

Telbivudine (LdT) Therapy of Chronic Hepatitis B

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Introduction

Telbivudine (LdT) is a cytosine nucleoside analogue with potent *in vitro* activity against the hepatitis B virus (HBV) and no activity against HIV or herpes viruses. Preclinical studies have shown that telbivudine has an excellent safety profile with no evidence of mitochondrial toxicity or genotoxicity. Pharmacokinetic and antiviral dose-response studies support the use of a single daily dose of 600 mg per day. Phase II studies showed that telbivudine is associated with significantly greater HBV suppression than lamivudine over the first year of treatment and beyond.

Clinical Trials of Telbivudine

Telbivudine has been evaluated in a large, randomized international phase III trial, referred to as the GLOBE Trial, in which the antiviral and clinical efficacy of telbivudine (LdT) are compared to that of lamivudine over a 2 year period. The primary data analysis is at 1 year, with second-year data targeted to longer assessments of efficacy and safety and to the post-treatment durability of HBeAg responses. This trial enrolled 1,367 patients with chronic hepatitis B, stratified by HBeAg status. To be eligible, patients had to have serum HBV DNA levels $> 10^6$ copies/ml by the COBAS AmpliCor™ PCR assay, ALT 1.3 to 10 times ULN, and compensated liver disease. The primary endpoint was a composite serologic endpoint termed Therapeutic Response (HBV DNA $< 10^5$ copies/mL, with either ALT normalization or HBeAg loss). Key secondary outcomes measures were histologic response, suppression of HBV DNA to $\leq 10^5$ copies/ml, clearance of HBV DNA to PCR-undetectable levels (< 300 copies/mL), normalization of ALT, and loss of HBeAg. At 1 year, viral resistance (based upon genotypic screening) developed in 2.6% of patients on telbivudine and 8.2% on lamivudine in the overall study population. The table below summarizes the results of the primary data analysis at 1 year.

	No.	Therapeutic Response	Histologic Response	HBV DNA Reduction (log copies)	PCR Undetectable	ALT Normal	HBeAg Loss
Telbivudine [#]	458	75%	65%	6.5	60%	77%	26%
Lamivudine [#]	463	67%	56%	5.5	40%	75%	23%
Telbivudine [*]	222	75%	66%	5.2	88%	74%	N/A
Lamivudine [*]	224	77%	66%	4.4	71%	79%	N/A

[#] HBeAg-positive; ^{*} HBeAg-negative; N/A, not applicable.

Two other large studies of telbivudine have been carried out. These include a second Phase III comparative trial of telbivudine and lamivudine in 332 Chinese patients using a similar study design to the GLOBE Trial. The rate of Therapeutic Response here was 87% with telbivudine and 64% with lamivudine, and telbivudine showed significantly greater ALT normalization (89 vs. 76%), HBeAg loss (31 vs. 20%), and antiviral efficacy (HBV DNA reduction and PCR-nondetectability) than lamivudine.

The therapeutic effects of telbivudine have also been compared to those of adefovir in a randomized controlled trial of 133 patients with HBeAg-positive chronic hepatitis B (see below for interim results at week 24):

	No.	HBV DNA Reduction (log copies)	HBV DNA <10 ⁵ copies/ml	PCR Undetectable	ALT Normal	HBeAg Loss
Telbivudine	44	6.4	95%	39%	61%	16%
Adefovir	89	5.1	57%	12%	63%	10%

Conclusions

Telbivudine has significantly greater antiviral efficacy than either lamivudine or adefovir in patients with chronic hepatitis B, with less primary treatment failure. The use of telbivudine is associated with a low rate of resistance at 1 year.

Research Needs

1. Telbivudine should be tested in combination with other (non-cytosine) nucleos(t)ide analogues, such as PMEAs with complementary resistance mechanisms, to evaluate possible enhanced efficacy and diminished resistance.
2. The optimal duration of therapy for hepatitis B is not known, for telbivudine and other nucleoside-nucleotide anti-HBV agents. The preclinical toxicologic profile of telbivudine appears favorable, and clinical safety to date appears good, but are there any safety issues associated with long-term use of telbivudine, other than risk of breakthrough due to viral resistance?
3. Does the profound and rapid reduction of HBV DNA associated with telbivudine translate to enhanced clinical effect? Telbivudine achieved significantly greater effects on several clinical efficacy parameters at one year, in the GLOBE study and the mainland China study, but additional data will be helpful to define the long-term clinical efficacy advantages of telbivudine.

References

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