Hepatitis B Goes Globe: Telbivudine as a New Treatment Option

Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et al.; Globe Study Group. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007; 357:2576-2588. (Reprinted with permission.)

Abstract

Background: **Reducing hepatitis B virus (HBV) replication to minimal levels is emerging as a key therapeutic goal for chronic hepatitis B.** ***Methods:*** **In this double-blind, phase 3 trial, 1370 patients with chronic hepatitis B were randomly assigned to receive 600 mg of telbivudine or 100 mg of lamivudine once daily. The primary efficacy end point was noninferiority of telbivudine to lamivudine for therapeutic response (i.e., a reduction in serum HBV DNA levels to fewer than 5 $\log_{10}$ copies per milliliter, along with loss of hepatitis B e antigen [HBeAg] or normalization of alanine aminotransferase levels). Secondary efficacy measures included histologic response, changes in serum HBV DNA levels, and HbeAg responses.** ***Results:*** **At week 52, a significantly higher proportion of HBeAg-positive patients receiving telbivudine than of those receiving lamivudine had a therapeutic response (75.3% vs. 67.0%, P=0.005) or a histologic response (64.7% vs. 56.3%, P=0.01); telbivudine also was not inferior to lamivudine for these end points in HBeAg-negative patients. In HBeAg-positive and HBeAg-negative patients, telbivudine was superior to lamivudine with respect to the mean reduction in the number of copies of HBV DNA from baseline, the proportion of patients with a reduction in HBV DNA to levels undetectable by polymerase-chain-reaction assay, and development of resistance to the drug. Elevated creatine kinase levels were more common in patients who received telbivudine, whereas elevated alanine aminotransferase and aspartate aminotransferase levels were more common in those who received lamivudine.** ***Conclusions:*** **Among patients with HBeAg-positive chronic hepatitis B, the rates of therapeutic and histologic response at 1 year were significantly higher in patients treated with telbivudine than in patients treated with lamivudine. In both the HBeAg-negative and the HBeAg-positive groups, telbivudine demonstrated greater HBV DNA suppression with less resistance than did lamivudine. (ClinicalTrials.gov number, NCT00057265 [ClinicalTrials.gov].)**

Comment

With approximately 400 million chronic hepatitis B virus (HBV) carriers being at risk for disease-related complications such as liver cirrhosis or hepatocellular carcinoma (HCC), hepatitis B represents a global health challenge. The Globe Study Group now reported data for the latest approved oral nucleoside analog, telbivudine (Tyzeka™, Idenix Pharmaceuticals; Sebivo™, Novartis).[1] This expands the options for the treatment of chronic HBV infection to now six approved antiviral agents (standard interferon, pegylated interferon, lamivudine, adefovir, entecavir, and telbivudine), plus at least three others (emtricitabine, clevudine, tenofovir) that are in late phases of clinical evaluation.[2] The freedom of choosing among these drugs, which have all been proven effective in the short term, raises the question of which patients should be assigned to which therapeutic regimen?

In the Globe study, treatment-naïve patients with hepatitis B e antigen (HBeAg)-positive (n = 921) or HBeAg-negative (n = 446) chronic HBV infection were randomly assigned to receive 600 mg telbivudine or 100 mg lamivudine once daily.[1] All patients had biochemical signs of liver inflammation (alanine aminotransferase > 1.3-fold upper limit of normal), relatively high HBV viral loads ($>10^6$ copies/mL) and no disease-related complications (for example, cirrhosis, HCC) or relevant comorbidities. The study cohort comprised mainly Chinese and non-Chinese Asian patients (about 80% of the HBeAg-positive and 65% of the HBeAg-negative individuals were of Asian ethnicity), consequently causing a predominance of HBV genotypes C and B in this study. The therapeutic and histologic response was analyzed at week 52, while the patients continued their treatment for another year. At week 52, telbivudine showed a (moderately) better response rate in patients who were HBeAg-positive than did lamivudine, whereas no significant difference in the therapeutic or histologic response was seen for patients who were HBeAg-negative. The most notable disparity between the two drugs was found for circulating HBV DNA levels: telbivudine administrations reduced serum HBV DNA more efficiently and more often below the detection limit of 300 copies/mL than lamivudine, in patients who were HBeAg-positive and HBeAg-negative.[1] Similar observations were reported from a smaller study comparing telbivudine and lamivudine in 332 Chinese patients, who were mostly HBeAg-positive.[3] Telbivudine was generally safe and well-tolerated, but elevated creatine kinase levels and occasional incidences of myopathy were specifically observed in telbivudine-treated patients.[1,3,4] Of note, potential interactions of telbivudine with other drugs—for example, statins—are not known at present.

