Clevudine Demonstrates Potent Antiviral Activity in Naïve Chronic Hepatitis B Patients

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Key Words

Hepatitis B virus • Post marketing surveillance • Viral replication • Viral breakthrough • Clevudine

Abstract

Objectives: Clevudine has demonstrated antiviral potency in the treatment of naïve chronic hepatitis B patients in pivotal studies. The objectives of this study were to evaluate the safety and efficacy of a 1-year treatment with clevudine in chronic hepatitis B patients. **Methods:** This is a post-marketing surveillance using case report forms which were submitted to the health authorities. **Results:** Analysis of individual data showed that hepatitis B virus (HBV) DNA after a 1-year treatment was <141,500 copies/ml in 96% of hepatitis B e antigen (HBeAg)-positive and 100% of HBeAg-negative patients. The proportion of patients with HBV DNA <2,000 copies/ml after a 1-year treatment was 74%: 71% of HBeAg-positive and 93% of HBeAg-negative patients. Most of the patients with HBV DNA below the detection limit with each

assay at week 24 showed sustained viral suppression up to week 48. The proportion of patients who showed normal alanine aminotransferase at week 48 was 86% in HBeAg-positive patients and 87% in HBeAg-negative patients. The rates of HBeAg-loss were 21%. Two patients showed viral breakthrough during treatment. **Conclusion:** Clevudine monotherapy demonstrates potent antiviral activity as well as biochemical and serological response with a 0.7% rate of viral breakthrough in naïve chronic hepatitis B patients.

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Introduction

Although effective vaccines are available in many countries, hepatitis B virus (HBV) infection is common and a major worldwide health threat. Chronic hepatitis B patients are at high risk of progression to cirrhosis, end-stage liver disease and primary hepatocellular carcinoma, which is associated with considerable mortality [1].

Approximately 15–40% of infected subjects will develop cirrhosis, liver failure or hepatocellular carcinoma [2].

Several oral antiviral agents are used for chronic HBV infection. Lamivudine has been shown to improve short-term outcome in some patients [3]. However, these treatments do not provide a cure or durable remission in the majority of patients. Lamivudine has a favorable safety profile; however, long-term therapy is required, which can lead to the selection of drug-resistant mutants [4, 5]. Adefovir dipivoxil and entecavir have the advantage of retaining antiviral activity against lamivudine-resistant HBV isolates and a lower risk of developing drug-resistant mutants [6, 7]. However, adefovir dipivoxil and entecavir also require long-term therapy, and discontinuation of therapy is associated with a prompt relapse to disease activity. An ideal regimen should be safe with more potent and sustained viral suppression, with a minimal chance of developing resistant mutants.

Clevudine [1-(2-deoxy-2-fluoro- β -L-arabinofuranosyl) thymine, L-FMAU], which is being marketed in Korea, is a nucleoside analogue of the unnatural β -L configuration that has potent activity against HBV and some activity against the Epstein-Barr virus *in vitro* [8]. The lack of cytotoxicity reflects the inability of human cellular DNA polymerases α , β , γ and δ to utilize the 5'-triphosphate of clevudine as a substrate [9]. Moreover, clevudine was found to have no effect on mitochondrial structure, DNA content or function [9].

A unique advantageous characteristic of clevudine is the prolonged and sustained suppression of viral replication even after withdrawal of treatment. Serum woodchuck hepatitis virus (WHV) DNA remained undetectable for up to 56 weeks after WHV-infected animals were given oral doses of clevudine (10 mg/kg daily) for 12 weeks [10]. It has been demonstrated that the sustained viral suppression is associated with a significant reduction of covalently closed circular DNA in hepatocytes [11].

In the pivotal phase III clinical trials [12, 13], clevudine demonstrated potent antiviral efficacy and significant biochemical improvement after 24 weeks of therapy. In hepatitis B e antigen (HBeAg)-positive chronic hepatitis B patients, clevudine (30 mg) produced highly potent antiviral activity [$-5.1 \log_{10}$ copies/ml change from baseline, 59% with negative HBV DNA (<300 copies/ml) by PCR at the end of 24-week treatment] and biological improvement leading to alanine aminotransferase (ALT) normalization (68% at week 24). In HBeAg-negative chronic hepatitis B patients, 92% of the patients had negative HBV DNA by PCR and 75% had normal ALT at the

end of 24 weeks of treatment. As already observed in animal models and in the previous clinical trials [14–16], sustained viral suppression and biochemical improvement were observed at 6 months post-treatment in these studies.

