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Entecavir *vs.* lamivudine in chronic hepatitis B patients with severe acute exacerbation and hepatic decompensation

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See Focus, pages 1108–1109

Background & Aims: We compared the mortality and treatment response between lamivudine (LAM) and entecavir (ETV) in chronic hepatitis B (CHB) patients with severe acute exacerbation and hepatic decompensation.

Methods: From 2003 to 2010 (the LAM group) and 2008 to 2010 (the ETV group), 215 and 107 consecutive CHB naïve patients with severe acute exacerbation and hepatic decompensation treated with LAM and ETV respectively, were recruited.

Results: At baseline, the LAM group had higher AST levels and end-stage liver disease (MELD) scores, and lower albumin levels than the ETV group. Univariate analysis showed that the LAM group had a higher rate of overall ($p = 0.02$) and liver-related mortality ($p = 0.052$) at week 24 than the ETV group, including in patients with acute-on-chronic liver failure. Multivariate analysis showed that MELD scores, ascites, and hepatic encephalopathy were independent factors for overall and liver-related mortality at week 24. ETV or LAM treatment was not an independent factor for mortality in all patients or patients with acute-on-chronic liver failure. The best cut-off value of MELD scores were 24 for 24-week liver-related mortality. The ETV group achieved better virological response (HBV DNA <300 copies/ml) than the LAM group at week 24 ($p = 0.043$) and 48 ($p = 0.007$). The T1753C/A mutation was also an independent predictor associated with overall and liver-related mortality at week 24.

Conclusions: The choice between ETV and LAM was not an independent factor for mortality in CHB patients with acute exacerbation and hepatic decompensation. Patients with ascites, hepatic encephalopathy, and MELD scores ⩾24 were associated with poor outcome and should be considered for liver transplantation.

Keywords: Hepatitis B virus; MELD scores; Liver-related mortality; Basal core promoter mutation; Hepatic encephalopathy.

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Abbreviations: ALT, alanine aminotransferase; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LAM, lamivudine; NA, nucleos(t)ide analogues; PCR, polymerase chain reactions.

Introduction

Hepatitis B virus (HBV) infection leads to approximately one million deaths annually worldwide [1]. A wide range of clinical manifestations have been established for chronic HBV infection, from asymptomatic carriers to severe chronic liver disease, including those with cirrhosis and hepatocellular carcinoma [2–4]. In some patients, spontaneous acute exacerbation of the disease occurs, which is characterized by very high serum alanine aminotransferase (ALT) level and jaundice [5,6]. This may progress to acute-on-chronic liver failure and death [7].

Oral nucleos(t)ide analogues (NA) therapy is able to suppress viral replication and can prevent hepatic decompensation in patients with advanced liver disease [8–10]. Owing to the high morbidity and mortality, most guidelines recommend rapid initiation of oral NA in chronic hepatitis B (CHB) patients with severe acute exacerbation and hepatic decompensation [11–13]. Lamivudine (LAM) was the first effective oral HBV replication suppressive agent and has been widely used in patients with severe acute exacerbation of CHB [8,14–16]. However, LAM treatment is associated with a high risk of drug resistance [17]. Entecavir (ETV) is a newer NA that led to suppression of HBV DNA replication to undetectable levels in 92% of naive HBeAg-positive patients through 5 years of treatment [18,19]. Resistance to ETV is rare in NA-naïve patients [20]. However, clinical data are inconsistent with regard to the efficacy and safety of ETV in patients with severe acute exacerbation of chronic hepatitis B [21–23]. A previous study showed that ETV treatment had higher short-term mortality rates than LAM treatment in patients with severe acute exacerbation of CHB [22].

Research Article

We compared the efficacy and safety of entecavir or lamivudine therapy in patients with severe acute exacerbation and hepatic decompensation. In addition, we compared the mortality rates between the two treatments and determined predictors of mortality.

