

Long-Term Effects of Telbivudine for Treatment-Naïve Chronic Hepatitis B-Associated Decompensated Cirrhosis

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ABSTRACT

AIM: To compare the effects of telbivudine (TBV) with entecavir (ETV) on hepatitis B virus (HBV)-infected decompensated cirrhosis.

METHODS: A total of 94 consecutive chronic hepatitis B patients with decompensated cirrhosis were recruited and retrospectively studied. Forty five patients were assigned to TBV group (600 mg/day) and 49 to ETV group (0.5mg/day), none of whom undertook antiviral treatment before.

RESULTS: At 2 years, TBV and ETV groups had comparable

cumulative rates of undetectable viremia (74.4% vs 88.0%, $p = 0.083$, by log-rank test) despite higher reduction of HBV-DNA levels in ETV group (-3.93 ± 0.22 vs -3.72 ± 0.24 , $p < 0.001$). TBV and ETV groups showed comparable HBeAg clearance or seroconversion rates, normalized alanine aminotransferase (ALT) proportions, Child-Turcotte-Pugh (CTP) and Model for end-stage liver disease (MELD) scores, cumulative rates of survival and hepatocellular carcinoma (HCC), and proportions of cirrhosis-associated complications. TBV group had significantly higher rates of drug-resistance (15.9% vs 0%, $p < 0.05$) and elevated creatine kinase (CK, 18.2% vs 4.0%, $p < 0.05$). Cox proportional hazard regression model revealed that pretreatment HBV DNA level was the only independent predictive factor for 2-year undetectable viremia [Hazard Ratio (HR): 0.627; 95% Confidence Interval (CI): 0.432-910, $p = 0.014$].

CONCLUSIONS: For hepatitis B-associated decompensated cirrhosis, TBV was comparable to ETV in viral suppression, biochemical and immunological responses, and clinical outcomes. However, TBV was associated with higher rates of drug-resistance and increased CK.

Key words: Telbivudine; Entecavir; Hepatitis B virus; Liver cirrhosis

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INTRODUCTION

It is estimated that there are more than 350 million hepatitis B virus (HBV) carriers in the world, and of this one million deaths occur each year due to various liver diseases^[1]. In china, chronic hepatitis B (CHB) is still a severe health problem that poses a heavy economic burden to the society, despite the 1992 universal intervention program that has greatly decreased the prevalence of HBV infection^[2]. According to a recent epidemiological study carried out in Zhejiang province, China, the adjusted carrier rate of HBsAg in the screened population was 6.13%, of whom, 17.5%

were with elevated alanine aminotransferase (ALT)^[3]. Both CHB patients and HBV carriers bear the risk of progression to cirrhosis, hepatic decompensation, hepatocellular carcinoma (HCC) and even liver failure^[4,5].

In CHB patients cirrhosis, long-term treatment with antiviral agents, mainly involving oral nucleos(t)ides (NAs), is imperative and beneficial. During the treatment, patients are required to be close monitored for detection of drug resistance and/or acute deterioration of liver function which manifests in the form of an increment of ALT level to above 10 folds the upper normal limit and above 2 folds the preliminary level^[6,7]. Patients with cirrhosis at compensated and decompensated stages are associated with different prognosis and predictors for survival and other clinical decompensating events such as variceal hemorrhage (VH), ascites and hepatic encephalopathy (HE)^[8]. In CHB patients with compensated or decompensated cirrhosis, entecavir (ETV) treatment had been reported to be an effective drug which resulted in sustained viral inhibition and improvement of histology^[9].

Currently, telbivudine (TBV) is not recommended as the first-line treatment option for the management of patients with chronic liver disease related to HBV infection. However, TBV is less expensive and thus more affordable than ETV for patients in developing countries. Besides, previous studies reported that long-term treatment with TBV was both effective and safe in CHB patients regardless of HBeAg status, and TBV was even more advantageous to ETV in clearing HBeAg^[10,11]. In the treatment of CHB-associated compensated cirrhosis, TBV was reported to be similarly effective in terms of clinical outcomes when compared to ETV^[12].

