Short-Term Efficacy of Tenofovir Alafenamide in Acute-On-Chronic Liver Failure: A Single Center Experience

Clinical Pathology
Volume 17: 1–7

DOI: 10.1177/2632010X241265858

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ABSTRACT

BACKGROUND: Patients with acute-on-chronic liver failure (ACLF) who take entecavir (ETV) and tenofovir disoproxil fumarate (TDF) experience a reduction in hepatic events and mortality. The effectiveness of tenofovir alafenamide (TAF) was not well investigated. This study was aim to compare the antiviral efficacy and mortality between TAF and ETV in patients with ACLF caused by the hepatitis B virus (HBV).

METHODS: One hundred and six patients with HBV-ACLF who received TAF (25 mg/day) and ETV (0.5 mg/day) for 12 weeks were analyzed. The primary endpoints were overall mortality and liver transplantation (LT) at week 12. Biochemical responses, virologic responses, mortality, drug safety, and side effects were evaluated.

RESULTS: At 4 and 12 weeks of TAF treatment, patients showed significantly higher HBV-DNA reduction ($P < .001$), higher HBV-DNA undetectability rates ($P < .001$), and lower HBV DNA levels ($P < .001$) in serum. Lower Child-Turcotte-Pugh (CTP) scores ($P = .003$) were observed at 4 weeks in the TAF group, although the CTP scores showed no difference between TAF group and ETV group at 12 weeks ($P = 1.143$). Lower alanine aminotransferase (ALT) levels of patients in the TAF group at week 4 and 12 were observed ($P = .023$ and $P < .0001$, separately). The mortality of TAF group was lower after 4 weeks of treatment ($P = .038$); however, the 2 groups had similar mortality rates at week 8 and 12. Among the causes of death in HBV-ACLF patients, we found the same incidence of liver-related problems in both groups ($P > .05$).

CONCLUSIONS: This study showed that ACLF patients with chronic HBV infection treated with TAF had a rapid decline in HBV DNA, a higher rate of ALT reduction and improved CTP scores compared to the ETV group, thereby improving patient survival.

KEYWORDS: Antiviral efficacy, acute-on-chronic liver failure, hepatitis B virus, tenofovir alafenamide

RECEIVED: August 31, 2023. **ACCEPTED:** June 11, 2024.

TYPE: Original Research

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This project was supported by grants from Henan Province Medical Science and Technology Tackling Provincial Ministry Key Project of China (No. SBGJ202102085).

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Hepatitis B virus (HBV) infection is one of the leading causes of chronic liver disease worldwide,[1,2] and present with different clinical manifestations, including HBV carriers, chronic hepatitis B (CHB), CHB reactivation, cirrhosis, hepatocarcinoma, etc.[3-5] Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by functional system failure and rapid hepatic decompensation.[6,7] The presence of active viral replication in patients with CHB can induce inflammatory responses and pathological changes in the liver, and the reactivation of HBV replication can lead to the development of ACLF. Clinically, ACLF patients have poor prognosis and high short-term mortality.[8,9] Liver transplantation (LT) is an effective treatment for ACLF patients, but not every family can afford the high medical costs. Nucleoside analogs (NAs) can reduce hepatocyte cell death by inhibiting viral DNA replication, thereby helping to prevent decompensation-related liver failure. Therefore, many guidelines recommend NAs as a critical therapeutic method for the onset of ACLF. Entecavir (ETV), tenofovir dioproxil fumarate (TDF) and tenofovir alafenamide (TAF) are recommended as first-line antiviral drugs for CHB patients.[10]

ETV and lamivudine (LAM) have been used in the treatment of ACLF as oral agents. LAM is the first NA registered for the treatment of CHB patients, and is also widely used in ACLF patients for many years.[11,12] Li et al[13] found that LAM can reduce the short-term mortality of ACLF patients. In addition, ETV showed stronger antiviral activity than LAM. Huang et al[14] analyzed 8 retrospective cohort studies and found that ETV had better long-term prognosis for ACLF patients than LAM patients, and the study also showed that ETV could alleviate the clinical manifestations caused by ACLF. The study by Park et al[15] also showed that patients treated with LAM tended to have higher mortality or require LT more frequently than patients treated with TDF or ETV. TDF is low drug resistance and has shown excellent anti-HBV activity in LAM-resistant patients.[16] Compared with placebo, TDF significantly improved 3-month outcomes in patients with HBV-ACLF.[17] In addition, Compared with ETV, TDF is superior to ETV in the treatment of HBV-ACLF in terms of rapid suppression of virus, improvement of liver function and short-term survival rate.[18] However, long-term use of TDF is nephrotoxic and

