

# A review of the use of telbivudine in the treatment of chronic hepatitis B

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**Abstract:** Chronic hepatitis B is a major global health problem. Fortunately there are currently a number of agents licensed in most countries to treat chronic hepatitis B, including the oral nucleos(t)ide agents lamivudine, adefovir, entecavir, telbivudine, and tenofovir, and the immune modulators interferon alfa-2b and peginterferon alfa-2a. Large clinical trials have shown potent suppression of viral replication with telbivudine and a good safety profile, and superiority of telbivudine over lamivudine and adefovir in head-to-head trials. The potential of resistance with use of telbivudine mandates careful monitoring and on-treatment strategies to avoid or reduce the development of resistance. This review article provides an overview of the pharmacokinetics, clinical efficacy, safety, and resistance profile of telbivudine.

**Keywords:** chronic hepatitis B, HBV, treatment of chronic hepatitis B, telbivudine

## Introduction

Chronic hepatitis B (CHB) is a global health problem, with more than 350 million people infected with hepatitis B virus (HBV) and a prevalence rate as high as 15% in certain endemic regions.<sup>1</sup> The worldwide mortality attributed to HBV infection is estimated at 620,000 deaths per year.<sup>2</sup> In the United States, it is estimated that approximately 1.4 million people are chronically infected with HBV.<sup>3</sup> CHB is associated with significant morbidity and mortality, and progression of liver disease can lead to cirrhosis with decompensation and hepatocellular carcinoma. With the high continuous flux of immigrant populations, even countries with previously low endemic rates of chronic HBV infection will be confronted with long-term management issues associated with CHB.

Medical management of CHB has evolved dramatically in the past decade. Increased knowledge of the natural history of chronic HBV infection and clinical data demonstrating improved outcomes with medical interventions have led to publication of various treatment guidelines aimed at providing direction regarding initiation and on-treatment management of antiviral therapy and monitoring of outcome measures.<sup>4–7</sup> The overall goals are timely initiation of antiviral therapy in the setting of active liver disease and management of available medications to achieve suppression of viral replication to low or undetectable levels, normalization of alanine aminotransferase (ALT) levels, and improvement in liver histologic changes. Additional therapeutic endpoints include loss of hepatitis B e antigen (HBeAg) with seroconversion to antibody to HBeAg (anti-HBe) in HBeAg-positive patients, avoidance of antiviral drug resistance, and ultimately, loss of hepatitis B surface antigen (HBsAg) with seroconversion to antibody to HBsAg (anti-HBs). Antiviral therapy has been shown to not only control HBV replication and improve underlying liver histology, but also reduce the likelihood of clinical deterioration in the setting of advanced fibrosis and the incidence of hepatocellular carcinoma.<sup>8–13</sup> Furthermore, in the post-transplant setting, optimal viral suppression is important for the prevention of recurrent CHB and potential loss of the transplanted organ.<sup>14</sup>

There are currently seven antiviral agents approved for treatment of CHB in the United States by the Food and Drug Administration (FDA) and also licensed in many other countries. Of the non-oral agents, which are immune modulators, the two approved medications are interferon alfa-2b and peginterferon alfa-2a. However, use of interferon-based therapy has several potential limitations,

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particularly a significant side effect profile and requirement for injections.<sup>7</sup> Advantages of interferon-based therapy are a fixed duration of treatment, absence of resistance and a higher rate of HBsAg loss and seroconversion compared with the oral agents. Since 1998, various oral nucleos(t)ide analogues have changed the treatment landscape for HBeAg-positive and HBeAg-negative CHB. The five FDA-approved oral agents are lamivudine, adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate. Although these agents have a somewhat similar mechanism of action and tolerability, they differ in terms of their potency at suppressing viral replication, genetic barrier to resistance, and rates HBeAg and HBsAg loss and seroconversion. As one of the newer nucleoside analogues, telbivudine received FDA approval in 2006 and is one of only two oral agents along with tenofovir labeled as pregnancy category risk B.<sup>15</sup> In this review, we will present the preclinical background, including the drug mechanism of action and preclinical data, as well as the clinical trials that led to the approval of telbivudine for the treatment of CHB.

