

Safety and efficacy of telbivudine for the treatment of chronic hepatitis B

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Abstract: Telbivudine was recently approved for the treatment of chronic hepatitis B. Phase III studies indicated its antiviral potency with 6- to 6.5-log copies/mL reductions in hepatitis B DNA levels at year 1, comparable to other potent agents such as entecavir or tenofovir. Genotypic resistance rates, however, reached 25% at year 2 in hepatitis B e-antigen positive subjects and 11% in hepatitis B e-antigen negative subjects, preventing it from becoming a preferred first-line drug for hepatitis B. Furthermore, its signature resistance mutation (a change from methionine to isoleucine at position 204 in the reverse transcriptase domain of the hepatitis B polymerase) also confers cross-resistance to entecavir, lamivudine, and emtricitabine. Telbivudine is well tolerated, with elevations in creatine phosphokinase being the most common abnormality observed in clinical trials. Most often, elevations were asymptomatic. Future research in hepatitis B will focus on the best ways to use existing therapies, including telbivudine, sequentially or in combination in order to maximize viral suppression and minimize the development of antiviral resistance.

Keywords: telbivudine, hepatitis B, antivirals, resistance

Chronic hepatitis B affects nearly 350 million people worldwide, with prevalence varying geographically, from >8% in areas of endemicity such as Asia and Sub-Saharan Africa to <1% in Western countries.¹ It is the leading cause of hepatocellular cancer,² present in 53% of cases. Chronic infection with hepatitis B can also lead to cirrhosis and its complications.

Over the past five years, the armamentarium of oral antiviral therapies against hepatitis B has grown from one nucleoside analogue (lamivudine) to three nucleoside analogues and two nucleotide analogues available in 2009. These oral agents joined the immunomodulatory drug interferon-alfa (along with its pegylated form) as treatment options for chronic hepatitis B.

One of the most recent hepatitis B drugs to become available is the L-nucleoside telbivudine, which was approved by the US Food and Drug Administration in October 2006, and in the European Union and China in 2007. As the options for hepatitis B therapy grow, it becomes important to consider the relative potencies and resistance profiles of each available agent to maximize long-term viral suppression and prevent development of virologic breakthrough. In this article, the trials leading to telbivudine's approval will be discussed, along with strategies for its potential incorporation into current treatment paradigms based on its comparative efficacy with other approved nucleoside analogues.

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Structure and pharmacokinetics

Telbivudine (β -L-2'-deoxythymidine) is a β -L-nucleoside analogue of thymidine that impairs hepatitis B virus (HBV) DNA replication by leading to chain termination. It differs from the natural nucleotide only with respect to the location of the sugar and base moieties, taking on an levorotatory configuration versus a dextrorotatory configuration as do the natural deoxynucleosides.³ Lamivudine and emtricitabine are also L-nucleosides. Telbivudine contains a hydroxyl group at the 3' position of the β -L-2'-deoxyribose sugar which confers specificity to HBV polymerase.³ Preclinical studies have shown no activity of telbivudine against human immunodeficiency virus (HIV), herpes simplex virus, varicella zoster virus, Epstein–Barr virus, adenovirus type-1, influenza, measles, or other viruses. It also does not appear to have any activity against the human cellular DNA polymerase. Although *in vitro* data have supported a lack of HIV activity, further *in vitro* data is needed. Entecavir, another HBV nucleoside analogue, was also not found to have HIV activity in preclinical *in vitro* HBV models. Clinical experience, however, confirmed suppression of HIV RNA and induction of HIV resistance with use of entecavir as monotherapy in HIV/HBV-coinfected patients.^{4,5} Indeed, one case report suggests that telbivudine may have some activity against HIV.⁶ Clearly, more clinical data is needed.

