A Dose-Finding Study of Once-Daily Oral Telbivudine in HBeAg-Positive Patients With Chronic Hepatitis B Virus Infection

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Current therapy for chronic hepatitis B is suboptimal as a result of limited durable response rates, cumulative viral resistance, and/or poor tolerability. Telbivudine has potent antiviral activity against hepatitis B virus (HBV) *in vitro* and in the woodchuck model and has a promising preclinical safety profile. In this first clinical study of telbivudine, safety, antiviral activity, and pharmacokinetics were assessed in 43 adults with hepatitis B e antigen–positive chronic hepatitis B. This placebo-controlled dose-escalation trial investigated 6 telbivudine daily dosing levels (25, 50, 100, 200, 400, and 800 mg/d); treatment was given for 4 weeks, with 12 weeks' follow-up. Serum HBV DNA levels were monitored via quantitative polymerase chain reaction. The results indicate that telbivudine was well tolerated at all dosing levels, with no dose-related or treatment-related clinical or laboratory adverse events. telbivudine plasma pharmacokinetics were dose-proportional within the studied dose range. Marked dose-related antiviral activity was evident, with a maximum at telbivudine doses of 400 mg/d or more. In the 800mg/d cohort, the mean HBV DNA reduction was 3.75 $\log_{10}$ copies/mL at week 4, comprising a 99.98% reduction in serum viral load. Correspondingly, posttreatment return of viral load was slowest in the high-dose groups. Viral dynamic analyses suggested a high degree of efficiency of inhibition of HBV replication by telbivudine and helped refine selection of the optimal dose. In conclusion, these results support expanded clinical studies of this new agent for the treatment of hepatitis B. (HEPATOLOGY 2004;40:719–726.)

Hepatitis B remains a significant global health problem. An estimated 350 million individuals with chronic hepatitis B virus (HBV) infection are at risk of progressive necroinflammatory liver disease.[1,2] Natural history studies indicate a link between level of persistent HBV replication and disease progression to cirrhosis and/or hepatocellular carcinoma.[3–7] Correspondingly, numerous clinical studies of interferon and anti-HBV nucleosides/nucleotides indicate that prolonged suppression of HBV replication can reverse hepatic necroinflammation, and several studies suggest that longer-term patient outcomes can improve with therapy.[8–12]

Alpha-interferon, lamivudine, and adefovir dipivoxil have been extensively studied for the treatment of patients with chronic hepatitis B. These agents allow clinical management of many patients, but overall efficacy and safety remain suboptimal. Interferon induces hepatitis B e antigen (HBeAg) seroconversion in perhaps 20%–35% of patients with pretreatment alanine aminotransferase (ALT) levels exceeding twice the upper limit of normal.[1,2,9] However, most patients fail to respond to interferon, and some patients are not eligible for interferon treatment because of advanced disease or concurrent medical conditions. Frequent side effects and a requirement for self-injection tend to limit enthusiasm for interferon among patients and physicians.

Orally bioavailable agents that directly inhibit HBV replication have improved treatment options for patients with hepatitis B. Treatment with lamivudine or adefovir suppresses viremia by 3–4 $\log_{10}$ after 1 year, reduces hepatic necroinflammatory activity, and increases the probability of HBeAg seroconversion.[1,10,11] Lamivudine is

Abbreviations: HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase.

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generally well tolerated except for occasional ALT flares associated with discontinuation of treatment or viral breakthrough.[10,13,14] With adefovir, a 12% HBeAg seroconversion rate was reported after 48 weeks of treatment in HBeAg-positive patients,[11] and while generally well tolerated at 10 mg/d, adefovir carries warnings for potentially severe posttreatment flares and potential nephrotoxicity.