Patients and methods

Patients

From 2003 to 2010 (the LAM group) and 2008 to 2010 (the ETV group), 215 and 107 consecutive CHB patients treated with LAM and ETV respectively were recruited in this study while they fulfilled the definition of spontaneous acute exacerbation of hepatitis and hepatic decompensation in both the Kaohsiung and the Keelung Chang Gung Memorial Hospital. Acute exacerbation of hepatitis was defined as an increase of serum ALT level to $\geqslant 5$ times the upper limit of normal (ULN) [11]. Because the definition of hepatic decompensation put forth by the 2012 Asian Pacific Association for the Study of the Liver (APASL) is "significant liver function abnormality as indicated by raised serum bilirubin and prolonged prothrombin time or occurrence of complications such as ascites" [11], we defined hepatic decompensation as serum bilirubin levels $\geqslant 3$ mg/ml and prolonged prothrombin time (PT) $\geqslant 3$ s and/or if patients developed ascites and/or features of hepatic encephalopathy and/or variceal hemorrhage in accordance with our previous reports [24–26]. All patients had positive hepatitis B surface antigen (HBsAg) for more than 6 months. Patients who had co-infection with hepatitis A virus, hepatitis C virus or hepatitis D virus by serological assays or had hepatocellular carcinoma or biliary obstruction by abdominal ultrasound at the start of treatment were excluded. Patients who received immunosuppressants or systemic corticosteroids were also excluded. All patients were antiviral treatment-naïve and received LAM 100 mg or ETV 0.5 mg daily. Cirrhosis was diagnosed by liver biopsy or ultrasound findings as coarse liver parenchyma with nodularity and small liver size and the presence of features of portal hypertension (e.g., thrombocytopenia, ascites, splenomegaly and/or varices). Of the 145 patients who were diagnosed with liver cirrhosis, 15 were diagnosed by biopsy. This study was approved by the Ethical Committee of Chang Gung Memorial Hospital.

Methods

All patients were followed up every 4–12 weeks during therapy. Additional weekly or biweekly visits were set up if ALT rose or were more than 5 times the ULN (ULN: 40 U/L) or hepatic decompensation. Follow-up studies included clinical assessment, conventional liver biochemical tests, and serological hepatitis B markers. Each patient was checked for HBV DNA quantitatively prior to therapy and every 6 months during treatment or at the time of biochemical breakthrough.

Definitions

The virological response (VR) was defined as serum HBV DNA levels <70 copies/ml during the on-treatment period [18]. The diagnostic criteria of acute-on-chronic liver failure was defined as: acute hepatic insult manifesting as jaundice [serum bilirubin $\geqslant 5$ mg/dl] and coagulopathy (INR $\geqslant 1.5$ or prothrombin activity <40%), complicated within 4 weeks by ascites and/or encephalopathy in patients with previously diagnosed or undiagnosed chronic liver diseases [27]. Biochemical breakthrough was defined as ALT levels >2 times ULN during continued treatment in patients who initially had ALT normalization. Virological breakthrough was defined as an increase in serum HBV DNA levels $\geqslant 1$ $\log_{10}$ copies/ml from nadir.

Serology

The presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HCV antibody and anti-HDV antibody was assessed using commercial assay kits (HBsAg EIA, Abbott, North Chicago, IL; HBeAg EIA, Abbott; anti-HCV, EIA 3.0, Abbott; anti-HDV, RIA, Abbott). Serum HBV DNA levels were analyzed using the COBAS AmpliPrep-COBAS TaqMan HBV test (CAP-CTM; Roche Molecular Systems, Inc., Branchburg, NJ, USA), with a lower detection limit of 70 copies/ml.

Direct sequencing of pre-S, HBV polymerase, basal core promoter (BCP), and precore regions

The sequences of pre-S, BCP and precore regions in sera were determined using nested polymerase chain reaction and direct sequencing, as described previously [28–30]. In BCP and precore regions, the variants of nucleotides 1753, 1762/1764, 1766/1768, 1896, and 1899 were analyzed in correlation with advanced liver diseases according to previous studies [30–32].

HBV genotyping

The HBV genotypes were assessed using restriction fragment length polymorphism on surface gene (between nucleotide positions 256 and 796), as described previously [33].

Data analysis

Data are displayed as means ± standard deviation (SD), proportions, or median (range). In comparing the values between two groups, χ^2 test was performed to analyze categorical variables and Student's *t* tests and Mann-Whitney U test were applied for continuous variables with normal and skewed distributions respectively. Cumulative incidences of HBeAg loss or seroconversion were analyzed by the Kaplan-Meier method with a log rank test. Univariate and multivariate analyses were carried out to identify baseline factors associated with mortality using the Cox proportional hazards regression models. Receiver operator characteristic (ROC) curve analysis was applied to define the best cut-off point of end-stage liver disease (MELD) scores for liver-related mortality. All statistical tests were two-sided, and a *p* value below 0.05 was accepted as statistically significant.

Results

Baseline characteristics of the study population

Baseline characteristics of the study population are presented in Table 1. Patients in the LAM group had higher AST levels and MELD scores, and lower albumin levels than the ETV group.

