

Expert Opinion

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Telbivudine: a new nucleoside analogue for the treatment of chronic hepatitis B

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Telbivudine, β -L-2'-deoxythymidine (LdT), is a new β -L-nucleoside analogue with potent inhibitory activity against the hepatitis B virus. In *in vitro* studies and animal models, telbivudine has demonstrated potent and specific antiviral activity against hepatitis B. Additionally, in preclinical animal toxicology studies, telbivudine showed no adverse side effects or adverse effects on mitochondrial function. The promising results of the early *in vitro* and animal telbivudine studies prompted the development and initiation of Phase I and II human clinical trials. The Phase I clinical study demonstrated that end-of-treatment virological response rates were better for telbivudine recipients at multiple dosing levels as compared with placebo patients. The subsequent Phase IIb human clinical study demonstrated superior antiviral efficacy of telbivudine, significantly better ALT normalisation and better hepatitis B e-antigen loss as compared with lamivudine. Telbivudine was well tolerated with no identified safety issues. Virological breakthrough with telbivudine was significantly lower than with lamivudine.

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1. Background

Chronic hepatitis B virus (HBV) infection constitutes a significant worldwide problem. It is estimated that 5% of the world's population is infected, which comprises ~ 350 million individuals [1]. It is anticipated that nearly 1 million individuals will die of HBV-related complications annually. Epidemiological studies have established a possible link between the level of persistent viral replication and disease progression to cirrhosis and hepatocellular carcinoma (HCC) [2-6]. In support of this, viral suppression can reverse necroinflammation and may improve long-term patient outcomes in HBV [7-11].

IFN- α was the first FDA-approved medication for the treatment of chronic HBV. With a defined duration of therapy, IFN- α can induce hepatitis B e-antigen (HBeAg) seroconversion in 20 – 35% of the patients [11-13]. Patients with active hepatitis, as documented by an alanine aminotransferase (ALT) elevation twice the upper limit of normal, respond the best to IFN- α . However, IFN- α therapy is contraindicated in patients with advanced liver disease or significant co-morbid medical conditions. Additionally, the multiple adverse side effects associated with therapy and the need for self-injection has limited overall enthusiasm in IFN- α for the treatment of chronic HBV.

Lamivudine, an oral nucleoside analogue, was the second FDA-approved medication for the treatment of chronic HBV. In clinical studies, lamivudine decreased HBV viral levels by 3 – 4 \log_{10} after 1 year of therapy, normalised serum ALT in 72% of patients and increased the probability of HBeAg seroconversion by ~ 12% over placebo [7,13]. Unfortunately, viral breakthrough remains problematic with lamivudine [7,14,15]. The incidence of lamivudine resistance ranges from 16 to 32% after 1 year of therapy to as high as 58% with 2 – 3 years of therapy in high-viraemic

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HBV patients [7,16-18]. Viral breakthrough most often occurs in patients with suboptimal initial viral suppression [15,19,20]. Furthermore, disease progression has been shown to resume following viral breakthrough.

Adefovir dipivoxil, an oral nucleotide analogue, was approved by the FDA for the treatment of chronic HBV in September 2003. An HBeAg seroconversion rate of 12% was reported after 48 weeks of treatment in HBeAg-positive chronic HBV patients [9]. Adefovir dipivoxil was also effective in suppressing HBV viral levels to < 400 copies/ml in 51% of HBeAg-negative chronic HBV patients after 48 weeks of therapy [21]. Viral breakthrough on adefovir dipivoxil occurred infrequently and was associated with the emergence of N236T and possibly A181V mutant HBV [22]. Resistance development was associated with increased ALT levels. Adefovir dipivoxil is also associated with potential nephrotoxicity.

Newer antiviral nucleoside analogues are currently undergoing evaluation in clinical trials for the treatment of chronic HBV patients. The aim of the current paper is to introduce and review current information on the nucleoside analogue telbivudine for the treatment of chronic HBV.

