ORIGINAL ARTICLE

Comparison of the efficacy of tenofovir and entecavir for the treatment of nucleos(t) ide-naïve patients with chronic hepatitis B

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Abstract

Background: An important goal in the treatment of chronic hepatitis B virus (HBV) infection is to prevent hepatocellular carcinoma and liver cirrhosis by suppressing HBV replication. Tenofovir and entecavir are effective viral suppression compounds. However, comparative data is scant, especially in Korea. This study compared tenofovir and entecavir concerning efficiencies and side effects.

Materials and Methods: We retrospectively reviewed data of nucleos (t) ide-naïve patients with chronic HBV infection. Independent variables reflecting virological response were evaluated, and the decline in serum HBV DNA levels, and side effects between tenofovir-and entecavir-treated patients were compared at treatment week 12, 24, and 48.

Results: At the end of 48 weeks, there was no statistical difference in the induction of undetectable levels of HBV DNA between the entecavir (82.5%) and tenofovir (69.2%) groups. Entecavir was more effective in reducing serum HBV DNA levels at 24 weeks of treatment (serum HBV DNA decline of 5.53 and 4.95 log10 units for entecavir and tenofovir, respectively; $P = 0.044$), but the rate of decline was similar at other weeks. There was no difference between the two groups in terms of side effects and discontinuance of treatment due to side effects.

Conclusions: Tenofovir is not significantly different from entecavir in virologic response and tolerability in the treatment of chronic HBV.

Key words: Chronic hepatitis B, entecavir, tenofovir

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Introduction

Hepatitis B virus (HBV) infection affects more than 400 million people worldwide and is associated with significant health problems. Approximately 25% of HBV infections ultimately lead to the development of cirrhosis or hepatocellular carcinoma (HCC).[1]

High serum HBV DNA level is a risk factor for progression to cirrhosis and development of HCC.[2] In patients positive and negative for hepatitis B e antigen (HBeAg), the sustained suppression of HBV DNA replication is associated with histological and clinical improvements due to the suppression of HBV DNA and hepatic necroinflammation.[3,4]

The primary goals for patients with chronic hepatitis B are to decrease the risk of liver disease progression, particularly to cirrhosis, liver failure, and HCC, which can be achieved if HBV replication can be suppressed in a sustained manner. Based on the evidence linking high HBV DNA levels to the development of complications of liver disease, patients with HBeAg-positive

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chronic hepatitis who have a substantial decrease in the level of HBV DNA and a loss of HBeAg from serum demonstrate histological improvement and reduction in disease progression. Loss of hepatitis B surface antigen (HBsAg) from serum with or without seroconversion to anti-HBs is considered the ideal end-point of therapy. However, this is infrequently achieved with currently available anti-viral agents, thus, undetectable or low levels of HBV DNA are the main therapeutic goals for decreasing the risk of developing cirrhosis and its complications in clinical practice.[5-7] 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.

Current treatment options for chronic HBV consist of nucleos(t)ide analogues and (pegylated) interferon. Antiviral treatment with nucleos(t)ide analogues aims at inhibiting viral polymerase activity.[8] In the treatment of chronic HBV infection, tenofovir and entecavir provide more powerful viral suppression and cause fewer resistant mutant HBV viruses than other anti-viral agents.[6] Two clinical studies to date have compared entecavir and tenofovir, but there were few cases.[9,10] Since tenofovir was only recently approved for the treatment of chronic hepatitis B in Korea, information on the efficacy of tenofovir in Koreans is scant.

The current study investigated the safety and efficacy of tenofovir compared with entecavir after 49 weeks of treatment in HBeAg-positive and HBeAg-negative chronic HBV patients who had not previously received a nucleos(t)ide analogue or interferon regimen.

Materials and Methods

Patients

Seventy-nine chronic HBV patients (52 males, 27 females) who received treatment with entecavir or tenofovir between January 2012 and April 2014 in the Liver Clinic of Samsung Changwon Hospital were investigated retrospectively. Patients ranged in age from 39 to 62 years. Inclusion criteria were sero-positive for HBsAg, elevation of serum alanine aminotransaminase (ALT) for at least 6 months (normal range: 7–38 IU/L for females and 4–53 IU/L for males), pretreatment HBV DNA positive, and use of tenofovir or entecavir monotherapy for 1 year. Serum HBV DNA levels were measured during treatment in the 1st year.

