A 24-Week, Parallel-Group, Open-Label, Randomized Clinical Trial Comparing the Early Antiviral Efficacy of Telbivudine and Entecavir in the Treatment of Hepatitis B e Antigen–Positive Chronic Hepatitis B Virus Infection in Adult Chinese Patients

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ABSTRACT

Background: Because drug-resistant strains of hepatitis B virus (HBV) have developed, and because serum HBV-DNA levels may rebound in patients who receive treatment with nucleoside/nucleotide analogues for up to 2 years, there remains a largely unmet clinical need for agents to induce potent virologic suppression in the initial stage of the disease course of HBV infection.

Objective: The aim of this work was to compare the early antiviral effectiveness of telbivudine and entecavir in the treatment of patients with hepatitis B e antigen (HBeAg)-positive HBV.

Methods: In this parallel-group, open-label trial, adult Chinese patients with previously untreated HBeAg-positive HBV (HBV-DNA concentration: ≥6 $\log_{10}$ copies/mL; alanine aminotransferase [ALT] level: ≥2 times the upper limit of normal) were randomized to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks. Blood samples were collected at the baseline and at 12 and 24 weeks after the treatment. The primary end point was the mean reduction from baseline in serum HBV-DNA concentration at week 24. Secondary end points included mean reduction from baseline in serum HBV-DNA concentration at week 12, the absence of serum HBV-DNA, absence of serum HBeAg, HBeAg seroconversion at week 24, the normalization of serum ALT at week 24, and occurrence of adverse events through week 24.

Results: A total of 131 patients were enrolled in the study: 91 men and 40 women, with a mean (SD) age of 32.5 (8.9) years. All patients were ethnic Han Chinese. The baseline demographic characteristics and serum HBV-DNA concentrations in the 2 treatment groups were well matched. Sixty-five patients were randomized to receive telbivudine and 66 to receive entecavir. The mean reductions from baseline in serum HBV-DNA were 4.99 and 4.69 $\log_{10}$ copies/mL at week 12, respectively, and 6.00 and 5.80 $\log_{10}$ copies/mL at week 24 (both time points, P = NS between groups). At week 12, HBV-DNA was undetectable in 43.1% (28/65) of the telbivudine group and 34.8% (23/66) of the entecavir group (P = NS); at week 24, it was undetectable in 67.7% (44/65) of the telbivudine group and 57.6% (38/66) of the entecavir group (P = NS). At week 12, HBeAg absence and seroconversion rates were significantly greater in the telbivudine group than the entecavir group (absence: 20.0% [13/65] vs 3.0% [2/66], respectively [P = 0.002]; seroconversion: 13.8% [9/65] vs 3.0% [2/66] [P = 0.030]). However, at week 24, HBeAg absence and seroconversion rates were comparable between the telbivudine and entecavir groups (absence: 36.9% [24/65] vs 28.8% [19/66] [P = NS]; seroconversion: 24.6% [16/65] vs 13.6% [9/66] [P = NS]). In addition, the normalization of ALT levels was observed in 78.5% (51/65) and 74.2% (49/66) of patients treated with telbivudine and entecavir, respectively, at week 24 (P = NS). The adverse events were upper respiratory tract infection (12.3% of telbivudine patients vs 9.1% of entecavir patients), fatigue (6.2% vs 7.6%), diarrhea (1.5% vs 3.0%), and coughing (0% vs 1.5%), most of which were mild to moderate. Elevated creatinine

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phosphokinase was noted in 8 telbivudine-treated patients (12.3%). There were no statistically significant differences in rates of adverse events between groups except for creatinine phosphokinase.

Conclusion: In this study of ethnic Han Chinese adults with previously untreated HBeAg-positive HBV infection, there were no statistically significant differences in effectiveness or tolerability between telbivudine 600 mg and entecavir 0.5 mg at the end of 24 weeks of treatment. ChiCTR.org identifier: ChiCTR-TRC-00000341. (*Clin Ther.* 2010;32:649–658) © 2010 Excerpta Medica Inc.

Key words: hepatitis B, HBV, HBeAg, telbivudine, entecavir, seroconversion.

