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Long-Term Treatment Efficacy and Safety of Clevudine Therapy in Naïve Patients with Chronic Hepatitis B

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Background/Aims: Clevudine (CLV) has potent antiviral activity against chronic hepatitis B (CHB) virus infection. The long-term efficacy and safety of CLV therapy in naïve patients with CHB were investigated. **Methods:** In this retrospective study, 152 naïve Korean patients with CHB who received 30 mg of CLV once daily for at least 12 months were investigated. **Results:** The cumulative rates at months 12, 24, and 36, respectively, were 65.8%, 74.7%, and 74.7% for undetectable serum hepatitis B virus (HBV) DNA (<12 IU/mL); 77.6%, 86.2%, and 86.2% for normalization of serum alanine aminotransferase (<40 IU/L); 17.6%, 23.5%, and 23.5% for hepatitis B e antigen (HBeAg) loss or seroconversion; and 6.6%, 22.5%, and 30.0% for viral breakthrough. HBeAg positivity (p=0.010), baseline serum HBV DNA level ≥6 $\log_{10}$ IU/mL (p=0.032) and detectable serum HBV DNA (≥12 IU/mL) at week 24 (p=0.023) were independently associated with the development of viral breakthrough. During follow-up, CLV-induced myopathy developed in 5.9% of patients. **Conclusions:** The results of long-term CLV therapy for the treatment of naïve patients with CHB showed a high frequency of antiviral resistance and substantial associated myopathy. Therefore, we advise that CLV should not be used as a first-line treatment for naïve patients given the availability of other more potent, safer antiviral agents. **(Gut Liver 2012;6:486-492)**

Key Words: Chronic hepatitis B; 2'-Fluoro-5-methylarabinosyluracil; Viral breakthrough; Muscular diseases

INTRODUCTION

Clevudine (1-[2-deoxy-2-fluoro-β-arabinofuranosyl] thymine) (CLV) is a pyrimidine analog with potent antiviral activity against hepatitis B virus (HBV).[1] CLV inhibits DNA-dependent DNA reverse transcription and priming by HBV polymerase.[2] Phase III clinical trial results showed that 24 weeks of CLV therapy had a potent and sustained antiviral effect without clinical evidence of viral resistance during the treatment period in both HBeAg-positive and HBeAg-negative chronic hepatitis B (CHB) patients.[3,4] The ability to maintain antiviral activity in a significant portion of patients following the discontinuation of therapy is a unique characteristic of CLV.

In a retrospective study, a 48-week course of CLV therapy was highly effective in CHB patients and the risk of developing resistance to CLV was increased in patients with cirrhosis and previous exposure to lamivudine.[5] In a double-blind randomized study, 48 weeks of CLV treatment was superior to lamivudine in suppressing HBV replication without the emergence of viral breakthrough in patients with hepatitis B e antigen (HBeAg)-positive CHB.[6] However, several studies reported that 48 weeks of CLV therapy resulted in an incidence of virologic breakthrough ranging from 3.4% to 9.4% in treatment-naïve patients with CHB.[7-9] Furthermore, several studies showed that long-term CLV therapy induces the depletion of mitochondrial DNA and leads to mitochondrial myopathy associated with myonecrosis.[10-12] Recently, a global clinical study of CLV sponsored by Pharmasset Inc. (Princeton, NJ, USA) was terminated voluntarily because of safety concerns about myopathy reported during marketing in South Korea (Pharmasset Inc. press release, April 20, 2009). CLV was approved for the treatment of CHB patients in South Korea in 2006 and is currently prescribed for

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CHB. The Korea Food & Drug Administration concluded that CLV-associated myopathy is infrequent, reversible, and not life threatening, and approved continued marketing of CLV based on extensive review of the safety data. However, to date, long-term clinical data on its antiviral efficacy and safety are limited. In this study, we investigated the antiviral efficacy and resistance of long-term CLV therapy and the development of CLV-associated myopathy in treatment-naïve CHB patients. We also analyzed factors associated with the development of virologic breakthrough.

