Original Article

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Current Role of Lamivudine Regarding Therapeutic Response and Resistance in Children with Chronic Hepatitis B

Suk Jin Hong, Yeo Hyang Kim, Byung-Ho Choe, Hyo Jung Park, Won-Young Tak* and Young-Oh Kweon*

*Departments of Pediatrics and *Internal Medicine, Kyungpook National University School of Medicine, Daegu, Korea*

Purpose: To identify the predictive factors of long-term therapeutic response or resistance to lamivudine treatment in children and adolescents with chronic hepatitis B.

Methods: Eighty one children and adolescents with chronic hepatitis B were included, who received lamivudine treatment for at least 6 months. Their condition was monitored for at least 12 months (12-88 months) thereafter. Twenty one (25.9%) were preschool children (age ≤ 6). For patients who had developed HBeAg seroconversion or breakthrough, univariate and multivariate analyses were used to identify the effects of age, gender, pretreatment alanine aminotransferase (ALT) and hepatitis B virus DNA levels.

Results: HBeAg seroconversion occurred in 49 (60.5%) of the 81 patients after the initiation of the lamivudine therapy. In 65 patients whom were monitored for over 24 months, the seroconversion rate was significantly higher in younger patients (*p*=0.040), especially in those patients of preschool age (age ≤ 6, *p*=0.031). The seroconversion rate was significantly higher in higher pretreatment ALT (*p*=0.003). The breakthrough occurred in 21 (25.9%) of the 81. The breakthrough rate was lower in younger aged patients (age ≤ 6), and with higher pretreatment ALT levels, but no significant difference.

Conclusion: Younger age is a good predictor of HBeAg seroconversion in children with long-term lamivudine treatment as well as high pretreatment ALT levels. **(Pediatr Gastroenterol Hepatol Nutr 2013; 16: 80~88)**

Key Words: Chronic hepatitis, Child, Lamivudine, Seroconversion, Therapeutics

INTRODUCTION

Serum hepatitis B virus (HBV) DNA clearance occurs in up to two thirds of children with HBeAg positive chronic hepatitis before reaching adulthood, though they have a high risk of chronic progressive liver diseases, including cirrhosis and hepatocellular carcinoma [1,2]. The goals of treatment are to decrease viral replications by obtaining HBeAg seroconversion, to normalize serum aminotransferase levels and liver histopathology, and to prevent long-term progressive liver diseases.

Lamivudine, an oral nucleoside analogue, effectively suppresses HBV replications and improves liver enzymes as well as liver histology of chronic hepatitis B in both adults and children [3,4]. Known predictive factors of therapeutic response with lamivudine are high histologic activity index (HAI) score [5], high pretreatment alanine aminotransferase (ALT) [5], low HBV DNA [6] and HBeAg level [7], duration of lamivudine therapy [8,9], and good compliance [10], amongst others.

However, studies for identifying the predictive factors in children are limited so far and most of the studies done at several centers were assessed at the end of 52 weeks treatment of lamivudine, though long-term treatment is essential for lamivudine therapy [5,6,11].

The objective of our study is to evaluate predictors of better therapeutic responses including virologic responses and HBeAg seroconversion, as well as lamivudine resistance during long-term lamivudine treatment in children and adolescents with chronic hepatitis B.

MATERIALS AND METHODS

Patient population

Eighty one children and adolescents (58 male and 23 female; age, 0.8-20 years, mean, 11.5 years) with chronic hepatitis B were enrolled consecutively in this prospective cohort study (Fig. 1). They received lamivudine for at least 6 months starting from March 1999 to August 2005. They were followed for at least 12 months (a mean period of 44.0±22.7 months) until August 2006 at the Department of Pediatrics and Division of Gastroenterology, Kyungpook National University Hospital, Korea.

The informed consent was obtained from the patients or their parents, and our study was approved by the Institutional Review Board of Kyungpook National University Hospital.

