A comparison of 48-week treatment efficacy between clevudine and entecavir in treatment-naïve patients with chronic hepatitis B

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Abstract

Purpose Clevudine and entecavir are currently available in Korea as antiviral drugs against chronic hepatitis B (CHB). We aimed to compare the efficacy of clevudine and entecavir therapy.

Methods Treatment-naïve CHB patients who received 30 mg of clevudine or 0.5 mg of entecavir a day were analyzed. Mean reduction of hepatitis B virus (HBV) DNA levels, complete virological response (cVR, undetectable HBV DNA by real-time PCR), biochemical response (recovery to normal ALT level), and hepatitis B e antigen (HBeAg) seroconversion rate at the 48th week of treatment were assessed.

Results A number of 59 patients in clevudine group and 61 patients in entecavir group were included. Mean HBV DNA reductions from baseline were similar in the clevudine and entecavir groups, -6.4 versus -6.8 $\log_{10}$ copies/mL in HBeAg-positive ($p = 0.417$) and -6.9 versus -7.0 $\log_{10}$ copies/mL in HBeAg-negative patients ($p = 0.640$). The proportion of patients who achieved cVR was not different between the two groups, 53 versus 55% in HBeAg-positive ($p = 1.000$) and 100 versus 95% in HBeAg-negative patients ($p = 0.452$). Biochemical response rates and

HBeAg seroconversion rates were also similar in both the groups. Two (3.4%) patients in clevudine group showed virologic breakthrough with rtM204I mutation using direct sequencing analysis. Clinical myopathy occurred in two (3.4%) patients in clevudine group.

Conclusion Mean reduction of viral loads was similar between clevudine and entecavir groups during 48 weeks. However, virologic breakthrough and significant myopathy were noted only in clevudine-treated patients. Therefore, more attention should be paid to patients receiving clevudine.

Keywords Hepatitis B virus · Clevudine · Entecavir

Introduction

Hepatitis B virus (HBV) infection is a major healthcare problem worldwide [1]. Currently approved oral antiviral agents for chronic hepatitis B (CHB) include lamivudine, adefovir dipivoxil, entecavir, telbivudine, and tenofovir dipivoxil fumarate worldwide, and clevudine in Korea and Philippines. At present, entecavir and tenofovir are widely recommended as first-line therapy for treatment-naïve CHB patients since these two drugs have shown superior virologic, biochemical, and histologic response and lower rate of developing drug-resistant mutants than lamivudine, adefovir, or telbivudine [2, 3].

Clevudine [1-(2-deoxy-2-fluoro- β -L-arabinofuranosyl)thymine, L-FMAU] is a nucleoside analog of the unnatural β -L configuration that has potent activity against HBV. Clevudine is efficiently phosphorylated by three intracellular enzymes to clevudine-triphosphate in target cells, which inhibits DNA polymerase by not incorporating into the viral DNA but rather binding to the polymerase [4, 5].

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A unique advantageous characteristic of clevudine is prolonged sustained suppression of viral replication even after withdrawal of treatment [4, 6, 7]. The sustained viral suppression has been demonstrated to be associated with significant reduction of covalently closed circular DNA (ccc-DNA) in hepatocytes [8, 9]. Clevudine has also showed potent antiviral activity, which was mean DNA reduction of -4.6 to $5.7 \log_{10}$ copies/mL in hepatitis B e antigen (HBeAg)-positive patients and $-3.7 \pm 4.9 \log_{10}$ copies/mL in HBeAg-negative patients over 48 weeks [10–13]. However, most studies about clevudine included heterogeneous populations and/or were performed without control.

In 2006, clevudine and entecavir were approved by Korean Food and Drug Administration (KFDA) for marketing. Recently, a global clinical study of clevudine sponsored by Pharmasset Inc. has been terminated voluntarily due to safety concern about myopathy reported during marketing in South Korea (Pharmasset Inc. press release, April 20, 2009). However, after extensive review of the safety data, KFDA concluded that clevudine-associated myopathy is infrequent, reversible, and not life threatening and approved continued marketing of clevudine. Therefore, we have had unique opportunity for head-to-head comparison between clevudine and entecavir.

This study was conducted to compare the efficacy of clevudine and entecavir at 48 weeks of treatment.

Materials and methods

This retrospective study was approved as an exemption from consent by the Institutional Review Board of Samsung Medical Centre. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the institution's Human Research Committee.