Overall and liver-related mortality by week 24 and extended follow-up

By week 24, overall, 62 patients died. Of these, 75.8% of the deaths (n = 47) occurred in the first month. Of the 62 mortality cases, 13 (12.1%) patients were in the ETV group and 49 (22.8%) patients were in the LAM group. The cumulative rate of overall mortality in LAM and ETV treatment at week 4, 12, and 24 was 16.8% and 9.4%, 21.2% and 10.3%, and 23.2% and 12.3% respectively ($p = 0.02$ by log rank test) (Fig. 1A). A total of 57 (91.9%) of the 62 deaths were liver-related. Five patients died from the following causes: sepsis (n = 3), intracranial hemorrhage (n = 1), and breast cancer with brain metastasis (n = 1). The cumulative rate of liver-related mortality in LAM and ETV treatment at week 4, 12, and 24 was 15.5% and 9.4%, 19.4% and 10.3%, and 21% and 12.3% respectively ($p = 0.052$) (Fig. 1B).

Among the 322 patients, 92 fulfilled the criteria of acute-on-chronic liver failure [27]. Of them, 48 died at week 24. The cumulative rate of overall mortality in LAM and ETV treatment at week 4, 12, and 24 was 46.2% and 25.9%, 57.6% and 29.6%, and 62.6% and 29.6% respectively. The cumulative rate of liver-related mortality in LAM and ETV treatment at week 4, 12, and 24 was 43.6% and 25.9%, 55.6% and 29.6%, and 60.9% and 29.6% respectively. The LAM group had a higher rate of overall ($p = 0.006$) and liver-related mortality ($p = 0.01$) than the ETV group.

Table 1. Comparisons of pretreatment clinical features between patients treated with lamivudine and entecavir.

	Lamivudine n = 215	Entecavir n = 107	*p* value
Age (yr)	49.5 ± 14.4	48.6 ± 14.1	0.58
Sex (male:female)	167:48	85:22	0.72
Treatment duration Median (range) (wk)	74 (0.5-285)	108 (1-208)	<0.001
HBeAg (+)	60 (27.9%)	35 (32.7%)	0.37
Cirrhosis	92 (42.8%)	53 (49.5%)	0.25
AST (U/L)	988.4 ± 793.6	805.8 ± 578.1	0.035
ALT (U/L)	1239.4 ± 941.7	1045.3 ± 782.8	0.08
Total bilirubin (mg/dl)	12.6 ± 8.7	11.6 ± 8.7	0.32
INR	2.0 ± 2.3	1.6 ± 0.7	0.10
Albumin (g/dl)	2.9 ± 0.8	3.3 ± 0.6	<0.001
Creatinine (mg/dl)	1.3 ± 1.5	1.1 ± 1.2	0.081
Platelet (1000/μl)	137.0 ± 72.8	144.1 ± 58.7	0.38
HBV DNA (log_{10} copies/ml)	6.5 ± 1.7	6.5 ± 1.9	0.70
HBV genotype			
B	151	75	0.24
C	30	22	
MELD score	23.2 ± 8.8	20.4 ± 6.7	0.004
Ascites	60 (27.9%)	28 (26.2%)	0.74
Variceal hemorrhage	13 (6%)	2 (1.7%)	0.16
Hepatic encephalopathy	37 (17.2%)	10 (9.3%)	0.06

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio of prothrombin time; MELD, end-stage liver disease.

Of the 239 patients with extended follow-up after 24 weeks (median 79 weeks, range 26–285 weeks), 9 died. Of them, 4 were associated with liver-related mortality (2 died due to new HCC with progression and liver failure at month 20 and 36, 1 died due to varices bleeding at month 17, 1 died due to spontaneous bacterial peritonitis with hepatorenal syndrome at month 10). Five patients died from the following causes: sepsis (n = 1), heart failure (n = 1), terminal lung cancer (n = 2), and small bowel sarcoma (n = 1). There were no differences in the rates of delayed overall ($p = 0.086$) and liver-related mortality ($p = 0.36$) after 24 weeks between the LAM and the ETV groups (mortality cases were included only for those who died after 6 months).

Baseline predictors for overall and liver-related mortality at week 24

By week 24, the baseline factors of patients with and without mortality are shown in Table 2. Overall, patients who died were old age, had higher rates of LAM therapy, HBeAg-negative status, cirrhosis, ascites, hepatic encephalopathy and T1753C/A mutation, had higher levels of bilirubin, INR, creatinine, HBV DNA and end-stage liver disease (MELD) scores, and had lower levels of albumin and platelet count than those who survived.

