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Lamivudine Maintenance Beyond One Year After HBeAg Seroconversion Is a Major Factor for Sustained Virologic Response in HBeAg-Positive Chronic Hepatitis B

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The reported durability of virologic response after successful lamivudine monotherapy is variable, and the question remains as to whether virologic responses can be maintained over an extended follow-up period. The aim of this study was to investigate posttreatment durability, the optimal duration of additional treatment after HBeAg clearance or seroconversion, and determinants for sustained virologic response (SVR) following lamivudine monotherapy in patients with HBeAg-positive chronic hepatitis B (CHB). From January 1999 to August 2004, 178 Korean patients with HBeAg-positive CHB were treated with lamivudine and achieved complete responses, defined as a loss of serum HBeAg and hepatitis B virus DNA, and alanine aminotransferase normalization. The mean duration of lamivudine monotherapy was 26 months (range, 12-77). SVR was maintained in 138 patients (77.5%). Host and viral factors were compared between 138 patients with SVR and 40 patients whose response was not sustained. The cumulative relapse rates increased from 15.9% at 1 year to 30.2% at 5 years, with a mean time to relapse after cessation of lamivudine of 12 months (range, 7-42). Most relapses occurred within 2 years after discontinuation of lamivudine (33/40, 82.5%). On multivariate analysis, age ≤ 40 years and additional treatment for more than 12 months after HBeAg clearance or seroconversion were independent factors for SVR. **Conclusion:** The lamivudine-induced virologic response was durable in patients under 40 years old and those receiving lamivudine for more than 12 months after HBeAg clearance or seroconversion. Age and additional treatment were major predictive factors for SVR. (HEPATOLOGY 2010;51:415-421.)

Abbreviations: ALT, alanine aminotransferase; anti-HBe, hepatitis B virus e antibody; CHB, chronic hepatitis B; CR, complete response; CRF, case report form; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus; IFN- α , interferon-alpha; ULN, upper limit of normal; SVR, sustained virologic response.

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Currently, a number of therapies for chronic hepatitis B (CHB) have been developed: interferon-alpha (IFN- α), lamivudine, adefovir dipivoxil, entecavir, tenofovir, and pegylated interferon-alpha (pegIFN- α).¹⁻³ Although they can all be considered first-line therapies for individuals with noncirrhotic liver disease, the degree of viral suppression achieved during treatment and the durability of response after treatment cessation appear to be the most important determinants of drug selection.

However, achieving a durable response has been hampered by drug resistance and the limited efficacy of antiviral agents. Since its introduction in the late 1990s, lamivudine has remained an important therapy for CHB, with many doctors and most patients opting for lamivudine rather than IFN- α .⁴⁻⁹ However, the efficacy of lamivudine is limited by the emergence of drug-resistant hepatitis B virus (HBV) mutants, restricting its use as a long-term therapy.¹⁰⁻¹³ Additionally, relapses after discontinuing antiviral therapy occur in a sizeable proportion of patients. Although there are no robust comparative data, the durability

of lamivudine treatment is generally considered to be less than that of IFN- α .¹⁴ Furthermore, studies of lamivudine treatment in Korean patients have reported lower rates of durability compared with studies of patients in Western countries.^{15,16}

Thus, there remain a number of questions regarding lamivudine therapy for CHB in terms of the appropriate duration of treatment, continuation of treatment after HBeAg seroconversion, and predictive factors for sustained HBeAg seroconversion. Recently, several factors have been reported to be associated with increased durability of lamivudine therapy, including longer duration of consolidation treatment, younger age, lower HBV DNA level at the time treatment was stopped, and genotype B.^{15,17-20} On the basis of these reports, the current American Association for the Study of Liver Diseases (AASLD) guidelines recommend that treatment should be continued until the patient has achieved HBeAg seroconversion and completed at least 6 months of additional treatment after the appearance of anti-HBe in patients with HBeAg-positive CHB.²¹ However, the number of patients in these studies was small (under 100) and the duration of the follow-up period was short (<3 years).

This retrospective analysis of a large multicenter cohort of Korean patients with HBeAg-positive CHB (predominantly genotype C) investigated posttreatment durability, the optimal duration of additional treatment after HBeAg clearance or seroconversion, and determinants for sustained virologic response (SVR) following lamivudine monotherapy.

