European Review for Medical and Pharmacological Sciences 2013; 17: 2467-2473

Comparison of tenofovir and entecavir in patients with chronic HBV infection

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Abstract. – BACKGROUND: Sustained suppression of serum HBV DNA levels with nucleos(t)ide analogues is the most important success obtained in the treatment of chronic HBV infection today. Tenofovir and entecavir provide more robust viral suppression.

AIM: The aim of this study is to compare tenofovir and entecavir in terms of viral kinetics, side effects and virological response in patients with chronic HBV infection.

PATIENTS AND METHODS: Patients with chronic hepatitis B treated with tenofovir or entecavir were included in this retrospective study. Using survey analysis, we evaluated independent variables reflecting virological response to treatment and determined whether use of tenofovir or entecavir was one of them. We compared the decline in serum HBV DNA levels at the 3rd, 6th, 12th, 18th and 24th months of treatment between two groups. We also compared entecavir and tenofovir in terms of side effect rates.

RESULTS: 117 patients [average age: 44 (20-73), 65 males (55.6%), 30 HBeAg positive (25.6%)] were enrolled in the study. Sixty-six patients (56.4%) used tenofovir and 51 (43.6%) patients used entecavir.

Virological response was better in patients using tenofovir (Odd's ratio of 1.796 and p = 0.014) and having high fibrosis score (Odd's ratio of 0.182 and p = 0.018). Entecavir was more effective in reducing serum HBV DNA levels at the 3rd month of treatment (serum HBV DNA decline of 4.45 and 3.96 log10 units for entecavir and tenofovir respectively, p = 0.031), but decline rates were similar at other months.

There was no difference between patient groups in terms of side effects and discontinuation of treatment due to side effects.

CONCLUSIONS: Patients with chronic HBV infection using tenofovir have better virological response than those using entecavir.

Key Words:
Entecavir, Tenofovir, Hepatitis B virus.

Introduction

Chronic hepatitis B virus (HBV) infection, being a contagious disease with high contamination rates and leading serious complications such as liver cirrhosis and hepatocellular carcinoma is a very important health problem in the whole world[1]. The best goal of the treatment is the loss of hepatitis B virus surface antigen (HBsAg), meaning the complete healing of the disease. However, unfortunately this can be rarely succeeded. The seroconversion in hepatitis B virus e antigen (HBeAg) during treatment is generally accompanied with the decrease of serum HBV DNA levels, albeit this decrease never signs complete cure and does not prevent from complications of liver disease. Because complete cure is rare, the most important goal of the treatment is to prevent from complications of chronic HBV infection. It is suggested that the decrease in serum HBV DNA levels with nucleos(t)ide analogues accompanies the decrease of decompensated liver disease and hepatocellular carcinoma risks[2,3]. Therefore, sustained suppression of serum HBV DNA levels with nucleos(t)ide analogues is the most important success obtained in the treatment of chronic HBV infection today. Lamivudine, telbivudine, adefovir, tenofovir and entecavir are the currently approved nucleos(t)ides in the treatment of chronic HBV infection. Tenofovir and entecavir provide more robust viral suppression and cause fewer resistant mutant HBV viruses than others[3]. In the literature, there are two clinical observational studies comparing entecavir and tenofovir, but the number of cases in these studies are small[4,5].

The purpose of this work is to compare tenofovir and entecavir in terms of viral kinetics, side effects and virological response in patients with chronic HBV infection.

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Patients and Methods

In this study, data of patients diagnosed with chronic HBV infection and treated with entecavir or tenofovir between March 2007, and January 2010 were evaluated retrospectively.

Inclusion Criteria

Patients complying with all the following criteria were included:

1. HBsAg positivity for at least six months
2. Pretreatment HBV DNA positivity
3. Use of tenofovir or entecavir monotherapy for at least three months
4. Serum HBV DNA levels have to be measured during treatment in first year three- then six-monthly

Exclusion Criteria

Patients complying with any of the following criteria were not included:

1. Active hepatitis C virus infection, HIV infection or hepatitis D virus infection
2. Habitual intravenous narcotic use
3. Malignity
4. Pregnancy
5. Liver transplantation
6. Autoimmune hepatitis
7. Hemochromatosis
8. Lamivudine use prior to entecavir treatment
9. Adefovir use prior to tenofovir treatment

Evaluated Variables

Data including patients' age, height, weight at the time of liver biopsy, gender, alcohol use, Knodell scores and fibrosis scores in the liver biopsy, prior treatment types received for chronic HBV infection, serum alanine aminotransferase (ALT) and HBV DNA levels prior to the treatment; total duration of treatment with tenofovir or entecavir, side effects, HBeAg positivity, serum HBV DNA levels at the 3rd, 6th, 12th, 18th and 24th months during tenofovir or entecavir treatment were recorded. Independent variables determining the virologic response to the treatment were found with survival analysis. Cumulative probability of virologic response were calculated in patients using entecavir and tenofovir.

