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Original Research Article

An Evaluation of the Effectiveness of Entecavir in Patients with Acute Chronic Hepatitis B liver Failure

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Abstract

Background: Entecavir has been shown to be effective in randomized controlled trials in highly selected patients with hepatitis B virus infection. Entecavir does not cure HBV and may not prevent complications of hepatitis B such as cirrhosis of the liver or liver cancer. The dose is double for people who have persistent hepatitis viremia (the presence of virus in the blood) while taking lamivudine or have lamivudine reesistance. It's recommended to take entecavir on an empty stomach, two hours before or after a meal. For some people, hepatitis B infection become chronic, meaning it lasts more than six months. Having chronic hepatitis B increases your risk of developing liver failour, liver cancer or cirrhosis a condition that permanently scares of the liver. ***Aims:*** This study aimed to evaluate the efficacy of in cronic hepatitis B patients in the real world setting. ***Methodology:*** In this study a total of 32 acute on chronic Hepatitis B liver failure patients (age > 18 years with both sexes but male predominant) were included in Hepatology department of Bangabandhu Sheikh Mujib Medical University, Dhaka during January 2013 to December 2015. The patients were randomized into two groups: Entecavir group (N=32) and followed at least for 03 months. ***Result:*** Table I shows the Majority 26(81.3%) patients were male and 6(18.7%) patients were female in entecavir group. Altered level of consciousness was found 14(43.8%) in entecavir group. Moderate ascites was found 26(81.3%) in entecavir group. Encephalopathy was found 16(50.0%) in entecavir group. The entecavir not statistically significant (p>0.05) of the groups. Table II shows Baseline investigation of the study patients (n=32). It was observed that mean total countwas found 10181.3±3594.1 /mm3 in entecavir group. Mean serum bilirubinwas found 22.0±5.7 mg/dl in entecavir group. Mean Rank ALT was found 18.0 U/L in entecavir group. Mean Rank AST was found 17.8 U/L in entecavir group. Mean prothrombin time was found 23.1±4.2 secant in entecavir group. Mean international normalized ratio was found 2.0±0.3 in entecavir group. Mean serum albumin was found 2.3±0.5 gm/dl in entecavir group. Mean serum creatinine was found and 0.85±0.31 mg/dl in entecavir group. Mean serum sodium was found 134.1±5.2 mmol/l in entecavir group. Mean serum potassium was found 3.7±1.0 mmol/l in entecavir group. Mean MELD scorewas found 26.5±2.0 in entecavir group. Mean Child Pugh scorewas found 12.0±1.5 in entecavir group. The mean entecavir was not statistically significant (p>0.05) of the groups. Liver function, Child Pugh score and MELD score improvement by three months after entecavir therapy: In entecavir patients, mean serum bilirubinwas found 22.0±5.7 mg/dl in pretreatment and 5.1±1.7 mg/dl at 90 days. Mean international normalized ratio was found 2.0±0.3 in pretreatment and 1.4±0.2 at 90 days. Mean serum albumin was found 2.3±0.5 gm/dl in pretreatment and 3.1±0.3 gm/dl at 90 days. Mean Child Pugh scorewas found 12.0±1.5 in pretreatment and 9.3±0.9 at 90 days. Mean MELD scorewas found 26.5±2.0 in pretreatment and 17.0±2.1 at 90 days. Negative Mean Ranks ALT was found 4.0 U/L and sum of Ranks 28.0 U/L. Positive mean rank and sum of rank 0.The difference were statistically significant (p<0.05) between two groups. Table VIII: Entecavir induced improvement of liver function, Child pugh score and MELD score three months after therapy (n=16). Conclusion: In conclusion entecavir is very potent anti-HBV drug with a high genetic barrier to resistance, highly effective in lamivudine-naïve CHB patients and most promising for their long term treatment but not very suitable for CHB patients harboring LAM resistant HBV mutants.

Keywords: Entecavir, hepatitis B, HBV.