2. Molecular structure

The chemical name of telbivudine is β -L-2'-deoxythymidine (LdT) or 1-(2-deoxy- β -L-ribofuranosyl)-5-methyluracil. Telbivudine is an unsubstituted, unmodified β -L-2'-nucleoside and is one of the natural nucleosides in the β -L-configuration, which also include β -L-2'-deoxycytidine (LdC) and β -L-2'-deoxyadenosine (LdA) [23,24]. Telbivudine was the first compound of this series. Telbivudine exhibits no chemical modifications and differs from its natural nucleoside only with respect to the stoichiometric relationship of its sugar and base moieties, the L-configuration versus the D-configuration (Figure 1). Seifer *et al.* demonstrated differences between compounds in the β -L-nucleoside series using strand-specific Southern hybridisation assays utilising cell culture-derived intracellular HBV nucleocapsids, and a panel of hepadnaviral *in vitro* polymerase assays [25]. They showed that telbivudine and LdC differed in their mode of action despite structural similarities, and that telbivudine differed in its mode of action compared with lamivudine. Additionally, telbivudine exerted a preferential effect on HBV second-strand (DNA-dependent) DNA synthesis compared with LdC and lamivudine, both of which strongly inhibited first-strand (RNA-dependent) DNA synthesis and depending on the assay, the preferential effect varied from two- to six-fold.

The β -L-nucleoside analogues, telbivudine, LdC and LdA, are the most potent and specific inhibitors of HBV replication in the HepG 2.2.15 cell culture assays [24,26]. Bryant *et al.* performed an extensive structure-activity analysis on telbivudine [24]. Indeed, structure-activity relationships (SAR) analyses indicate telbivudine to be the most potent inhibitor of HBV replication with a half-maximal effective concentration (EC_{50}) of 0.19 μ M in HepG 2.2.15 cells [26]. The key to the

HBV specificity of telbivudine is the hydroxyl (-OH) group in the 3'-position of the β -L-2'-deoxyribose sugar (Figure 1), which confers unique anti-HBV activity [24]. Loss or substitution of the 3'-OH results in loss of HBV antiviral activity, suggesting an intimate role of the 3'-OH group in establishing affinity with the HBV polymerase [24,26].

Telbivudine must be activated by phosphorylation and is efficiently metabolised to the 5'-triphosphate derivatives in HepG2 and human hepatocytes in primary culture [24]. Telbivudine is metabolised to the active triphosphate (LdTTP) species via redundant kinases (i.e., deoxycytidine kinase and thymidine kinase 1 among others) [26]. The intracellular 5'-triphosphorylated form is responsible for inhibition of the viral polymerase and is the most potent form with a median inhibitory concentration (IC_{50}) of 0.24 μ M, as demonstrated by inhibition of woodchuck hepatitis virus (WHV) DNA polymerase [24]. Inhibition of viral replication occurs via a direct interaction of the 5'-triphosphate metabolite of telbivudine with the viral polymerase [26]. This inhibition probably occurs at the stage of reverse transcription of pregenomic RNA and/or the stage of synthesis of HBV second-strand DNA [24,26]. This inhibition results in obligate chain termination of DNA synthesis by internal incorporation of L-dNMP into viral DNA. The exact mechanism is unknown, and other mechanisms cannot be excluded, including inhibition of RNase H activity, priming of reverse transcriptase, or coordination of intracellular virion assembly, and these other potential mechanisms are currently being studied [24,26]. The triphosphate species, however, is not a substrate for human DNA polymerase- α , - β or - γ , even at concentrations as high as 100 mM [24,26].

The β -L-nucleosides are orally bioavailable agents and have been shown to have potent, selective and specific activity against hepadnaviruses. However, the β -L-nucleosides are not active or have only limited activity against other viruses such as herpes simplex virus (HSV) or human immunodeficiency virus (HIV). Although the activity of telbivudine in patients with lamivudine resistance has not been evaluated clinically, the β -L-nucleosides are not effective against some lamivudine (YMDD)-resistant mutants *in vitro*.

In *in vitro* studies and animal models, telbivudine has demonstrated potent and specific antiviral activity against HBV. In the woodchuck model, telbivudine achieves a > 8 \log_{10} copies/ml drop in serum WHV DNA level with 4 weeks of treatment [26]. In addition, in preclinical animal toxicology studies at doses \leq 1000 mg/kg/day, telbivudine showed no adverse side effects or adverse effects on mitochondrial function [24,26]. *In vitro*, telbivudine is highly specific for HBV, with no significant activity against other viruses such as HSV or HIV.