We describe here the results of 48 weeks of clevudine treatment to see the viral suppression potency and resistance profile.

Patients and Methods

Post-marketing surveillance was performed to evaluate the safety and efficacy of clevudine in the naïve chronic hepatitis B patients. The protocol and case report form was approved by the health authorities before starting.

Patients who started clevudine monotherapy between February 2007 and June 2007 were included in this surveillance. Efficacy parameters included serum HBV DNA, ALT and serology for HBeAg.

For the detection of HBV DNA values, CMHA [Hybrid Capture II Kit; Digene, Gaithersburg, Md., USA; limit of detection (LOD) of 141,500 copies/ml, 63 patients], bDNA (Bayer HealthCare LLC, Tarrytown, N.Y., USA; LOD of 2,000 copies/ml, 156 patients) and PCR [LOD of 125 copies/ml by real-time PCR and 300 copies/ml by Amplicor PCR (Roche Molecular Systems, Branchburg, N.J., USA); 125 patients] were used. Laboratory tests were measured at each clinical site. The proportion of patients with HBV DNA $<141,500$ copies/ml and $<2,000$ copies/ml were evaluated. At each time-point, patients with missing data were excluded from the analysis at that time-point.

Biochemical response was defined as a normalization of serum ALT. Serological response was assessed during the surveillance period. HBeAg-loss was defined as the disappearance of HBeAg, and HBeAg seroconversion was defined as HBeAg disappearance combined with the appearance of anti-HBe [16].

Viral breakthrough, which was defined as 1 $\log_{10}$ -increase from nadir, was assessed during treatment. For the evaluation of viral breakthrough, patients using CMHA for HBV DNA titration were excluded due to the LOD.

The safety analysis included all adverse events, serious adverse events and laboratory abnormalities which were recorded over 1 year. The safety evaluation was evaluated every 4 weeks and efficacy evaluation was scheduled every 12 weeks.

Results

Patients

The data from the 344 patients treated with clevudine (30 mg) from several hospitals and clinics were collected and analyzed. Among them, 274 patients were HBeAg-positive and 70 patients were HBeAg-negative before clevudine treatment. All patients were Korean, of which 229 (67%) were male and 115 (33%) were female. All patients, except 10 (3 HBeAg-positive, 7 HBeAg-negative),

showed HBV DNA levels of more than 141,500 copies/ml before clevudine treatment.

The majority of patients (98%) had ALT values more than the upper limit of normal before clevudine treatment.

Sixty-three patients did not finish treatment: 1 because of viral breakthrough, 35 because of patient withdrawal, 25 because of financial difficulty and 2 due to loss of follow-up.

Antiviral Activity

Table 1 displays the efficacy data. The proportion of patients with HBV DNA <141,500 copies/ml after a 1-year treatment was 96%: 96% of HBeAg-positive and 100% of HBeAg-negative. The proportion of patients with HBV DNA <2,000 copies/ml after the 1-year treatment was 74%: 71% of HBeAg-positive and 93% of HBeAg-negative.

After the 1-year clevudine therapy, 3% of the patients experienced treatment failure. All of them were HBeAg-positive at baseline. In this surveillance, treatment failure was defined as not achieving a >2 log₁₀-decrease from baseline and maintaining a HBV DNA level over the LOD for 1 year.

Ninety-two percent of the patients who showed HBV DNA below the detection limit with each assay at week 24 showed sustained viral suppression up to week 48.

At baseline, median ALT was 116.5 IU/l. After the 1-year treatment, 86% of HBeAg-positive and 87% of HBeAg-negative patients had normal ALT. HBeAg-loss was observed in 21%, and 13% had HBeAg seroconversion.

