Role of tenofovir and telbivudine in treatment of hepatitis B related acute on chronic liver failure

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ABSTRACT

Introduction: ACLF is characterized by acute deterioration of liver function in patients with chronic liver disease. HBV is one of the most important causes of both acute insult and underlying chronic liver disease in ACLF. Reactivation of HBV is one of the common causes of ACLF in our region. ACLF requires multiple organ support and is associated with high short and medium term mortality. This is the reason why early, rapid reduction of HBV DNA is essential in treating ACLF-B. **Methods:** Consecutive patients of ACLF-B due to spontaneous reactivation of HBV (ALT> 5xULN or >2 x baseline and HBV DNA >20,000 IU/ml) were randomized into tenofovir group (300mg/day) and telbivudine group (600mg/day) along with standard medical treatment. Clinical and laboratory parameters were evaluated at baseline, day-7, day-14, day-30 and day-90. HBV DNA was evaluated at baseline and after three months of therapy. Primary end point was survival or death at three months. Secondary end point was improvement of liver function assessed by Child-Turcotte Pugh score and MELD score at three months. **Results:** 30 patients were enrolled in the study and 15 of them received tenofovir and 15 patients received telbivudine. Most of the baseline parameters showed no difference except serum AST and serum creatinine level that showed statistically significant difference between two groups. After antiviral therapy both groups showed significant clinical improvement along with CTP and MELD scores. However statistically significant improvement between tenofovir and telbivudine groups was only seen with MELD score. Survival rate was 80% in tenofovir group and 60% in telbivudine group, but this was not statistically significant. Low serum albumin at baseline was predictor of mortality. **Conclusion:** In patients of ACLF-B, antiviral therapy with both tenofovir and telbivudine improve liver function, but there is no statistically significant difference in survival between tenofovir and telbivudine.

Keywords: ACLF-B, HBV, telbivudine, tenofovir

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Introduction

Acute on chronic liver failure (ACLF) is characterized by acute deterioration of liver function in patients with chronic liver disease.[1] Asian-Pacific Association for the Study of Liver Disease (APASL) defines ACLF as an acute hepatic insult

manifesting as jaundice and coagulopathy, complicated within 4 weeks by clinical ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease/cirrhosis and is associated with a high 28-day mortality.[2]

Chronic hepatitis B virus (HBV) infection is a serious health problem worldwide. It has been estimated that more than 2,00,000 and 3,00,000 chronic HBV-infected people die worldwide each year due to HBV-related liver cirrhosis and hepatocellular carcinoma (HCC).[3] Some CHB patients develop acute exacerbations of HBV leading to liver failure and even death. ACLF-B is associated with mortality ranging from 30% to 70%.[4] Liver transplantation remains only definitive therapy for patients with ACLF, but limited donor availability, high cost and lack of availability limit its usefulness in the management of patients of ACLF. Besides many patients cannot eventually be transplanted due to hemodynamic instability, raised intracranial pressure, reduced cerebral perfusion pressure and bacterial and/or fungal infections. Mortality due to ACLF-B may be prevented with antiviral therapy drugs during the golden window period. It is assumed that antiviral drugs reduce HBV load and reduce hepatocyte death with improved survival outcome.[5] It has been shown that nucleos (t) ide analogues significantly reduce HBV DNA[6] with significantly lower 3-month mortality (44.8% vs. 73.3%) and also reduced reactivation (1.80% vs. 18.4%).[4]

Methodology

It was an observational study carried out on patients admitted at the in-patient department of Department of Hepatology, Bangabandhu Sheikh Mujib Medical University, Dhaka. Prior to the commencement of this study, the research protocol was approved by the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka. Clinically suspected patients of ACLF-B were admitted through the out-patient department. Necessary investigations were done after admission. Patients of ACLF-B of age >18 years of both sexes were enrolled as study population. Patients of ACLF-B with undetectable HBV DNA, underlying cirrhosis due to any other etiology other than HBV, patients testing positive for anti-HAV IgM, anti-HEV IgM and anti-HCV IgM, coexistent HCC, patients on antiviral, cytotoxic, or immune-modulator drugs and with co-morbidity like heart failure, malignancy and uncontrolled diabetes were excluded. In all, 30 patients were recruited. After enrollment, the patients were randomized into two groups (A and B). Group A was selected for tenofovir and group B for telbivudine. Tenofovir 300 mg orally daily was given on an empty stomach at least 1 h before or 2 h after breakfast and telbivudine 600 mg orally daily in the morning along with standard medical therapy and was followed up for next 3 months. Data were collected on admission, at days 7, 14, 30, and 90. In case of death, cause of death was evaluated.