In the literature, reports about the effects of TBV on CHB-associated decompensated cirrhosis are limited. Our study aimed to investigate this subject by comparing TBV with ETV in terms of antiviral potency, biochemical and serological responses, and long-term clinical outcomes.

Table 1 Baseline characteristics of patients in TBV and ETV groups.

	TBV (n=44)	ETV (n=50)	*P value
Female, n(%)	9/44 (20.5%)	12/50 (24.0%)	0.68
Age(year)	49.5 ± 12.5	52.5 ± 10.6	0.201
HBeAg positivity	8/44 (18.2%)	8/50 (16.0%)	0.779
HBV-DNA (log ₁₀ copies/mL)	6.82 ± 0.75	6.81 ± 0.48	0.951
Albumin, g/L	31.8 ± 7.1 [†]	28.3 ± 6.2	0.012
ALT, U/L	74.1 ± 93.8	98.7 ± 162.4	0.379
AST, U/L	87.4 ± 109.5	113.5 ± 196.4	0.437
Total bilirubin, μmol/L	38.5 ± 41.5	50.2 ± 49.6	0.221
Creatinine, μmol/L	73.2 ± 14.1	70.2 ± 14.7	0.307
PT(s)	18.4 ± 3.3 [†]	20.4 ± 5.1	0.023
INR	1.59 ± 0.30	1.75 ± 0.50	0.055
WBC, 10 ⁹ /L	3.55 ± 1.42	3.86 ± 2.16	0.426
Hemoglobin, g/L	116.6 ± 30.6	117.0 ± 27.1	0.954
Platelets, 10 ⁹ /L	95.5 ± 67.8	80.4 ± 46.4	0.206
CTP score	7.89 ± 2.46	8.80 ± 2.44	0.075
MELD score	11.2 ± 4.2	12.8 ± 5.1	0.097
Ascites	22/44(50.0%)	29/50(58.0%)	0.437
Episodes of variceal bleeding	13/44(29.5%)	15/50(30.0%)	0.962
Episodes of encephalopathy	4/44(9.1%)	7/50(14.0%)	0.46

TBV: telbivudine; ETV: entecavir; ALT: alanine aminotransferase; AST: aspartate aminotransferase; PT: prothrombin time; INR: international normalized ratio; WBC: white blood cell; CTP: Child-Turcotte-Pugh; MELD: model for end stage liver disease; [†]*p*, by χ^2 test or Student's *t*-test; ^{*}*P* < 0.05 compared to entecavir group.

METHODS

Patients

During July 2012-January 2016, a total of 97 consecutive patients with HBV-infected decompensated cirrhosis were recruited and retrospectively evaluated at the Second Affiliated Hospital of Kunming Medical University. None of the patients undertook antiviral treatment before. The study protocol was approved by the ethics committee of our hospital and informed consent was obtained from every patient. Three subjects (3.1%) were excluded in the analysis due to failure to comply with the scheduled follow-up visits. Of the remaining 94 patients, 45 were assigned to TBV group (600 mg/day) and 49 to ETV group (0.5 mg/day). Allergic reaction was recorded in 1 subject after taking TBV and thus switched to ETV. Cirrhosis was confirmed according to clinical, radiological, or histological evaluation. Decompensated cirrhosis was defined as cirrhosis complicated with ascites, VH, HE or spontaneous bacterial peritonitis (SBP) or Child-Turcotte-Pugh (CTP) score of seven or more^[13,14].

Baseline HBV DNA levels were above 1,000 copies/mL in all recruited cases. A patient was excluded if: (1) co-infection with hepatitis A, C, D, E virus or Human immunodeficiency virus (HIV); (2) excessive alcohol intake (> 40 grams per day in males and 20 grams per day in females); (3) HCC diagnosis was confirmed by radiological approaches including Doppler-ultrasonography (Doppler-USG), computed tomography (CT), and/or magnetic resonance imaging (MRI), and/or alpha-fetoprotein (AFP) tests.