Patients

Treatment-naïve patients who visited Samsung Medical Centre, Seoul, Korea from January 2007 to March 2008 and received clevudine 30 mg or entecavir 0.5 mg a day over 48 weeks were examined. Whether a patient would receive clevudine or entecavir was determined by the patients themselves after being informed of the benefits and risks of the two drugs, and the last follow-up visit was completed before April 2009. The adherence to prescribed medication was confirmed by telephone, and the poor compliance was defined when actual dose administered was less than six times a week.

A diagnosis of CHB was made either histologically or clinically. The clinical diagnostic criteria for CHB included documented hepatitis B surface antigens (HBsAg) over a

6-month period and HBV DNA $>10^5$ copies/mL with elevated serum alanine aminotransferase (ALT) levels before the initial antiviral therapy. Patients with cirrhosis or hepatocellular carcinoma were excluded. Cirrhosis was identified based on histologic evidence or any clinical feature of portal hypertension, such as esophagogastric varices, ascites, hepatic encephalopathy, and imaging features that were suggestive of cirrhosis on sonographic examination or computed tomography. Patients who had history of habitual alcohol ingestion (≥ 30 g per day), co-infection with chronic hepatitis C or human immunodeficiency virus, severe obesity (body mass index ≥ 28 kg/m²), autoimmune disease such as autoimmune hepatitis, or hepatic infiltrative disease were excluded. With scrupulous reviewing chart, cases of insufficient baseline characteristics that can make analysis impossible were excluded.

Efficacy evaluation

Serum ALT was measured with an enzymatic assay. Serum HBsAg, antibodies to HBsAg, HBeAg, and antibodies to HBeAg (anti-HBe) were detected by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Serum HBV DNA was quantified by real-time polymerase chain reaction (PCR) assay, the COBAS Taq-Man HBV quantitative test (Roche Molecular Systems Inc., Branchburg, NJ, USA), which had a lower limit of quantification of 60 copies/mL (12 IU/mL).

Mean reduction of HBV DNA levels, complete virological response (cVR), biochemical response, and HBeAg sero-conversion rate at 48th week of treatment were assessed. A cVR was defined as undetectable DNA by real-time PCR assay within 48 weeks of therapy. A partial virological response was defined as a decrease in HBV DNA of more than $1 \log_{10}$ copies/mL but still detectable HBV DNA by real-time PCR assay at 48th week. Primary non-response was defined as a decrease in serum HBV DNA of less than $2 \log_{10}$ copies/mL after at least 24 weeks of therapy. Biochemical response was defined as recovery to normal ALT level.

Genotypic analysis

Genotypic analysis was performed in patients showing virologic breakthrough. In order to identify emerging HBV polymerase substitutions that may be associated with resistance, PCR amplification was performed by using the following primers: external primers were forward primer for reverse transcriptase (RTF) (5'-tat gtt gcc cgt ttg tcc tc-3', position 460–479) and reverse primer for reverse transcriptase (RTR) (5'-tga cat act ttc caa tca ata gg-3', position 970–992). Internal primers were nested forward primer for reverse transcriptase (RTNF) (5'-aaa acc ttc gga cgg aaa ct-3', position 574–593) and nested reverse primer for

reverse transcriptase (RTNR) (5'-tgc ggt aaa gta ccc caa ct-3', position 895–914). The PCR amplified DNA was purified by using QIAquick PCR purification kit (QIAGEN, Hilden, Germany). Purified DNA was treated with an ABI Prism BigDye Terminator v3.1 Cycle Sequencing kit (Applied Biosystems, CA, USA). The primers used for direct sequencing were RTNS and RTNR. DNA sequencing was performed in both directions and was analyzed on an Applied Biosystems 3130 Genetic Analyzer (Applied Biosystems, Foster city, CA, USA). The rtL180M and rtM204V/I/S were considered as clevudine-associated mutations.

Clinical myopathy

As for patients who show muscular symptoms, such as pain or weakness, serum creatinine phosphokinase (CK) and lactate dehydrogenase (LDH) level were measured. Patients with muscular symptom with elevated CK level were defined as having clinical myopathy. Those who had taken other causes to induce myopathy, such as excessive exercise, traumatic muscle injury, lipid-lowering agent, recent high-dose glucocorticoid treatment, neuromuscular blocking drug, alcohol abuse, chloroquine or amiodarone, were excluded.

Statistical analysis

Statistical significance for comparison was evaluated by the Mann–Whitney *U* test and Pearson's χ^2 test. Those analyses were performed using SAS software (Version 8.2, Cary, NC, USA). Differences were considered significant when the *p* value was less than 0.05.