3. Predinical *in vitro* and animal studies

In *in vitro* analysis, β -L-2'-deoxynucleosides inhibit hepadnaviruses HBV, duck HBV and woodchuck WHV, but

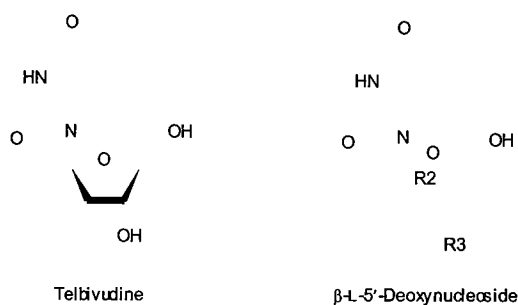


Figure 1. Chemical structure of telbivudine and LdT Series β-L-5'-deoxynucleoside. A hydroxyl group (-OH) at position R3 confers specific HBV antiviral activity for telbivudine.

HBV: Hepatitis B virus; LdT: β-L-2'-deoxythymidine.

do not inhibit HIV-1, HSV-1 or HSV-2, varicella-zoster virus, Epstein-Barr virus, cytomegalovirus, adenovirus-1, influenza type A and B viruses, measles virus, para-influenza virus type 3, rhinovirus type 5, or respiratory syncytial virus type A at concentrations as high as 200 μM [24,26]. *In vitro* studies have shown that telbivudine inhibits HBV replication. Bryant *et al.* [24] analysed and quantitated HBV inhibition with telbivudine using the human hepatoma 2.2.15 cell line and found that the EC₅₀ of telbivudine was 0.19 μM.

Telbivudine is efficiently converted to LdTTP, which peaks at 30 μM at 24 h [26]. In HepG2 cells, telbivudine was extensively phosphorylated, and its 5'-triphosphate metabolite was the predominant species by 24 h (ranging from 7.43 to 27.7 pmol/10⁶ cells), compared with LdTMP (8.09 pmol/10⁶ cells) and LdTDP (2.87 pmol/10⁶ cells) [27]. In primary human hepatocytes, telbivudine was again extensively phosphorylated predominantly to the 5'-triphosphate species in 24 h (16.5 pmol/10⁶ cells), compared with LdTMP (15.2 pmol/10⁶ cells) and LdTDP (2.49 pmol/10⁶ cells) [27]. The intracellular half-life (t_{1/2}) of telbivudine in HepG2 cells is ≥ 15 h [27]; therefore, even after 24 h, the intracellular concentration of telbivudine remains well above the IC₅₀ as previously described in addition to the IC₅₀ found in studies for the WHV DNA polymerase [26]. In the cynomolgous monkey, telbivudine declined in a bi-exponential manner, to eventually reach undetectable levels by 8 h [26], suggesting that telbivudine clearance is variable and higher in monkeys (t_{1/2} = 1.5 h) compared with woodchucks (t_{1/2} = 3.5 h).

Telbivudine was nontoxic in *in vitro* studies. Specifically, in human DNA polymerase assays, telbivudine had no cytotoxic effect on human hepatoma cell line 2.2.15, primary human peripheral blood monocyte (PBM) cells, human foreskin fibroblasts, or other mammalian and avian cell types even at concentrations > 100 μM [24,26].

Human bone marrow (BM) stem cells in primary culture serve as good predictors of potential nucleoside-induced hepatotoxicity [24,26]. Telbivudine did not affect BM stem cells (colony-forming unit of granulocyte-macrophage [CFU-GM] or burst-forming

units-erythroid [BFU-E] precursors) in clonogenic assays, suggesting that telbivudine is highly selective and that its phosphorylated metabolite is nontoxic *in vivo* [24,26]. In genotoxicity assays, telbivudine was not mutagenic in the *Salmonella typhimurium* nor the *Escherichia coli* plates at concentrations as high as 5000 μg/plate [26]. In the Chinese hamster ovary (CHO) assay, no chromosomal aberrations were noted after exposure to telbivudine at concentrations as high as 5000 μg/plate [26]. In the mouse micronucleus assay, telbivudine was not clastogenic at concentrations ≤ 2000 mg/kg [26].

