Establishment of Individual Prediction Model for Treatment Response in HBeAg-Positive Chronic Hepatitis B Patients on Lamivudine Monotherapy

Wonseok Kang

Department of Medicine

The Graduate School, Yonsei University

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Directed by Professor Kwang-Hyub Han

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Wonseok Kang

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This certifies that the Master's Thesis
of Wonseok Kang is approved.

Thesis Supervisor : Kwang-Hyub Han

Thesis Committee Member : Kwan Sik Lee

Thesis Committee Member : Kyung Soo Park

The Graduate School
Yonsei University

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ABSTRACT

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Wonseok Kang

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Kwang-Hyub Han)

Background: Although the emergence of lamivudine-resistant strains is becoming a problem in the treatment of chronic hepatitis B, lamivudine is still the first-line drug in many countries, because of its long-term safety profile and relatively inexpensive cost. Therefore, it would be beneficial to screen lamivudine responders prior to lamivudine treatment. The aim of this study was to assess the predictors of lamivudine treatment response and to establish an individual prediction model for HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients on lamivudine monotherapy.

Methods: In this multi-center trial, retrospective analysis of 748 consecutive patients (Male:Female, 570:178) with HBeAg-positive chronic hepatitis B on lamivudine monotherapy was performed between January 1999 and August 2004. The median age was 43.0 years (range, 19-79). Multivariate analysis

was conducted to identify factors associated with HBeAg seroconversion, and probability of HBeAg seroconversion was calculated in a logistic regression model. The probability (Pr) of HBeAg seroconversion was classified into high (Pr≥50%), intermediate (30<Pr<50%), and low (Pr≤30%) response group, and was then validated using a new set of patients, enrolled between January 2005 and December 2006.

Results: The duration of lamivudine monotherapy was 34.2 ± 0.7 months (mean ± SD). The cumulative HBeAg seroconversion rates were increased from 26.1% at 12 months to 50.7% at 96 months. In the multivariate analysis, age (OR=0.974, 95% CI: 0.961-0.988, p<0.001), pretreatment serum ALT level (OR=1.001, 95% CI: 1.000-1.002, p=0.014), and pretreatment serum HBV DNA level (OR=0.749, 95% CI: 0.651-0.862, p<0.001) were significant factors associated with HBeAg seroconversion. Based on the data from 748 HBeAg-positive chronic hepatitis B patients, an individual prediction model was established. The cumulative HBeAg seroconversion rate at 72 months for high, intermediate, and low response group was 66.0%, 48.5%, and 21.8%, respectively (p<0.001).

Conclusion: An individual prediction model was developed based on the predictors of HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients on lamivudine monotherapy. This model seems feasible and may facilitate screening lamivudine responders prior to the commencement of antiviral treatment.

Key words : prediction model, chronic hepatitis B, lamivudine, antiviral therapy

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I. INTRODUCTION

Chronic hepatitis B virus (HBV) infection is a major public health problem worldwide affecting more than 400 million people, of whom approximately 75% are of Asian ethnicity.[1-3] Individuals chronically infected by HBV are at risk of developing chronic liver disease, cirrhosis and hepatocellular carcinoma.[4]

The goal of therapy for chronic hepatitis B is to eliminate or significantly suppress viral replication and prevent the progression of liver disease to cirrhosis, hepatocellular, and death.[5] Loss of HBsAg, although highly desirable, is rarely attained with short-term antiviral therapy, and thus, is not a

realistic goal for antiviral treatment. Therefore, the primary aim of treatment is to reduce and maintain serum HBV DNA at the lowest possible levels, to promote histologic improvement, and to promote alanine aminotransferase (ALT) normalization. Persistence of positive hepatitis B e antigen (HBeAg) and high HBV DNA level are well-known risk factors for progression of liver disease and development of hepatocellular carcinoma, and hence, in patients who are HBeAg-positive before antiviral therapy, an additional goal of treatment is achieving loss of HBeAg with seroconversion to the antibody to HBeAg (anti-HBe). HBeAg seroconversion is preferable, because achievement of complete HBeAg seroconversion indicates a high likelihood that the benefit will persist once the patient is off therapy, enabling the clinician to discontinue treatment at some point after the seroconversion.[6-9]

Antiviral therapy in patients with chronic hepatitis B is associated with improved outcome. Currently, six drugs are available for the management of chronic HBV infection in Korea: interferon-alfa, pegylated interferon, lamivudine, adefovir dipivoxil, entecavir, and clevudine.