## Preclinical Background

Telbivudine ( $\beta$ -L-2'-deoxythymidine,  $C_{10}H_{14}N_2O_5$ ) is an unmodified nucleoside analogue of naturally-occurring thymidine. This compound differs from thymidine only in the spatial orientation of a hydroxyl group (-OH) on the sugar moiety. Telbivudine was first identified as a potential antiviral agent using a drug screen selecting for molecules with selective activity against HBV in HepG2.2.15 tissue culture assays. *In vitro* assays demonstrated selective and strong inhibition of HBV replication without any appreciable activity against human immunodeficiency virus (HIV) or other non-hepadnaviridae viruses. In addition, the same hydroxyl group that distinguishes telbivudine from thymidine plays an important structural role that mediates the effectiveness of telbivudine against members of the hepadnavirus family. Furthermore, telbivudine appears to have no activity against cellular polymerases at concentrations up to 100  $\mu$ M. Once inside the cell, inhibition of HBV DNA polymerase occurs at a low  $IC_{50}$  of 0.19  $\mu$ M. A pharmacokinetics study revealed a long intracellular half-life of 14 hours, which allows telbivudine to remain above its therapeutic  $IC_{50}$  and be amenable to daily dosing.<sup>16</sup>

Upon entry into the hepatocyte, telbivudine undergoes phosphorylation by nonselective thymidine kinases and eventually is converted to its active form, telbivudine 5'-triphosphate. HBV has one key enzyme endowed with multiple vital functions including RNA- and DNA-dependent DNA polymerase activity.<sup>17</sup> It is believed that telbivudine competes with thymidine, the natural substrate, for binding to the active side of the viral DNA polymerase. Incorporation of telbivudine 5'-triphosphate causes DNA chain termination and inhibition of viral replication. *In vitro* studies have demonstrated that telbivudine preferentially inhibits DNA-dependent DNA replication, which occurs following RNA-dependent DNA synthesis, a step inhibited by lamivudine.<sup>18</sup> Modeling of drug-polymerase interactions revealed that telbivudine occupies the active site of the DNA polymerase in a manner structurally and energetically similar to the natural substrate,<sup>19</sup> consistent with its high affinity.

Preclinical evaluation for drug cytotoxicity was quite favorable. *In vitro* cellular toxicity assays showed little or no evidence of cytotoxicity at concentrations greater than 100  $\mu$ M in various cellular systems including hepatocyte cell lines, peripheral blood mononuclear cells, and primary cultures of human bone marrow stem cells (which are used as a gauge for hematotoxicity). Similarly, there was no effect on mitochondrial DNA content or alterations in the morphology in hepatocyte cell line following short-term exposure. Animal studies designed to access acute and subacute toxicity were equally encouraging. In addition, there was no evidence of mutagenicity in animal and cell line studies, a finding that was in agreement with previous experiments documenting that telbivudine was not a substrate of cellular DNA polymerases.<sup>20,21</sup>

Since the approval of telbivudine for treatment of CHB, a number of studies have analyzed the development of drug resistance and cross-resistance to other available nucleoside and nucleotide analogues. For example, cellular assays have shown that telbivudine maintains its antiviral activity in hepatocyte cell lines that harbor replicating HBV bearing resistant mutation(s) to tenofovir (A194T), adefovir (N236T, A181V) and lamivudine (M204V). However, these studies also reveal that telbivudine has decreased antiviral activity against HBV bearing a common lamivudine-resistant mutant, L180M/M204V/I.<sup>22</sup> Overall, preclinical evaluation has demonstrated the safety

of telbivudine in cell line and animal systems and the current focus is to seek an understanding of the development of telbivudine resistance and its implication to management of CHB.

## Telbivudine Pharmacokinetics

The initial trial designed to study pharmacokinetics and determine optimal dosing for telbivudine also provided early evidence of its potency. A phase I/IIa clinical trial, conducted over a four-week period with a 12-week follow-up, compared escalating drug dosages (50 mg to 900 mg) to a placebo control. The population targeted was HBeAg-positive patients with elevated serum HBV DNA levels at least 7 log<sub>10</sub> copies/mL and serum ALT below 5 times the upper limit of normal (ULN).<sup>23</sup> Findings from this study provided important data on drug pharmacokinetics, tolerability, and short-term efficacy including: 1) rapid absorption and reaching maximal plasma concentration an average of three hours following oral administration; 2) absence of serious adverse events and no dose limiting toxicities at all dosing levels; and 3) a favorable early virologic response following short-term drug exposure. There was a dose-dependent decrease in serum HBV DNA with the highest level of suppression of 3.75 log<sub>10</sub> copies/mL in the highest dose group by week 4. Not only did the higher dosages result in better viral suppression, they also demonstrated the slowest return of viremia to pretreatment levels following cessation of treatment. All telbivudine dosages showed a steep reduction in the viral load in the first week of treatment with a gradual downward decline through the end of therapy at week 4. This is similar to the biphasic response with other antiviral therapies where the rapid first-phase drop in serum HBV DNA corresponds to reduction in clearance of plasma virions and inhibition of replication, whereas the second phase represents net loss of HBV infected cells.<sup>23</sup>