MATERIALS AND METHODS

1. Patients

This retrospective study included treatment-naïve CHB patients treated with CLV (30 mg) daily for more than 12 months. Two hundred and sixty-eight patients with CHB were treated with CLV 30 mg daily from March 2007 to August 2011 at Chonbuk National University Hospital. CHB was defined as a detectable serum hepatitis B surface antigen (HBsAg) level for more than 6 months and a serum HBV DNA level of $\geq 10^5$ copies/mL (or ≥20,000 IU/mL) with an elevated serum alanine aminotransferase (ALT) level. Of the 268 patients, 152 who received CLV for more than 12 months were included in this study. We excluded 116 patients due to follow-up loss (which included transfer to other clinics; 52 patients), a duration of CLV therapy of <12 months (30 patients), a previous history of treatment with nucleoside analogues (21 patients), decompensated liver cirrhosis (five patients), HCC (six patients), and co-infection with hepatitis C virus (two patients). However, we included patients who discontinued CLV within 12 months due to viral breakthrough or adverse effects, including CLV-induced myopathy. This study was conducted in compliance with the World Medical Association Declaration of Helsinki and was approved by the ethics committee at our institution.

2. Evaluation of treatment efficacy and safety

Serum ALT was measured with an enzymatic assay. Serum HBsAg, antibodies to HBsAg, HBeAg, and antibodies to HBeAg were detected by electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). Serum HBV DNA was quantified by real-time polymerase chain reaction (PCR) and 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).

The mean reduction in HBV DNA levels, virological response, biochemical response, and HBeAg loss or seroconversion rate during the treatment period were assessed. A virological response was defined as undetectable serum HBV DNA by real-time PCR (<12 IU/mL) during the treatment period. A biochemical response was defined as normalization of the serum ALT level (<40 IU/L). Primary nonresponse and viral breakthrough were analyzed to evaluate viral resistance. Primary nonresponse was defined as a decrease in serum HBV DNA less than 2 $\log_{10}$ copies/mL after at least 24 weeks of therapy. Viral breakthrough was defined as an increase in the serum HBV DNA level greater than 1 $\log_{10}$ from the nadir during continued treatment. In those cases, restriction fragment mass polymorphism technology was used to analyze the drug resistance mutation.

Side effects of CLV therapy were analyzed retrospectively by reviewing medical records and laboratory data during the treatment period. CLV-associated myopathy was defined as elevation of serum creatinine phosphokinase (CK) to more than twice the upper normal limit and the presence of myopathy-related symptoms (weakness of skeletal muscles, fatigue, myalgia, and weight loss) during CLV therapy. Patients with other reasons for myopathy, such as excessive exercise, traumatic muscle injury, lipid-lowering agents, recent high-dose glucocorticoid treatment, neuromuscular blocking drugs, alcohol abuse, chloroquine, or amiodarone, were excluded. The myopathy associated with CLV therapy was not well defined initially through clinical trials. Therefore, serum CK was not checked regularly in this study. Only patients who presented progressive proximal muscular weakness were tested for serum CK level.

3. Statistical analysis

Results are reported as means with standard deviations. HBV DNA levels were logarithmically transformed for analysis. Continuous variables were compared using the two-tailed Student's t-test. Categorical data were analyzed using the Fisher's exact test. Mean reductions in serum HBV DNA levels from baseline were compared by repeated measures analysis of variance. Cumulative probabilities for virological response, biochemical response, serological response, and viral breakthrough were evaluated by Kaplan-Meier analysis and compared between HBeAg-positive and HBeAg-negative patients by log-rank test. The logistic regression analysis was used to identify the univariate and multivariate risk factors for viral breakthrough. A two-tailed p-values <0.05 were considered statistically significant. Data was collated in Microsoft Excel (Microsoft Excel 2007; Microsoft Co., Seattle, WA, USA) and analyzed using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Baseline characteristics of study patients

