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Tenofovir versus Entecavir in Treatment of Chronic Hepatitis B Virus with Severe Acute Exacerbation

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Tenofovir disoproxil fumarate (TDF) and entecavir (ETV) are effective antivirals recommended as first-line monotherapies for treatment of chronic hepatitis B (CHB) infection. This study aimed to compare the short-term efficacies of TDF and ETV in the treatment of CHB with severe acute exacerbation. From 2008 to 2013, 189 consecutive treatment-naive CHB patients receiving TDF ($n = 41$) or ETV ($n = 148$) for severe acute exacerbation were enrolled. The primary endpoint was overall mortality or receipt of liver transplantation by week 24. The baseline characteristics were comparable between these two groups. By week 24, 8 (19% [95% confidence interval {CI}, 7% to 32%]) patients in the TDF group and 26 (18% [95% CI, 11 to 24%]) patients in the ETV group died ($n = 30$) or received liver transplantation ($n = 4$) ($P = 0.749$). The two groups of patients developed similar rates of liver-related complications and achieved comparable biochemical and virological responses at week 24. Cox regression analysis showed that baseline viral DNA level ($P = 0.002$), hypertension ($P = 0.002$), model for end-stage liver disease (MELD) score ($P = 0.01$), platelet count ($P = 0.005$), early presence (within 4 weeks) of ascites ($P = 0.005$), hepatic encephalopathy ($P = 0.002$), and hepatorenal syndrome ($P < 0.001$) were independent factors for mortality or liver transplantation. Among the patients who survived by week 24, there was no difference between the two groups in the percentage of patients who had a serum creatinine increase of ≥0.5 mg/dl from baseline (6.7% [95% CI, 0% to 16%] versus 2.0% [95% CI, 0% to 4.8%] in the TDF and ETV groups, respectively; $P = 0.231$), whereas a significant reduction in the estimated glomerular filtration rate (eGFR) was found in the two groups ($P = 0.001$ for both). In conclusion, TDF and ETV produce a similar treatment response and clinical outcome in patients with severe acute exacerbation of CHB.

Chronic hepatitis B virus (HBV) infection is a major global health issue, affecting around 370 million people worldwide (1). Patients with chronic hepatitis B (CHB) are at a significantly increased risk for the development of liver failure, cirrhosis, and hepatocellular carcinoma (HCC) (2). In its natural course, up to 30% of CHB patients experience a spontaneous reactivation of hepatitis every year (3). Severe acute exacerbation of CHB characterized by high serum alanine aminotransferase (ALT) level, jaundice, and hepatic decompensation leads to a high mortality rate, ranging from 30 to 70% (4, 5). Most guidelines recommend treatment with oral nucleos(t)ide analogues (NUCs) for CHB patients with severe acute exacerbation as soon as possible (6–8). Liver transplantation is the salvage treatment if medical therapy fails; however, this is neither readily available nor feasible in many parts of the world where HBV is highly endemic (5, 9).

Lamivudine (LAM) was the first effective oral HBV replication-suppressive agent and has been widely used in patients with severe acute exacerbation of CHB (4, 10). However, this therapy is limited by the high risks of virological breakthrough and drug resistance (11). Entecavir (ETV) is a newer potent NUC against HBV, with rare resistance in NUC-naive patients (12). Although the clinical data are inconsistent with regard to the efficacy and safety of ETV in CHB patients with severe acute exacerbation (13–17), recent studies have shown similar rates of short-term mortality between LAM and ETV treatment in such patients (15–17). In particular, our previous study based on a large cohort demonstrated that the choice between ETV and LAM was not an independent factor for mortality in CHB patients with acute exacerbation (17).