Blood tests and radiologic imaging

At the entry of study, all recruited patients undertook Doppler-USG and CT or MRI imaging. Viral infection panel, including HAV, HBV, HCV, HDV, HEV and HIV was tested by immunoassays (Abbott Laboratories, Chicago, IL). HBV DNA was quantified by real-time fluorescent PCR test (CAP-CTM; Roche Molecular Systems, Inc., Branchburg, NJ, USA), with detection limits of 500 copies/mL. The remaining blood tests were performed by technicians in the clinical laboratory department.

Follow-up protocol

Followed-up visits at an interval of three to six months were carried out in our institution. During the visits, physical exam and clinical reviews regarding compliance, side effects, decompensating events associated with liver cirrhosis were evaluated in each subject. Biochemical tests, coagulation panel, HBV immunological markers, and HBV DNA levels, Doppler-USG or CT were also carried out in every patient. We calculated the scores of CTP^[15] as well as model for end-stage liver disease (MELD)^[16] according to the proposed approaches.

Clinical endpoints

The major endpoints were 2-year cumulative rates of undetectable viremia, ALT normalization, and changes of CTP and MELD scores. 2-year cumulative rates of survival, HCC, immunological and biochemical responses, antiviral resistance, and side effects during the treatment were also noted.

Statistical analysis

Data were analyzed by SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA). Categorical variables were reported as proportions and compared by Chi-square test, and continuous variables were expressed as mean ± standard deviation (SD) or median (range)

and compared by Student's *t*-test or Mann–Whitney test. Survival rates were calculated by Kaplan–Meier method and compared by log-rank test. Cox univariate and multivariate regressions were employed to analyze significant pretreatment predictors of undetectable viremia. Statistical significance was taken as a two-sided *p* value <0.05.

RESULTS

Pretreatment features

Table 1 shows the pretreatment features of all subjects. The proportions of male subjects in TBV and ETV groups were similar (79.5% vs 76.0%, *p* = 0.680). Age, HBeAg positive rates, HBV DNA values in TBV group was comparable to ETV group. TBV group had markedly higher albumin levels and lower prothrombin time (PT) as compared to ETV (*p* < 0.05). Other laboratory indices, CTP and MELD scores, rates of decompensating events such as ascites, VH and HE in TBV and ETV were not statistically different (*p* > 0.05).

Therapeutic Results

Virological and immunological responses

As shown in Table 2, after 1 year of treatment, undetectable viremia rate in TBV group was comparable to ETV group (72.5% vs. 86.0%, *p* = 0.112). After 2 years of treatment, undetectable viremia rate in TBV was also comparable to ETV group (77.1% vs. 86.7%, *p* = 0.266). Figure 1 shows the undetectable viremia rates in TBV and ETV groups during the study. Using Kaplan–Meier method, we further calculated the 2-year cumulative rates of undetectable viremia, which were still not significantly different between TBV group and ETV group (74.4% vs. 88.0%, *p* = 0.083, by log-rank test) (Figure 2).

Table 2 Virological and immunological responses in TBV and ETV groups during the study.

