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Early Viral Kinetics of Telbivudine and Entecavir: Results of a 12-Week Randomized Exploratory Study with Patients with HBeAg-Positive Chronic Hepatitis B[▽]

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We characterized the early viral kinetic profiles of telbivudine and entecavir and the effects of these potent nucleoside analogs on hepatitis B virus (HBV) DNA and alanine aminotransferase levels in adults with hepatitis B e antigen-positive compensated chronic hepatitis B. Forty-four patients were enrolled in this open-label, parallel-group, multicenter study and randomized to receive telbivudine or entecavir for 12 weeks. Reductions in hepatitis B virus DNA and alanine aminotransferase levels from baseline to weeks 2, 4, 8, and 12 were assessed. Viral kinetic parameters, including viral clearance per day, loss of infected cells per day, and efficiency of inhibition of viral production, were estimated by using a biphasic mathematical model. Statistical analyses were limited to descriptive analyses. The 2 treatment groups achieved similar reductions in HBV DNA and alanine aminotransferase levels. Mean reductions in levels of hepatitis B virus DNA at week 12 were 6.6 ± 1.6 and 6.5 ± 1.5 $\log_{10}$ copies/ml for the telbivudine- and entecavir-treated patients, respectively. There were no significant differences between groups in values for mean viral clearance per day, mean loss of infected cells per day, or efficiency of blocking viral production. The safety profiles for both medications were favorable. During the first 12 weeks of treatment, telbivudine and entecavir demonstrated similar antiviral potencies, resulting in a rapid and profound suppression of serum hepatitis B virus DNA and reduction of alanine aminotransferase levels. No differences in the effects of these 2 agents on early viral kinetics were observed. Both medications were well tolerated.

Chronic hepatitis B (CHB) affects approximately 350 million individuals worldwide; when left untreated, it may lead to liver-related sequelae including cirrhosis, decompensated liver disease, and hepatocellular carcinoma (2, 5, 21). Clinical experience has shown that the early and profound suppression of hepatitis B virus (HBV) DNA replication is the primary goal of treatment and that the sustained suppression of serum hepatitis B virus (HBV) DNA levels below the limit of detection is associated with improved long-term virological and biochemical response rates (21, 24, 40). Therapeutic options for the treatment of patients with CHB have expanded with the licensure of several potent oral nucleoside (nucleotide) analogs (NAs), including entecavir, telbivudine, and tenofovir, that induce a rapid and profound suppression of serum HBV DNA levels. These agents have established superior efficacy over lamivudine and adefovir in large registrational trials (4, 15, 27); however, limited head-to-head comparative data exist for the more potent NAs in current clinical use (32).

An analysis of viral kinetics using established mathematical models during the first few weeks of antiviral therapy is useful for summarizing important features of the early response and provides valuable information by efficient comparisons of different treatment regimens even when relatively small samples are involved (11, 31, 34). Characterization of early viral kinetics during oral NA treatment can be used to predict subsequent virological responses, allowing clinicians to choose the most appropriate drugs and optimize the patient response to therapy (1, 6, 14). Data from studies of oral NAs have revealed different patterns of viral kinetics with these agents during the early phase of treatment (16–18, 20, 28, 34). Initial clinical trials of telbivudine have demonstrated profound (>2 $\log_{10}$ copies/ml) reductions in serum HBV DNA levels at as early as 1 week of treatment (17). Similar findings were reported for a phase II, 24-week, double-blind study of entecavir in patients with hepatitis B e antigen (HBeAg)-positive CHB (18). The present randomized, open-label, parallel-group, multicenter, phase IIIb trial was conducted to characterize the early viral kinetics, efficacy, and safety of telbivudine and entecavir in treatment-naïve patients with HBeAg-positive compensated CHB. The primary objective of this study was

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to assess reductions in serum HBV DNA levels and changes in other parameters of viral kinetics during 12 weeks of treatment.