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INTRODUCTION

The term ACLF was first used in 1995 to describe a condition in which two insults to the liver are operating simultaneously, one of them are being ongoing and chronic while the other being acute [1]. Acute on chronic liver failure (ACLF) is an increasingly recognized distinct disease entity encompassing an acute deterioration of liver function in patients with chronic liver disease [2]. Although there are no widely accepted diagnostic criteria for ACLF, two representative consensus definitions are commonly used. Asia-Pacific Association for the Study of Liver Disease has defined 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 high 28-day mortality [3]. Acute on chronic liver failure (ACLF) is currently recognized as a specific entity characterized by acute deterioration of liver function in the context of compensated or even decompensated, but hitherto stable, cirrhosis [4]. Chronic hepatitis B virus (HBV) infection is a serious health problem because of its worldwide distribution and its potential adverse sequelae, including cirrhosis and hepatocellular carcinoma (HCC) [5]. It was estimated that more than 200,000 and 300,000 chronic HBV carriers worldwide die of liver cirrhosis and HCC, respectively, each year [6]. On the other hand short term prognosis of patients with spontaneous severe acute exacerbation of CHB leading to ACLF-like presentation is extremely poor, with a high mortality ranging from 30% to 70% [7]. The acute episodes vary depending on the geographic region and the population under study. They include both infectious and noninfectious causes. It was also appreciated that the major etiologic agents responsible for precipitating ACLF are quite distinct in the East and the West. Alcohol and drugs constitute the majority of acute insults in the West, where as infectious etiologies predominate in the East. The difference in the etiologies of ACLF between the East and the West reflects the differences in the etiology of the underlying chronic liver disease in the different geographic regions as well. Among the infectious etiologies, reactivation of hepatitis B virus (HBV) infection is one of the major causes of ACLF in the Asian region [8]. Reactivation may be either spontaneous or due to intensive chemotherapy or immunosuppressive therapy [9], immune restoration after highly active antiretroviral therapy for HIV [10], treatment related [11], or reactivation of the occult HBV infection by rituximab (anti-CD20)-based chemotherapy [12]. Similarly, reactivation of hepatitis C virus infection has also been reported, especially after immunosuppressive therapy [13]. The other very important infectious etiology of the acute event is super infection with hepatitis E virus, predominantly in patients in the Indian subcontinent [14]. Mahtab *et al*. [15], has reported that HEV is also the commonest acute insult for ACLF in Bangladesh. Various bacterial, parasitic, and fungal infections may affect the liver. Spirochetal, protozoal, helminthic, or fungal organisms may directly infect the liver, whereas bacterial or parasitic infection may spread to the liver from other sites [16]. These infections may lead to liver failure in patients with underlying chronic liver disease. Among the noninfectious etiologies, alcoholic hepatitis is the major cause of acute deterioration in stable known or unknown chronic liver diseases, more often in the western countries [17]. Hepatotoxic drugs and herbal indigenous medicines are important causes for liver failure in the Asia–Pacific region [18]. Acute variceal bleeding has been included as one of the events to define hepatic decompensation in the natural history of cirrhosis [19]. Recent publications from the West have shown that major surgical procedures could pose an acute insult to liver [20].

METHODOLOGY

The study was carried outfrom From January 2013 to December 2015Randomized clinical trial at the Inpatient Department of the Department of Hepatology, BSMMU, while patients were admitted through the Outpatient Department of the same Department. Acute on chronic hepatitis B liver failure patients (age >18 years of both sexes) were enrolled as study population. Inclusion criteria: Age: > 18 years, Sex: both sexes, Bilirubin ≥ 5 mg/dl, Coagulopathy (international normalized ratio ≥ 1.5), Complicated by ascites and/or encephalopathy within 4 weeks. Patients with chronic liver disease due to HBV infection.