	TBV (n=44)	ETV (n=50)	* <i>p</i> value
Virological response			
Serum HBV DNA undetectable, No. (%)			
0.5 year	24/44 (54.5)	34/50 (68.0)	0.181
1 year	29/40 (72.5)	43/50 (86.0)	0.112
2 year	27/35 (77.1)	39/45 (86.7)	0.266
Reduction of serum HBV DNA level (log 10 copies/mL), No.			
0.5 year	-3.22 ± 0.26 (n = 44) ^Δ	-3.42 ± 0.29 (n = 50)	0.001
1 year	-3.59 ± 0.27 (n = 40) ^Δ	-3.88 ± 0.20 (n = 50)	0
2 years	-3.72 ± 0.24 (n = 35) ^Δ	-3.93 ± 0.22(n = 45)	0
Immunological response			
HBeAg loss, No. (%)			
1 year	4/8(50.0)	2/8(25.0)	0.302
2 years	5/7(71.4)	3/8(37.5)	0.189
HBeAg seroconversion, No. (%)			
1 year	2/8(25.0)	1/8(12.5)	0.522
2 years	4/7(57.1)	1/8(12.5)	0.067
HBsAg loss, No. (%)			
1 year	1/40(2.5)	2/50(4.0)	0.884
2 years	2/35(5.7)	2/45(4.4)	0.796
HBsAg seroconversion, No. (%)			
1 year	1/40(2.5)	1/50(2.0)	0.873
2 years	0/35(0)	1/45(2.2)	0.375

TBV: telbivudine; ETV: entecavir; #*p*, by χ^2 test or Student's *t*-test; ^Δ*P*<0.01 compared to ETV group.

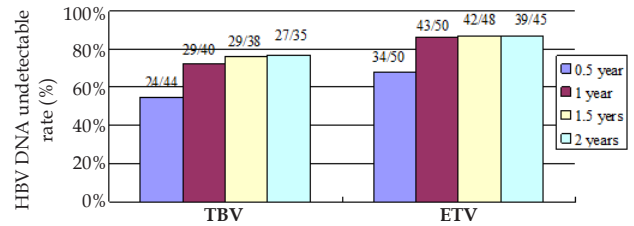


Figure 1 Virological response at the follow-up period in telbivudine and entecavir group.

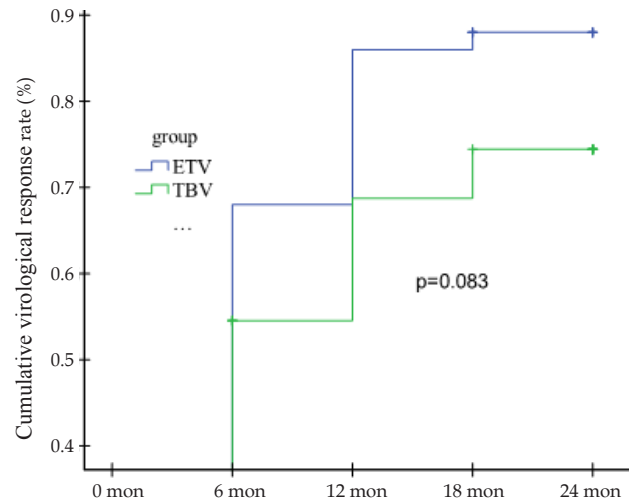


Figure 2 Cumulative virological response at 2 years between the two groups as determined by the Kaplan-Meier method (log rank test, *p* = 0.083).

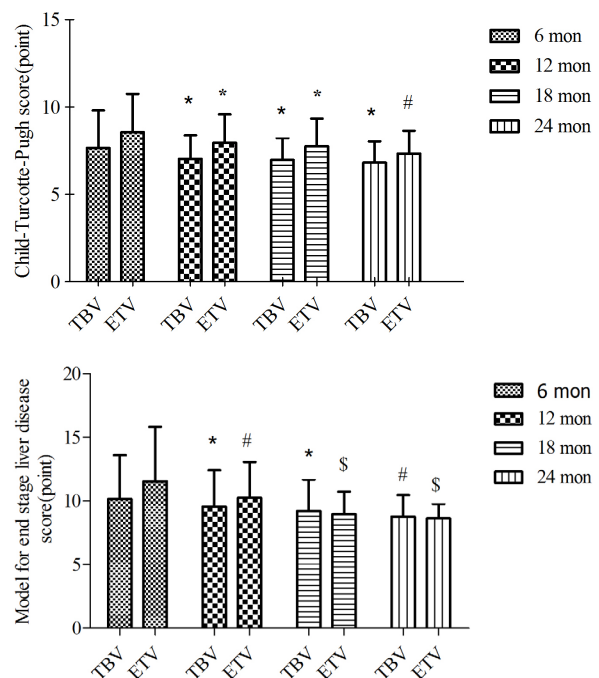


Figure 3 a,b Child-Turcotte-Pugh score and Model for End Stage Live Disease score at each time point during the study. **p*<0.05, #*p*<0.01, \$*p*<0.001 compared to at baseline (by student *t*-test).