MATERIALS AND METHODS

Study design and patients. Eligible patients were aged ≥18 years and had HBeAg-positive CHB with a clinically confirmed diagnosis of compensated liver function (a total serum bilirubin level of ≤2.5 mg/dl, a prothrombin time ≤3 s longer than normal or an international normalized ratio of ≤1.5, a serum albumin level of ≥3 g/dl, and no history of variceal bleeding or hepatic encephalopathy). Eligible patients also had detectable hepatitis B surface antigen (HBsAg) for ≥24 weeks prior to screening. Other inclusion criteria at screening were serum HBV DNA levels of ≥7 $\log_{10}$ copies/ml, as determined by a Cobas Amplicor DNA PCR-based assay (Roche Molecular Diagnostics, Branchburg, NJ), a serum alanine aminotransferase (ALT) level 1.3× to 10.0× the upper limit of normal (ULN), and evidence of chronic liver inflammation documented upon previous liver biopsy within 24 months of the study or by a history of elevated serum ALT levels on ≥2 occasions within a 6-month period. Exclusion criteria included coinfection with hepatitis C virus, hepatitis delta virus, or human immunodeficiency virus; the use of interferon or other immunomodulatory agents within 12 months of screening or any previous treatment with oral NA agents; and conditions requiring the frequent, chronic, or prolonged use of systemic corticosteroids or hepatotoxic or nephrotoxic medications. A total of 44 patients were randomized in a 1:1 ratio to receive telbivudine at 600 mg/day (n = 23) or entecavir at 0.5 mg/day (n = 21) for 12 weeks. The study was conducted in full compliance with the ethical principles of the Declaration of Helsinki and was consistent with Good Clinical Practice guidelines and applicable local regulatory requirements. Informed consent was obtained from each subject in writing prior to randomization.

Efficacy assessments. All efficacy assessments were performed on the intent-to-treat (ITT) population, which consisted of all patients who were randomized to 1 of the 2 treatment groups, received ≥1 dose of study drug, and had undergone ≥1 postbaseline assessment of serum HBV DNA levels. Efficacy measures included serum HBV DNA, HBsAg, antibody to HBsAg (anti-HBs), HBeAg, antibody to HBeAg (anti-HBe), and ALT levels, which were obtained at screening; baseline (day 1 prior to dosing); days 2, 3, 5, 8, 10, 12, 15, 22, 29, 43, 57, and 85 of treatment; and weeks 14 and 16 after treatment. Serum HBsAg, anti-HBs, HBeAg, and anti-HBe levels were assessed at a central laboratory by using standard commercially available enzyme-linked immunoassays.

HBV DNA quantification. Serum HBV DNA levels were evaluated at a central laboratory by using the Cobas Amplicor HBV Monitor, which utilizes PCR methods and semiautomated sample readout technologies (threshold for detection, 300 copies/ml). Prediluted serum samples were analyzed to detect the range of HBV viremia commonly reported for patients with CHB and active viral replication (6 to 9 $\log_{10}$ copies/ml). Diluted samples were retested in an undiluted formulation if they were negative for HBV DNA. Additionally, the Cobas TaqMan HBV assay (Roche Molecular Systems, Branchburg, NJ) was also used to determine HBV DNA levels for the mathematical modeling of early viral kinetics because of the wider dynamic range of this assay than with the Cobas Amplicor HBV Monitor assay.

Viral kinetics. Viral kinetic parameters were estimated with a biphasic mathematical model of HBV DNA by using compartments of free virus, infected cells, and uninfected target cells (28, 33). The dynamics of the compartment of the target cells were modeled by using a biphasic model as proposed previously (10, 28). Maximum-likelihood estimation (MLE) methods for the viral kinetic parameters entailed the fitting of a nonlinear differential equation system via the least-squares approach from the serum HBV DNA data collected during the treatment period. To obtain these estimates, we used our own MATLAB routines to calculate the log-likelihood function as an objective function for maximization, including existing routines for stiff differential equation system solvers inside this function and overall nonlinear optimization of the objective function for individual patient data (MathWorks Inc., Natick, MA). A characterization of viral kinetics was made by estimating the efficiency of blocking new virus production (ε) and the half-lives of both free virions (c) and infected hepatocytes (δ). Here, as in previously reported studies, the efficiency of blocking *de novo* virus production (ε) is defined as the ratio of virus production during and before treatment in the compartment model, with values of 0% to 100% (28, 33).