As expected for any antimicrobial agent, drug-resistant HBV variants have been selected in patients receiving prolonged treatment with lamivudine or adefovir. The cumulative risk for emergence of lamivudine-resistant (YMDD-mutant) HBV strains increases to 50% or more with 3 years of therapy in high-viremic HBeAg-positive patients.[15] Drug resistance occurs most often in patients with suboptimal initial viral suppression.[13,16,17] Although loss of therapeutic response is variable, liver disease may resume after viral breakthrough with lamivudine, occasionally with severe ALT flares.

Adefovir resistance is associated with the emergence of N236T and possibly A181V mutant HBV strains.[18–20] The 2-year incidence of adefovir resistance appears to be relatively infrequent in lower-viremic HBeAg-negative patients.[19] The development of resistance is also associated with increased ALT levels.

Further optimization of antiviral therapy for hepatitis B is needed to improve rates of durable response with safe, orally bioavailable agents. More potent agents that offer more profound HBV suppression may improve results for key efficacy end points such as HBeAg seroconversion, ALT normalization, and liver histology while minimizing drug resistance.[13,17]

Telbivudine (β-L-2′-deoxythymidine, telbivudine) is an orally-bioavailable L-nucleoside with potent and specific antiviral activity against HBV *in vitro* and in animal models.[21,22] In woodchucks, telbivudine suppresses serum HBV DNA by over 8 $\log_{10}$ copies/mL with 4 weeks of treatment.[22] telbivudine has no significant effect on human DNA polymerases α, β, or γ or on mitochondrial function, and there have been no adverse findings in preclinical animal toxicology studies at chronic dosing up to 1,000 mg/kg/d.[21,22]

This report describes a human phase I/II clinical trial of telbivudine. The study was a double-blind, placebo-controlled dose-escalation study of the safety, antiviral efficacy, and pharmacokinetics over 4 weeks of 6 different daily doses of telbivudine in HBeAg-positive patients with compensated chronic hepatitis B.

Patients and Methods

Study Design. The dose-escalation design involved sequential investigation of 6 daily doses of telbivudine (25 mg, 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg). At each dosing level, a cohort of 7 eligible patients with HBeAg-positive chronic hepatitis B was randomized at a ratio of 6:1 to receive telbivudine or matching placebo once daily. Patients were treated for 4 weeks and followed for an additional 12 weeks after discontinuation of treatment.

Pharmacokinetics of plasma telbivudine were evaluated over 8 hours following the first dose and at steady state between weeks 2 and 4. Plasma levels of telbivudine were measured with a validated high performance liquid chromatographic assay with mass spectrometric detection. The assay lower limit of quantitation was 0.1 μg/mL, and intra- and interday precision and accuracy (percent deviation) were below 10%. Blood samples for viral load measurement were obtained at baseline and weekly through week 8, and thereafter every other week through week 16. Serum HBV was quantified at the central study laboratory using the COBAS Amplicor polymerase chain reaction assay for HBV DNA (Roche Diagnostics, Branchburg, NJ) (lower limit of detection: 300 genome copies/mL).

The 6 different dosing levels were investigated sequentially. When at least 6 patients from a dose cohort completed treatment through week 4, escalation to the next higher dose was discussed and agreed upon by the study investigators if one of the following criteria were met: (1) at least 6 of 7 patients within the cohort had completed treatment through week 4 without a protocol-defined dose-limiting toxicity or (2) 2 additional patients had completed treatment through week 4 if 2 of the initial 7 patients had developed a dose-limiting toxicity. Dose-limiting toxicities were specified in the protocol as: a prothrombin time of more than 3 seconds above control; a serum albumin level less than 30 g/L; grade 3 or greater elevation of total bilirubin, creatinine, or amylase; grade 4 ALT elevation ($>10 \times$ baseline) with any evidence of hepatic insufficiency; or any other grade 4 clinical or laboratory toxicity considered by the investigator to be at least reasonably or possibly related to the study drug.

Patients. Eligible patients included adults 18 years of age or older, with chronic hepatitis B documented by the presence of hepatitis B surface antigen in the serum for at least 6 months prior to the start of the study. The minimum serum HBV DNA level was 1×10^7 copies/mL or more at screening. Patients were documented to be HBeAg-positive for at least 1 month with serum ALT levels below 5 times the upper limit of normal.