Telbivudine is rapidly absorbed, reaching peak concentration within 2.5 to 3 hours after dosing.⁷ Absorption is not affected by food intake, and therefore, it may be taken with or without a meal, with comparable maximum plasma concentration (C_{max}), time to maximum concentration (T_{max}) and area under the plasma concentration-time curve (AUC_{0-t}).⁸ Once taken up into the hepatocyte, it is efficiently phosphorylated into its active 5'-triphosphorylated form by host cellular kinases. The half-life of the activated drug is long (>14 hours), making once-daily administration of a 600 mg dose appropriate. It is eliminated unchanged through passive diffusion into the urine, with a renal clearance similar to that of creatinine. Therefore, dosage adjustment is required in renal impairment,⁹ with extension of the dosing interval for creatinine clearance less than 50 mL/minute.¹⁰ For patients on hemodialysis, the dose is 600 mg every 96 hours (every four days), given after dialysis, as a four-hour dialysis session causes a 23% decrease in total exposure if the dosage is given prior to the session.⁹ Telbivudine is neither an inducer nor inhibitor of human CYP450 enzymes. No changes in its pharmacokinetics were observed in patients with mild, moderate or severe hepatic impairment so no dosage modifications are required in these patients.¹¹

Clinical efficacy

Hepatitis B therapy cannot cure infection and has not been shown to improve mortality or development of hepatocellular carcinoma,¹² although in theory reduction of viral replication and amelioration of hepatic inflammation should decrease the likelihood of progression to the complications of hepatitis B. The efficacy of hepatitis B therapies are therefore measured by such surrogate endpoints as HBV DNA suppression, normalization of biochemical markers (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), loss of hepatitis B e antigen (HBeAg) and seroconversion to hepatitis B e antibody (anti-HBe), and loss of hepatitis B surface antigen (HBsAg). Because most antiviral therapies need to be given for prolonged periods of time, there is growing interest in development of drugs or drug strategies that have low rates of drug resistance when used for many years. More emphasis has been recently placed on an agent's "genetic barrier to resistance" when deciding its place in treatment algorithms, as exemplified by the recommendation against using lamivudine as a first-line agent in antiviral-naïve patients due to high rates of resistance.¹³

The approval of telbivudine was based on several large, double-blind, multicenter, randomized studies comparing telbivudine to other approved hepatitis B agents. The largest of these was the phase III international GLOBE trial, which enrolled 1370 HBeAg-positive and HBeAg-negative antiviral-naïve subjects and randomized them to receive either 600 mg of telbivudine or 100 mg of lamivudine once daily.¹⁴ A second phase III trial (study 015), identical in design and intervention, enrolled 332 patients in China only.¹⁵ Telbivudine has also been compared to adefovir in randomized, open-label study in HBeAg-positive patients (study 018).¹⁶

In the GLOBE trial, the primary outcome was a "therapeutic response" which was defined as a decrease in the HBV DNA level to <5 log copies/mL along with either a loss of HBeAg or ALT normalization. Secondary outcomes were histologic response, change in HBV DNA levels, HBeAg loss, HBsAg loss, HBeAg seroconversion, HBsAg seroconversion, and normalization of ALT. The authors also looked for virologic breakthrough, defined as a >1 log copies/mL increase in HBV DNA over nadir. Treatment-emergent resistance mutations were screened for in anyone with virologic breakthrough as well as those with detectable HBV DNA at prespecified timepoints. The Chinese trial used decrease in HBV DNA at one year as the primary endpoint. Secondary endpoints included the proportion of subjects with HBV DNA < 5 log copies/mL and proportion undetectable

at one year, normalization of ALT, HBeAg loss, HBeAg seroconversion and therapeutic response, as defined in the GLOBE trial.

The GLOBE study included 683 patients randomized to receive telbivudine (458 HBeAg-positive and 222 HBeAg-negative) and 687 patients randomized to receive lamivudine (463 HBeAg-positive and 224 HBeAg-negative). Results through year 2 are summarized in Table 1. In this study, telbivudine showed a more potent HBV DNA reduction at one year compared to lamivudine in both HBeAg-positive and HBeAg-negative patients, with an average drop of -6.45 log copies/mL drop in HBeAg-positive patients

and -5.23 log copies/mL in HBeAg-negative patients in the telbivudine groups, nearly a full log over changes in the lamivudine groups. The mean time to HBV DNA negativity was also shorter with telbivudine, 34 weeks versus 39 weeks with lamivudine in HBeAg-positive ($P < 0.001$) and 20 weeks versus 26 weeks with lamivudine in HBeAg-negative ($P < 0.001$). The less dramatic virologic results seen in HBeAg-negative patients may reflect their lower HBV DNA levels at baseline (9.5 log copies/mL in HBeAg-positive versus 7.4 to 7.7 log copies/mL in HBeAg-negative). Telbivudine also outperformed lamivudine for therapeutic response, with 75% to 85% of HBeAg-positive patients and

