

# Comparative role of tenofovir versus entecavir for treating patients with hepatitis B virus-related acute on chronic liver failure

Sharker M. S. Hossain<sup>1</sup>, Mamun A. Mahtab<sup>2</sup>, Dulal C. Das<sup>2</sup>,  
Sheikh M. Noor-E-Alam<sup>2</sup>, Ayub A. Mamun<sup>2</sup>, Md. Sakirul I. Khan<sup>3</sup>,  
Sheikh M. F. Akbar<sup>4</sup>, Md. Zakiur Rahman<sup>5</sup>, Salimur Rahman<sup>2</sup>

<sup>1</sup>Department of Medicine, Kurmitola General Hospital, Dhaka, <sup>2</sup>Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh, <sup>3</sup>Departments of Anatomy and Embryology, and <sup>4</sup>Gastroenterology and Metabology, Ehime University Graduate School of Medicine, Ehime, Japan, <sup>5</sup>Department of Primary Care and Microbiology, Brahminbaria Medical College, Brahminbaria, Bangladesh

## ABSTRACT

**Introduction:** The aim of the study was to compare the safety and efficacy of tenofovir versus entecavir for treatment of naive acute on chronic liver failure (ACLF) due to hepatitis B virus (HBV) (ACLF-B). **Methods:** Thirty-two patients aged 14-65 years were enrolled in the study. Diagnosis of ACLF was confirmed by clinical condition, biochemical analysis, and virological data. The causes of both chronic liver damages and acute insult in all patients were HBV. They were expressing HBV DNA in the sera, positive for IgM anti-HBc, had increased levels of serum bilirubin, compromised prothrombin time; and more than 50% patients had encephalopathy. The standard dose of tenofovir and entecavir was given. **Results:** The antiviral effects of tenofovir and entecavir were evident as most patients became negative for HBV DNA in the sera after 90 days of therapy. Also, the levels of serum bilirubin, CTP (Child-Turcotte-Pugh) and MELD (model for end-stage liver disease) score exhibited significant improvement due to antiviral therapy. Although the improvement of liver functions, and liver damages were detected in patients receiving both tenofovir and entecavir, the survival of the patients was significantly higher in those receiving tenofovir compared to entecavir-treated patients. **Conclusion:** This prospective study with limited number patients provides a challenge to assess the real potential of tenofovir over entecavir as therapeutic option for ACLF-B by conducting a multicenter clinical trial enrolling patient of different races and background.

**Keywords:** Acute on chronic liver failure, entecavir, HBV, tenofovir

## Introduction

Acute on chronic liver failure (ACLF) is an intractable liver disease characterized by rapid downhill course and high

short-term mortality.<sup>[1,2]</sup> However, ACLF is also unique as unlike decompensated liver cirrhosis, the course of ACLF can be reversed if proper management can be initiated early. In this context, management strategy of ACLF is of utmost importance. ACLF develops in patients with chronic liver disease due to one or more acute insult resulting in aberrant immune responses. The acute insult may arise from activation of or flare of the causative agent of the underlying chronic liver diseases, like same or similar viruses, alcohol or others.<sup>[1,2]</sup> These points are

**Address for correspondence:** Dr. Mamun A. Mahtab, Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Bangladesh. Postal Address: House # 109, Road # 4, Block # B, Banani, Dhaka-1213, Bangladesh.  
E-mail: shwapnil@agni.com

Received: 23-11-2020

Revised: 16-02-2021

Accepted: 10-04-2021

Published: 30-07-2021

### Access this article online

#### Quick Response Code:



Website:  
www.jfmpc.com

DOI:  
10.4103/jfmpc.jfmpc\_2299\_20

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Hossain SM, Mahtab MA, Das DC, Noor-E-Alam SM, Mamun AA, Khan MS, *et al.* Comparative role of tenofovir versus entecavir for treating patients with hepatitis B virus-related acute on chronic liver failure. J Family Med Prim Care 2021;10:2642-5.

of importance during the management of ACLF patients. In most Asian countries, hepatitis B virus (HBV) represents a major etiology of chronic infection leading to chronic liver diseases and flare of HBV represents acute insult of ACLF in a majority of patients of ACLF. If appropriate treatment can be initiated early in ACLF, favorable prognosis can be expected.<sup>[3]</sup> Several evolving therapies such as immune therapy, stem cells therapy and other modes of therapies have been proposed for almost all sorts of intractable liver diseases.<sup>[4-8]</sup> These therapeutic endeavors are yet to be tested in ACLF.