Patients and Methods

Patients. From January 1999 to August 2004, a total of 748 patients with HBeAg-positive CHB infection were treated with lamivudine. This study was a retrospective, multicenter trial. All patients were recruited from seven medical institutions in Korea. Patients enrolled in this study met the following entry criteria: they were 18-75 years of age, the presence of serum HBsAg and HBeAg was observed for at least 6 months, they had elevated serum alanine aminotransferase (ALT) on two occasions, and the presence of HBV DNA had been documented on two occasions. Candidates were required to have compensated liver disease. Consecutive patients were treated with lamivudine for at least 12 months. The exclusion criteria were as follows: the presence of antibody to human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV), a history of malignancy, or evidence of other forms of liver disease.

Complete response (CR) was defined as normalization of serum ALT level, loss of serum HBV DNA, as deter-

mined using the Digene Hybrid Capture II HBV DNA Test (Digene, Gaithersburg, MD; cutoff value = 1.4×10^5 copies/mL), and HBeAg clearance (Abbott Diagnostics, Wiesbaden, Germany). According to the 2004 AASLD guidelines, patients in whom HBeAg seroconversion had occurred were maintained on treatment for >3 months after seroconversion was confirmed. In patients who had developed only clearance, treatment was also continued for >3 months after clearance, differing from the continuation-of-treatment recommended in the guidelines. CR was achieved in 287 of 748 patients (38.4%). Of these 287 patients, 178 patients were followed for at least 6 months and discontinued lamivudine treatment after CR, whereas 109 patients continued lamivudine treatment after CR. However, 101 of 748 patients (13.2%) were lost to follow-up. In 360 of 748 patients (48.1%), lamivudine was switched to a new antiviral agent or a new viral agent was added, due to primary nonresponse or virologic breakthrough (Fig. 1).

Methods. Serum HBeAg, anti-HBe, HBV DNA, and ALT were tested every 3-6 months during lamivudine therapy (or as necessary) and after drug cessation. Patients who maintained CR for more than 6 months after cessation of lamivudine therapy were classified as having SVR. Relapsers were defined as patients with reappearance of serum HBV DNA after drug cessation. The cumulative relapse rates and the predictors for SVR were evaluated.

Statistical Analyses. Data are expressed as means \pm standard error or median (range). Student's *t*-test, Fisher's exact test, and the chi-squared test were used for comparisons of variables between groups. The Kaplan-Meier method was used to calculate the cumulative rates of relapse. To determine predictive factors for SVR, multivariate analysis using Cox's regression model was performed. Statistical analysis was performed using Statistical Package for Social Science software v. 12.0 (SPSS, Chicago, IL). A *P*-value less than 0.05 was deemed statistically significant.

Results

Patient Characteristics. Of the patients, 178 were followed for at least 6 months and discontinued lamivudine treatment after CR. The characteristics at baseline are shown in Table 1; 129 (72.5%) patients were male, and the mean age was 39 years (range, 21-71). The mean baseline serum ALT level was 265.1 IU/L (range, 48-678). The mean baseline serum HBV DNA level was 7.8 log₁₀ copies/mL (range, 5.2-9.4). The mean duration of lamivudine treatment was 26 months (range, 12-77), and the mean total follow-up period was 53 months (range, 24-90).