Mitochondrial toxicity, seen with many HIV nucleoside analogues (zidovudine, stavudine, didanosine and zalcitabine) and previously with fialuridine (FIAU), manifests as decreased mitochondrial DNA (mtDNA) and/or altered mitochondrial morphology, which leads to increased lactic acidosis and hepatic steatosis [26]. β-L-2'-deoxynucleosides have not been shown to affect mitochondrial function or morphology. Bryant *et al.* performed mitochondrial and cytotoxicity studies with telbivudine in HepG2 cells [24]. Telbivudine, when exposed to HepG2 cells for 14 days, did not reveal any adverse effect on lactic acid production, mtDNA content or mitochondrial morphology.

On the basis of the promising *in vitro* studies, subsequent animal studies were initiated. Standing *et al.* performed acute (single-dose) and subacute (28-day) dosing studies in several animals [26]. In Sprague-Dawley rats and cynomolgous monkeys, there were no telbivudine-related effects on body weight, food consumption, or biochemical tests seen during the acute and subacute dosing studies. In addition, no macroscopic or microscopic pathological abnormalities were seen. Based on these rat and monkey studies, the 'no observed adverse effect level' (NOAEL) of telbivudine was determined to be 2000 mg/kg. In the woodchuck HBV model, there were again no telbivudine-related adverse effects in weight loss or biochemical tests during acute and subacute studies [26]. In addition, end-of-treatment liver biopsies showed no evidence of hepatic steatosis in woodchucks.

Bridges *et al.* studied the effects of telbivudine orally administered to animals for longer duration [28]. No overt signs of toxicity were observed in rats given telbivudine for 6 months or monkeys given telbivudine for 9 months at maximal doses of 1000 mg/kg/day. No drug-related effects were observed with regard to body weight, food consumption or biochemical serum tests. At necropsy, there were no changes in gross organ weight nor macroscopic or microscopic lesions noted that were attributable to telbivudine. Accordingly, on the basis of these observations, the NOAEL for telbivudine was 1000 mg/kg/day in rats and monkeys. Further long-term follow-up observations revealed no teratogenicity in rats and rabbits. Specifically, no telbivudine-related fetal effects on body weight, sex distribution, or external, skeletal or visceral malformations were noted. Thus, the NOAEL for fetal development was also 1000 mg/kg/day.

The WHV model has been shown to be a good predictor of candidate antiviral drug activity and safety of nucleoside

analogues for the treatment of human HBV [24,26]. Despite slower oral absorption and lower bioavailability in woodchucks as compared with monkeys, volume of distribution was identical in monkeys and woodchucks [26]. Strandring *et al.* studied the efficacy of telbivudine administered to woodchucks at a dose of 10 mg/kg/day for 4 weeks with 8 weeks of follow up [26]. WHV DNA levels were measured using branched DNA (bDNA) and polymerase chain reaction (PCR)-based assays. WHV DNA levels decreased by 8 log₁₀ while on treatment, but returned to near baseline levels during follow up. Interestingly, a decline in WHV surface antigen was also noted. The decline in WHV surface antigen paralleled the decline in WHV DNA level, but the onset of decline lagged a week behind WHV DNA decline. WHV surface antigen levels continued to decline after drug removal prior to rebounding. This finding is compelling, as in the woodchuck HBV model, WHV surface antigen decline has been correlated with clearance of covalently closed-circular DNA (ccDNA) in infected hepatocytes.

Bryant *et al.* studied the efficacy of telbivudine administered to woodchucks at a dose of 10 mg/kg/day for 12 weeks [24]. WHV DNA level determinations demonstrated significant inhibition within the first few days of therapy, which was maintained throughout the treatment period. Telbivudine induced a nearly 8 log₁₀ decrease in WHV DNA, though rebound to near baseline levels occurred within 4 – 8 weeks after drug withdrawal. In comparison, lamivudine at equivalent doses demonstrated only a 0.5 log₁₀ decline in WHV DNA during the same time period, probably due to the lower oral bioavailability of lamivudine and phosphorylation in woodchucks [29,30]. Thus, in the woodchuck model, Bryant *et al.* concluded that unmodified telbivudine was well tolerated and caused no drug-related toxicity through 12 weeks of treatment and 4 weeks of follow up.

Strandring *et al.* studied the efficacy of combination therapy with telbivudine and LdC in the woodchuck model [26]. In combination, 1 mg/kg/day of both drugs reduced WHV DNA by as much as 11 log₁₀, which is significantly more than either drug alone. Following drug removal, the time to rebound was significantly delayed with combination therapy. In addition, WHV surface antigen also dramatically decreased with combination therapy.