INTRODUCTION

Although more than 20 years have elapsed since the availability of an effective vaccine to prevent hepatitis B virus (HBV) infection, the virus continues to play an important role in human disease, infecting ~350 million people worldwide.[1] An estimated >1 million people die annually from HBV-related disease, such as hepatic cirrhosis or hepatocellular carcinoma.[2] It has been reported that the risk of developing hepatic cirrhosis and hepatocellular carcinoma is directly proportional to serum HBV-DNA concentration, a measure of viral load.[3,4] With the advent of the oral nucleoside/nucleotide analogues, the incidence of the complications of chronic HBV infection has declined.[5,6] However, the clinical benefits of these nucleoside/nucleotide analogues are limited because of the emergence of resistant strains and the low rate of a sustained response (ie, the serum HBV-DNA level rebounds in many patients following treatment lasting up to 2 years).[7–10] Several studies have reported that the initial viral response (ie, the decrease in the serum HBV-DNA level during the first 12 and 24 weeks of treatment) is a useful predictor for the emergence of resistant virus in patients with chronic HBV infection.[11,12] Thus, in patients with a prolonged treatment, the more the viral load declines in the initial stage of treatment, the better the outcome will be.[13] Therefore, an unmet clinical need remains for agents that are able to induce potent virologic suppression in the initial stage of the disease course.

It has been reported that telbivudine and entecavir are associated with better outcomes compared with other nucleoside/nucleotide analogues (eg, lamivudine, adefovir) that have been approved by the Chinese health authority, the State Food and Drug Administration, based on direct measures of antiviral efficacy (such as HBV-DNA detection) and on several clinical measures (such as alanine aminotransferase [ALT] and HBV serologic tests).[14–16] Entecavir has a high genetic barrier to resistance; more mutations are required to produce a reduction in susceptibility.[4] In addition, treatment with telbivudine, also a nucleoside analogue, has a higher rate of hepatitis B e antigen (HBeAg) seroconversion than other analogues.[17] Moreover, both drugs can suppress HBV replication rapidly and effectively (ie, to undetectable range in ~4 weeks).[18]

Recent studies have reported that antiviral efficacy for chronic HBV infection and the emergence of drug resistance are closely related to the degree of viral suppression achieved within the first 24 weeks of therapy.[19,20] However, a search of the literature did not identify any published direct comparisons of these agents for the treatment of patients with chronic HBV infection. Therefore, we designed this prospective, parallel-group, open-label, randomized clinical trial to compare the early antiviral effectiveness of telbivudine and entecavir in the treatment of patients with HBeAg-positive chronic HBV infection.

PATIENTS AND METHODS

This study was conducted in agreement with the ethical principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of the First Affiliated Hospital of Wenzhou Medical College, consistent with the Good Clinical Practice Guideline. The study was performed according to Consolidated Standards of Reporting Trials checklist criteria.[21] Written informed consent was obtained from each patient before the initiation of the study.

Patients

Outpatients at the First Affiliated Hospital of Wenzhou Medical College were eligible for the trial if they were aged 18 to 65 years, had HBeAg-positive chronic HBV infection and compensated liver disease with a serum ALT value ≥2 times the upper limit of normal (ULN), and had never received treatment with nucleosides or nucleotides for HBV. In addition, to evaluate the virologic suppressive effect of the 2 drugs of interest, patients were required to have a serum HBV-DNA concentration ≥6 $\log_{10}$ copies/mL at screening. Based on the investigators' clinical experience, HBV-DNA concentrations were categorized as follows: level 1,

HBV-DNA 6 $\log_{10}$ to <7 $\log_{10}$ copies/mL; level 2, HBV-DNA 7 $\log_{10}$ to <8 $\log_{10}$ copies/mL; and level 3, HBV-DNA ≥8 $\log_{10}$ copies/mL. The data were analyzed by a blinded, independent investigator.

Patients were excluded if they had evidence of infection with HIV, or hepatitis C or D viruses. Other exclusion criteria included pregnancy, breastfeeding, alcohol abuse (ie, use of alcoholic beverages to excess on individual occasions or as a regular practice), other forms of liver disease, and impaired renal function. In addition, patients with muscular diseases or baseline serum creatinine phosphokinase (CPK) >190 U/L were also excluded.

Patients were randomized according to a random number table to receive oral telbivudine 600 mg* or oral entecavir 0.5 mg,† once daily, for 24 weeks. Adherence to the treatment was assessed by patient diary. Blood samples were collected at the baseline, 12-week, and 24-week assessments for biochemical and hematologic examinations, including evaluation of liver and renal function. Fasting blood samples were obtained from an antecubital vein, and the samples were used for the analysis. The laboratory of the First Affiliated Hospital of Wenzhou Medical College performed all of the tests.