On the other hand, nucleoside analogs (NUC) are antivirals capable of blocking HBV replication by acting on polymerase enzyme, which is essential for viral replication. These drugs are also capable of restoring host immunity in these patients. Clinical trials have shown that NUCs can induce negativity or significant decrease of HBV-DNA, negativity and seroconversion to hepatitis B e antigen (HBeAg) and negativity of hepatitis B surface antigen (HBsAg).<sup>[3,9-14]</sup> NUCs have also resulted in containment of fibrosis and prevention of hepatocellular carcinoma (HCC) in some patients. Different NUCs have been used in patients with ACLF with an HBV background (ACLF-B).<sup>[13-15]</sup> Garg *et al.* have reported that tenofovir significantly reduces HBV-DNA levels, improves Child-Turcotte-Pugh (CTP) and Model for end stage liver disease (MELD) scores and reduces mortality in ACLF-B patients.<sup>[15]</sup>

## Methods

A total of 32 patients with ACLF were enrolled in this study. This study was conducted at the Department of Hepatology at Bangabandhu Sheikh Mujib Medical University, Dhaka. The study protocol was approved by the Institutional Review Board (IRB) of the university. Ethical approval was obtained on 15, November 2012. ACLF was diagnosed on the basis of Consensus Recommendation of Asia-Pacific Association of Study for the Liver (APASL). Chronic HBV infection was confirmed by HBsAg-positivity and negativity of all other causes of chronic liver diseases. The HBV as acute insult was shown by expression of anti-HBc Immunoglobulin M (IgM) and negativity of IgM antibody to hepatitis A virus (HAV), hepatitis C virus (HCV), drugs, alcohol and autoimmunity. Also, the patients were not on antiviral therapy.

Out of the 32 patients, 16 patients were treated by entecavir (0.5 mg/day) and the rest 16 patients received tenofovir (300 mg/day). The patients received entecavir or tenofovir on the basis of their consecutive appearance at the hospital. Informed written consent was obtained from all study subjects. In addition, all patients received standard medical care, including intravenous antibiotics, albumin infusion, supervised diet, lactulose and close-care monitoring as indicated. Enteral or parenteral nutrition was provided to those patients where caloric requirement was not fulfilled orally.

Clinical assessments and laboratory investigations were done weekly for the first 2 weeks and at the time of deterioration or 90 days after

therapy commencement. The primary endpoints were improvement in CTP and MELD scores and reduction in HBV-DNA levels and the secondary endpoint of the study was survival at 3 months. Date and cause were documented for each death.

Statistical analyzes were carried out by statistical package for social sciences version for windows (SPSS Inc., Chicago, IL, USA). Chi-square test was used to analyze the categorical variables. Student's, paired t-test, Mann-Whitney U-test and Wilcoxon test were used for continuous variables. *P* value (<0.05) was considered as statistically significant. The study was approved by the IRB of the Bangabandhu Sheikh Mujib Medical University, Dhaka.

## Results

The age of the patients were  $43.8 \pm 13.1$  years in tenofovir group and  $44.2 \pm 12.3$  years in the entecavir group. Majority of the patients were male in both tenofovir (93.7%) and entecavir group (81.3%). As shown in Table 1, all the patients in both tenofovir and entecavir groups had different degrees of ascites and evidences of clinical jaundice. Encephalopathy was found 10 (62.5%) in tenofovir group and 8 (50.0%) in entecavir group.

The biochemical data have been shown in Table 2 and there was no statistically significant difference regarding data of biochemical parameters between the two groups. All the patients were expressing HBV-DNA in the sera; HBeAg was positive in 6 (37.5%) patients in the tenofovir group and 7 (43.8%) in the entecavir group.