Every patient was received standard medical treatment including intravenous antibiotics, lactulose, supervised diet, and close monitoring. Patients were also treated with albumin and proton pump inhibitors when required. Enteral or parenteral nutrition was ensured to those patients where caloric requirement was not fulfilled orally.

All data were presented as mean ± SD and analyzed by SPSS. Qualitative data were analyzed by Chi-square test and quantitative data were be analyzed by Student's *t*-test. The Wilcoxon rank sum was used to compare laboratory parameters and measurement obtained in the first and last visits. A statistically significant result was considered when *P* value < 0.05.

Table 1: Distribution of the study patients by demographic variables

Demographic variables	Tenofovir group (*n*=15)		Telbivudine group (*n*=15)		*P*
	n	%	*n*	%	
Age (in years)					
≤50	10	66.7	11	73.3	
>50	5	33.3	4	26.7	
Mean±SD	43.5	±13.5	44.0	±14.3	[a]0.922[ns]
Range (min, max)	23	, 70	25	,78	
Sex					[b]0.542[ns]
Male	13	86.7	14	93.3	
Female	2	13.3	1	6.7	
Marital status					
Married	14	93.3	15	100.0	[b]0.500[ns]
Unmarried	1	6.7	0	0.0	
Occupational status					
Service	8	53.3	10	66.7	
Farmer	2	13.3	1	6.7	[b]0.926[ns]
Teacher	1	6.7	1	6.7	
Business	2	13.3	2	13.3	
Housewife	2	13.3	1	6.7	

ns=not significant, [a]*P*-value reached from unpaired *t*-test, [b]*P*-value reached from Chi-square test

Table 2: Distribution of the study patients by symptom and sign

Presenting complaints	Tenofovir group (*n*=15)		Telbivudine group (*n*=15)		*P*
	n	%	*n*	%	
Yellow coloration of eye and urine	15	100.0	15	100.0	-
If yes (days)					-
Mean±SD	27.7	±11.6	33.7	±13.4	0.200[ns]
Range (min, max)	15	, 45	15	, 60	
Abdominal swelling and/or legs swelling	15	100.0	15	100.0	
If yes (days)					
Mean±SD	17.3	±9.1	22.0	±10.5	0.200[ns]
Range (min, max)	7	, 30	7	, 45	
Altered level of consciousness	4	26.7	3	20.0	
If yes (days)					
Mean±SD	4.2	±1.2	5.1	±1.9	0.132[ns]
Range (min, max)	3	, 7	5	,7	

ns=not significant

Table 3: Baseline investigations of the study patients					
Investigation	Tenofovir group (*n*=15)		Telbivudine group (*n*=15)		*P*
	Mean	±SD	Mean	±SD	
Hb (gm/dl)	11.2	±1.8	10.9	±1.5	0.623[ns]
Range (min-max)	7.5	, 14	8.5	, 14	
Total count (/mm³)	8726.7	±2229.5	9140.0	±3765.2	0.717[ns]
Range (min-max)	4000	, 12000	2100	, 16000	
Platelet count (/mm³)	188666.7	±102111.1	196333.3	±134874.4	0.861[ns]
Range (min-max)	50000	, 480000	40000	, 500000	
Alpha feto protein (ng/ml)	95.7	±227.9	66.2	±76.6	0.638[ns]
Range (min-max)	1.3	, 904	0.69	, 242	
ALT (U/L)	376.7	±211.1	249.6	±137.9	0.061[ns]
Range (min-max)	75	, 828	69	, 493	
AST (U/L)	328.5	±167.3	197.8	±110.6	0.017[s]
Range (min-max)	113	821	21	, 396	
Serum sodium (mmol/l)	132.0	±6.3	130.5	±8.3	0.581[ns]
Range (min-max)	119	, 142	113	, 144	
Serum potassium (mmol/l)	4.0	±0.8	3.9	±0.7	0.718[ns]
Range (min-max)	2.7	, 6.0	2.9	, 5.2	
Prothrombin time (s)	21.6	±3.4	21.3	±3.1	0.802[ns]
Range (min-max)	18	, 28.9	18.5	, 28.8	
INR	1.84	±0.27	1.80	±0.27	0.688[ns]
Range (min-max)	1.51	, 2.45	1.5	, 2.4	
Serum albumin (gm/dl)	2.5	±0.5	2.3	±0.5	0.282[ns]
Range (min-max)	1.5	, 3.4	0.93	, 3.0	
Serum creatinine (mg/dl)	1.1	±0.4	2.3	±0.5	0.001[s]
Range (min-max)	0.4	, 1.9	0.93	, 3.0	
Serum bilirubin (mg/dl)	19.3	±7.1	17.9	±7.9	0.613[ns]
Range (min-max)	9	, 32.1	9.1	, 35.3	
CTP score	12.2	±0.8	12.1	±0.8	0.734[ns]
Range (min-max)	11	, 14	11	, 14	
MELD score	25.3	±2.7	25.6	±5.4	0.848[ns]
Range (min-max)	21	, 29	21	, 39	
Esophageal varix	9 (60.0%)		11 (73.3%)		0.438[ns]