Telbivudine is predominately cleared unchanged by the kidneys. There is very little hepatic metabolism and no dose adjustment is required for hepatic impairment.<sup>24,25</sup> Drug clearance is linearly proportional to renal function and occurs mainly through passive diffusion. Consequently, dose adjustment is required for patients with significant renal disease. In patients with creatinine clearance between 30 and 49 mL/min, the recommended dosing is 600 mg every two days; for CrCl < 30 mL/min,

dosing is 600 mg every three days; and for patients with end-stage renal disease on hemodialysis, dosing is 600 mg every four days. Since telbivudine is effectively removed by hemodialysis, the drug should be given following dialysis sessions.<sup>26</sup>

## Phase II Study

With the success of the phase I/IIa clinical study, a phase IIb trial was designed to determine the one-year safety and efficacy profile and investigate the potential role of combination drug therapy. This was a randomized, double-blind, multicenter study of 104 treatment-naïve HBeAg-positive patients with well-compensated liver disease treated for one year with either 400 mg or 600 mg of telbivudine alone or in combination with 100 mg of lamivudine or with lamivudine monotherapy.<sup>23</sup> In addition to assessing typical endpoints of HBeAg-positive CHB (suppression of HBV DNA, HBeAg loss and seroconversion, ALT normalization, and resistance rate), this study also stratified the degree of HBV DNA suppression at week 24 with different measures of treatment outcomes at week 52.

This phase II study showed that telbivudine demonstrated greater efficacy and potency than lamivudine over a 1-year period. The superior potency of telbivudine was first noted at week 4 and extended to week 52, and treatment was associated with a median reduction of serum HBV DNA levels from baseline of greater than 6 log<sub>10</sub> for telbivudine-treatment arms compared to 4.66 log<sub>10</sub> reduction with lamivudine alone. There was no statistical difference in terms of the viral suppression between the two different doses of telbivudine monotherapy arms. Importantly, the study showed no evidence of additional potency when telbivudine was combined with lamivudine. At the end of the week 52, telbivudine had a better or equal outcome for all endpoints compared to lamivudine, with patients on telbivudine monotherapy having a significantly higher rate of undetectable viral suppression compared to lamivudine (61% vs. 32%, respectively). Those on combination therapy had an intermediate level of undetectable HBV DNA at 49% but showed no statistical difference compared to telbivudine monotherapy. All treatment arms were effective at normalizing ALT levels by week 52 with 86% of patients on telbivudine, 78% on telbivudine/lamivudine combination therapy, and 63% of lamivudine patients achieving this endpoint. For HBeAg loss

and seroconversion rate, telbivudine-treated patients performed better than those on lamivudine alone or in combination therapy. No patients in any of the treatment arms had HBsAg loss or seroconversion during the one-year treatment period.

Notably, this study helped establish the importance of obtaining an early virologic response at 24 weeks and using this response as a predictor of achieving important endpoints at week 52. For example, all patients who had undetectable serum HBV DNA at week 24 were able to maintain complete viral suppression at week 52. In addition, there was a strong, inverse relationship between patients who achieved HBeAg loss at 52 weeks with the level of viral suppression at 24 weeks. Forty-three percent of patients with undetectable HBV DNA levels at week 24 had HBeAg loss compared to only 7% in those with HBV DNA levels elevated  $>4 \log_{10}$  copies/mL. Thus, the 24-week time point should be used as an important marker of the efficacy of telbivudine therapy. The predictive value of viral suppression at week 24 on subsequent antiviral efficacy of therapy and the incidence of resistance at year 1 and year 2 have been highlighted in the description of a 'roadmap' concept of on-treatment monitoring and decision making during antiviral therapy.<sup>6</sup>

Although oral nucleoside therapy was well tolerated, the main adverse effects of therapy were related to the development of viral resistance. At week 52, viral breakthrough was seen in 15.8% of patients on lamivudine, 4.5% on telbivudine, and interestingly, in 12.2% on telbivudine/lamivudine combination therapy. The predominant mutation associated with telbivudine resistance was M204I, which also conveys resistance to lamivudine and partial resistance to entecavir.<sup>5</sup> Furthermore, there was no viral breakthrough at the end of the trial in patients who had  $<3 \log_{10}$  copies/mL at week 24 whereas 19% to 26% of patients with viral load  $>3 \log_{10}$  copies/mL had developed viral resistance. Thus, this trial provided important insights regarding the one-year efficacy of telbivudine, the ineffectiveness of combination therapy with telbivudine plus lamivudine, and the importance of the 24-week time point as a predictor of response and risk of developing viral resistance.