Exclusion criteria included: history or evidence of decompensated liver disease; pregnancy or breast-feeding; unwillingness to use a barrier method of contraception; coinfection with hepatitis C or D virus or human immu-

nodeficiency virus; any prior nucleoside analogue treatment; treatment with interferon or corticosteroids within 6 months of baseline; a hemoglobin level of less than 6.2 mmol/L; an absolute neutrophil count of less than 1.5×10^9/L; a platelet count of less than 100×10^9/L; a creatinine level of more than 133 μmol/L; serum amylase and pancreatic amylase/lipase levels of more than 1.5 times the upper limit of normal; an alpha-fetoprotein level of more than 20 ng/mL with follow-up ultrasonographic features of hepatocellular carcinoma; other clinically important diseases; or current abuse of alcohol or illicit drugs.

Written informed consent was obtained from all patients. The trial was approved by the Ethics Committees of the two trial centers and was conducted under Good Clinical Practice standards, with local regulatory authorization and Investigational New Drug authorization by the U.S. Food and Drug Administration.

Data Analyses. For efficacy analysis, the evaluable population was defined as all patients who received the study drug for the entire 4-week treatment period, were at least 90% compliant with the study drug (determined by pill count) and had no major protocol violations. The population for safety assessments included all patients who received any amount of the study drug.

Single-dose and steady-state telbivudine pharmacokinetics were analyzed using a noncompartmental approach. Evaluated pharmacokinetic parameters included maximum plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration time curve from time zero to infinity ($AUC_{0-\infty}$), and observed terminal phase half-life (T½).

Serum HBV DNA levels and changes from baseline in HBV DNA levels over time were tabulated by treatment group using descriptive statistics. Virological response was defined as a 2 log or more decrease in serum HBV DNA levels during the 4-week treatment period. The proportion of virological responders was analyzed at each time point for each treatment group.

Using data on quantitative changes in serum HBV DNA levels, the anti-HBV dose–response relationship for telbivudine was analyzed in three ways: (1) descriptive statistics for changes in serum HBV DNA levels; (2) predicted maximal effect (E_{max}) modeling; and (3) viral dynamics analyses. E_{max} modeling has been used to assess the quantitative dose–response relationship for a number of antiviral and oncology agents.[23–25] E_{max} modeling estimates the drug dose needed to achieve a given level of antiviral effect, in a defined time period, as a proportion of E_{max}. In the E_{max} equation, $E = \text{Dose} \times E_{max}/(ED_{50} + \text{Dose})$. Here E is the antiviral activity defined, for each dose, as the median percent viral load reduction at week 4. For each patient, percent reduction $= (V_0 - V_{week4})/V_0$, where V_0 and V_{week4} are the viral loads at baseline and week 4, respectively. ED_{50} is the telbivudine dose producing a 50% viral load reduction. E_{max} is defined as the expected maximum effect (complete loss of detectable serum HBV DNA) and is set to 1. In this study, ED_{50} was estimated by fitting the model to median percent viral load reductions from the 6 dose cohorts, using the GLM procedure of SAS (version 8.0, SAS Institute Inc, Cary, NC).

Viral dynamic modeling has been used to characterize plasma viral load changes that occur after initiation of hepatitis B treatment.[26–29] Previous reports indicated a biphasic response to antiviral therapy: a rapid first-phase reduction in serum HBV DNA, reflecting clearance of plasma virions and inhibition of HBV replication, and a second, more prolonged phase of HBV DNA decline corresponding to net loss of HBV-infected cells.[26–28] For the viral dynamic analyses, two approaches were taken: a model-independent approach assessed dose-related HBV DNA reductions during week 1 and weeks 2–4 of treatment, and a viral dynamics model utilized equations previously described.[27] The modeling equation is given as:

$$V(t) = V_0 e^{-ut} + \frac{(1-\epsilon)uV_0}{(u-a)}(e^{-at} - e^{-ut})$$

In this equation, $V(t)$ = viral load at time (t), V_0 = viral load at baseline, a = the clearance rate constant of infected cells, u = the clearance rate constant free virions, and ϵ = the degree of inhibition of viral replication. Model estimates of virion (u) and infected cell (a) clearance rate constants were used to calculate the half-life of virions (as 0.693/u) and infected cells (as 0.693/a).