Table 1 Results of the phase III GLOBE trial comparing telbivudine 600 mg daily to lamivudine 100 mg daily in nucleoside-naïve hepatitis B e-antigen positive and e-antigen negative subjects^{13,18}

HBeAg-positive subjects						
	Year 1			Year 2		
	Telbivudine 600 mg/day (n = 458)	Lamivudine 100 mg/day (n = 463)	P	Telbivudine 600 mg/day (n = 458)	Lamivudine 100 mg/day (n = 463)	P
Therapeutic response	75.3%	67.0%	0.005	63.3%	48.2%	<0.001
Histologic Response	64.7%	56.3%	0.01			
Mean change in HBV DNA (log copies/mL)	-6.45	-5.34	<0.001			
Undetectable HBV DNA	60%	40.4%	<0.001	55.6%	38.5%	<0.011
ALT normalization	77.2%	74.9%	0.42	69.5%	61.7%	<0.05
HBeAg loss	25.7%	23.3%	0.40	35.2%	29.2%	0.056
HBeAg seroconversion	22.5%	21.5%	0.73	29.6%	24.7%	0.095
Virologic response	25.7%	22.8%	0.32			
Viral breakthrough	5.9%	15.9%	<0.001	28.8%	46.9%	<0.001
Viral resistance	5.0%	11.0%	<0.001	25.1%	39.5%	<0.001
Primary treatment failure	4.7%	13.4%	<0.001	1.3%	1.3%	0.993
HBeAg-negative subjects						
	Telbivudine 600 mg/day (n = 222)	Lamivudine 100 mg/day (n = 224)	P	Telbivudine 600 mg/day (n = 222)	Lamivudine 100 mg/day (n = 224)	P
Therapeutic response	75.2%	77.2%	0.62	77.5%	66.1%	0.007
Histologic response	66.6%	66.0%	0.90			
Mean change in HBV DNA (log copies/mL)	-5.23	-4.40	<0.001			
Undetectable HBV DNA	88.3%	79.3%	<0.001	82.0%	56.7%	<0.001
ALT normalization	74.4%	79.3%	0.24	77.8%	70.1%	0.073
Viral breakthrough	2.3%	12.5%	<0.001	12.2%	31.7%	<0.001
Viral resistance	2.2%	10.7%	<0.001	10.8%	25.9%	<0.001
Primary treatment failure	0.4%	2.7%	<0.06	0.5%	0.9%	0.567

Notes: Therapeutic response = suppression of HBV DNA to <5 log copies/mL + either loss of HBeAg OR ALT normalization.

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

63% to 71% of HBeAg-negative patients experiencing this endpoint. Primary treatment failure (failure of treatment to suppress HBV DNA to <5 log copies/mL) seems to be rare with telbivudine, occurring in $<5\%$ of study subjects in GLOBE and study 015.

After one year of telbivudine, the HBeAg loss rates and HBeAg seroconversion rates were no different from lamivudine in the GLOBE trial, with HBeAg loss rates of 25.7% and 23.3% for telbivudine and lamivudine, respectively ($P = 0.40$) and 22.5% and 21.5% for HBeAg seroconversion ($P = 0.73$). By year 2, however, telbivudine gained a slight, though not statistically significant advantage, with HBeAg loss rates of 35% and HBeAg seroconversion rates of nearly 30%. HBsAg loss and HBsAg seroconversion were low with both treatments, as they have been with other nucleoside analogues.

ALT normalization occurred commonly with telbivudine and lamivudine in both HBeAg-positive and HBeAg-negative subjects. Overall, 77% of HBeAg-positive subjects and 75% of HBeAg-negative subjects had ALT normalization at year 1, and nearly 70% of HBeAg-positive subjects and 78% of HBeAg-negative subjects reached this endpoint at year 2. The lower proportion having normal ALT at year 2 among HBeAg-positive patients may reflect the higher rate of viral breakthrough and resistance seen in year two in this group (see later discussion). The favorable effect on ALT, a marker of inflammation, was also mirrored by improvements in histology on paired liver biopsies at baseline and one year, which were seen in 65% to 66% of the telbivudine-treated patients, significantly more than the proportion of HBeAg-positive patients treated with lamivudine with a histological response (56%, $P = 0.01$).