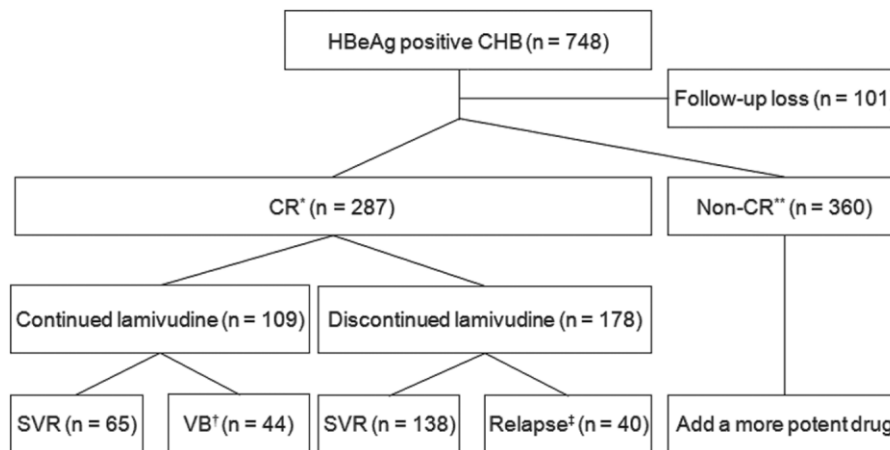


Fig. 1. Clinical outcomes in 748 patients with HBeAg-positive CHB treated with lamivudine monotherapy. The figure shows the flow diagram for 748 patients enrolled in the present study. *Complete response was defined as normalization of serum ALT level, loss of serum HBV DNA (cutoff value = 1.4×10^5 copies/mL), and HBeAg clearance. **Noncomplete response was defined as primary nonresponse and virologic breakthrough. †Virologic breakthrough was defined as reappearance of serum HBV DNA (cutoff value = 300 copies/mL) while on treatment, after achieving CR in a medication-compliant patient. ‡Relapse was defined as reappearance of serum HBV DNA (cutoff value = 1.4×10^5 copies/mL) after drug cessation. Abbreviations: CHB, chronic hepatitis B; CR, complete response; SVR, sustained virologic response; VB, virologic breakthrough.

Long-Term Clinical Outcomes. Among 178 patients who discontinued lamivudine treatment after CR, 138 patients (77.5%) maintained SVR. The mean times to HBeAg clearance and seroconversion were 13 months (range, 3-36) and 16 months (range, 3-36), respectively. The cumulative relapse rates at 1, 2, 3, 4, and 5 years were 15.9%, 23.0%, 26.4%, 30.2%, and 30.2%, respectively (Fig. 2A). The mean time to relapse after cessation of lamivudine was 12 months (range, 7-42). Most relapses occurred within 2 years after discontinuation of lamivudine (33/40, 82.5%).

Of patients with HBeAg clearance only, 25 (14%) were followed up. Of them, eight patients relapsed, with virologic breakthrough, and 17 patients showed SVR. HBeAg had reverted to positive in six patients and two patients progressed to HBeAg-negative CHB. Thus, the posttreatment durability of HBeAg clearance alone upon discontinuation of lamivudine was 68% (17/25) at 5 years.

Patients with HBeAg seroconversion ($n = 153$) were also followed. The cumulative relapse rates at 1, 2, 3, 4, and 5 years were from 13.6% at 1 year to 28.3% at 5 years (Fig. 2B). Of these, 32 patients relapsed with virologic breakthrough and 121 patients showed SVR. HBeAg reverted to positive in 25 patients and seven patients progressed to HBeAg-negative CHB.

Predictive Factors of Sustained Virologic Response. Differences between the 40 patients with relapse and 138 patients with SVR in terms of age, baseline ALT, and baseline HBV DNA were investigated. In univariate analysis, significant predictive factors for SVR were age (years; mean, 41.8 ± 11.1 vs. 38.1 ± 10.0 ; $P = 0.048$), baseline serum ALT (IU/L; mean, 215.5 ± 155.1 vs. 279.5 ± 240.4 ; $P = 0.048$), additional treatment duration after HBeAg clearance (months; mean, 7.9 ± 7.0 vs. 17.9 ± 12.4 ; $P < 0.001$), and additional treatment duration after HBeAg seroconversion (months; mean, 7.1 ± 5.9 vs. 14.1 ± 11.6 ; $P < 0.001$). In particular, when the duration of additional lamivudine treatment after HBeAg clearance or seroconversion was stratified into 6- and 12-month intervals, the cumulative relapse rates were significantly lower in patients with an additional treatment duration of ≥ 12 months ($P < 0.001$). Gender, baseline

Table 1. Baseline Characteristics of the Patients

Characteristic	HBeAg (+) CHB n = 178 (%)
Male:female	129:49
Mean age (years)	39.0 ± 10.3
≤ 40	101 (56.7)
> 40	77 (43.3)
Mean serum ALT (IU/L)	265.1 ± 225.3 (48-678)
> 1 and ≤ 2 times ULN*	14 (7.9)
> 2 and ≤ 5 times ULN*	73 (41.0)
> 5 and ≤ 10 times ULN*	61 (34.3)
> 10 and < 20 times ULN*	30 (16.9)
Mean serum HBV DNA (\log_{10} copies/mL)	7.8 ± 1.0 (5.2-9.4)
≤ 8.0	94 (52.8)
> 8.0	84 (47.2)
Family history of CHB	56 (31.5)
Previous IFN- α therapy	17 (9.6)
Mean treatment duration, months (range)	26 (12-77)
Mean total follow-up duration, months (range)	53 (24-90)

Values are expressed as mean \pm standard error of the mean.