Interestingly, ETV treatment resulted in markedly higher reductions in BV-DNA levels compared to TBV at various follow-up points ($p < 0.01$) (Table 2). In 16 subjects who were HBeAg positive at baseline, TBV treatment resulted in similar 1-and 2-year HBeAg loss or seroconversion rates to ETV, which may be due to limited number of HBeAg-positive patients (Table 2). HBsAg loss occurred in one subject in TBV group, and HBsAg loss and seroconversion occurred in another subject in ETV group after 2 years of treatment.

Table 3 shows the analyses of Cox univariate and multivariate regressions, which showed that baseline HBV DNA was the only independent predictor of undetectable viremia in both univariate analysis (Hazard Ratio(HR): 0.620; 95% Confidence Interval (CI): 0.457-0.841, $p=0.002$) and multivariate analysis (HR: 0.627; 95% CI: 0.432-0.910, $p=0.014$).

Biochemical response

As shown in Table 4, TBV and ETV groups showed comparable 1- and 2-year ALT and aspartate aminotransferase (AST) normalization rates ($P > 0.05$). When compared to at baseline, both TBV and ETV treatments resulted in markedly improved levels of albumin, total bilirubin (TBIL) and PT at 2 years ($p < 0.05$). In ETV group, serum albumin, TBIL also prominently improved at 1 year and international normalized ratio (INR) prominently improved at 2 years ($p < 0.05$) than at baseline. Notably, compared to ETV, TBV treatment resulted in markedly improved levels of albumin, TBIL and PT at 1 or 2 years ($p < 0.05$), which was compatible with the pretreatment levels. Despite CTP and MELD scores in TBV and ETV groups were not significantly different during the study, these two scores were prominently improved since 1 year when compared to pretreatment scores (Figure 3).

Clinical results

As presented in Table 5, TBV and ETV groups had similar length of follow-up periods (24.9 ± 7.3 vs. 27.1 ± 5.0 months, $p = 0.094$). In total, 14 deaths occurred at the follow-up period due to: VH ($n = 6$), hepatic failure ($n = 4$), lung infection ($n = 1$), SBP ($n = 1$), and HCC ($n = 2$). The 2-year cumulative rates of survival and HCC, and incidences of other decompensating events, such as VH, HE, SBP, and hepatorenal syndrome were comparable between TBV group and ETV group ($p > 0.05$).

Drug resistance

At the follow-up period, seven subjects developed drug resistance (1st year: one HBeAg-positive subject who died without HBeAg seroconversion at 15 months, and two HBeAg-negative subjects; 2nd year: four HBeAg-negative subjects) in TBV group, as compared to none in ETV group ($p < 0.05$). Among these patients, mild elevation of ALT levels was detected in only two patients, one with 210 U/L and the other 320 U/L. All these patients were subjected to genetic tests for YMDD mutation. Of these patients, only two were tested positive for rtM204I mutation, and added adefovir (ADV). Both patients tolerated well and showed undetectable viremia within six months after the rescue therapy (Table 5).

Adverse events

In TBV group, one subject developed skin eruption over the body after taking TBV for 2 weeks and he was switched to ETV. In ETV group, one male patient complained of headache. Elevated creatine kinase (CK) was more frequent in TBV group than ETV group (18.2% vs. 4.0%, $p < 0.05$), which were asymptomatic. Mild lactic acidosis was accidentally noted in 2 subjects who had low blood oxygen saturation and undertook arterial blood gas analysis in ETV

Table 3 Univariate and multivariate analysis for the factors predictive of virological response at 2 years.