Included were 152 patients (Table 1) with a mean age of 46.1 years, with 57 (37.5%) men, 49 (32.3%) patients with cirrhosis, and 90 (59.2%) who were HBeAg-positive. The median baseline serum ALT was 160 IU/L and serum HBV DNA was 6.4 $\log_{10}$ IU/mL. The median treatment duration was 23.4 months (range, 12 to 54 months). Baseline characteristics are compared between HBeAg-positive and HBeAg-negative patients in Table 1. HBeAg-positive patients were younger and had higher baseline

Table 1. Baseline Patient Characteristics

Characteristic	Total (n=152)	HBeAg-positive (n=90)	HBeAg-negative (n=62)	p-value*
Age, yr	46.1±11.1	44.6±11.7	48.3±10.1	0.046
Male sex	57 (37.5)	30 (52.6)	27 (47.0)	0.201
Cirrhosis†	49 (32.3)	25 (27.8)	24 (38.7)	0.156
Platelets, $\times 10^3/mm^3$	160.0±59.7	160.3±61.0	159.6±59.0	0.949
Serum AST, IU/L	117.8±133.8	161.0±160.9	134.6±74.1	0.061
Serum ALT, IU/L	160.2±191.1	177.1±218.1	135.6±141.0	0.189
GGT, IU/L	86.1±83.0	94.4±95.6	73.5±57.8	0.134
Total bilirubin, mg/dL	1.1±1.1	1.1±1.1	1.1±1.4	0.864
Creatinine, mg/dL	0.8±0.8	0.8±0.2	0.8±0.2	0.287
Serum HBV DNA, $\log_{10}$ IU/mL	6.4±1.5	7.0±1.2	5.6±1.4	0.043

Data are presented as mean±SD or number (%).
HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma glutamyl peptidase; HBV, hepatitis B virus.
*Comparison between HBeAg-positive and HBeAg-negative patients; †All patients had compensated cirrhosis.

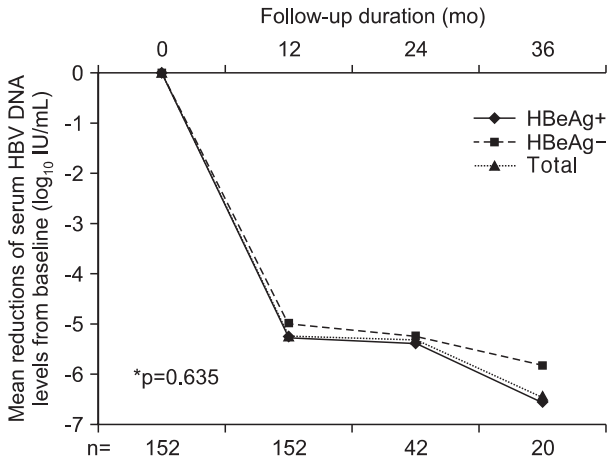

Fig. 1. Mean reduction in serum hepatitis B virus (HBV) DNA ($\log_{10}$ IU/mL) from baseline during treatment.
*Comparison between hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients based on an analysis of variance.

serum HBV DNA levels than the HBeAg-negative patients (44.6 $\log_{10}$ IU/mL vs 48.3 $\log_{10}$ IU/mL, p=0.046; 7.0 $\log_{10}$ IU/mL vs 5.6 $\log_{10}$ IU/mL, p=0.043), but other baseline characteristics were not significantly different between the two groups.

2. Virological, biochemical, and serological responses

Overall mean reductions in serum HBV DNA levels from baseline were -5.25 at 12 months, -5.32 at 24 months, and -6.47 $\log_{10}$ IU/mL at 36 months (Fig. 1). The mean reductions in serum HBV DNA levels from baseline were not significantly different between HBeAg-positive and HBeAg-negative patients (-5.29 $\log_{10}$ IU/mL vs -5.01 $\log_{10}$ IU/mL at 12 months, -5.39 $\log_{10}$ IU/mL vs -5.26 $\log_{10}$ IU/mL at 24 months, and -6.57 $\log_{10}$ IU/mL vs -5.83 $\log_{10}$ IU/mL at 36 months; p=0.635) (Fig. 1).