The study was designed to assess the effect of tenofovir versus entecavir in equal number of ACLF-B patients and the follow up was planned for 90 days. At 90 days, out of the total 32 patients, a total of 20 (62.5%) patients survived. Out of them, 13 (81.2%) received tenofovir for 90 days, whereas 7 (43.7%) belonged to the entecavir group. The difference was statistically significant ( $P < 0.05$ ) between two groups. Hepatorenal syndrome, hepatic encephalopathy, hypokalemia,

**Table 1: Distribution of the study patients by symptom and sign**

	Tenofovir group (n=16)		Entecavir group (n=16)		P
	n	%	n	%	
Symptom					
Yellowish eye and urine	16	100.0	16	100.0	-
Abdominal swelling and/or legs swelling	16	100.0	16	100.0	-
Ascites					
Mild	5	31.3	1	6.3	
Moderate	11	68.8	13	81.3	0.089
Severe	0	0.0	2	12.5	
Encephalopathy					
Present	10	62.5	8	50.0	0.476
Absent	6	37.5	8	50.0	

**Table 2: Baseline investigation of the study patients**

Parameters	Tenofovir group (n=16)		Entecavir group (n=16)		P
	Mean	±SD	Mean	±SD	
Total count (/mm <sup>3</sup> )	10580.0	±4818.6	10181.3	±3594.1	0.792
Range (min-max)	2010	-20000	4000	-85000	
Serum bilirubin (mg/dL)	19.8	±7.4	22.0	±5.7	0.353
Range (min-max)	9.8	-33.5	9.6	-30.3	
ALT (U/L)					
Mean rank	15.0		18.0		0.366
Sum of Ranks	240.0		288.0		
AST (U/L)					
Mean rank	15.2		17.8		0.429
Sum of ranks	243.0		285.0		
Prothrombin time (sec)	22.1	± 3.3	23.1	± 4.2	0.459
Range (min-max)	17.3	-29.5	17.0	-32.6	
INR	1.9	±0.3	2.0	±0.3	0.353
Range (min-max)	1.5	-2.5	1.6	-2.8	
Serum albumin (gm/dL)	2.1	±0.6	2.3	±0.5	0.313
Range (min-max)	1.2	-3.2	1.2	-2.9	
Serum creatinine (mg/dL)	0.98	±0.27	0.85	±0.31	0.215
Range (min-max)	0.3	-1.3	0.2	-1.2	
Sodium (mmol/L)	133.4	±5.3	134.1	±5.2	0.708
Range (min-max)	122	-141	125	-145	
Potassium (mmol/L)	4.1	±0.7	3.7	±1.0	0.199
Range (min-max)	3.2	-5.9	2.1	-5.2	
MELD score	25.0	±3.1	26.5	±2.0	0.114
Range (min-max)	19.0	-30.7	23.0	-29.8	
Child-Turcotte Pugh score	12.1	±1.3	12.0	±1.5	0.841
Range (min-max)	10	-14	9	-15	

hypokalemia plus hyponatremia, and septicemia were found to be related with death of patients in both the groups and there was not a statistically significant difference between these groups.

According to study design, the comparison of different clinical parameters and the effects of tenofovir versus entecavir was possible among the patients who survived; 13 in tenofovir group and 7 in entecavir group.

Regarding different clinical scores of liver damages, the CTP score was  $12.1 \pm 1.3$  and  $12.0 \pm 1.5$  at baseline in tenofovir and entecavir group, respectively. After 90 days of therapy, CTP score improved to  $7.2 \pm 1.3$  in tenofovir group and  $9.3 \pm 0.9$  in entecavir group. Similarly, MELD score improved due to antiviral therapy (baseline; tenofovir group vs entecavir group;  $25.0 \pm 3.1$  vs  $26.5 \pm 2.0$ ; after 90 days of therapy; tenofovir group vs entecavir group;  $9.3.0 \pm 3.2$  vs  $17.0 \pm 2.1$ ).

