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Original Article

Clinical efficacy of tenofovir and entecavir in the treatment of chronic hepatitis B infection in patients naïve to nucleosides and their analogues therapy

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Abstract: Objective: To compare the clinical efficacy and safety of tenofovir and entecavir in chronic hepatitis B patients naïve to nucleosides and their analogues. Methods: A total of 196 patients with chronic hepatitis B, who were naïve to nucleosides and their analogues, were enrolled in this single-blinded controlled study from January 2014 to January 2015. The patients were randomly assigned to tenofovir group (98 cases) or entecavir group (98 cases) for 48-week antiviral therapy. The levels of hepatitis B virus (HBV) and alanine aminotransferase (ALT) before and after the treatment, the median time of HBV DNA negative conversion and ALT normalization, the rate of HBeAg seroconversion and virological breakthrough, and the incidences of adverse reactions during treatment were recorded and compared between the two groups. Results: There were no significant differences in baseline between the two groups. While after the treatment, though the levels of HBV DNA and ALT in both groups were significantly decreased compared to those at pre-treatment, there was no significant intra-group difference. The median time of HBV DNA negative conversion was 16 and 13 weeks in tenofovir and entecavir groups respectively (P=0.220) and the time of ALT normalization were 24 weeks for both groups (P=0.806). Meanwhile, after the treatment, the HBeAg serum conversion rate was 8.3% in tenofovir group and 7.1% in entecavir group without difference between the groups (P=0.811), and the virological breakthrough rates in both groups were 0. During the treatment, no serious adverse reaction or death was observed. Conclusion: Tenofovir and entecavir both can effectively inhibit the replication of HBV and alleviate liver injury with low incidences of adverse reactions.

Keywords: Chronic hepatitis B, nucleoside analogues, tenofovir, entecavir, clinical efficacy

Introduction

Chronic hepatitis B (CHB), an infectious disease caused by hepatitis B virus (HBV), is characterized by fatigue, nausea, abdominal distension and liver pain [1]. Besides, it causes liver fibrosis, liver cirrhosis and even progresses to liver cancer when the lobular structure is damaged [2]. Globally, it was enumerated that about 701,800 people died from CHB or its complications including cirrhosis and liver cancer in 2015 [3]. CHB is also a health burden in China as the prevalence of hepatitis B surface antigen was as high as 7.2% [4].

Early antiviral therapy, which can inhibit the transcription of HBV *in vivo*, is vital to delay the progression of CHB [5, 6]. Therefore, nucleoside analogs such as lamivudine, adefovir, entecavir, etc., are widely used clinically for the treatment of CHB, especially, tenofovir and entecavir have been demonstrated as the most potent oral antiviral agents for hepatitis B E antigen (HBeAg) positive patients in the first years of CHB treatment [7] and recommended as preferred initial antiviral drugs in several treatment guidelines for CHB from USA and Europe [5, 6]. Many previous studies have compared the efficacy and safety of tenofovir and entecavir among CHB patients, however, the results were inconsistent. Which one is more effective based on specific endpoints like complete viral suppression, HBeAg clearance and seroconversion, is still controversial [8-11]. Besides, most of these studies were not randomized controlled trials, which limited the credibility of the evidences. In this study, we performed a randomized controlled trial to compare the efficacy and safety of tenofovir and entecavir, aiming to provide more powerful evidences for clinical CHB treatment.

Table 1. Demographical and clinical data of the patients in two groups

Characteristics	Tenofovir group (n=98)	Entecavir group (n=98)	*P* value
Gender (male/female)	60/38	58/40	0.772
Age (range)	28~46	29~51	
Age (mean ± SD)	35.9±10.6	36.1±9.8	0.446
BMI (kg/m^2)	23.09±2.91	22.81±2.88	0.499
Family history of HBV infection (n/%)	45/45.9%	42/42.9%	0.666
Smoking history (n/%)	49/50.0%	37/37.8%	0.084
Drinking history (n/%)	34/36.7%	40/40.8%	0.377
HBeAg (+) (n/%)	60/61.2%	56/59.2%	0.561

Table 2. The levels of HBV DNA before and after treatment in two groups (mean ± sd)

HBV DNA (U/ml)	Tenofovir group (n=98)	Entecavir group (n=98)	*P* value
Before treatment	6.56±0.66	6.73±0.81	0.109
After treatment	4.16±0.71	4.20±1.10	
Difference	2.40±0.35	2.53±0.41	0.162
P value	0.013	0.015	