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affects bone metabolism, which is not preferred for people with kidney disease and the elderly.[19] In contrast to TDF, TAF, a novel oral phosphonamidite prodrug of tenofovir, has a high intracellular exposure in the liver and has a higher renal and bone safety profile than TDF.[20] However, as a new drug, there are a few data on the impact of TAF on clinical outcomes of short-term efficacy in HBV-related ACLF, and TAF is not inferior to TDF in antiviral efficacy with higher renal and bone safety. In consequence, this study retrospectively compared the antiviral efficacy of TAF and ETV in patients with HBV-ACLF.

Patients and Methods

From January 1, 2017, to June 30, 2020, patients with continuous HBV infection who were admitted to the hospital were assessed and selected for this retrospective study. A total of 106 ACLF patients with HBV infection were contained in this study. The following were the inclusion requirements: (1) HBsAg positive for at least 6 months; (2) Meeting the definition of ACLF proposed by the 2012 Asia Pacific Association for the Study of the Liver (APASL), an acute hepatic insult manifesting as jaundice (serum total bilirubin, ⩾5 mg/dL) and coagulopathy (international normalized ratio, ⩾1.5 or prothrombin activity, <40%) complicated within 4 weeks by clinical ascites and/or encephalopathy in patients with chronic liver disease or cirrhosis; (3) 18-60 years old; and (4) No other virus infection was found, including HAV, HCV, HEV, epstein-Barr virus, cytomegalovirus infection. The exclusion criteria were as follows: (1) Patients with positive results for anti-HDV and anti-HIV positive patients; (2) Patients with positive results for autoimmune liver disease, such as antinuclear antibody; (3) Patients with alcohol liver disease; (4) Patients with hepatocellular carcinoma; (5) Patients with data loss; (6) Pregnant patients. This study was approved by the Independent Ethics Committee of the First Affiliated Hospital of Zhengzhou University (Ethical approval number: 2023-KY-1038-001).

Virological and Liver Function Tests

Clinical assessments and routine examinations were collected at weeks 4, 8, and 12, and followed for >6 months until death or liver transplantation. The monitored data are as follows: (1) the level of serum HBV DNA (⩾20 IU/mL) and HBV markers (HBsAg, HBsAb, HBeAg, HBeAb, HBcAb); (2) Liver and kidney function tests, including alanine aminotransferase (ALT), aspartate transaminase (AST), albumin (ALB), total bilirubin (TBIL), urea, creatinine, estimated glomerular filtration rate (eGFR); (3) International standardized ratio for PTA and coagulation function.

Clinical Outcome Assessment

The aim of this study was to evaluate the safety and efficacy of TAF for the short-term treatment of HBV-ACLF patients. Liver transplantation (LT) or overall mortality are both adverse consequences of treatment, thus overall mortality or LT at week 12 was considered as the first endpoint. The secondary endpoints were reduction in ALT and bilirubin levels, CTP scores, virological response, presence of viral mutations, and seroconversion of hepatitis B e-antigen (HBeAg) in patients with HBeAg positivity at baseline.

Management and Follow-Up

Both TAF and ETV are first-line antivirals, so we divided them into the TAF group and the ETV group according to their choice of medication. Patients in the TAF group received TAF 25 mg orally once daily; patients with ETV received ETV 0.5 mg orally once daily. Patients' follow-up commenced upon the initiation of NAs. Patients were administered NA treatment for at least 3 months until liver transplantation or death. Moreover, all patients received standard medical care, such as complete bed rest, supportive care, regular liver protection medication, and control of intestinal microbiology. The levels of ALT and HBV DNA were monitored for >6 months. Throughout the follow-up period, clinical and test data, side effects, and patient compliance were all tracked. Liver function parameters, positivity for HBeAg, and serum HBV DNA levels were regularly checked at each follow-up. Figure 1 presents an overview of the research population's treatment distribution data.