Baseline factors	Univariate analysis		
	HR	95% CI	P value
HBV DNA	0.62	0.457-0.841	0.002

HR: hazard ratio; CI: confidence interval; TBIL: total bilirubin; INR: international normalized ratio.

Table 4 Biochemical response and hepatic function improvement during the study in TBV and ETV groups.

	TBV (n = 44)	ETV (n = 50)	*P value
Biochemical response			
Normalization of ALT levels, No. (%)			
1 year	30/40 (75.0)	43/50 (86.0)	0.185
2 years	28/35 (80.0)	38/45 (84.4)	0.604
Normalization of AST levels, No. (%)			
1 year	28/40 (70.0)	42/50 (84.0)	0.112
2 years	27/35 (77.1)	38/45 (84.4)	0.407
Albumin(g/L)			
1 year	34.0 ± 5.3 (n = 40) [*]	31.3 ± 3.8 (n = 50) ^β	0.01
2 years	34.8 ± 5.1 (n = 35) ^{α,Δ}	31.9 ± 3.8 (n = 45) ^β	0.007
Total bilirubin(μmol/L)			
1 year	27.4 ± 12.3 (n = 40)	33.3 ± 16.1 (n = 50) ^α	0.052
2 years	24.5 ± 8.1 (n = 35) ^{α,Δ}	30.3 ± 12.7 (n = 45) ^β	0.015
Creatinine(μmol/L)			
1 year	70.7 ± 10.6 (n = 40)	69.9 ± 14.1 (n = 50)	0.767
2 years	69.4 ± 9.9 (n = 35)	68.4 ± 13.5 (n = 45)	0.714
Prothrombin time(s)			
1 year	17.4 ± 2.3(n = 40) ^Δ	19.1 ± 3.1 (n = 50)	0.005
2 years	16.9 ± 1.8(n = 35) ^{α,Δ}	18.2 ± 2.4 (n = 45) ^β	0.007
International normalized ratio(INR)			
1 year	1.52 ± 0.22(n = 40)	1.61 ± 0.28 (n = 50)	0.075
2 years	1.48 ± 0.17(n = 35)	1.57 ± 0.24 (n = 45) ^α	0.052

TBV: telbivudine; ETV: entecavir; ALT: alanine aminotransferase; AST: aspartate aminotransferase; *p, by χ^2 test or Student's t-test; ^β $p < 0.05$, ^α $p < 0.01$ compared to ETV group, ^α $p < 0.05$, ^β $p < 0.01$ compared to baseline levels.

Table 5 Cirrhotic complications and drug-related adverse events during the study.

	TBV (n=44)	ETV (n=50)	*P value
Follow-up(month)	24.9 ± 7.3	27.1 ± 5.0	0.094
Mortality	9/44 (20.5%)	5/50 (10.0%)	0.155
Cumulative survival rate	79.50%	90.00%	0.141 [‡]
HCC rate	5/44 (11.4%)	6/50 (12.0%)	0.924
Cumulative HCC rate	11.70%	12.70%	0.883 [‡]
Variceal bleeding	9/44 (20.5%)	8/50 (16.0%)	0.576
Bacterial peritonitis	3/44 (6.8%)	5/50 (10.0%)	0.581
Hepatic encephalopathy	5/44 (11.4%)	9/50 (18.0%)	0.367
Hepatorenal syndrome	0/44 (0%)	1/50 (2.0%)	0.346
Virological breakthrough, No.(%)			
1 year	3/40 (7.5%)	0/50 (0%)	0.049
2 years	4/35 (11.4%)	0/45 (0%)	0.02
Drug-related adverse events, No.(%)			
Allergic reactions	1/45 (2.2%) [§]	0/50 (0%) [§]	
Headache	0/44 (0%)	1/50 (2.0%)	
Elevated CK	8/44 (18.2%)	2/50 (4.0%)	
Lactic acidosis	0/44 (0%)	2/50 (4.0%)	

TBV: telbivudine; ETV: entecavir; [§]one patient switched to ETV due to allergic reaction to TBV; HCC: hepatocellular carcinoma; CK: creatine kinase; *p, by χ^2 test; [‡]p, by log rank test.

group without interruption of the treatment (Table 5).