For many years, interferon-alfa, the first agent approved for treating chronic hepatitis B, was the only treatment specifically approved for patients with chronic hepatitis B. However, it has been reported to be effective only in a minority of patients, and furthermore, virologic relapse after interferon-alfa-induced viral suppression is common in endemic areas of HBV infection, especially Korea.[10, 11]

Lamivudine, the first nucleoside analogue approved for the treatment of chronic hepatitis B, inhibits viral reverse-transcriptase activity as a competitive inhibitor of deoxycytidine triphosphate.[12] Since it was officially

introduced in Korea in the late 1990s, lamivudine has been widely prescribed for initial treatment for chronic hepatitis B infection. By suppressing HBV replication, lamivudine brings about decreased level or disappearance of HBV DNA in the patient's serum, HBeAg, normalization of serum ALT level, and histological improvement.[13-15]

As discontinuation of therapy often leads to reactivation of HBV, long-term therapy is necessary for many patients with chronic hepatitis B infection. Yet, the emergence of drug-resistant mutations from substitutions at M204I/V within the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the HBV polymerase gene, has been a major limitation in long-term lamivudine treatment.[14-21] The selection of lamivudine-resistant YMDD variants can lead to marked viral rebound, increases in serum ALT levels, hepatitis flares, or even liver decompensation and death from hepatic failure.[21-25] As a result, newer nucleos(t)ide analogues, which are associated with more potent viral suppression and a lower chance of the emergence of drug resistant HBV variants, have been introduced to the market.[26-32]

Despite the introduction of the newer nucleos(t)ide analogues, however, lamivudine is still used as the first-line drug for the treatment of chronic hepatitis B in many places, because of its well-established long-term safety and efficacy profile, and additionally, relatively inexpensive cost.[33] Many patients have been successfully treated long-term in the past with lamivudine with persistently undetectable serum HBV DNA for many years. For the reason that there is a certain proportion of patients who shows long-term favorable response to lamivudine treatment, tailored the antiviral therapy according to the patient features and clinical circumstances is necessary.[34]

Hence, so as to maximize individualized therapy for chronic hepatitis B patients, it is still an important issue to screen patients who are more likely to be responsive to lamivudine with a lower chance of developing lamivudine-resistant variants before initiating the antiviral treatment.

The aim of this study was to assess the predictors of lamivudine treatment response and to develop and validate an individual prediction model for HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients on lamivudine monotherapy.

II. MATERIALS AND METHODS

1. Study Population

In this multi-centered, retrospective cohort study, data were collected from consecutive patient files and medical records held at seven medical institutions in Korea, including Yonsei, Yeungnam, Keimyung, Hanyang, Soonchunhyang, Kwandong University and National Health Institute Corporation Ilsan Hospital. 748 patients with HBeAg-positive chronic hepatitis B who were given lamivudine 100 mg daily from January 1999 to August 2004 were selected for the study set. For the validation set, 396 patients with HBeAg-positive chronic hepatitis B who started lamivudine therapy between January 2005 and December 2006 were consecutively enrolled, and data were collected. Patients were considered eligible if they were 18 years of age or older, had positive HBsAg and HBeAg for more than 6 months, had elevated serum HBV DNA level (at least 1.4×10^5 copies/mL), and had elevated serum ALT level more than twice the upper limit of normal for more than two successive months. Patients were excluded if they had decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or received immunosuppressive agents. Moreover, patients with co-infections such as human immunodeficiency virus (HIV), hepatitis C virus (HCV) or hepatitis D virus (HDV), or other concomitant liver diseases such as autoimmune liver disease and hemochromatosis were excluded.

2. Definition

HBeAg seroconversion was defined as loss of HBeAg and detection of anti-HBe in the patient's serum, which was previously HBeAg-positive and anti-HBe-negative. Virologic response was defined as undetectable serum HBV DNA levels. Virologic breakthrough was defined as increase in serum HBV DNA level by greater than 1.0 $\log_{10}$ copies/mL above nadir after achieving a virologic response during continued therapy.

3. Study Methods

A. Data collection

The clinical and laboratory data of the patients were recorded with retrospective chart review. Clinical evaluation included general characteristics of the patients such as gender, age, family history, and treatment duration. Laboratory variables included serum biochemistry data such as serum ALT levels, serologic markers of HBV infection, and serum HBV DNA levels. HBsAg, anti-HBs, HBeAg, and anti-HBe were determined by commercially available enzyme immunoassays (Dade Behring, Marburg, Germany). Serum HBV DNA level was determined by detection of HBV DNA by Hybrid Capture II HBV DNA assay (Digene Diagnostics Inc., Bestivelle, MD, USA), and the lower limit of detection for HBV DNA test was 1.4×10^5 copies/mL. The upper limit of normal for serum ALT was 40 IU/L.

B. Statistical Analysis

The values were expressed as mean ± standard error of mean or median (range) as appropriate. HBV DNA levels were reported as $\log_{10}$ copies/mL.