### Phase III Clinical Trials

In two published phase III clinical trials,<sup>27,28</sup> the efficacy of telbivudine was compared to adefovir and, in the second study (GLOBE trial), telbivudine

was compared with lamivudine. Adefovir was the only nucleotide analogue available for the treatment of CHB until 2008, when tenofovir received FDA approval in the United States and several other countries. An international multicenter study was undertaken to compare the efficacy of telbivudine to adefovir for one year and to define the role of switching drug therapy.<sup>27</sup> This was an open label, controlled, randomized study involving 135 treatment-naïve HBeAg-positive patients enrolled in one of three treatment arms: telbivudine 600 mg a day, adefovir 10 mg a day, or adefovir for 24 weeks with switch to telbivudine until the completion of the trial period. Similar to other studies, all patients had ALT at least 1.3 to  $10 \times$  ULN and serum HBV DNA level at least  $6 \log_{10}$  copies/mL.

This study showed that, head-to-head, telbivudine was more potent than adefovir in achieving early reduction in HBV viral load. Separation of mean serum HBV DNA level was noted as early as week 2 of therapy. At the 24-week time point, telbivudine had achieved a mean reduction of HBV DNA of  $6.3 \log_{10}$  copies/mL compared to  $4.97 \log_{10}$  copies/mL in the adefovir arm. In addition, more patients obtained complete viral suppression by 24 weeks in the telbivudine group (39%) compared to the adefovir group (12%). At the end of the 1-year treatment period, more patients in the telbivudine arm achieved therapeutic endpoints than those receiving adefovir. This study also demonstrated that patients who switched from adefovir to telbivudine at week 24 had improved outcomes measured at week 52. For example, by week 52, complete viral suppression was greatest in the telbivudine group (60%) followed by the adefovir-to-telbivudine group (54%) and the adefovir group (40%). Furthermore, HBeAg seroconversion followed a similar pattern with the highest rate noted in telbivudine group (28%) followed by adefovir-to-telbivudine (24%) and adefovir (19%). All treatment groups obtained high rates of ALT normalization and there was no statistical difference among the different arms.

Similar to the earlier phase IIb clinical trial, this study again demonstrated the importance of the week 24 time point in predicting future viral response. The degree of viral suppression at week 52 was directly proportional to demonstrated efficacy at week 24. Those patients in the telbivudine group who obtained serum HBV DNA less than  $3 \log_{10}$  copies/mL at week 24 had a 94%



rate of undetectable viral load at week 52. On the other hand, of the patients who had an HBV DNA level greater than  $3 \log_{10}$  at week 24, only 25% had undetectable viral load at week 52. Similarly, the viral response at week 24 was equally predictive of future responses for HBeAg loss and seroconversion and ALT normalization.

Side effects on telbivudine and adefovir in this trial were minimal, but viral breakthrough and resistance for both drugs were noteworthy. Specifically, 2% in the telbivudine arm, 29% in the adefovir arm, and 11% in the adefovir-to-telbivudine arm experienced primary treatment failure, defined as the inability to obtain at least two consecutive HBV DNA values less than  $5 \log_{10}$  copies/mL after at least 24 weeks of therapy. Importantly, viral breakthrough, defined as a  $1 \log_{10}$  increase in serum HBV DNA from nadir value on therapy, was seen in both telbivudine and adefovir treatment arms but only after completion of at least 24 weeks of therapy and was more frequently seen in patients with a residual serum HBV DNA  $> 3 \log_{10}$  copies/mL. Resistance rate at the end of one year was 4.4% in the adefovir group and 6.8% in the telbivudine group. At the end of the trial, no viral breakthrough was seen in those who completed only 24 weeks of adefovir therapy prior to switching to 24 weeks of telbivudine, which was internally consistent with the risk of developing viral resistance after at least 24 weeks of single drug therapy. No serious adverse side effects were

seen, although all treatment arms had similar levels of minor side effects. Reports of elevated creatine kinase and mild myopathy were noted, but these cases required no additional medication dose adjustment. In a head-to-head comparison, telbivudine appears to be more effective at suppressing viral replication and has a higher HBeAg loss and seroconversion rate compared to adefovir.