Tenofovir disoproxil fumarate (TDF), which has been available since 2008, is another rapidly acting oral NUC that has been shown to be highly effective in suppressing HBV replication (18). TDF has shown excellent activity against HBV in both LAM-naive and LAM-resistant patients (19). In a small randomized controlled study, TDF was shown to significantly reduce HBV DNA levels, improve Child-Turcotte-Pugh (CTP) and model for end-stage liver disease (MELD) scores, and reduce mortality in patients with severe spontaneous reactivation of CHB compared to those factors in the placebo group (20). However, its safety and effectiveness should be further evaluated in more patients.

In this study, we compared the short-term efficacy, safety, and clinical outcomes of severe acute exacerbation in CHB patients treated with TDF or ETV, which have been recommended oral first-line therapies for CHB (6–8).

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TABLE 1 Comparisons of baseline characteristics between patients treated with tenofovir or entecavir

Characteristic[a]	Data (mean ± SD or no. [%]) for patients treated with: Tenofovir ($n = 41$)	Entecavir ($n = 148$)	P
Age (yr)	49.8 ± 13.1	50.6 ± 14.7	0.758
Male gender	30 (73)	106 (72)	1.000
Body mass index (kg/m^2)	24.1 ± 3.5	24.6 ± 4.4	0.518
Diabetes mellitus	7 (17)	26 (18)	1.000
Hypertension	9 (22)	39 (26)	0.686
Cirrhosis	8 (20)	50 (34)	0.088
HBV DNA ($\log_{10}$ copies/ml)	7.0 ± 1.9	6.5 ± 1.9	0.076
HBeAg positive	14 (34)	42 (28)	0.562
AST (U/liter)	880 ± 837	857 ± 706	0.855
ALT (U/liter)	1,104 ± 918	1,084 ± 830	0.890
Total bilirubin (mg/dl)	8.8 ± 7.3	10.6 ± 7.7	0.172
Albumin (g/dl)	3.5 ± 0.7	3.3 ± 0.6	0.060
Creatinine (mg/dl)	1.0 ± 1.0	1.1 ± 1.4	0.837
Estimated GFR (MDRD)	102 ± 48	92 ± 33	0.118
INR	1.7 ± 0.7	1.7 ± 0.9	0.738
Platelet (10^3/μl)	139 ± 65	144 ± 69	0.658
MELD score	20.0 ± 6.6	20.6 ± 6.7	0.586

[a] HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease (in ml/min/1.73 m^2); INR, international normalized ratio of prothrombin time; MELD, model for end-stage liver disease.

MATERIALS AND METHODS

Patients. From January 2008 to December 2013, consecutive CHB patients treated with TDF or ETV who fit the definition of severe acute exacerbation of CHB in single medical center were recruited in this study. Severe acute exacerbation of CHB was defined as an elevation of serum ALT level to ≥5 times the upper limit of normal (ULN) (7), accompanied by a raised serum bilirubin level of ≥3 mg/ml, prolonged prothrombin time of ≥3 s, and/or occurrence of complications, such as ascites or hepatic encephalopathy (4, 17). All patients were positive for hepatitis B surface antigen (HBsAg) for >6 months. Patients who had coinfection with human immunodeficiency virus (HIV), hepatitis A virus, hepatitis C virus (HCV), hepatitis D virus (HDV), or hepatitis E virus by serological assays or had HCC or biliary obstruction by imaging studies at the start of treatment were excluded. Patients who had evidence of drug-induced injury or who received immunosuppressants or systemic corticosteroids were also excluded. Cirrhosis was diagnosed by ultrasound findings as coarse liver parenchyma with nodularity and small liver size, as well as the presence of features of portal hypertension (21).

Treatment and follow-up. The patients were antiviral treatment naive and received 300 mg of TDF or 0.5 mg of ETV daily. All patients were followed up at weeks 1, 2, 4, 8, and 12 and then every 12 weeks after. The follow-up studies included clinical assessment and conventional biochemical and blood tests. HBV DNA levels were checked at baseline, week 12, and week 24.