For all patients, predictive factors associated with overall and liver-related mortality at week 24 are presented in Tables 3 and 4. Cox regression analysis showed that higher MELD scores, and the presence of ascites and hepatic encephalopathy were independent factors for overall and liver-related mortality. The choice between ETV and LAM was not an independent factor for overall or liver-related mortality.

For 92 patients who had acute-on-chronic liver failure, Cox regression analysis showed that MELD scores (HR: 1.07, 95% CI:

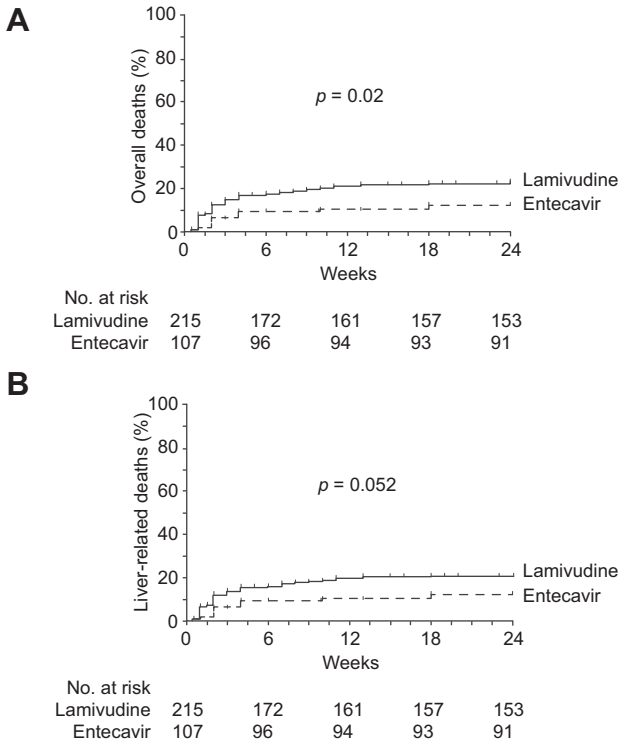

Fig. 1. Overall and liver-related death at week 24 in patients on entecavir and lamivudine treatment. (A) Overall death and (B) liver-related death.

Research Article

1.04–1.10), and the presence of variceal hemorrhage (HR: 2.17, 95% CI: 1.08–4.36) and hepatic encephalopathy (HR: 2.93, 95% CI: 1.54–5.60) were independent factors for overall mortality; and MELD scores (HR: 1.07, 95% CI: 1.04–1.10) and hepatic encephalopathy (HR: 2.79, 95% CI: 1.45–5.37) were independent factors for liver-related mortality. The choice between ETV and LAM was not an independent factor for overall or liver-related mortality.

By extended follow-up after week 24, Cox regression analysis showed that only old age was an independent factor for delayed overall (HR: 1.06, 95%: 1.01–1.11, $p = 0.023$) and liver-related (HR: 1.13, 95%: 1.03–1.25, $p = 0.013$) mortality.

Biochemical and virological response within week 48

In our study, of the 322 patients, 15 were lost to follow-up, 20 had no data of HBV DNA and 3 changed to other drugs (2 entecavir, 1 telbivudine) at week 24 of treatment. At week 48 of treatment, 28 were lost to follow-up, 13 had no data of HBV DNA and 4 changed to other drugs (3 entecavir, 1 telbivudine). No patient was prematurely stopped due to side effects of drugs.

Although the baseline ALT levels were higher (borderline significant) in the LAM group, there was no significant difference in mean ALT levels between the ETV and the LAM groups from week 1 to week 36 (Fig. 2A). However, the ETV group had a significantly lower mean ALT level (28.5 ± 13.7 *vs.* 33.8 ± 22.1, $p = 0.048$) and a higher rate of ALT normalization than the LAM group (74/85 *vs.* 106/140, $p = 0.039$) at week 48.

In comparison, there was no significant difference in bilirubin levels between the ETV and the LAM groups at the baseline and week 1. However, the ETV group had a significant or borderline lower bilirubin level at week 2, 4, and 12 (Fig. 2B). There was no significant difference in bilirubin levels between the ETV and the LAM groups from week 24 to week 48 onwards (Fig. 2B). The analysis of bilirubin normalization showed that there was no significant difference in bilirubin normalization between the ETV and the LAM groups from week 4 to week 48 onwards. The analysis of the decline in bilirubin level within 4 weeks revealed that the ETV group had a faster decline in bilirubin level at week 2 than the LAM group (2.7 ± 6.1 *vs.* 0.8 ± 6.9, $p = 0.027$). There was no significant difference in the decline of bilirubin level at week 1 (1.2 ± 4.2 *vs.* 0.5 ± 6.2, $p = 0.33$) and week 4 (5.4 ± 5.7 *vs.* 4.5 ± 7.3, $p = 0.29$) between ETV and the LAM groups.