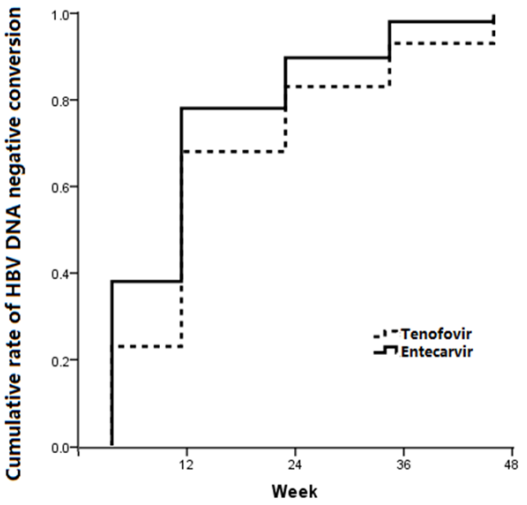

Figure 1. The cumulative rates of HBV DNA negative conversion in two groups. No significant difference of HBV DNA negative conversion was observed between the two groups (Log rank =1.504, P=0.220).

Materials and methods

Study design and patients

This study is a prospective, randomized, single-blinded, controlled study that was reviewed and approved by the Institutional Review Board of hospital. A total of 196 patients diagnosed with CHB in our hospital from January 2014 to January 2015 were enrolled in this study and equally randomized to two treatment arms by a computer generated random sequence. Tenofovir and entecavir were provided in identical formats in terms of shape, size, texture and packing.

The inclusion criteria: the patients whose diagnosis met the criteria and the indications of 2010 guidelines for the prevention and treatment of chronic hepatitis B in China [8]; patients who had no history of nucleoside or nucleotide analogs application; patients who had no use of antiviral drugs in the past half year. The exclusion criteria: patients who were infected with other hepatotropic virus, or suffered drug-induced liver diseases, alcoholic liver disease or autoimmune liver disease, tumor, serious complications in heart, kidney, brain and other organs; patients who were in pregnancy or lactation. There was no limitation on age, gender, ethnicity, course of HBV infection, liver function or serum HBeAg serological test.

Treatment and follow-up

All the patients were firstly given supportive and hepato-protective treatment, including balancing the water, electrolyte and albumin, with particular attention paid to the occurrence of CHB related complications. Then, they were given 48-week antiviral therapy. To be specific, patients in tenofovir group were administrated tenofovir tablets (Wei Ruide, Gilead Science) with a dose of 300 mg/d, while patients in entecavir group were treated with entecavir (Baraclude Bristol production) with a dose of 0.5 mg/d. During the treatment, patients were demanded a review at 4th, 12th, 24th, 36th and 48th week since the beginning of the treatment. Their HBV DNA levels, HBeAg serological status and serum ALT concentrations were measured at each visit, and information about adverse reactions was also collected.

Outcome measurements

The main outcome measurements were the reductions of HBV DNA levels and ALT concen-

Table 3. The levels of ALT in two groups

ALT(U/L)	Tenofovir group (n=98)	Entecavir group (n=98)	*P* value
Before treatment	135.3±33.4	130.5±31.9	0.305
After treatment	52.7±9.8	46.7±11.2	
Difference	86.2±12.7	83.8±13.1	0.194
P value	<0.001	<0.001	

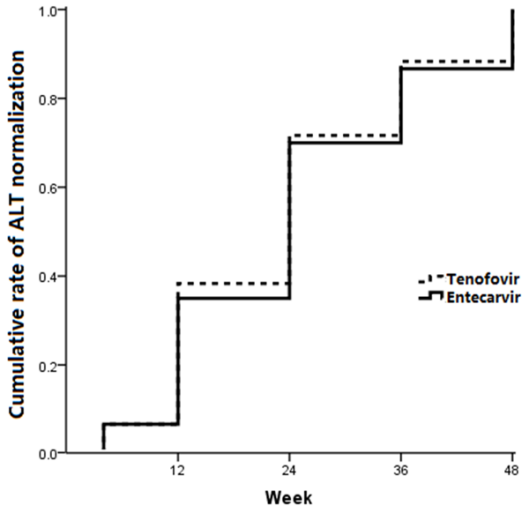

Figure 2. The cumulative rates of ALT normalization in two groups. Tenofovir and Entecavir group had the same median time of ALT normalization.

trations at the end of 48-week treatment from baseline. The secondary outcome measurements included the median time of HBV DNA negative conversion and ALT normalization, the rates of HBeAg seroconversion and virological breakthrough. In addition, the incidences of adverse reactions during treatment of each group were recorded and compared.