Continuous variables were compared with Student's *t*-test and categorical variables with chi-squared test or Fisher's exact test as appropriate. Time-to-event (survival) analysis was carried out using Kaplan-Meier estimates to draw out the cumulative HBeAg seroconversion rate curves. Univariate and multivariate analyses were performed using logistic regression models of relevant prognostic variables to construct the prediction model based on the risk index formula, and the equality of survival distribution was analyzed using Log-Rank test. All of the statistical tests were two-tailed and a *p*-value of < 0.05 was considered statistically significant. All procedures were performed using the SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA).

III. RESULTS

1. Patient Characteristics

Patient demographics and standard laboratory tests at the time of commencing lamivudine monotherapy are summarized in Table 1. The median age of the 748 patients (570 males, 178 females) was 43.0 years (range, 19 – 79). The mean pretreatment serum ALT level was 226.6 ± 8.4 IU/L. The mean pretreatment HBV DNA level was 7.97 ± 0.4 $\log_{10}$ copies/mL. The mean duration of LAM treatment was 34.2 ± 0.7 months, and the mean follow up duration was 47.4 ± 0.8 months.

Table 1. Baseline characteristics of HBeAg-positive CHB patients (*n* = 748)

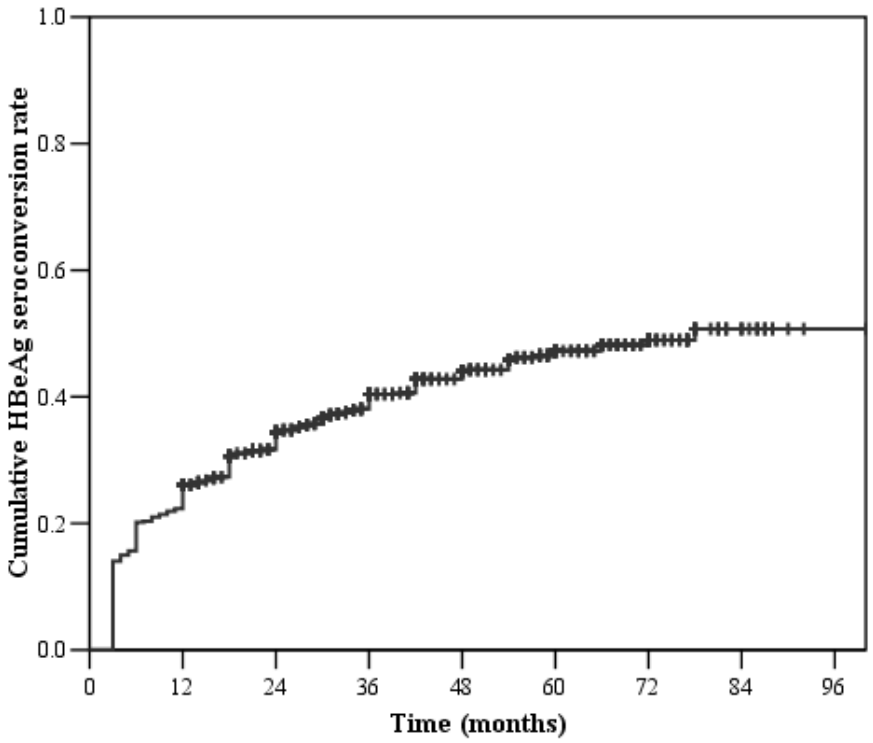
Variables		
Gender	Male, *n* (%)	570 (76.2)
	Female, *n* (%)	178 (23.8)
Median age, years (range)		43.0 (19 – 79)
Pretreatment serum ALT (IU/mL)		226.6 ± 8.4
Pretreatment HBV DNA ($\log_{10}$ copies/mL)		7.97 ± 0.4
Lamivudine treatment duration (months)		34.2 ± 0.7
Follow up duration (months)		47.4 ± 0.8

Results are given as mean ± standard error of mean, unless otherwise indicated. CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus.

2. Cumulative HBeAg Seroconversion Rates

Among the 748 patients, 316 (42.2%) achieved HBeAg seroconversion. Figure 1 represents the cumulative HBeAg seroconversion rates of the 748 HBeAg-positive chronic hepatitis B patients. The cumulative HBeAg seroconversion rates were from 26.1% at 12 months to 50.7% at 96 months.

Figure 1. Cumulative HBeAg seroconversion rate



3. Predictors of HBeAg Seroconversion

Table 2 shows the comparisons of variables according to HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients. In the univariate and multivariate analyses of the study set population, age (OR = 0.974, 95% CI: 0.961-0.988, $p < 0.001$), pretreatment serum ALT level (OR = 1.001, 95% CI: 1.000-1.002, $p = 0.014$), and pretreatment serum HBV DNA level (OR = 0.749, 95% CI: 0.651-0.862, $p < 0.001$) were independent factors for HBeAg seroconversion (Table 3).