ns=not significant, s=significant, CTP=Child-Turcotte Pugh. *P*-value reached from unpaired *t*-test

Table 4i: Distribution of the study patients by HBeAg, anti-HBe and anti-HBc IgM					
Variables	Tenofovir group (*n*=15)		Telbivudine group (*n*=15)		*P*
	n	%	*n*	%	
HBeAg					
Positive	7	46.7	10	66.7	0.269[ns]
Negative	8	53.3	5	33.3	
Anti-HBe					
Positive	3	20.0	3	20.0	1.000[ns]
Negative	12	80.0	12	80.0	
Anti-HBc IgM					
Positive	9	60.0	8	53.3	0.704[ns]
Negative	6	40.0	7	46.7	

s=significant, ns=not significant. P-value reached from Chi-square test

Result

The mean age was found 43.5 ± 13.5 years in tenofovir group and 44.0 ± 14.3 years in telbivudine group. The majority patients were males in both groups [Table 1]: 100.0% patients in both groups had jaundice and ascites. Altered level of consciousness was found 26.7% in tenofovir group and 20% in telbivudine group [Table 2].

Mean Child–Turcotte Pugh (CTP) score was 12.2 ± 0.8 in tenofovir group and 12.1 ± 0.8 in telbivudine group, while mean Model of end stage liver disease (MELD) score was 25.3 ± 2.7 in tenofovir group and 25.6 ± 5.4 in telbivudine group [Table 3]. Virological status of the study patients is shown in Tables 4(i) and 4(ii).

All patients in both groups had coagulation failure. Liver failure was seen 86.7% in tenofovir group and 66.7% in telbivudine group, cerebral failure in 26.7% in tenofovir group and 20% in telbivudine group, kidney failure in 26.7% in tenofovir group and 20% in telbivudine group, while circulatory failure seen in 6.7% cases in both groups [Table 5].

Pretreatment CTP score was 12.2 ± 0.8 in tenofovir group and 12.1 ± 0.8 in telbivudine group. After 3 months of therapy, CTP score was 7.5 ± 2.0 in tenofovir group and 7.5 ± 1.9 in telbivudine group. The differences were not statistically significant (*P* > 0.05)

Table 4ii: Distribution of the study patients by HBV DNA in two groups at baseline

	Mean±SD		P
	Tenofovir group (*n*=15)	Telbivudine group (*n*=15)	
*HBV DNA (IU/ml)	4.1±1.0	4.8±1.5	0.143[ns]
Range (min-max)	2.3,5.8	2.2, 7.4	

*HBV DNA data value changed from LOG transformation. ns=not significant

Table 5: Distribution of the study patients by organ failure between two groups

	Tenofovir group (*n*=15)		Telbivudine group (*n*=15)		P
	n	%	*n*	%	
Liver failure					
Serum bilirubin >12 mg/dl	13	86.7	10	66.7	0.194[ns]
Coagulation failure					
INR >1.5	15	100.0	15	100.0	-
Cerebral failure					
HE	4	26.7	3	20.0	0.500[ns]
Kidney failure					
Serum creatinine >1.2 mg/dl	4	26.7	3	20.0	0.500[ns]
Circulatory failure					
DBP <70 mm Hg	1	6.7	1	6.7	0.758[ns]

s=significant, ns=not significant, HE=hepatic encephalopathy. P-value reached from Chi-square test