Safety assessments. Adverse events (AEs) and laboratory abnormalities were monitored throughout the treatment phase. Laboratory abnormalities were graded for severity according to criteria adapted from the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health (7). Safety assessments included hematological assessments, blood chemistry, urinalysis, regular measurement of vital signs (heart rate, diastolic and systolic blood pressure, and weight), and physical examination. ALT flares were defined as ALT elevations >2× the baseline and >10× the ULN, according to the guidelines of the American Association for the Study of Liver Diseases (26). Grade 3 to 4 creatine kinase (CK) elevations were defined as CK levels of >7× the ULN.

TABLE 1. Demographic and baseline characteristics

Parameter	Value for treatment group	
	Telbivudine (n = 23)	Entecavir (n = 21)
Mean age (yr) (SD)	36.2 (9.62)	33.4 (8.82)
No. (%) of patients of gender		
Male	18 (78.3)	12 (57.1)
Female	5 (21.7)	9 (42.9)
No. (%) of patients with Asian and South Korean race and ethnicity	23 (100.0)	21 (100.0)
Mean patient height (cm) (SD)	170.5 (7.16)	166.2 (7.32)
Mean patient wt (kg) (SD)	68.8 (10.79)	64.2 (17.54)
No. (%) of patients with time since diagnosis of CHB		
Within past 6 mo	0 (0.0)	0 (0.0)
<1 yr but >6 mo	2 (8.7)	1 (4.8)
≥1 yr ago	21 (91.3)	20 (95.2)
No. (%) of patients with liver biopsy performed in last 2 years		
Yes	15 (65.2)	13 (61.9)
No	8 (34.8)	8 (38.1)
Baseline HBV DNA level ($\log_{10}$ copies/ml)		
Mean (SD)	10.29 (1.6)	9.72 (1.7)
Median	9.9	9.5
Range (min, max)	7.84, 13.05	5.77, 12.71
Baseline ALT level (IU/liter)		
Mean (SD)	163.1 (125.2)	170.2 (152.7)
Median	116	110
Range (min, max)	51,559	73,644

Statistical methods. Statistical analyses used descriptive statistics to characterize reductions in HBV DNA levels due to the small sample size. Serum HBV DNA levels were plotted over time by treatment group and visit. Changes in individual patient HBV DNA levels from baseline to week 12 were plotted similarly. The difference in reductions in HBV DNA and ALT levels between telbivudine and entecavir was also described, along with its 95% confidence interval (CI) based on the MLE model.

The safety population included all patients who received ≥1 dose of study medication and completed ≥1 postbaseline safety assessment. All data analyses apart from viral kinetic analyses were performed by an independent clinical research organization (Rho Inc., Chapel Hill, NC) by using SAS statistical software (version 9.1).

RESULTS

Patient disposition. Treatment groups were balanced with respect to demographics and baseline characteristics (Table 1). The proportion of males was higher in the telbivudine group than in the entecavir group (78.3% versus 57.1%). Patients