Acute insult by reactivation of HBV or HBV flare. Exclusion criteria: Age <18 years, Acute insult caused by HEV, HAV, drugs, alcohol etc. Decompensated cirrhosis of liver. Acute on chronic hepatitis B liver failure patient with undetected HBV DNA. Patients with chronic liver disease due to HCV infection, NASH etc. Coexistent hepatocellular carcinoma (HCC), Serum creatinine >1.5 mg/dl. Pregnancy Patients on antiviral drugs, Patients on immunomodulator therapy, Patients on cytotoxic/immunosuppressive therapy, Co-morbidity like heart failure, any malignancy, uncontrolled diabetes etc. Patients unwilling to take part in the study. Sampling technique: Purposive (judgment) sampling, Sample size: 32. Patient with clinical suspicion of ACLF were admitted in Department of Hepatology from Outpatient Department. The diagnosis of ACLF was confirmed after proper evaluation and investigations. The study was conducted fulfilling all criteria of good clinical practice according to the Declaration of Helsinki. Written informed consent in Bengali for inclusion into the trial was obtained from all study subjects. Shortly after admission, the patients were enrolled and randomized into two groups with one group receiving tenofovir and other group receiving entecavir. The potential benefits and risks of the use of tenofovir and entecevir and the non-availability of liver transplantation facilities were explained to them. Every

alternate patient received tenofovir and entecavir respectively. Tablet tenofovir (300mg) was given orally daily to half of the patients while the other half received tablet entecavir (0.5mg) orally daily according to APASL ACLF Management Guideline of 2014. Both drugs were administered in empty stomach (at least 2 hours before or 2 hours after meals) along with standard medical therapy and the patients were followed up for 03 months. Permanent address, present address, mobile and land phone number of all patients were recorded and close liaison was maintained with all patients. Patients and/or their relatives were contacted over telephone and by post reminding of them of their follow up visits, in case they were not admitted in the Department of Hepatology, BSMMU at the time of a particular follow up. All adverse events were recorded describing their nature (local or systemic), intensity and the necessary treatment to relieve them according to WHO guidelines (WHO technical report series No. 850, 1995), the intensity degrees of which are as follows: No adverse reaction, Mild; it does not require treatment, Moderate; it requires treatment and disappears with treatment, Severe; it puts the patient's life in danger or produces death. It requires prolonged hospitalization, produces significant or persistent disability or congenital malformations. Dose modification of tenofovir and entecavir was done according to CrCL level in appropriate cases. In case of tenofovir group, If CrCL 30 to 49 ml/min: 300 mg orally every 48 hours, If CrCL 10 tO 29 ml/min:300 mg orally every 72 to 96 hours. In case of entecavir group with renal Impairment; if CrCL> 50 usual dose of entecavir was 0.5mg once daily, if CrCL 30 to < 50, dose was 0.25 mg once daily or 0.5 mg every 48 hours, if Cr CL 10 to < 30 , dose was 0.15 mg once daily, or 0.5 mg every 72 hours. Close liaison was maintained with colleagues at Government hospitals (upozilla health complexes and sadar hospitals) closest to the residences of the study subjects as well as with colleagues of private hospitals, where they received treatment, had they fallen ill after discharge from the Department of Hepatology, BSMMU. Cause, time and date of death was recorded in case of every study subject who expired from the hospital records of Department of Hepatology, BSMMU or respective Government or private hospitals in case of deaths of every study subject. Data were collected using a preformed data collection sheet (questionnaire). Base line information was collected from the patient and/or their relatives. All information regarding clinical features was recorded in a data collection sheet. Fasting plasma glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, prothombin time (INR), serum albumin, serum creatinine, serum electrolyte, CBC and alpha fetoprotein (AFP) were done at the Department of Biochemistry, BSMMU, while abdominal ultrasound and upper gastrointestinal (GI) endoscopy were done at the Department of Radiology and Imaging and Department of Hepatology, BSMMU respectively. Severity of the liver disease was assessed by Child-Turcotte Pugh score (CTP) and model for endstage liver disease (MELD) score. Virological tests were done at Department of Virology, BSMMU. For the diagnosis of HBV serology included tests for hepatitis B surface antigen (HBsAg).

Data were collected with a structured form filled by the investigator after interviewing with the sample unit and were presented as tables. Statistical analysis was carried out by the software SPSS version 23.

