Early Entecavir Treatment for Chronic Hepatitis B with Severe Acute Exacerbation

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A previous study found that lamivudine, if started early enough, may improve the chance of survival in chronic hepatitis B virus (HBV) with severe acute exacerbation (SAE). The aim of this study was to investigate the effect of early entecavir treatment before the bilirubin level exceeds 20 mg/dl for chronic HBV with SAE. Consecutive patients with chronic HBV with SAE and a serum bilirubin level of <20 mg/dl who received lamivudine or entecavir were enrolled. Short-term (4 months) survival was evaluated. One hundred fourteen patients received lamivudine, and 53 patients received entecavir. The baseline characteristics were similar for the two groups except that the entecavir group was older and had a lower alanine aminotransferase (ALT) level. Three patients (8.0%) in the entecavir group and 9 patients (7.9%) in the lamivudine group died ($P = 1.000$). If only patients who started antiviral treatment before serum bilirubin level rose to more than 15 mg/dl were included, 3 patients (8.3%) in the entecavir group and 3 patients (3.0%) in the lamivudine group died ($P = 0.189$). If only patients with an HBV DNA level higher than 10^5 copies/ml and a bilirubin level lower than 15 mg/dl were included, 5 out of 40 patients (12.5%) in the entecavir group died and 1 out of 59 patients (1.7%) in the lamivudine group died. Multivariate analysis found that entecavir treatment was associated with more mortality than lamivudine ($P = 0.035$). Early entecavir treatment in patients with high viral load is associated with more short-term mortality than lamivudine for chronic HBV with severe acute exacerbation.

Chronic hepatitis B virus (HBV) infection is a major global health problem, with an estimated 400 million HBV carriers worldwide (1). In the natural history of chronic HBV, spontaneous acute exacerbation (AE) is not uncommon, with a cumulative incidence of 10 to 30% every year (2–5). These exacerbations can be mild, but some patients may develop hepatic decompensation and even death (6, 7).

Lamivudine (LAM) is the first approved antiviral agent for HBV. Lamivudine is effective and safe for the treatment of compensated and decompensated chronic HBV infection (8–10). Several nonrandomized studies have found that lamivudine did not increase the survival rate for the treatment of chronic HBV with severe AE (SAE) (11, 12). A recent study by Chien et al. found that early lamivudine treatment before the bilirubin level is above 20 mg/dl is associated with an improved outcome (13). Another recent study by Sun et al. also found that lamivudine treatment can improve the outcome for patients with a Model for End-Stage Liver Disease (MELD) score less than 30 (14). However, lamivudine is associated with a high resistance rate (15). In randomized studies, entecavir (ETV) demonstrated superior antiviral efficacy to and a lower resistance rate than lamivudine (16, 17). However, a recent study from Hong Kong unexpectedly demonstrated that entecavir resulted in an increased short-term mortality rate over that of lamivudine in chronic HBV with severe AE (18). The aim of this study was to investigate the effect of early entecavir use for the treatment of chronic HBV with severe AE.

MATERIALS AND METHODS

Consecutive patients with chronic hepatitis B with severe AE admitted to Kaohsiung Veterans General Hospital from January 2000 to December 2006 who received lamivudine and from July 2008 to December 2012 who received entecavir were included. All patients had a history of HBV infection for more than 6 months. Severe AE was defined as abrupt rise of

alanine aminotransferase (ALT) to more than $5 \times$ the upper limit of normal (ULN; the ULN is 40 U/liter), accompanied by a total bilirubin level of more than 2.0 mg/dl or prolongation of the prothrombin time (PT) by more than 3 s. Patients with alcohol use of more than 30 g/day, who took hepatotoxic agents, and who had evidence of liver cirrhosis or hepatocellular carcinoma were excluded. Patients with a total bilirubin level of more than 20 mg/dl before antiviral treatment were excluded. Patients who had previously received antiviral therapy including interferon or nucleoside or nucleotide analogues were also excluded. Liver cirrhosis was diagnosed by histology or by characteristic ultrasonography findings (19).

Liver biochemistry values, including serum albumin, bilirubin, aspartate transaminase (AST), ALT, PT, creatinine, complete blood counts, and HBV DNA were determined upon admission to the hospital. The liver biochemistry data, PT, and renal function were monitored once or twice per week until the patients' conditions stabilized. All biochemical tests were performed in the clinical pathology laboratories of Kaohsiung Veterans General Hospital using routine automated techniques. The serological markers HBsAg, HBeAg, IgM anti-HBc, and IgM anti-HAV were assayed by immunoenzymatic assay (Abbott Laboratories, Ltd., Germany). Anti-HCV was assayed using an enzyme immunoassay (EIA) kit (Abbott Laboratories, Ltd., Germany). The quantification of HBV DNA was performed by real-time PCR as previously described (20).