*The upper limit of normal ALT levels is less than 40 IU/L.

Abbreviations: HBeAg (+), HBeAg positive; CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal; IFN- α , interferon alpha.

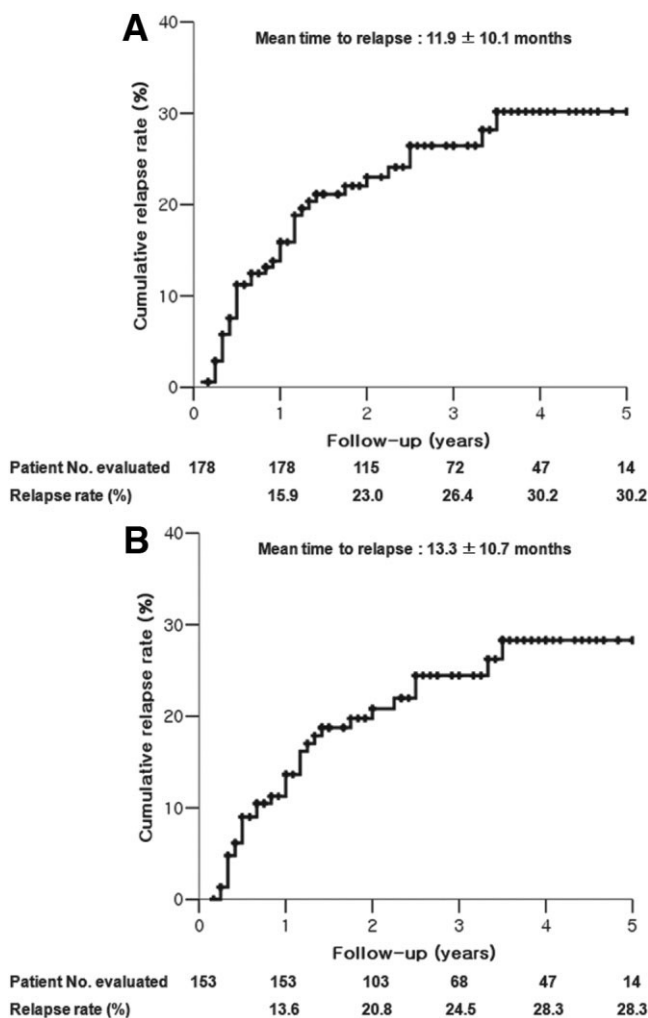


Fig. 2. Among (A) 178 patients who discontinued lamivudine monotherapy after CR the cumulative relapse rate increased from 15.9% at 1 year to 30.2% at 5 years. HBeAg seroconversion was observed in (B) 153 patients. Among them the cumulative relapse rate increased from 13.6% at 1 year to 28.3% at 5 years.

HBV DNA, family history, and previous INF- α treatment were not significantly different between patients with relapse and SVR (Table 2).

Multivariate Cox regression analysis revealed that patients with age ≤ 40 years (odds ratio [OR], 1.950; 95% confidence interval [CI], 1.031-3.689; $P = 0.040$), additional treatment duration after HBeAg clearance ≥ 12 months (OR, 9.259; 95% CI, 4.184-20.408; $P < 0.001$), and additional treatment duration after HBeAg seroconversion ≥ 12 months (OR, 14.292; 95% CI, 6.791-34.285; $P < 0.001$) were independent determinants of SVR (Table 3).

At 5 years the cumulative relapse rates were higher in patients >40 years (≤ 40 vs. >40 years, 24.6% vs. 36.9%; $P = 0.039$; Fig. 3A) and those with additional treatment duration after HBeAg clearance of <12 months (<12 vs. ≥ 12 months, 61.9% vs. 8.7%; $P < 0.001$; Fig. 3B).