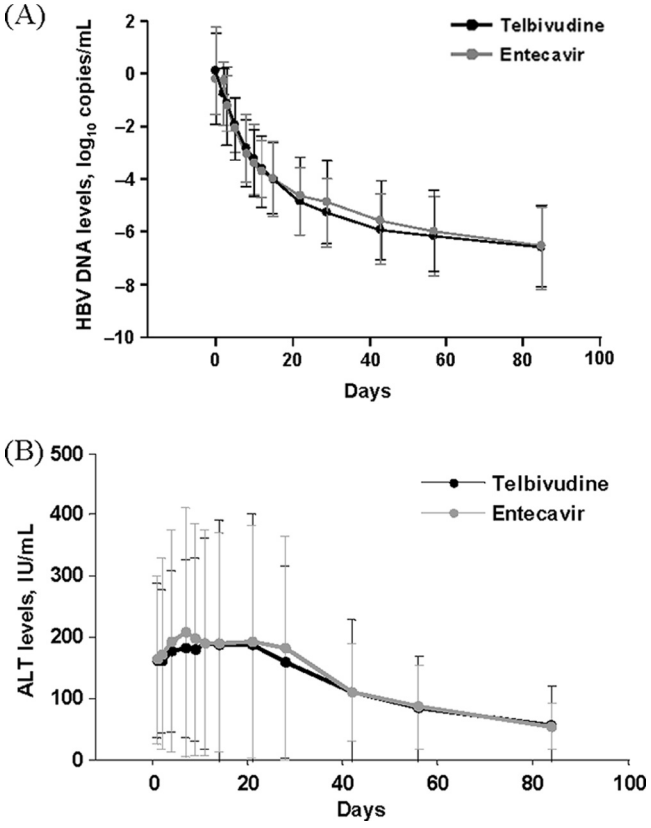

FIG. 1. Effects of telbivudine and entecavir on early serum HBV and ALT kinetics. (A) Mean (± standard deviation [SD]) change from baseline in $\log_{10}$ HBV DNA levels with telbivudine and entecavir. (B) Mean (±SD) ALT levels over time with telbivudine and entecavir.

were well matched for time since the diagnosis of CHB. Patients in the telbivudine group had higher baseline mean serum HBV DNA levels (10.29 ± 1.6 versus 9.72 ± 1.7 $\log_{10}$ copies/ml) and lower mean ALT levels (163.1 ± 125.2 versus 170.2 ± 152.7 IU/liter) than patients in the entecavir group. All randomized patients completed treatment, and there were no treatment discontinuations.

Efficacy. All patients responded well to treatment, and no patient experienced primary treatment failure (<1 $\log_{10}$ reduction in serum HBV DNA from baseline) or virological rebound. From baseline to week 12, all patients experienced a ≥2-$\log_{10}$ reduction in HBV viral load, and the mean reductions in HBV DNA levels were similar for the telbivudine and entecavir groups (6.6 ± 1.6 and 6.5 ± 1.5 $\log_{10}$ copies/ml, respectively) (Fig. 1A). Changes from baseline to week 12 in $\log_{10}$-transformed HBV DNA levels for individual patients were also comparable between the 2 treatment groups (Fig. 2). From mean baseline HBV DNA levels of 10.29 ± 1.6 $\log_{10}$ copies/ml (telbivudine) and 9.72 ± 1.7 $\log_{10}$ copies/ml (entecavir), 2 patients receiving telbivudine (8.7%) and 6 patients receiving entecavir (28.6%) achieved undetectable HBV DNA levels by treatment week 12.

The reductions in ALT levels from baseline to week 12 were similar for both treatment groups, with all patients experiencing a 4-fold decrease. The mean reductions in ALT levels from baseline to week 12 were similar for the telbivudine and entecavir groups (108.0 ± 147.87 and 116.3 ± 162.81 IU/liter, respectively) (Fig. 1B). At treatment week 12, patients in the telbivudine and entecavir groups achieved mean ALT levels of 55.1 and 54.0 IU/liter, respectively.

Viral kinetics. The evaluation of viral kinetic parameters for the ITT population revealed no significant differences between the 2 treatment groups for values for mean viral clearance per day, mean loss of infected cells per day, or efficiency factor of blocking viral production (Table 2). As shown in Fig. 2, the data supported the biphasic model for viral kinetics. Only a few patients showed a deviation in 1 quantification from a biphasic pattern, and only 1 patient treated with telbivudine showed a deviation in 2 quantifications. This patient was excluded when

TABLE 2. Viral kinetic parameters for telbivudine and entecavir

Parameter	Value for treatment group		*P*
	Telbivudine[a] (*n* = 23)	Entecavir (*n* = 21)	
Mean viral clearance rate ± SD (1/day)	0.809 ± 0.390	1.002 ± 0.082	0.314
Mean rate of infected cell loss ± SD (1/day)	0.075 ± 0.023	0.071 ± 0.028	0.627
Mean efficiency factor (%) of blocking virus production ± SD	99.1 ± 1.3	99.2 ± 0.9	0.736

[a] The value for 1 patient in the telbivudine group was excluded, as this patient showed a deviation from the biphasic pattern in viral kinetic modeling.