Also, the levels of serum bilirubin, albumin and INR (international normalized ratio) showed positive modulation due to therapy for 90 days by both tenofovir and entecavir. These biochemical parameters and indices of liver damages significantly improved due to both tenofovir and entecavir therapy ( $P < 0.05$ ). All patients of tenofovir group and entecavir group were expressing HBV-DNA at baseline before the start of therapy. After 90 days of therapy,

HBV-DNA became negative in all the 13 surviving patients of tenofovir group and 6 of 7 surviving patients of entecavir group.

## Discussion

There have been many approaches to address the management issue of ACLF. One approach is to target the pathogenesis of the disease as a whole irrespective of etiology. Recently, our group has shown the efficacy of granulocyte colony-stimulating factor and erythropoietin in improving the outcome of ACLF. However, in this particular study, we addressed the etiology of ACLF in improving management outcome.<sup>[16]</sup> The primary objective of this study was to assess if antiviral therapy improves the natural course of ACLF-B in the context of Bangladesh. The secondary objective was to assess the relative contribution of two commonly used antiviral drugs, tenofovir and entecavir in this context, in Bangladeshi patients.

In fact, the role of antiviral drugs in combatting HBV-ACLF has been shown by other investigators.<sup>[17-22]</sup> In most cases, they evaluated the efficacy of tenofovir or entecavir on the basis of their study design. The study presented here is a pilot study of prospective nature and the patients were enrolled to receive either tenofovir or entecavir on a consecutive basis. Although, a proper randomization was not possible in this type of study, this was designed to avoid bias in patient selection as much as possible.

Almost comparable antiviral potential of tenofovir and entecavir was recorded in this study comparing the HBV-DNA load before starting the therapy and 90 days after the therapy. Also, the effects of both tenofovir and entecavir on CTP and MELD scores as well as on serum bilirubin and albumin were shown. They positively modulated these parameters and a role of antiviral drug for management of ACLF is highlighted in this communication, as has been shown by others.

However, tenofovir revealed potent survival benefit in these patients (13 of 16 patients survived) compared to entecavir (7 of 16 patients survived) ( $P < 0.05$ ). These facts indicate that a multicenter study should be conducted in patients with various genotypes and races to assess the real impact of tenofovir in ACLF-B patients. Also, it remains to be assessed if an antiviral drug is effective in ACLF with only chronic liver diseases due to HBV or when the acute insult of ACLF is by HBV. There are some inherent limitations of this study, such as the comparatively small sample size. The survival of ACLF-B patients with tenofovir is very distinct, but the mechanisms underlying this could not be explored in this study. It represents the complexity of management of these patients and it may be postulated that tenofovir bears some immune regulatory properties in addition to antiviral potentials.

## Conclusion

ACLF is a life-threatening disease with high mortality and few recognized treatment options. Hepatitis B virus-related ACLF is

particularly of concern in the Asia-Pacific region because the main burden of liver disease related to hepatitis B is in this part of the world. From that perspective this study ushers new hope in the management of hepatitis B-related ACLF. It is also important for general practitioners to be updated about this disease and its management since they are the ones who provide the backbone of healthcare in a vast majority of the Asia-Pacific countries.

### Acknowledgement

The study was conducted at the Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