Results

Patient Population

Treatment was completed satisfactorily for all telbivudine recipients with no dose-limiting toxicities at all dosing levels; therefore, all dose escalations were unanimously approved by the clinical investigators and study team. In total, 43 HBeAg-positive patients (75% males) were enrolled, with a median age of 34 years (range: 20–64). One patient withdrew voluntarily from the trial at week 2 and was thus excluded from the efficacy-evaluable population and replaced per protocol. On decoding, this patient was found to have been receiving placebo. One patient met all protocol-mandated criteria for inclusion in the efficacy evaluable population, but pharmacokinetic analysis showed minimal plasma telbivudine levels. When queried, the patient acknowledged discarding his study medication and was therefore excluded from the efficacy-evaluable population.

Table 1. Baseline Demographic and Disease Characteristics

		telbivudine						
	Placebo	25 mg/d	50 mg/d	100 mg/d	200 mg/d	400 mg/d	800 mg/d	All telbivudine
N	7	6	6	6	6	6	6	36
Age (mean years ± SD)	30.9 ± 9.8	31.7 ± 7.5	32.0 ± 8.4	38.7 ± 11.6	29.4 ± 7.8	32.5 ± 10.0	41.8 ± 16.5	34.3 ± 10.9
Sex (% male)	86	83	50	83	67	67	100	75
Weight (mean kg ± SD)	68.0 ± 13.4	72.5 ± 17.2	63.3 ± 17.2	59.4 ± 17.2	62.6 ± 9.1	63.6 ± 8.5	66.3 ± 9.9	64.6 ± 13.4
Serum HBV DNA (mean $\log_{10}$ copies/mL ± SD)	8.3 ± 1.2	9.9 ± 1.1	8.8 ± 0.8	9.0 ± 1.0	7.9 ± 0.8	8.2 ± 0.6	8.7 ± 1.3	8.8 ± 1.1
Serum ALT (median IU/mL, range)	33 (27–78)	68 (22–75)	30 (24–139)	63 (21–163)	81 (20–169)	126 (22–545)	52 (31–243)	58 (20–545)

NOTE. All patients were ethnically Asian and seropositive for hepatitis B surface antigen and hepatitis B e antigen.

Table 1 lists baseline demographic and disease characteristics. The placebo group represents the pooled placebo patients, one from each dose cohort. All telbivudine groups and the placebo group were comparable with regard to baseline characteristics. All patients were ethnically Asian.

Pharmacokinetics

telbivudine was rapidly absorbed after oral administration with a mean T_{max} ranging from 0.8–2.8 hours postdosing across cohorts. Single dose and steady-state C_{max} and $AUC_{0-\infty}$ ranged from 0.20–5.46 μg/mL and 1.1–47.5 μg/mL × hour, respectively. Both measures of systemic exposure increased linearly with the administered doses. At steady state, values for C_{max} and $AUC_{0-\infty}$ were approximately 50% higher than those obtained after a single dose, which is indicative of a sustained plasma exposure with a once-daily regimen. The elimination of telbivudine from plasma was apparently monophasic over the 8-hour sampling period, with an observed mean terminal half-life ($t_{1/2}$) ranging from 2.5–5.0 hours across cohorts.