Inclusion and exclusion criteria

All 81 patients treated with lamivudine had HBsAg and HBeAg positive, anti-HBs and anti-HBe negative, elevated HBV DNA ($>$10 pg/mL, with a lower limit of detection of 0.5 pg/mL) for at least 6 months, and serum ALT values more than 1.3×ULN (times the upper limit of the normal range) for at least 3 months without a 1 log drop of HBV DNA decrement before treatment.

Patients were excluded if they had received any agents affecting treatment results such as systemic antiviral agents, corticosteroids, cytotoxic agents, or immunosuppressive drugs within the past 6 months. Patients were also excluded if they were coinfected with the hepatitis C virus or if they had decompensated liver diseases or other causes of liver disease such as Wilson disease or steatohepatitis by ultrasonography and/or biopsy. The hepatitis D virus or human immunodeficiency virus was not examined
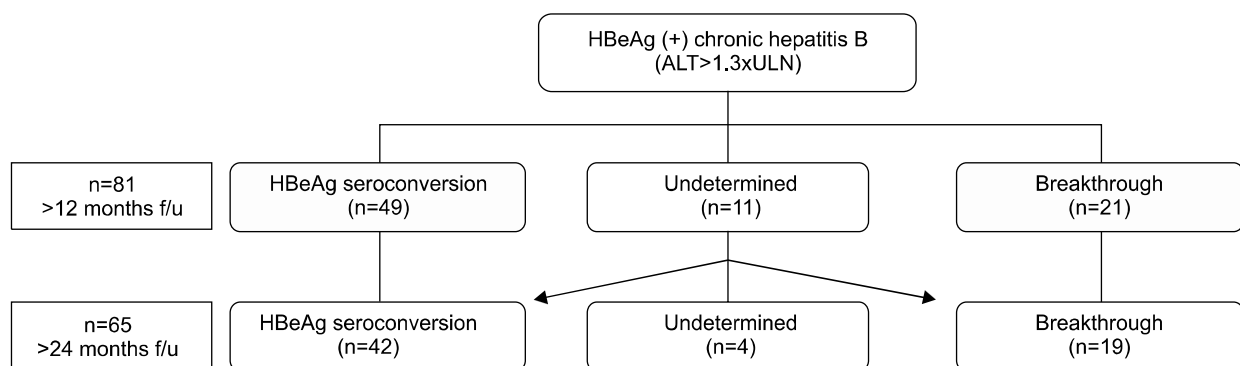

Fig. 1. Algorithm of treatment for HBeAg (+) chronic hepatitis B. Analysis was done for 81 and 65 patients who have followed-up for over 12 months and 24 months, respectively. ×ULN: times the upper limit of the normal range, f/u: follow-up.

because of its extremely rare incidence in Korean children and adolescents.

Treatment and follow-up of patients

Lamivudine, at a dose of 3 mg/kg orally (maximal dose 100 mg, tablet or syrup), once daily, was given for at least 6 months. The patients who completely responded with normalized ALT, undetectable HBV DNA, and HBeAg/anti-HBe seroconversion continuously received lamivudine therapy for at least 6 additional months after HBeAg/anti-HBe seroconversion. Thereafter, lamivudine treatment was stopped. If breakthrough developed during the lamivudine therapy, it was given for 6-12 additional months. After that, YMDD mutation was assessed along with discontinuation of lamivudine if there were no more therapeutic responses. Virologic breakthrough was defined as ≥ 1 $\log_{10}$ increase in HBV DNA on two consecutive occasions after clearance in serum after an initial virologic response (HBV DNA <4 $\log_{10}$ copies/mL after 6 months on treatment) or an initial decline in HBV DNA by >2 $\log_{10}$ copies/mL during lamivudine treatment.

The follow-up monitoring was performed one month after the initiation of lamivudine therapy and every 2-3 months until the end of therapy. The patients with complete response (HBeAg/anti-HBe seroconversion and HBV DNA negativization) were followed up at 2-3 month intervals for 6 months and then every 3-6 months thereafter. Periodic evaluation included clinical history, physical examination, aspartate aminotransferase, ALT, and serologic HBV markers (HBsAg and anti-HBs, HBeAg and anti-HBe, HBV DNA).