Table 6: CTP score at different follow-up two groups

CTP score	Mean±SD		P
	Tenofovir group (*n*=15)	Telbivudine group (*n*=15)	
Pretreatment	12.2±0.8	12.1±0.8	0.162[ns]
Day 7	11.2±1.2	11.8±1.1	0.164[ns]
Day 14	10.8±1.1	10.7±1.5	0.836[ns]
Day 30	9.2±1.5	9.1±1.4	0.851[ns]
Day 90	7.5±2.0	7.5±1.9	1.000[ns]

CTP=Child-Turcotte Pugh, ns=not significant

Table 7: MELD score at different follow-up in both groups

MELD score	Mean±SD		P
	Tenofovir group (*n*=15)	Telbivudine group (*n*=15)	
Pretreatment	25.3±2.7	25.6±5.4	0.848[ns]
Day 7	24.3±4.9	23.7±4.0	0.725[ns]
Day 14	23.2±3.9	21.2±4.8	0.271[ns]
Day 30	19.3±3.9	19.6±4.4	0.704[ns]
Day 90	12.08±2.84	14.41±1.76	0.043[s]

ns=not significant, s=significant

Table 8: Cause of death of the study patients

Outcome	Tenofovir group (*n*=3)		Telbivudine group (*n*=6)		P
	n	%	*n*	%	
HE	1	33.3	2	33.3	0.861[ns]
HRS	1	33.3	1	16.7	0.590[ns]
HE + HRS	1	33.3	2	33.3	1.000[ns]
HRS + variceal bleeding	0	0.0	1	16.7	0.477[ns]

ns=not significant, HE=hepatic encephalopathy, HRS=hepatorenal syndrome

between two groups [Table 6]. On the other hand, pretreatment MELD score was 25.3 ± 2.7 in tenofovir group and 25.6 ± 5.4 in telbivudine group. After 3 months of therapy, MELD score was 12.08 ± 2.84 in tenofovir group and 14.41 ± 1.76 in telbivudine group. MELD score significantly improved in tenofovir group than telbivudine group [Table 7].

Hepatic encephalopathy (HE) was the cause of death in 33.3% patients in both groups, hepatorenal syndrome (HRS) in 33.3% patients in tenofovir group and 16.7% in telbivudine group and HE plus HRS was found 33.3% in both groups. HRS and variceal bleeding was the cause of death in 16.7% in telbivudine group [Table 8]. Mean serum albumin was 2.6 gm/dl in the survivors and 2.4 gm/dl in those who died. Difference in serum albumin was statistically significant (*P* < 0.05) between the two groups.

Discussion

In this study, there is a significant improvement in CTP and MELD scores after 3 months of tenofovir therapy. Similarly, an Indian study showed significant improvement in MELD score in tenofovir group but not in placebo group in ACLF-B.[7] In our study, telbivudine group also showed a significant improvement in CTP and MELD scores. Although no significant difference was found in CTP score between two groups, MELD score showed a better improvement in tenofovir group than telbivudine, which was statistically significant.

After 3 months of antiviral therapy, 80% survived in tenofovir group and 60% in telbivudine group, but there was no statistically significant difference between the groups. A Chinese group has also demonstrated better survival in ACLF-B with telbivudine compared placebo.[8]

There is also significant clinical improvement (i.e., jaundice, ascites, and HE) in both groups, but not significant between groups. Our study did not observe any adverse event in either group. However, in two patients, renal dose adjustment for tenofovir was required due to HRS. Garg and colleagues have shown in their study that in ACLF-B, none of the patients developed significant renal failure that could be attributed to tenofovir.[7]

Various baseline parameters were analyzed to predict mortality. Serum bilirubin, INR, creatinine, HBV DNA and MELD score were higher among the dead but none of these were statistically significant. Serum albumin was higher in the survivor group, which was statistically significant.

Various evolving therapies have recently been shown for the management of chronic liver diseases. The present antiviral therapeutic approach with those novel approaches would be useful for the patients with ACLF.[9-12]

Conclusion

This study was done to compare the outcome with tenofovir and telbivudine in the patients with ACLF-B. It can be concluded that both groups experienced significant improvement of serum bilirubin, albumin, INR, and CTP and MELD scores. Both groups also have HBV DNA suppression. However, tenofovir therapy significantly improved MELD score compared to telbivudine therapy. Survival rate was also higher in tenofovir group than telbivudine group at 3 months, but this was not statistically significant.

Conflicts of interest

There are no conflicts of interest.

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