Virological Response

A pronounced decline of serum HBV DNA occurred in all telbivudine-treated patients over the 4-week treatment period (Fig. 1). At 4 weeks, treatment with 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg telbivudine resulted in mean decreases from baseline of 2.5, 2.68, 3.19, 2.89, 3.63, and 3.75 $\log_{10}$ copies/mL, respectively, compared with a mean 0.13 $\log_{10}$ decrease in the placebo group (see Fig. 1). The lower-than-expected HBV DNA reduction for the 200mg/d cohort, compared with the results for the 100mg/d cohort, may have been due to the lower baseline viremia level in the 200mg/d group (*i.e.*, 1.1 $\log_{10}$ lower than the 100mg/d group).

Only one telbivudine-treated patient failed to achieve protocol-defined virological response (*i.e.*, a 2 $\log_{10}$ or greater reduction in serum HBV DNA levels at week 4). This patient was in the lowest-dose group (25 mg/d) and exhibited a 1.2 log reduction in HBV DNA at week 4. No placebo recipients achieved a 2 $\log_{10}$ reduction in HBV DNA levels; therefore, virological response was significantly more common in telbivudine recipients (97% vs. 0%, $P < .0001$). Posttreatment, serum HBV DNA levels returned toward baseline levels in an overall dose-related manner, with the slowest return of viremia in the 400 and 800mg/d dose groups (see Fig. 1).

Additional Assessments of Dose–Response Relationship

E_{max} *Model.* Figure 2 illustrates the relationship between telbivudine dose and reduction of serum HBV DNA levels at week 4 in the fitted E_{max} model. The empiric dose–response data from this trial conformed well to the fitted E_{max} equation and indicated that there was a marked increase in antiviral effect at doses of 25–200 mg/d, with diminishing increases in effect at doses above 200 mg/d. The E_{max} curve in Fig. 2 also clearly illustrates

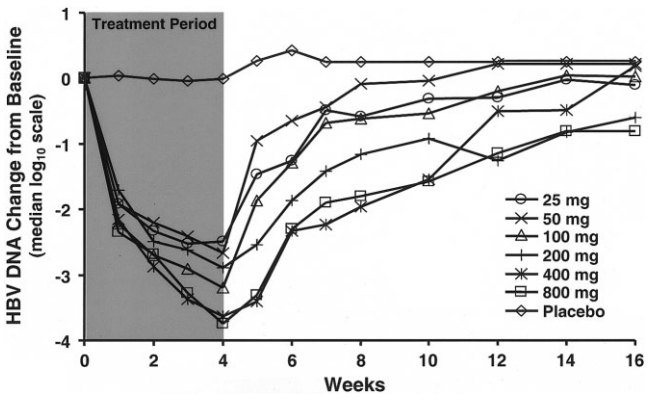

Fig. 1. Effect of telbivudine treatment on serum HBV DNA levels. Serum HBV DNA levels were assessed during and after telbivudine treatment using the Roche COBAS Amplicor assay (Roche Diagnostics, Branchburg, NJ). Doses of 25–800 mg once daily were compared with placebo. HBV, hepatitis B virus.

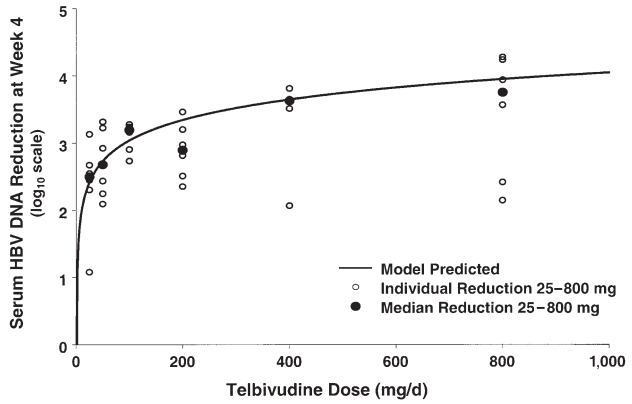

Fig. 2. E_{max} modeling of dose-response data. An E_{max} model in the form of E = dose × E_{max}/(ED_{50} + Dose) was fitted to the median percent viral load reduction at week 4 (percent reduction = (V_0 − V_{week4})/V_0 × 100%) from the 25–800-mg dose cohorts. E_{max} was fixed to 100%, the expected maximum antiviral effect. For presentation purposes, percent reduction was converted to log_{10} reduction. HBV, hepatitis B virus.