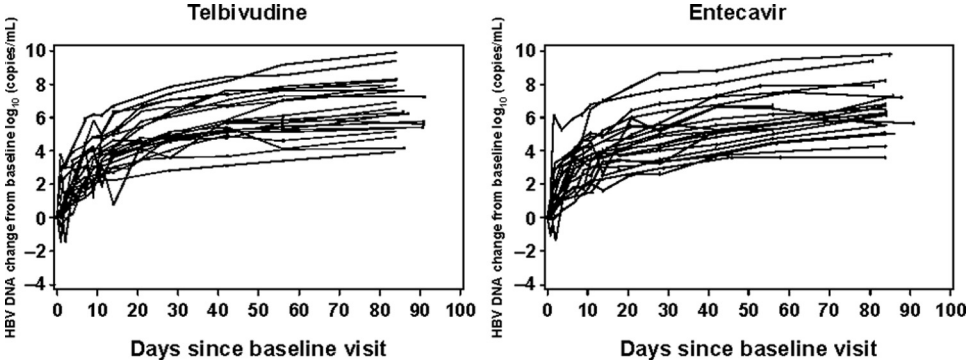

FIG. 2. Change from baseline in $\log_{10}$-transformed HBV DNA over time by patients (ITT population).

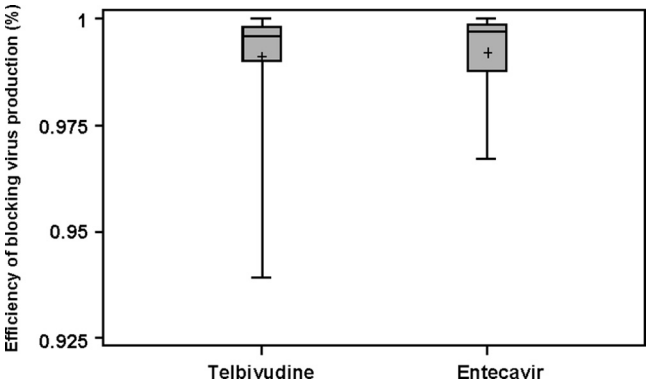

FIG. 3. Box plots for the efficiency of blocking virus protection by treatment group (ITT population). The boxes show the ranges between the 25% and 75% quintiles (the middle half of the estimated parameters). The median is shown by the line, and the mean is indicated by the cross. The vertical lines represent the range (the smallest and largest values in each case).

the following results were calculated, but statistical significances were comparable when this patient was included. The mean viral clearance was 0.809 ± 0.390/day for patients administered telbivudine compared with 1.002 ± 0.816/day for patients administered entecavir ($P = 0.314$). The mean rates of infected cell loss were estimated to be 0.075 ± 0.023 and 0.071 ± 0.023 (1/day) for the telbivudine and entecavir groups, respectively ($P = 0.627$). The mean efficiency factors for the inhibition of virus production also did not differ significantly between the 2 treatment groups: 99.1% ± 1.3% and 99.2% ± 0.9% for the telbivudine and entecavir groups, respectively ($P = 0.736$). Box plots for the efficiency of viral production confirmed that there were no significant differences between these groups (Fig. 3).

Safety. Treatment with telbivudine and entecavir was well tolerated, with favorable safety profiles and mostly mild-to-moderate AEs. Of the 21 entecavir-treated patients, 13 (61.9%) experienced drug-related AEs, compared with only 9 (39.1%) of the 23 telbivudine-treated patients (Table 3). Mild-to-moderate elevations in blood CK levels were reported for 3 (14.3%) of the entecavir-treated patients but none of the telbivudine-treated patients. ALT flares were observed for 3 (13.0%) and 1 (4.8%) of the telbivudine- and entecavir-treated patients, respectively. The majority of ALT flares occurred during the first 4 weeks of treatment. Peripheral neuropathy and muscular weakness were not reported for either treatment group.

DISCUSSION

This study provides the first head-to-head comparison of the viral kinetic profiles of telbivudine at 600 mg/day and entecavir at 0.5 mg/day for treatment-naïve patients with HBeAg-positive compensated CHB. Early reductions in serum HBV DNA levels were similar for the patients who received telbivudine and entecavir. Viral kinetic parameters were also comparable between the 2 groups with respect to viral clearance per day, rate of infected cell loss per day, and efficiency of blocking viral replication. Both treatments demonstrated favorable safety profiles and were well tolerated, although a higher rate of AEs was reported for the entecavir-treated patients.