The cumulative rates of virologic response (serum HBV DNA levels <12 IU/mL) were 65.8% at 12 months, 74.7% at 24 months, and 74.7% at 36 months (Fig. 2A). HBeAg-positive patients had a significantly lower cumulative virologic response at months 12, 24, and 36 compared to HBeAg-negative patients (53.8% vs 83.6%, 59.7% vs 95.3%, and 59.7% vs 95.3%, p<0.001) (Fig. 2A). The cumulative rates of biochemical response (serum ALT <40 IU/L) were 77.6% at 12 months, 86.2% at 24 months, and 86.2% at 36 months (Fig. 2B). The cumulative biochemical response was not significantly different between HBeAg-positive patients and HBeAg-negative patients (75.8% vs 80.3% at 12 months, 87.1% vs 85.8% at 24 months, and 87.1% vs 85.8% at 36 months, p=0.677) (Fig. 2B). Among 90 HBeAg-positive patients, the cumulative rates of serologic response (HBeAg loss or HBeAg seroconversion) were 17.6% at 12 months, 23.5% at 24 months, and 23.5% at 36 months (Fig. 2C). The cumulative rates of viral breakthrough were 6.6% at 12 months, 22.5% at 24 months, and 30.0% at 36 months. HBeAg-positive patients showed significantly higher cumulative viral breakthrough than HBeAg-negative patients (8.9% vs 3.2% at 12 months, 28.9% vs 14.1% at 24 months, and 38.9% vs 14.1% at 36 months, p=0.028) (Fig. 2D). When we analyzed genotypic mutations for the patients who developed viral breakthrough, the cumulative rates of genotypic resistance were 4.6% at 12 months, 16.1% at 24 months, and 24.2% at 36 months. The cumulative rates of genotypic resistance were also significantly higher in HBeAg-positive patients compared to HBeAg-negative patients (5.6% vs 3.2% at 12 months, 23.7% vs 6.3% at 24 months, and 35.9% vs 6.3% at 36 months, p=0.002).

3. Factors associated with viral breakthrough and rescue therapy

Among 152 patients, 37 developed viral breakthrough during the treatment period. Univariate analysis to analyze factors related to the viral breakthrough showed HBeAg positivity (p=0.001), baseline serum HBV DNA level (p=0.041), baseline