The smaller study 015 completed in China, randomized 147 HBeAg-positive and 20 HBeAg-negative patients to telbivudine and 143 HBeAg-positive and 22 HBeAg-negative patients to lamivudine. The results were strikingly similar to the results from the GLOBE study, indicating little ethnic variation in the efficacy of telbivudine.^{15,17} HBV DNA reduction was -6.3 log copies/mL in HBeAg-positive patients and -5.5 log copies/mL in HBeAg-negative patients, again a nearly 1 log increase over the changes seen in lamivudine-treated patients at one year. ALT normalization at one year was seen in 87% of HBeAg-positive and 100% of HBeAg-negative patients treated with telbivudine. Although HBeAg loss occurred more often with telbivudine than lamivudine at one year (31% vs 20%, $P = 0.047$), HBeAg seroconversion was not statistically significant (25% vs 18%, $P = 0.14$). Sixty-seven percent of telbivudine-treated HBeAg-positive patients

became undetectable by PCR assay at year 1, while therapeutic response was seen in 85% of telbivudine patients versus only 62% of lamivudine subjects ($P < 0.001$). No patient experienced HBsAg loss or HBsAg seroconversion.

Participants in both the GLOBE and study 015 were offered participation in a phase IIIb extension study offering two years additional treatment with continued monitoring of treatment responses. Ninety-three HBeAg-positive patients with HBeAg seroconversion and HBV DNA < 300 copies/mL met the criteria for entrance into the rollover protocol.¹⁸ Of these 93 patients, 77% maintained HBeAg seroconversion and HBV DNA < 300 at year 3. All had maintained HBeAg loss, but only 93% maintained HBeAg seroconversion. Among six patients who lost anti-HBe, six had low levels of HBV DNA (<5 log copies/mL). Ninety-one percent of patients maintained normal ALT at year 3. Therefore, for those responding to telbivudine, the response appears durable. HBeAg-positive subjects in GLOBE were also offered the option of stopping study drug if HBeAg loss had been maintained for 24 weeks with an undetectable HBV DNA. Of the 38 telbivudine patients who elected to do so, 82% sustained HBeAg loss through the last study visit after a median post-treatment follow up of 29.1 weeks.¹⁹

Telbivudine has also been compared to adefovir in one trial in HBeAg-positive patients.¹⁶ In this randomized, controlled, open-label study telbivudine 600 mg daily for 52 weeks was compared to adefovir 10 mg daily for 52 weeks or 24 weeks of adefovir followed by 24 weeks of telbivudine, with approximately 45 patients randomized to each group. The investigators found no differences at week 52 between any of the groups with regard to reduction in HBV DNA, proportion of subjects with undetectable HBV DNA by PCR assay, biochemical response, HBeAg loss, or HBeAg seroconversion (Table 2). There was, however, a statistically significant difference between the amount of HBV DNA reduction at week 52 and the residual HBV DNA level at this time point in favor of telbivudine by almost 1 log copies/mL. There was also a much higher primary failure rate in both adefovir groups (29% in the adefovir only group, 11% among the adefovir to telbivudine group, and 2% in the telbivudine only group) which was statistically significant. This is consistent with prior data confirming the suboptimal antiviral activity of adefovir against hepatitis B and its relative lack of potency compared to other available hepatitis B agents.²⁰

Combination therapy

In the treatment of HIV, combination therapy with nucleoside analogues is standard care and well established as superior

Table 2 Telbivudine (LdT) 600 mg daily versus adefovir (ADV) 10 mg daily versus adefovir 10 mg for 24 weeks then telbivudine 600 mg daily for 24 weeks in nucleoside naïve hepatitis B e-antigen-positive patients (Week 52 results)¹⁵