The values are expressed as means $\pm$ standard deviations. Categorical variables were analyzed with chi-square test or Fisher's exact test as ap-

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TABLE 1 Demographic and clinical data in patients under entecavir or lamivudine treatment before bilirubin level reached >20 mg/dl

Parameter	Value for group		<i>P</i>
	Entecavir (<i>n</i> = 53)	Lamivudine (<i>n</i> = 114)	
Age (yrs) ^a	49 ± 13	43 ± 15	0.006
Sex (M/F ^b)	38/15	88/26	0.446
AST (U/liter) ^a	838 ± 690	1,051 ± 1,010	0.166
ALT (U/liter) ^a	1,287 ± 788	1,629 ± 1,011	0.031
Albumin (g/dl) ^a	3.6 ± 0.6	3.5 ± 0.5	0.183
Bilirubin (mg/dl) ^a	6.3 ± 4.5	7.7 ± 5.1	0.087
Creatinine (mg/dl) ^a	0.9 ± 0.2	0.9 ± 0.2	0.943
Prothrombin time (INR) ^a	1.4 ± 0.5	1.5 ± 0.5	0.308
Platelet (cells × 10 ⁹ /ml) ^a	156 ± 59	175 ± 60	0.071
HBeAg (positive/negative)	15/38	47/67	0.123
HBV DNA (×10 ⁵ copies/ml) ^a	1,442 ± 338	1,642 ± 448	0.783
Mortality	6/53 (11.3%)	9/114 (7.9%)	0.325

^a Data presented as means ± standard deviations.^b M, male; F, female.

appropriate, and continuous variables were analyzed by Mann-Whitney test. Logistic regression test was applied to analyze the independent association of various variables with the outcome. A *P* value of <0.05 was regarded as significant.

This study was approved by the Institutional Review Board of Kaohsiung Veterans General Hospital (VGHKS13-CT7-13).

RESULTS

In patients who fulfilled the inclusion and exclusion criteria, 53 received entecavir (ETV), and 114 received lamivudine (LAM). The findings for baseline ASL, bilirubin, prolongation of PT, platelets, albumin, HBV DNA level, and HBeAg status were similar for the two groups. Patients in the ETV group were older than those in the LAM group and had a lower level of ALT (Table 1). Six out of 53 patients (11.3%) in the ETV group died, and 9 out of 114 patients (7.9%) in the LAM group died. The observed difference in the mortality rate between ETV and LAM group is not statistically significant (*P* = 0.325). All of the deaths in ETV or LAM group were caused by liver failure. If only patients who received antiviral treatment before the bilirubin level rose by more than 15 mg/dl were included, patients in the ETV group were older than those in the LAM group and had a lower level of ALT. The baseline AST, bilirubin, prolongation of PT, platelets, albumin, HBV DNA level, and HBeAg status were similar for the two groups (Table 2). Five out of 50 patients (10%) in the ETV group died, and 3 out of 100 patients (3%) in the LAM group died. The observed difference in the mortality rate between ETV and LAM groups is not statistically significant (*P* = 0.083). In patients with a baseline HBV DNA level higher than 10⁵ copies/ml who had started antiviral treatment before the bilirubin level was greater than 15 mg/dl, those in the ETV group were older than those in the LAM group and had a lower level of ALT, but the findings for the baseline AST, bilirubin, prolongation of PT, platelets, albumin, HBV DNA level, and HBeAg status were similar between the two groups (Table 3). Five out of 40 patients (12.5%) in the ETV group died, and 1 out of 59 patients (1.7%) in the LAM group died. Multivariate analysis showed that ETV treatment (relative risk, 17.6; 95% confidence interval, 1.230 to 251.0; *P* = 0.035) and prothrombin time international normalized ratio (INR) (relative risk, 16.3; 95% confi-

TABLE 2 Demographic and clinical data in patients under entecavir or lamivudine treatment before bilirubin level reached >15 mg/dl