RESULT

Table I shows the Majority 26(81.3%) patients were male and 6(18.7%) patients were female in entecavir group. Altered level of consciousness was found 14(43.8%) in entecavir group. Moderate ascites was found 26(81.3%) in entecavir group. Encephalopathy was found 16(50.0%) in entecavir group. The entecavir not statistically significant ($p>0.05$) of the groups. Table II shows Baseline investigation of the study patients (n=32). It was observed that mean total countwas found 10181.3±3594.1 /mm^3 in entecavir group. Mean serum bilirubinwas found 22.0±5.7 mg/dl in entecavir group. Mean Rank ALT was found 18.0 U/L in entecavir group. Mean Rank AST was found 17.8 U/L in entecavir group. Mean prothrombin time was found 23.1±4.2 secant in entecavir group. Mean international normalized ratio was found 2.0±0.3 in entecavir group. Mean serum albumin was found 2.3±0.5 gm/dl in entecavir group. Mean serum creatinine was found and 0.85±0.31 mg/dl in entecavir group. Mean serum sodium was found 134.1±5.2 mmol/l in entecavir group. Mean serum potassium was found 3.7±1.0 mmol/l in entecavir group. Mean MELD scorewas found 26.5±2.0 in entecavir group. Mean Child Pugh scorewas found 12.0±1.5 in entecavir group. The mean entecavir was not statistically significant ($p>0.05$) of the groups. Liver function, Child Pugh score and MELD score improvement by three months after entecavir therapy: In entecavir patients, mean serum bilirubinwas found 22.0±5.7 mg/dl in pretreatment and 5.1±1.7 mg/dl at 90 days. Mean international normalized ratio was found 2.0±0.3 in pretreatment and 1.4±0.2 at 90 days. Mean serum albumin was found 2.3±0.5 gm/dl in pretreatment and 3.1±0.3 gm/dl at 90 days. Mean Child Pugh scorewas found 12.0±1.5 in pretreatment and 9.3±0.9 at 90 days. Mean MELD scorewas found 26.5±2.0 in pretreatment and 17.0±2.1 at 90 days. Negative Mean Ranks ALT was found 4.0 U/L and sum of Ranks 28.0 U/L. Positive mean rank and sum of rank 0.The difference were statistically significant ($p<0.05$) between two groups. Table VIII: Entecavir induced improvement of liver function, Child pugh score and MELD score three months after therapy (n=16

Table-I: Sex distribution of the study patients

Sex	n=32	%
Male	26	81.3
Female	6	18.7
Total	32	100

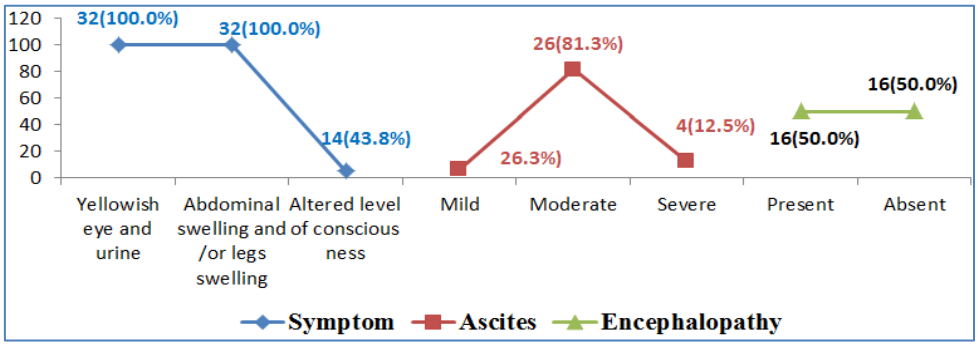

Fig-I: Distribution of the study patients bysymptom and sign (n=32)

Table-III: Entecavir induced improvement of liver function, Child pugh score and MELD score three months after therapy (n=32)

