

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

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Background/aims: Chronic hepatitis B virus infection is an important cause of morbidity and mortality. Tenofovir disoproxil fumarate and entecavir were licensed for the treatment of hepatitis B virus infection. We evaluated the first 12 months of chronic hepatitis B treatments with tenofovir and entecavir and compared their efficiencies. **Methods:** The study enrolled 94 chronic hepatitis B patients with compensated liver disease. The entecavir group consisted of 29 patients who received entecavir 0.5 mg/day and the tenofovir group consisted of 65 patients who received tenofovir 245 mg/day. There was no statistically significant demographic or HBeAg status difference between the groups. Patients returned to the clinic every four weeks for laboratory assessments of serum chemical and hematologic values, liver function and for documentation of any adverse events. Hepatitis B serologic markers and HBV-DNA levels were assessed every 12 weeks. The primary efficacy endpoint was a plasma HBV-DNA level of less than 400 copies/ml over 48 weeks. **Results:** At the end of 48 weeks, treatment with either tenofovir or entecavir resulted in clinically important suppression of HBV-DNA, as 71.3%. There was no statistical difference in inducing undetectable levels of HBV-DNA between the entecavir (69%) and tenofovir (72.3%) groups. Furthermore, no side effect as an increase in creatinine was seen. HBeAg seroconversion was seen in only one patient in the entecavir group, but in no patients of the tenofovir group. **Conclusions:** In the first year of treatment for chronic hepatitis B, virologic response and tolerability did not differ significantly between tenofovir and entecavir. Both drugs are safe and efficacious for patients infected with HBV.

Key words: Chronic hepatitis B, entecavir, tenofovir

Kronik hepatit B'li naiv hastaların tedavisinde tenofovir ve entekavirin etkinliğinin karşılaştırılması

Amaç: Kronik hepatit B virus enfeksiyonu morbidite ve mortalitenin önemli bir nedenidir. Tenofovir disoproksil fumarat ve entekavir, hepatit B virus enfeksiyonu tedavisinde ruhsatlı ilaçlardır. Biz, kronik hepatit B'nin tenofovir ve entekavir ile 12 aylık tedavi sonuçlarını değerlendirdik ve bu ilaçların etkinliklerini karşılaştırdık. **Yöntem ve Gereç:** Çalışma kompanse karaciğer hastalığı olan 94 kronik hepatit B hastasını içerdi. Entekavir grubu 0.5 mg/gün entekavir alan 29 hastayı, tenofovir grubu 245 mg/gün tenofovir alan 65 hastayı içerdi. Gruplar arasında demografik verilerde ve HBeAg durumunda istatistiksel bir farklılık yoktu. Hastalar karaciğer fonksiyonları, yan etkiler, kan sayımları ve biyokimyasal tetkikler için her 4 haftada bir kontrol edildiler. Hepatit B göstergeleri ve HBV-DNA seviyeleri 12 haftada bir değerlendirildi. Birincil etkinlik sonlanma noktası 48 hafta sonunda plazma HBV-DNA seviyesinin 400 kopya/ml altında bulunmasıydı. **Bulgular:** 48 haftalık tedavi sonunda tenofovir veya entekavirle tedavi, HBV-DNA'nın %71.3 olarak belirlenen klinik olarak önemli bir supresyonu ile sonuçlandı. Entekavir ve tenofovir gruplarında HBV-DNA'nın tesbit edilemeyecek seviyelere düşmesinde (%69 ve %72.3) istatistiksel bir fark yoktu. Kreatin düzeyinde artış gibi herhangi bir yan etki de gözlenmedi. HBeAg serokonversiyonu entekavir grubunda sadece bir hastada gözlemlendi, tenofovir grubunda ise hiçbir hastada görülmedi. **Sonuç:** Kronik Hepatit B tedavisinin ilk yılında, virolojik cevap ve tolerabilite, tenofovir ve entekavir grubunda anlamlı bir fark göstermedi. Her iki ilaç da Hepatit B virusu ile enfekte hastalarda etkili ve güvenliydi.