## GLOBE Trial

The GLOBE trial, the largest of the phase III clinical studies of the treatment of CHB, was a two-year international collaboration comparing the efficacy of telbivudine to lamivudine (Table 1).<sup>28</sup> This multicenter, randomized, double-blind study compared standard doses of telbivudine to lamivudine. This study enrolled 1,370 treatment-naïve HBeAg-positive and HBeAg-negative CHB patients with baseline ALT between  $1.3 \times$  to  $10 \times$  ULN, serum HBV DNA greater than  $6 \log_{10}$  copies/mL and compatible pretreatment liver histologic findings. In all, there were 921 HBeAg-positive and 446 HBeAg-negative CHB patients. This study demonstrated that telbivudine was more potent than lamivudine at reducing serum HBV DNA levels in both HBeAg-positive and HBeAg-negative patients. This marked difference between the two drugs was reflected in an early separation of the serum HBV DNA levels starting at week 12

**Table 1.** Results of GLOBE trial at year 2.<sup>29</sup>

	HBeAg-positive patients		HBeAg-negative patients	
	Lamivudine N = 463	Telbivudine N = 458	Lamivudine N = 224	Telbivudine N = 222
Therapeutic response (%)	48.2	63.3 <sup>a</sup>	66.1	77.5 <sup>d</sup>
Mean HBV DNA reduction from baseline (log copies/mL)	-4.4	-5.7 <sup>b</sup>	-4.2	-5.2 <sup>b</sup>
HBV DNA undetectable by PCR (%)	38.5	55.6 <sup>a</sup>	56.7	82 <sup>a</sup>
ALT normalization (%)	61.7	69.5 <sup>b</sup>	70.1	77.8 <sup>e</sup>
HBeAg seroconversion (%)	24.7	29.6 <sup>c</sup>	n/a	n/a
Viral breakthrough (%)	46.9	28.8 <sup>a</sup>	31.7	12.2 <sup>a</sup>
Viral resistance (%)	39.5	25.1 <sup>a</sup>	25.9	10.8 <sup>a</sup>
Primary treatment failure (%)	12.3	4.0 <sup>b</sup>	2.7	0 <sup>b</sup>

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

Primary treatment failure = HBV DNA levels  $> 5 \log_{10}$  copies/mL at end-of-treatment; therapeutic response = a reduction in HBV DNA level to  $< 5 \log_{10}$  copies/mL plus either HBeAg loss or ALT normalization; viral resistance = viral breakthrough with treatment-emergent resistance mutations confirmed by genetic sequencing; viral breakthrough = increase in serum HBV DNA to  $\geq 1 \log_{10}$  copies/mL above the nadir value on 2 consecutive occasions.

<sup>a</sup> $P = < 0.001$ , <sup>b</sup> $P = < 0.05$ , <sup>c</sup> $P = 0.095$ , <sup>d</sup> $P = 0.007$ , <sup>e</sup> $P = 0.073$ .

for HBeAg-positive and at week 8 for HBeAg-negative patients. By week 52, 60% of HBeAg-positive and 88.3% of HBeAg-negative telbivudine treatment group achieved undetectable HBV DNA as compared to lamivudine (40.4% and 71.4%, respectively). In addition, the mean time to complete viral suppression was shorter in the telbivudine group (34 weeks) compared to lamivudine group (39 weeks).

Aside from the efficacy of telbivudine at viral suppression, many other study endpoints were similar between lamivudine and telbivudine at the end of one year. By week 52, the number of patients achieving HBeAg loss and seroconversion was not statistically different between the telbivudine and lamivudine groups. Both treatment groups also achieved a high level of ALT normalization by week 52. Patients with high baseline ALT levels (greater than  $2.5 \times \text{ULN}$ ) achieved higher rates of HBeAg loss and seroconversion compared to those with lower baseline ALT, a fact that is reflected in the current use of elevated ALT as a prerequisite for initiation of treatment. Similar to previous studies, there was less than 1% HBsAg loss and seroconversion rate during this 1-year trial. Primary failure, defined as persistently elevated HBV DNA greater than  $5 \log_{10}$  after at least 24 weeks of therapy, was seen predominantly in the lamivudine group but was statistically significant only in the HBeAg-positive patients. The GLOBE trial also reinforced the importance of early viral suppression, again demonstrating the usefulness of the 24-week time point as a predictor of later outcome measures for both lamivudine and telbivudine monotherapy.