Not all current pharmacological interventions against CHB are equally effective for all patients, and there is compelling evidence that distinct patterns of viral kinetics are associated with differential responses to treatment regimens (30). These variations might be attributed to a variety of underlying factors that have yet to be identified but are likely to include HBV genotype, baseline ALT level and HBeAg status, and previous treatment history for CHB and may also depend on varying pharmacokinetics (30, 33, 36). We used a basic biphasic model that simplifies comparisons with recent results and fits well with our data. Recently suggested advanced models for viral kinetic analysis include ongoing assessments of serum HBV DNA, HBeAg, HBsAg, and ALT levels and proliferation processes of infected cells to provide estimates of the number of virions produced and cleared daily, the half-lives of infected cells, and the expected time to elimination of virus-producing cells. This additional complexity may facilitate the prediction of a long-term response and allow individualized treatment based on further research (1, 6, 25, 33).

The viral kinetic analyses presented here are consistent with data from previous reports demonstrating that the decline in serum HBV DNA levels over the first 12 weeks of treatment was biphasic for both drugs (17, 19, 35). The initial first phase, characterized by a rapid decline in HBV DNA levels, lasted up to 10 days and was followed by a second phase characterized by a gradual decline in HBV DNA levels. No difference was observed between telbivudine and entecavir in the rates of the

TABLE 3. Incidence of adverse events

Adverse event[a]	No. (%) of adverse events for group	
	Telbivudine ($n = 23$)	Entecavir ($n = 21$)
ALT level increased	3 (13.0)	1 (4.8)
Upper respiratory tract infection	1 (4.3)	2 (9.5)
Chest discomfort	1 (4.3)	1 (4.8)
Abdominal discomfort	1 (4.3)	0 (0.0)
Abdominal pain, upper	1 (4.3)	0 (0.0)
AST level increased	1 (4.3)	0 (0.0)
Conjunctival hyperemia	1 (4.3)	0 (0.0)
Dyspnea	1 (4.3)	0 (0.0)
Gingival bleeding	1 (4.3)	0 (0.0)
Hypophosphatemia	1 (4.3)	0 (0.0)
Myalgia	1 (4.3)	0 (0.0)
Neutropenia	1 (4.3)	0 (0.0)
Thrombocytopenia	1 (4.3)	0 (0.0)
Blood CK level increased	0 (0.0)	3 (14.3)
Nausea	0 (0.0)	2 (9.5)
Facial edema	0 (0.0)	1 (4.8)
Headache	0 (0.0)	1 (4.8)
Hordeolum	0 (0.0)	1 (4.8)
Insomnia	0 (0.0)	1 (4.8)
Myringitis	0 (0.0)	1 (4.8)
Nasopharyngitis	0 (0.0)	1 (4.8)
Proteinuria	0 (0.0)	1 (4.8)
Vaginal hemorrhage	0 (0.0)	1 (4.8)
Vomiting	0 (0.0)	1 (4.8)
Total	9 (39.1)	13 (61.9)

[a] Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase.

biphasic decline and the rate of reductions in HBV DNA levels during the second phase of viral clearance. The findings reported here are similar to those of early viral kinetic analyses of entecavir recently reported for an open-label, multicenter, phase IIIb study by Leung et al. In that study, entecavir led to an early and superior reduction in HBV DNA levels compared with adefovir in nucleoside-naïve HBeAg-positive patients with CHB (19). Patients treated with entecavir demonstrated mean reductions in serum HBV DNA levels of 6.23 $\log_{10}$ copies/ml at week 12; these reductions were evident by week 2. Consistent with data from the previous report, we observed a >3.5-fold reduction from the baseline in mean serum HBV DNA levels with entecavir; this reduction was evident as early as day 2 of treatment and was sustained through week 12 of treatment. Additionally, the mean estimate of efficacy (99.2%) of entecavir in our study is consistent with the reported mean estimate of efficacy (99.9%) reported by Leung et al. despite the use of a slightly different mathematical model in the latter study (19). In the absence of direct comparative studies, and based on evidence from viral kinetic analyses, it is tempting to speculate that the superior efficacy of telbivudine over adefovir in clinical trials with patients with HBeAg-positive CHB (3) may be due to a greater early antiviral activity of telbivudine.