Continuation of Lamivudine Treatment. Among 287 patients with CR, 109 patients received prolonged lamivudine therapy after CR (Fig. 1). Sixty-five (59.6%) patients maintained undetectable HBV DNA by polymerase chain reaction (PCR) (<300 copies/mL) at the time of last follow-up (mean total follow-up duration, 51.8 months), whereas 44 (40.4%) patients had detectable HBV DNA after CR. Among 44 patients, 21 patients developed virologic breakthrough along with lamivudine-resistant mutations during an additional treatment for a median duration of 33 months (range, 5-83). Of the 21 patients with a lamivudine-resistant mutation, 12 patients had both rtM204I and rtL180M mutations, six patients had both rtM204V and rtL180M mutations, and three patients had the rtM204I mutation only.

Discussion

Spontaneous HBeAg clearance and seroconversion predict long-lasting suppression of HBV, reduced infectivity, and improved clinical prognosis. Thus, lamivudine-induced HBeAg clearance and seroconversion have been considered a potential endpoint for stopping antiviral treatment.²² Although long-term lamivudine therapy increases HBeAg clearance and/or seroconversion rates, there is still a risk of increased frequency of virologic breakthrough.^{23,24} Additionally, lamivudine-induced HBeAg clearance or seroconversion is not durable in Asian patients, and viral relapse occurs more frequently in patients with a shorter duration of additional lamivudine therapy after HBeAg clearance or seroconversion.^{15,16,18} Thus, the optimal duration of lamivudine therapy has yet to be determined.

In accordance with the AASLD practice guidelines, HBeAg seroconversion remains the most desirable endpoint for the treatment of HBeAg-positive CHB, although other treatment endpoints in some clinical studies have included undetectable levels of HBV DNA, normalization of serum ALT, and HBeAg clearance.^{21,25,26} A longer duration of consolidation lamivudine therapy after both HBeAg clearance and seroconversion was strongly associated with the probability of SVR. More precisely, additional lamivudine treatment for ≥ 12 months after HBeAg seroconversion was a stronger predictor than that after HBeAg clearance (OR 14.292 vs. 9.259). Both HBeAg clearance and seroconversion were appropriate parameters for the cessation of lamivudine in this study. Our data suggest that prolonged additional therapy (i.e., ≥ 12 months after HBeAg clearance or seroconversion) might be needed to achieve SVR in Asian patients. As most relapses occurred within 2 years after discontinuation of lamivudine (82.5%), our results also suggest that patients with HBeAg clearance should be closely moni-

Table 2. Univariate Analysis of Predictive Factors for Sustained Virologic Response Among 178 Patients Who Stopped Lamivudine After Complete Response

Variable	Relapser* n = 40 (%)	SVR† n = 138 (%)	P Value
Male:female	32:8	97:41	0.226
Mean age (years)	41.8 ± 11.1	38.1 ± 10.0	0.048
≤40	17 (42.5)	84 (60.9)	
>40	23 (57.5)	54 (39.1)	0.039
Baseline serum ALT (IU/L)	215.5 ± 155.1	279.5 ± 240.4	0.048
>1 and ≤2 times ULN‡	3 (7.5)	11 (8.0)	
>2 and ≤5 times ULN‡	22 (55.0)	51 (37.0)	
>5 and ≤10 times ULN‡	8 (20.0)	53 (38.4)	
>10 and <20 times ULN‡	7 (17.5)	23 (16.7)	0.136
Baseline HBV DNA (log ₁₀ copies/mL)	7.9 ± 1.0	7.7 ± 1.0	0.334
≤8.0	19 (47.5)	75 (54.4)	
>8.0	21 (52.5)	63 (45.7)	0.445
Family history of CHB	12 (30.8)	44 (32.1)	0.873
Previous IFN-α therapy	6 (15.4)	11 (8.0)	0.170
HBeAg seroconversion	32 (80.0)	121 (87.7)	0.218
Mean additional treatment duration after HBeAg clearance (months)	7.9 ± 7.0	17.9 ± 12.4	<0.001
<6 vs. ≥6	12:28 (30.0:70.0)	24:114 (17.4:82.6)	0.080
<12 vs. ≥12	32:8 (80.0:20.0)	29:109 (21.0:79.0)	<0.001
Mean additional treatment duration after HBeAg seroconversion (months)	7.1 ± 5.9	14.1 ± 11.6	<0.001
<6 vs. ≥6	13:19 (40.6:59.4)	22:99 (18.2:81.8)	0.007
<12 vs. ≥12	22:10 (68.8:31.3)	36:85 (29.8:70.2)	<0.001

*Relapsers were defined as patients having reappearance of serum HBV DNA after drug cessation.