Table 2. Comparisons of variables according to HBeAg seroconversion in HBeAg-positive CHB patients

Variables		HBeAg seroconversion	
		Not achieved (n = 432)	Achieved (n = 316)
Gender	Male, n (%)	335 (77.5)	235 (74.4)
	Female, n (%)	97 (22.5)	81 (25.6)
Age (years)		43.9 ± 0.5	40.7 ± 0.6
Pretreatment serum ALT (IU/mL)		205.9 ± 8.7	254.9 ± 15.9
Pretreatment HBV DNA (log_{10} copies/mL)		8.1 ± 0.1	7.8 ± 0.1

Results are given as mean ± standard error of mean, unless otherwise indicated.

CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus.

Table 3. Univariate and multivariate analysis of variables according to HBeAg seroconversion in HBeAg-positive CHB patients

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Gender (Male:Female)	0.840	0.599 – 1.179	0.313	-	-	-
Age (years)	0.974	0.960 – 0.987	< 0.001	0.974	0.961 – 0.988	< 0.001
Pretreatment serum ALT (IU/mL)	1.001	1.000 – 1.002	0.006	1.001	1.000 – 1.002	0.014
Pretreatment HBV DNA (log_{10} copies/mL)	0.772	0.673 – 0.885	< 0.001	0.749	0.651 – 0.862	< 0.001

CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus; OR, odds ratio; CI, confidence intervals.

Table 4. Logistic regression analysis of maximum likelihood estimates for HBeAg seroconversion in HBeAg-positive CHB patients

Variables	β	S.E.	P-value	Exp(β)
Constant	2.8844	0.6676	<0.0001	17.893
Age (years)	-0.0262	0.0071	0.0002	0.974
Pretreatment serum ALT (IU/mL)	0.000915	0.0004	0.0138	1.001
Pretreatment HBV DNA (log_{10} copies/mL)	-0.2889	0.0715	0.0001	0.749

CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus; S.E., standard error; Exp, exponential.

4. Model building: Individual Prediction Model for HBeAg Seroconversion

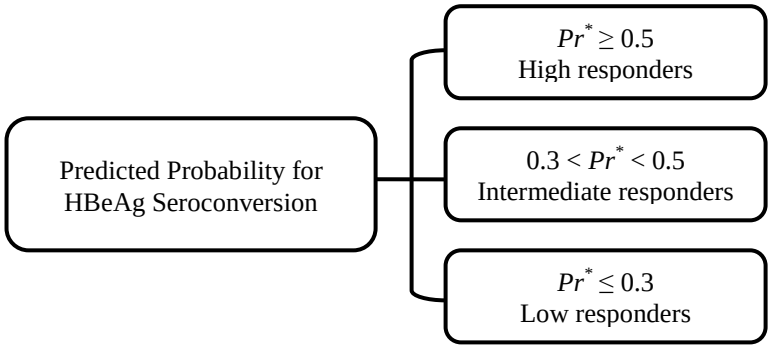
Based on the three variables – age, pretreatment serum ALT level, and pretreatment HBV DNA level – an individual prediction model (risk index formula) for HBeAg seroconversion was constructed (Table 4). The regression formula (risk index) for prediction of HBeAg seroconversion is:

Risk index (RI) for HBeAg seroconversion = e^{A}

The probability of HBeAg seroconversion = RI/(RI+1)

where A = 2.8844 + [-0.0262 x Age (year)] + [0.000915 x pretreatment serum ALT level (IU/L)] + [-0.2889 x pretreatment HBV DNA level ($\log_{10}$ copies/ml)]

Figure 2. Classification of lamivudine response group in accordance with the probability of HBeAg seroconversion



* *Pr*: Probability of HBeAg seroconversion

All possible probabilities for HBeAg seroconversion of 748 patients were calculated and realigned, and two arbitrary cut-off values were selected to exclude spontaneous HBeAg seroconversion rate from the accumulated HBeAg seroconversion rate during the lamivudine treatment period. Based on the cut-off values, the probability of HBeAg seroconversion was categorized into high (Pr ≥ 50%), intermediate (30% < Pr < 50%), and low (Pr ≤ 30%) response groups as depicted in Figure 2. In the high response group, 55.5% of the patients achieved HBeAg seroconversion whereas in the low response group, 19.4% achieved HBeAg seroconversion (Table 5).