	Telbivudine	Adefovir	Adefovir → telbivudine	P (LdT vs ADV)	P (switch vs ADV)
HBV DNA reduction (log copies/mL)	-6.56	-5.99	-6.44	0.11	0.18
Undetectable HBV DNA	60%	40%	54%	0.07	0.20
Mean HBV DNA (log copies/mL)	3.01	4.00	3.02	0.004	<0.01
ALT normalization	79%	85%	85%	0.45	0.98
HBeAg loss	30%	21%	26%	0.25	0.53
HBeAg seroconversion	27%	18%	24%	0.34	0.51
Primary treatment failure	2%	29%	11%	0.008	0.042

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

to sequential monotherapy.²¹ *In vitro* pharmacologic data in HBV support additive antiviral effects by the Loewe additivity model and the Bliss independence model when adefovir and telbivudine were applied to transfected HepG2 cells.²² These same models also demonstrated additive antiviral effects when telbivudine was combined with either entecavir or tenofovir *in vitro*.²³

Similarly convincing clinical data in HBV are lacking, with *de novo* nucleoside (or nucleoside/nucleotide) combinations failing to show improved efficacy over monotherapy.^{24–26} In these studies, rates of HBeAg loss, HBeAg seroconversion, magnitude of HBV DNA suppression and proportion undetectable at one year have not differed among subjects randomized to dual therapy versus monotherapy. Most studies have been too short to show a benefit on prevention of drug resistance, which is one of the primary benefits to combination therapy in HIV. Furthermore, many of the clinical combination therapy studies in HBV have studied less potent drugs (adefovir) or drugs with high rates of resistance (lamivudine) in combination and have not included newer, potent drugs with higher genetic barriers to resistance.

Telbivudine has been studied in combination with lamivudine for HBeAg-positive chronic hepatitis B.²⁴ Subjects were randomized to receive lamivudine alone, telbivudine at one of two doses alone or lamivudine plus telbivudine at one of two doses together. The telbivudine groups were later pooled for analysis. At week 52, the lamivudine group (n = 19) had a -4.66 log copies/mL drop in HBV DNA compared to a greater than 6 log copies/mL drop in both the monotherapy (n = 44) and combination (n = 41) telbivudine groups. The proportion of subjects with undetectable HBV DNA at week 52 was significantly less in the lamivudine group (32%) than in either of the telbivudine groups which were not significantly different from one another (61% in the telbivudine

monotherapy group and 49% in the combination therapy group). There were no differences among the three groups with regard to ALT normalization, HBeAg loss, HBeAg seroconversion, or therapeutic response. Virologic breakthrough occurred in 3/19 (15.8%) of lamivudine patients, 2/44 (4.5%) of telbivudine patients, and 5/41 (12.2%) of combination therapy patients. Two lamivudine breakthroughs had the rtM204I mutation and one had rtM204V + L180M. Both telbivudine breakthroughs carried the rtM204I mutation. In the combination group, three patients had rtM204I, one had M204V+L180M and one had wild-type HBV. As discussed later, telbivudine and lamivudine are now known to share the same pattern of resistance so it is unlikely that they would now be used together in combination therapy.

Safety

Because of its specificity for hepatitis B and selectivity for the viral polymerase rather than the host cellular polymerase, there are few adverse effects associated with the use of telbivudine. Preclinical²⁷ and phase 1 and 2 studies⁷ showed no major toxicities associated with its use in humans. In the phase III GLOBE and study 015, there were no serious adverse events that led to drug discontinuation or death.^{14,15} In both of these studies, elevations in the creatine phosphokinase (CPK) were seen more frequently and were higher than in those subjects receiving lamivudine. Grade 3/4 CPK elevations occurred in 12.9% of telbivudine subjects versus 4.1% of lamivudine patients in the GLOBE trial ($P < 0.001$) after a mean time of 56.9 weeks to first elevation. There were no cases of rhabdomyolysis, although one case was associated with a symptomatic myopathy, which was reported as a serious adverse event.¹⁹ In most cases, the elevations in CPK were not correlated with musculoskeletal symptoms, and were transient, resolving with the next laboratory check.