The baseline HBV DNA was similar in both groups. The mean HBV DNA in the ETV and the LAM groups was 2.2 ± 0.6 and 2.5 ± 1.1 log copies/ml at week 24 ($p = 0.015$), and 2.0 ± 0.4 and 2.4 ± 1.2 log copies/ml at week 48 ($p = 0.003$), respectively. The number of patients in the ETV and the LAM groups with undetectable HBV DNA was 65 out of 87 (74.7%) and 80 of 130 (61.5%) at week 24 ($p = 0.043$), and 77 of 84 (91.7%) and 100 out of 129 (77.5%) at week 48 ($p = 0.007$), respectively. At week 48, the LAM group had a higher HBV resistant mutant rate than the ETV group (8/129 *vs.* 0/84, $p = 0.023$).

Among the 95 patients with HBeAg-positive disease (60 LAM, 35 ETV), the LAM group had a higher cumulative incidence of HBeAg loss and HBeAg seroconversion compared to

Table 2. Comparisons of pretreatment clinical features between patients with and without mortality at week 24 of treatment.

	No mortality n = 260	Mortality n = 62	*p* value
Age (yr)	47.0 ± 14.3	58.3 ± 10.0	<0.001
Sex (male:female)	207:53	45:17	0.23
HBeAg (+)	83 (31.9%)	12 (19.4%)	0.051
Cirrhosis	101 (38.8%)	44 (71.0%)	<0.001
AST (U/L)	908.5 ± 640.9	1008.3 ± 1037.8	0.34
ALT (U/L)	1223.1 ± 853.8	988.4 ± 1037.4	0.063
Total bilirubin (mg/dl)	10.6 ± 7.6	19.0 ± 9.6	<0.001
INR	1.6 ± 1.8	2.9 ± 2.2	<0.001
Albumin (g/dl)	3.2 ± 0.6	2.6 ± 0.7	<0.001
Creatinine (mg/dl)	1.0 ± 0.8	2.4 ± 2.5	<0.001
Platelet (1000/μl)	147.4 ± 68.6	105.8 ± 56.9	<0.001
HBV DNA (log_{10} copies/ml)	6.4 ± 1.8	7.0 ± 1.8	0.05
HBV genotype B C	 195 45	 33 7	 0.85
Lamivudine: entecavir use	166:94	49:13	0.023
MELD score	19.8 ± 5.2	32.7 ± 10.3	<0.001
Ascites	47 (18.1%)	41 (66.1%)	<0.001
Variceal hemorrhage	3 (1.2%)	12 (19.4%)	<0.001
Hepatic encephalopathy	10 (3.8%)	37 (59.7%)	<0.001
T1753C/A	25/237	10/40	0.011
A1762T/G1764A	132/237	22/40	0.94
G1896A	184/237	30/40	0.71
Pre-S deletions	67/230	8/39	0.27

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio of prothrombin time; MELD, end-stage liver disease.

JOURNAL OF **HEPATOLOGY**

Table 3. Univariate and multivariate analysis of factors predictive of 24-week overall mortality.

Variable	Comparison	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (yr)	Increase per one year	1.05 (1.03-1.07)	<0.001		
Sex (male:female)	Male *vs.* female	0.73 (0.42-1.27)	0.26		
HBeAg (+)	Yes *vs.* no	0.54 (0.29-1.01)	0.053		
Cirrhosis	Yes *vs.* no	3.29 (1.90-5.69)	<0.001		
AST (U/L)	≥1000 *vs.* <1000	1.12 (0.67-1.87)	0.67		
ALT (U/L)	≥1000 *vs.* <1000	0.41 (0.24-0.70)	0.001		
Total bilirubin (mg/dl)	Increase per one mg/dl	1.08 (1.06-1.11)	<0.001		
INR	Increase in ratio	1.10 (1.05-1.15)	<0.001		
Creatinine (mg/dl)	Increase per one mg/dl	1.28 (1.19-1.38)	<0.001		
Platelet (1000/μl)	Increase per 1000/μl	0.99 (0.98-0.99)	<0.001		
HBV DNA (log_{10} copies/ml)	Increased per one log_{10}	1.18 (1.002-1.40)	0.047		
HBV genotype	C *vs.* B	0.89 (0.39-2.0)	0.77		
Antiviral therapy	Entecavir *vs.* lamivudine	0.50 (0.27-0.91)	0.024		
MELD score	Per score	1.12 (1.10-1.14)	<0.001	1.09 (1.06-1.11)	<0.001
Ascites	Yes *vs.* no	6.34 (3.74-10.73)	<0.001	2.30 (1.32-4.0)	0.003
Variceal hemorrhage	Yes *vs.* no	7.16 (3.79-13.54)	<0.001		
Hepatic encephalopathy	Yes *vs.* no	14.59 (8.70-24.48)	<0.001	6.29 (3.55-11.15)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio of prothrombin time; MELD, end-stage liver disease.