The primary endpoint was overall mortality or liver transplantation by week 24. The secondary endpoints included liver-related complications (ascites, variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome). The biochemical response (normalization of ALT and total bilirubin level) and virological response at week 24 were compared between these two groups. Informed consent was obtained from each patient. This study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethics committees of Chang Gung Memorial Hospital, Kaohsiung, Taiwan.

Laboratory assays. The presence of hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), anti-HCV antibodies, and anti-HDV antibodies was assessed using commercially available kits (HBsAg enzyme immunoassay [EIA], HBeAg EIA, anti-HCV EIA 3.0, and anti-HDV radioimmunoassay, respectively; all from Abbott, North Chicago, IL). 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. The HBV genotypes were determined using restriction fragment length polymorphism on the surface gene sequence and amplified by PCR with nested primers, as described previously (22).

Statistical analysis. The continuous data were expressed as the mean ± standard deviation, and the categorical data were expressed as the number (percentage). Comparisons of differences in the categorical data between the groups were performed using the chi-square test or Fisher's exact test. The distributions of the continuous variables were analyzed by the Student t test or Mann-Whitney U test, where appropriate. A paired t test was performed to compare the variables, such as ALT, bilirubin, and HBV DNA levels, and estimated glomerular filtration rate (GFR) in serial mea-

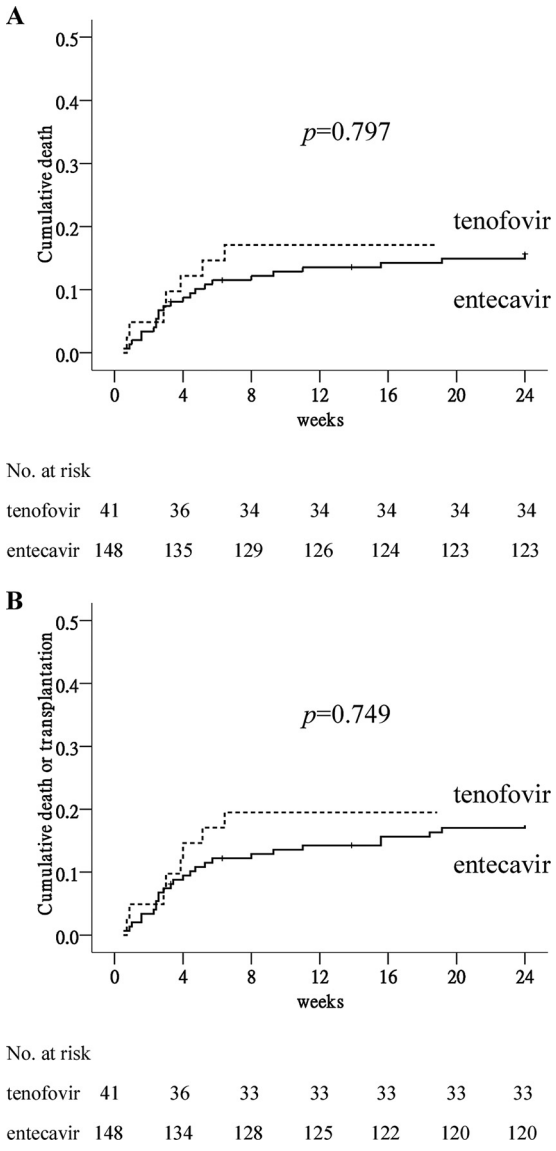

FIG 1 Cumulative rate of overall mortality or liver transplantation by week 24 in patients treated with tenofovir and entecavir. (A) Overall mortality. (B) Overall mortality or liver transplantation.