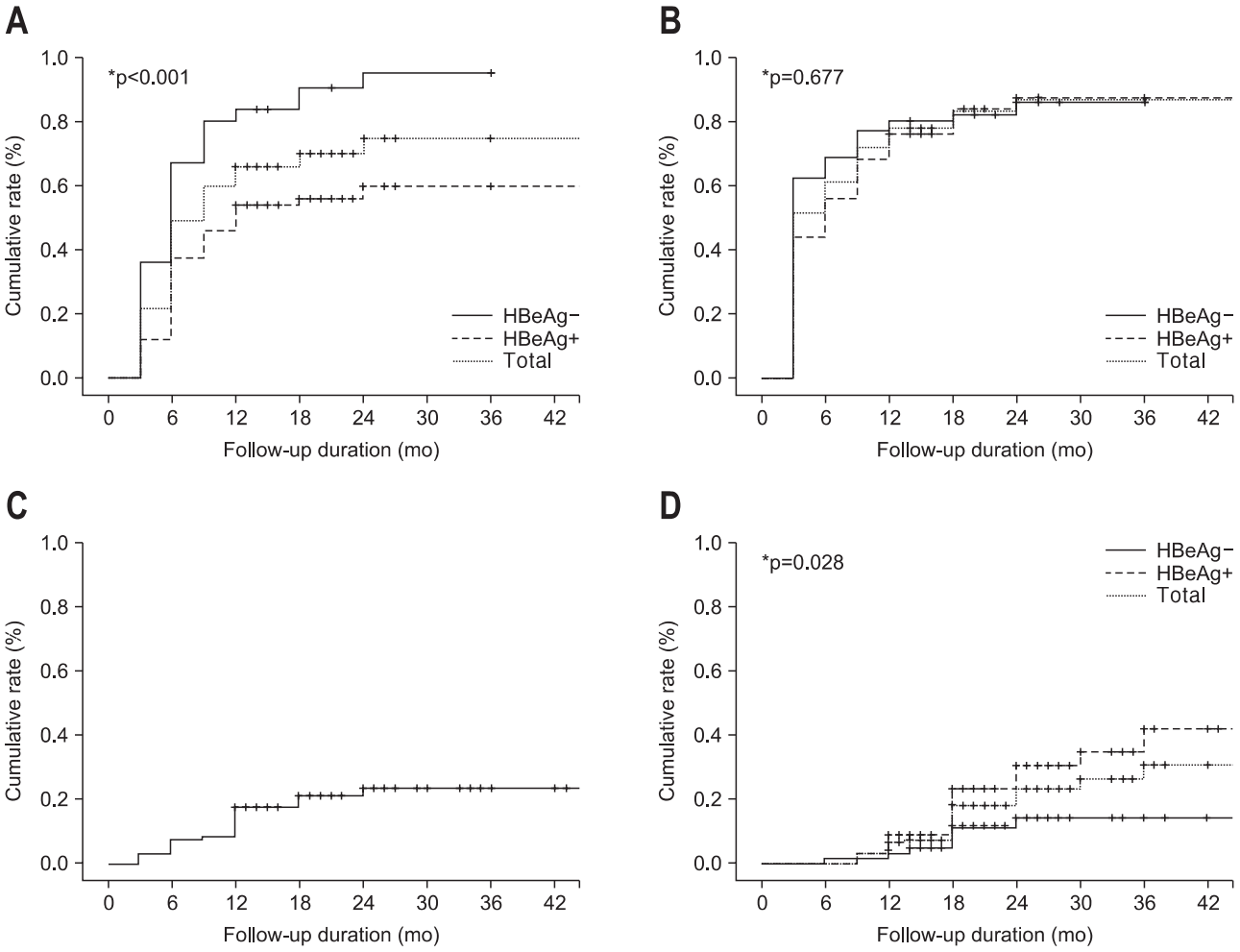

Fig. 2. Cumulative rates of treatment response during clevudine therapy. (A) Cumulative rates of the virologic response (serum hepatitis B virus DNA level <12 IU/mL). (B) Cumulative rates of the biochemical response (serum alanine aminotransferase level <40 IU/L). (C) Cumulative rates of the serologic response (hepatitis B e antigen [HBeAg] loss or seroconversion). (D) Cumulative rates of viral breakthrough.
*Comparison between HBeAg-positive and HBeAg-negative patients based on a log-rank test.

Table 2. Factors Associated with Viral Breakthrough during Clevudine Therapy (Univariate Analysis)

Characteristic	With viral breakthrough (n=37)	Without viral breakthrough (n=115)	p-value
Age, yr	44.7±11.4	46.5±11.1	0.387
Male	18 (48.6)	39 (33.9)	0.107
Cirrhosis	10 (27.0)	39 (33.9)	0.436
HBeAg positivity	30 (81.1)	61 (53.0)	0.001
Platelets, $\times 10^3/mm^3$	156.8±63.5	161.8±58.7	0.664
Serum AST, IU/L	98.6±72.8	124.6±147.9	0.159
Serum ALT, IU/L	124.3±89.0	171.7±212.7	0.056
Baseline serum HBV DNA level, $\log_{10}$ IU/mL	6.7±1.0	6.2±1.5	0.041
Baseline serum HBV DNA level (≥6 $\log_{10}$ IU/mL)	32 (86.4)	68 (59.1)	0.002
Detectable serum HBV DNA (≥12 IU/mL at wk 24)	23 (62.2)	41 (35.7)	0.001