HBsAg, HBeAg and antibodies were assayed by commercial enzyme immunoassays (Behringer ELISA Processor III; BEP III, Dade Behringer Diagnostics, Marburg, Germany) by the year 1999 or electrochemiluminescence immunoassay (ECLIA method, Roche Diagnostics Corporation, Indianapolis, IN, USA) thereafter, and HBV DNA was measured quantitatively on manual blot hybridization by the year 2000 or on a hybrid capture II HBV DNA assay (DML 2000 System, Digene, Gaithersburg, MD,

USA) thereafter, of which the detection limit was 0.5 pg/mL.

Evaluation of efficacy and resistance

For patients followed up for over 12, 18, and 24 months after the initiation of lamivudine, the seroconversion and breakthrough rates were compared according to age differences (≤ 6 yr, $6<\ \leq 15$ yr, $15<\ \leq 20$ yr), pretreatment ALT and HBV DNA levels in the HBe Ag seroconversion group and breakthrough group, respectively.

HBeAg seroconversion was defined as losses of HBeAg and concomitant developments of anti-HBe after initiating the treatment.

Univariate and multivariate analyses were applied for patients with HBeAg seroconversion or with breakthrough according to age, gender, pretreatment ALT and HBV DNA levels.

Statistical analysis

The data were analyzed using a χ^2 test or Fisher's exact test for association between two qualitative variables: ANOVA test for the comparison of continuous variables such as age, pretreatment ALT, and HBV DNA levels. Logistic-regression analysis was used in lamivudine responsive or resistant groups to assess factors related to the rate of therapeutic responses after adjustment for the following baseline factors: ALT level, HBV DNA level, and age.

All statistical analysis was performed using statistical software (SAS ver. 9.13; SAS Institute, Cary, NC, USA) and a standard personal computer system (Samsung Magic Station M2950; Samsung, Seoul, Korea). p-values below 0.05 were considered to indicate statistical significances.

RESULTS

Baseline characteristics

Baseline demographics of the lamivudine treated groups according to age difference were compared in Table 1.

Twenty one (25.9%) of the 81 patients were preschool children (age≤ 6), thirty one (38.3%) were

Table 1. Baseline Demographics and Clinical Characteristics of Lamivudine Treated Group according to Age Difference

Age (yr)	≤6 (n=21)	6<≤15 (n=31)	15<≤20 (n=29)	p-value	Total (n=81)
Sex (Male : Female)	12 : 9	19 : 12	27 : 2	0.006	58 : 23
Tx duration (mo)	20.3 (12-38)	23.9 (7-67)	23.7 (9-54)	0.48	22.9±11.5 (7-67)
Follow-up duration (mo)	43.8 (14-88)	41.0 (12-87)	45.8 (9-88)	0.72	43.4±22.4 (12-88)
PreTx ALT level (IU/L)					
≤2×ULN	72.5 (63-82) (n=4)	66.5 (59-80) (n=6)	65.0 (48-80) (n=5)	0.51	67.6±9.6 (48-82) (n=15)
2<≤5×ULN	126.0 (85-195) (n=15)	127.2 (85-199) (n=19)	170.9 (118-204) (n=7)	0.007	134.2±35.3 (85-204) (n=41)
>5×ULN	299 (222-376) (n=2)	457.7 (221-1,012) (n=6)	425.4 (214-1,267) (n=17)	0.78	423.0±267.1 (214-1,267) (n=25)
Total	132.3±70.6	179.4±188.7	301.8±259.0	0.008	211.0±207.3 (48-1,267)
PreTx HBV DNA level (pg/mL)					
≤100	28.5 (17-40) (n=2)	24.5 (22-27) (n=2)	39.9 (15.8-53.2) (n=6)	0.76	30.4±13.1 (15.8-53.2) (n=10)
100<≤353	202.3 (105-330) (n=6)	244.7 (154-323) (n=10)	183.7 (127.2-340.9) (n=6)	0.30	216.5±78.8 (105-340.9) (n=22)
>353	>353 (n=13)	>353 (n=19)	>353 (n=17)	0.33	>353 (n=49)
Total	279.0±116.5	296.9±96.4	251.8±136.5		276.1±117.4