TABLE 2 Clinical outcomes of patients with severe acute exacerbation of chronic hepatitis B treated with tenofovir or entecavir

Outcome	No. (%) in patients treated with: Tenofovir ($n = 41$)	Entecavir ($n = 148$)	P
Liver-related complications			
Ascites	14 (34)	49 (33)	1.000
Within 4 wk	11 (27)	40 (27)	
Between 4 and 24 wk	3 (7)	9 (6)	
Hepatic encephalopathy	7 (17)	27 (18)	1.000
Within 4 wk	5 (12)	16 (11)	
Between 4 and 24 wk	2 (5)	11 (7)	
Hepatorenal syndrome	3 (7)	10 (7)	1.000
Within 4 wk	2 (5)	8 (5)	
Between 4 and 24 wk	1 (2)	2 (1)	
Variceal bleeding	0 (0)	2 (1)	1.000
Death	7 (17)	23 (16)	0.811
Within 4 wk	5 (12)	13 (9)	
Between 4 and 24 wk	2 (5)	10 (7)	
Liver transplantation	1 (2)	3 (2)	1.000
Within 4 wk	1 (2)	1 (1)	
Between 4 and 24 wk	0 (0)	2 (1)	

surements. The cumulative incidences of mortality or emergent liver transplantation were analyzed by the Kaplan-Meier method with a log rank test. Univariate and multivariate analyses were carried out to identify independent factors using the Cox proportional hazards regression models. All statistical tests were 2-tailed, and a P value of <0.05 was considered statistically significant.

RESULTS

Baseline characteristics. Forty-one and 148 patients who fulfilled the inclusion criteria received TDF and ETV treatment, respectively. The baseline characteristics of the study population are shown in Table 1. There were no significant differences regarding the demographic, virological, and laboratory characteristics between these two groups.

Overall mortality or liver transplantation and liver-related complications by week 24. By week 24, 7 (17% [95% confidence interval {CI}, 5% to 29%]) patients in the TDF group and 23 (16% [95% CI, 10% to 21%]) patients in the ETV group died (Fig. 1A, $P = 0.797$). Of these, 60% ($n = 18$) of the deaths occurred in the first month (Table 2). All of the deaths were liver related. In addition, 1 patient (2% [95% CI, 0% to 7%]) in the TDF group and 3 patients (2% [95% CI, 0% to 4%]) in the ETV group received living-donor liver transplantation because of progressive liver failure. The reasons for mortality without transplantation were no available living donor or refusal in 13 patients, old age (>70 years) in 9 patients, history of malignancy in 4 patients, refractory sepsis in 3 patients, and schizophrenia in 1 patient. The cumulative rates of overall mortality or liver transplantation were similar between the TDF and ETV groups ($P = 0.749$) (Fig. 1B).

As shown in Table 2, the patients in the two groups had comparable rates of liver-related complications, including ascites, hepatic encephalopathy, hepatorenal syndrome, and variceal bleeding.

Factors associated with overall mortality or liver transplantation by week 24. Comparisons between the patients with and without mortality or liver transplantation by week 24 of treatment are shown in Table 3. Old age, diabetes mellitus (DM), hypertension, cirrhosis, higher levels of HBV DNA, bilirubin levels, international normalized ratio (INR) of prothrombin time, and MELD scores, lower levels of albumin, estimated GFR, platelet count, early (within 4 weeks) presence of ascites, hepatic encephalopathy, and hepatorenal syndrome were associated with mortality or liver transplantation. By a Cox proportional hazard model, hypertension (hazard ratio [HR], 3.49; $P = 0.002$), higher HBV DNA levels (HR, 1.51; $P = 0.002$), higher MELD scores (HR, 1.10; $P = 0.01$), lower platelet count (HR, 0.99; $P = 0.005$), early presence of ascites (HR, 3.35; $P = 0.005$), hepatic encephalopathy (HR, 4.36; $P = 0.002$), and hepatorenal syndrome (HR, 7.34; $P < 0.001$) were independent factors associated with overall mortality or liver transplantation (Table 4).