Statistical analysis

Statistical software package SPSS (version 21.0, IBM Company, Chicago, IL) was applied for data analysis.

Continuous variables were expressed as mean ± standard deviations. The levels of HBV DNA and ALT before and after treatment between two groups were analyzed with independent t test, and their pre- and post-treatment differences in each group were compared with paired t test. Categorical variables were expressed as numbers and percentages and analyzed by chi-square test or fisher exact test. Kaplan-Meier method was used to analyze cumulative rate of HBV DNA negative conversion and ALT normalization, while the median time of HBV DNA negative conversion and ALT normalization in each group were compared using the Log-rank tests. Intention-to-treat (ITT) analysis was used, and for those dropped out during the follow-up, the last available measurement prior to withdrawal from the study is retained in the analysis. P<0.05 (two-tailed test) was considered to be statistically significant.

Results

Patients' demographics

The demographic and clinical parameters of the two groups are listed in **Table 1**, and no statistically significant difference between the two groups was found (all P>0.05). At the end of treatment, there were 8 (3 dropped out at 36th week, 5 dropped out at 48th week) and 10 (3 dropped out at 36th week, 7 dropped out at 48th week) patients dropped out in tenofovir and entecavir group with completion rates of 91.8% and 87.8% respectively (P=0.621).

The levels of HBV DNA in two groups

As shown in **Table 2**, the baselines of HBV DNA in tenofovir and entecavir groups were (6.56± 0.66) U/ml and (6.73±0.81) U/ml, respectively, and the comparison showed no significant differences (P>0.05). After one year of treatment, their HBV DNA levels respectively dropped to (4.16±0.71) U/ml, (4.20±1.10) U/ml which were considerably lower than those before treatment in each group (all P<0.05), but there was no significant difference between the two groups (P=0.162).

The median time of HBV DNA negative conversion in two groups

As shown in **Figure 1**, Kaplan-Meier survival analysis showed that cumulative rate of HBV DNA negative conversion was increased with the extension of antiviral time in both groups. The median time of HBV DNA negative conversion was 16, 13 weeks in tenofovir group and entecavir group without significant difference between the two groups (Log rank =1.504, P=0.220).

The levels of ALT in two groups

As shown in **Table 3**, the baselines of ALT in tenofovir group and entecavir group were

Table 4. HBeAg seroconversion rate and virological breakthrough rate in the two groups (n/%)

Characteristics	Tenofovir group (n=60)	Entecavir group (n=56)
HBeAg seroconversion	5/8.3	4/7.1
Virological breakthrough	0	0

(135.3±33.4) U/L and (130.5±31.9) U/L respectively, and difference between the two groups had no significance (P>0.05). After one year of treatment, the levels of ALT in tenofovir and entecavir groups decreased to (52.7±9.8) U/L and (46.7±11.2) U/L, which were notably lower than those before treatment (P<0.001), but there was no significant difference between the two groups (P=0.194).

The median time of ALT normalization in two groups

As shown in **Figure 2**, Kaplan-Meier survival analysis showed that cumulative rate of ALT normalization was increased with an extension of antiviral time in both groups. The median time of ALT normalization was 24 weeks in both groups without significant difference between the two groups (Log rank =0.06, P=0.806).

HBeAg seroconversion rate and virological breakthrough rate in the two groups

There were 60 and 56 HBeAg (+) patients in tenofovir and entecavir group respectively at baseline (**Table 1**). Among these HBeAg (+) patients, 3 in tenofovir group and 4 in Entecavir group dropped out at 48th week. As shown in **Table 4**, after one year of the treatment, the HBeAg seroconversion rate was 8.3% (5/60) and 7.1% (4/56) in tenofovir and entecavir groups respectively, without significant difference between the two groups (P=0.811). No virological breakthrough was observed in both groups.

Adverse reactions

During the treatment, 4 (4.1%) and 6 (6.1%) cases were observed that creatine kinase (CK) level increased by more than twice the upper limit of normal levels in tenofovir and entecavir group respectively (P=0.516), and the maximal values of CK were 366 U/L and 466 U/L respectively. However, all these increases were transient, which returned to normal level at week 36. All the patients had no adverse events related to CK, such as myolysis and lactic acidosis. Besides, no severe adverse reactions including abnormal renal function, heart failure and death were observed during the treatment.