Effectiveness and Safety Assessments

As noted previously, the objective of this study was to compare the early antiviral effects of telbivudine and entecavir. The primary effectiveness end point was the mean reduction in serum HBV-DNA concentration as determined by polymerase chain reaction (PCR) assay at week 24, after adjusting for the baseline value.

Secondary efficacy end points were mean reduction in serum HBV-DNA concentration at week 12, after adjusting for the baseline value; the absence of serum HBV-DNA (ie, undetectable HBV-DNA concentration of <500 copies/mL); the normalization of serum ALT (ie, ≤1 × ULN); absence of HBeAg (ie, disappearance of serum HBeAg); and HBeAg seroconversion (ie, absence of serum HBeAg plus the development of anti-HBe antibody) at week 24. In addition, adverse events (AEs), including symptoms, signs, and clinical laboratory abnormalities (such as increased serum CPK) within 24 weeks were monitored, and discontinuations were recorded.

ALT and CPK were detected by the Karmen method,[22] which has been routinely performed according to the manufacturer's instructions in the First Affiliated Hospital of Wenzhou Medical College since 2000. Serum HBV-DNA concentrations were measured by quantitative PCR assay (Amplicor HBV Monitor Test, Roche Diagnostics, Basel, Switzerland; limit of quantitation: 500 copies/mL) before the administration of the first dose of study drugs and weeks 12 and 24 after the treatment.[14,23] HBV serologic tests for HBV surface antigen, HBeAg, anti-HBs antibody, and anti-HBe antibody were conducted with a modular immunoassay analyzer (Modular Analytics E170, Roche Diagnostics) within 2 weeks before administration of the first dose of study drugs and at weeks 12 and 24 after the treatment, according to the manufacturer's instruction (Freedom Evolyzer 150, Tecan Group Ltd., Männedorf, Switzerland). Laboratory personnel were blinded to participants' treatment group.

Statistical Analysis

To detect a difference of 0.5 $\log_{10}$ copies/mL in the mean reduction from baseline of serum HBV-DNA concentrations at week 24 between telbivudine-treated and entecavir-treated groups, with an SD of 1 within each group, a 2-sided significance level of 0.05, 80% power, and an expected dropout rate of 5%, ≥65 patients per treatment group were needed.[24] The data were expressed as the mean and SD for continuous variables with normal distribution, as the median and range for discrete variables, and as counts or percentages for qualitative variables. Data were analyzed based on the intent-to-treat principle.[25]

The Kolmogorov-Smirnov test was applied to determine whether the sample data were likely to be derived from a normal distribution population. A *t* test or ANOVA was used for normally distributed data, and the Wilcoxon signed rank test or Mann-Whitney *U* test was used for nonparametric continuous data. The χ^2 test or Fisher exact test was used to compare the difference in proportions between the treatment groups. $P < 0.05$ was considered statistically significant. All statistical tests were performed using SPSS, version 13.0 (SPSS Inc., Chicago, Illinois). Estimates of proportions were based on all evaluable patients, with missing data assumed to represent treatment failure.

*Trademark: Sebivo® (Beijing Novartis Pharma Ltd., Beijing, China).

†Trademark: Baraclude® (Bristol-Myers Squibb Company, Princeton, New Jersey).

RESULTS

Study Population

A total of 286 patients were screened, and 155 patients were excluded due to various reasons. Therefore, a total of 131 patients were randomized to receive either telbivudine (n = 65) or entecavir (n = 66) treatment (**Figure**). This intent-to-treat group included 91 men and 40 women, with a mean (SD) age of 32.5 (8.9) years. All patients were ethnic Han Chinese, and the baseline demographic characteristics and serum HBV-DNA concentrations of the 2 treatment groups were well matched (**Table I**).

Review of the patient diaries indicated good compliance. Three patients were lost to follow-up; 1 was treated with telbivudine (HBV-DNA level 2), and 2 were treated with entecavir (HBV-DNA levels 1 and 3, respectively). Another patient in the telbivudine group (HBV-DNA level 3) did not take the drug regularly. Thus, 64 patients in the telbivudine group (20, 29, and 15 patients with HBV-DNA levels 1, 2 and 3, respectively) and 63 patients in the entecavir group (19, 26, and 18 patients with HBV-DNA levels 1, 2 and 3) completed the 24-week treatment (**Figure**).