TABLE 3 Comparisons of clinical features between patients with and those without mortality or liver transplantation by week 24 of treatment

Feature[a]	Data (mean ± SD or no. [%]) for patients with: No mortality or transplantation ($n = 155$)	Mortality or transplantation ($n = 34$)	P
Age (yr)	47.6 ± 13.6	61.9 ± 11.5	<0.001
Male gender	114 (74)	22 (65)	0.300
Body mass index (kg/m^2)	24.4 ± 3.8	25.0 ± 5.9	0.474
Diabetes mellitus	22 (14)	11 (32)	0.022
Hypertension	32 (21)	16 (47)	0.002
Cirrhosis	37 (24)	21 (62)	<0.001
TDF/ETV	33/122	8/26	0.819
HBV DNA ($\log_{10}$ copies/ml)	6.4 ± 1.9	7.3 ± 1.7	0.021
HBeAg positive	50 (32)	6 (18)	0.101
HBV genotype B/C[b]	53/17	8/0	0.189
AST (U/liter)	858 ± 711	879 ± 840	0.884
ALT (U/liter)	1,126 ± 839	917 ± 878	0.194
Total bilirubin (mg/dl)	9.5 ± 6.9	13.7 ± 9.9	0.003
Albumin (g/dl)	3.4 ± 0.6	3.0 ± 0.6	0.001
Creatinine (mg/dl)	1.0 ± 1.1	1.5 ± 2.0	0.059
Estimated GFR (MDRD)	98 ± 35	78 ± 43	0.004
INR	1.6 ± 0.8	2.3 ± 0.9	<0.001
Platelet (10^3/μl)	151 ± 70	107 ± 46	0.001
MELD score	19.3 ± 5.3	25.9 ± 9.2	<0.001
Ascites[c]	29 (19)	22 (65)	<0.001
Hepatic encephalopathy[c]	7 (5)	14 (41)	<0.001
Hepatorenal syndrome[c]	0 (0)	10 (29)	<0.001

[a] TDF, tenofovir; ETV, entecavir; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease (in ml/min/1.73 m^2); INR, international normalized ratio of prothrombin time; MELD, model for end-stage liver disease.
[b] Available in 78 patients.
[c] Developed within 4 weeks.

Biochemical and virological response. As shown in Fig. 2A, the rates of decline in serum ALT levels were very similar between the TDF and ETV groups. Although bilirubin increased and peaked at week 2 in the TDF group, there was no significant difference in the serum bilirubin levels at each point between these two groups (Fig. 2B). Among the patients who survived by week 24, 26 of 31 (84% [95% CI, 70% to 98%]) in the TDF group had ALT level normalization compared to 93 of 114 (82% [95% CI, 74% to 89%]) patients in the ETV group ($P = 1.0$). Also, the normalization rate of the serum bilirubin level was not different between these two groups.

TABLE 4 Univariate and multivariate analyses of factors associated with mortality or liver transplantation by week 24 of treatment

Factor comparison[a]	Univariate analyses		Stepwise multivariate analyses	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age, per 1 year increase	1.07 (1.04–1.10)	<0.001		
Gender, male vs female	0.711 (0.35–1.44)	0.342		
BMI, per 1 kg/m^2 increase	1.03 (0.95–1.11)	0.509		
DM, yes vs no	2.43 (1.18–4.98)	0.016		
Hypertension, yes vs no	2.96 (1.51–5.81)	0.002	3.49 (1.57–7.76)	0.002
Cirrhosis, yes vs no	4.15 (2.08–8.30)	<0.001		
Antiviral drug, TDF vs ETV	1.14 (0.52–2.51)	0.750		
HBV DNA, per $\log_{10}$ copies/ml increase	1.30 (1.04–1.61)	0.021	1.51 (1.17–1.96)	0.002
HBeAg positive, yes vs no	0.47 (0.19–1.12)	0.089		
HBV genotype, B vs C	0.033 (0–38.77)	0.345		
ALT, per 1 U/L increase	1.00 (1.00–1.00)	0.198		
Total bilirubin, per 1 mg/dl increase	1.07 (1.03–1.11)	0.001		
Albumin, per 1 g/dl increase	0.40 (0.23–0.68)	0.001		
Creatinine, per 1 mg/dl increase	1.17 (1.02–1.35)	0.024		
INR, increase in ratio	1.32 (1.13–1.54)	<0.001		
Platelet, per 10^3/μl increase	0.99 (0.98–0.99)	0.001	0.99 (0.98–0.99)	0.005
MELD, per score	1.14 (1.09–1.19)	0.001	1.10 (1.02–1.18)	0.01
Ascites,[b] yes vs no	6.06 (3.00–12.27)	<0.001	3.35 (1.44–7.81)	0.005
Hepatic encephalopathy,[b] yes vs no	9.16 (4.59–18.27)	<0.001	4.36 (1.71–11.09)	0.002
Hepatorenal syndrome,[b] yes vs no	24.06 (10.47–55.30)	<0.001	7.34 (2.52–21.43)	<0.001