Grade 3/4 elevations in CPK were also seen with more frequency in the telbivudine group in study 015 (8.4% versus 3.0% in the lamivudine group) but this did not reach statistical significance ($P = 0.06$).¹⁵ The only other serious adverse event not related to muscle enzymes or myopathy associated with telbivudine was one instance of liver failure which occurred with an episode of virologic breakthrough that occurred with the development of telbivudine resistance in the GLOBE trial.¹⁹ Post-marketing reports have added additional case reports of myopathy and CPK elevations to the literature,^{28,29} as well as case reports of neuralgia and numbness and cardiac arrhythmia.²⁹ The mechanisms for myopathy and peripheral neuropathy are not clear. Other nucleoside analogues, such as fialuridine, have been associated with mitochondrial toxicity leading to distortions of cell energy metabolism with subsequent lactic acidosis, myopathy, peripheral neuropathy and hepatic steatosis through inhibition of the mitochondrial DNA polymerase gamma.^{30,31} Preclinical studies in animals did not demonstrate any mitochondrial toxicity with telbivudine²⁷ and thus far, there is no clinical evidence that this is the mechanism underlying the observed myopathies in clinical trials. Animal studies of telbivudine showed axonopathic changes in the sciatic nerves and spinal cord of cynomolgus monkeys receiving the drug for nine months, but telbivudine's role in pathogenesis was determined to be equivocal.²⁷

Telbivudine resistance

Because hepatitis B cannot be eradicated,³² long-term suppression of viral replication remains the therapeutic goal, either by induction of HBeAg seroconversion via drug therapy or by long-term maintenance therapy with antivirals (usually the only choice in HBeAg-negative chronic hepatitis B). A few studies have reported sustained responses after discontinuation of antiviral therapy after two to three years of sustained virological suppression in HBeAg-negative disease,^{33,34} but clinical and virologic relapses are frequent with this approach.

The biggest hindrance to long-term virologic suppression of HBV DNA is the development of drug resistance. With lamivudine, the HBV drug with the lowest genetic barrier to resistance, rates of failure and genotypic resistance are 17% after one year of therapy and increase to 70% after four years.³⁵ In HIV-coinfected patients, lamivudine-resistant HBV develops even more quickly, with nearly 95% of patients resistant after four years of treatment.^{36,37} In contrast, the drug with highest genetic barrier to resistance (requiring three mutations in the reverse transcriptase gene) has a rate of only 1.2% after six years of therapy in nucleoside-naïve

patients.³⁸ Long-term data on tenofovir are not yet available. To date, no mutations conferring resistance to tenofovir have been conclusively identified, although clinical failures are well-described.^{39–42} Adefovir falls somewhere in the middle, with resistance rates of 0%, 3%, 11%, 18%, and 29% in years 1 through 5, respectively.⁴³

In the GLOBE trial, telbivudine breakthrough and genotypic resistance rates varied by the HBeAg status of the subjects. Among HBeAg-positive subjects, virologic breakthrough at one year was about 6%, with genotypic resistance seen in 5%.¹⁴ The corresponding rates in HBeAg-negative subjects were 2.3% for virologic breakthrough and 2.2% for genotypic resistance. By year 2, 28.8% of HBeAg-positive subjects had breakthrough and 25% had resistance. Among HBeAg-negative subjects, the rates were less than half, with breakthrough in 12% and resistance in 10.8%. Rates were comparable at year 1 in the Chinese study (study 015).¹⁵ Subjects experiencing virologic breakthrough in GLOBE were successfully salvaged with adefovir, either as add-on therapy or in substitution for telbivudine.⁴⁴

Hepatitis B resistance is conferred by mutations in the reverse transcriptase domain of the HBV polymerase. For telbivudine, resistance is conferred by a single mutation at position rt204 that changes methionine to isoleucine (rtM204I).¹⁴ Secondary mutations rtL80I/V and L80I/V + L180M can accompany this signature mutation in approximately 2% and 0.3% of cases, respectively.¹⁴ This signature mutation, rtM204I, is also one of the signature mutations for lamivudine (the other being rtM204V).⁴⁵ Therefore, patients failing telbivudine are unlikely to respond to lamivudine. There is *in vitro* data to suggest that telbivudine may retain activity against rtM204V single mutants, suggesting that this cross-resistance may not be bidirectional.⁴⁶ Clinical data to support the use of telbivudine after lamivudine failure with rtM204V are lacking, and such a strategy cannot be recommended without more data.