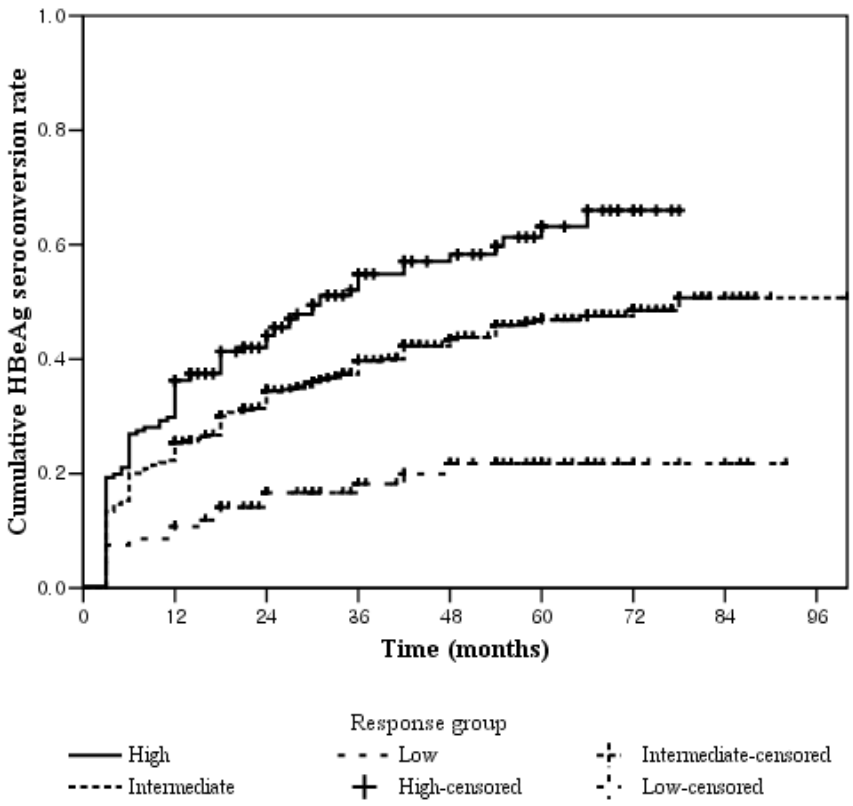
Table 5. Distribution of HBeAg CHB patients with HBeAg seroconversion in accordance with the individual prediction model in the estimation set ($p < 0.001$)

		HBeAg Seroconversion		Total
		Not achieved	Achieved	
Response group, *n* (%)	Low	75 (80.6)	18 (19.4)	93 (12.4)
	Intermediate	280 (57.9)	204 (42.1)	484 (64.7)
	High	77 (45.0)	94 (55.5)	171 (22.9)
Total		432 (57.8)	316 (42.2)	748 (100.0)

The cumulative rate of HBeAg seroconversion according to the individual prediction model reveals that there is a significant difference in the cumulative HBeAg seroconversion rates between the response groups, as shown in Figure 3 ($p < 0.001$). For the high response group, the cumulative HBeAg seroconversion rates at 12, 24, 36, and 60 months were 36.3%, 44.1%,

54.9%, and 63.1%, respectively. For the intermediate response group, the cumulative HBeAg seroconversion rates at 12, 24, 36, and 60 months were 25.4%, 34.4%, 39.7%, and 46.8%, respectively. The cumulative HBeAg seroconversion rate for the low response group was 10.8% at 12 months, 16.6% at 24 months, 18.2% at 36 months, 21.8% at 60 months, and remained unchanged throughout the follow up period.

Figure 3. Cumulative rate of HBeAg seroconversion in accordance with the individual prediction model in the estimation set ($p < 0.001$)



5. Validation of Individual Prediction Model

Table 6 shows baseline patient demographics and laboratory tests of the validation set population. The median age of the 396 patients (280 males, 116 females) was 41.0 years (range, 18 – 77). The mean pretreatment serum ALT level was 170.0 ± 10.6 IU/L. The mean pretreatment HBV DNA level was 7.4 ± 0.1 $\log_{10}$ copies/mL. The mean follow up duration was 22.3 ± 0.5 months. Compared with the study set population, patients in the validation set were younger in age ($p = 0.011$), had lower serum ALT levels ($p < 0.001$) and pretreatment HBV DNA levels ($p < 0.001$), and shorter follow up duration period ($p < 0.001$).

