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Survival Rate in Patients with HBV-ACLF after Three Months of Antiviral Therapy

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Abstract | **Original Research Article**

Background: A virus which primarily causes inflammation of he liver. The hepatitis B virus can be transmitted in several ways including blood transfusion, needle sticks, body piercing and tattooing using unsterile instruments, dialysis, sexual and evenless intimate close contact, and childbirth. Acute on chronic liver failure (ACLF) is an acute hepatic insult manifested 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. It is associated with high 28-day mortality rate ranging from 30% to 70%. Reactivation of Hepatitis B virus infection and super infection with hepatitis A or E are the major causes of ACLF in the Asian region. Liver transplantation is the only definitive therapy though it is not available everywhere and not feasible always. Again MARS therapy (Molecular Adsorbent Recirculating System) didn't reduce mortality significantly. So, antiviral therapy should be started as soon as possible in patients with ACLF due to Hepatitis B irrespective of DNA and ALT status to improve hepatic dysfunction and rescue the patients from mortality. ***Aims:*** This randomized clinical trial was carried out with an aimto see survival among patients with acute on chronic hepatitis B liver failure 03 months after the antiviral (Tenofovir or Entecavir) therapy. ***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: Tenofovir group (N=16) and Entecavir group (N=16) and followed at least for 03 months. ***Result:*** The total study population was 32 Tenofovir and Entecavir ware 15, 13(86.66) tenofovir and entecavir of 7 days. 6(60.00) tenofovir and entecavir of 8-15 days. 1(14.28) tenofovir and entecavir of 16-28 days. Table-1 demonstrated the Intervention by antiviral at different time of survival rate after three month of early intervention by antiviral (Tenofovir or Entecavir) therapy in HBV-ACLF patients improves survival rate. (n=32). The total study population was 32 Tenofovir and Entecavir ware 15, 2(13.33) had tenofovir and entecavir of 7 days. 4(40.00) tenofovir and entecavir of 8-15 days. 6(85.71) tenofovir and entecavir of 16-28 days. Table II demonstrated the Intervention by antiviral at different time of survival rate after three month of early intervention by antiviral (Tenofovir or Entecavir) therapy in HBV-ACLF patient's death rate. (n=32. The total study population was 32, Outcome Tenofovir was 9(56.3) had survive and 7(43.7) had death. Outcome entecavirwas 3(18.8) had survive and 13(81.02) had death. Figure I show the Outcome of the ACLF patients three months after the antiviral therapy of Intervention by antiviral at different time of survival rate.And lastly, Out of 07 patients,who got antiviralinterventionwithin 16-28 days of ACLF development or appearance of jaundice and ascites, survivalrate and death rate after three month was 01(14.28%) and 06 (85.71%), respectively($p<0.05$).Conclusion: Currently no curative therapy is available. The therapies available to date in habit virus replication, but need to be given long-term. As long as infectedpeople cannot from an adequate immune response, the virus will survive.

Keywords: Antiviral Therapy, Survival Rate, Acute on chronic liver failure (ACLF).

INTRODUCTION

A virus which primarily causes inflammation of the liver. The hepatitis B virus can be transmitted in several ways including blood transfusion, needle sticks, body piercing and tattooing using unsterile instrumwnts, dialysis, sexual and evenless intimate close contact, and childbirth. Several antiviral medications including entecavir, tenofovir, lamivudine, adefovir and telbivudine can heip fight the virus and

slow its ability to damage your liver these drugs are taken by mouth. 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 a 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].

METHODOLOGY

The study was carried out from 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 Bliver 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. 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 CrCL 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), hepatitis B e antigen (HBeAg), immunoglobulin M (IgM) anti-HBc, total anti-HBc and anti-HBe done by commercially available enzyme-linked immunoassays. HBV DNA estimation was done with the real-time polymerase chain reaction (PCR) method and anti HCV was done by commercially available enzyme-linked immunoassays. Anti HEV IgM and anti HAV IgM were also done by commercially available enzyme-linked immunoassays for diagnosis of acute insult. Every patient received standard medical treatment including intravenous antibiotics, albumin infusion, supervised diet, lactulose, bowel wash and intensive care monitoring. Enteral or parenteral nutrition was provided to those patients where caloric requirement was not fulfilled by mouth. Clinical assessment (appetite, sleep pattern, level of consciousness, bowel habit, color of stool and urine, urine output, jaundice, flapping tremor, ascitis etc.) and investigations CBC, ALT, AST, total bilirubin, prothombin time (INR), serum albumin, serum creatinine, serum electrolyte, and serum lactate were done weekly for first two weeks, at the time of deterioration and at day 90. HBV DNA level and ultrasound of abdomen were repeated at day 90. Patients were discharged on the basis of clinical and biochemical improvement. Increase appetite, feeling of wellbeing, reduction of ascites and serum bilirubin below 5 mg/ dl were the basic criteria for hospital discharge in this study. Besides patients were discharged on risk bond, if they were unwilling to continue treatment being admitted in the Department of Hepatology, BSMMU despite not meeting the basic discharge criteria. The primary endpoints were reduction of serum bilirubin, improvement in CTP and MELD scores and reduction in HBV DNA levels and secondary endpoint of the study was survival at 3 months. The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-Square test was used to analyze the categorical variables, shown with cross tabulation. Student, paired t-test, Mann-Whitney U-test and Wilcoxon test were used for continuous variables. P values <0.05 was considered as statistically significant. Prior to the commencement of this study, the research protocol was approved by the Institutional Review Board (IRB) of BSMMU. Objectives of the study along with its procedure, methods, risks and benefits of this study were explained to the patients in easily understandable local language and then informed, written consent in Bengali was taken from each patient. Patients were assured that all information and records will be kept confidential and that the procedure would be beneficial for both the physicians and the patients in making rational approach in case management.