At the end of the 2-year trial, telbivudine continued to be more potent than lamivudine in viral suppression.<sup>29</sup> At the week 104 time point, 55.6% of HBeAg-positive and 82% of HBeAg-negative patients in the telbivudine group attained undetectable serum HBV DNA compared to 38.5% and 56.7% of the lamivudine group, respectively. Similar to the week 52 endpoint, both treatment arms continued to demonstrate high levels of ALT normalization and HBeAg loss. Patients with ALT greater than  $2 \times \text{ULN}$  continued to have better treatment outcomes. In this selective population, those HBeAg-positive patients on telbivudine achieved a mean reduction of  $6.1 \log_{10}$  copies/mL in their plasma HBV DNA with 61% obtaining undetectable viral load whereas those HBeAg-positive patients with baseline ALT less

than  $2 \times \text{ULN}$  had a mean reduction of only  $5.0 \log_{10}$  copies/mL in serum HBV DNA and undetectable viral load in 43%. Additionally, elevated baseline ALT also predicted better rates of HBeAg loss and seroconversion with patients in the telbivudine arm significantly outperforming those on lamivudine.

The two-year GLOBE trial also provided data on the sustainability of HBeAg loss and seroconversion after discontinuation of oral antiviral therapy. Patients who discontinued antiviral therapy following HBeAg loss and who continued to receive at least six additional months of therapy were followed. In this population, there was a high rate of sustained HBeAg loss in 82% of the telbivudine group and in 89% of the lamivudine group. Follow-up of these patients for 29–32 weeks, depending on the treatment arm, revealed that a majority of these patients obtained seroconversion. Patients on telbivudine maintained HBeAg seroconversion during follow-up at a rate of 98% at 12 weeks, 94% at 24 weeks, and 86% at 52 weeks, which was similar to values achieved on lamivudine for the same follow-up period (100%, 95%, 93%, respectively).<sup>30</sup>

A significant endpoint evaluated in the GLOBE trial was change in histology during antiviral therapy. This study evaluated and compared liver histology at baseline and after one year on nucleoside therapy. Both lamivudine and telbivudine treatment resulted in improved mean Knodell histologic index. In the majority of patients with pretreatment bridging fibrosis and an Ishak fibrosis score between 4 and 6 (with 6 indicative of cirrhosis), improvement in histology was seen in both HBeAg-positive and HBeAg-negative patients. No histologic data was available at week 104. Furthermore, evaluation of these pre- and on-treatment liver biopsies also revealed that lamivudine and telbivudine resulted in reductions in both the intrahepatic HBV DNA and cccDNA with no statistical difference between the treatment arms.<sup>31</sup> Overall, the GLOBE trial demonstrated that patients on telbivudine derive histologic benefit from oral nucleoside therapy.

One of the major concerns with the use of antiviral therapy is the development of resistance; the GLOBE trial year two data provides further insight into this cumulative risk with use of telbivudine. By week 52 of therapy, viral resistance in the telbivudine group was seen in 5% of HBeAg-positive and 2.3% of HBeAg-negative patients

compared to that in the lamivudine group, 11% and 10.7% respectively. By week 104, viral resistance continued to increase in both treatment arms, with a resistance rate of 25.1% of HBeAg-positive and 10.8% of HBeAg-negative patients in the telbivudine group compared to 39.5% and 25.9%, respectively, in the lamivudine group. As seen previously, the signature mutation for telbivudine was M204I. Other minor mutations were described but these occurred only in the presence of the M204I mutation. Additionally, mutations at codon A181 and L229 were reported but these mutations were not associated with viral breakthrough.