In addition, the rtM204I mutation is a prerequisite for the development of entecavir resistance. Failure of entecavir is rare in nucleoside naïve patients because three mutations must develop for resistance to occur.^{47–49} In addition to a substitution at rt204 (either rtM204V or M204I), changes must also occur at two other positions (I169, T184, S202, or M250).⁵⁰ This had led to much different long-term entecavir resistance rates in nucleoside-naïve patients (1.2% at six years)³⁸ versus those with pre-existing lamivudine resistance, where the cumulative rate of entecavir virologic breakthrough at four years was 39.5%.⁵¹ Since lamivudine and telbivudine share the same signature mutation, it should

follow that telbivudine-experienced patients would also not respond as well to entecavir as nucleoside-naïve patients.

Adefovir and tenofovir do not share this same mutation pattern as telbivudine. Resistance to adefovir is conferred by a mutation at position rt236 from asparagine to threonine, which confers a 7- to 13-fold reduction in HBV susceptibility to the drug.⁵² A mutation from alanine to threonine at position rt181 is also associated with adefovir resistance, albeit at a lower level.⁵³ No definitive tenofovir mutations have been described to date, although rtA194T has been identified in some clinical failures.^{40,54} Others have not confirmed these findings.⁵⁵ None of these adefovir or tenofovir mutations have been associated with reduced response to telbivudine either clinically or *in vitro*,^{46,54} suggesting little or no cross-resistance between it and these nucleotide analogues.

Incorporation of telbivudine into treatment algorithms

As the landscape of HBV treatment has become more complex, the choice of initial treatment has become increasingly important in maximizing potency and minimizing antiviral resistance. When considering these factors, telbivudine falls in the middle of the nucleos(-)ide pack for both, as discussed above. Its place in the HBV armamentarium is therefore ill-defined.

Several sets of guidelines on the treatment of chronic hepatitis B have been published by professional societies.^{13,56–58} While each are in general agreement about when HBV therapy is indicated, they each pose slightly different recommendations regarding the choice of initial therapy and the specific role of telbivudine in the sequencing of available antivirals. The American Association for the Study of Liver Disease (AASLD) Guidelines and the European Association for the Study of the Liver (EASL) Guidelines both recommend entecavir or tenofovir as first-line agents when nucleos(-)ide analogues are being chosen for therapy.^{13,58} A second US guideline (the US Treatment Algorithm, compiled by an expert panel of hepatologists) also endorses entecavir or tenofovir as first-line nucleoside analogues.⁵⁶ In contrast, the Asian–Pacific consensus statement on the management of chronic hepatitis B for 2008 considers lamivudine, adefovir, entecavir, and telbivudine all to be first-line agents for hepatitis B (tenofovir has not yet become available there).⁵⁷ The first three guidelines base their recommendations on the relative potencies and high genetic barriers of resistance for entecavir and tenofovir which make them superior to the other options. With the high burden of disease in Asia and the Pacific Islands, the authors of the Asian-Pacific

consensus statement acknowledge the need for clinicians to consider drug availability, affordability, and patient choice when making therapeutic decisions. Given the similar rates of HBeAg loss and seroconversion with the agents available there, they felt there was not enough evidence to support recommending one drug over another when all other factors were also considered. Regarding telbivudine specifically, the AASLD guidelines state that “telbivudine monotherapy has a limited role in the treatment of hepatitis B”. There are no specific situations in the AASLD guidelines in which telbivudine is considered a drug of choice. The EASL guidelines are similar, although they do recommend telbivudine as an option in the rare situation where HBV needs to be treated in the absence of HIV.