Value: mean (range), total value: mean±standard deviation. yr: years old, Tx: treatment, preTx: pretreatment, ALT: alanine aminotransferase, ×ULN: multiples of upper limit of the normal range (39 IU/L), HBV: hepatitis B virus. p-value analyzed by ANOVA test among 3 age groups.

school children (6<age≤15), and twenty nine (35.8%) were adolescents (15<age≤20). Sixty one patients (75.3%) had family history of hepatitis B (56 maternal, 4 paternal, 1 brother). There was no significant difference between the groups in treatment and follow-up duration, pretreatment HBV DNA levels, and pretreatment ALT levels (≤2×ULN, >5×ULN). The number of male was significantly larger (p=0.006) and pretreatment ALT level (2<≤5×ULN) were significantly higher (p=0.007) in lamivudine treated adolescents.

Overall therapeutic efficacy and resistance to lamivudine treatment over 12 or 24 months follow-up

Baseline demographics and clinical characteristics of the lamivudine treated group according to seroconversion or breakthrough 12 months after the initiation of the treatment were compared. There was no significant difference between the seroconversion and breakthrough groups in sex, age, pretreatment ALT levels and pretreatment HBV DNA levels (>100). Treatment duration was significantly longer (p=0.026) in the breakthrough group.

The HBeAg seroconversion and breakthrough occurred in 49 (60.5%) and 21 (25.9%) respectively, of the 81 patients treated with lamivudine. The seroconversion rate was significantly higher in those with higher pretreatment ALT level (p=0.013) but there was no significantly different seroconversion rate in sex, age, pretreatment HBV DNA levels. Eleven (13.6%) of 81 patients were neither completely responsive to lamivudine, nor resistant to therapy (i.e. HBeAg positive, HBV DNA negative state) 12 months after the initiation of lamivudine.

The HBeAg seroconversion and breakthrough occurred in 42 (64.6%) and 19 (29.2%) respectively, of the 65 patients treated with lamivudine for over 24 months. The number of undetermined children reduced to four (6.2%) out of 65 patients 24 months after the initiation of therapy.

Seroconversion rate by minimal follow-up duration

Seroconversion rate according to age, pretreatment ALT and pretreatment HBV DNA levels were compared by minimal follow-up duration in Table 2.

The HBeAg seroconversion occurred in 49 (60.5%), 45 (63.3%), 42 (64.6%) respectively, of the 81, 71, and 65 patients monitored for over 12, 18, and 24 months after the initiation of the treatment. In patients monitored for over 24 months, the seroconversion rate was significantly higher in the younger group (p=0.040), especially in those patients of preschool age (age$\leq$6, odds ratio [OR]=6.29 vs. age$>$15, p=0.031, Fig. 1).

Furthermore, HBsAg disappeared in 8 (50.0%) out of 16 children of preschool age (age$\leq$6), whereas only one (3.8%) out of 26 patients over age 6. The rate of HBsAg loss was significantly higher in preschool age group (age$\leq$6, [OR]=25 vs. age$>$6, p=0.001).

The seroconversion rate was significantly higher in patients with greater pretreatment ALT level (p=0.003), especially in patients with an increased level more than 5 times the upper limit of normal ($\leq$2$\times$ULN OR=1 vs. 2$<$ $\leq$5$\times$ULN OR=2.82, 2.91, 3.11 vs. $>$5$\times$ULN OR=8.00, 8.55, 10.80) at follow-up duration for over 12, 18, and 24 months (p=0.013, p=0.016, p=0.003 vs. $\leq$2$\times$ULN) respectively, but there was no significantly different seroconversion rate in sex, pretreatment HBV DNA levels.