Anahtar kelimeler: Kronik hepatit B, entekavir, tenofovir

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INTRODUCTION

Hepatitis B virus (HBV) infection is a significant global health problem, affecting more than 400 million people worldwide. Although the majority never develop significant liver disease, around 25% of those with HBV infection ultimately develop cirrhosis or hepatocellular carcinoma (1). The goal of therapy in patients with chronic hepatitis B (CHB) is the prevention of cirrhosis, hepatocellular carcinoma and HBV-related mortality (2).

Current treatment options for CHB consist of nucleos(t)ide analogues and (pegylated) interferons. Antiviral treatment with nucleos(t)ide analogues aims at inhibiting viral polymerase activity (3). Nucleoside analogues include lamivudine, telbivudine and entecavir, while nucleotide analogues include adefovir and tenofovir. While interferon has been limited by its poor tolerability and significant side effect profile, the efficacy of oral agents has been hampered by the necessity of prolonged use and emergence of resistance (4). As with most of the oral agents, prolonged duration of therapy is associated with an increasing rate of antiviral drug resistance.

Lamivudine leads to resistance at a rate of approximately 20% of patients per year and can reach 65-70% after 4-5 years of therapy (5). Telbivudine is another nucleoside analogue. It has potent antiviral activity, and after one year of therapy, 60% of HBeAg-positive and 88% of HBeAg-negative patients achieved undetectable levels of serum HBV-DNA (6). However, telbivudine is also associated with a high rate of viral resistance. In HBeAg-positive patients, resistance rates have been reported as 5% and 25%, while in HBeAg-negative patients, these are 2.3% and 11% at 1 and 2 years, respectively (7). Among nucleoside analogues, entecavir has a greater potency and a lower resistance (8). Entecavir is a member of the cyclopentane group and is rapidly phosphorylated to the active intracellular 5'-triphosphate form that is a very potent inhibitor of viral polymerase activity by inhibiting both minus- and plus-strand DNA synthesis (9). The rate of entecavir resistance is minimal (1.2%) in treatment-naive patients after five years of therapy (10). However, in lamivudine-refractory patients, the cumulative probability of entecavir resistance at years 1 through 5 is 6%, 15%, 36%, 46%, and 51%, respectively (10).

The nucleotide adefovir dipivoxil is active against lamivudine-resistant virus-carrying codon 204

mutations, and was used not only as a first-line therapy but also as a rescue therapy for patients with lamivudine resistance (11). However, the development of rtN236T or rtA181V/T mutations offers resistance to adefovir, and this resistance has been demonstrated at 1, 2, 4, and 5 years of therapy at a rate of 0%, 3%, 18%, and 29%, respectively (12). Tenofovir disoproxil fumarate is a nucleotide analogue that is a reverse transcriptase inhibitor recently approved by the United States Food and Drug Administration for the treatment of CHB infection in adults (13). It is structurally very similar to adefovir, but it exhibits more potent inhibitor activity against both wild type and lamivudine-resistant strains. Clinical trials had shown that tenofovir effectively controls HBV replication in patients with both HBeAg- positive and -negative diseases, with approximately 75% and 93%, respectively (1). The rtA194T mutation has been implicated as conferring tenofovir resistance, but to date, no tenofovir resistance phenotype has been reported in patients treated for up to two years (1).

Although there are studies comparing the efficacy of entecavir and adefovir or tenofovir and adefovir, there are limited data about the comparison of these two potent agents: tenofovir and entecavir. The aim of the current study was to investigate the safety and efficacy of entecavir, as compared with tenofovir, in HBeAg-positive and -negative CHB patients who had not previously received a nucleoside analogue or interferon regimen, after 48 weeks of treatment.