Results of the detailed kinetic analysis performed in the current study are also consistent with the findings of a recently reported study by Shi et al. comparing the short-term efficacies and safety of telbivudine and entecavir at weeks 12 and 24 of treatment of HBeAg-positive Chinese patients with CHB (32). For this patient population, no difference in the mean reduction in HBV DNA levels was observed between the treatment groups (5.27 copies/ml with telbivudine and 5.36 copies/ml with entecavir), and the proportions of patients with normalized ALT levels were similar (52.5% with telbivudine and 60.0% with entecavir; $P > 0.05$) at week 12. In contrast to our findings, Shi et al. reported no difference in the rates of undetectable serum HBV DNA levels between the groups at treatment week 12. In the current study, although no difference in viral kinetics and the suppression of HBV DNA was observed, a higher proportion of patients treated with entecavir achieved undetectable viremia at treatment week 12. These differences may be related to the small patient population in our study and the observation from the GLOBE trial that the rate of PCR negativity for the telbivudine-treated patients increased markedly between weeks 12 and 24 of treatment (23). The findings of Shi et al. further extend the analysis presented in the current study by demonstrating the value of the early and profound suppression of HBV DNA on the rate of HBeAg seroconversion. Although HBeAg seroconversion occurs rarely during the first 3 months of oral NA therapy for most HBeAg-positive patients, Shi et al. reported higher rates of HBeAg seroconversion in telbivudine-treated patients than in entecavir-treated patients at treatment weeks 12 (20% versus 5%; $P = 0.043$) and 24 (27.5% versus 17.5%; $P > 0.05$) (32). The high rate of early HBeAg seroconversion observed by Shi et al. may be indicative of an additional mechanism of action for telbivudine in the suppression of HBV replication. Preliminary data suggest that telbivudine exerts a dual antiviral effect by stimulating the host immune system and directly inhibiting viral replication (8, 37). It was previously postulated that this putative benefit may contribute to the high HBeAg seroconversion rates observed for long-term follow-up studies of continuous telbivudine treatment for patients with HBeAg-positive CHB (12, 13). The effect of telbivudine on the host immune response and the magnitude of HBeAg seroconversion merits further investigation.

The early and profound suppression of serum HBV DNA with oral NAs correlates with sustained viral suppression below the limits of detection, improvement of liver histology, and low rates of antiviral resistance (22, 24, 29, 39, 40). Yuen et al. previously demonstrated the importance of HBV DNA suppression by week 24 of treatment to prevent the emergence of antiviral resistance with lamivudine (39). More recently, those authors also reported that HBV DNA levels of <2,000 copies/ml at treatment week 4 are predictive of outcomes at 5 years for lamivudine-treated patients (38). A rapid decline in HBV viral load (≥3 log copies/ml) at week 12 was also reported to be an important predictor of the subsequent response to adefovir therapy (9). In the GLOBE trial, the largest trial with patients with CHB, patients with undetectable HBV DNA levels at week 12 or 24 had better outcomes at 2 years than did patients with HBV DNA levels of >4 $\log_{10}$ copies/ml (40). A multivariate analysis from GLOBE, including baseline variables and treatment response at week 24, found that undetectable HBV DNA after 24 weeks of telbivudine treatment was the strongest predictor for all 2-year clinical end points (40). In that analysis, treatment week 12 was too early to determine the treatment response or predict 2-year outcomes with telbivudine (23). Our findings are consistent with those from the GLOBE trial, as the majority of patients receiving telbivudine and entecavir had detectable HBV DNA levels at treatment week 12. Head-to-head studies are needed to further evaluate the predictive value of the early virological response with telbivudine, entecavir, and tenofovir alone or in combination to assess the potential benefit of *de novo* combination treatment.

The findings from this study indicate that based on the 12-week treatment response, telbivudine and entecavir are well tolerated, demonstrate equivalent potency in the suppression of early HBV replication, and exhibit similar viral kinetic profiles for treatment-naïve patients with HBeAg-positive compensated CHB. This information may assist physicians in their choice of antiviral agent for the treatment of patients with CHB. Additionally, the assessment of viral kinetic responses of patients with different clinical characteristics that may influence the response to treatment, such as HBV genotype and decompensated CHB, may further refine the results from this first head-to-head comparison of telbivudine and entecavir.

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