Table 4. Univariate and multivariate analysis of factors predictive of 24-week liver-related mortality.

Variable	Comparison	Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (yr)	Increase per one year	1.05 (1.03-1.07)	<0.001		
Sex (male:female)	Male *vs.* female	0.84 (0.46-1.54)	0.58		
HBeAg (+)	Yes *vs.* no	0.48 (0.24-0.94)	0.033		
Cirrhosis	Yes *vs.* no	4.13 (2.29-7.55)	<0.001		
AST (U/L)	≥1000 *vs.* <1000	1.28 (0.76-2.18)	0.36		
ALT (U/L)	≥1000 *vs.* <1000	0.46 (0.26-0.80)	0.006		
Total bilirubin (mg/dl)	Increase per one mg/dl	1.09 (1.06-1.11)	<0.001		
INR	Increase in ratio	1.10 (1.04-1.15)	<0.001		
Creatinine (mg/dl)	Increase per one mg/dl	1.28 (1.19-1.38)	<0.001		
Platelet (1000/μl)	Increase per 1000/μl	0.99 (0.98-0.99)	<0.001		
HBV DNA (log_{10} copies/mL)	Increased per one log_{10}	1.16 (0.98-1.37)	0.086		
HBV genotype	C *vs.* B	0.67 (0.26-1.73)	0.41		
Antiviral therapy	Entecavir *vs.* lamivudine	0.55 (0.30-1.02)	0.059		
MELD score	Per score	1.12 (1.09-1.14)	<0.001	1.08 (1.06-1.11)	<0.001
Ascites	Yes *vs.* no	6.86 (3.92-12.02)	<0.001	2.70 (1.42-4.64)	0.002
Variceal hemorrhage	Yes *vs.* no	7.07 (3.64-13.74)	<0.001		
Hepatic encephalopathy	Yes *vs.* no	13.83 (8.07-23.68)	<0.001	6.0 (3.32-10.87)	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; INR, international normalized ratio of prothrombin time; MELD, end-stage liver disease.

the ETV group ($p = 0.021$ and 0.046 respectively, by log rank test, Fig. 3). The baseline factors including age, sex, AST, ALT, bilirubin, INR, MELD scores, creatinine, HBV genotype, HBV DNA levels and the selection of antiviral agents were analyzed for HBeAg loss or seroconversion. The LAM group (HR: 2.01, 95% CI: 1.10–3.69, $p = 0.023$) was an independent predictor for HBeAg loss, and the higher baseline AST level (HR: 1.001, 95% CI: 1.000–1.001, $p = 0.014$) for HBeAg seroconversion.

MELD score cut-off value as predictor of 24-week liver-related mortality

Because pretreatment MELD score was the significant factor for mortality, we analyzed the best cut-off value of this parameter for 24-week liver-related mortality. The areas under the ROC curve of MELD score were 87.7. A cut-off level of MELD score at 23.61 could give the maximum sum of sensitivity (86%) and spec-

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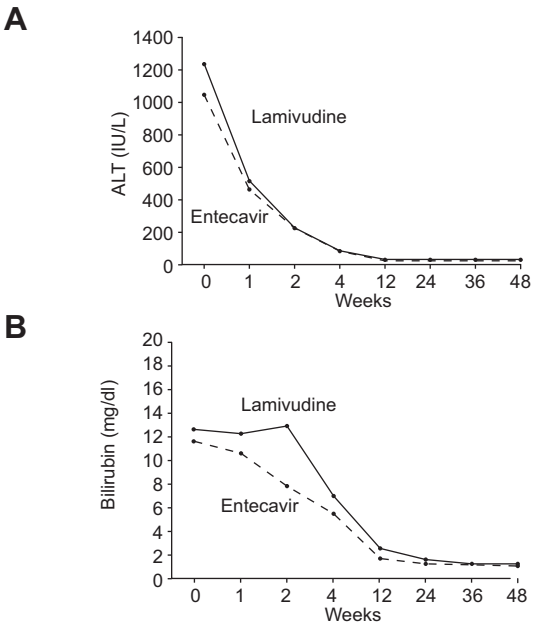

Fig. 2. Serial mean ALT and bilirubin levels at week 48 in patients on entecavir and lamivudine treatment. (A) ALT and (B) bilirubin levels.