Two patients (0.7%) showed viral breakthrough (1 log₁₀-increase from the nadir during treatment) during therapy.

During the 1-year treatment, 7 patients (3%) experienced >5-times the upper limit of normal in ALT, which resolved without any special treatment. Adverse events reported during the 1-year treatment were ALT elevation and creatine elevation, both of which resolved without any treatment.

Discussion

Clevudine (30 mg once daily) produced highly potent antiviral activity and biochemical improvement in naïve chronic hepatitis B patients when used as monotherapy.

Clevudine exerted potent viral suppression from baseline in serum HBV DNA, leading to a high proportion of

Table 1. Summary of serum HBV DNA and ALT response

	Total	Clevudine 30 mg	
		HBeAg-positive	HBeAg-negative
Serum HBV DNA <141,500 copies/ml			
Week 12	171/288 (59)	128/236 (54)	43/52 (83)
Week 24	213/274 (78)	178/236 (75)	35/38 (92)
Week 36	235/256 (92)	199/220 (91)	36/36 (100)
Week 48	246/256 (96)	215/225 (96)	31/31 (100)
Serum HBV DNA <2,000 copies/ml			
Week 12	65/232 (28)	42/184 (23)	23/48 (48)
Week 24	113/219 (52)	86/186 (46)	27/33 (82)
Week 36	143/205 (70)	116/174 (67)	27/31 (87)
Week 48	152/206 (74)	127/179 (71)	25/27 (93)
Normal ALT			
Week 12	142/292 (49)	95/233 (41)	47/59 (80)
Week 24	194/285 (68)	161/245 (66)	33/40 (83)
Week 36	207/264 (78)	176/225 (78)	31/39 (80)
Week 48	232/271 (86)	200/234 (86)	32/37 (87)

Figures in parentheses represent percentages.

patients (96% in HBeAg-positive and 100% in HBeAg-negative patients) achieving serum HBV DNA levels <141,500 copies/ml. Seventy-one percent of the HBeAg-positive patients and 93% of the HBeAg-negative patients had HBV DNA <2,000 copies/ml.

It is known that the viral response at week 24 is a predictor of viral response during long-term therapy [17]. Our results also showed that 92% of the patients with viral suppression up to the detection limit with each assay at week 24 maintained viral response up to week 48. Most of the patients who showed HBV DNA below the detection limit with each assay at week 24 showed sustained viral suppression up to week 48.

In addition, clevudine showed a good biochemical and serological response after the 1-year treatment. Eighty-six percent of the patients showed normal ALT after the 1-year treatment and, with the exception of 3 patients, all patients showed ALT values ≤2 × ULN after the 1-year treatment. Furthermore, 21% of the patients had HBeAg-loss and 13% had HBeAg seroconversion after the 1-year treatment.

Two patients (0.7%) showed viral breakthrough (1 log₁₀-increase from the nadir during treatment) during the 1-year treatment. One of them showed viral suppression to <300 copies/ml at week 24 and then viral breakthrough to 5,310 copies/ml at week 48 with normal ALT.

In the pivotal phase III trials [12, 13], no clevudine resistance was observed during the 24-week treatment. During the 1-year treatment in this surveillance, 0.7% showed viral breakthrough, which demonstrates that the emergence of resistance with clevudine is very low for 1 year.

In this surveillance, 37 patients with cirrhosis (compensated or decompensated) were included. Among the 12 cirrhotic patients who completed the 1-year treatment, 10 showed viral suppression to the LOD and normal ALT after the 1-year treatment. Twenty-five patients discontinued the surveillance due to financial difficulty without relation to clevudine, as they were not covered by the

insurance system in the early phase of clevudine marketing. These results prove that clevudine also shows very rapid and potent viral suppression in hepatitis B-related cirrhosis patients, even though only a small number of patients were included in this surveillance. Further studies on a larger scale may be needed to clarify the safety of clevudine in patients with cirrhosis. In conclusion, our data showed that clevudine seems to be one of the most potent antiviral agents among the agents currently being marketed [18–20]. Clevudine's strong viral suppression and low rate of resistance development would be very helpful in the treatment of chronic hepatitis B patients.

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