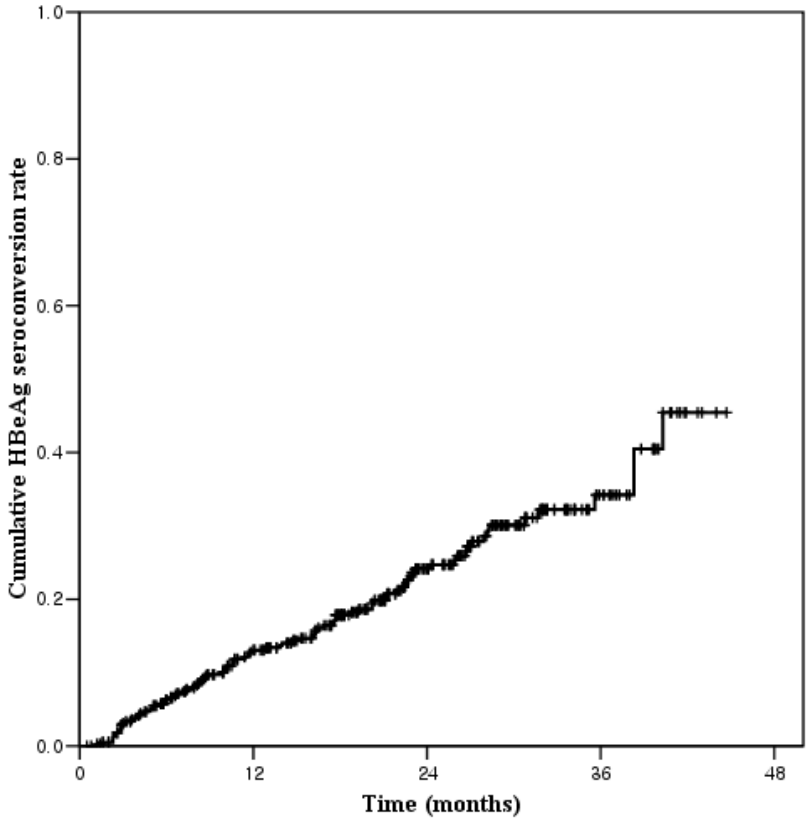
Table 6. Baseline characteristics of HBeAg-positive CHB patients in the validation set (*n* = 396)

Variables		
Gender	Male, *n* (%)	280 (70.7)
	Female, *n* (%)	116 (29.3)
Median age, years (range)		41.0 (18 – 77)
Pretreatment serum ALT (IU/mL)		170.0 ± 10.6
Pretreatment HBV DNA ($\log_{10}$ copies/mL)		7.4 ± 0.1
Follow up duration (months)		22.3 ± 0.5

Results are given as mean ± standard error of mean, unless otherwise indicated.

CHB, chronic hepatitis B; ALT, alanine aminotransferase; HBV, hepatitis B virus.

Figure 4. Cumulative HBeAg seroconversion rate of the validation set



The cumulative HBeAg seroconversion rates were from 13.1% at 12 months to 34.2% at 36 months (Figure 4). For the high response group, the cumulative HBeAg seroconversion rates at 12, 24, and 36 months were 16.2%, 30.1%, and 45.5%, respectively. For the intermediate response group, the cumulative HBeAg seroconversion rates at 12, 24, and 36 months were 11.1%, 22.5%, and 27.5%, respectively. The cumulative HBeAg seroconversion rate for the low response group was 13.3% at 12 months, and remained unchanged

throughout the follow up period (Figure 5).

Based on the predefined categorization, 30.7% of the high response group gained HBeAg seroconversion, and 11.5% of the low response group achieved HBeAg seroconversion (Table 7).

According to the individual prediction model, there was a significant difference in the cumulative rate of HBeAg seroconversion between high response group and intermediate and low response group as shown in Figure 5 (p = 0.0149).

Figure 5. Cumulative rate of HBeAg seroconversion in accordance with the individual prediction model in the validation set (p = 0.0149)

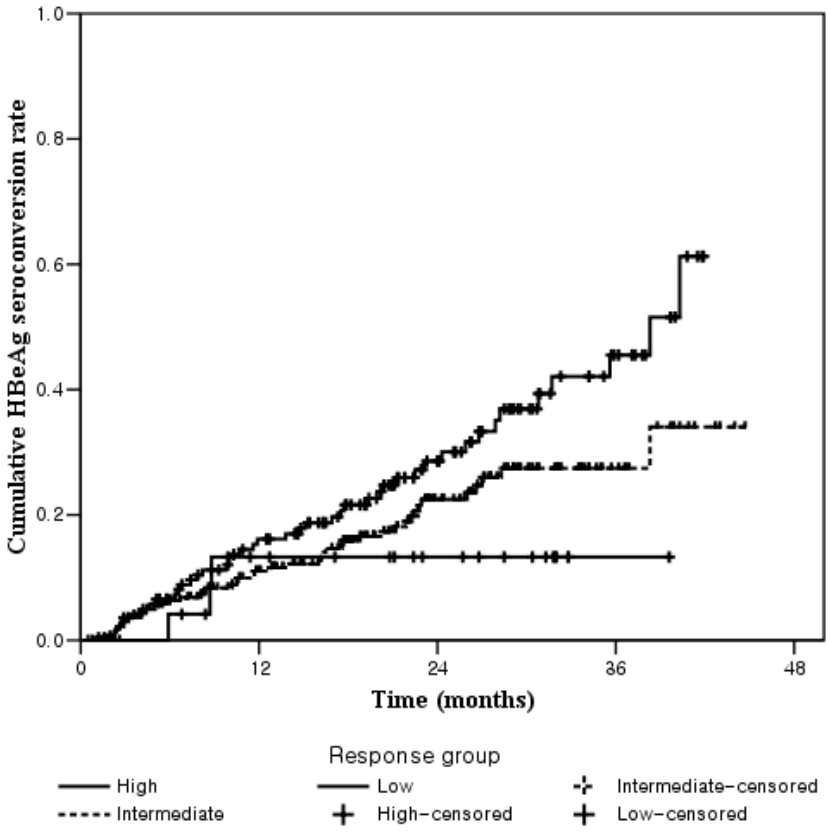


Table 7. Distribution of HBeAg CHB patients with HBeAg seroconversion in accordance with the individual prediction model in the validation set ($p < 0.013$)