Primary End Point

At week 24, the mean reductions in serum HBV-DNA concentration in the telbivudine and the entecavir groups were 6.00 $\log_{10}$ and 5.80 $\log_{10}$ copies/mL, respectively (P = NS between groups). When stratified by baseline HBV-DNA concentration, the mean reductions in HBV-DNA concentration were not significantly different between the telbivudine and entecavir groups (6.02 $\log_{10}$ vs 5.73 $\log_{10}$ copies/mL in level 1; 6.05 $\log_{10}$ vs 5.42 $\log_{10}$ copies/mL in level 2; and 5.91 $\log_{10}$ vs 6.41 $\log_{10}$ copies/mL in level 3).

Secondary End Points

At week 12, the mean reductions from baseline in serum HBV-DNA concentration in the telbivudine-

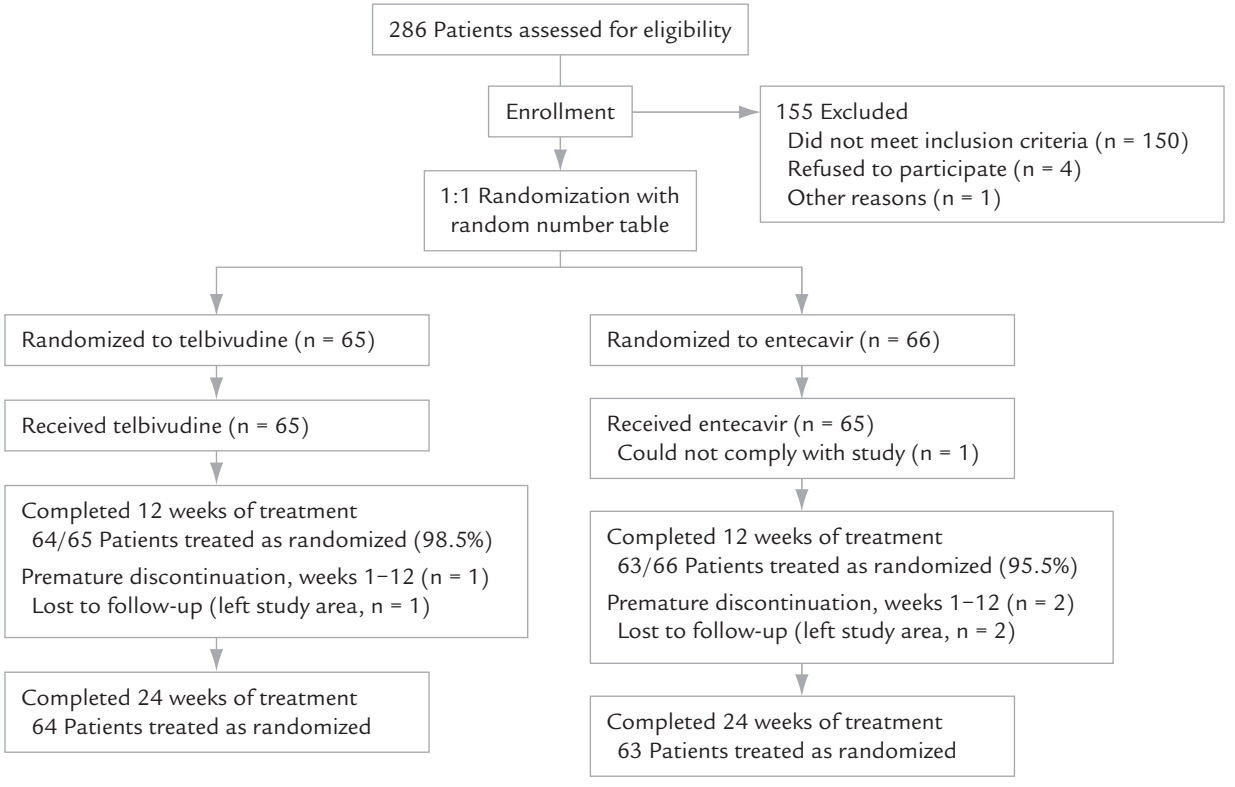

Figure. Disposition of patients in a parallel-group, open-label trial that randomized adult Han Chinese patients with previously untreated hepatitis B e antigen–positive hepatitis B virus infection to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks.