Results

Of 130 eligible patients, seven patients were transferred to the community hospital for patients' convenience, and

three patients were excluded due to poor compliance (Fig. 1). Analysis was performed on per protocol basis unless otherwise indicated. Baseline characteristics including age, sex, liver function test, prothrombin time, platelet counts, and HBV DNA levels were quite similar in clevudine and entecavir groups (Table 1).

Virologic response

HBeAg-positive patients (78)

At 48th week, 52.8% (19/36) in clevudine group and 54.8% (23/42) in entecavir group showed cVR (Fig. 2a), and its proportion was not significantly different between the two groups (Table 2). Mean reduction of serum HBV DNA level over 48 weeks was -6.4 ± 2.0 and $-6.8 \pm 1.6 \log_{10}$ copies/mL from baseline in clevudine and entecavir groups, respectively ($p = 0.417$; Fig. 3). Most of the decrements occurred within the first 24 weeks in both the groups ($-5.8 \pm 1.5 \log_{10}$ copies/mL in clevudine group vs. $-6.1 \pm 1.5 \log_{10}$ copies/mL in entecavir group, $p = 0.158$).

HBeAg-negative patients (42)

Among 42 HBeAg-negative patients, all patients who received clevudine (23/23) and 94.7% of patients who received entecavir (18/19) showed cVR (Fig. 2a), and its proportion was not significantly different between the two groups ($p = 0.452$; Table 2). Mean reduction in serum HBV DNA levels over 48 weeks was not different between clevudine- and entecavir-treatment groups (-6.9 ± 1.0 vs. $-7.0 \pm 0.8 \log_{10}$ copies/mL, $p = 0.640$; Fig. 3). Major reduction occurred within 24 weeks in both the groups ($-6.6 \pm 1.2 \log_{10}$ copies/mL in clevudine group vs. $-6.6 \pm 1.2 \log_{10}$ copies/mL in entecavir group, $p = 0.752$).

Fig. 1 Flow chart of this study. CLV clevudine, ETV entecavir, LC liver cirrhosis, HCC hepatocellular carcinoma, CHB chronic hepatitis B

Table 1 Baseline characteristics of the patients

Variables	HBeAg-positive			HBeAg-negative		
	Clevudine (n = 37)	Entecavir (n = 42)	<i>p</i> value	Clevudine (n = 23)	Entecavir (n = 19)	<i>p</i> value
Age (years)	42.4 ± 8.8	42.8 ± 11.2	0.845	44.5 ± 10.6	45.2 ± 6.3	0.919
Sex (male:female)	27:9	29:13	0.560	15:8	16:3	0.163
Body weight (kg)	66.0 ± 11.0	69.4 ± 10.5	0.177	67.7 ± 11.6	71.5 ± 11.7	0.546
ALT (U/L)	243.6 ± 179.8	230.0 ± 193.0	0.093	187.5 ± 134.2	215.6 ± 241.6	0.445
Total bilirubin (mg/dL)	1.4 ± 1.6	2.0 ± 4.2	0.461	1.2 ± 0.9	1.3 ± 0.8	0.611
Albumin (mg/dL)	4.0 ± 0.3	3.9 ± 0.3	0.167	4.1 ± 0.3	4.1 ± 0.3	0.769
Prothrombin time INR	1.1 ± 0.1	1.2 ± 0.2	0.214	1.1 ± 0.1	1.1 ± 0.1	0.988
Platelet ($\times 10^3/\text{mm}^3$)	182.0 ± 42	171.2 ± 45.0	0.297	181.3 ± 54.2	161.3 ± 42.6	0.240
HBV DNA level ($\log_{10}$ copies/mL)	8.2 ± 1.2	8.3 ± 1.3	0.623	6.9 ± 1.0	7.2 ± 1.0	0.456

ALT alanine aminotransferase, HBV hepatitis B virus

Fig. 2 Proportion of patients achieving complete virologic response (a) and biochemical response (b) at 48th week

Biochemical response

HBeAg-positive patients (78)

Normalization of ALT at 48 weeks was observed in 83.3% (30/36) in clevudine and 83.3% (35/42) in entecavir group ($p = 1.000$; Fig. 2b).

HBeAg-negative patients (42)

In HBeAg-negative patients, 78.3% (18/23) and 73.7% (14/19) in clevudine and entecavir group showed biochemical response, respectively ($p = 1.000$; Fig. 2b).