Discussion

The globe epidemic of hepatitis B virus infections has imposed a huge burden on the development of economy and public health. Every year, millions of people died of liver cirrhosis and hepatocellular carcinoma caused by CHB. It is widely believed that the elimination of hepatitis B virus replication can effectively reduce the liver inflammation and necrosis, thus improve the life quality and survival of patients [12, 13]. Currently, nucleotide analogs, which are widely used as the main antiviral drugs in the treatment of hepatitis B infection clinically, have been confirmed that they can effectively inhibit HBV replication and alleviate hepatic fibrosis or cirrhosis [14, 15]. Among them, tenofovir and entecavir are the best options for the first-line antiviral treatment in China [16].

Previous study has indicated that as a reverse transcriptase inhibitor, tenofovir can effectively suppress HBV replication in both HBeAg-positive and -negative patients [17]. Entecavir, a deoxyguanosine nucleoside analogue, can also inhibit HBV replication, so that it can be used as a replacement therapy in patients with lamivudine resistance, and its drug resistance usually occurs in 10 years [18, 19]. Some studies and systematic reviews have compared their efficacy and safety in CHB patients, however, the results were inconsistent [9, 20-23]. A meta-analysis suggested that tenofovir is a better choice for chronic HBV patients than entecavir as it has more potent suppression on HBV viral load and has a similar safety profile with entecavir [24], while another systematic review considered that these two drugs were similarly effective and safe for chronic HBV patients. A recent cohort study found that during the follow-up of 12 months, the HBV DNA levels were similarly suppressed in both entecavir and tenofovir groups, but HBV DNA decreasing level was more obvious in tenofovir group than that in entecavir group in hepatitis HBeAg positive patients [25]. Besides, there was a systematic review that showed a significant difference in undetectable HBV-DNA in a 3-month follow-up

period in entecavir group compared to tenofovir group, however, no significant difference was found in the long-term period [21]. In this study, at the end of 48 weeks of treatment, the pre- and post-treatment differences of HBV DNA were apparently in each group, but there was no significant difference between the two groups (P>0.05). We further analyzed cumulative rate of HBV DNA negative conversion in both groups, which not only is not affected by the level of HBV DNA, but also has high accuracy in reflecting the ability of HBV replication, and the result turned out that the cumulative rate of HBV DNA negative conversion was increased with the extension of antiviral time in both groups, and there was no significant difference between the two groups, suggesting that both of these two nucleoside analogues could inhibit the replication of HBV DNA effectively.

ALT, an important indicator of liver function evaluation, can be released to serum upon the damage in the liver cells caused by virus, therefore, the serum level of ALT is proportional to the degree of liver damage. In this study, after 48 weeks treatment, although ALT levels were evidently decreased compared to that of pretreatment in each group, there was no significant difference between the two groups. In addition, further analysis showed that cumulative rate of ALT normalization was increased with the extension of antiviral time in each group, which was in accordance with some other studies [9, 26], indicating both of these two drugs can drastically improve liver function.

In addition, our study also showed that after the treatment, no significant difference in HBeAg seroconversion and virological breakthrough rate was observed between the two groups (P>0.05), while another study reported that the virological breakthrough appeared more frequent in entecavir group, though rate of HBeAg seroconversion was similar in both groups [26]. The reason for the inconsistency was suspected to be connected with the shorter duration of treatment in our study than that of the studies mentioned above. Therefore, more long-term trials are needed to confirm the true differences in terms of these endpoints. Furthermore, no abnormal renal function, heart failure or death was recorded in both groups during the treatment, meanwhile, the elevated level of CK in most patients were mild to moderate, and all of them recovered to normal after rest, indicating the well tolerated and safe of these two drugs which were all consistent with the previous studies [24, 27].

The main merit of this study is the prospective, randomized, controlled, blinded study design and relatively large sample size, which provided further evidences for the comparison of efficacy and safety between tenofovir and entecavir. However, subjective bias might occur as the design was single blinded. Additionally, the follow-up was relatively short in our study, thus long-term efficacy and safety of these two drugs should be evaluated in the future.

To conclude, both tenofovir and entecavir is effective and safe in the treatment of CHB in patients naïve to nucleoside analogues, and both can inhibit the replication of HBV DNA and alleviate liver injury with less adverse reactions.

Disclosure of conflict of interest

None.

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