Parameter	Value for group		<i>P</i>
	Entecavir (<i>n</i> = 50)	Lamivudine (<i>n</i> = 100)	
Age (yrs) ^a	49 ± 13	42 ± 14	0.002
Sex (M/F ^b)	36/14	78/22	0.424
AST (U/liter) ^a	809 ± 667	1,037 ± 1,024	0.156
ALT (U/liter) ^a	1,258 ± 741	1,629 ± 1,021	0.023
Albumin (g/dl) ^a	3.7 ± 0.6	3.5 ± 0.6	0.144
Bilirubin (mg/dl) ^a	5.7 ± 3.7	6.4 ± 3.8	0.273
Creatinine (mg/dl) ^a	0.9 ± 0.2	0.9 ± 0.2	0.480
Prothrombin time (INR) ^a	1.3 ± 0.3	1.4 ± 0.3	0.393
Platelet (cells × 10 ⁹ /ml) ^a	157 ± 59	174 ± 60	0.081
HBeAg (positive/negative)	15/35	43/57	0.086
HBV DNA (×10 ⁵ copies/ml) ^a	1,507 ± 348	1,770 ± 478	0.741
Mortality	5/50 (10%)	3/100 (3%)	0.082

^a Data presented as means ± standard deviations.^b M, male; F, female.

dence interval, 2.24 to 118.3; *P* = 0.006) were associated with a greater mortality (Table 4).

DISCUSSION

In this study, we found that in chronic HBV with AE and a high viral load, early ETV treatment before the bilirubin level exceeds 15 mg/dl is associated with more short-term mortality than LAM treatment.

Several nonrandomized studies have found that lamivudine did not increase the survival rate for the treatment of chronic HBV with severe AE (11, 12). A recent study by Sun et al. found that lamivudine treatment can improve the outcome for patients with a MELD score less than 30 (14). Another recent study by Chien et al. found that early lamivudine treatment before the bilirubin level exceeds 20 mg/dl is associated with an improved outcome, but in patients with a bilirubin level of ≥20 mg/dl, lamivudine treatment did not have survival benefit over the control (14). In this study, if we enrolled only patients who received antiviral therapy before bilirubin level rose to more than 15 mg/dl and with a HBV DNA

TABLE 3 Demographic and clinical data in patients with an HBV DNA level of >10⁵ copies/ml under entecavir or lamivudine treatment before bilirubin level reached >15 mg/dl

Parameter	Value for group		<i>P</i>
	Entecavir (<i>n</i> = 40)	Lamivudine (<i>n</i> = 59)	
Age (yrs) ^a	49 ± 14	40 ± 15	0.002
Sex (M/F ^b)	27/13	43/16	0.654
AST (U/liter) ^a	890 ± 718	1,277 ± 1,243	0.079
ALT (U/liter) ^a	1,277 ± 752	1,826 ± 1,120	0.008
Albumin (g/dl) ^a	3.7 ± 0.6	3.5 ± 0.6	0.068
Bilirubin (mg/dl) ^a	5.6 ± 3.5	6.8 ± 3.7	0.088
Creatinine (mg/dl) ^a	0.9 ± 0.2	0.9 ± 0.2	0.606
Prothrombin time (INR) ^a	1.4 ± 0.4	1.4 ± 0.4	0.292
Platelet (cells × 10 ⁹ /ml) ^a	150 ± 55	164 ± 49	0.188
HBeAg (positive/negative)	13/27	29/30	0.147
HBV DNA (×10 ⁵ copies/ml) ^a	1,809 ± 3,747	2,311 ± 5,358	0.609

^a Data presented as means ± standard deviations.^b M, male; F, female.

TABLE 4 Factors associated with overall mortality at 4 months in patients with HBV DNA $> 10^5$ copies/ml under entecavir or lamivudine treatment before bilirubin level > 15 mg/dl

Parameter	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age (yrs)	1.060	0.999–1.125	0.054			
Sex (M/F ^a)	2.154	0.241–19.28	0.493			
AST (U/liter)	1.000	1.000–1.001	0.221			
ALT (U/liter)	1.000	0.999–1.001	0.836			
Albumin (g/dl)	0.440	0.113–1.713	0.236			
Bilirubin (mg/dl)	1.248	0.988–1.578	0.064			
Creatinine (mg/dl)	5.395	0.177–14.40	0.334			
Prothrombin time (INR)	8.693	1.694–44.59	0.010	16.3	2.240–118.3	0.006
Platelet (cells $\times 10^9$ /ml)	0.999	0.983–1.015	0.888			
HBV DNA ($\times 10^5$ copies/ml)	1.000	1.000–1.000	0.590			
ETV vs LAM	8.286	0.930–73.86	0.058	17.6	1.230–251.0	0.035

^a M, male; F, female.