Data are presented as mean±SD or number (%).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBV, hepatitis B virus.

serum HBV DNA level ≥6 $\log_{10}$ IU/mL (p=0.002), and detectable serum HBV DNA (≥12 IU/mL) at week 24 (p=0.001) to be significant (Table 2). However, on multivariate analysis, HBeAg positivity (odds ratio [OR], 4.65; 95% confidence interval [CI], 1.437 to 15.050; p=0.010), baseline serum HBV DNA level ≥6 $\log_{10}$ IU/mL (OR, 3.78; 95% CI, 1.123 to 12.732; p=0.032), and

Table 3. Factors Associated with Viral Breakthrough during Clevudine Therapy (Multivariate Analysis)

	OR	95% CI	p-value
HBeAg positivity	4.65	1.437–15.050	0.010
Baseline serum HBV DNA level (log_{10} IU/mL)	0.92	0.586–1.439	0.709
Baseline serum HBV DNA level (≥6 log_{10} IU/mL)	3.78	1.123–12.732	0.032
Detectable serum HBV DNA (≥12 IU/mL at wk 24)	2.82	1.157–6.867	0.023

OR, odds ratio; CI, confidence interval; HBV, hepatitis B virus.

detectable serum HBV DNA (≥12 IU/mL) at week 24 (OR, 2.82; 95% CI, 1.157 to 6.867; p=0.023) were independently associated with the development of viral breakthrough (Table 3).

Among 37 patients with viral breakthrough, 26 patients had a CLV-resistant mutation (rtM204I±rtL180M) by restriction fragment mass polymorphism analysis. Of the other 11 patients, seven were not analyzed for a genotypic mutation and four patients had no mutation conferring CLV-resistance. Of the 11 patients associated with viral breakthrough without mutation, seven were confirmed to have shown poor medication compliance by review of medical records. Of 26 patients with a CLV-resistant mutation, 18 patients changed to combination therapy with adefovir plus lamivudine, four patients switched to entecavir 1.0 mg monotherapy, three patients changed to combination therapy with adefovir plus CLV, and one patient changed to combination therapy with adefovir plus telbivudine. Mean duration of follow-up after rescue therapy was 76.3±41.0 weeks. Assessment of response to rescue therapy at week 48 showed a serum HBV DNA non-detectability (<12 IU/mL) rate of 6/19 (31.6%), a serum ALT normalization rate of 17/19 (89.5%), and HBeAg loss or seroconversion rate of 2/15 (13.3%).

4. Safety and CLV-associated myopathy

During the treatment period, CLV was safe and tolerable to most patients. Common side effects included fatigue, pruritis, headache, and dyspepsia, but all were mild. Of 152 patients, 32 (21.1%) patients discontinued CLV therapy because of CK elevation, myopathy-related symptoms, patient concern, or other causes (Table 4). In 20 (13.2%) patients, elevation of serum CK level occurred during CLV therapy and in 9 (5.9%), myopathy-related symptoms (weakness of skeletal muscle, fatigue, myalgia, and weight loss) occurred. Among 20 patients with an elevated serum CK level during CLV treatment, 11 were less than three times the upper normal limit and nine displayed an increase in serum CK greater than two times the upper normal limit. CLV-associated myopathy, defined as elevation of the serum CK level above two times the upper normal limit and the presence of myopathy-related symptoms in this study, developed in nine (5.9%) patients (Table 4). The mean time to the development of myopathy was 14.5 months and all patients improved after CLV discontinuation. The mean time to myopathy improvement was 2.6 months (range, 1 to 6 months). We analyzed and compared baseline clinical factors, such as, age, sex, presence of cirrhosis, HBeAg positivity, platelet counts, baseline serum AST, serum ALT, and serum HBV DNA levels, in patients complicated and not complicated by myopathy. However, we found no significant predictors of CLV-associated myopathy.