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

It was observed that more than two third (68.8%) patients belonged to age ≤50 years in tenofovir group and 13(81.3%) in entecavir group. The mean age was found 43.8±13.1 years in tenofovir group and 44.2±12.3 years in entecavir group. The mean difference was not statistically significant (p>0.05) between two groups. Majority (93.7%) patients were male in tenofovir group and 13(81.3%) patients in entecavir group. The difference was not statistically significant (p>0.05) between two groups. Figure-1 show Age and Sex distribution of the study patients. 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. Which was statistically significant (p<0.05) between two groups. At pretreatment, mean Rank ALT was found 15.0 U/L in tenofovir group and 18.0 U/L in entecavir group. At 1st follow up (7 days) mean Rank ALT was found 16.4 U/L and 16.6 U/L in tenofovir and entecavir group respectively. At 2nd follow up (14 days) mean Rank ALT was found 15.9 U/L in tenofovir group and 17.1 U/L in entecavir group. At 3rd follow up (90 days) mean Rank ALT was 9.0 U/L and 13.3 U/L in tenofovir and entecavir group respectively. The mean Rank ALT was not statistically significant (p>0.05) between two groups. At pretreatment, mean Rank AST was found 15.2 U/L in tenofovir group and 17.8 U/L in entecavir group. At 1st follow up (7 days) mean Rank AST was found 16.4 U/L and 16.6 U/L in tenofovir and entecavir group respectively. At 2nd follow up (14 days) mean Rank AST was found 15.7 U/L in tenofovir group and 17.3 U/L in entecavir group. At 3rd follow up (90 days) mean Rank AST was 9.5 U/L and 12.3 U/L in tenofovir and entecavir group respectively. The mean

Rank AST was not statistically significant (p>0.05) between two groups. At pretreatment, mean INR was found 1.9±0.3 mg/dl in tenofovir group and 2.0±0.4 mg/dl in entecavir group. At 1st follow up (7 days) mean INR was found 1.7±0.4 mg/dl and 2.0±0.6 mg/dl in tenofovir and entecavir group respectively. At 2nd follow up (14 days) mean INR was found 1.6±0.4 mg/dl in tenofovir group and 1.9±0.6 mg/dl in entecavir group. At 3rd follow up (90 days) mean INR was 1.1±0.1 mg/dl and 1.4±0.2 mg/dl in tenofovir and entecavir group respectively. Mean INR was not statistically significant (p>0.05) between two groups in 3rd follow up (90 days). At pretreatment, mean serum creatinine was found 0.9±0.3 mg/dl in tenofovir group and 0.8±0.3 mg/dl in entecavir group. At 1st follow up (7 days) mean serum creatinine was found 1.2±0.7 mg/dl and 0.9±0.3 mg/dl in tenofovir and entecavir group respectively. At 2nd follow up (14 days) mean serum creatininewas found 1.4±1.1 mg/dl in tenofovir group and 0.9±0.3 mg/dl in entecavir group. At 3rd follow up (90 days) mean serum creatinine was 0.8±0.3 mg/dl and 1.1±0.3 mg/dl in tenofovir and entecavir group respectively. Mean serum creatinine was statistically significant (p<0.05) between two groups in 3rd follow up (90 days) In 1stfollow up, Child-Turcotte Pugh score was found 10.4±1.5 in tenofovir group and 11.9±1.4 in entecavir group. At 3rd follow up, Child-Turcotte Pugh score was found 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. Figure II and Table I show Serum bilirubin, ALT (U/L), AST, INR and creatinine (mg/dl), Meld, Child-Turcotte Pugh in different follow up of Tenofovir Group, Serum bilirubin, ALT (U/L), AST, INR, Creatinine (mg/dl), Meld, Child-Turcotte Pugh in different follow up of Entecavir Group.At 90 days, total 20 (62.5%) patients were survive. Out of them 13(81.2%) in tenofovir group and 7(43.7%) in entecavir group. The difference was statistically significant (p<0.05) between two groups.