Variable	Pretreatment n=32		At 90 days (n=14)		P value
	Mean	±SD	Mean	±SD	
S. Bilirubin (mg/dl)	22.0	±5.7	5.1	±1.7	a0.001s
INR	2.0	±0.3	1.4	±0.2	a0.001s
Serum albumin (gm/dl)	2.3	±0.5	3.1	±0.3	a0.001s
Child-Turcotte Pugh score	12.0	±1.5	9.3	±0.9	a0.001s
MELD score	26.5	±2.0	17.0	±2.1	a0.001s

s= significant [a]P value reached from paired t-test [b]P value reached from Wilcoxon test

Table-II: Baseline investigation of the study patients (n=32)

Symptom	Entecavir		P value
	Mean	±SD	
Total count (/mm^3)	10181.3	±3594.1	[a]0.792[ns]
Range (min-max)	4000	-85000	
Serum bilirubin (mg/dl)	22.0	±5.7	[a]0.353[ns]
Range (min-max)	9.6	-30.3	
ALT(U/L)			[b]0.366[ns]
Mean Rank	18.0		
Sum of Ranks	288.0		
AST (U/L)			[b]0.429[ns]
Mean Rank	17.8		
Sum of Ranks	285.0		
Prothrombin time (sec)	23.1	± 4.2	[a]0.459[ns]
Range (min-max)	17.0	-32.6	
INR	2.0	±0.3	[a]0.353[ns]
Range (min-max)	1.6	-2.8	
Serum albumin (gm/dl)	2.3	±0.5	[a]0.313[ns]
Range (min-max)	1.2	-2.9	
Serum creatinine (mg/dl)	0.85	±0.31	[a]0.215[ns]
Range (min-max)	0.2	-1.2	
Sodium (mmol/l)	134.1	±5.2	[a]0.708[ns]
Range (min-max)	125	-145	
Potassium (mmol/l)	3.7	±1.0	[a]0.199[ns]
Range (min-max)	2.1	-5.2	
MELD score	26.5	±2.0	[a]0.114[ns]
Range (min-max)	23.0	-29.8	
Child-Turcotte Pugh score	12.0	±1.5	[a]0.841[ns]
Range (min-max)	9	-15	

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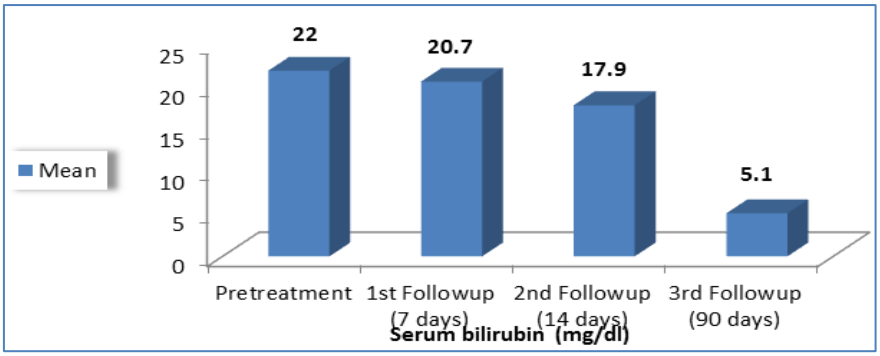

Fig-II: Showing Serum bilirubin in different follow up

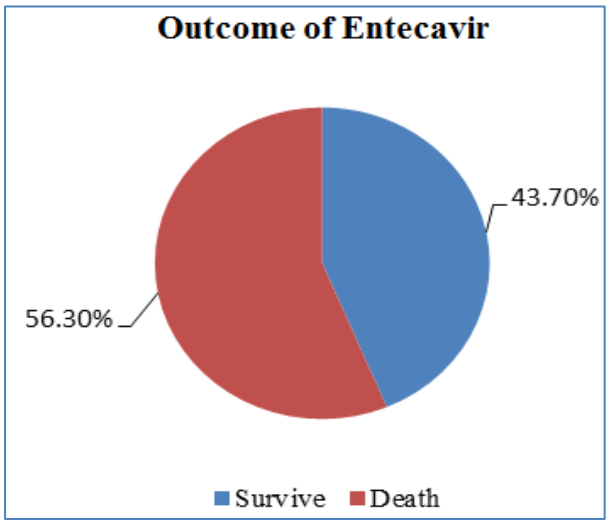

Fig-III: Showing outcome of evaluation of the effectiveness of Entecavir in patients with acute on chronic hepatitis B liver failure