Table 4. Safety of CLV Therapy and CLV-Associated Myopathy

Safety issue	Incidence
Drug discontinuation	32 (21.1)
CK elevation	20 (13.2)
Myopathy-related symptoms	9 (5.9)
Patient's concern	7 (4.6)
Others	5 (3.3)
CK elevation	20 (13.2)
<×2 UNL	11 (7.2)
≥×2 UNL	9 (5.9)
CLV-associated myopathy	9 (5.9)

Data are presented as number (%). CLV-associated myopathy was defined as an elevation in the serum CK level above two times the upper limit of normal and the presence of myopathy-related symptoms (skeletal muscle weakness, fatigue, myalgia, and weight loss) during CLV therapy.
CLV, clevudine; CK, creatinine phosphokinase; UNL, upper normal limit.

DISCUSSION

In this study, long-term CLV therapy showed potent antiviral suppression and biochemical response in treatment-naïve CHB patients. However, CLV was associated with the development of substantial viral breakthrough. Furthermore, CLV-associated myopathy was observed in a small proportion of patients, although this was reversible with discontinuation of therapy.

A previous randomized study on CLV reported that 73% of patients achieved undetectable serum HBV DNA levels at week 48.[6] Direct head-to-head comparisons are not available, but this degree of HBV DNA reduction by CLV at week 48 compared favorably to entecavir 0.5 mg daily (67%) and telbivudine 600 mg daily (60%).[13,14] In our study, long-term CLV therapy showed cumulative rates of virologic response of 65.8% at 12 months, 74.7% at 24 months, and 74.7% at 36 months. In subgroup analysis, the virologic response was significantly lower in HBeAg-positive patients compared to HBeAg-negative patients (53.8% vs 83.6% at 12 months, 59.7% vs 95.3% at 24 months, and 59.7% vs 95.3% at 36 months, p<0.001). The rates of virologic response among HBeAg-positive patients in our study

were lower than in previous CLV studies.[5,6] We suspect that the main reason for this discrepancy is a difference in the sensitivity of the serum HBV DNA measurement methods. We used a more sensitive method to measure serum HBV DNA, the COBAS TaqMan HBV quantitative test (12 IU/mL lower limit of quantification), while previous studies used an Amplicor PCR assay (300 copies/mL lower limit of quantification). Recently, the proportion of patients who achieved virologic response (serum HBV DNA level <12 IU/mL) with 48 weeks of CLV treatment was reported to be 53% in HBeAg-positive and 100% in HBeAg-negative patients,[9] similar to our results.

In previous studies, CLV treatment led to a high frequency (78% to 84.7%) of serum ALT normalization at 48 weeks.[5-9] Similarly, our study also showed high cumulative rates of biochemical response (serum ALT <40 IU/L) (77.6% at 12 months, 86.2% at 24 months, and 86.2% at 36 months), and this was not significantly different between HBeAg-positive and negative patients. In addition, the rate of HBeAg loss or HBeAg seroconversion in our study (17.6% at 12 months, 23.5% at 24 months, and 23.5% at 36 months) was similar to previous studies (18% to 25% at week 48).[5,6,9]