- Sarin SK, Kumar A, Almeida JA, Chawla YK, Fan ST, Garg H, *et al.* Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL). *Hepatology* 2009;3:269-82.
- Sarin K, Kumar C, Abbas Z, Amarapurkar D, Bihari C, Chan AC, *et al.* Acute-on-chronic liver failure: Consensus recommendations of the Asian Pacific Association for the Study of the Liver (APASL) 2014. *Hepatology* 2014;8:453-71.
- Philips CA, Sarin SK. Potent antiviral therapy improves survival in acute on chronic liver failure due to hepatitis B virus reactivation. *World J Gastroenterol* 2014;20:16037-52.
- Al Mahtab M, Mohammad Fazle Akbar S, Chandra Podder D, Kumar Saha P, Jahan M, Begum L, *et al.* Relationship between hepatitis B viral deoxyribonucleic acid load and hepatocellular carcinoma. *Euroasian J Hepatogastroenterol* 2014;4:66-7.
- Hussain MM, Al Mahtab M, Islam S, Ahmed N, Rahman S, Khan M. Therapy targeting stem cell in patients with decompensated cirrhosis of liver in a tertiary treatment care center of Bangladesh. *Euroasian J Hepatogastroenterol* 2017;7:111-2.
- Mahtab MA, Alam SMN, Moben AL, Raihan R, Alam MA, Rahim MA, *et al.* Therapy targeting stem cells in patients with decompensated cirrhosis of liver in a tertiary treatment care center of Bangladesh. *Euroasian J Hepatogastroenterol*, 2017;7:113-5.
- Al Mahtab M, Mf Akbar S, Begum M, Islam MA, Rahim MA, Noor-E-Alam SM, *et al.* Stem cell therapy for cirrhosis of liver in Bangladesh: Specific design compatible for developing country. *Euroasian J Hepatogastroenterol* 2018;8:121-5.
- Mf Akbar S, Al-Mahtab M, Khan SI. Nature of host immunity during hepatitis B virus infection and designing immune therapy. *Euroasian J Hepatogastroenterol* 2018;8:42-6.
- Wiegand J, van Bommel F, Berg T. Management of chronic hepatitis B; status and challenges beyond treatment guidelines. *Semin Liver Dis* 2010;30:361-7.
- Lin CL, Kao JH. Recent advances in the treatment of chronic hepatitis B. *Expert Opin Pharmacother* 2011;12:2025-40.
- Hadziyannis SJ. Milestones and perspectives in viral hepatitis B. *Liver Int* 2011;31(Suppl 1):129-34.
- Liaw YF. Natural history of chronic hepatitis B virus infection and long-term outcome under treatment. *Liver Int* 2009;29(Suppl 1):100-7.
- Lin SM, Sheen IS, Chien RN, Chu CM, Liaw YF. Long-term beneficial effect of interferon therapy in patients with chronic hepatitis B virus infection. *Hepatology* 1999;29:971-5.
- Garg H, Sarin SK, Kumar M, Garg V, Sharma BC, Kumar A, *et al.* Tenofovir improves the outcome in patients with spontaneous reactivation of hepatitis B presenting as acute-on-chronic liver failure. *Hepatology* 2011;53:774-80.
- Lin B, Pan CQ, Xie D, Xie S, Zhang X, Wu B, *et al.* Entecavir improves the outcome of acute on chronic liver failure due to the acute exacerbation of chronic hepatitis B. *Hepatology* 2013;7:460-7.
- Haque MN, Mahtab MA, Das DC, Noor-E-Alam SM, Mamun AA, Khan MS, *et al.* Effect of granulocyte colony-stimulating factor and erythropoietin on patients with acute-on-chronic liver failure. *Euroasian J Hepatogastroenterol* 2020;10:64-7.
- Lai J, Yan Y, Mai L, Zheng YB, Gan WQ, Ke WM. Short-term entecavir versus lamivudine therapy for HBeAg-negative patients with acute-on-chronic hepatitis B liver failure. *Hepatobiliary Pancreat Dis Int* 2013;12:154-9.
- Gao L, Trinh HN, Li J, Nguyen MH. Tenofovir is superior to entecavir for achieving complete viral suppression in HBeAg-positive chronic hepatitis B patients with high HBV DNA. *Aliment Pharmacol Ther* 2014;39:629-37.
- Sun LJ, Yu JW, Zhao YH, Kang P, Li SC. Influential factors of prognosis in lamivudine treatment for patients with acute-on-chronic hepatitis B liver failure. *J Gastroenterol Hepatol* 2010;25:583-90.
- Shi Y, He J, Wu W, Huang J, Yang Y, Sheng J, *et al.* The Efficacy and safety of nucleoside (t) ide analogues in the treatment of HBV-related acute-on-chronic liver failure: A meta-analysis. *Ann Hepatol* 2013;12:364-72.
- Cui YL, Yan F, Wang YB, Song XQ, Liu L, Le XZ, *et al.* Nucleoside analogue can improve the long-term prognosis of patients with hepatitis B virus infection associated acute on chronic liver failure. *Dig Dis Sci* 2010;55:2373-80.
- Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354:1001-10.