Table I. Baseline demographic characteristics, serum alanine aminotransferase (ALT), and DNA concentrations of adult Han Chinese patients with previously untreated hepatitis B e antigen–positive hepatitis B virus (HBV) infection who were randomized to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks in a parallel-group, open-label trial.*

Variable	Telbivudine (n = 65)	Entecavir (n = 66)	*P*
Age, mean (SD), y	31.6 (8.7)	33.5 (9.1)	0.244
Sex, no. (%)			
Male	49 (75.4)	42 (63.6)	0.144
Female	16 (24.6)	24 (36.4)	
ALT, mean (SD), U/L	167.3 (100.4)	160.3 (89.8)	0.675
HBV-DNA concentration, mean (SD), $\log_{10}$ copies/mL			
Overall	7.45 (0.69)	7.51 (0.85)	0.671
Baseline HBV-DNA level 1	6.67 (0.27)	6.45 (0.27)	0.016
Baseline HBV-DNA level 2	7.49 (0.28)	7.56 (0.29)	0.383
Baseline HBV-DNA level 3	8.41 (0.24)	8.50 (0.26)	0.303

*Baseline HBV-DNA concentrations were categorized as follows: level 1, HBV-DNA 6 $\log_{10}$ to <7 $\log_{10}$ copies/mL (telbivudine, n = 20; entecavir, n = 20); level 2, HBV-DNA 7 $\log_{10}$ to <8 $\log_{10}$ copies/mL (telbivudine, n = 30; entecavir, n = 26); and level 3, HBV-DNA ≥8 $\log_{10}$ copies/mL (telbivudine, n = 15; entecavir, n = 20).

treated and the entecavir-treated groups were 4.99 $\log_{10}$ and 4.69 $\log_{10}$ copies/mL, respectively (*P* = NS between groups). Similarly, when adjusted for baseline level, the mean reductions in HBV-DNA concentration did not differ significantly between the telbivudine and entecavir groups (5.00 $\log_{10}$ vs 5.11 $\log_{10}$ copies/mL in level 1; 5.28 $\log_{10}$ vs 4.29 $\log_{10}$ copies/mL in level 2; and 4.44 $\log_{10}$ vs 4.82 $\log_{10}$ copies/mL in level 3).

Furthermore, at week 12, the proportion of patients with undetectable HBV-DNA was 43.1% (28/65) in the telbivudine group and 34.8% (23/66) in the entecavir group (χ^2 = 0.933; *P* = NS between groups; **Table II**). In the telbivudine group, the proportion of patients with undetectable HBV-DNA was 60.0% (12/20), 46.7% (14/30), and 13.3% (2/15), when the baseline HBV-DNA level was 1, 2, or 3, respectively. Among patients treated with entecavir, the corresponding proportions were 60.0% (12/20), 30.8% (8/26), and 15.0% (3/20) (**Table II**). There were 2 patients in whom the reduction of serum HBV-DNA level was <1 $\log_{10}$ copies/mL: 1 had received telbivudine (baseline HBV-DNA level 1), and the other had received entecavir (baseline HBV-DNA level 2). HBV-DNA concentrations remained ≥5 $\log_{10}$ copies/mL in 9 patients treated with telbivudine and in 10 patients treated with entecavir.

At 24 weeks, HBV-DNA was undetectable in an additional 16 telbivudine-treated and 15 entecavir-treated patients, yielding overall proportions of patients with undetectable HBV-DNA of 67.7% (44/65) and 57.6% (38/66), respectively (χ^2 = 0.987; *P* = NS between groups; **Table II**). However, HBV-DNA concentrations remained ≥5 $\log_{10}$ copies/mL in 6 patients who received telbivudine; 2 of them later rebounded (ie, HBV-DNA was undetectable at week 12 but increased to ≥5 $\log_{10}$ copies/mL or more at week 24). Four patients who received entecavir still had HBV-DNA levels ≥5 $\log_{10}$ copies/mL at 12 weeks; however, none of them rebounded. Only 1 patient, who received telbivudine, experienced a mild increase in HBV-DNA (ie, concentration was undetectable at week 12, but increased to <5 $\log_{10}$ copies/mL at week 24) without ALT elevation.

The normalization of serum ALT was documented in 36 (55.4%) telbivudine-treated and 38 (57.6%) entecavir-treated patients at week 12 (χ^2 = 0.064; *P* = NS between groups), and in 51 (78.5%) telbivudine-treated and 49 (74.2%) entecavir-treated patients at week 24 (χ^2 = 0.323; *P* = NS between groups; **Table III**).