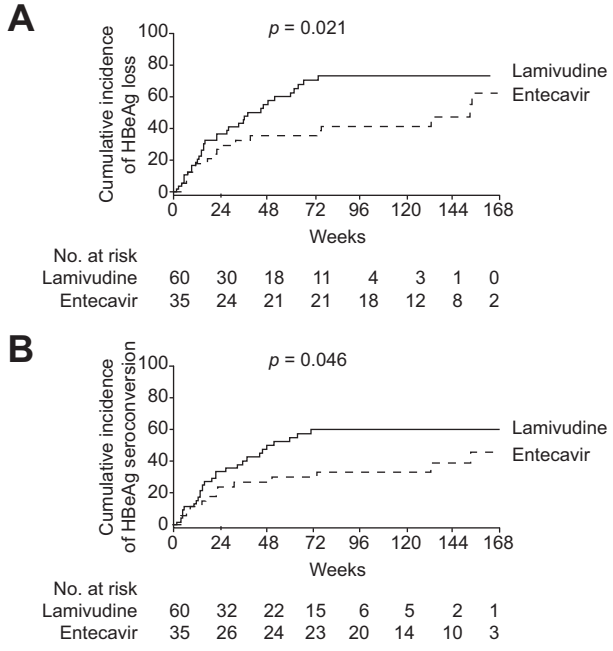

Fig. 3. HBeAg loss and seroconversion in patients on entecavir and lamivudine treatment. (A) HBeAg loss and (B) HBeAg seroconversion.

ificity (80.4%) to predict 24-week liver-related mortality. Among the 222 patients who had MELD score <24, 9 (4.1%) died at week 24. On the contrary, among the 100 patients who had MELD score ⩾24, 48 (48%) died at week 24 (p <0.001). Compared to patients with MELD score <24, the hazard ratio of liver-related mortality was 16.62 in patients with pretreatment MELD score ⩾24 (95% CI, 8.13–34; p <0.001).

For the analysis of 92 patients who had acute-on-chronic liver failure, the areas under the MELD score ROC curve was 83.5. A MELD score cut-off level at 29.67 provided the maximum sum of sensitivity (60.9%) and specificity (93.5%) to predict 24-week liver-related mortality. Among the 60 patients who had MELD scores <30, 18 (30%) died at week 24. On the contrary, among the 32 patients who had MELD scores ⩾30, 28 (87.5%) died at week 24 (p <0.001). Compared to patients with MELD scores <30, the hazard ratio for liver-related mortality was 5.69 in patients with pretreatment MELD scores ⩾30 (95% CI, 3.02–10.74; p <0.001).

Analysis of pre-S deletions, mutations in BCP, and precore regions for predicting week 24 mortality

Direct sequencing of pre-S, BCP and precore genes was performed in 277 patients whose pre-treatment serum was available. Univariate analysis showed that only the T1753C/A mutation was associated with overall (p = 0.009 by log rank test) or liver-related mortality (p = 0.013) at week 24. Pre-S deletions, T1762/A1764, T1766/A1768, A1896, and A1899 mutations were not associated with overall or liver-related mortality in these 277 patients. Furthermore, Cox regression analysis showed that the T1753C/A mutation was an independent predictor associated with overall (HR: 2.52, 95% CI: 1.16–5.47) or liver-related mortality (HR: 2.62, 95% CI: 1.2–5.71) at week 24 after adjusting for other baseline factors included in Table 2.

Discussion

A recent study reported that ETV treatment is associated with increased short-term mortality in patients with severe acute exacerbation of CHB [22]. In that study, the number of patients on ETV was relatively small. Furthermore, the ETV group was older than the LAM group [22]. In our study, we analyzed the 320 patients who experienced severe acute exacerbation of CHB in both Kaohsiung (in southern Taiwan) and Keelung (in northern Taiwan) Chang Gung Memorial Hospitals. Thus, this study represented a larger cohort of this illness than found in any previous studies. We found that the LAM group, as compared to the ETV group, was associated with increased short-term (24 weeks), but not long-term (>24 weeks) mortality. For the analysis of subgroups, compared to the ETV group, the LAM group increased short-term mortality in patients with acute-on-chronic liver failure. However, patients treated with ETV or LAM had some differences at baseline. The LAM group had higher baseline AST levels and MELD score than the ETV group, which might explain the higher mortality in the LAM group. Thus, our result revealed that neither overall nor liver-related mortality was associated with the choice of LAM or ETV after adjusting for baseline factors for all patients and patients with acute-on-chronic liver failure. Our result was consistent with the recent studies which demonstrated that the ETV and the LAM groups showed similar short-mortality rates in patients with HBV-related acute-on-chronic liver failure [34,35] or in CHB patients with decompensation [23]. Tenofovir is another newer potent, oral acyclic nucleotide analog that has been shown to be highly effective in suppressing HBV replication [36]. A recent study showed that compared with the placebo group, tenofovir significantly improved MELD scores and reduces mortality in patients with acute-on-chronic liver