Statistical Analyses

The clinical data was analyzed by SPSS 18.0. The t-test was used to compare numeric variables with normal distributions from the independent groups. The comparison of categorical variables was performed by chi-square test. All data were processed in 2-tailed tests and $P < .05$ indicated statistical difference.

Results

Study characteristics

Two hundred and fifty-three ACLF patients were screened between January 1, 2017 and June 30, 2020. Among them, 106 patients were finally selected in this research, whose characteristics are presented in Table 1. We divided the following patients into TAF group (N = 40) and ETV group (N = 66) (Figure 1). The baseline is the period of time when patients have been selected in the study but have not yet started NAs treatment. There was no significant difference in baseline characteristics such as sex, age, chemical factors, HBV DNA load (Table 1).

Virological response

HBV DNA decreased rapidly in the TAF and ETV groups during treatment. We observed the HBV DNA load at the antiviral baseline at weeks 4 and 12. The loss rate of HBeAg at 12 weeks was also found. Compared with baseline, the HBV DNA load in the TAF group decreased from (5.64 ± 0.68)

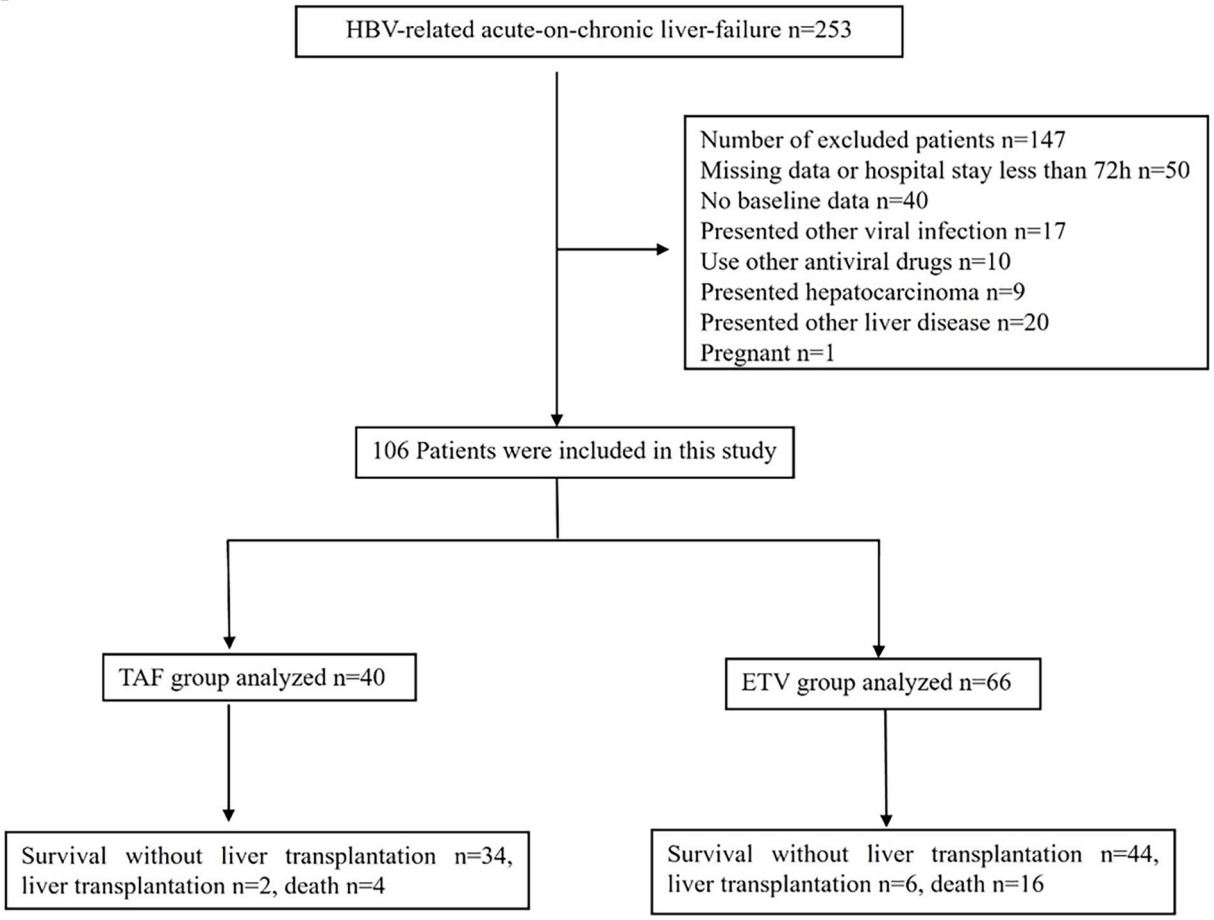

Figure 1. Patient inclusion flow chart.

$\log_{10}$ IU/mL to (3.55 ± 0.75) $\log_{10}$ IU/mL at 4 weeks; the HBV DNA load in the ETV group decreased from (5.38 ± 0.838) $\log_{10}$ IU/mL to (4.34 ± 0.62) $\log_{10}$ IU/mL ($P < .001$). The HBV DNA load decreased to (2.01 ± 1.04) $\log_{10}$ IU/mL in the TAF group and (3.53 ± 0.64) $\log_{10}$ IU/mL in the ETV group at 12 weeks ($P < .001$). We compared the HBV DNA load in the 2 groups and found that TAF rapidly reduced the HBV DNA load at 4 and 12 weeks (Figure 2). Moreover, 72.5% of patients in the TAF group and 60.6% of patients in the ETV group exhibited a decline in HBV DNA load of > 2 $\log_{10}$ IU/mL after 4 weeks ($P < .001$), and 25% and 13.64% of TAF and ETV patients exhibited a negative HBV DNA load after 12 weeks of antiviral therapy ($P < .001$), respectively.