Multivariate analyses were used to assess the pure effects of age and pretreatment ALT, which were controlled by age, gender, pretreatment ALT and HBV DNA levels. None of these interactions were significant. The multivariate analyses' adjusted odds ratio in preschool children (age$\leq$6) was 13.99 times (95% confidence interval [CI], 1.61-121.0, p=0.0169) that of adolescents (age$>$15). The multivariate analyses' adjusted odds ratio in higher pretreatment ALT ($>$5$\times$ULN) levels was 46.72 times (CI, 4.54-480.87, p=0.0012) that of those in lower ALT ($\leq$2$\times$ULN) levels.

Breakthrough rate by minimal follow-up duration

Breakthrough rate according to age, pretreatment ALT and pretreatment HBV DNA levels were compared by minimal follow-up duration in Table 3.

Breakthrough occurred in 21 (25.9%), 19 (29.2%) respectively, of the 81, and 65 patients monitored for over 12, 24 months after the initiation of the

Table 2. HBeAg Seroconverion Rate by Minimal Follow-up Duration according to Age, Pretreatment ALT levels, and Pretreatment HBV DNA Levels

	$\geq$12 months (n=81)		$\geq$24 months (n=65)	
	Seroconversion (N/%) (n=49)	OR (CI)	Seroconversion (N/%) (n=42)	OR (CI)
Age (yr)				
$\leq$6 (n=21, 18)	16 (76%)	2.60 (0.75-9.01)	16 (89%)*	6.29 (1.19-33.35)
6$<$ $\leq$15 (n= 31, 22)	17 (55%)	0.99 (0.36-2.73)	12 (55%)	0.94 (0.30-2.99)
15$<$ $\leq$20 (n=29, 25)	16 (55%)	1	14 (56%)	1
PreTx ALT levels (IU/L)				
1.3$<$ $\leq$2$\times$ULN (n=15, 14)	5 (33%)	1	5 (36%)	1
2$<$ $\leq$5$\times$ULN (n=41, 30)	24 (59%)	2.82 (0.82-9.76)	19 (63%)	3.11 (0.83-11.66)
$>$5$\times$ULN (n=25, 21)	20 (80%)[†]	8.00 (1.87-34.23)	18 (86%)[†]	10.80 (2.10-55.65)
PreTx HBV DNA levels (pg/mL)				
10$<$ $\leq$100 (n=11, 10)	9 (82%)	3.50 (0.68-17.95)	8 (80%)	2.55 (0.47-13.77)
100$<$ $\leq$353 (n=22, 19)	13 (59%)	1.12 (0.40-3.13)	12 (63%)	1.09 (0.35-3.44)
$>$353 (n=48, 36)	27 (56%)	1	22 (61%)	1

Value: mean (range), OR: odd ratio, CI: 95% confidence interval, yr: years old, Tx: treatment, PreTx: pretreatment, ALT: alanine aminotransferase, $\times$ULN: multiples of upper limit of the normal range, HBV: hepatitis B virus. *p=0.040 by chi-square test (cf. multivariate analyses adjusted OR=13.99), [†]p=0.013 by chi-square test, [†]p=0.003 by chi-square test (cf. multivariate analyses adjusted OR=46.72).

Table 3. Breakthrough Rate by Minimal Follow-up Duration according to Age, Pretreatment ALT levels, and Pretreatment HBV DNA levels

	≥12 months (n=81)		≥24 months (n=65)	
	Breakthrough (N/%) (n=21)	OR (CL)	Breakthrough (N/%) (n=19)	OR (CL)
Age (yr)				
≤6 (n= 21, 18)	3 (14%)	0.44 (0.10, 1.90)	2 (11%)	0.27 (0.05, 1.44)
6<≤15 (n=31, 22)	10 (32%)	1.250 (0.412, 3.790)	9 (47%)	1.47 (0.45, 4.86)
15<≤20 (n=29, 25)	8 (28%)	1	8 (42%)	1
PreTx ALT levels (IU/L)				
1.3<≤2×ULN (n=15, 14)	6 (40%)	1	6 (43%)	1
2<≤5×ULN (n=41, 30)	12 (29%)	0.62 (0.18, 2.13)	10 (33%)	0.67 (0.18, 2.45)
>5×ULN (n=25, 21)	3 (12%)	0.21 (0.04, 1.00)	3 (14%)	0.22 (0.04, 1.12)
PreTx HBV DNA levels (pg/mL)				
10<≤100 (n=11, 10)	2 (18%)	0.67 (0.13, 3.53)	2 (20%)	0.50 (0.09, 2.73)
100<≤353 (n=22, 19)	7 (32%)	1.40 (0.46, 4.25)	5 (26%)	0.71 (0.21, 2.45)
>353 (n=48, 36)	12 (25%)	1	12 (33%)	1