We searched if tenofovir or entecavir use is one of the variables determining virologic response. Besides we compared the decline in serum HBV DNA levels in groups using tenofovir and entecavir at 3rd, 6th, 12th, 18th and 24th months of therapy.

Evaluation of Liver Histology

Liver biopsy specimens were evaluated using Knodell Scoring System. Patients were divided into two groups according to fibrosis score as stage 0-2 and 3-4.

Serum HBV DNA Measurements

Serum HBV DNA levels were measured with RT-PCR (Real time-polymerase chain reaction) (BioRad iCycler iQ system (San Diego, CA, USA; Quiagen DNA isolation kit, Hilden, Germany; detection limit 20 IU/mL) method. Serum HBV DNA levels were expressed as $\log_{10}$ Units.

Definition of Virologic Response

Virologic response to tenofovir and entecavir treatment was defined as HBV DNA seronegativity (< 20 IU/ml) with polymerase chain reaction (PCR).

Definition of Drug-Induced Side Effects

The observed symptoms and abnormal clinical and laboratory findings resolving with discontinuation were considered drug-induced side effects. Increase in serum creatinine levels exceeding upper normal limit was considered drug-related renal side effect.

Statistical Analysis

Data were evaluated with SPSS-17 (SPSS Inc., Chicago, IL, USA) statistical packet program. Entecavir and tenofovir groups were compared Mann Whitney U test and chi-square test. Cox regression analysis was used in search of variables determining virologic response. Variables significantly associated with virologic response by univariable Cox regression analysis entered into a multivariable model. The cumulative risk of virologic response in patients groups treated tenofovir or entecavir was estimated by the Kaplan-Meier method and the statistical significance of the difference was examined by log-rank test. All statistical tests were two-sided and p value below 0.05 was considered significant.

Results

On hundred seventeen patients were included in this study. Their median (min.-max.) age was

Table I. Comparison of tenofovir and entecavir groups in term of baseline variables.

	Entecavir group n = 51 (43.6%)	Tenofovir group n = 66 (56.4%)	*p* value
Age (years)*	41 (20-73)	45 (22-66)	0.31
Gender (male)**	28 (54.9%)	37 (56.1%)	0.90
Body-mass index*	25 (15-37)	25 (15-37)	0.59
Knodell score*	9 (5-14)	9 (2-14)	0.36
Fibrosis score*	3 (0-4)	1.5 (1-4)	0.06
Patients with grade 3-4 fibrosis **	26 (54.2%)	27 (45%)	0.34
Pretreatment serum ALT level (U/L)*	56 (10-264)	66.5 (14-284)	0.43
Pretreatment serum HBV DNA level (×10^3 Ü/mL)*	117 (0.17-7130000)	5500 (0.14-1110000)	0.08
HBeAg-positive patients**	12 (23.5%)	18 (27.3%)	0.64
Patients consuming alcohol**	14 (27.5%)	7 (10.6%)	0.17

*Median (range); **Number (%) of patients.

44 (20-73) years. Sixty-five (55.6%) of them were male. Thirty (25.6%) of them were HBeAg positive.

Sixty-six (56.4%) patients used tenofovir and 51 (43.6%) patients used entecavir. Entecavir and tenofovir groups were not different in term of baseline parameters (Table I).

Variables affecting virologic response were tenofovir treatment, low serum HBV DNA levels, advanced age and severe fibrosis score in univariable Cox regression analysis (Table II). Multivariable Cox regression analysis showed that severe fibrosis and tenofovir treatment independently determined virologic response (Table II). We realized that median virological response month was 6 (standard error 8,61) in tenofovir group and 12 (standard error 1.34) in entecavir group by Kaplan Meier analysis ($p = 0.007$).

The cumulative probabilities of virologic responses in 3rd, 6th. 12th, 18th and 24th months of treatment were 28.8%, 54.1%, 80.8%, 97.6% ve 100% in tenofovir and 25.5%, 33.8%, 60.9%, 85.8% ve 95.3% in entecavir group, respectively.