Whichever drug is chosen as first-line, the monitoring for development of resistance is paramount to ongoing care. HBV DNA levels and ALT levels should be measured every three to six months. It is typical to see a rise in HBV DNA prior to biochemical flare. When this occurs, assessment of adherence to therapy should be confirmed. If adherence is determined to be acceptable, drug resistance is the most likely cause of the rise in HBV DNA, and therapy should be modified immediately, to achieve the best outcomes and avoid flare of hepatitis. The choice of salvage therapy and whether to add on or switch depends on the drug used for initial therapy. The AASLD guidelines, EASL guidelines, and US treatment algorithm, which all recommend entecavir or tenofovir first-line, recommend a switch to or add on of the other if resistance occurs. If the initial therapy was something besides entecavir or tenofovir, the salvage drug becomes more complex. Add-on telbivudine would be an option for those failing adefovir or tenofovir. The Asian–Pacific consensus statement offers little guidance for those who develop resistance; recommendations are consistent with known cross-resistance patterns for the agents used.

The US treatment algorithm introduces another approach to HBV treatment based on viral kinetic responses on treatment, or the “HBV Roadmap Concept”. This concept grew, in part, from data in the GLOBE study of telbivudine that HBV DNA suppression at week 24 (or lack thereof) could predict HBeAg loss and seroconversion at week 104.⁵⁹ In that study, among patients with HBV DNA > 4 log copies/mL at week 24 of telbivudine, HBeAg seroconversion was 10% at week 104 compared to 86% in those with undetectable HBV DNA at week 24. Rates of resistance were also correlated with week 24 response, with 6% resistance at week 104 among subjects with undetectable HBV DNA at week 24 and 49% resistance rate in those with HBV DNA > 4 log copies/mL.¹⁹

The algorithm recommends an assessment of antiviral efficacy at week 24 for patients beginning HBV therapy. If the patient has experienced a complete response (HBV DNA negative by polymerase chain reaction), the same therapy can be continued with appropriate monitoring. If the virologic response is inadequate (>2000 IU/mL, or $>10,000$ copies/mL), a more potent drug should be added, and monitoring continued every three months. If there has been a partial virologic response (HBV DNA > 60 to <2000 IU/mL or >300 to $<10,000$ copies/mL), the change depends on the initial drug used. For drugs with a low genetic barrier to resistance (lamivudine, telbivudine), a second drug with a different genetic mutation profile should be added. For drugs with a high genetic barrier to resistance (tenofovir, entecavir), the patient should continue to be monitored every three months with no drug added. For patients on a drug with suboptimal viral potency (adefovir, telbivudine), physicians should continue to monitor until 48 weeks and then add another more potent drug that is not cross-resistant if not fully suppressed.⁵⁶

To date, there have been no specific studies of telbivudine in the setting of pre- or post-liver transplantation.

Summary and future directions

The last five years have emerged as a new era in the treatment of chronic hepatitis B. Advances in therapeutics and the approval of new drugs have been accompanied by a better understanding of natural history and pathogenesis, as well as better diagnostics. There are few new drugs for hepatitis B in the pipeline, with the agent farthest along in development, clevudine, halted for problems with muscle toxicity.⁶⁰ Therefore, future directions in hepatitis B therapy will focus on using the available drugs most effectively, either through logical sequential therapy or combinations of drugs to delay the development of drug resistance. In addition, methods of cost-efficiently determining resistance mutations will need to be developed and made commercially available as treatment failure becomes more complex. Results of genotypic testing can then be used to inform later therapeutic decisions.

Telbivudine remains a drug searching for its niche in the hepatitis B world. Although it has potent viral suppression, high resistance rates keep it from being a preferred agent. As an L-nucleoside, its signature mutation, rtM204I, confers full cross-resistance to lamivudine and partial cross-resistance to entecavir. Cross-resistance to emtricitabine (currently being investigated for hepatitis B) is also predicted. Therefore, use as initial therapy not only causes the loss of itself as a treatment option, but also the loss of several other

agents, including the most potent and durable option for hepatitis B, entecavir. Telbivudine's role now is best defined as add-on therapy for the nucleotide analogues (adefovir or tenofovir) when a suboptimal or partial virologic response is observed at week 48 or when resistance develops to one of these agents. Other possibilities for use that should be investigated include prophylaxis before chemotherapy in hepatitis B carriers or as prophylaxis in liver transplant recipients of hepatitis B core antibody-positive livers. In both these scenarios, telbivudine offers an option with less chance of resistance than the currently used lamivudine, albeit at higher cost. Consequently, telbivudine will remain a "B" list drug in the "B" world.

Disclosures

The authors report no conflicts of interest in this work.

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