Table II. Response to treatment, as indicated by the mean reduction in serum DNA and the proportion of undetected DNA (intent-to treat analysis) in a parallel-group, open-label trial that randomized adult Han Chinese patients with previously untreated hepatitis B e antigen–positive hepatitis B virus (HBV) infection to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks.*

Treatment Response	Telbivudine (n = 65)	Entecavir (n = 66)	*P*
12 Weeks			
Reduction in serum HBV-DNA concentration, mean (SD), $\log_{10}$ copies/mL			
Total	4.99 (2.10)	4.69 (2.16)	0.261
Baseline HBV-DNA level 1	5.00 (2.18)	5.11 (1.88)	0.429
Baseline HBV-DNA level 2	5.28 (2.17)	4.29 (2.47)	0.411
Baseline HBV-DNA level 3	4.44 (1.84)	4.82 (1.96)	0.890
Proportion of patients with undetectable HBV-DNA concentration, % (n/N)†			
Total	43.1 (28/65)	34.8 (23/66)	0.334
Baseline HBV-DNA level 1	60.0 (12/20)	60.0 (12/20)‡	>0.999
Baseline HBV-DNA level 2	46.7 (14/30)‡	30.8 (8/26)	0.224
Baseline HBV-DNA level 3	13.3 (2/15)	15.0 (3/20)‡§	>0.999
24 Weeks			
Reduction in serum HBV-DNA concentration, mean (SD), $\log_{10}$ copies/mL			
Total	6.00 (2.07)	5.80 (2.16)	0.350
Baseline HBV-DNA level 1	6.02 (1.68)	5.73 (1.44)	0.037
Baseline HBV-DNA level 2	6.05 (2.18)	5.42 (2.51)	0.153
Baseline HBV-DNA level 3	5.91 (2.46)	6.41 (2.20)	0.885
Proportion of patients with undetectable HBV-DNA concentration, % (n/N)†			
Total	67.7 (44/65)	57.6 (38/66)	0.232
Baseline HBV-DNA level 1	85.0 (17/20)	75.0 (15/20)‡	0.695
Baseline HBV-DNA level 2	66.7 (20/30)‡	53.8 (14/26)	0.327
Baseline HBV-DNA level 3	46.7 (7/15)	45.0 (9/20)‡§	0.992

*Baseline HBV-DNA concentrations were categorized as follows: level 1, HBV-DNA 6 $\log_{10}$ to <7 $\log_{10}$ copies/mL; level 2, HBV-DNA 7 $\log_{10}$ to <8 $\log_{10}$ copies/mL; and level 3, HBV-DNA ≥8 $\log_{10}$ copies/mL.
† Defined as <500 copies/mL.
‡ 1 Patient lost to follow-up.
§ 1 Patient did not comply with the study protocol.

HBeAg Absence and Seroconversion

At week 12, significantly more patients in the telbivudine group than the entecavir group had no HBeAg (20.0% [13/65] vs 3.0% [2/66]; $\chi^2 = 9.301$; $P = 0.002$), as well as HBeAg seroconversion (13.8% [9/65] vs 3.0% [2/66]; $\chi^2 = 4.981$; $P = 0.030$). However, at week 24, HBeAg absence was comparable between the telbivudine and entecavir groups (36.9% [24/65] vs 28.8% [19/66]; $\chi^2 = 0.983$; P = NS), as was HBeAg seroconversion (24.6% [16/65] vs 13.6% [9/66]; $\chi^2 = 2.556$; P = NS) (**Table III**).

Adverse Events

The AEs reported in either the telbivudine or entecavir group were upper respiratory tract infection (12.3% [8/65] vs 9.1% [6/66], respectively), fatigue (6.2% [4/65] vs 7.6% [5/66]), diarrhea (1.5% [1/65] vs 3.0% [2/66]), and coughing (0% vs 1.5% [1/66]), most of which were

Table III. Effects of treatment on alanine aminotransferase (ALT) and hepatitis B e antigen (HBeAg) in a parallel-group, open-label trial that randomized adult Han Chinese patients with previously untreated HBeAg-positive hepatitis B virus (HBV) infection to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks.*