4. Human clinical studies

The promising results of the early *in vitro* and animal telbivudine studies prompted the development and initiation of Phase I and II human clinical trials. In the initial Phase I/II 5-dose-escalation study, an excellent safety profile prompted a protocol amendment to include a sixth dose of telbivudine at 800 mg/day. In this study, six healthy men and six healthy women were administered telbivudine for 7 days in escalating doses. Pharmacokinetic (PK) and safety data were the primary study goals. An ancillary study was performed to assess potential drug interactions between telbivudine 200 mg/day and lamivudine

100 mg/day with a 14-day treatment course in 16 healthy subjects. Zhou *et al.* presented the results of these preliminary studies [31]. Telbivudine was rapidly absorbed, reaching maximal concentration with 0.75 – 3.13 h. Peak plasma concentrations after first-dose administration and at steady-state increased linearly with increasing dose, and the steady-state drug levels were ~ 1.5 times the drug level after first-dose administration. In addition, for doses > 100 mg/day, substantially higher predosing trough drug levels were seen, suggesting a slower second-phase elimination for telbivudine. No serious dose-related adverse effects were seen in all telbivudine patients compared with placebo, and there was no apparent accumulation of telbivudine after steady-state was achieved. Finally, in the ancillary study, there were no telbivudine–lamivudine interactions noted with regard to PK and safety.

The excellent results achieved in the early human PK and safety studies led to the Phase I/II clinical trial in patients with chronic HBV. Lai *et al.* published the results of this human Phase I/II clinical trial in 2004 [32]. This double-blind, placebo-controlled dose-escalation study was the first human trial with telbivudine in patients with chronic HBV. All the patients in this study were Asians with compensated HBeAg-positive chronic HBV. Baseline HBV viral levels were > 7 log₁₀ copies/ml in all patients. The safety, PKs and antiviral efficacy of telbivudine administered over 4 weeks at sequentially escalating doses of 25, 50, 100, 200, 400 and 800 mg/day were studied. Patients were randomised 6:1 (telbivudine:placebo), thus, in total, 43 patients (6 telbivudine patients at each dosing level + 6 placebo patients + 1 patient who declined the trial after enrolment) were enrolled. At all doses, telbivudine was well tolerated and exhibited no serious clinical adverse events, dose-limiting toxicities or laboratory abnormalities. Telbivudine was rapidly absorbed following oral administration, reaching peak serum levels from 0.8 to 2.8 h post dosing. Steady-state drug levels were 50% higher than post single-dose levels, indicative of sustained plasma levels with a once-daily dosing regimen. Drug elimination from plasma was monophasic over an 8-h sampling period with a mean terminal t_{1/2} ranging from 2.5 to 5 h.

The week 4 end-of-treatment (ETR) virological response rates were better for all telbivudine recipients in all dosing levels as compared with placebo patients (Figure 2). The mean decrease of HBV DNA from baseline with telbivudine 25, 50, 100, 200, 400 and 800 mg, and placebo was 2.5, 2.68, 3.19, 2.89, 3.63 and 3.75 log₁₀, respectively, compared with placebo, 0.13 log₁₀. Indeed, no placebo patients achieved a 2 log₁₀ decline in HBV DNA. Thus, overall ETR virological response was significantly greater for all telbivudine recipients (97%) as compared with placebo (0%) (p < 0.0001). All doses of telbivudine lead to steep 2 log₁₀ reductions, corresponding to first-phase viral clearance. In follow up, 16-week post-treatment HBV DNA levels showed a return towards baseline in an overall dose-related manner with the slowest return occurring in the 400 and 800 mg/day doses, although a 16-week sustained