Serologic response

Among the 78 HBeAg-positive patients, 25.0% (9/36) in clevudine group and 31.0% (13/42) in entecavir group had

HBeAg loss. Among those, 22.2% (8/36) in clevudine group and 26.2% (11/42) in entecavir group showed HBeAg seroconversion. There was no significant difference in seroconversion rates (Table 3).

Resistance

At 48th week, two HBeAg-positive patients in clevudine group showed the virologic breakthrough. Genotypic analysis by direct sequencing revealed the rtM204I mutations in YMDD motif of HBV polymerase gene in those patients. Clinical and laboratory data of those patients are described in Table 4.

Adverse events

Two patients who received clevudine demonstrated the proximal muscle weakness at the visit of 48th week.

Table 2 Comparison of virologic response at week 48 between clevudine and entecavir

Variables	HBeAg-positive			HBeAg-negative		
	Clevudine (<i>n</i> = 36)	Entecavir (<i>n</i> = 42)	<i>p</i> value	Clevudine (<i>n</i> = 23)	Entecavir (<i>n</i> = 19)	<i>p</i> value
Complete VR	19 (52.8%)	23 (54.8%)	1.000	23 (100%)	18 (94.7%)	0.452
Partial VR	17 (47.2%)	19 (45.2%)		0 (0.0%)	1 (5.3%)	
Primary NR	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Biochemical response	30 (83.3%)	35 (83.3%)	1.000	18 (78.3%)	14 (73.7%)	1.000

VR virologic response, NR non-response

Fig. 3 Mean reduction of HBV DNA levels through 48th week. CLV clevudine, ETV entecavir**Table 3** Serologic response at weeks 24 and 48 in HBeAg-positive patients

	Clevudine (<i>n</i> = 36)	Entecavir (<i>n</i> = 42)	<i>p</i> value
HBeAg seroconversion at 24 weeks (<i>n</i>)	6 (16.7%)	9 (21.4%)	0.595
HBeAg seroconversion at 48 weeks (<i>n</i>)	8 (22.2%)	11 (26.2%)	0.684

Concurrently, blood tests showed elevated serum CK and LDH levels. Both of the symptoms and laboratory abnormalities were resolved following cessation of clevudine (Table 5).

Intention-to-treat analysis (data not shown)

In the intention-to-treat population, there were 60 clevudine-treated patients and 70 entecavir-treated patients (Fig. 1). The cVR occurred in 19 of 36 patients in clevudine group and 23 of 47 patients in entecavir group in HBeAg-positive patients (52.8 vs. 49.0%, $p = 0.146$). In HBeAg-negative patients, the cVR rate was higher in clevudine group (95.8%) than in entecavir group (78.3%), but no statistical difference was noted (23/24 vs. 18/23, $p = 0.112$). Seroconversion rate at 48th week was 22.2% in clevudine group and 26.2% in entecavir group. This

analysis showed no significant difference between two drugs ($p = 0.684$).

Discussion

Although this study has limitation as a retrospective analysis, baseline characteristics of the patients in the two groups were well balanced. The patients were from a single tertiary referral center with unified follow-up protocol. Virologic response in all patients was assessed using the most sensitive real-time PCR assay. Recently, there has been similar attempt to compare clevudine with entecavir [13]. However, the details in methods, such as enroll criteria, definition of end point, and follow-up protocol, are different from this study.

In this study, entecavir showed potent antiviral activity without emergence of drug-resistant mutants, like reports from previous clinical trials. Clevudine also showed potent antiviral activity in treatment-naïve CHB patients quite similar to entecavir up to 48 weeks. Mean reduction of HBV DNA level from baseline was -5.8 and -6.4 $\log_{10}$ copies/mL at weeks 24 and 48 in HBeAg-positive patients. In HBeAg-negative patients, mean DNA reduction was more marked with -6.6 and -6.9 $\log_{10}$ copies/mL at weeks 24 and 48. It is remarkable that HBV DNA decreased to undetectable level by real-time PCR in all the HBeAg-negative patients at 48th week. In addition, clevudine and entecavir showed rapid suppression of HBV DNA during the first 24 weeks of therapy, which is important predictor for a good virologic response and lower rate of development of drug-resistant mutants [14]. In spite of lower virologic response rate, overall viral reductions were greater in this study than in other reports, which can be attributed to the highest sensitivity of detection method (COBAS TaqMan HBV quantitative test; lower quantitation limit <60 copies/mL). The HBeAg seroconversion rates, 22.2% in clevudine group and 26.2% in entecavir group, were comparable to prior data.