[a] CI, confidence interval; TDF, tenofovir; ETV, entecavir; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; ALT, alanine aminotransferase; INR, international normalized ratio of prothrombin time; MELD, model for end-stage liver disease.
[b] Developed within 4 weeks.

The mean ± standard deviation HBV DNA levels in the TDF group and the ETV group were 2.9 ± 0.8 and 2.7 ± 1.3 log copies/ml at week 12 ($P = 0.535$) and 2.4 ± 0.7 and 2.2 ± 0.5 log copies/ml at week 24 ($P = 0.154$), respectively (Fig. 2C). The numbers of patients in the TDF and ETV groups with undetectable HBV DNA levels were 10 of 23 (43% [95% CI, 22% to 65%]) and 54 of 102 (53% [95% CI, 43% to 63%]), respectively, at week 24 ($P = 0.491$).

Overall renal safety. There were no patients who discontinued antivirals early due to drug side effects. Among the patients who survived by week 24, 2 of 30 (6.7% [95% CI, 0% to 16%]) patients in the TDF group and 2 of 99 (2.0% [95% CI, 0% to 4.8%]) patients in the ETV group had a confirmed change in serum creatinine from baseline of 0.5 mg/dl at week 24 ($P = 0.231$). The significant factors associated with serum creatinine increase of ≥0.5 mg/dl from baseline were old age ($P = 0.035$), hypertension ($P = 0.039$), and low baseline estimated GFR ($P = 0.035$).

There was no significant difference in the estimated GFRs between the TDF and the ETV groups at baseline, weeks 1, 2, 4, 12, and 24 (Fig. 2D). However, a significant reduction in the estimated GFR was found at week 24 in both groups (108 to 87 ml/min/1.73 m^2, $P = 0.001$ in the TDF group and 92 to 84 ml/min/1.73 m^2, $P = 0.001$ in the ETV group, respectively) (Fig. 2D).

DISCUSSION

There is growing evidence to suggest that treatment for CHB with severe acute exacerbation or decompensated liver disease should use the most effective NUCs where available (9, 23). Despite the absence of randomized controlled trials with NUCs, they appear to improve survival (mean survival, almost 80%) in CHB patients with severe acute exacerbation compared to that without antiviral therapy (mortality or transplantation rate, nearly 50%) (24). The survival benefit is more evident if therapy starts early enough (before serum bilirubin level rise of >20 mg/dl or a MELD score of ≤30) (4, 25). In addition, a rapid decline in viral load has been considered a predictor of good outcome (25).