DISCUSSION

It's well established that antiviral treatment is associated with improved clinical outcomes in patients with severe fibrosis or cirrhosis. Compared to decompensated cirrhosis, antiviral treatment with TBV was associated with higher ALT normalization rates and HBV-DNA negativity rates, and lower drug-resistance rates at 12 weeks; antiviral treatment in compensated cirrhosis was also associated with alleviated esophageal varix and significantly improved liver stiffness, which emphasized the importance of early antiviral treatment in patients of such severe liver disease^[17].

In patients with cirrhosis, antiviral treatment with oral NA(s) usually should be maintained indefinitely. Among oral NAs, tenofovir (TDF) or ETV are more preferable due to their high antiviral potency and minimal risk of drug-resistance, and lamivudine (LAM) should not be used due to high drug-resistance potential in such cohort of patients^[7]. ADV possesses low antiviral efficacy and have the potential of renal toxicity, thus it is not a good option for patients with cirrhosis^[18]. In contrast, TBV treatment results in higher rates of HBeAg seroconversion than other oral NAs, and it has renoprotective effects in patients with chronic HBV infection^[19,20]. Therefore, TBV seems to be a good treatment option for patients with cirrhosis, particularly decompensated cirrhosis. However, reports about the effects of TBV in patients with decompensated cirrhosis are still very limited.

For patients with CHB, previous studies had reported that TBV treatment, regardless of the HBeAg status, was superior to LAM in terms of viral inhibition, ALT normalization, and drug resistance; TBV was similar to LAM in frequency of adverse events, though TBV was associated with higher frequency of increased CK levels^[10,11,21]. For CHB patients who were HBeAg-positive and NA-naïve, TBV was reported to be comparably effective in viral inhibition, ALT normalization; TBV was associated with higher proportions of HBeAg loss and seroconversion; both drugs were safe and well tolerated; but TBV was associated with higher rates of drug resistance as well as elevated CK, as compared to ETV^[11,22-25]. Moreover, long-term ETV treatment can cause regression of liver fibrosis or cirrhosis, and can result in substantial histological improvement in the majority of NA-naïve CHB patients^[26].

As mentioned before, long-term and adequate antiviral treatment can enhance clinical outcomes in patients with severe fibrosis or cirrhosis. Cirrhotic patients are required to undertake long-term antiviral treatment, during when drug resistance and viral flares should be closely monitored^[7]. For patients with compensated cirrhosis, previous studies reported that prolonged and sufficient antiviral therapy could stabilize patients and prevent the progression to decompensated liver disease^[27,28]. Patients with decompensated cirrhosis require prompt initiation of antiviral treatment irrespective of HBV DNA levels, as which can prevent hepatic decompensation caused by viral reactivation^[7]. In the literature, ETV or TBV had been evaluated for the efficacy and safety in the management of patients with HBV-infected decompensated cirrhosis. Shim *et al*^[29] investigated the efficacy of ETV in 70 HBV-infected patients with decompensated cirrhosis and compared the virological responses of 55 patients who were treated for one year (decompensated group) with those of 144 patients with CHB or compensated cirrhosis (compensated group), which concluded that one-year primary ETV treatment was similarly effective in both compensated and decompensated cirrhosis, and it improved CTP

and MELD scores. Singal *et al*^[30] in a meta-analysis reported that 1-year treatment for patients with HBV-infected decompensated cirrhosis using all oral antiviral agents, including ETV, LAM, ADV, TBV and TDF, led to improved virological, biochemical and clinical indices; the efficacies of LAM and TBV were limited by drug-resistance, and ADV was limited by its antiviral potency and slow onset of action; it still required more studies on TDF and ETV to determine the optimal agent(s) for treatment-naïve patients and in those with drug-resistance. Thus, the optimal oral antiviral agent for HBV-related decompensated cirrhosis was still not established.

