore was not a good representative of the patients with chronic HBV infection in our society. Treatment duration in our study was at least 3 months and we need to further follow the patients to evaluate outcomes of long-term treatment duration.

In summary, we found high treatment response rate to Tenofovir in Iranian patients with chronic HBV infection. Tenofovir in our population resulted in virological, serological, and biochemical response rates comparable to other populations.

Considering availability and the lower costs of this drug compared with other treatments in our society, Tenofovir can be recommended as the first-line therapy of chronic HBV infection in treatment-native patients in Iran.

AUTHORS' CONTRIBUTION

Concept and design: BP & PA. Clinical studies: BA & PA Data acquisition and analysis: BP. Literature search: BP. Manuscript preparation, editing and review: MKH, PA.

Financial support and sponsorship

This study was supported by the Isfahan University of Medical Sciences (grant no. 394266).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004;11:97-107.
2. Ott JJ, Stevens GA, Groeger J, Wiersma ST. Global epidemiology of hepatitis B virus infection: New estimates of age-specific HBsAg seroprevalence and endemicity. Vaccine 2012;30:2212-9.
3. Alavian SM, Fallahian F, Lankarani KB. The changing epidemiology of viral hepatitis B in Iran. J Gastrointestin Liver Dis 2007;16:403-6.
4. Shakeri MT, Foghanian B, Nomani H, Ghayour-Mobarhan M, Nabavinia MS, Rostami S, *et al.* The prevalence of hepatitis B virus infection in mashhad, iran: A population-based study. Iran Red Crescent Med J 2013;15:245-8.
5. Keyvani H, Sohrabi M, Zamani F, Poustchi H, Ashrafi H, Saeedian F, *et al.* A population based study on hepatitis B virus in Northern Iran, Amol. Hepat Mon 2014;14:e20540.
6. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, Han KH, *et al.* Asian-Pacific consensus statement on the management of chronic hepatitis B: A 2008 update. Hepatol Int 2008;2:263-83.
7. Lok AS, McMahon BJ. Chronic hepatitis B: Update 2009. Hepatology 2009;50:661-2.
8. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012;57:167-85.
9. Scaglione SJ, Lok AS. Effectiveness of hepatitis B treatment in clinical practice. Gastroenterology 2012;142:1360-8.e1.
10. Buti M, Oyagüez I, Lozano V, Casado MA. Cost effectiveness of first-line oral antiviral therapies for chronic hepatitis B: A systematic review. Pharmacoeconomics 2013;31:63-75.
11. Ghany MG, Doo EC. Antiviral resistance and hepatitis B therapy. Hepatology 2009;49 5 Suppl:S174-84.
12. Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. Hepatology 2009;49 5 Suppl:S185-95.
13. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, Wong DK, *et al.* Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: A systematic review and Bayesian meta-analyses. Gastroenterology 2010;139:1218-29.
14. Lin CL, Kao JH. The clinical implications of hepatitis B virus genotype: Recent advances. J Gastroenterol Hepatol 2011;26 Suppl 1:123-30.
15. Marcellin P, Lau GK, Bonino F, Farci P, Hadziyannis S, Jin R, *et al.* Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic

hepatitis B. N Engl J Med 2004;351:1206-17.
16. Janssen HL, van Zonneveld M, Senturk H, Zeuzem S, Akarca US, Cakaloglu Y, *et al.* Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: A randomised trial. Lancet 2005;365:123-9.
17. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, *et al.* Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. N Engl J Med 2005;352:2682-95.
18. Dienstag JL, Schiff ER, Wright TL, Perrillo RP, Hann HW, Goodman Z, *et al.* Lamivudine as initial treatment for chronic hepatitis B in the United States. N Engl J Med 1999;341:1256-63.
19. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. N Engl J Med 2006;354:1001-10.
20. Lai CL, Shouval D, Lok AS, Chang TT, Cheinquer H, Goodman Z, *et al.* Entecavir versus lamivudine for patients with HBeAg-negative chronic hepatitis B. N Engl J Med 2006;354:1011-20.
21. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, *et al.* Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007;357:2576-88.
22. Köklü S, Tuna Y, Gülsen MT, Demir M, Köksal AS, Koçkar MC, *et al.* Long-term efficacy and safety of lamivudine, entecavir, and tenofovir for treatment of hepatitis B virus-related cirrhosis. Clin Gastroenterol Hepatol 2013;11:88-94.
23. Lai CL, Chien RN, Leung NW, Chang TT, Guan R, Tai DI, *et al.* A one-year trial of lamivudine for chronic hepatitis B. Asia Hepatitis Lamivudine Study Group. N Engl J Med 1998;339:61-8.
24. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, Chang TT, Kitis G, Rizzetto M, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-negative chronic hepatitis B. N Engl J Med 2003;348:800-7.
25. Marcellin P, Chang TT, Lim SG, Tong MJ, Sievert W, Shiffman ML, *et al.* Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. N Engl J Med 2003;348:808-16.
26. Marcellin P, Heathcote EJ, Buti M, Gane E, de Man RA, Krastev Z, *et al.* Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. N Engl J Med 2008;359:2442-55.
27. Chan HL, Chan CK, Hui AJ, Chan S, Poordad F, Chang TT, *et al.* Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. Gastroenterology 2014;146:1240-8.
28. van Bömmel F, Wünsche T, Mauss S, Reinke P, Bergk A, Schürmann D, *et al.* Comparison of adefovir and tenofovir in the treatment of lamivudine-resistant hepatitis B virus infection. Hepatology 2004;40:1421-5.
29. van Bömmel F, de Man RA, Wedemeyer H, Deterding K, Petersen J, Buggisch P, *et al.* Long-term efficacy of tenofovir monotherapy for hepatitis B virus-monoinfected patients after failure of nucleoside/nucleotide analogues. Hepatology 2010;51:73-80.
30. Murray KF, Szenborn L, Wysocki J, Rossi S, Corsa AC, Dinh P, *et al.* Randomized, placebo-controlled trial of tenofovir disoproxil fumarate in adolescents with chronic hepatitis B. Hepatology 2012;56:2018-26.
31. Gordon SC, Krastev Z, Horban A, Petersen J, Sperl J, Dinh P, *et al.* Efficacy of tenofovir disoproxil fumarate at 240 weeks in patients with chronic hepatitis B with high baseline viral load. Hepatology 2013;58:505-13.
32. Fung S, Kwan P, Fabri M, Horban A, Pelemis M, Hann HW, *et al.* Randomized comparison of tenofovir disoproxil fumarate vs emtricitabine and tenofovir disoproxil fumarate in patients with lamivudine-resistant chronic hepatitis B. Gastroenterology 2014;146:980-8.
33. Gao L, Trinh HN, Li J, Nguyen MH. Tenofovir is superior to entecavir for achieving complete viral suppression in HBeAg-positive chronic hepatitis B patients with high HBV DNA. Aliment Pharmacol Ther 2014;39:629-37.