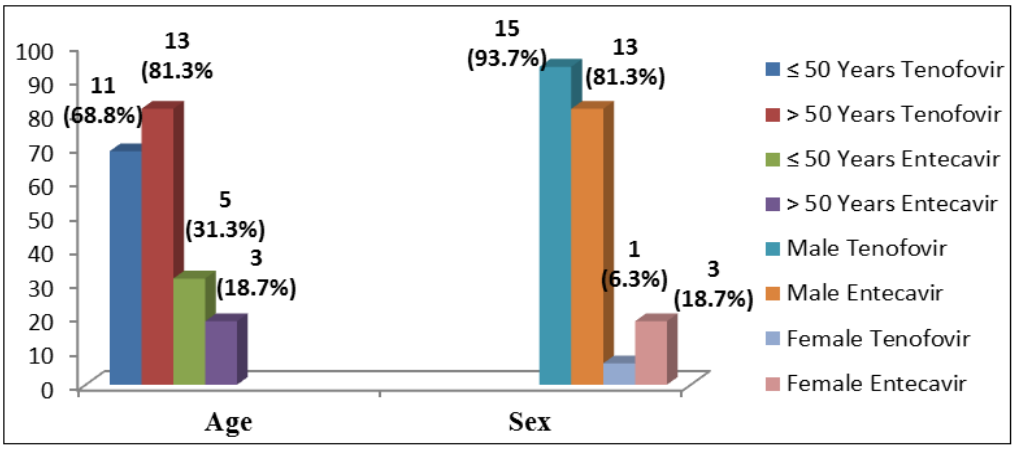

Fig-1: Age and Sex distribution of the study patients

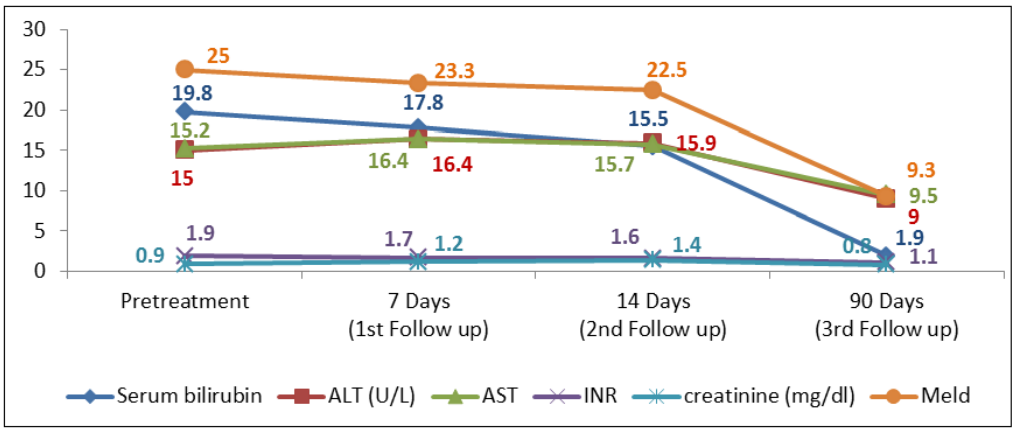

Fig-2: Serum bilirubin, ALT (U/L), AST, INR and creatinine (mg/dl), Meld, Child-Turcotte Pugh in different follow up of Tenofovir Group

Table-1: Serum bilirubin, ALT (U/L), AST, INR, Creatinine (mg/dl), Meld, Child-Turcotte Pugh in different follow up of Entecavir Group

	Serum bilirubin	ALT (U/L)	AST	INR	Creatinine (mg/dl)	Child-Turcotte Pugh
Pretreatment	22	18	17.8	2	0.8	12
7 Days (1st Follow UP)	20.7	16.6	16.6	2	0.9	11.9
14 Days (2nd Follow UP)	17.9	17.1	17.3	1.9	0.9	11.3
90 Days (3rd Follow UP)	5.1	13.3	12.3	1.4	1.1	9.3