		HBeAg Seroconversion		Total
		Not achieved	Achieved	
Response group, *n* (%)	Low	23 (88.5)	3 (11.5)	26 (6.6)
	Intermediate	186 (80.9)	44 (19.1)	230 (58.1)
	High	97 (69.3)	43 (30.7)	140 (35.4)
Total		306 (77.3)	90 (22.7)	396 (100.0)

CHB, chronic hepatitis B.

IV. DISCUSSION

Sustained suppression of viral replication and achieving loss of HBeAg and/or seroconversion to anti-HBe in HBeAg-positive patients are the most important goals in the treatment of chronic HBV infection.[35] Among these goals, HBeAg seroconversion is a desirable goal, because achievement of complete HBeAg seroconversion usually predicts long-lasting suppression of HBV, reduced infectivity and an improved clinical prognosis.[8, 36]

In the current study, an individual prediction model for HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients on lamivudine monotherapy was developed from routinely measured and easily available clinical and laboratory variables.

Predictors associated with HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients on lamivudine monotherapy were patient's age, pretreatment serum ALT level, and pretreatment serum HBV DNA level. Pretreatment serum HBV DNA level was negatively associated with the probability of HBeAg seroconversion, as previously reported.[35, 37-39] Although there has been conflicting data on the affect of age and pretreatment serum ALT level on the treatment outcome of antiviral therapy using nucleos(t)ide analogues in HBeAg-positive chronic hepatitis B patients, younger age and higher serum ALT level at the initiation of antiviral therapy were associated with higher probability of HBeAg seroconversion in the current study.[35, 37, 39, 40] It could be postulated that patients with higher serum ALT levels undergo more intense immune responses, and thus, have a higher change of HBeAg

seroconversion.

The role of genotypes as a treatment predictor in chronic hepatitis B has not been clearly defined and remains controversial.[41-45] Although there is an increasing evidence that HBV genotype may be an important predictor of treatment outcome of interferon-based therapy, the role of HBV genotypes in nucleos(t)ide analogue antiviral therapy remains controversial. In Korea, more than 95% of chronic hepatitis B patients are infected with genotype C, and thus, individual HBV genotyping was not performed in the current study, with an assumption that the only a minority of patients have HBV genotypes other than genotype C.[46-48]

The cut-off values for the response group categorization in the individual prediction model were selected under the background of natural history of chronic hepatitis B infection and reported long-term treatment results of lamivudine therapy. According to the literature, the annual rate of spontaneous HBeAg seroconversion is approximately 15-20%, and therefore the lower cut-off value of 30% was chosen roughly to exclude spontaneous HBeAg seroconversion rate from the accumulated HBeAg seroconversion rate during the lamivudine treatment period.[49-51] The incidence of HBeAg seroconversion at 5 years of lamivudine treatment is approximately 50%, and hence it was chosen for the upper cut-off value for the individual prediction model.[5]

The HBeAg seroconversion rate in the validation set was lower than that in the study set. In this cohort of 748 patients of the study set, 50.7% achieved HBeAg seroconversion with up to 96 months, which is comparable with the results of previous studies.[5, 52] On the other hand, 45.4% achieved HBeAg seroconversion with up to 48 months. Similar to the literature, the chance of

HBeAg seroconversion increased with time, thus it could be postulated that the study set showed a higher HBeAg seroconversion rate compared to that of the validation set, owing to a longer duration of lamivudine treatment.[15, 25, 53, 54] Therefore if the follow up duration of the validation set was extended to a longer period of time, HBeAg seroconversion rate might rise to a comparable level.

In both of the study and the validation sets, the cumulative HBeAg seroconversion rate increased with time significantly in the high response group. The cumulative HBeAg seroconversion rate increased from 36.3% at 1 year to 63.2% at 5 years in the high response group of the study set, and 16.2% at 1 year to 61.3% at 4 years in the high response group of the validation set, respectively.

On the contrary, the cumulative HBeAg seroconversion rate of the low response groups of both sets remained at a low level from the early period of time. In the study set, the cumulative HBeAg seroconversion rate was 10.8% at 1 year and increased to 21.8% at 4 years, but no longer increased up to 7 years. In the validation set, the cumulative HBeAg seroconversion rate was 13.3% at 1 year and remained the same throughout the follow up period.