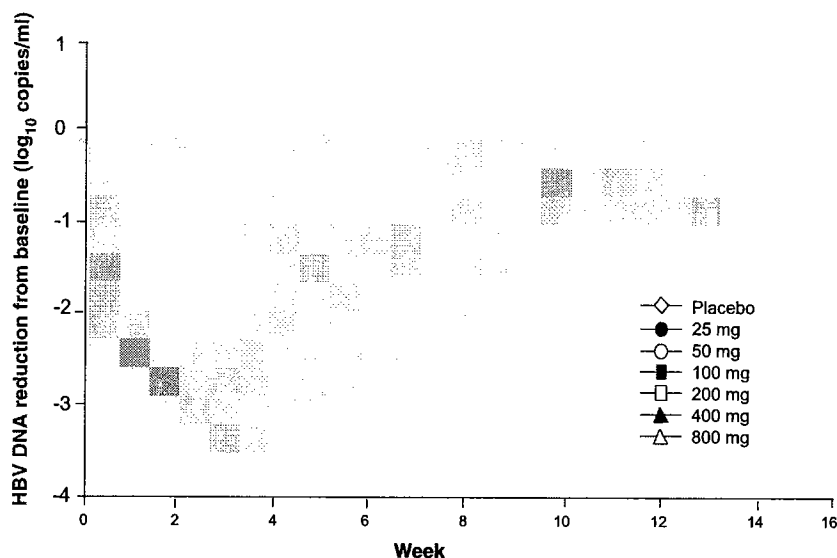


Figure 2. Viral suppression in a Phase I/II dose-escalating study.

HBV: Hepatitis B virus.

virological suppression of $\sim 1 \log_{10}$ below baseline was seen with the 200- and 800-mg/day telbivudine doses (Figure 2).

Neumann *et al.* performed an exploratory analysis of the data from the Phase I/II dose-escalating trial to evaluate changes in HBV viraemia during the 4-week treatment phase, then the 8-week follow-up phase [33]. A total of 36 treatment-naïve, HBeAg-positive patients were ultimately included in this analysis. HBV DNA viral levels were quantified using the Roche COBASTM PCR assay. A biphasic decline in HBV viraemia was noted with the inflection occurring during the second week of therapy. The week-1 slope, which represents the first-phase viral decline, was consistent with the known $t_{1/2}$ of HBV virions of 12–24 h and was not dependent on the dose of telbivudine (telbivudine effectiveness = 98.8% at doses of 25–200 mg and 99.4% at doses of 400–800 mg). However, the slower second-phase decline was significantly dose dependent ($0.27 \log_{10}/\text{week}$ for 25–100 mg and $0.41 \log_{10}/\text{week}$ for 200–800 mg) ($p < 0.01$). The authors speculated that the current viral kinetics model did not adequately explain the slower second-phase decline and postulated a third functional compartment of latently infected cells that contributes to this slower decline. Finally, they found that post-treatment viral relapse was significantly delayed in those receiving the 200- to 800-mg doses of telbivudine ($p < 0.002$).

The encouraging results obtained in the Phase I/II clinical trials led to the design and initiation of the multi-centre, international Phase IIb human clinical trial. This study included 104 patients with HBeAg-positive chronic HBV enrolled from five countries and began accrual in early 2001. The study design was a double-blind, randomised format

comparing five treatment arms (telbivudine 400 and 600 mg/day, telbivudine 400 mg/day plus lamivudine 100 mg/day, telbivudine 600 mg/day plus lamivudine 100 mg/day, and lamivudine 100 mg/day). Lai *et al.* performed a week-12 interim analysis [34]. There were no reported serious adverse events or discontinuations for adverse events. Furthermore, there were no treatment-related clinical adverse events or laboratory abnormalities. The week 12 analysis revealed greater HBV DNA suppression in the telbivudine-containing arms (mean decline $4.3 - 5.1 \log_{10}$) versus the lamivudine monotherapy arm (mean decline $3.9 \log_{10}$), and this difference in viral suppression widened after week 4, indicating better second-phase HBV clearance in the telbivudine-containing arms.

The 1-year efficacy and safety results of the Phase IIb clinical study have been presented by several investigators [35-37]. As previously stated, 104 patients from five countries enrolled. All study treatment arms were well tolerated. HBV DNA suppression at week 52 was significantly greater for the telbivudine monotherapy and telbivudine plus lamivudine treatment arms than the lamivudine monotherapy arm (6.09 and 5.99 versus $4.57 \log_{10}$, respectively; Figure 3). HBV DNA detected by PCR at week 52 was significantly greater for the telbivudine monotherapy arms (64%) as compared with the lamivudine monotherapy arm (32%), but interestingly, the combination of telbivudine plus lamivudine (49%) was worse than telbivudine monotherapy (64%). ALT normalisation at week 52 was significantly better for telbivudine monotherapy (86%) as compared with lamivudine monotherapy (63%), and again, telbivudine monotherapy was better than the combination of telbivudine plus lamivudine (78%) at