Patients complying with any of the following criteria were not included: (1) Active hepatitis C virus infection, human immunodeficiency virus infection, or hepatitis D virus infection; (2) habitual intravenous narcotic use; (3) malignancy; (4) pregnancy; (5) liver transplantation; (6) autoimmune hepatitis; (7) hemochromatosis; (8) lamivudine use prior to entecavir treatment; and (9) adefovir use prior to tenofovir treatment.

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

Every patient who received tenofovir or entecavir underwent a check-up for biochemical, serological and virological parameters at an outpatient clinic, at least every 3 months.

Observed symptoms and abnormal clinical and laboratory findings that resolved with discontinued therapy were considered drug-induced side effects. Serum calcium and phosphorus levels were regularly measured every 3 months to detect tenofovir-related nephrotoxicity. Increase in serum creatinine levels exceeding the upper normal limit was considered a drug-related renal side effect. Data including age, gender, body mass index, platelet count, prothrombin, gamma-glutamyltransferase (GGT), creatinine, bilirubin, albumin, alkaline phosphatase (ALP), aspartate transaminase (AST), ALT levels, HBeAg status, serum HBV DNA levels prior to treatment; and total duration of treatment with tenofovir or entecavir, side effects, ALT levels, HBeAg positivity, serum HBV DNA levels at week 12, week 24, and week 48 during tenofovir or entecavir treatment were recorded. Independent variables determining the virologic response to the treatment were identified with survival analysis. The decline in serum HBV DNA levels was compared in patients treated with tenofovir and entecavir at week 12, 24, and 48 of therapy. Liver cirrhosis was diagnosed by comprehensively reviewing laboratory findings (e.g., thrombocytopenia or prolonged prothrombin time), endoscopic findings (e.g., esophageal varix or gastric varix), and abdominal ultrasound or abdominal computerized tomography, in patients with underlying liver disease.

Assays

Hepatitis B surface antigen, HBeAg, and hepatitis B e antibody (anti-HBe) were assayed with second-generation enzyme-linked immunosorbent assay. All patients underwent blood testing for liver biochemistry (ALT, AST, ALP, GGT, albumin, and bilirubin), complete blood count, prothrombin time, and renal biochemistry before the commencement of therapy. Serum HBV DNA levels were measured with real time-PCR (RT-PCR). Serum HBV DNA levels were expressed as log10 units. HBsAg, anti-HBs, HBeAg, and anti-HBe were tested by electrochemiluminescence immunoassay (MOUDULAR E170; Roche Diagnostics, IN, USA). Levels of serum HBV-DNA were quantified using a RT-PCR assay (COBAS Tagman™ HBV Test Kit; Roche Molecular Systems Inc., USA); the lower limit of HBV DNA quantification was 20 IU/ml.

Statistical analyses

Data were evaluated with SPSS Statistics version 19 (IBM, Armonk, NY, USA). Entecavir and tenofovir

groups were compared using the Mann–Whitney U-test, independent *t*-test Chi-square test, and Fisher's exact test. Cox regression analysis was used in search of variables determining virologic response. Variables significantly associated with virologic response by univariable Cox regression analysis were entered into a multivariable model. All statistical tests were two-sided, and $P < 0.05$ was considered significant.

