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• *BASIC RESEARCH* •

Relationship between body surface area and ALT normalization after long-term lamivudine treatment

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Abstract

AIM: To further evaluate the relationship between BSA and the effects of lamivudine in a greater number of cases and over a longer period of observation than in our previous evaluation.

METHODS: We evaluated 249 patients with chronic hepatitis B. The effects of treatment for one year (n = 249), two years (n = 147), and three years (n = 72) were evaluated from the levels of serum ALT and HBV-DNA, as biological and virological effects (undetectable levels by PCR), respectively. Moreover, several variables that could influence the response to treatment, including ALT, albumin, bilirubin, platelet counts, BSA, HBV-DNA, and HBeAg were analyzed.

RESULTS: For 1-year treatment, multivariate analysis revealed that BSA (P = 0.0002) was the only factor for the biological effect, and that ALT (P = 0.0017), HBV-DNA (P = 0.0004), and HBeAg (P = 0.0021) were independent factors for the virological effect. For 2-year treatment, multivariate analysis again showed that BSA (P = 0.0147) was the only factor for the biological effect, and that ALT (P = 0.0192) and HBeAg (P = 0.0428) were independent factors for the virological effect. For 3-year treatment, multivariate analysis, however, could not reveal BSA (P = 0.0730) as a factor for the normalization of ALT levels.

CONCLUSION: BSA is a significant predictor for the normalizing the effect of lamivudine therapy on ALT for an initial 2-year period, suggesting that lamivudine dosage should be based on the individual BSA.

Key words: Lamivudine; Hepatitis B virus; Body surface area; Dose; Long-term treatment

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INTRODUCTION

Chronic hepatitis B is an important cause of morbidity and mortality resulting from cirrhosis-related liver failure and hepatocellular carcinoma (HCC)[1-3]. Lamivudine is an oral nucleoside analog approved for the treatment of chronic hepatitis B. It inhibits viral DNA replication by means of chain termination, and competitively inhibits viral polymerase. A daily dosage of lamivudine of 100 mg has been accepted worldwide for the treatment for chronic hepatitis B, since early studies showed that there was no

significant difference in the effect of lamivudine at doses of 100 and 300 mg[4,5]. However, to establish ideal dosages in those studies, efficacy was mainly evaluated by measuring hepatitis B virus (HBV)-DNA, and the assay used was much less sensitive than the polymerase chain reaction (PCR) assay. Studies in which HBV-DNA was measured by PCR assay reported an additional viral suppressive activity with high doses (300 mg) of lamivudine for 24 wk[6]. In addition to the limits imposed by the assay methods that were used, the observation periods in the studies on lamivudine doses of 100-300 mg were limited to a period of 12[4] or 24 wk[5]. Although the effect of doses greater than 100 mg on the emergence of YMDD mutants has not been evaluated, baseline body mass index has been reported to be significantly related to the emergence of HBV mutants during lamivudine treatment in patients co-infected with HBV and human immunodeficiency virus-1 (HIV-1)[7]. In a previous study of 134 patients treated for 23.1 mo(mean observation period), body surface area (BSA) was shown to be an independent factor contributing to the effects of lamivudine treatment[8]. In the present study, to further confirm these results, we evaluated the relationship between BSA and the effects of lamivudine effects in a greater number of patients and for longer observation periods than those in the previous report.

MATERIALS AND METHODS

Patients

Criteria for entry into this study were as follows: (a) the patients had not been treated with lamivudine previously; (b) they had chronic hepatitis caused by HBV, and persistent abnormal levels of alanine aminotransferase (ALT); and (c) patients with HCC were excluded. A total of 249 patients with chronic hepatitis B were evaluated. They had been treated with 100 mg of lamivudine for more than 1 year at Kyushu University Hospital and its affiliated hospitals (Table 1). For all the patients, the existence of serum HBV-DNA was confirmed by transcription-mediated nucleic acid amplification (TMA) assay ($10^{3.7}$-$10^{8.7}$ genome equivalents/mL; 3.7-8.7 log genome equivalents [LGE]/mL) (Chugai Diagnostic Science, Tokyo, Japan) or by a Roche Monitor kit ($10^{2.6}$-$10^{7.6}$ copies/mL; 2.6-7.6 log copies/mL) (Roche Diagnostics, Tokyo, Japan) before the treatment. None of the patients dropped out and all were treated with 100 mg/d lamivudine until the end of the observation period. After the start of medication, basic hepatic function and serum levels of HBV-DNA were measured at least every 3 mo for all the patients. The efficacy of lamivudine was evaluated from the serum levels of ALT and HBV-DNA, as biological and virological effects, respectively. The categories for the biological evaluation based on serum ALT were as follows: (1) sustained responder (SR) ALT: the serum levels of ALT decreased and remained at less than 30 U/L continuously during the observation period; and (2) non-responder (NR) ALT: the serum ALT was more than 30 U/L at the end of the observation. Similarly, the categories for the virological evaluation based on HBV-DNA were: (1) SR-HBV: serum HBV-DNA decreased to levels undetectable by PCR (<2.6 log copies/mL) and remained negative continuously during the observation period; and (2) NR-HBV: serum HBV-DNA was detectable at the end of the observation period (>2.6 log copies/mL). BSA was calculated using the method of DuBois.