Biochemical and serological responses

The Child-Turcotte-Pugh (CTP) scores and ALT level in the TAF and ETV groups were observed, and found that there was not significantly difference in the CTP scores between these 2 groups at baseline ($P = .79$). In addition, the CTP scores of TAF-treated patients were lower than that of ETV-treated patients at 4 weeks ($P < .01$). The change trend of CTP scores showed no difference between the 2 groups at week 12 ($P = .097$) (Figure 2). Compared with the baseline value, there was a significant difference in the CTP scores between TAF and ETV groups after 12 weeks treatment ($P < .0001$, $P < .0001$, respectively). There was not significantly difference in the ALT levels between 2 groups at baseline ($P = .437$). At 4 weeks, the ALT level in the TAF group were lower than that in the ETV group ($P = .023$), and the same results were found at 12 weeks ($P < .0001$).

Short-term mortality rate in the ACLF groups

We assessed the effect of ETV and TAF on short-term mortality in ACLF patients, and calculated the mortality in these 2 groups. No subjects died within the first 2 weeks. Five patients died and 6 patients were transferred to the liver transplantation department in the first 4 weeks, including 1 patient in the TAF group (2.50%) and 10 patients in the ETV group (15.15%) ($\chi = 4.286$, $P = .038$). Six patients (15%) in the TAF group and 22 patients (33.33%) in the ETV group passed away or underwent LT surgery at the end of 12 weeks. There was no significant difference in the percent survival between the 2 groups ($\chi = 3.53$, $P = .06$) (Figure 3). We also investigated the causes of

Table 1. Baseline characteristics of the enrolled patients.