In the literature, few studies directly compared the efficacy of TBV with ETV for the treatment of patients with HBV-infected decompensated cirrhosis. In a randomized trial comparing the efficacy and safety of TBV with LAM in treatment-naïve CHB-associated decompensated cirrhosis, TBV treatment was associated with a prominent alleviation in glomerular filtration, better virological and biochemical responses compared to LAM and was also associated with a trend towards improvement in survival^[20]. In another long-term study by Kim HR *et al*^[31] which compared the efficacy of TBV with ETV for the treatment of antiviral-naïve CHB-associated cirrhosis, TBV treatment resulted in similar improvement of liver function, but lower viral inhibition and higher drug resistance rates than ETV. In our study, TBV treatment achieved comparable cumulative rates of undetectable viremia despite lower reduction of HBV DNA levels, and similar ALT normalization rates; TBV was associated with higher rates of drug-resistance and increased CK, consistent with the results observed in HBeAg-positive CHB patients^[11,22-25]. Moreover, our study showed that the improvement of CTP and MELD scores, 2-year cumulative survival rates and HCC development, and rates of complications related to cirrhosis were not statistically different between TBV and ETV, which may favor TBV since it was less expensive and was associated with improved glomerular filtration^[20]. The discrepancy in antiviral efficacy between our study and the study by Kim HR *et al*^[31] could be explained by the patient selection criteria and statistical analytic method: the recruited patients in our study were those with decompensated cirrhosis, while patients in the latter were those with cirrhosis (decompensated or not was not specified); antiviral efficacy in our study was analyzed by Kaplan–Meier method and log-rank test, while antiviral efficacy in the latter was by intention-to-treat analysis.

Previous studies showed that TBV was associated with better immunological response in terms of HBeAg loss and seroconversion compared to ETV^[11,22-25]. In the present study, TBV treatment resulted in similar HBeAg clearance and seroconversion rates to ETV, which was probably due to limited number of HBeAg-positive patients. For TBV-resistant patients, our policy was adding ADV for rescue therapy before 2015, when rescue therapy with TDF was not widely accepted in China^[32]. After adding ADV, the two patients with TBV-resistance and rtM204I mutation achieved undetectable viremia within six months without severe adverse events.

It is not clear which oral antiviral agent was optimal in survival benefit for the management of patients with CHB-associated decompensated cirrhosis. As mentioned previously, Chan *et al*^[20] reported that TBV resulted in a trend towards improved survival than LAM. In our study, cumulative survival rates in TBV and ETV groups were comparable, which was in line with previous studies^[20]. In our study, TBV and ETV treatment resulted in similar HCC incidence, which was in line with previous report that antiviral treatment did not completely eliminate the risk of HCC

development in patients with cirrhosis^[33].

In our study, increased CK was more frequent in TBV group, though it did not cause treatment interruption. Patients with highly impaired liver function (MELD score above 20) were at risk of developing lactic acidosis, and thus ETV should be cautiously applied^[34]. In this study, three patients in ETV group had lactic acidosis which resolved shortly without discontinuing ETV therapy. During the study, renal impairment was not observed in any patient.

This study has several limitations: first, it was retrospective in design; second, group assignment was not randomized; third, HBeAg clearance and seroconversion rates may be underestimated due to limited number of HBeAg-positive patients. However, this study directly compared the safety and efficacy of TBV with ETV with a 2-year follow-up period, which provided useful information for clinical practitioners.

In conclusion, TBV was comparably effective in virological, biochemical and clinical responses to ETV in the treatment of CHB-associated decompensated cirrhosis, but TBV was associated with higher rates of drug-resistance and CK increment.

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