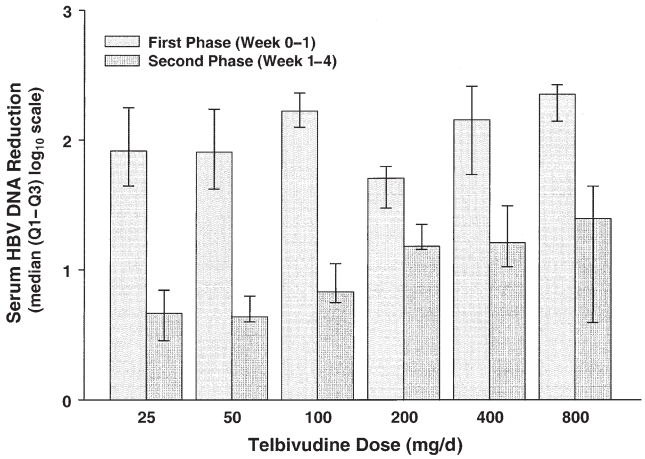

Fig. 3. Serum HBV DNA reductions from baseline by response phase. Serum HBV DNA reductions were determined for each telbivudine dose level. Light grey bars indicate the reduction from pretreatment baseline that occurred during first-phase viral clearance (week 0–1). Dark grey bars indicate the incremental reduction from baseline that occurred during second-phase viral clearance (weeks 1–4). HBV, hepatitis B virus.

that near-maximal reductions of viral load are achieved with telbivudine doses in the range of 400–800 mg/d.

Viral Dynamics. All doses of telbivudine resulted in steep, approximately 2 log_{10} reductions in viral load in the first week of treatment, corresponding to first-phase clearance in a viral dynamics perspective (see Fig. 1). In contrast, viral load reductions observed between day 7 and the end of treatment showed a more gradual downward slope, suggesting that viral clearance was entering a second phase. In the model-independent, empiric analysis of HBV DNA reductions during telbivudine treatment, dose-proportionality was evident for the second phase (weeks 2–4) but not for the first phase of clearance (week 1), as shown in Fig. 3. This observation may have been due to the fact that all telbivudine doses were quite active (>2 log_{10} HBV DNA reduction in week 1). In any case, it suggested a potential use of viral dynamics analyses for fine resolution of dose–response relationships.

Application of the viral dynamics model to viral load data yielded an estimated half-life of free virions of 17.7–32.8 hours, which is consistent with the approximately 1-day half-life for HBV virions previously reported.[26–29] The substantial overlap between dosing groups suggested that the estimated half-life for free virions was independent of dose. However, the estimated half-life of infected cells (a) exhibited an inverse relationship to dose, decreasing from 17.2 days at the 25mg/d dose to 8.4 days at the 800-mg/d dose (Fig. 4). This relationship confirms the similar results obtained with the model-independent approach described in the previous section. Importantly, the dose proportionality for estimates of infected cell half-life was more clearly evident up to the 400 and 800mg/d dosing levels in the quantitative viral dynamic modeling, which is consistent with the E_{max} results.

Safety

Telbivudine was well tolerated at all doses. There were no serious adverse events and no dose-limiting toxicities. All reported adverse events were mild or moderate in intensity, and most were not attributed to study treatment. Treatment-emergent adverse events (those occurring on treatment and up to 24 hours after completion of treatment)—regardless of whether or not they were attributed to the study drug—are listed in Table 2. There was no appreciable pattern of dose-related or treatment-related