TDF and ETV are both effective antiviral agents and have been reported to be well tolerated in patients with decompensated liver disease. However, there are no head-to-head comparisons of TDF and ETV for the treatment of CHB with severe acute exacerbation. Furthermore, little information is available about the clinical efficacy and safety of TDF in such patients (20). In this study, we compared the short-term efficacy, safety, and clinical outcomes of severe acute exacerbation in naive CHB patients treated with TDF or ETV. Our data showed that patients receiving TDF or ETV developed the similar rates of liver-related complications, including ascites, hepatic encephalopathy, hepatorenal syndrome, and variceal bleeding. In addition, the cumulative rates of mortality or liver transplantation by week 24 were comparable between these two groups and were similar to those previously reported in patients treated with ETV (13, 17). These results demonstrated that the efficacies of TDF and ETV were similar in the treatment of naive patients with severe acute exacerbation of CHB. However, in treatment-experienced patients, further studies are necessary to confirm these findings. Although this study was not randomly controlled, our analysis with two groups with very similar baseline characteristics might provide important data for use in clinical practice.

There are some observational studies comparing TDF and ETV in terms of their antiviral responses to CHB (26, 27). These studies reported that the decline in serum HBV DNA levels and HBV DNA negativity rates were not different between TDF and ETV treatments for CHB (26, 27). A recent meta-analysis also confirmed that no differences were observed in the ALT normaliza-

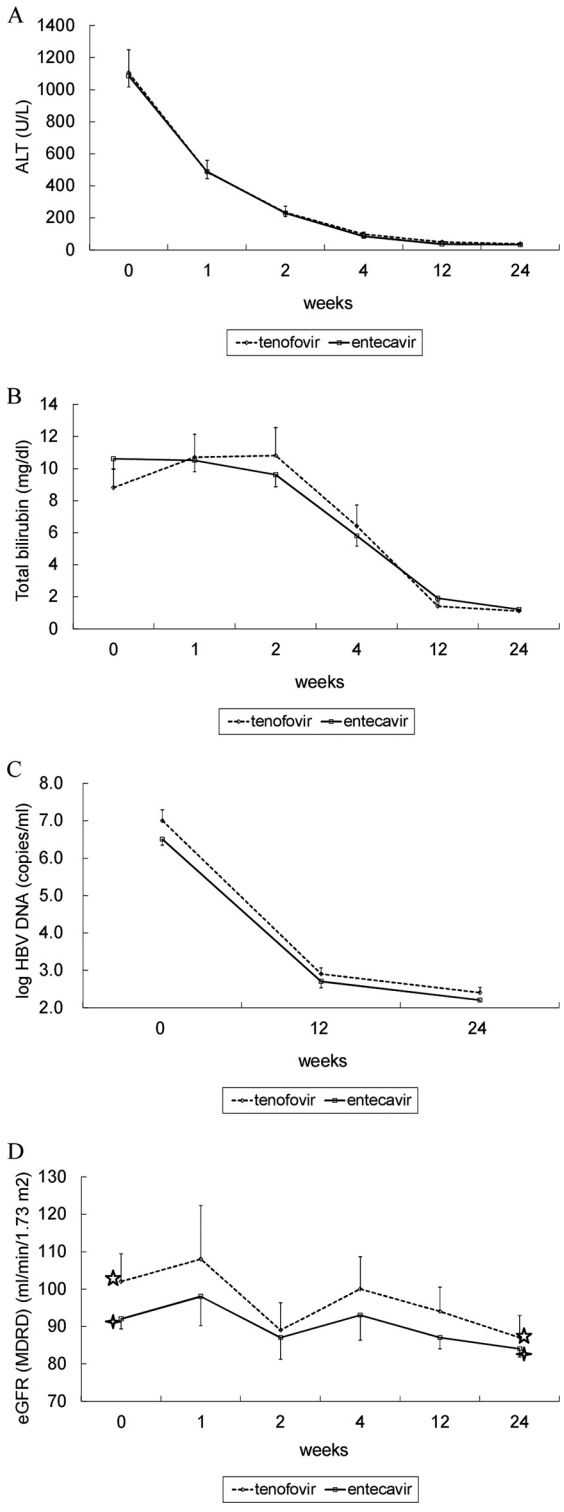

FIG 2 Serial mean ALT (A), total bilirubin (B), HBV DNA (C), and estimated GFR (eGFR) (D) levels by week 24 in patients treated with tenofovir and entecavir. (D) ☆, $P < 0.05$; ✧, $P < 0.05$ by paired *t* test. The data are presented as mean ± standard error of the mean ([SEM]). MDRD, modification of diet in renal disease.

tion rates and HBeAg seroconversion rates after 24 weeks and 48 weeks of TDF or ETV therapy (28). In our study, we found that TDF and ETV achieved comparable biochemical and virological responses at week 24 in CHB with severe acute exacerbation. Nevertheless, the long-term responses with TDF and ETV should be monitored in prolonged therapy.