Value: mean (range), OR: odd ratio, CL: confidence limits, yr: years old, PreTx: pretreatment, ALT: alanine aminotransferase, ×ULN: multiples of upper limit of the normal range, HBV: hepatitis B virus.

Table 4. Seroconverion and Breakthrough Rate by Minimal 12 or 24 Months Follow-up Duration according to Age and Pretreatment ALT levels

Follow-up periods	Response/resistance rate	Age≤6, preTx ALT>2×ULN	Age>6, preTx ALT≤2×ULN	p
≥12 months	Seroconversion rate	14/17 (82.4%)	3/11 (27.3%)	0.0062*
	Breakthrough rate	1/17 (5.9%)	4/11 (36.4%)	0.0618
≥24 months	Seroconversion rate	14/14 (100%)	3/10 (30.0%)	0.0003*
	Breakthrough rate	0/14 (0%)	4/10 (40.0%)	0.0198*

PreTx: pretreatment, ALT: alanine aminotransferase, ×ULN: multiples of upper limit of the normal range. *Fisher's exact test.

treatment.

YMDD mutation was found in 14 (82.4%) among 17 tested patients who have developed breakthrough.

Seroconversion and breakthrough rate according to age and pretreatment ALT levels

The seroconverion and breakthrough rate of the preschool aged children with higher pretreatment ALT levels (age≤6, pretreatment ALT>2×ULN) were 14/17 (82.4%) and 1/17 (5.9%), compared to 3/11 (27.3%) and 4/11 (36.4%) of school aged children with lower pretreatment ALT levels (age>6, pretreatment ALT≤2×ULN), applying a minimal 12 months follow-up duration (p=0.0062, Table 4).

In addition, the seroconverion and breakthrough rate of the preschool aged children with higher pretreatment ALT levels were 14/14 (100%) and 0/14

(0%), as compared to 3/10 (30.0%) and 4/10 (40.0%) of school aged children with lower pretreatment ALT levels, applying a minimal 24 months follow-up duration (p=0.0003 and 0.0198) (Table 4).

DISCUSSION

Chronic hepatitis B in children is treated with interferon-alpha and lamivudine, of which therapeutic responses of lamivudine are associated with a pretreatment state of low HBV DNA level and high ALT level [5,6]. The cumulative HBeAg seroconversion rates were 28% and 39% at 1 and 2 years, respectively after the initiation of lamivudine treatment in 519 Korean adults [7]. In children, the cumulative seroconversion rates were 34% and 68% at 1 and 2 year after initiation of lamivudine treatment, respectively

[4]. This suggested that long-term lamivudine treatment in children had better effects of improving HBeAg seroconversion rates than in adults.

The efficacy after 12 months of lamivudine treatment was not better than that of interferon alpha in children [12,13]. However, the authors have demonstrated in previous studies that lamivudine had a better therapeutic effect than interferon-alpha two years after the initiation of treatment and lesser adverse effects [4].

Although the longer lamivudine treatment induced the higher seroconversion rate, the risk of viral resistance increased with development of YMDD mutations and breakthrough hepatitis [14]. In Korean adult studies, the incidence of YMDD mutations were 8%, 36%, and 52% at 1, 2, and 3 year, respectively [7,15]. In addition, relapse is frequent if lamivudine is discontinued before or immediately after HBeAg seroconversion [7,15,16].