On the other hand, the genotypic resistance inducing virologic breakthrough developed in 3.4% in clevudine-treated patients, whereas no resistance occurred in

Table 4 Clinical and laboratory data of two patients showing virologic breakthrough

Age	Sex	Initial HBeAg	Initial ALT (U/L)	Initial HBV DNA (CPM)	Nadir HBV DNA (CPM)	HBV DNA on breakthrough (CPM)	Mutation type
49	M	Positive	103	1.8×10^8	7.5×10^2	6.6×10^7	rtM204I
58	M	Positive	226	4.4×10^9	6.5×10^4	1.2×10^7	rtM204I

ALT alanine aminotransferase, HBV hepatitis B virus, CPM copies/mL

Table 5 Characteristics of two patients presenting clinical myopathy

Age	Sex	Initial HBeAg	Initial ALT (U/L)	Initial HBV DNA (CPM)	Type of response	ALT at week 48 (U/L)	HBV DNA at week 48 (CPM)	Duration of CLV before symptom (days)	CK (U/L)	LDH (U/L)	Recovery time (days)
41	M	Positive	87	4.2×10^9	pVR	32	1.1×10^4	371	601	604	70
51	M	Positive	212	8.6×10^7	pVR	36	7.7×10^4	342	545	467	64

ALT alanine aminotransferase, HBV hepatitis B virus, CPM copies/mL, CLV clevudine, CK creatine kinase, LDH lactate dehydrogenase, pVR partial virologic response

entecavir-treated patients. Cumulative incidence of clevudine-resistance in treatment-naïve patients has been reported as 0.7–10.0% up to 48 weeks [12, 15, 16]. Mutation of rtM204I in reverse transcriptase was the major signature associated with clevudine-resistance, as presented in the previous reports [11, 15, 17]. In this study, clevudine-resistance occurred in patients with quite high levels of baseline HBV DNA, which is a well-known risk factor for emergence of resistance in other nucleos(t)ide analogs [14, 18–20]. Considering that the mutation of rtM204 shows cross-resistance against other L-nucleoside, such as lamivudine, emtricitabine, and telbivudine, the addition of nucleotide analogs including adefovir and tenofovir may be preferred for patients with clevudine-resistant CHB.

In a period following the announcement of Pharmasset Inc., several cases of myopathy were reported to be associated with long-term therapy with clevudine, which was characterized by depletion of mitochondrial DNA [15, 21–23]. However, KFDA approved continued marketing based on that the risk of infrequent and reversible adverse event was not prior to the advantage of continuing clevudine (<http://www.kfda.go.kr>). In this study, two patients (3.4%) complained about proximal muscular weakness with corresponding elevation of muscle enzyme at 48th week, which disappeared after cessation of clevudine. The incidence of clevudine-associated myopathy was reported variable as 2.9–14.6% and almost always resolved after discontinuation [10, 13, 15, 24–26]. Although development of myopathy has been reported in other nucleos(t)ides analogs as well, such as lamivudine, adefovir, and tenofovir, the causal relationship was not elucidated [27]. In phase III GLOBE study about telbivudine, clinically overt

myopathy occurred in 0.3% of patients though asymptomatic grade 3/4 CK elevations encountered in 12.9% of patients at 104th week [28]. Given the incidence of clevudine-associated myopathy demonstrated in previous reports included only overt episodes by retrospective investigations, it is possible that asymptomatic CK elevations may be more prevalent than we are aware of.

Our study has several limitations. First, this is a retrospective study. It is possible that patients who showed good response were likely to be selected or trivial side effects that physicians did not care about might be missed. To improve methodological limitation, we did not demonstrate the outcome of clevudine only but compared with entecavir during same period. Besides, a virologic response was assessed strictly using real-time PCR, with lowest cut-off. Second, we did not perform histologic assessment. Instead, the clinical criterion to distinguish cirrhosis was applied. Third, the analysis to detect genotypic resistance was performed in only patients showing virologic breakthrough using a less sensitive method and direct sequencing assay [29]. If regular check up for genotypic resistance with more sensitive assay were available in all patients, more mutations might be identified. Fourth, the evaluation of antiviral activity requires outcome of more than 1 year. Accordingly, we are willing to follow up patients enrolled who are taking clevudine.

In conclusion, mean reduction of viral loads was similar between clevudine and entecavir groups during 48 weeks. However, virologic breakthrough and significant myopathy were noted only in clevudine-treated patients. Therefore, more attention should be paid to patients receiving clevudine, and additional long-term data about these problems are warranted in large number of patients.

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