MATERIALS AND METHODS

Patients

Ninety-four CHB patients (58 males, 36 females) followed between 2008 and 2010 in the Liver Clinics of Adana Numune Research and Training Hospital, Çukurova University School of Medicine, and Bakırköy Sadi Konuk Training and Research Hospital and treated with entecavir or tenofovir were investigated retrospectively. Patients were between 18 and 73 years of age and eligible for inclusion if they fulfilled the following criteria: (1) Seropositive for HBsAg, elevation of serum alanine aminotransaminase (ALT) for at least six months (normal range: 13-31 u/L for females and 13-53 u/L for males) and detectable serum HBV-DNA; (2) No evidence of hepatocellular carcinoma based on the clinical criteria and ultrasound examination; (3) No evidence of hepatitis C virus, hu-

man immunodeficiency virus or hepatitis D virus infection; and (4) Creatinine clearance of more than 70 ml per minute. Liver biopsy was performed within six months of entry. The liver histology was studied according to criteria of Ishak (14), which comprise two major components: necroinflammation and fibrosis. Patients were excluded from the study if they had previous nucleos(t)ide analogue or interferon-alfa therapy within 24 weeks before the randomization.

Analysis

Of the 94 patients included in the study, 39 were classified as HBeAg-positive and 55 as HBeAg-negative CHB, respectively. Among these patients, no case was histologically diagnosed as cirrhosis. Ten HBeAg-positive and 19 HBeAg-negative cases received entecavir treatment and 29 HBeAg-positive and 36 HBeAg-negative cases received tenofovir treatment. All patients were followed every four weeks for until week 48. Plasma samples were routinely assessed for hematological variables (e.g. leukocyte and platelet counts and levels of creatinine, ALT, aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), albumin, and bilirubin) every four weeks for documentation of any adverse events. Hepatitis B serological markers (HBeAg, anti-HBe and HBsAg) and HBV-DNAs were assessed every 12 weeks. The primary efficacy endpoint at week 48 was an HBV-DNA level of <400 copies/ml. Secondary efficacy endpoints at week 48 were HBeAg seroconversion (HBeAg loss and the appearance of HBe antibody) and normalization of serum ALT.

Assays

Hepatitis B surface antigen (HBsAg), HBeAg and hepatitis B e antibody (anti-HBe) (Abbott Laboratories, North Chicago, IL, USA) were assayed with the 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 commencement of therapy. Serum HBV-DNA was measured with the TaqMan polymerase chain reaction assay (TaqMan HBV Assay, Roche Diagnostics; lower limit of quantification = 35 copies/ml).

Statistical Analysis

All statistical analyses were performed using the Statistical Program for Social Sciences (SPSS 18.0.0 for Windows; SPSS Inc., Chicago, IL, USA).

The Mann-Whitney U test was used for continuous variables with skewed distribution and chi-squared with Yates correction for continuity or Fisher's exact test for categorical variables. The primary endpoint was HBV-DNA level <400 copies/ml. A secondary analysis was performed to identify factors that were associated with the endpoint at the end of follow-up. Factors that were significant in the univariate analysis were subsequently incorporated into a logistic regression analysis to identify the most important factors associated with endpoint at the end of the follow-up. Statistical significance was defined as $p < 0.05$.

RESULTS

Serum HBV-DNA and ALT levels of the patients at baseline and at weeks 12, 24, 36, and 48 of the entecavir and tenofovir treatments are shown in Table 1.

Among the HBeAg-negative patients, at week 48, 27 tenofovir-treated patients (75%) and 13 entecavir-treated patients (68%) achieved HBV-DNA <400 copies/ml ($p = 0.89$). 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 7.5 log₁₀ copies/ml for tenofovir and 7.4 log₁₀ copies/ml for entecavir. At week 12, the mean HBV-DNA level was 5.2 log₁₀ copies/ml for tenofovir and 4.9 log₁₀ copies/ml for entecavir. Primary response, defined as 1-log₁₀ copies/ml or more decrease in serum HBV-DNA level within 12 weeks of the commencement of antiviral therapy, was achieved in all patients in the entecavir and tenofovir groups.