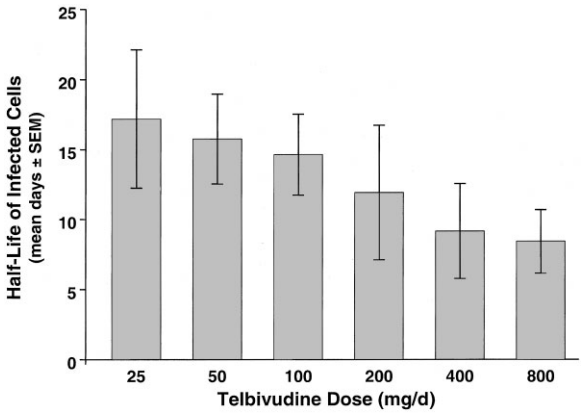

Fig. 4. Estimated half-life of infected cells—viral dynamic model. A viral dynamic model[27] was fitted to individual viral load data obtained during the 4-week treatment period for the patients in the 6 telbivudine dosing cohorts (25, 50, 100, 200, 400, 800 mg/d). Model estimates of virion (u) and infected cell (a) clearance rate constant were used to calculate half-lives of 0.693/u and 0.693/a, respectively.

Table 2. Number of Patients With Adverse Events During Treatment, Regardless of Attributability

Adverse Event	Placebo (n = 7)	Telbivudine 25 mg (n = 6)	50 mg (n = 6)	100 mg (n = 6)	200 mg (n = 6)	400 mg (n = 6)	800 mg (n = 6)	All telbivudine (n = 36)
At least one adverse event	1	1	3	2	1	2	4	13
Influenza			1	2		1	3	7
Cough			1				1	2
Pyrexia			1			1		2
Sore throat			1	1				2
Acne						1		1
Back pain						1		1
Dry mouth			1					1
Fatigue							1	1
Haemaluria present							1	1
Headache			1					1
Hypercholesterolaemia					1			1
Menstruation irregular		1						1
Sinusitis							1	1
Vertigo						1		1
Appetite decreased	1							
Dyspepsia	1							
Insomnia	1							
Nausea	1							

(telbivudine vs. placebo) clinical adverse events or laboratory abnormalities.

Overall, the safety profile of telbivudine appeared comparable to placebo. During treatment, increases in aminotransferases were the most commonly observed grade 1 and 2 laboratory abnormalities. These were observed at similar rates in the telbivudine and placebo patients. No grade 4 abnormalities were seen during treatment, and the only grade 3 abnormalities observed were an episode of hyperglycemia in a placebo patient and an elevated serum GGT level in a patient receiving 400 mg telbivudine. During follow-up, one patient each in the 50-mg/d and 100-mg/d treatment groups experienced transient grade 3 elevation in aminotransferases.

Discussion

In this first human trial, telbivudine induced marked dose-proportional suppression of serum HBV DNA levels in HBeAg-positive adults with chronic hepatitis B, with mean serum HBV DNA reductions of 3.63–3.75 $\log_{10}$ copies/mL after 4 weeks at dosags of 400–800 mg/d. Most patients achieved at least a 2 $\log_{10}$ reduction in HBV DNA levels in the first week of treatment. This high degree of viral suppression appears to be unprecedented for an anti-HBV agent after 4 weeks of treatment.[11,30,31]

Telbivudine was absorbed rapidly after oral dosing with C_{max} reached within 1–3 hours. Pharmacokinetic parameters of drug exposure were dose-proportional in the studied dose range. telbivudine exhibited an apparent single distribution/elimination phase with a short observed terminal half-life. Plasma telbivudine exposure was higher at steady state than after a single dose, suggesting the presence of a second, slower elimination phase, which was not observed in this study because of the short (8-hour) sampling period. Recent healthy volunteer studies with sampling periods up to 32 hours confirmed the existence of a second elimination phase that has an observed half-life of 12–20 hours (unpublished data). The long half-life of plasma telbivudine ensures a sustained exposure to the drug when dosed once daily.