Accordingly, complete HBeAg seroconversion is hardly achieved in the low response group, thus there is a higher probability of developing virologic breakthrough during the lamivudine therapy. Once virologic breakthrough has taken place, adding adefovir dipivoxil to lamivudine treatment may be an answer to the treatment plan, yet it would be less cost-effective than choosing a newer and potent antiviral drug, such as entecavir, in the beginning of antiviral treatment for the patients in the low response group.

Likewise, for the treatment-naïve patients of younger age with high serum ALT levels and low HBV DNA levels, favorable response to lamivudine is anticipated. In such patients, treating with lamivudine would be cost-effective than with high barrier drugs as entecavir.

The patients in the intermediate response group showed a moderate increase in cumulative HBeAg seroconversion rate in both of the study and the validation set. In this case, antiviral therapy may be started with lamivudine and perform on-treatment monitoring of the serum HBV DNA at 12 weeks to determine primary treatment failure. Patients with complete suppression of serum HBV DNA level at 12 weeks of therapy may be continued with lamivudine as early virologic response monitoring at 12 weeks predicts HBeAg seroconversion (data not shown). Further studies are need for determining new, tailored antiviral treatment strategies for the patients in the intermediate group.

The major limitation of this study was that the validation study was carried out in a single institution with a shorter follow up duration compared to that of the study set population. For this reason, the significant differences between the response groups were not clear. Due to these limitations, further studies with a long-term accumulated data would be necessary.

V. CONCLUSION

In conclusion, an individual prediction model for HBeAg seroconversion in HBeAg-positive chronic hepatitis B patients on lamivudine monotherapy was developed from routinely measured and easily available clinical and laboratory variables. For the patients in the high response group, commencing antiviral therapy with lamivudine for the long-term management would be appropriate, for they are likely to have favorable outcomes with lamivudine. Further studies are needed for the patients in the intermediate response group. Lamivudine monotherapy is not recommended for the patients in the low response group. This individual prediction model is expected to contribute to establishing new, tailored antiviral treatment guidelines for chronic hepatitis B patients.

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ABSTRACT (IN KOREAN)

HBeAg 양성 만성 B형 간염 환자에서 라미부딘의 치료 효과 및 예측모형의 개발

<지도교수 한 광 협>

연세대학교 대학원 의학과

강 원 석

배경: B형 간염바이러스의 증식을 억제하는 라미부딘은 만성 B형 간염에서의 장기적인 효용성 및 안정성이 밝혀져 있으나 최근 약제 내성 바이러스가 출현함에 따라 문제가 되고 있으나 경제적인 측면과 장기간 연구된 약제 안정성으로 인하여 라미부딘은 아직까지도 만성 B형 간염 치료에 있어서 널리 쓰이고 있다. 따라서 라미부딘 내성 바이러스의 발생 가능성이 적고 라미부딘 치료에 효과적인 반응을 보이는 환자들을 선별하는 것이 중요하다.

방법: 1999년 1월부터 2006년 8월까지 라미부딘 1일 100mg씩 6개월 이상 단독 치료를 받은 만성 B형 간염 환자 중 HBeAg 양성인 환자 748명을 대상으로 분석하였다. 단변량 및 다변량 분석을 통하여 HBeAg 혈청전환의 예측인자를 구한 뒤 로지스틱 회귀 분석을 이용하여 HBeAg 혈청전환의 확률을 산출하고 예측모형을 개발하였다. 예측 모형에 따라 고반응군(Pr≥50%), 중간반응군(30<Pr<50%), 저반응군(Pr≤30%)으로 분류한 뒤 2005년 1월부터 2006년 12월까지 라미부딘을 새로 투약 받은 환자 396명을

대상으로 예측모형을 검증하였다.

결과: 라미부딘 단독치료의 중앙 기간은 34.2개월이었다. HBeAg의 누적 혈청전환율은 12개월째 26.1%에서 96개월째 50.7%로 증가하였다. HBeAg 혈청전환의 예측인자로는 환자의 나이(OR=0.974, 95% CI: 0.961-0.988, p<0.001), 치료전 ALT 수치(OR=1.001, 95% CI: 1.000-1.002, p=0.014), 그리고 치료 전 HBV DNA 수치(OR=0.749, 95% CI: 0.651-0.862, p<0.001)였다. 예측모형을 바탕으로 한 고반응군, 중간반응군, 저반응군에서의 HBeAg의 72개월 누적 혈청전환율은 각각 66.0%, 48.5%, 21.8% 이었다 (p<0.001).

결론: HBeAg 양성 만성 B형 간염 환자에서 라미부딘 단독 치료시 HBeAg 혈청전환 예측모형을 개발하였다. 이 예측 모형을 통하여 항바이러스 치료를 시작하기 전 라미부딘 치료의 반응을 예측함으로써 새로운 항바이러스 치료 가이드라인을 형성하는 데 도움이 될 것으로 생각된다.

핵심되는 말 : 예측모형, 만성 간염, 라미부딘, 치료