†Sustained virologic response (SVR) was defined as a complete response sustained > 6 months after the end of lamivudine therapy.

‡The upper limit of normal ALT levels is less than 40 IU/L.

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal; IFN-α, interferon alpha.

Table 3. Multivariate Cox Regression Analysis of Predictive Factors Associated with Sustained Virologic Response

Variable	Odds Ratio	95% CI	P Value
Age (years)			
≤40	1.950	1.031-3.689	0.040
>40	1.0		
Baseline serum ALT (IU/L)			
>1 and ≤2 times ULN*	1.0		
>2 and ≤5 times ULN*	2.623	0.777-8.853	0.120
>5 and ≤10 times ULN*	1.452	0.378-5.586	0.587
>10 and <20 times ULN*	2.573	0.653-10.148	0.177
Baseline serum HBV DNA (log ₁₀ copies/mL)			
≤8.0	1.0		
>8.0	1.462	0.771-2.773	0.245
Additional treatment duration after HBeAg clearance(months)			
<12	1.0		
≥12	9.259	4.184-20.408	<0.001
Additional treatment duration after HBeAg Seroconversion (months)			
<12	1.0		
≥12	14.292	6.791-34.285	<0.001

* The upper limit of normal ALT levels is less than 40 IU/L.

Abbreviations: ALT, alanine aminotransferase; HBV, hepatitis B virus; ULN, upper limit of normal.

tored for relapse with follow-up testing of HBV DNA and HBeAg for up to 2 years after discontinuation of lamivudine monotherapy.

Several reports have evaluated the durability of HBeAg seroconversion with lamivudine therapy, resulting in a wide range of durable HBeAg seroconversion rates.^{14,27} In a study by van Nunen et al.,¹⁴ the relapse rates after HBeAg seroconversion were reported as 42% and 54% after 1 and 3 years, respectively. Song et al.¹⁵ also reported high relapse rates, of 36% and 49% after 1 and 2 years, respectively. Our results (13.6% at 1 year to 28.3% at 5 years), in contrast, are more similar to those reported by Dienstag et al.,²⁷ with 1- and 3-year relapse rates of 14% and 28%, respectively. It is difficult to explain these disparate results. However, differences in the duration of lamivudine therapy may partially account for the different relapse rates. The lamivudine treatment duration for subjects in the van Nunen et al. and Song et al. studies was as short as 6 months for some subjects, whereas the minimum duration of therapy in the study by Dienstag et al. and our study was 12 months.^{14,15,27} Thus, the longer duration of treatment may have resulted in lower relapse rates.

Data from this Korean cohort indicate that the durability of HBeAg seroconversion in patients with CHB was similar to the durability of ≈70% reported in non-Asian