DISCUSSION

A total of 32 acute on chronic hepatitis B liver failure patients (age > 18 years with both sexes) in Hepatologydepartment of Bangabandhu Sheikh Mujib Medical University, Dhaka, during January 2013 to December 2015, were included in this study. Patients were randomized into two groups by one group received Tenofovir and other group received Entecavir. Both groups received standard of care and appropriate nutritional support including albumin, Intravenous antibiotics and Lactulose etc. as indicated.

In this study it was observed that more than two third 11(68.8%) patients belonged to age ≤50 years in tenofovir group and 13(81.3%) in entecavir group. The mean age was 43.8±13.1 years in tenofovir group and 44.2±12.3 years in entecavir group. No difference was found between the two groups. Similar age distribution has been seen in clinical trials involving HBV-ACLF patients by Lai *et al*. [21], Garg *et al*. [22], and Chang *et al*. [23]. In this current series male predominance was seen in both groups, (93.7%) in tenofovir group and 81.3% in entecavir group. Similar observations regarding male predominance has also been observed in studies by Guzelbulut *et al*. [24], Garg *et al*. [1], Bommel *et al*. [25] Lai *et al*. [21] and Chang *et al*. [23]. In this series all baseline investigation reports were almost similar between the two groups and no significant ($p>0.05$) difference was observed. Similar observations were made in studies with HBV related ACLF patients by Garg *et al*. [22] and Chang *et al*. [23]. Similarly no significant difference ($p>0.05$) was seen in the size of oesophagealvarices of the patients in the two groups which is similar to the study by Garg *et al*. [22]. In terms of the primary serological outcomes, Zuo *et al*. [26] found that the entecavir was similar to tenofovir in terms of HBsAg loss and HBe Agseroconversion both having minimal influence on both HBsAg loss and HBeAgseroconversion. In this current study HBeAg was found to be positive in 37.5% patients in tenofovir group and 43.8% in entecavir group. HBV DNA was found to be >20000 IU/ml in 50% in tenofovir group and 56.2% in entecavir group, which were almost alike. In the study by Zuo *et al*. [26] 65 of the 128 patients (50.8%) non-naive patients treated with entecavir had HBV-DNA levels<400 copies/ml, whereas 83 of 138 patients (60.1%) in the tenofovir group had HBVDNA levels<400 copies/ml. In their study Guzelbulut *et al*. [28] had HBeAg positivity in 6 (30.0%) in tenofovir group and 20.8% in entecavir group. The difference was not statistically significant ($p>0.05$). Garg *et al*. [22] observed the mean HBV DNA $7.5x10^5$ IU/ml, with range from $1.7x10^4$-$3.1x10^7$ IU/ml. Bommel *et al*. [25] showed HBeAg-positive in 65.0% in tenofovir group. The above findings are comparable with the current study.Entecavir and tenofovir are currently preferred for the treatment of decompensated cirrhosis because of greater antiviral potency and a high genetic barrier to resistance [29]. In a multinational study, 191 patients with decompensated cirrhosis (mean CTP score 8.8, Model for End-Stage Liver Disease [MELD] score 17.1) were treated with entecavir or adefovir for up to 96 weeks [30]. Entecavir was more effective in viral suppression, and also caused improvement or stabilization in both scores. However there are few direct comparisons between entecavir and tenofovir in decompensated cirrhosis. In a randomized, controlled study by Liaw *et al*. [30] of 112 patients with mildly decompensated cirrhosis (average MELD score 11, CTP score 7), HBV DNA at week 48 was undetectable in 71% of tenofovir-treated patients and 73% treated with entecavir. In this present study in tenofovir