DISCUSSION

The primary goal for chronic HBV patients is to achieve the maximum treatment benefit possible from current NUCs' therapies in order to prevent complications including hepatic failure, cirrhosis and hepatocellular carcinoma (HCC). To achieve this aim, long-term suppression of HBV replication is necessary. The aim of antiviral treatment for HBV-ACLF is to reduce viral load at an appreciably high rate, thereby promoting reduction in hepatocyte cell death and improved survival outcomes by prevention of decompensation related multiorgan complications in this group of severely ill patients. This randomized clinical trial was carried out with an aim to measure serum bilirubin, CTP score, MELD score and HBV DNA load among patients with acute on chronic hepatitis B liver failure 03 months after the antiviral (tenofovir or entecavir) therapy and to see survival of patients at 3 months among patients with acute on chronic hepatitis B liver failure 03 months after the antiviral (tenofovir or entecavir) therapy. A total of 32 acute on chronic hepatitis B liver failure patients (age > 18 years with both sexes) in Hepatology department 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., [17], Garg et al., [18] and Chang et al., [16]. 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., [19], Garg et al., [18], Bommel et al., [20], Lai et al., [17] and Chang et al., [16]. 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., [18] and Chang et al., [16]. 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., [18]. In terms of the primary serological outcomes, Zuo et al., [21] found that the entecavir was similar to tenofovir in terms of HBsAg loss and HBeAgseroconversion 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., [21] 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., [19] 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., [18] observed the mean HBV DNA $7.5x10^5$ IU/ml, with range from $1.7x10^4$-$3.1x10^7$ IU/ml. Bommel et al., [20] 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 [22]. 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 [23]. 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., [23] 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., [18] 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., [18] 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 entecavir treated 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., [24] 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., [17] 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. Bing Liang et al., [24] 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 [25] 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., [26] 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., [27], 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., [28] also observed that entecavir prevents disease progression in ACLF patients. However Chen et al., [29] 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 current study it was observed that at 90 days 12 patients expired, out of whom 3 and 9 were respectively in tenofovir and entecavir groups. In tenofovir group cause of death was 1 had hepatorenal syndrome with hepatic encephalopathy, 1 hepatorenal syndrome with hepatic encephalopathy with hypokalaemia and 1 patient had hepatic encephalopathy with septiceamia. On the other hand, among the patients who expired in the entacavir group, 2 had hepatic encephalopathy with septiceamia, 3 hepatic encephalopathy with hepatorenal syndrome, 1 hepatorenal syndrome with septiceamia, 1 hepatic encephalopathy with hypokalaemia, 1 hepatorenal syndrome with hepatic encephalopathy with hyperkalaemia with hyponatremia and 1 had hepatic encephalopathy with hyponatremia. Similar observations have been made by Garg et al., [18] where 17 (63.0%) patients died. Most 12 (82.0%) deaths occurred because of development of multiorgan failure. Multiorgan failure resulted due to progressive liver failure, leading to renal failure (12/17 [70.0%]) and hepatic encephalopathy (15/17 [88.0%]). Most of these patients required mechanical ventilation as their respiratory parameters deteriorated. None of them could be weaned off the ventilator due to multiorgan failure and the patients succumbed to the disease. 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., [29] 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., [21] 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., [30] 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., [32] 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 [33].

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., [34] documented that tenofoviris highly effective in suppressing HBV replication, Guzelbulut et al., [19] 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. More than 2 log reduction in HBV DNA levels at 2 weeks was found to be an independent predictor of survival in ACLF [18]. The impact of anti-viral therapy on survival has been evaluated by different researchers. Shi et al., [35] evaluated the impact of anti-viral therapy on long-term recurrence of liver failure while Garg et al., [18] and Hu et al., [36] evaluated effect of short-term HBV DNA inhibition in HBV-related ACLF patients. Nucleos(t)ide analogue treatment reduced 3-months mortality of HBV-ACLF patients. This was in line with prior report that ACLF patients with high baseline viral load (HBV DNA $\geq 10^5$ copies/mL) had poorer short-term prognosis than those with low viremia [37]. Furthermore, even in the treatment group, only patients with a rapid decline of HBV DNA had a better prognosis [18, 33]. It suggested that viral factors participated in the pathogenesis of this severe hepatic necro-inflammation and decompensation. Therefore, appropriate antiviral therapy might prevent or at least slow down the progression of liver necro-inflammation and allow hepatic regeneration.

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 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., [18] 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 [38] observe in HBV-ACLF patient wihEntecavir; 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. Tenofovir significantly reduces HBV-DNA levels, improves CTP and MELD scores, and reduces mortality in patients with severe spontaneous reactivation of CHB presenting as ACLF. Reduction in HBV-DNA levels at 2 weeks should be a desirable goal and is a good predictor of survival. Garg et al., [18] demonstrated that tenofovir therapy in ACLF patients significantly reduced the serum HBV DNA levels, improved the CTP and thereby reduced mortality, which are consistent with the current study. In another study

CONCLUSION

In HBV-ACLF patients, the use of nucleoside and nucleotide analogs has clear survival benefit, which is significantly higher with Tenofovir. Early intervention by antiviral therapy improve survival rates of HBV-ACLF patients and early intervention by tenofovir improves more survival.

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