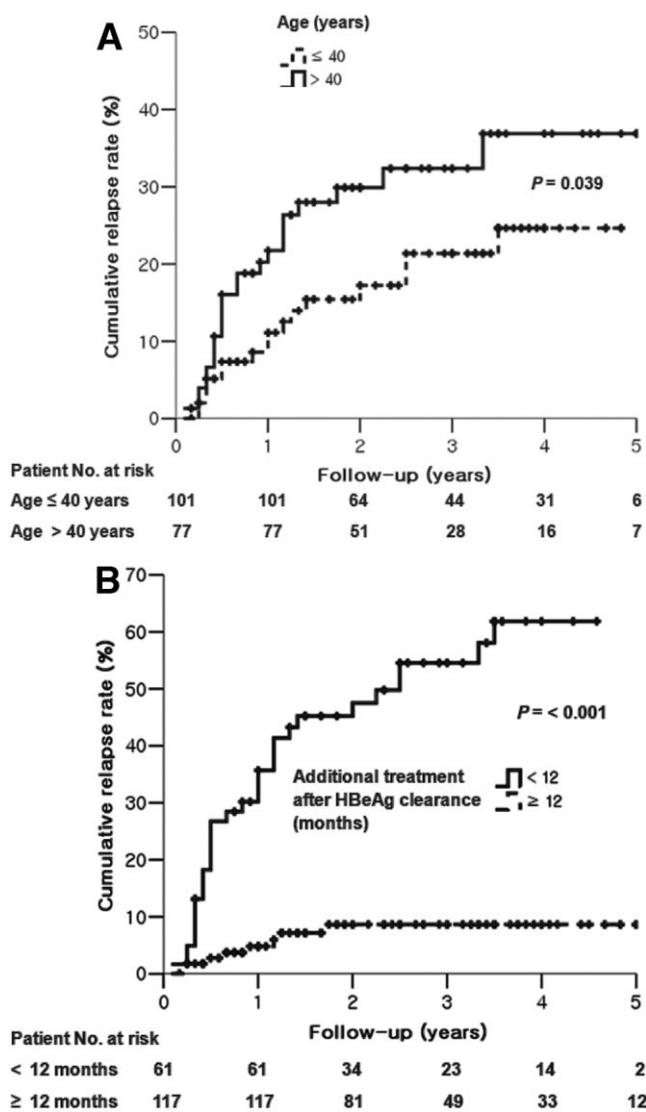


Fig. 3. The cumulative relapse rates were higher in (A) patients >40 years (≤ 40 vs. >40 years, 24.6% vs. 36.9%; $P = 0.039$) and (B) those with additional treatment duration after HBeAg clearance <12 months (<12 vs. ≥ 12 months, 61.9% vs. 8.7%; $P < 0.001$).

patients.²⁷ Other Korean studies have reported lower rates of durability (50%–60%), which may in part be related to small patient numbers, and/or shorter duration of treatment before and after HBeAg seroconversion.^{15–19}

SVR was previously found to be associated with longer duration of additional treatment, younger age, lower HBV DNA level at the time treatment was stopped, and genotype B.^{15,17–20} However, the number of patients in these studies was smaller than in our study (under 100 vs. 178 patients). Also, the duration of treatment and additional treatment after HBeAg seroconversion were shorter than in our study (mean 13 vs. 26 months and mean 4.5 vs. 12.4 months, respectively). In our study, age and the duration of additional lamivudine treatment after HBeAg clearance or seroconversion were predictive factors for SVR.

A major limitation of this multicenter, large-scale cohort study was the use of a relatively insensitive HBV DNA assay. It is possible that this low sensitivity was partly responsible for the apparent relatively low relapse rates after CR. More sensitive HBV DNA assays would be required to evaluate this issue definitively.

We subanalyzed 51 patients with SVR who had been followed for more than 4 years after 2004, using a more sensitive assay (the COBAS TaqMan 48 analyzer, Roche Molecular Systems, Branchburg, NJ; with a lower limit of detection of 300 copies/mL). The mean HBV DNA level was 429 copies/mL (range, <300 –1,296). The percentage of relapse could have been higher if more sensitive HBV DNA assays had been used during the study period. However, there was no virological rebound (HBV DNA level $>10,000$ copies/mL) in 51 patients who completed at least 12 months of additional treatment after HBeAg clearance or seroconversion.

Interestingly, despite prolonged lamivudine treatment after CR, 21 of 109 (19.3%) patients experienced lamivudine-resistant mutations and virologic breakthrough. These data suggest that lamivudine could be stopped after optimal additional treatment in patients who have achieved HBeAg clearance or seroconversion. However, additional studies are needed because new antiviral agents that have low resistance and more potent antiviral efficacy could provide different insights into prolonged therapy.

In conclusion, the lamivudine-induced virologic response was durable in patients under 40 years old and receiving lamivudine for more than 12 months after HBeAg clearance or seroconversion in CHB that was predominantly genotype C. Future long-term prospective and comparative data are needed to evaluate the durability of lamivudine-induced HBeAg clearance or seroconversion according to HBV genotype, given the continuing use of long-term lamivudine monotherapy in the management of CHB.

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