Previous studies have identified several important indicators of poor prognosis in CHB with severe exacerbation. These included the presence of cirrhosis, high bilirubin level and INR, high CTP score, high MELD score, low albumin level, and low platelet count (4, 5, 16). Consistent with these studies (4, 5, 16), our patients with mortality or liver transplantation had significantly high baseline HBV DNA level and MELD score, low platelet count, early presence of ascites, hepatic encephalopathy, and hepatorenal syndrome. In particular, metabolic factors, including DM and hypertension, were also significantly associated with higher rates of primary adverse outcomes, although DM was not shown to be an independent variable on multivariate analysis. Currently, there are limited data regarding the relationship between chronic HBV infection and metabolic factors (29, 30). Wong et al. (29) demonstrated that coincidental metabolic syndrome in CHB patients increased the risk of liver fibrosis progression, independent of viral load and hepatitis activity. Another study showed that metabolic factor-related hepatic steatosis was significantly associated with antiviral treatment failure in CHB patients (30). In our study, we provide the first evidence that hypertension is one of the significant factors of poor prognosis in patients with severe acute exacerbation of CHB, and further studies are warranted to explore the possible mechanism of this factor.

Nephrotoxicity may be a concern with TDF, based on evidence from the postmarketing surveillance of patients receiving TDF for HIV infection (31), but so far, this problem seems to be less evident in CHB patients. In clinical trials, creatinine clearance rates remained stable over 4 years, with <1% of CHB patients having confirmed increases of 0.5 mg/dl in serum creatinine levels (32). In comparison, the degree of serum creatinine increase of ≥0.5 mg/dl from baseline appeared to be higher in our patients, with a correspondingly significant decrease in the estimated GFR at week 24. These results might be attributed to a number of pathogenic mechanisms, such as renal hypoperfusion, drug-induced nephrotoxicity, or systemic inflammatory response during severe acute exacerbation of CHB (33). However, there was no significant difference in the estimated GFRs between the TDF and the ETV groups over the treatment course, suggesting that the renal safety of TDF was the same as that of ETV for treating patients with severe acute exacerbation of CHB. Instead, old age, hypertension, and low baseline estimated GFR significantly correlated with a serum creatinine increase of ≥0.5 mg/dl from baseline.

Our study has some limitations, the most important being that the treatment assignment was not done by randomization. Nevertheless, we believed that the bias was small, since the two groups of patients had very similar baseline characteristics. Ideally, a randomized controlled trial to compare the efficacy between entecavir and tenofovir is needed, but such a trial appears to be very difficult to perform, considering that these cases do not occur frequently; therefore, it is almost impossible to have two arms that are adequately numerous and homogenous for statistical evaluation. Second, there was no untreated arm for use as a control in our study. This might be because NUCs can be provided by the National Health Insurance for severe acute exacerbation of CHB in

Taiwan; thus, most such patients were already under NUC treatment. Although the number of patients on TDF was relatively small, this study has been the largest cohort with this condition to date.

In conclusion, our data indicate that TDF and ETV produce a similar treatment response and clinical outcome in patients with severe acute exacerbation of CHB. There was no significant difference in terms of renal safety between these two groups. Baseline HBV DNA level, hypertension, MELD score, platelet count, early presence of ascites, hepatic encephalopathy, and hepatorenal syndrome were independent factors affecting primary adverse outcomes by week 24.

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