Statistical analysis

The baseline characteristics of the patients prior to the beginning of the lamivudine therapy are expressed as mean±SD for the quantitative variables. In order to determine the contribution of these variables to the effect of the treatment, univariate and multivariate logistic analyses were performed. For multivariate logistic analysis, we analyzed BSA as an independent factor contributing to the effects of lamivudine treatment variables that showed χ^2 values of more than 1.0 in the univariate logistic

Table 1 Baseline characteristics of patients treated for 1 year[1]

	Total (range)	SR-ALT	NR-ALT	SR-DNA	NR-DNA
n	249	150	99	183	66
Male/female	180/67	99/51	82/17	127/54	53/13
ALT (U/L)	211.1±402.4 (16-4491)	242.1±424.2	163.6±363.6	240.3±462.2	128.8±88.1
Albumin (g/dL)	3.8±0.6 (2.2-4.9)	3.8±0.6	3.8±0.6	3.8±0.6	3.9±0.6
Bilirubin (mg/dL)	1.3±1.7 (0.1-12.9)	1.4±1.8	1.2±1.5	1.4±1.9	1.0±1.1
Platelet (10^4/mL)	14.1±6.1 (2.6-35.5)	14.2±5.8	14.0±6.5	13.9±6.2	14.9±5.6
BSA (m^2)	1.70±0.20 (1.25-2.17)	1.66±0.17	1.75±0.18	1.69±0.18	1.73±0.18
HBV-DNA					
≤5 (LEG/mL)	31	20	11	29	2
5< ≤6	33	18	15	27	6
6< ≤7	68	41	27	52	16
7<	117	71	46	75	42
HBeAg +/-	135/110	83/64	52/46	84/96	51/14
Age (yr)	48.6±11.6 (19-73)				
CH/LC [Child A/B/C]	162/87 [61/11/15]				

[1]Data are shown as mean±SD.

model. *P* value less than 0.05 was considered statistically significant.

RESULTS

The effects of lamivudine for 1 year were analyzed in a total of 249 patients (Table 1), of which 150 (60.2%) were identified as SR-ALT and 99 (39.8%) as NR-ALT, and 183 (73.5%) were identified as SR-DNA and 66 (26.5%) as NR-ALT (Table 1). To evaluate the contribution of the variables to the effect of treatment, univariate and multivariate logistic analyses were performed. In the univariate logistic analysis, BSA and ALT in the biological evaluation, and ALT, albumin, bilirubin, platelet count, BSA, HBV-DNA, and HBeAg in the virological evaluation, had χ^2 values of more than 1.0 (Table 2). Therefore, we used these factors as variables for multivariate logistic analysis. The results of multivariate analysis revealed that BSA was the only significant factor for the improvement of ALT levels (χ^2 = 14.3, P = 0.0002), and ALT, albumin, HBV-DNA and HBeAg were independent factors for the disappearance of serum HBV-DNA (ALT: χ^2 = 9.8, P = 0.0017; albumin: χ^2 = 5.1, P = 0.0238; HBV-DNA: χ^2 = 12.6, P = 0.0004; and HBeAg: χ^2 = 9.5, P = 0.0021) (Table3).

The effects of 2-year therapy were evaluated in 147 patients (Table 4). Of these patients, 75 (51.0%) were identified as SR-ALT and 72 (49.0%) as NR-ALT, while 85 (57.8%) were identified as SR-DNA and 62 (42.2%) as NR-ALT (Table 5). In the univariate logistic analysis, bilirubin, platelet count and BSA in the biological evaluation, and ALT, bilirubin, platelet, BSA and HBeAg in the virological evaluation, were selected (χ^2>1.0) (Table 5). Multivariate analysis revealed that BSA was the only significant factor in the biological effects (χ^2 = 5.6, P = 0.0147), and ALT and HBeAg were independent factors in the virological effects (ALT: χ^2 = 5.5, P = 0.0192; and HBeAg: χ^2 = 4.1, P = 0.0428) (Table 6).