The decline in serum HBV DNA levels at 3rd month was more prominent with entecavir than tenofovir, but there was no difference at 6th, 12th, 18th, and 24th months of therapy in this respect (Table III, Figure 2).

In the study population, HBsAg status was determined each year with ELISA method and HBsAg loss were not seen in any patient. Because serum HBV DNA levels did not increase in any patients during treatment, tenofovir and entecavir resistance tests were not performed. Nine (7.7%) patients had side effects. There was no difference between the two treatment groups in terms of side effect rates and discontinuation of treatment due to side effects. Treatments were interrupted in one (2%) patients using entecavir due to serious allergic reaction and in two (3%) patients using tenofovir due to generalized body pain.

In patients developed generalized body pain during tenofovir use, serum creatinine and lactic acid levels were normal and no muscle pathology explaining this pain were found in electromyography. Pain was started in first month of treat-

Table II. The results of uni- and multivariate logistic regression analyses which determined the virologic response to the treatment.

	Univariate Cox analysis			Multivariate Cox analysis		
	95% confidence interval	Odd's ratio	*p*	95% confidence nterval	Odd's ratio	*p*
Age (years)	1.017	1.002-1.033	0.029			
Fibrosis score*	1.223	1.007-1.485	0.043	1.282	1.044-1.574	0.018
Pretreatment HBV DNA level	1	1-1	0.043			
Tenofovir or entecavir use	0.632	0.418-0.956	0.03	1.796	1.125-2.867	0.014
HBeAg status	0.644	0.401-1.034	0.069			

Data related to gender, body-mass index, Knodell score, serum alanine aminotransferase level and alcohol using were not expressed in this table, because these variables were not found statistically significant.

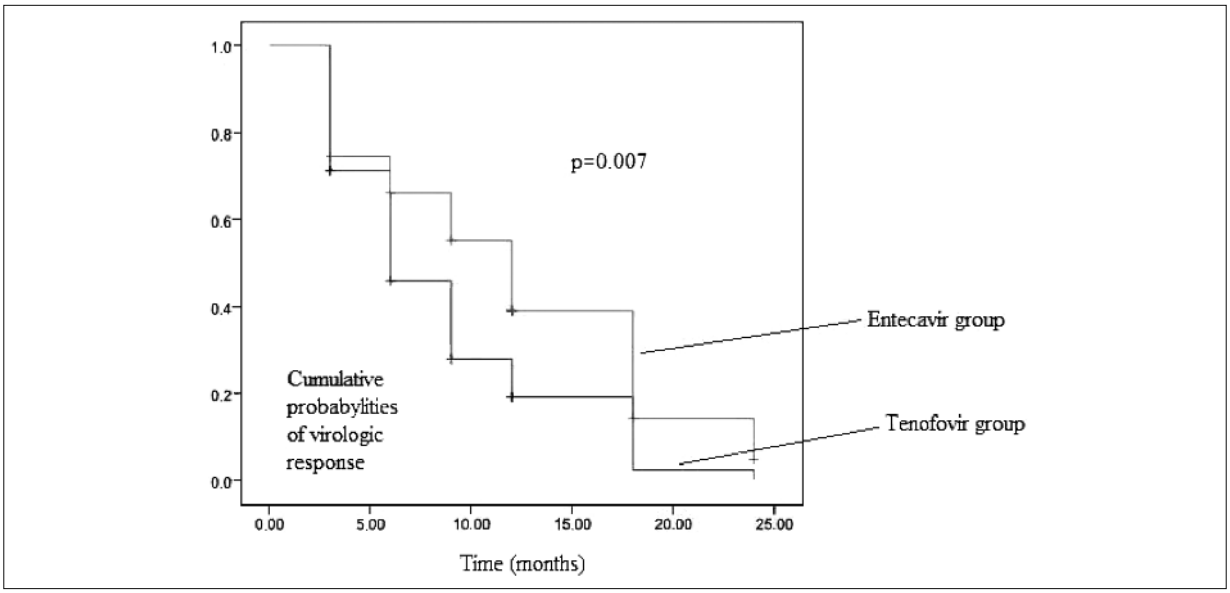

Figure 1. Kaplan-Meier curve showing the effects of the used drug types on virologic response to the treatment.

ment and disappeared when the tenofovir treatment interrupted. Exacerbation of hepatitis was not seen in any patient.