Results

Totally, 79 patients had an average age of 49.1 ± 10.5 years. Thirty-nine (49.4%) patients were treated with tenofovir and 40 (50.6%) patients were treated with entecavir. Seven (17.5%) of 40 patients in the entecavir group and 6 (15.4%) of 39 patients in the tenofovir group had liver cirrhosis at the time of introduction of antiviral treatment. Entecavir and tenofovir groups were not different in term of baseline parameters [Table 1]. In our study, follow-up data were obtained for all patients who were initially included in this study without loss. Declines in serum HBV DNA levels and rate of undetectable HBV DNA at week 24 were more prominent with entecavir than tenofovir ($P = 0.03$), but there was no difference at weeks 12 and 48 of therapy. At week 48 of therapy, 33 of 40 (82.5%) patients in the entecavir group and 27 of 39 (69.2%) patients in the tenofovir group achieved undetectable HBV

Table 1: Baseline comparison of tenofovir and entecavir groups

Variable	Entecavir group (*n*=40)	Tenofovir group (*n*=39)	*P*
Age, years	50.60 (11.66)	47.79 (9.39)	0.244
Gender (%)			
Female	14 (35.0)	13 (33.3)	0.876
Male	26 (65.0)	26 (66.7)	
BMI	23.18 (2.41)	23.25 (2.65)	0.903
Albumin (g/dL)	3.62 (0.78)	3.85 (0.60)	0.137
Total bilirubin (mg/dL)	1.46 (1.50)	1.67 (2.99)	0.713
INR	1.15 (0.26)	1.05 (0.26)	0.146
ALP (IU/L)	104.93 (38.13)	90.00 (36.65)	0.087
Platelet ($\times 10^3$/uL)	131.10 (58.23)	151.94 (54.02)	0.103
GGT (IU/L)	85.32 (112.75)	83.35 (84.19)	0.652
Creatinine (mg/dL)	0.81 (0.21)	0.83 (0.15)	0.508
Pretreatment AST (IU/L)	214.58 (392.31)	163.38 (258.77)	0.344
Pretreatment ALT (IU/L)	200.55 (337.50)	205.28 (327.49)	0.677
HBeAg-positive patients (%)	22 (55.0)	18 (45.0)	0.432
Pretreatment HBV DNA level ($\times 10^3$ IU/mL)	6.38 (1.21)	6.24 (1.24)	0.079

Number in brackets represent SD or percentage. INR=International normalized ratio; ALP=Alkaline phosphatase; GGT=Gamma-glutamyl transferase; SD=Standard deviation; AST=Aspartate transaminase; ALT=Alanine aminotransaminase; HBeAg=Hepatitis B e antigen; HBV=Hepatitis B virus; BMI=Body mass index

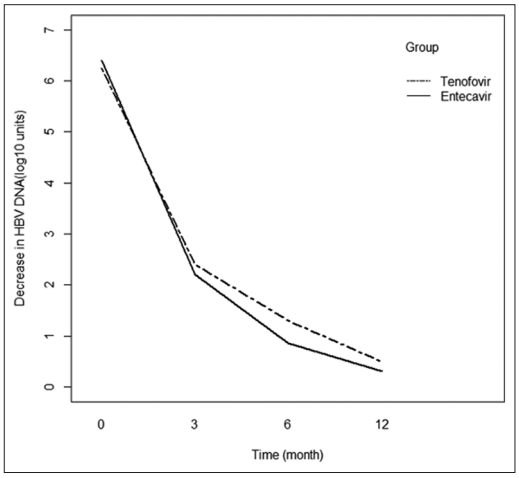

Figure 1: Decrease in serum hepatitis B virus DNA levels in tenofovir and entecavir groups during treatment (log10 units)

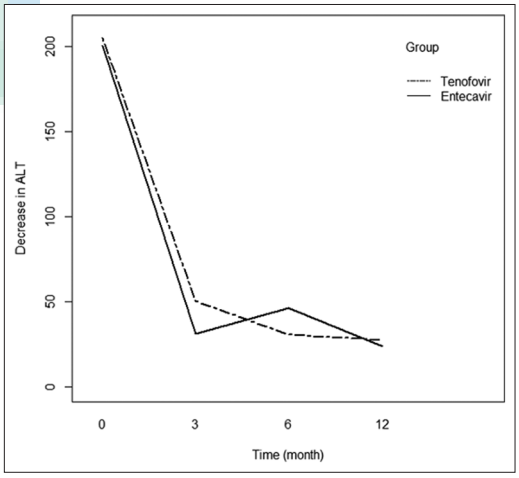

Figure 2: Decrease in serum alanine aminotransaminase levels in tenofovir and entecavir groups during treatment (IU/L)