Among the HBeAg-positive patients, at week 48, 20 tenofovir-treated patients (69%) and 7 entecavir-treated patients (70%) achieved HBV-DNA <400 copies/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 7.6 log₁₀ copies/ml for tenofovir and 8.2 log₁₀ copies/ml for entecavir. At week 12, the mean HBV-DNA level was 7.2 log₁₀ copies/ml for tenofovir and 6.8 log₁₀ copies/ml for entecavir. Primary response was achieved in 9 patients (90%) in the entecavir group and 28 patients (97%) in the tenofovir group ($p = 0.84$).

Among all patients treated, 72.3% of patients who received tenofovir versus 69% of patients who received entecavir had HBV-DNA suppression to <400 copies/ml ($p = 0.75$). In total, no patients expe-

Table 1. The comparison of the results of the groups

	Entecavir			Tenofovir		
	HBeAg+	HBeAg-	Total	HBeAg+	HBeAg-	Total
Number (%) of patients	10 (34)	19 (66)	29 (100)	29 (45)	36 (55)	65 (100)
Histology						
-Mean HAI±SD	8.9±4.1	10.6±3.6	9.7±3.9	9.7±4.4	8.6±3.6	9.2±4.0
-Mean fibrosis±SD	2.9±1.8	2.9±1.1	2.9±1.5	2.5±1.8	2.3±1.5	2.4±1.7
Mean HBV-DNA±SD (log IU/ml)						
-Baseline	8.2±8.5	7.4±7.7	7.9±8.3	7.6±7.7	7.5±7.7	7.6±7.7
-12 th week	6.8±7.3	4.9±5.4	6.3±7.1	7.2±7.9	5.2±5.9	6.8±7.7
-24 th week	6.5±7.0	4.7±5.3	6.0±6.8	4.6±5.3	4.2±4.8	4.4±5.1
-36 th week	4.2±4.4	3.6±4.2	3.9±4.3	4.5±5.2	3.9±4.6	4.3±5.0
-48 th week	4.9±5.4	3.2±3.8	4.5±5.2	3.3±3.8	3.3±3.8	3.3±3.8
Mean ALT±SD (IU/L)						
-Baseline	117±91	67±47	84±69	69±45	151±235	114±181
-12 th week	36±20	28±21	31±21	72±117	48±28	59±81
-24 th week	32±23	21±7	25±15	57±97	43±32	49±69
-36 th week	34±23	22±7	26±15	45±45	37±21	40±34
-48 th week	26±11	23±8	24±9	37±24	32±16	34±20
Number (%) of patients with virologic response (HBV-DNA <400 copies/ml)	7 (70)	13 (68)	20 (69)	20 (69)	27 (75)	47 (72.3)

HAI: Histology activity index. SD: Standart deviation.

rienced virological breakthrough during the 48 weeks of treatment.

Elevations in ALT levels occurred rarely during treatment and were observed with similar frequencies in the two treatment groups. No biochemical breakthrough was noted in the two groups. The proportions of patients showing normalized serum ALT levels at weeks 12, 24, 36, and 48 did not differ significantly between the two groups. No patients in the tenofovir group or the entecavir group had HBsAg loss. HBeAg seroconversion was seen in only one patient in the entecavir group, but in no patient in the tenofovir group.

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.

After multivariate analysis with adjustment for baseline variables (sex, age, HBeAg status, serum HBV-DNA, ALT, AST, total bilirubin and albumin levels, prothrombin time) for all 94 patients in both groups, none was inversely associated with serum HBV-DNA negativity at week 48.

Both drugs were effective in inducing undetectable levels of HBV-DNA and normalization of ALT levels, and there was no statistically significant difference between them. There were also no significant differences between the side effects including serum creatinine values.