failure [37]. However, it remains unclear whether tenofovir appears to be superior to lamivudine for mortality and treatment response in patients with severe acute exacerbation and hepatic decompensation.

A previous study showed that the independent factors associated with adverse outcome for the parameters in patients with severe exacerbation of HBV were preexisting cirrhosis, high Child-Pugh score, low albumin level, high bilirubin level, prolonged PT, and low platelet count [38]. Chien *et al.* reported that LAM may prevent fatality if therapy starts early enough or before the serum bilirubin level rises over 20 mg/dl [24]. Similarly, another study showed that LAM treatment can significantly decrease the mortality of patients with a MELD score of 20–30, but has no effect on those with a MELD score higher than 30 [39]. In our study, we found that MELD scores, ascites, and hepatic encephalopathy at baseline were independent predictors for overall and liver-related mortality at week 24. The best cut-off value of MELD scores was 24. This parameter was similar with our previous study [40]. Thus, patients with ascites, hepatic encephalopathy, and MELD scores $\geqslant$24 should be considered for liver transplantation in CHB patients with acute exacerbation and hepatic decompensation.

Wang *et al.* reported that there was a slower decline in bilirubin level in the ETV group than the LAM group [22]. However, our study found that the serum mean bilirubin level in the LAM-treated patients peaked at week 2, which was not the case for ETV-treated patients. In our study, higher AST and ALT levels were associated with delayed decreasing or even rising bilirubin level. The LAM group had higher baseline AST and ALT levels than the ETV group. Thus, the LAM group had an exaggerated immune response and exacerbated liver injury, which may be related with a later peaking of the serum bilirubin level than in the ETV group.

The role of pre-S deletions, precore and core promoter mutations in causing severe exacerbation is still controversial. A previous study found that precore and core promoter mutations did not affect the outcome in patients with severe exacerbation of CHB [38]. In our study, precore mutation A1896 and basal core promoter mutations T1762/A1764 were not associated with mortality. However, the T1753C/A mutation was an independent predictor for mortality at week 24. A previous study showed that the precore mutation A1896 and the core promoter mutation at nt 1753 and 1754 were found more frequently in fulminant hepatitis than in acute self limited hepatitis [41]. Thus, the T1753C/A mutation may contribute to predicting the clinical outcome of HBV-associated severe acute exacerbation.

Moreover, high rate of HBeAg loss and seroconversion was observed in both the ETV and the LAM groups. This may be due to the strong immune response in patients with severe acute exacerbation of HBV. In a previous clinical trial, high ALT at baseline was associated with an increased rate of HBeAg seroconversion [42]. However, our study showed that the LAM group had a higher cumulative rate of HBeAg loss or seroconversion than the ETV group. The LAM group and pretreatment AST level were independent factors for HBeAg loss and seroconversion respectively. Further studies are needed to confirm this finding.

Our study was a retrospective study and had a few limitations. First, serum HBV DNA quantification or HBV gene sequencing were not performed for all patients because serum from some patients was unavailable. Second, the treatment assignment was not done by randomization. Thus, there were some differences in the baseline characteristics of patients treated with ETV and LAM.

In conclusion, the selection between ETV and LAM treatment was not an independent predictor for mortality in CHB patients with acute exacerbation and hepatic decompensation. The ETV group achieved the better virological response and lower resistance rates than the LAM groups in the longer treatment. However, the LAM group had higher rates of HBeAg loss or seroconversion. Hepatic encephalopathy, ascites, and MELD scores at baseline were independent predictors for short-term mortality. The T1753C/A mutation was also an independent predictor associated with short-term mortality. It suggests that patients with severe acute exacerbation of CHB who have ascites, hepatic encephalopathy, and MELD scores $\geqslant$24 have high mortality rates, in which cases, liver transplantation should be considered.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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