	Week 12			Week 24		
Treatment Response	Telbivudine (n = 65)	Entecavir (n = 66)	*P*	Telbivudine (n = 65)	Entecavir (n = 66)	*P*
ALT normalization, % (n/N)†						
Total	55.4 (36/65)	57.6 (38/66)	0.800	78.5 (51/65)	74.2 (49/66)	0.570
Baseline HBV-DNA level 1	65.0 (13/20)	60.0 (12/20)‡	0.744	75.0 (15/20)	85.0 (17/20)‡	0.695
Baseline HBV-DNA level 2	60.0 (18/30)‡	57.7 (15/26)	0.861	83.3 (25/30)‡	69.3 (18/26)	0.213
Baseline HBV-DNA level 3	33.3 (5/15)	55.0 (11/20)*‡§	0.203	73.3 (11/15)	70.0 (14/20)‡§	>0.999
HBeAg absence, % (n/N)						
Total	20.0 (13/65)	3.0 (2/66)	0.002	36.9 (24/65)	28.8 (19/66)	0.321
Baseline HBV-DNA level 1	30.0 (6/20)	10.0 (2/20)	0.235	50.0 (10/20)	60.0 (12/20)‡	0.525
Baseline HBV-DNA level 2	20.0 (6/30)	0 (0/26)	0.025	36.7 (11/30)‡	15.4 (4/26)	0.129
Baseline HBV-DNA level 3	6.7 (1/15)	0 (0/20)	0.429	20.0 (3/15)	15.0 (3/20)‡§	>0.999
HBeAg seroconversion, % (n/N)						
Total	13.8 (9/65)	3.0 (2/66)	0.030	24.6 (16/65)	13.6 (9/66)	0.110
Baseline HBV-DNA level 1	20.0 (4/20)	10.0 (2/20)	0.661	30.0 (6/20)	30.0 (6/20)‡	>0.999
Baseline HBV-DNA level 2	16.7 (5/30)‡	0 (0/26)	0.055	30.0 (9/30)‡	3.8 (1/26)	0.014
Baseline HBV-DNA level 3	0 (0/15)	0 (0/20)	–	6.7 (1/15)	10.0 (2/20)‡§	>0.999

*Baseline HBV-DNA concentrations were categorized as follows: level 1, HBV-DNA 6 $\log_{10}$ to <7 $\log_{10}$ copies/mL; level 2, HBV-DNA 7 $\log_{10}$ to <8 $\log_{10}$ copies/mL; and level 3, HBV-DNA ≥8 $\log_{10}$ copies/mL.
† Defined as ALT ≤1 × the upper limit of normal.
‡ 1 Patient lost to follow-up.
§ 1 Patient did not comply with the study protocol.

of mild to moderate severity (all, *P* = NS between groups; **Table IV**). All AEs resolved after appropriate measures to manage these symptoms, such as prevention of cough, fluid infusion, and rest. An increase in serum CPK at week 24 was observed in 8 telbivudine-treated patients (12.3%), but the increase was <2 × ULN, without clinical symptoms, in all cases. No patient in the entecavir group experienced increased serum CPK. There were no other clinical laboratory abnormalities in the 2 groups, no serious AEs were observed, and no patients withdrew from the study because of AEs.

DISCUSSION

The findings of the present study indicate that treatment with either telbivudine or entecavir for 24 weeks produced reductions in serum HBV-DNA of 6.00 $\log_{10}$ and 5.80 $\log_{10}$ copies/mL, respectively, in patients with HBeAg-positive chronic HBV infection. HBV-DNA was undetectable in 67.7% (44/65) and 57.6% (38/66) of telbivudine-treated and entecavir-treated patients at the end of 24 weeks, and ALT levels were normalized in 78.5% (51/65) and 74.2% (49/66), respectively. In addition, HBeAg absence and HBeAg seroconversion were achieved in 36.9% (24/65) and 24.6% (16/65) of telbivudine-treated patients and 28.8% (19/66) and 13.6% (9/66) of entecavir-treated patients. To our knowledge, this is the first published clinical trial with a direct head-to-head comparison of the antiviral effects of telbivudine and entecavir in nucleoside-naive, HBeAg-positive patients with compensated chronic HBV infection. The results suggest that both telbivudine and entecavir have rapid antiviral activity in the early treatment stage of the disease.

In the present study, HBV-DNA was undetectable within 24 weeks in more than half of patients in both

Table IV. All adverse events through 24 weeks of treatment in a parallel-group, open-label trial that randomized adult Han Chinese patients with previously untreated hepatitis B e antigen–positive hepatitis B virus infection to receive telbivudine 600 mg or entecavir 0.5 mg daily for 24 weeks.