DISCUSSION

Large long-term studies have shown that the risk of developing cirrhosis and hepatocellular carcinoma is directly proportional to the serum HBV-DNA level (15,16). With the currently approved treatment options, the main goal of treatment is complete suppression of viral replication, because persistent HBV viremia is associated with development of liver cirrhosis and hepatocellular carcinoma. Furthermore, a rapid virological response after initiation of nucleos(t)ide analogue treatment is associated with lower rates of antiviral drug resistance in the long term (17). By implication, treatments that reduce HBV-DNA may prevent progression of liver disease in patients with CHB. These results are supported by Liaw *et al.* (18), who showed that for patients with HBeAg-negative or HBeAg-positive CHB who had cirrhosis or advanced fibrosis, treatment with lamivudine slowed the progression of liver disease, presumably by suppressing viral replication and decreasing the resultant necroinflammatory response. Among patients with HBeAg-negative and -positive CHB who had not previously been treated with a nucleoside analogue, the rates of histological improvement, virological response and normalization of ALT levels were significantly higher at 48 weeks with entecavir than with lamivudine (19-21). In different studies, entecavir produced more rapid and significantly greater suppression of HBV-DNA than adefovir in nucleoside-naïve patients,

but in the studies comparing with lamivudine-resistant or adefovir-resistant groups, it had limited efficacy (17,22-24).

In patients with compensated chronic HBV infection, tenofovir was superior to adefovir dipivoxil with respect to the primary endpoint of antiviral efficacy, and tenofovir is a highly effective rescue drug for HBV-infected patients with altered response to treatment with lamivudine and adefovir (25-28).

Woo et al. (8) and Dakin et al. (29) recently conducted two different meta-analyses evaluating the relative efficacy of nucleosides and nucleotides for treatment of nucleoside- and nucleotide-naïve patients. In Dakin's study, 13 trials were included in the analyses. The trials' study population included HBeAg-positive, treatment-naïve patients. They demonstrated that 94% of patients achieved HBV-DNA <300 copies/ml after one year with tenofovir, compared with 73% for entecavir, 50% for adefovir and 38% for lamivudine. There were no statistically significant differences between nucleos(t)ides in HBeAg seroconversion at one year (29). Woo and her colleagues, in their Bayesian meta-analysis, reviewed 20 trials - 15 in HBeAg-positive patients and 8 in HBeAg-negative patients (3 of these studies evaluated both HBeAg-positive and -negative patients). They concluded that, in the first year of treatment for CHB, tenofovir and entecavir are the most potent oral antiviral agents for HBeAg-positive patients and teno-

fovir is most effective for HBeAg-negative patients. In HBeAg-positive patients, tenofovir was most effective in inducing undetectable levels of HBV-DNA (probability 88%), normalization of ALT level (66%), HBeAg seroconversion (20%), and HBsAg loss (5%), and third in histological improvement of the liver (53%). Entecavir was most effective in improving liver histology (56%), second for inducing undetectable levels of HBV-DNA (61%) and normalization of ALT levels (70%), and third in loss of HBsAg (1%). In HBeAg-negative patients, tenofovir was the most effective in inducing undetectable levels of HBV-DNA (94%) and improving liver histology (65%) (8).

In our study, we had limitations because of its retrospective design. We had the pre-treatment but not post-treatment biopsies. Further, the number of the patients is limited. However, except for these limitations, this is an important study because there are limited studies comparing the efficacy and potency of tenofovir and entecavir. Our comparative analysis demonstrates that there was no statistically significant difference between the groups in achieving <400 copies/ml HBV-DNA, HBeAg seroconversion, decline in HBsAg titer, and ALT normalization.

In conclusion, in the first year of treatment for CHB, tenofovir and entecavir have equal potency for HBeAg-positive and -negative patients. Nevertheless, further randomized, prospective studies including more patients are warranted.

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