	TAF (N = 40)	ETV (N = 66)	*P* VALUE
Age (years)	52.35 ± 6.58	53.70 ± 6.28	.902
Male (n%)	36 (90.0)	59 (89.39)	.261
HBeAg positive (%)	14 (35.0)	32 (48.48)	.833
HBV-DNA (log_{10} IU/mL)	5.64 ± 0.68	5.38 ± 0.838	.864
ALT (U/L)	424.79 (223-1110)	451.85 (221-1106)	.437
AST (U/L)	410.98 (219-881)	424.9 (227-773)	.106
TBIL (μmol/L)	378.79 (223.1-678.9)	380.69 (234.1-678.5)	.935
DBIL (μmol/L)	255.28 (112.7-347.3)	240.15 (101.3-342.3)	.300
ALB (g/L)	30.31 ± 2.72	30.65 ± 2.53	.509
Urea (mmol/L)	5.81 (3.21)	5.60 (2.77)	.865
Creatinine (μmol/L)	76.25 (29.81)	69.78 (23.46)	.552
eGFR (mL/min/1.73 m^2)	101.53 (40.45)	110.76 (50.87)	.296
Platelets ($\times 10^9$/L)	110.98 ± 27.48	116.62 ± 23.86	.268
PTA (%)	29.28 ± 5.54	28.48 ± 6.18	.509
Ascites (n%)	17 (42.5)	28 (42.42)	.922
Child-Pugh class C (n%)	8 (20)	9 (13.64)	.387
MELD score	23.57 ± 4.37	24.75 ± 3.36	.622

Data are number (%), mean ± standard deviation, or median (range).
Abbreviations: ALT, glutamic-pyruvic transaminase; AST, glutamic-oxalacetic transaminase; TBIL, total bilirubin; DBIL, direct bilirubin; ALB, albumin; PTA, prothrombin time activity; MELD, model for end-stage liver disease.

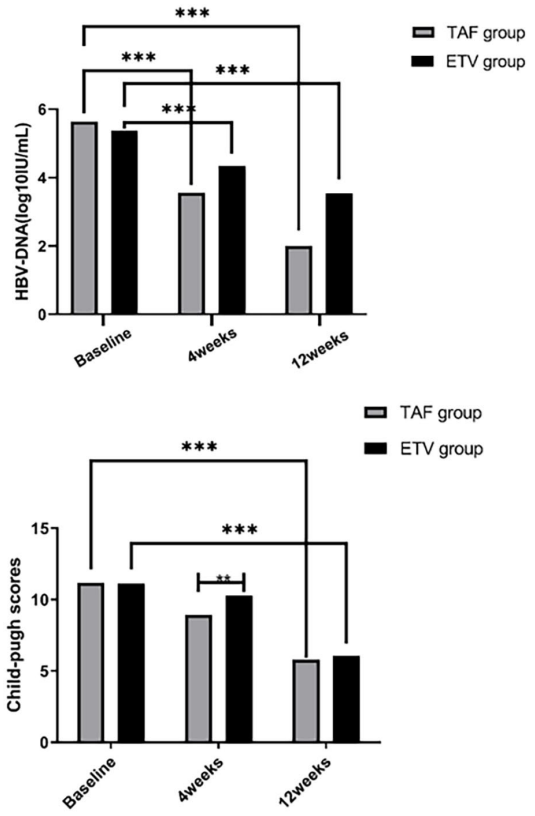

Figure 2. Dynamic changes in the HBV-DNA and Child-Pugh scores in the TAF and ETV groups. $^{**}P < .01$, $^{***}P < .001$.

death, including ACLF-related hepatorenal syndrome (HRS), spontaneous bacterial peritonitis (SBP), septicemia and variceal bleeding. Table 2 showed that the rates of liver-relevant complications in the 2 groups were similar ($P > .05$). The comparison of clinical features of patients with or without death or LT after 12 weeks of treatment is shown in Table 3. Cirrhosis, advanced age, CTP score, higher TBIL levels, model for end-stage liver disease (MELD) score, international normalized ratio (INR) of prothrombin time, ascites, lower platelet count, and hepatic encephalopathy were associated with mortality or LT (Table 3).

Safety and side effects

All patients tolerated therapy during the study period, and no patients adjusted the dose of antiviral agents or early discontinued antiviral therapy in this study. Moreover, none of the patients developed significant lactic acidosis, renal failure, or bone effects that could be attributed to TAF and ETV.