Data about the incidence of viral resistance during long-term CLV therapy are limited. In a randomized study, no resistance was found in the CLV group during the 48-week treatment period.[6] However, several studies from Korea reported that 48 weeks of CLV therapy resulted in a viral breakthrough incidence ranging from 3.4% to 9.4% in treatment-naïve patients with CHB.[7-9] In our study, the cumulative rates of viral breakthrough substantially increased with treatment duration from 6.6% at month 12 to 30.0% at month 36. Similarly, the cumulative rates of genotypic resistance increased with treatment duration. Resistance was associated with prior treatment with nucleos(t)ide analogs or, in treatment-naïve patients, with high baseline HBV DNA levels, and a slow decline in HBV DNA levels. Furthermore, during treatment with lamivudine, adefovir or telbivudine, a partial virological response at 24 or 48 weeks (detectable as HBV DNA in a real-time PCR assay) was associated with a higher incidence of resistance.[14-16] Our study also found that HBeAg positivity (p=0.010), baseline serum HBV DNA level ≥6 $\log_{10}$ IU/mL (p=0.032) and detectable serum HBV DNA (≥12 IU/mL) at week 24 (p=0.023) were significantly associated with viral breakthrough. Accordingly, resistance should be identified as early as possible before clinical breakthrough (increased ALT) using HBV DNA monitoring and early rescue therapy should be started as soon as viral load increases. Furthermore, as recommended in the current treatment guidelines,[17,18] early treatment adaptation is needed for patients with partial virologic response to CLV therapy.

Identification of the pattern of resistance mutations should be used to adapt therapeutic strategies. Mutation of rtM204I in the reverse transcriptase gene had a major role in CLV-resistance, whereas several additional mutations could have a compensatory function in HBV replication.[19] In this study, 26 patients showed CLV-resistance mutations, with 20 patients carrying the rtM204I mutation and 6 with the rtM204I+rtL180M mutation. *In vitro* susceptibility assays demonstrated that the rtM204I mutation confers resistance to other L-nucleoside analogs such as lamivudine, emtricitabine, telbivudine, and entecavir. Accordingly, nucleotide analogs such as adeforvir and tenofovir or a combination regimen including these drugs could be the best options for patients with CLV-resistance. Furthermore, in our study, 11 patients showed virologic breakthrough without evidence of CLV-resistant mutation. It is mainly associated with poor medication compliance, but, it is possible to be associated with unknown resistance conferring mutation. During follow-up of these 11 patients, four showed a further reduction in serum HBV DNA level with continued CLV therapy, but the other seven showed a persistently elevated viral load and were rescued with another regimen.

Although the safety profile of CLV based on short-term clinical trials is similar to placebo,[3,4] several studies have reported an association between the emergence of myopathy and CLV therapy.[10-12] The incidence of CLV-associated myopathy varies by report. CLV-associated myopathy is characterized by clinical features of motor weakness in the proximal muscle of the lower extremities or asthenia with elevation of more than two of serum CK, lactate dehydrogenase, and lactate levels.[12] The pathologic features of mitochondrial toxicity strongly suggest that myopathy is mediated by mitochondrial dysfunction due to long-term CLV therapy.[10,12] Discontinuation of CLV appears to be sufficient for the management of myopathy. In this study, a substantial proportion (21.1%) of patients discontinued CLV therapy because of CK elevation, myopathy-related symptoms, patient concern for safety, or other causes. Indeed, CLV-associated myopathy developed in nine (5.9%) patients in whom the mean time to myopathy development was 14.5 months and all improved after CLV discontinuation. Therefore, careful medical examination along with periodic tests for muscle enzymes should be performed to detect subclinical myopathy without overt muscle weakness during long-term CLV therapy.

Our study had several limitations. First, it was retrospective, so patients who showed a good response were likely to be selected, and detailed analysis of side effects that physicians did not ask about might have been limited. Second, the analysis to identify genotypic resistance was performed in only patients showing viral breakthrough. Third, by the nature of retrospective analysis and the strict definition of myopathy in this study, the incidence of myopathy might have been underestimated. For example, the diagnosis of myopathy could not be made in the presence of muscle weakness if there is no result of CK. Fourth, because there was no definite guideline for withdrawal of CLV therapy in relation to myopathy, discontinuation of CLV therapy was dependent on physician's judgment.

In conclusion, long-term CLV therapy in treatment naïve pa-

tients with CHB showed high frequency of antiviral resistance and substantial myopathy development. Therefore, we advise that CLV should not be recommended as a first-line treatment for naïve patients given the availability of other more potent and safer antiviral agents.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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