Finally, the effects of 3-year therapy were evaluated in 72 patients (Table 7). Of these patients, 33 (45.8%) were identified as SR-ALT and 39 (54.2%) as NR-ALT, while

Table 2 Univariate analysis of the effects of lamivudine treatment for 1 year

Variables	χ^2	P
Biological effects		
ALT (U/L)	2.963405	0.0852
Albumin (g/dL)	0.230408	0.6312
Bilirubin (mg/dL)	0.934082	0.3338
Platelet count (10^4/mL)	0.097459	0.7549
BSA (m^2)	15.96269	<0.0001
HNV-DNA (LEG/mL)	0.000983	0.9750
HBeAg	0.275000	0.6000
Virological effects		
ALT (U/L)	8.293809	0.0040
Albumin (g/dL)	3.353949	0.0670
Bilirubin (mg/dL)	3.258437	0.0711
Platelet count (10^4/mL)	1.331910	0.2485
BSA (m^2)	2.586640	0.1078
HNV-DNA (LEG/mL)	14.38010	0.0001
HBeAg	19.51400	<0.0001

Table 3 Multivariate analysis on the effects of lamivudine treatment for 1 year

Variables	χ^2	P
Biological effects		
ALT (U/L)	1.921529	0.1657
BSA (m^2)	15.96269	0.0002
Virological effects		
ALT (U/L)	9.797455	0.0017
Albumin (g/dL)	5.106762	0.0238
Bilirubin (mg/dL)	0.450406	0.5021
Platelet count (10^4/mL)	0.009626	0.9218
BSA (m^2)	2.222164	0.1360
HNV-DNA (LEG/mL)	12.64904	0.0004
HBeAg	9.476967	0.0021

Table 4 Baseline characteristics of patients treated for 2 years[1]

	Total (range)	SR-ALT	NR-ALT	SR-DNA	NR-DNA
n	147	75	72	85	62
Male/female	112/35	52/23	60/12	62/23	50/12
ALT (U/L)	221.6±493.5 (17-4491)	258.9±548.5	182.3±428.2	291.3±626.3	122.2±132.0
Albumin (g/dL)	3.8±0.6 (2.2-4.9)	3.8±0.5	3.8±0.6	3.8±0.5	3.9±0.6
Bilirubin (mg/dL)	1.5±2.1 (0.3-12.9)	1.7±2.5	1.3±1.7	1.7±2.6	1.0±1.1
Platelet (10^4/mL)	13.8±6.2 (3.4-33.6)	12.9±5.4	14.6±6.8	13.1±5.5	14.9±5.6
BSA (m^2)	1.71±0.18 (1.30-2.17)	1.67±0.18	1.76±0.17	1.70±0.18	1.73±0.18
HBV-DNA					
≤5 (LEG/mL)	18	11	7	12	6
5< ≤6	20	7	13	11	9
6< ≤7	42	23	19	26	16
7<	69	35	34	38	31
HBeAg +/–	82/65	41/34	41/31	41/45	41/20
Age (yr)	48.9±11.4 (19-73)				
CH/LC [Child A/B/C]	95/54 [43/3/8]				

[1] Data are shown as mean±SD.

38 (52.8%) were identified as SR-DNA and 34 (47.2%) as NR-DNA (Table 8). In the univariate logistic analysis, albumin, platelet count, BSA, and HBeAg in the biological evaluation, and no variables in the virological evaluation, were selected (χ^2>1.0) (Table 8). Multivariate analysis did not reveal BSA as a factor for predicting the biological efficacy of lamivudine therapy $\chi^2 = 3.2$, $P = 0.0730$) (Table 9).