However, unlike interferon, there is no fixed duration of treatment in a nucleoside analogue. Therefore, the discontinuation of lamivudine, irrespective of therapeutic response, is not acceptable after treatment of a fixed duration. Lamivudine should be continued until at least 6 months after HBeAg seroconversion to reduce relapse [17]. For these reasons, it is necessary to assess patients treated for an additional period over 6-12 months after HBeAg seroconversion, for the identification of the best predictive factors.

Though therapeutic response is increased by longer lamivudine treatment, only a few studies have been published about long-term treatment of lamivudine in children to date. Until now, previous studies have shown that predictive factors for the therapeutic response to lamivudine were high HAI score[5], high pretreatment ALT [5], low HBV DNA [6] and HBeAg level [7], duration of lamivudine therapy [8,9], and good compliance [10], amongst others. However, most of the above studies were assessed by only therapeutic response to 52 weeks of lamivudine [5,6].

Pretreatment ALT levels and HAI scores have been suggested to have values in predicting therapeutic response, but age, gender, previous interferon therapy, baseline weight, HBV DNA, and BMI had no value as predictors to lamivudine treatment, demonstrated in a randomized, double-blind, placebo-controlled, and multicenter trial of lamivudine in children for 52 weeks [5].

However, in our study, the seroconversion rate was significantly higher in patients of preschool age (age$\leq$6) monitored for over 24 months, but insignificant if following-up was not done for more than 12 months. The univariate and multivariate analyses which adjusted odds ratio in preschool children (age $\leq$6) was 6.29 and 13.99 times higher than adolescents (age$>$15) respectively, which suggests that lamivudine treatment has a better therapeutic effect at a younger age. In addition, when ALT levels were $>$5$\times$ULN, the HBeAg seroconversion rates were significantly higher than those with lower pretreatment ALT levels. Plus, in preschool aged children with ALT levels greater than 2$\times$ULN, the seroconversion rate was 100% and breakthrough rate was 0%, which were far better results than the group with age$>$6 and ALT$<$2$\times$ULN ($p<0.05$). This data is in line with the higher HBsAg loss rate in preschool children [18].

In our study, HBeAg seroconversion occurred in 49/81 (60.5%) and 42/65 (64.6%) patients who were followed-up for at least over 12 and 24 months, respectively, after the initiation of the treatment. This represented higher efficacy rates than those in adults and other pediatric studies though most have been infected perinatally [5,19-22]. This result could be partially contributed by compliance and higher pretreatment ALT levels of enrolled patients as well as including young children.

Breakthrough occurred in 21 (25.9%) among 81 patients who received treatment, and were monitored for more than 12 months in our study, which is consistent with the results in the authors' previous study; breakthrough rates are 1 year 15.7% (8/51), 2 year 24.4% (10/41), with lower resistances than other studies [11,23].

Based on our study, efficacy rates in preschool children with chronic hepatitis B who received suffi-

cient duration of lamivudine were higher, and resistance seemed to occur less than in school children or adolescent patients. Compared to previous studies with a 1-year monitoring period, younger age was proven to be a good predictor, but only if there was monitoring for over 2 years, suggesting that studies with a long-term treatment period are required to find predictors of nucleoside analogue. The authors believe that lamivudine should be used for at least 12 months and an additional 12 months after HBeAg/anti-HBe seroconversion in order to get a good therapeutic response, even in preschool children. Nevertheless, pretreatment ALT should be higher than 2×ULN to reduce the resistances.

The limitations of our study are as below. First, by ethical reason, there is no untreated or interferon-treated control group because this is a long-term follow-up study. Second, the pretreatment mean ALT level ($2 < \leq 5 \times ULN$) was significantly higher ($p=0.007$) in lamivudine treated adolescents than in children, which could have slightly improved the therapeutic response of adolescents, but did not. Although the high ALT 10-20 times ULN were included in our study, their HBV DNA was not that low for spontaneous HBeAg seroconversion.

In conclusion, the predictors of therapeutic responses include younger age and high pretreatment ALT levels for long-term lamivudine treatment in children with chronic hepatitis B. The authors advocate that lamivudine could be the first therapeutic option for pre-school children in Korea where the insurance coverage of new nucleos(t)ides for children are still not permitted [24,25].

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