Comparing the results from the Globe study to prior large studies with the other nucleoside (nucleotide) analogs illustrates that telbivudine has an excellent potency with respect to its ability to suppress HBV DNA (Table 1). This corresponds to decent results in short-term mea-

Table 1. Comparison of Different Nucleoside/Nucleotide Analogs in the Treatment of Chronic HBV Infection After 1 Year of Therapy

Characteristic	Telbivudine	Lamivudine	Adefovir	Entecavir
HBeAg-positive patients				
ALT normalization	77%	75%	48%	68%
Histologic response	65%	56%	53%	72%
HBeAg (HBsAg) loss	26 (<1)%	23 (<1)%	24 (<1)%	22 (2)%
Serum HBV DNA undetectable	60%	40%	21%	67%
HBeAg-negative patients				
ALT normalization	74%	79%	72%	78%
Histologic response	67%	66%	64%	70%
Serum HBV DNA undetectable	88%	71%	51%	90%
Genotypic antiviral resistance				
Year 1	7%	24%	0%	0%
Year 2/3/4	?	38/49/67%	3/11/18%	0/1/?%
Cost of therapy per year	$5,811	$2,482	$6,647	$8,694
Side effects/concerns	myopathy?	minor	nephrotoxicity	minor

Efficacy data for telbivudine and lamivudine were extracted from the Globe Study,[1] data for adefovir and entecavir were extrapolated from other similar studies with treatment-naïve patients (modified from Hoofnagle et al.[2]). For antiviral resistance, genotypic resistance (detection of mutation with or without virological breakthrough) for telbivudine is given according to Lai et al.[1] and for other antivirals from larger analyses.[2] Costs for therapy as published by Hoofnagle et al.[2] In telbivudine-treated patients, elevated creatine kinase levels and occasional incidences of myopathy have been reported.[1,3,4]

sures for treatment efficacy, such as biochemical and histological response, or HBeAg loss for patients who were HBeAg-positive. Given the increasing body of evidence about a direct association between circulating HBV DNA and disease-related complications such as liver cirrhosis or HCC,[5] telbivudine's robust suppression of HBV DNA could likely be beneficial in the long run. However, this needs to be investigated in adequate studies on long-term outcomes, and could be hampered by an unfavorable feature of telbivudine, namely, its resistance profile. In the Globe study, 6.8% of all telbivudine recipients in the study harbored the M204I mutation associated with telbivudine (as well as lamivudine) resistance[6]; virological resistance developed in 5% of the patients who were HBeAg-positive and 2.2% of the patients who were HBeAg-negative after 52 weeks of telbivudine.[1] This is significantly more than in adefovir-treated patients[4] and than was observed for entecavir or tenofovir.[2]

Although the approval of telbivudine certainly expands treatment options for chronic HBV infection, telbivudine is not compellingly superior to the other antivirals (Table 1). Ideally, telbivudine's remarkable potency should be combined with agents that could manage to lose hepatitis B surface antigen and to achieve a sustained response (pegylated interferons?) and/or nucleotide agents with a lower and nonoverlapping viral resistance profile (tenofovir? adefovir?). Unfortunately, these issues remain unresolved until large studies comparing new combinations and new therapeutic concepts are conducted. At present, the practical management of patients should be based on the potency and resistance profile of the available agents, severity of liver disease or comorbid illnesses, history of exposure to antivirals, but also pretreatment HBV DNA level and possible need for rapid viral suppression.[7] In this respect, telbivudine is a new option, though not the ultimate answer.

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References

1. Lai CL, Gane E, Liaw YF, Hsu CW, Thongsawat S, Wang Y, et al. Telbivudine versus lamivudine in patients with chronic hepatitis B. N Engl J Med 2007;357:2576-2588.
2. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok AS. Management of hepatitis B: summary of a clinical research workshop. HEPATOLOGY 2007; 45:1056-1075.
3. Hou J, Yin YK, Xu D, Tan D, Niu J, Zhou X, et al. Telbivudine versus lamivudine in Chinese patients with chronic hepatitis B: Results at 1 year of a randomized, double-blind trial. HEPATOLOGY 2007;47:447-454.
4. Chan HL, Heathcote EJ, Marcellin P, Lai CL, Cho M, Moon YM, et al. Treatment of hepatitis B e antigen positive chronic hepatitis with telbivudine or adefovir: a randomized trial. Ann Intern Med 2007;147:745-754.
5. Tacke F, Trautwein C. Serum hepatitis B virus DNA level as a risk predictor for liver disease complications. Nat Clin Pract Gastroenterol Hepatol 2006;3:426-427.
6. Tacke F, Manns MP, Trautwein C. Influence of mutations in the Hepatitis B Virus genome on virus replication and drug resistance - implications for novel antiviral strategies. Curr Med Chem 2004;11:2667-2777.
7. Feld JJ, Ghany MG. Evolution of therapy for chronic hepatitis B: progressing from the simple to the complex. Ann Intern Med 2007;147:806-808.

Published online in Wiley InterScience (www.interscience.wiley.com).
DOI 10.1002/hep.22299
Potential conflict of interest: Drs. Trautwein and Tacke received grants from Novartis, Bristol-Myers Squibb, and Gilead.