patients, mean Child Pugh score was 12.1±1.3 in pre-treatment and 7.2±1.3 at 90 days, while mean MELD score was 25.0±3.1 in pre-treatment and 9.3±3.2 at 90 days. It was observed that S. Bilirubin, INR, ALT, Child-Turcotte Pugh score and MELD score had significant ($p<0.05$) decline at 90 days in tenofovir group. Serum albumin increased significantly ($p<0.05$) at 90 days in this group, which indicates that the present study showed tenofovir significantly improves serum bilirubin, serum albumin, Child-Turcotte Pugh (CTP) and model for end stage liver disease (MELD) scores 3 months after therapy. In the surviving patients Garg *et al*. [1] found there was a significant improvement in the, serum bilirubin, Child-Turcotte Pugh (CTP) and model for end stage liver disease (MELD) scores in the tenofovir group, whereas these parameters did not change significantly in the placebo group. In this present study it was observed that in tenofovir group, all patients had detectable HBV DNA during pretreatment and 13 patients was undetected HBV DNA at 90 days ($p<0.05$). Garg *et al*. (2011) reported that tenofovir significantly reduced HBV DNA levels from baseline 6.64 log to 4.07 ($P<0.05$) at day 15 and to 3.04 at day 90 ($P<0.05$). In the placebo group, out of the 10 surviving patients at day 15 HBV DNA values could be obtained in nine. None of these nine patients had >2 log reduction at day 90.

In this current study, on the other hand, it was observed that among entecavirtreated patients mean Child Pugh score improved from 12.0±1.5 in pre-treatment to 9.3±0.9 at 90 days ($p<0.05$). Similarly mean MELD score also improved from 26.5±2.0 at pretreatment to 17.0±2.1 at 90 days ($p<0.05$). It was further observed that s. bilirubin, INR and ALT declined significantly ($p<0.05$) at 90 days in entecavir group with serum albumin increasing significantly ($p<0.05$) at 90 days in this group. Bingliang *et al*. [31] showed that entecavir improves the outcome of acute on chronic liver failure due to the acute exacerbation of chronic hepatitis B. Entecavir treatment significantly improved disease severity scores including Chid–Turcotte Pugh(CTP),model for end-stage liver disease (MELD),and MELD sodium (MELD–Na). In the study by Lai *et al*. [37] entacavir was shown to rapidly and significantly improve liver functions tests.

In this present study it was observed that in entecavir arm, all patients had detectble HBV DNA at baseline and 6 had undetected HBV DNA at 90 days. The difference was statistically significant ($p<0.05$) between two groups. Bingliang *et al*. [21] showed all entecavir treated subjects achieved an undetectable HBV DNA level (<500 copies/ml; 100%vs 7.9%, $p<0.001$). In the study by Guan and Lui [32] nearly 50% of the entecavir treated patients had a clinically significant decrease in their CTP score of >2 points. However 12 patients (22.0%) showed no change in their CTP score and 4 patients had aggravation or their liver disease with worsening CTP scores. Similarly in another study, Lai *et al*. [21] reported that entecavir resulted in significantly higher rates of histologic, virologic and biochemical improvements compared to lamivudie in patients with HBeAg-negative chronic hepatitis B who had not previously received a nucleoside analogue. The findings are comparable with the current study. HBV-ACLF has been associated with extremely high short term mortality ranging from 30-70% according to reports documented by Tsubota *et al*. [7] and Tsang *et al*. [19], but patients receiving nucleos(t)ide analogues had significantly lower short-term mortality than those in control group. In this present study it was observed that at 90 days, 81.2% in tenofovir group were alive compared to 43.7% in entacavir group ($p<0.05$). Wong *et al*. [34] also observed that entecavir prevents disease progression in ACLF patients. However Chen *et al*. [33] did not observe any improvement in MELD score and liver function, including serum bilirubin, in 55 entecavir treated HBV decompensated cirrhotics with acute exacerbation of HBV. In this study short-term suppression of HBV replication offered no benefit on survival. In this present study it was observed that serum bilirubin level was also similar between two groups at pretreatment, 1st follow up (7 days) and 2nd follow up (14 days) but declined from pretreatment to 1st follow up (7 days) and 2nd follow up (14 days) in both groups. In 3rd follow up, serum bilirubin was found 1.9±2.0 mg/dl in tenofovir group and 5.1±1.6 mg/dl in entecavir group ($p<0.05$). Serum bilirubin level declined significantly more in tenofovir group. Chen *et al*. [35] treated 55 patients with severe acute exacerbation of HBV leading to decompensation with entecavir, comparing them with 74 other patients who were not treated with nucleoside analogs. Entecavir greatly reduced HBV replication in different periods of therapy ($P<0.05$), but the MELD score and liver function (ALT, albumin, bilirubin and PT) showed no significant change. These results suggested that short-term suppression of HBV replication with entecavir may not slow down the progression of liver failure in patients with chronic severe hepatitis B. Zuo *et al*. [26] has shown that tenofovir was not significantly better than entecavir with regard to reducing the serum HBV-DNA at 24 weeks, but tenofovir had better overall efficacy than entecavir at 48 weeks. In addition, our subgroup analysis comparing treatment naïve and non-naïve patients indicate that for treatment naïve patients, tenofovir was significantly better than entecavir in suppressing HBV-DNA. There was however no difference for NUC non-naïve patients. These findings are consistent with several other studies. Both Gao *et al*. [36] and Lin *et al*. [31] showed that tenofovir was significantly more effective than entecavir at achieving complete viral suppression in HBeAg-positive, nucleos(t)ide-naïve chronic HBV patients with a high baseline HBV-DNA level (HBV-DNA load >6 log10 IU/mL). Finally, meta-analysis by Wiens *et al*. [37] concluded that tenofovir had the highest probability of achieving undetectable HBV DNA at 12 months of