Table 2: Results of uni- and multivariable logistic regression analyses determining the virologic response to treatment

Covariate	Univariable Cox analysis			Multivariable Cox analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, years	0.993	0.948-1.041	0.782	0.956	0.903-1.011	0.116
Pretreatment HBV DNA level	1.000	1.000-1.000	0.079	1.000	1.000-1.000	0.670
Pretreatment ALT level	0.999	0.998-1.001	0.393	1.000	0.998-1.001	0.116
Tenofovir or entecavir use	0.500	0.180-1.389	0.184	0.329	0.102-1.057	0.329
HBeAg status	4.533	1.461-4.062	0.009	5.978	1.634-21.874	0.007

CI=Confidence interval; HR=Hazard ratio; HBV=Hepatitis B virus; ALT=Alanine aminotransaminase; HBeAg=Hepatitis B e antigen

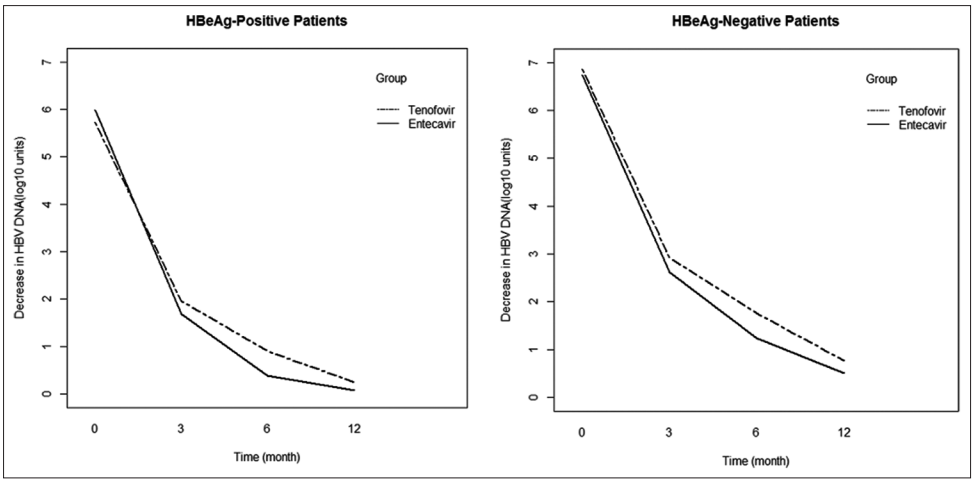

Figure 3: Decrease in serum hepatitis B virus DNA levels in tenofovir and entecavir groups during treatment (log10 units) in hepatitis B e (HBe) antigen-negative and HBe-positive patients

DNA (P = 0.260). Serum HBV DNA levels decreased by 6.07 ± 1.23 log IU/mL in the entecavir group and 5.75 ± 1.19 log IU/mL in the tenofovir group from baseline at week 48 of therapy (P = 0.251) [Figure 1].

The decline in serum ALT levels at week 12 was more prominent with entecavir than tenofovir (P = 0.07), but there was no difference at weeks 24 and 48. At week 48 of therapy, serum ALT levels were normalized in 36 of 41 (95.1%) patients in the entecavir group and in 34 of 39 (87.1%) patients in the tenofovir group (P = 0.185) [Figure 2]. Elevations in ALT levels occurred rarely during treatment.

After multivariate analysis with adjustment for baseline variables (age, serum ALT levels, serum HBV DNA levels, tenofovir or entecavir use, and HBeAg negativity) for all 79 patients in both groups, Our results indicate that positive test results at the pretreatment baseline for HBeAg showed a significant relationship to 48 week undetectable serum HBV DNA results [Table 2].