### Prediction of the Outcome of Telbivudine Therapy

In a subsequent analysis of the GLOBE trial, multivariate logistic regression analysis was employed to evaluate baseline and early on-treatment variables predicting optimal outcomes of telbivudine therapy.<sup>32</sup> Undetectable HBV DNA at week 24 of treatment was the strongest predictor of optimal outcomes for HBeAg-positive and HBeAg-negative patients. A combination of pretreatment characteristics with the response at week 24 identified subgroups with the best outcomes. For HBeAg-positive patients with baseline HBV DNA  $< 9 \log_{10}$  copies/mL and ALT levels  $\geq 2 \times \text{ULN}$  ( $n = 80$ ), 71% (57/80) had undetectable HBV DNA at week 24. In this population, the following outcomes were achieved at year 2 of therapy: undetectable HBV DNA in 89% (51/57), HBeAg seroconversion in 52% (25/48), and antiviral telbivudine resistance in 1.8% (1/57). For HBeAg-negative patients with baseline HBV DNA  $< 7 \log_{10}$  copies/mL ( $n = 91$ ), 95% (86/91) had undetectable HBV DNA at week 24. In these patients, the following outcomes were achieved at year 2 of therapy: undetectable HBV DNA in 91% (78/86) and antiviral telbivudine resistance in 2.3% (2/86). These parameters, especially the serum HBV DNA level at week 24 of telbivudine therapy, are important clinically to guide on-treatment management.<sup>6</sup> Thus, telbivudine is a good option for treatment of chronic hepatitis B in the subset of patients with low levels of HBV DNA and high ALT levels.

### Telbivudine Adverse Events

There was no statistical difference between the two treatment arms in terms of the frequency of adverse events in the GLOBE trial.<sup>28</sup> The majority

of patients reported at least one adverse event and many also reported minor events. The most common symptoms were frequently not attributed to therapy (upper respiratory tract infection, nasopharyngitis) and other symptoms were constitutional, i.e. fatigue, headache, nausea. Serious adverse events associated with telbivudine were reported in 5% of those taking the medications and included myopathy, liver failure in a patient with viral breakthrough, and elevated creatine kinase levels. Grade 3/4 ( $7 \times \text{ULN}$ ) creatine kinase elevations were seen in 12.9% of those receiving telbivudine (compared to 4.1% of lamivudine recipients), but the level of elevation did not correlate with patient symptoms. These elevated creatine kinase levels were noted at a mean period of 56.9 weeks into therapy and were frequently transient. Two cases of myopathy characterized by muscle pain and weakness associated with moderately elevated creatine kinase levels were reported in patients treated with telbivudine, and both cases resolved after drug discontinuation. Grade 3/4 elevation in aminotransferase levels and ALT flares were less common in the telbivudine group compared to lamivudine. Overall, telbivudine appears to have a favorable side effect profile with published safety data extending to two years.

Although the combination of peginterferon and lamivudine has no clinical benefit over peginterferon alone, there is still enthusiasm for the use of combination therapy with peginterferon and a more potent nucleos(t)ide agent.<sup>7</sup> It is thus important to note that peginterferon plus telbivudine therapy should be avoided, as a small pilot study showed that 8 of 48 (17%) of patients with chronic hepatitis B treated with this regimen developed a moderately severe peripheral neuropathy.<sup>33</sup> On the other hand, it is theoretically appealing to consider the use of telbivudine in combination with an oral nucleotide agent, such as tenofovir, for the treatment of chronic hepatitis B. However, studies of other combinations, such as lamivudine plus adefovir, failed to show improved therapeutic responses.<sup>34</sup> The potential advantage of such a combination might be a lower rate of antiviral drug resistance with long-term administration, but drugs such as tenofovir and entecavir have absent or very low rates of resistance with administration up to five years and potential demonstration of a small difference in resistance rates compared with a



combination of two oral agents would take a very large study conducted over many years.<sup>7</sup>

## Expert Commentary

As demonstrated in several published clinical trials, telbivudine is a potent and safe nucleoside analog with potent inhibition of HBV replication, and is comparable to all available oral agents in terms of achieving important therapeutic endpoints. More specifically, telbivudine can rapidly suppress the HBV DNA levels, normalize ALT, can improve liver histology in a subset of patients, and promote HBeAg loss and seroconversion. Equally important, these studies also revealed the importance of the 24-week time point in the treatment management of patients on telbivudine. Patients who do not obtain a serum HBV DNA level  $< 4 \log_{10}$  copies/mL by week 24 are less likely to achieve later therapeutic endpoints and are at a significantly higher risk of developing drug resistance. The signature telbivudine resistance mutation, a single nucleotide exchange at M204I, confers resistance not only to telbivudine, but also to lamivudine and partially to entecavir. Thus, the use of telbivudine for management of CHB must take into account not only the therapeutic advantages associated the drug, but also the long-term cumulative risk of developing viral resistance, which in many cases can result in cross-resistance to other available oral agents.