Descriptive statistics (mean and median values) for serum HBV DNA reductions in this study indicated that telbivudine doses above 400 mg/d are associated with maximal antiviral effects for this agent. This conclusion was supported by 2 additional analyses of the telbivudine dose–response relationship: E_{max} pharmacodynamic modeling and viral dynamic modeling. Interestingly, in the viral dynamic analyses there was no discernible effect of increasing telbivudine dose on serum HBV DNA suppression during the first week of treatment, representing the first phase of viral clearance. The steep HBV DNA decline observed with all doses in the first week of telbivudine treatment suggests that in viral dynamics terms, the efficiency of telbivudine-mediated inhibition of HBV replication is very high. During the second phase of viral clearance, corresponding to weeks 2–4 of treatment in this study, there was a noticeable influence of telbivudine dose on the observed increment in antiviral effect. In the model-independent analysis of HBV DNA reduction data, second-phase viral clearance appeared to increase progressively up to doses of 200 mg/d.

Viral dynamics modeling confirmed the model-independent findings and supported an empiric use of viral dynamics modeling for dose optimization. The viral dynamics model assumes that no productively infected cells are produced during therapy.[27] However, with incomplete inhibition of viral replication, viral reinfection undoubtedly persists in proportion to residual viral load, which in turn is influenced by the dose of the antiviral drug. In this circumstance, model-derived estimates of infected cell half-life are higher than the true intrinsic half-life, and estimates of infected cell half-life decrease as viral suppression increases and hepatocyte reinfection is reduced. In this paradigm, therefore, the optimal dose of telbivudine would be the dose associated with the minimum estimate of infected cell half-life. It is important to note, however, that this empiric use of viral dynamics was not designed to assess the potential effect of telbivudine or various virus and host factors on the true half-life of HBV-infected cells.

In this study, application of the quantitative viral dynamics model produced an estimated half-life of plasma virions of approximately 1 day, and virion half-life appeared to be independent of dose and comparable to data previously reported.[26–29] In contrast, viral suppression during the second phase of viral clearance was clearly dose-related up to doses of 400–800 mg/d, according to both viral dynamics modeling and model-independent analyses. Estimates of the half-life of infected cells were progressively shorter with higher doses of telbivudine, decreasing to 8.4 days at the highest (800 mg/d) dose. This value is somewhat lower than published estimates obtained from treatment with lamivudine, adefovir, and entecavir,[26–29] although caution is warranted in comparing these calculations because of potentially different methods and patient populations in the previous studies. Head-to-head clinical comparisons could establish the relative antiviral potencies and clinical efficacies of telbivudine and other agents in patients with chronic hepatitis B.

Using the E_{max} model applied to these study data, a 600mg/d dose of telbivudine (which was not used in this study) is predicted to produce an approximately 50% (*ca.* 0.2 $\log_{10}$) greater antiviral effect than the 400mg/d dose, and nearly as good an effect as the 800mg/d dose (only 0.1 $\log_{10}$ less), while preserving a convenient, easily palatable tablet size. Based on the complementary E_{max} and viral dynamics analyses of the telbivudine dose–response relationship, doses of 400 and 600 mg/d were selected for further evaluation in a phase IIb clinical trial.

The higher doses of telbivudine tested here (400 and 800 mg/d) were associated with a slower rebound of HBV DNA on cessation of therapy. This delayed return of viremia at high dosing levels is consistent with loss of infected cells during treatment, as suggested by the viral dynamics analyses. The clinical importance of this observation has yet to be established; however, a more gradual return of virus may lead to less frequent and/or less severe immunological rebound when the drug is withdrawn following longer-term therapy.

Telbivudine was well tolerated over 4 weeks of treatment throughout the dose range tested. These clinical results are consistent with the encouraging results of preclinical toxicology studies and with mode of action studies that showed a high degree of selectivity of telbivudine-triphosphate for the HBV polymerase, compared with cellular DNA polymerases.[21,22]

In conclusion, this study showed telbivudine to be well tolerated and capable of highly potent suppression of HBV replication in patients with chronic hepatitis B. Ongoing phase IIb and phase III trials will determine if the profound antiviral effects of telbivudine are associated with correspondingly improved clinical outcomes.

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