Among the HBeAg-positive patients, at week 48, 18 tenofovir treated patients (46.2%) and 23 entecavir treated patients (56.1%) achieved HBV DNA <20 IU/mL (P = 0.89). The average reduction in serum HBV DNA level at week 12 was similar in patients treated with entecavir and tenofovir. The baseline HBV DNA level was 6.86 log10 IU/mL for tenofovir and 6.73 log10 IU/mL for entecavir. At week 12, the mean HBV DNA level was 2.92 log10 IU/mL for tenofovir and 2.61 log10 IU/mL for entecavir. Primary response, defined as 1 log10 IU/mL or more decrease in HBV DNA serum level within 12 weeks of the commencement of antiviral treatment, was achieved in all patients in the entecavir and tenofovir groups [Figure 3].

Among the HBeAg-negative patients, at week 48, 21 tenofovir-treated patients (53.8%) and 18 entecavir treated patients (43.9%) achieved HBV DNA <20 IU/mL (P = 0.86). The mean reduction in serum HBV-DNA level at week 12 was similar in patients treated with entecavir and tenofovir. The baseline HBV DNA level was 5.73 log10 IU/mL for tenofovir and 5.98 log10 IU/mL for entecavir. At week 12, the mean HBV-DNA level was 1.96 log10 IU/mL for tenofovir and 1.69 log10 IU/mL for entecavir. Primary response was achieved in all patients in the entecavir and tenofovir groups [Figure 3].

Patients in both treatment groups did not display HBsAg loss. HBeAg seroconversion was evident in only three patients in the entecavir group. Three (3.7%) patients had side effects. Two patients had abdominal pain following the use of tenofovir, and one patient had dizziness following the use of entecavir. However, both drugs were well-tolerated and clinically significant side effects were not showed. A significant increase in creatinine was not observed during the observation period. Three months (M3), 6 months (M6) and 12 months (M12) after starting tenofovir, there was no significant change in mean calcium (M3: 9.1 mg/dL, M6: 8.9 mg/dL, M12: 9.0 mg/dL) and mean phosphorus levels (M3: 3.5 mg/dL, M6: 3.4 mg/dL, M12: 3.4 mg/dL).

Discussion

Our principal aim was to elucidate the safety and efficacy of tenofovir as compared with entecavir through week 48. The most important goal for the treatment of chronic HBV infection is to prevent HCC and liver cirrhosis by suppressing HBV replication. Entecavir and tenofovir are drugs that have been recently added to the treatment roster against chronic HBV infection. Both potently inhibit viral replication. Entecavir acts in three separate steps and has stronger activity than adefovir and lamivudine.[11-14] Tenofovir is less nephrotoxic than adefovir and so can be used in higher doses. Accordingly, its' activity is stronger than adefovir.[15-17]

Several studies have reported different virologic response rates using tenofovir and entecavir. The virologic response rate at week 48 of tenofovir treatment was 73%, 80.3%, and 97% in separate studies.[11,15,18] Virologic response rates associated with entecavir use are reportedly 12–37.5%, 43.9–76%, 55–93%, 95.8%, and 79–85% at week 12, 24, 48, 72, and 96 of treatment, respectively.[12,13,19]

Two studies have comparing entecavir and tenofovir in terms of antiviral response rates at week 48 of treatment. In one study, 24 patients used tenofovir and 20 patients used entecavir; response rates were not significantly different. Also, the decline in serum HBV DNA levels was not different from the HBV DNA negativity rate.[9] In the other study, the entecavir group consisted of 29 patients and the tenofovir group consisted of 65 patients. There was no difference between entecavir (69%) and tenofovir (72.3%) groups in terms of virologic response at 48 weeks of treatment.

The present findings are consistent with the two aforementioned studies. The proportions of patients who achieved undetectable HBV DNA in the entecavir and tenofovir group was 82.5% and 69.2%, respectively. While a higher proportion of patients who received entecavir achieved undetectable HBV DNA than that of those who received tenofovir, the difference was not statistically significant. But, at week 24, the virologic response (55.0% vs. 20.5%) was higher in patients treated with entecavir. The results are likely explained by the small number of patients at treatment week 24.