At the time of its FDA approval in 2006, telbivudine was the fourth oral antiviral agent available for treatment of CHB. Since the approval of telbivudine, one additional oral agent, tenofovir, was approved by the FDA. Both entecavir and tenofovir are equally or more potent than telbivudine at achieving many of the same therapeutic endpoints (viral suppression and HBeAg loss and seroconversion). However, unlike telbivudine, entecavir and tenofovir have a high barrier to the development of antiviral resistance. For example, in lamivudine-naïve patients, the 1-year resistance rate for both entecavir and tenofovir is 0%.<sup>35</sup> Accordingly, many treatment guidelines now advocate for use of entecavir or tenofovir as first-line oral antiviral agents as both agents are capable of accomplishing the two important goals of therapy—potent and effective control of viral replication, and low likelihood of developing antiviral drug resistance.<sup>5,7</sup>

However, there is still a potential role for telbivudine in the management of CHB. Although

telbivudine is not recommended as a first-line agent given the low barrier to antiviral resistance and the risk of developing cross-resistance, there is still a role for this drug in selected cases. For example, post-hoc analysis of the GLOBE trial has shown that patients with low levels of serum HBV DNA and, in patients with HBeAg-positive chronic hepatitis B, more than 2-fold elevation of ALT levels, have a high success rates with undetectable HBV DNA at year 2 of therapy (89% to 95%), loss of HBeAg (52%), and low rates of antiviral drug resistance (1.8% and 2%).<sup>32</sup> Thus, telbivudine is a good treatment option in these subsets of patients. Telbivudine should also be considered as one of the agents of choice for short-term treatment during pregnancy. However, it is worthwhile to add a word of caution that hepatitis flares, including severe and fatal rebound, may occur following discontinuation of treatment in spite of good HBV DNA suppression. Telbivudine, which is pregnancy category B, is ideal for rapid viral suppression in lamivudine-naïve pregnant patients. However, experience with the use of telbivudine in pregnancy is limited, and tenofovir, which is also pregnancy category B, is also an option. Finally, as noted earlier, telbivudine is not active against HIV, and thus telbivudine or telbivudine/adeфовir combination therapy may be a treatment option for HIV and HBV coinfecting patients who are not candidates for HIV antiretroviral therapy as they do not cause HIV resistance.<sup>7</sup>

Use of telbivudine as a second-line or third-line agent in patients who are not treatment-naïve should be considered with caution. A resistance profile by laboratory testing would be helpful in patients who have demonstrated prior potential or documented resistance to lamivudine or entecavir based on a breakthrough rise in serum HBV DNA levels while undergoing treatment. The presence of M204I or L180M/M204V/I mutations should preclude the use of telbivudine. In addition, monitoring for appropriate viral response after 24 weeks of therapy is crucial and an appropriate switch to a different agent is indicated in the absence of an adequate viral suppression at this time point. In the current treatment of CHB, many effective oral antiviral agents are now available, and judicious use of these medications is necessary to achieve optimal control of this chronic infection while reducing the risk of the development of antiviral drug resistance.



There is only limited experience in the management of telbivudine resistance, and guideline recommendations are primarily based on general principles of salvage treatment of resistance that involves the addition of a nucleotide agent such as adefovir or tenofovir when resistance to a nucleoside agent develops.<sup>4,7</sup> In the GLOBE trial, a limited number of patients with documented telbivudine resistance were treated with either continued telbivudine therapy with the addition of adefovir (n = 19) or with discontinuation of telbivudine and subsequent switch to adefovir (n = 5).<sup>29</sup> After 16 weeks of adefovir therapy, the mean serum HBV DNA decreased 4.3 log<sub>10</sub> and 3.7 log<sub>10</sub> copies/mL, respectively, in these two groups. In addition, one patient in each group lost HBeAg while being treated with adefovir. Based on the licensure and superiority of tenofovir over adefovir, tenofovir might now be preferred for salvage treatment of antiviral drug resistance that develops with the use of a nucleoside analogue such as telbivudine.<sup>5,7</sup> What remains uncertain is which strategy, to add-on or to switch, is preferred, although general principles and experience with high rates of adefovir resistance when patients with lamivudine resistance were switched to adefovir would support the addition of tenofovir to a patient with telbivudine antiviral drug resistance.

## Disclosures

The authors have no conflicts of interest to disclose.

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