Discussion

The most important target of the treatment of chronic HBV infection is to prevent from hepatocellular carcinoma and liver cirrhosis by suppression of the HBV replication.[6] Entecavir and tenofovir are drugs that recently added to the armamentarium against chronic HBV infection and it has been shown that both of them strongly inhibit viral replication. Entecavir inhibits viral replication in three separate steps so it has been suggested that entecavir is a stronger antiviral than adefovir and lamivudine[6-8]. Tenofovir is less nephrotoxic than adefovir, so it can be used higher doses. Therefore, it's activity is stronger than adefovir[9,10]. There are two observational studies comparing entecavir and tenofovir in terms of antiviral response rates at 48th week of the treatment[4,5]. In one of these studies, 24 patients used tenofovir and 20 patients used entecavir, and response rates were similar[4]. Also, it was reported that the decline in serum HBV DNA levels and HBV DNA negativity rates were not different. In other study, entecavir group consisted of 29 patients and tenofovir group consisted of 65 patients[5]. There was no difference between entecavir (69%) and tenofovir (72.3%) groups in terms of virologic response at 48 weeks of treatment. In our study, the decline in serum HBV DNA levels at the 48th week of the treatment was also similar in two treatment groups; however, HBV DNA negativity rates were higher in tenofovir group.

In literature, different virologic response rates were reported in patients using tenofovir and entecavir[7-9,11-20]. It has been reported the virologic response rate at the 48th week of the tenofovir treatment is between 73 and 97 per cent[9,11,21]. Findings in our study were consistent with these

Table III. Decrease in serum HBV DNA levels in tenofovir and entecavir groups at different months of treatment (log units).

		Entecavir group	Tenofovir group	*p*
Months of treatment	3	4.45 (0.93-7.966)	3.96 (0.14-7.74)	0.031
	6	3.84 (0.93-6.43)	4.88 (0.84-7.74)	0.931
	12	4.25 (0.93-6.65)	5.12 (0.84-7.74)	0.706
	18	4.25 (0.93-6.91)	5.12 (0.84-7.74)	0.952
	24	4.25 (0.93-7.37)	5.12 (0.84-7.74)	0.498

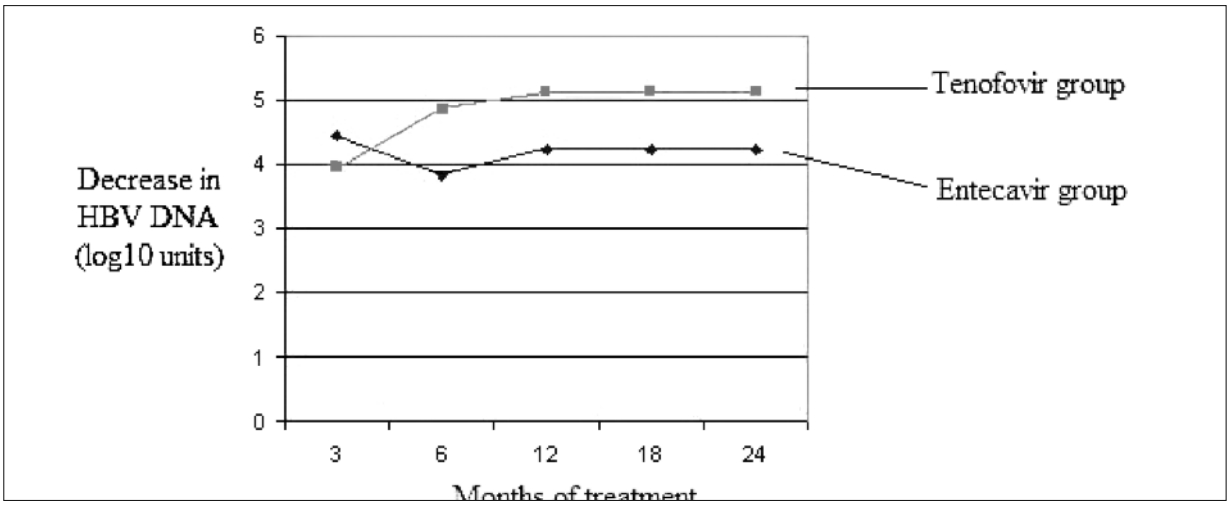

Figure 2. Decrease in serum HBV DNA levels in tenofovir and entecavir groups at different months of treatment (log_{10} units).

studies. In published reports, virologic response rates associated with entecavir use were 12-37.5%, 43.9-76%, 55-93%, 95.8% and 79-85% at 12th, 24th, 48th, 72nd and 96th weeks of the treatment, respectively[7,8,13-20]. The results in our study and in the literature were consistent, but our 96th weeks' result (95.3 per cent) was higher than reported in the literature. However, we think that this can be explained with low patient number at this treatment months in our study.