treatment for HBeAg-positive patients out of the 5 approved nucleos(t)ide analog therapies for chronic HBV. Several studies have indicated that if the reduction in DNA of >2 logs could be achieved within 2 weeks, the survival could be improved. This could be related to the suppression of hepatocellular necrosis and cytokine release [38]. In this study it was observed that in 3rd follow up, 13 (100.0%) patients was found undetected HBV DNA in tenofovir group and 6(85.7%) in entecavir group (p>0.05). Although Menne *et al*. [39] documented that tenofovir is highly effective in suppressing HBV replication, Guzelbulut *et al*. [40] reported that entecavir and tenofovir are similarly effective in nucleos(t)ide-naive chronic hepatitis B patients with a high viral load and/or high fibrosis scores. All these support our observation of better survival in HBV-ACLF with anti-virals as well as the better outcome with tenofovir compared to entecavir. In their study, Chen *et al*. [35] showed no significant change in MELD score and parameters of liver function (albumin, bilirubin and PT) with entecavir. These results suggested that short-term suppression of HBV replication may not slow down the progression of liver failure in patients with severe acute exacerbation of HBV leading to decompensation. We have also similar observation where tenofovir was clearly superior to entecavir in terms of survival of HBV- ACLF patients. In this current study it was observed that on 1st follow up, Child-Turcotte Pugh score was 10.4±1.5 in tenofovir group and 11.9±1.4 in entecavir group. At 3rd follow up, Child-Turcotte Pugh score was 5.8±1.1 in tenofovir group and 9.3±0.9 in entecavir group. Which were statistically significant (p<0.05) between two groups. Garg *et al*. [22] observed in the surviving patients, there was a significant improvement in the Child-Turcotte Pugh (CTP) and significant decline in the HBV DNA levels in the tenofovir group, whereas these parameters did not change significantly in the placebo group. However, Shouval [41] observe in HBV-ACLF patient wih Entecavir; there is prolonged jaundice, encephalopathy and ascites in entecavir group, more liver-related mortality in entecavir group and short-term mortality high in entecavir group, but faster reduction in viral load. The findings also comparable with the present study.

CONCLUSION

In conclusion entecavir is very potentanti-HBVdrug with a high genetic barrier to resistance, highly effective in lamivudine-naïve CHB patients and most promising for their long term treatment but not very suitable for CHB patients harboring LAM resistant HBV mutants.

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