Telbivudine

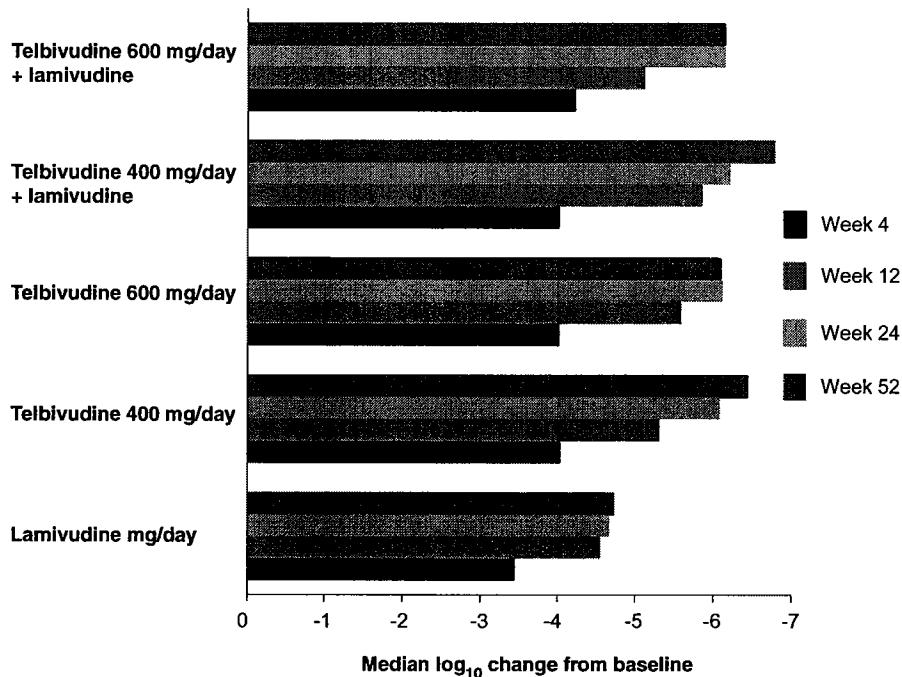


Figure 3. 52-Week viral suppression in a Phase IIb study.

normalising ALT. HBeAg loss at week 52 was better in the telbivudine monotherapy arms (33%) as compared with lamivudine monotherapy (28%) or the combination of telbivudine plus lamivudine (17%). For the telbivudine-containing treatment arms, antiviral efficacy at week 52 was equivalent between Asian and non-Asian patients. Thus, the 1-year antiviral results of the Phase IIb study indicate that telbivudine monotherapy is better than lamivudine monotherapy throughout; however, no advantage is evident using combination therapy with telbivudine plus lamivudine over telbivudine alone. The explanation for this observed antagonism with combination therapy is unknown, but competition between the nucleoside analogues, given their similar chemical structures, is theoretically possible. Data regarding durability of HBeAg loss and HBeAg seroconversion is currently unavailable, as post-treatment follow up from the Phase IIb study is ongoing.

At week 52 in the Phase IIb study, viral breakthrough occurred in 11 patients. Of the patients receiving lamivudine monotherapy, 4 of 19 (21.1%) developed viral breakthrough; two patients developed the M204I mutation, one patient developed the L180M and M204V mutations, and one patient developed delayed YMDD mutant formation on retesting 8 weeks later. Of the patients receiving telbivudine monotherapy, 2 of 44 (4.5%) developed viral breakthrough, which is significantly fewer compared with lamivudine ($p < 0.05$). The M204I mutation was detected in both these patients. Finally, 5 of 41 (12.2%) patients receiving combination therapy with telbivudine plus lamivudine developed viral

breakthrough: three patients developed the M204I mutation, one patient developed the L180M and M204V mutations, and one patient had wild-type virus suggesting possible non-compliance with therapy. To date, no *in vitro* studies of susceptibility of telbivudine-resistant HBV to other antiviral agents have been performed.