It has been seen in literature that in studies examining the variables which affects the virologic response rates to tenofovir treatment, included HIV/HBV co-infected patients[11,12,21]. In one of the such studies, HIV/HBV co-infected 45 patients were treated with lamivudine or lamivudine plus tenofovir combination and genotypes were emerged as the independent variable affecting the response rates[11]. In this study, pretreatment serum HBV DNA levels had no effect on the response rates. In another study including 31 HIV/HBV co-infected patients, the lower pretreatment serum HBV DNA levels and the use of lamivudine with tenofovir were seen as factors affecting virologic response, but genotype had no such effect[12]. In a study including twenty eight patients co-infected with HIV/HBV, HBV DNA levels were decreased below 200 copies/ml in 21 (75%) patients using tenofovir and the time to HBV DNA negativity was longer in patients with high pretreatment serum HBV DNA levels and HBeAg-positivity[21]. In this study, it was shown that serum ALT levels, fibrosis scores, duration of HIV infection, HBV genotype, serum HIV RNA levels and the numbers of CD_4 positive T lymphocyte had no effect on the time to virologic response. In another study evaluating 160 patients treated with entecavir; HBeAg negativity and lower pretreatment serum HBV DNA levels were the independent variables affecting the virologic response to the treatment[14]. In another study, 114 cases using entecavir were analysed and virological response at 3rd month were found to be the independent variable of virological response at the end of treatment[15]. In a study with 57 HBeAg-positive patients; the lower pretreatment HBV DNA and HBsAg levels and higher ALT levels affected the virologic responses at 24th months[22]. In our study, patients treated with entecavir or tenofovir were evaluated together dissimilarly to the above-mentioned studies and tenofovir treatment and severe fibrosis were found as independent variables. In our study, pretreatment serum HBV DNA levels did not affect treatment response. This may be resulted from that serum HBV DNA levels may fluctuate in cases with chronic HBV infection and we used single HBV DNA value instead of an average value.

We yielded that HBeAg status does not affect the virological response to treatment. This situation may be resulted from low number of HBeAg positive cases.

In our study, decrease in serum HBV DNA levels was higher in patients using entecavir comparing to patients using tenofovir at the 3rd month of treatment, but there was no difference after 3rd month of treatment in this respect. We concluded that this may be resulted from that both drugs make HBV DNA level negative after 3rd month of treatment.

Both drugs suppress serum HBV DNA level at the same level; however, in our study we concluded that virological response defined as HBV DNA negativity by PCR method is higher in the patients using tenofovir. Entecavir is effective as tenofovir in HBV DNA suppression, but is incompetent for complete negativity. Failure of complete HBV DNA negativity during treatment may cause drug resistance in long term therapy. However, we did not detect any emergence of entecavir resistance in two years period. We think it may be due to short follow up duration in our study.

In the largest study on side effects of tenofovir; 10343 patients receiving tenofovir-based antiretroviral treatment were followed up four years and at the end of the fourth year, increased creatinine levels were reported in two per cent of the patients[23]. During follow-up period, serum creatinine levels did not exceed normal upper limit in any patients who use tenofovir. Gastrointestinal side effects including nausea, vomiting and diarrhea were the most common side effects of tenofovir treatment in literature[9,23]. In our study, upper abdominal pain occurred in 1 patient following tenofovir use. The reason for low appearance of gastrointestinal side effects was probably that, the mild effects were not recorded in patient files. In a study, back pain and headache related to tenofovir were reported in 7% and 13% of patients, respectively[9]. In our study, in 5 (7.6%) patients using tenofovir, generalized body pain was reported and this side effect caused in 2 patients to discontinue the treatment. We didn't detect such a side effect in entecavir group. Serious adverse events causing the interruption of the entecavir treatment were rare in literature[16,18,19]. The results obtained in our study were consistent with these findings. There was no difference between the two treatment groups in terms of side effect rates and discontinuation of treatment due to side effects; however, low number of patients developing side effects makes this result less reliable.

Conclusions

It was demonstrated that patients with chronic HBV infection treated with tenofovir had higher virologic response rates than patients treated with entecavir, and there were no differences between two groups in terms of side-effects.

Acknowledgements

We thank Dr Gunay Can for his assistance in statistical evaluation of the study.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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