Adverse Event	Patients, No. (%) Telbivudine (n = 65)	Entecavir (n = 66)	*P*
Upper respiratory tract infection	8 (12.3)	6 (9.1)	0.551
Fatigue	4 (6.2)	5 (7.6)	>0.999
Diarrhea	1 (1.5)	2 (3.0)	>0.999
Coughing	0	1 (1.5)	>0.999
Increased creatinine phosphokinase*	8 (12.3)	0	0.003

*Defined as >174 U/L.

the telbivudine and entecavir groups. It has been suggested that the suppression of HBV-DNA at 24 weeks correlates with treatment outcome at 1 year.[26] Furthermore, we compared the antiviral efficacies of the 2 drugs in patients with different baseline HBV-DNA concentrations, which gave a more detailed message. It was noted that, in 2 patients treated with telbivudine, HBV-DNA concentration was undetectable at week 12 but rebounded to 5 $\log_{10}$ copies/mL at week 24. Another patient treated with telbivudine had an undetectable HBV-DNA concentration at week 12; the concentration increased slightly by week 24, but was still <5 $\log_{10}$ copies/mL. It has been reported that HBV-DNA rebound during treatment with telbivudine is associated with viral resistance development or treatment discontinuation.[16,27,28] Serum HBV-DNA rebound and flare-up were not observed during treatment with entecavir in the present study. However, given the small sample size, the results of the present study are not sufficient for comparisons of the rates of rebound and flare-up in patients with chronic HBV infection who are treated with telbivudine or entecavir.

In previous trials that evaluated the 2 drugs separately, HBeAg seroconversion was reported in 24.4% to 31% of telbivudine-treated patients and 11% to 21% of entecavir-treated patients.[27,29,30] In the present study, differences in HBeAg absence and HBeAg seroconversion did not vary significantly between the telbivudine and entecavir groups at week 24. However, these results may vary with prolonged follow-up. The present study also observed that HBeAg absence and seroconversion mainly occurred in the patients with baseline HBV-DNA between 6 $\log_{10}$ and <8 $\log_{10}$ copies/mL; in all the patients with HBeAg absence and seroconversion, HBV-DNA concentrations were reduced to <3 $\log_{10}$ copies/mL.

The present study found that treatment with telbivudine or entecavir for 24 weeks was associated with comparably high rates of ALT normalization (78.5% and 74.2%, respectively). In fact, ALT levels had normalized in 56.5% (74/131) of all patients by 12 weeks of treatment. This early effect on liver function is of particular clinical importance because it has been reported that rapid ALT normalization may reduce the risk of drug resistance.[11,31]

Treatment with telbivudine and entecavir was generally well tolerated in the present study. The most common AEs were upper respiratory tract infection and fatigue, which occurred in comparable proportions of telbivudine-treated and entecavir-treated patients. No serious AEs were reported, and all AEs resolved after appropriate treatment.

Serum CPK increase was observed in 8 telbivudine-treated patients (12.3%); however, the CPK level in all 8 of these patients remained <2 × ULN and was not accompanied by any clinical symptoms. Further investigations are required to determine whether long-term telbivudine treatment leads to a significant and sustained increase in CPK levels and subsequent serious AEs. In the present study, no entecavir-treated patients experienced CPK increases during the 24-week treatment.

There are a few potential limitations in the present study. First, it was an open-label study, which may lead to selection bias. Second, the sample size was relatively small. Finally, the follow-up was only 24 weeks. However, it must be emphasized that the aim of the present

study was to compare the short-term antiviral effects of telbivudine and entecavir in the treatment of HBeAg-positive chronic HBV infection, and 24 weeks is the generally accepted timeline for evaluation of short-term effectiveness.[32] Nevertheless, longer, randomized, double-blind, controlled clinical trials are needed to confirm the preliminary findings of the present study. Future studies should also incorporate quantitative studies of e and s antigens, in addition to serum ALT values, to provide a comprehensive understanding of the response to inhibition of HBV-DNA replication.

CONCLUSION

In this study of ethnic Han Chinese adults with previously untreated HBeAg-positive HBV infection, there were no statistically significant differences in effectiveness or tolerability between telbivudine 600 mg and entecavir 0.5 mg at the end of 24 weeks of treatment.

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