Lai *et al.* and Poynard *et al.* performed exploratory analysis of pooled data from the Phase IIb clinical trial to evaluate viral suppression and how it predicts HBeAg loss, ALT normalisation, and resistance development [38,39]. The week-24 HBV DNA level was found to be predictive of the clinical outcomes above (Table 1). Specifically, HBeAg loss was greatest when the week-24 HBV DNA was < 1000 copies/ml. In addition, no viral breakthrough was seen in patients achieving HBV DNA < 1000 copies/ml by week 24. Similar trends were also noted for HBV DNA levels at week 12 and 16.

Telbivudine is predominantly cleared by the kidneys with minimal metabolism and elimination via the hepatic route. Zhou *et al.* [40] studied the PK profile of telbivudine administered to patients with renal impairment and hepatic impairment with regard to peak concentration and overall drug exposure (area under the curve [AUC]). A total of 29 patients were enrolled into the renal impairment study: 8 normal patients, 8 patients with mild renal impairment (creatinine clearance [CrCl] = 50 – 80 ml/min), seven patients with moderate renal impairment (CrCl = 30 – 49 ml/min), and 6 patients with severe renal impairment (CrCl < 29 ml/min). A total of 24 patients were enrolled into the hepatic impairment study: six normal patients, six patients with Child-Pugh A

Table 1. Results of exploratory analysis of pooled data from a Phase III study.

Serum HBV DNA level at week 24 (copies/ml)	Percent response at week 52			
	BQL	QL – 10 ³	10 ³ – 10 ⁴	> 10 ⁴
HBeAg response	47	38	10	7
PCR non-detectability of HBV DNA	100	62	23	7
ALT normalisation	90	88	71	56
Viral breakthrough	0	0	19	26

BQL: Below quantitation level (< 200 copies/ml by COBAS Amplicor PCR); HBeAg: Hepatitis B e-antigen; HBV: Hepatitis B virus; PCR: Polymerase chain reaction; QL: quantitation level.

disease, six patients with Child-Pugh B disease, and six patients with Child-Pugh C disease. In patients with renal impairment, the AUC was two- to threefold higher in subjects with moderate and severe renal impairment when dosing was normalised to 600 mg/day, suggesting that telbivudine needs to be dose reduced in renally impaired patients either by reducing daily dose or increasing dosing interval. However, the results showed the PK profiles were comparable in subjects with normal and impaired hepatic function. This latter finding has prompted a clinical trial evaluating the antiviral efficacy of telbivudine in patients with mildly decompensated hepatitis B cirrhosis, which is currently ongoing.

5. Expert opinion

Telbivudine is one of the new β -L-nucleoside analogues with potent antiviral activity against HBV. Telbivudine is an obligate chain terminator, incorporating into HBV DNA, and exerts a preferential effect on second-strand DNA-dependent DNA synthesis. The 5'-triphosphate metabolite of telbivudine is the active compound, and although it exerts potent antiviral activity against HBV, it does not serve as a substrate for human polymerase, thus predicting no *in vivo* toxicity. In the woodchuck model, telbivudine achieves a > 8 log₁₀ copies/ml drop in serum WHV DNA level with 4 weeks of

treatment. In addition, in preclinical animal toxicology studies at doses \geq 1000 mg/kg/day, telbivudine showed no adverse side effects or mitochondrial toxicity.

The promising results of the early *in vitro* and animal studies paved the way for Phase III human clinical trials. These studies demonstrated an excellent safety profile for telbivudine with a favourable PK profile. Subsequent Phase IIB human clinical studies demonstrated superior antiviral efficacy of telbivudine, with a > 6 log₁₀ viral suppression, significantly better ALT normalisation and better HBeAg loss as compared with lamivudine. Telbivudine was well tolerated with no identified safety issues. Virological breakthrough with telbivudine was also significantly lower than lamivudine. Based on these preliminary findings, telbivudine may be considered a viable alternative to lamivudine as first-line therapy for patients with chronic HBV in the future.

On the basis of this promising data, a large, multicentre, international Phase III study of telbivudine was initiated and is currently ongoing. This study (designated GLOBE) has enrolled 1370 patients with compensated HBeAg-positive or HBeAg-negative chronic HBV. In addition, exploratory analysis of telbivudine in patients with impaired hepatic function has been promising, and a randomised, controlled clinical study of telbivudine in patients with mildly decompensated cirrhosis is currently ongoing.

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