level greater than 10^5 copies/ml, the LAM treatment group had a mortality rate of 1.7%. The mortality rate for this study is similar to that for the study by Chien et al., who found that no patients who received LAM treatment before the bilirubin level exceeded 20 mg/dl died (13). Previous studies found that ETV has better antiviral efficacy and lower resistance rate than LAM in chronic HBV (16, 17). However, a recent nonrandomized study from Hong Kong found that ETV treatment was associated with increased short-term mortality compared with LAM treatment in patients with chronic HBV and severe AE (18). Our study demonstrated that early ETV treatment did not result in decreased survival, compared with early LAM treatment, if the HBV viral load was not considered, but in patients with a higher HBV viral load, early ETV treatment resulted in a worse outcome than LAM treatment.

A previous study by our group found that for patients with chronic HBV with severe AE who had not received antiviral treatment, the HBV DNA level was not associated with an adverse outcome (21). This is consistent with the findings of another study from Hong Kong (22). For patients who received LAM treatment, several studies have also found that the baseline HBV DNA level was not related to survival (11–13). In the study by Chien et al., a lower HBV DNA level was shown to be associated with a higher bilirubin level (13). Some patients with chronic HBV with severe AE actually did not have a high HBV DNA level. In this study, we also found that the baseline HBV DNA level was not associated with the outcome of antiviral treatment. In the subgroup analysis for this study, which included only patients with an HBV DNA level higher than 10^5 copies/ml, early LAM treatment appeared to result in improved survival compared with ETV treatment. The significance of HBV DNA level and the outcome of antiviral therapy for chronic HBV with severe AE require more studies to clarify.

The clinical course of chronic HBV with AE can be divided into four stages according to the change of HBV DNA level. In the ascending limb, a HBV DNA level less than 10^5 copies/ml is stage I and a level greater or equal to 10^5 copies/ml is stage II. In the descending limb, a HBV DNA level greater or equal to 10^5 copies/ml is stage III and a level less than 10^5 copies/ml is stage IV. Patients in stage I are usually asymptomatic and will seldom seek medical help. Therefore, in clinical practice, patients who visit the hospital due to chronic HBV with SAE are usually in stage II, III, or IV. If patients visited the doctor at stage IV, the immune storm

due to flare-up of HBV has already been initiated and become exacerbated, so success of antiviral treatment is not anticipated. Besides, patients in stage IV have a low HBV DNA level which is also declining rapidly, so the benefits of antiviral treatment are expected to be low. The study from Chien et al. found that early lamivudine treatment before the bilirubin level exceeds 20 mg/dl is associated with an improved outcome (14), but that study did not determine the level of viral load at which LAM treatment is beneficial. Previous studies with patients of chronic HBV with SAE did not demonstrate significant benefits for lamivudine treatment. This may be due to the fact that these studies used not only stage II and III patients but also stage IV patients. The only randomized study from India, which found that tenofovir is associated with a better survival rate than the control, enrolled only patients with an HBV DNA level of more than 10^5 copies/ml. It is believed that if this study had also used patients with an HBV DNA level of less than 10^5 copies/ml, the benefit of tenofovir may probably disappear. A recent study by Hsu et al. (23) compared the outcomes of LAM and ETV treatment in decompensated HBV. But the study used patients with high and low viral loads, and the outcomes of ETV and LAM treatment were not different. In this study, if we enrolled patients with high and low viral loads, the outcomes of LAM and ETV treatment were similar, but if only patients with a high viral load were considered, LAM had a significantly higher survival rate than ETV.

This study has some limitations. This was not a randomized study, and the number of cases in the ETV treatment group was relatively small. Further randomized studies are required to determine whether ETV or LAM treatment produces a better treatment outcome for chronic HBV with severe AE. Since general patient care is expected to improve over time, the higher mortality in the more recent cohort receiving entecavir treatment was a negative bias and further supported the result of this study. Besides, patients in the ETV group were older than those in the LAM group, but multivariate analysis did not identify age as an independent factor of mortality. In the study by Wong et al., age was also not shown to be significantly associated with the outcome of entecavir or lamivudine treatment in chronic HBV patients with SAE (18). Similarly, in the study by Chien et al., age was also not shown to be associated with the outcome of lamivudine treatment in chronic HBV patients with SAE (13). The difference in the age of the two groups did not explain the inferior outcome of ETV.

Conclusions. Early entecavir treatment in patients with high

viral load is associated with more short-term mortality than lamivudine in chronic HBV with severe acute exacerbation.

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