Presently, age, serum ALT levels, serum HBV DNA levels, and the use of tenofovir or entecavir 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 independent variables affecting virologic response to the treatment.[20] In another study, 114 cases using entecavir were analyzed; the virological response at month 3 was an independent variable of virological response at the end of treatment.[21] 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 24 months.[22]

In our study, HBeAg negativity was an independent variable. The mean HBV DNA level at week 48 was 0.50 log10 IU/mL for tenofovir and 0.76 log10 IU/mL for entecavir in HBeAg-positive patients. The mean HBV DNA at week 48 was 0.08 log10 IU/mL for tenofovir DF and 0.25 log10 IU/mL for entecavir in HBeAg-negative patients. The results support the suggestion that tenofovir and entecavir are potent therapies for the treatment of HBeAg-negative and HBeAg-positive chronic HBV infection.

Pretreatment serum HBV DNA levels did not affect treatment response. This may have been due to the fluctuation of serum HBV DNA levels in cases with chronic HBV infection and may again be explained by the small number of the patient at the treatment months. No emergence of entecavir resistance was apparent at 48 weeks. However, this time may be too short for resistance to develop.

Both drugs were well tolerated, and no clinically significant side effects were reported. No significant increase in creatinine was observed during or at the end of the observation period. Though serum calcium and phosphorus both remained largely unchanged, and no worsening effect on phosphatemia was observed 12 months after introduction of tenofovir in treatment, more attention has to be paid to the monitoring of serum calcium and phosphorus levels, since long-term treatment with tenofovir could increase risk of defective urinary phosphorus reabsorption, which can induced abnormal bone mineral density. Two patients had abdominal pain following tenofovir use, and one patient had dizziness following entecavir use. Since this study was initiated, several other research studies have addressed this comparison between entecavir and tenofovir.[23-28] The simultaneous presence of these studies illustrates the timeliness and critical nature of this presentation and the concurrent research, which is all critical to the study of the anti-viral agents. Batirel *et al*. reported that tenofovir and entecavir appear to have similar efficacy in CHB patients, despite results indicating that 7% of patients on entecavir therapy had a virological breakthrough, while none of the patients on tenofovir therapy did.[23] In the studies by Ozaras *et al*. and Dogan *et al*., tenofovir and entecavir demonstrated comparable virologic efficacies.[25,27] These results are in close agreement with our study. However, these finding do not correspond with some studies that reported that tenofovir has a better virologic response compared to entecavir.[24,26]

Research assessing the long-term effects of entecavir and tenofovir is indeed an important topic. Idilman *et al*. found entecavir and tenofovir effectively maintained virological and biochemical responses through 4 years of therapy in CHB with/without liver cirrhosis.[29] Serum creatinine levels and creatinine clearance remained stable over time in both agents in that study. Köklü *et al*. also reported that entecavir and tenofovir were well tolerated and similarly safe agents for long-term use in patients with compensated or decompensated cirrhosis from HBV infection.[30] However, although entecavir and tenofovir, are known to be effective for long-term use and have relatively few side effects according to these studies, it is still necessary to monitor long-term potential risks. Clinical practice guidelines from the European Association for the Study of the Liver suggested that NUCs therapy can be stopped 12 months after anti-HBe seroconversion.[31] However they also recommend that NUCs therapy may be continued until HBsAg clearance, especially in patients with cirrhosis, since a proportion of patients who discontinue NUCs treatment after anti-HBe seroconversion may require retreatment

due to failure to sustain their virological response. These guidelines are also applied to patients receiving entecavir and tenofovir treatment.

Major limitation of this study is its retrospective design and just 49 week follow-up period, which calls for caution in interpreting the data presented. However, since tenofovir only recently entered the Korean market, there is no preliminary data and this study provides not only 1-year observations, but also a baseline for further study.

Conclusion

The comparative efficacy and potency of tenofovir and entecavir have not been well studied. Despite the noted limitations, this study demonstrates that there was no statistically significant difference between patients treated with tenofovir or entecavir in achieving <20 IU/mL HBV-DNA, HBeAg seroconversion, decline in HBsAg titer, and ALT normalization. In conclusion, in the 1st year of treatment for CHB, tenofovir and entecavir have equal potency for HBeAg-positive and HBeAg-negative patients. A long-term follow-up study is required to report more clinical, and virological outcomes, and prospective studies are still needed to clarify these.

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