Discussion

HBV infection is the leading cause of ACLF in Asian countries. The current guidelines recommend that NAs should be started immediately in all HBV-infected patients at presentation.[21] Increasing studies has shown that NAs antiviral therapy is an effective treatment for patients with liver failure.[22,23]

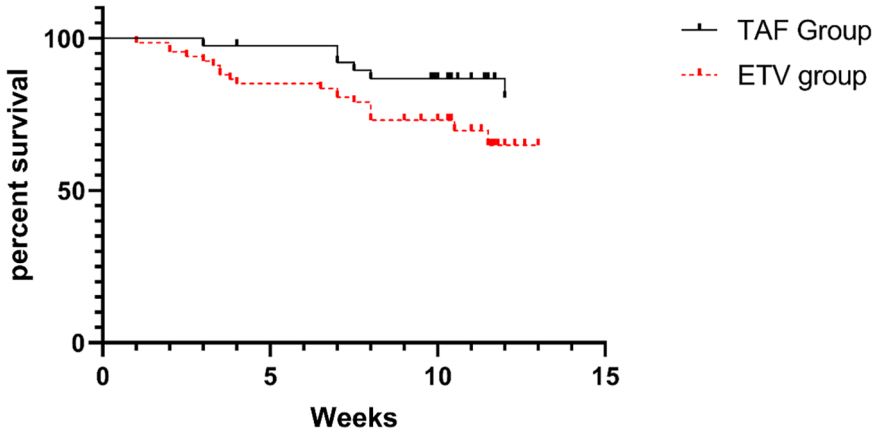

Figure 3. Cumulative survival analysis of patients in the TAF and ETV groups.

Table 2. Cause of death in the population.

CAUSE OF DEATH	TAF GROUP (N = 6)		ETV GROUP (N = 22)		*P*-VALUE
	N	%	N	%	
ACLF with HRS	2	33.33	6	27.27	.771
ACLF with SBP	1	16.67	6	27.27	.595
ACLF with variceal bleeding	1	16.67	6	27.27	.595
ACLF with septicemia	2	33.33	4	18.18	.423

Abbreviations: TAF, tenofovir alafenamide; ETV, entecavir; ACLF, acute-on-chronic liver failure; HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

Table 3. Comparisons of the baseline clinical features between patients by week 12 of treatment.

FEATURES	PATIENTS SURVIVED (N = 78)	DIED OR RECEIVED LT (N = 28)	*P* VALUE
Age (years)	52.17 ± 6.44	56.25 ± 5.49	<.0001
Male (n%)	70 (89.74)	25 (89.29)	.833
ETV/TAF	48/30	18/10	.492
HBeAg positive (n%)	46 (58.97)	16 (57.14)	.830
HBV DNA load (log_{10} IU/ML)	5.27 ± 0.80	5.53 ± 0.60	.119
ALT (U/L)	431.99 ± 169.50	448.04 ± 178.56	.673
AST (U/L)	384.99 ± 148.06	421.19 ± 157.42	.269
TBIL (μmol/L)	350.83 ± 100.16	459.39 ± 118.03	<.0001
INR	1.41 ± 0.34	1.65 ± 0.23	.001
Platelets ($\times 10^9$/L)	123.15 ± 20.02	90.89 ± 23.14	<.0001
PTA (%)	122.96 ± 20.25	90.89 ± 23.14	<.0001
Ascites (n%)	26 (33.33)	19 (67.86)	.002
CTP score	8.27 ± 2.65	10.79 ± 2.27	<.0001
MELD score	27.37 ± 5.37	30.27 ± 4.37	.003
Cirrhosis (n%)	15 (19.23)	19 (67.86)	<.0001
Hepatic encephalopathy (n%)	5 (6.41)	8 (28.57)	.005

Data are number (%), mean ± standard deviation.
Abbreviations: TAF, tenofovir alafenamide; ETV, entecavir; ALT, glutamic-pyruvic transaminase; AST, glutamic-oxalacetic transaminase; TBIL, total bilirubin; INR, international normalized ratio; CTP, Child-Turcotte-Pugh; MELD, model for end-stage liver disease.