DISCUSSION

In this present study, we found that BSA was a significant factor that could contribute to the normalization of serum ALT (biological response) after the treatment with lamivudine for an initial 2-year period. Body weight was also a significant factor contributing to the effects of lamivudine treatment (data not shown). Because χ^2 values of BSA were higher than those of body weight and BSA is determined with body weight and height, we used BSA as a variable for statistical analysis. We initially reported that BSA was an independent factor contributing to both the biological and virological responses[8]. The difference in the contribution to the virological response between the present and the previous study might be attributed to the differences in the criteria used to evaluate treatment effects. In our previous study, we used a third category in addition to SR and NR transient responder (TR) which included patients with serum ALT levels that initially decreased to less than 30 U/L but increased to more than 30 U/L during the subsequent observation period (TR-ALT), and the patients in whom serum HBV-DNA initially decreased to undetectable levels (<2.6 log copies/mL) but became positive again during the subsequent observation period (TR-DNA). Regardless of the differences in evaluation criteria, both studies clearly demonstrated that BSA independently contributed to the normalization of ALT in the patients treated with lamivudine for an initial 2-year period. Because the pharmacokinetics of lamivudine correlate with body weight, as is the case with many other drugs[9], it is reasonable to conclude that patients with lower BSA would have achieved higher blood concentrations

Table 5 Univariate analysis of the effects of lamivudine treatment for 2 years

Variables	χ^2	*P* values
Biological effects		
ALT (U/L)	0.962196	0.3266
Albumin (g/dL)	0.279331	0.5971
Bilirubin (mg/dL)	1.384215	0.2394
Platelet count (10^4/mL)	2.943368	0.0862
BSA (m^2)	8.339371	0.0039
HNV-DNA (LEG/mL)	0.009964	0.9205
HBeAg	0.077000	0.7810
Virological effects		
ALT (U/L)	8.990505	0.0027
Albumin (g/dL)	0.643271	0.4225
Bilirubin (mg/dL)	3.176521	0.0747
Platelet count (10^4/mL)	2.064207	0.1508
BSA (m^2)	1.060739	0.3030
HNV-DNA (LEG/mL)	0.546020	0.4598
HBeAg	5.595000	0.0180

Table 6 Multivariate analysis of the effects of lamivudine treatment for 2 years

Variables	χ^2	*P* values
Biological effects		
Bilirubin (mg/dL)	0.496757	0.4809
Platelet count (10^4/mL)	0.572997	0.4491
BSA (m^2)	2.263849	0.0147
Virological effects		
ALT (U/L)	5.482584	0.0192
Bilirubin (mg/dL)	0.983777	0.3212
Platelet count (10^4/mL)	1.098891	0.2945
BSA (m^2)	0.714246	0.3980
HNV-DNA (LEG/mL)	0.592857	0.4413
HBeAg	4.101478	0.0428

Table 7 Baseline characteristics of patients treated for 3 years

	Total (range)	SR-ALT	NR-ALT	SR-DNA	NR-DNA
n	72	33	39	38	34
Male/female	53/19	21/12	32/7	27/11	26/8
ALT (U/L)	198.6±437.2 (18-3545)	200.0±229.0	197.5±562.1	191.2±218.0	207.2±602.6
Albumin (g/dL)	3.8±0.5 (2.5-4.9)	3.7±0.4	4.0±0.5	3.8±0.5	3.9±0.5
Bilirubin (mg/dL)	1.5±2.1 (0.3-12.9)	1.6±2.2	1.5±2.3	1.6±2.2	1.5±2.4
Platelet (10^4/mL)	13.8±6.2 (3.9-33.6)	11.6±4.6	15.1±6.9	13.3±5.8	13.8±6.5
BSA (m^2)	1.71±0.18 (1.30-2.17)	1.75±0.17	1.66±0.19	1.69±0.17	1.73±0.20
HBV-DNA					
≤5 (LEG/mL)	7	4	3	4	3
5< ≤6	15	4	11	6	9
6< ≤7	17	11	6	13	4
7<	33	14	19	15	18
HBeAg +/–	41/31	21/12	20/19	22/16	19/15
Age (yr)	49.5±11.1 (21-73)				
CH/LC [Child A/B/C]	43/29 [25/0/4]				

[1] Data are shown as mean±SD.