TAF and ETV are the first-line NAs recommended by the International Liver Disease Guidelines.[24,25] TAF is a phosphonamidite prodrug of tenofovir. Long-term treatment with TAF is superior to TDF in terms of biochemical response rate. In addition, TAF is superior to TDF in terms of bone metabolism and renal safety.[26] The study found that TDF had better short-term efficacy (3 months) than ETV, but TDF may not be better than ETV during the 6-months treatment period in the viral suppression and liver function improvement.[27] There were no differences between the TDF and ETV treatment groups in the prevention of HCC in patients with chronic hepatitis B.[28-30] Therefore, this study was based on real-world research to explore the short-term efficacy of TAF and ETV in ACLF patients and found that TAF was superior to ETV in improving viral suppression, HBeAg loss, CTP score, and survival benefit in short-term treatment.

Our study found that in terms of the virological suppression, HBV DNA was inhibited faster in TAF group than in ETV group. 72.5% and 60.6% of patients in the TAF and ETV groups, respectively, presented a decline in HBV DNA load >2 $\log_{10}$ IU/mL after 4 weeks of treatment. In addition, 25% of patients in the TAF group exhibited negative HBV DNA load after 12 weeks of therapy. Our data also showed that the reduction rates of ALT and AST levels in TAF patients were much higher than that in ETV patients. As for the CTP scores, there was a significant declining trend in the TAF group compared with the ETV group throughout the course of therapy. The above results indicated that the antiviral efficacy of TAF was superior to that of ETV. Our study first proved that TAF could control HBV DNA and produce positive effects such as high ALT reduction rates and improved liver function in ACLF patients.

Moreover, TAF achieved a high survival rate in HBV-ACLF patients after the first 4 weeks. At 12 weeks, the death/LT rate in the TAF group was 15.00%, significantly lower than the ETV group (33.33%), which may be related to the faster improvement in biochemical markers and shorter duration of disease with early antiviral therapy with TAF. Other research groups confirmed that an early and rapid antiviral treatment contributes to reduce short-term mortality in patients with HBV-ACLF.[31] However, we found that the difference in survival rate at 12 weeks of treatment was not statistically significant, as indicated by power = 56.58% by power analysis, so this conclusion still needs to be revalidated by enlarging the sample size. The pathogenesis of ACLF is very complex. Casulleras et al[32] reported that massive release of inflammatory mediators led to serious tissue damage. Li et al[33] confirmed that HBV can aggravate immune-metabolism disorders in patients with HBV-ACLF. We hypothesized that despite antiviral therapy, the reduction of HBV DNA load to a lower level and the processes of immune and metabolic disorder would still drive the occurrence and progression of HBV-ACLF during the study period.

One previous study also examined important indicators of poor prognosis in patients with ACLF,[34-37] including cirrhosis, HBeAg positivity, HBV DNA load, high CTP score, MELD score, high AST, ALT and TBIL levels, INR, and low platelet counts. We also observed the relationship between the above factors and mortality in ACLF patients. Our data found that patients who received LT surgery or died were accompanied by older age, cirrhosis, high TB levels, CTP scores, MELD scores and INR, low platelet counts, ascites, or hepatic encephalopathy. Meanwhile, the safety and side effects of antiviral agents were observed in this study and found that no patients suffered serious adverse events such as lactic acidosis, renal impairment during treatment.

Our study has limitations, the main one being the short follow-up period, the small number of subjects in both groups, and no data on bone metabolism were collected. Therefore, further long-term follow-up studies and more large-scale randomized controlled studies are needed to validate these findings.

Conclusions

In conclusion, antiviral therapy with TAF is safe and effective in HBV-infected ACLF patients. Compared to the ETV group, TAF therapy could result in a rapid reduction of HBV DNA and a higher rate of ALT reduction in HBV-ACLF patients. Moreover, the CTP scores of patients in the TAF group tended to decrease significantly compared with those of the ETV group. TAF is better than ETV in improving survival and virological response in the treatment of HBV-ACLF.

Acknowledgements

None.

Author Contribution

Zhiqin Li: Conceptualization, Funding Acquisition, Resources, Supervision, Writing—original draft, Writing—review & editing. Ruirui Zhu: Investigation, Formal Analysis, Writing—original draft, Writing-review & editing. Jianxia Dong: Investigation, Formal Analysis, Writing—review & editing. Yinghui Gao: Investigation, Formal Analysis, Writing—review & editing. Jingya Yan: Investigation, Formal Analysis, Writing—review & editing.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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