Table 8 Univariate analysis of the effects of lamivudine treatment for 3 years

Variables	χ^2	*P* values
Biological effects		
ALT (U/L)	0.000598	0.9805
Albumin (g/dL)	5.541899	0.0186
Bilirubin (mg/dL)	0.100733	0.7510
Platelet count (10^4/mL)	6.242535	0.0125
BSA (m^2)	4.393544	0.0361
HNV-DNA (LEG/mL)	0.001477	0.9693
HBeAg	1.113000	0.2915
Virological effects		
ALT (U/L)	0.023922	0.8771
Albumin (g/dL)	0.565446	0.4315
Bilirubin (mg/dL)	0.010128	0.9198
Platelet count (10^4/mL)	0.137799	0.7105
BSA (m^2)	0.805305	0.3695
HNV-DNA (LEG/mL)	0.065438	0.7981
HBeAg	0.030000	0.8633

Table 9 Multivariate analysis of the effects of lamivudine treatment for 3 years

Variables	χ^2	*P* values$_\chi$
Biological effects		
Albumin (g/dL)	0.865354	0.3522
Platelet count (10^4/mL)	2.391260	0.1220
BSA (m^2)	3.213451	0.0730
HBeAg	1.252959	0.2630

of lamivudine, although we did not actually monitor the concentration of lamivudine. Recent reports suggest that the baseline body mass index is significantly related to the emergence of HBV mutation during lamivudine treatment (300 mg/d, >6 mo) in patients co-infected with HBV and HIV-1[7]. Therefore, the results of our studies again question whether a lamivudine dosage of 100 mg/d is adequate, particularly for long-term treatment.

The standard lamivudine dose of 100 mg daily was based on early studies in which doses of 25, 100, and 300 mg were compared for 12[4] or 24 wk[5]. Because there were no significant differences reported in the rates of non-detection of HBV-DNA and normalization of ALT levels between the 100 and 300 mg doses, the dose of 100 mg has become a well-accepted therapeutic standard[4,5]. However, several factors should be considered when evaluating the results of these studies, including the number of patients, duration of treatment, emergence of lamivudine-resistant mutants over long-term treatment, and detection limits for HBV-DNA.

In the present study, we found that there was a significant difference in the contribution of BSA to the biological effect, although the differences in the mean values of BSA between SR-ALT and NR-ALT were relatively small. Therefore, it is possible that previous studies failed to detect a significant contribution of BSA to the effects of lamivudine because of the smaller number of patients examined. The major drawback of lamivudine monotherapy is the emergence of resistant HBV with mutations of the tyrosine-methionine-aspartate-aspartate (YMDD) motif. The incidence of these mutants rises from 15-20% in the first year of therapy to 40% by the second year, and to 67% by the fourth year[10]. In some cases, fatal liver failure subsequent to the emergence of the mutant was reported[11]. Therefore, observation periods of 24 wk may not be adequate for detecting the emergence of lamivudine-resistant mutants. In our evaluation of HBV-DNA, the rates of NR-DNA were found to be 26.5%, 42.2%, and 57.2% in patients who were positive for HBV-DNA (>2.6 log copies/mL) by the first, second, and third year, respectively. Although we did not confirm YMDD mutation in all cases of NR-DNA, the increase in NR-DNA ratio might be attributable to the emergence of mutants. Concomitant with the increases in HBV-DNA seen over the 3-year period, the NR-ALT ratio rose from 39.8% in the first year to 49.0% by the second year and to 54.8% by the third year in the present study, suggesting that the emergence of mutants could abolish the contribution of BSA to biological effects in the third year. Further studies will be needed to confirm whether BSA affects the incidence of YMDD mutants.

In previous studies that showed no difference in the effects of 100 and 300 mg lamivudine on HBV-DNA levels (as aforementioned)[4,5], HBV-DNA was measured quantitatively by liquid hybridization assay (Abbott Laboratories), which has a detection limit of 10^7 geq/mL[12]. Honkoop *et al*[6] studied the efficacy of 100 and 300 mg lamivudine in viral suppression for 24 wk using a semi-quantitative PCR method with a detection limit of 10^2-10^3 geq/mL. In the present study, we used a Roche Monitor kit, which has detection limit of 2.6 log copies/mL, and could not find a significant relationship between BSA and the virological effect of lamivudine. Chun *et al*[13], reported that there was no significant correlation between viral replication and liver damage in chronic hepatitis B. Hence, it seems reasonable that we did not find a contribution of BSA to the virological effects of treatment. Further study will be needed to evaluate dose-dependent lamivudine effects on viral suppression including the emergence of mutants which could directly affect the viral load.

In conclusion, we have shown that BSA is a statistically significant and potentially important factor for predicting the efficacy of lamivudine therapy for chronic hepatitis B. A noteworthy finding in our study was that small differences in BSA might significantly influence the effect of lamivudine treatment, suggesting that a small increase in lamivudine dose might markedly increase its therapeutic efficacy. We believe that a long-term clinical trial with higher-dose lamivudine treatment in a large number of cases is warranted, since lamivudine will continue to be a first-line treatment for HBV.

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