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Early Intervention by Antiviral (Tenofovir or Entecavir) Therapy in HBV-ACLF Patients Improves Survival Rate.

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Abstract:
Background:*HBV-ACLF was defined as acute deterioration of liver function andextrahepatic organ failure in patients underlying HBV-related chronic liver disease regardless of cirrhosis status. 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 aim to 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 I 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:** *In HBV-ACLF patients, the use of nucleoside and nucleotide analogs has clear survival benefit, which is significantly higher with Tenofovir. Early interventions by antiviral therapy improve survival rates of HBV-ACLF patients and early intervention by tenofovir improves more survival.*

Key Words:*Tenofovir, Entecavir, HBF (Hepatitis B Virus), ACLF (Acute-on-chronic liver failure).*

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I. Introduction

HBV-ACLF was defined as acute deterioration of liver function andextrahepatic organ failure in patients underlying HBV-related chronic liver disease regardless of cirrhosis status. 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 (Sarin et al. 2009). 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 (Jalan et al. 2012). 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 (Sarin et al. 2014). Acute-on-chronic liver failure (ACLF) is a complicated syndrome that can cause rapid deterioration in patients with chronic liver disease, associated with high-level mortality[1]. Several large, prospective multicentre studies have shown that patients with ACLF have extremely bad prognoses; the 28-day mortality rate ranges from 30% to 90%[2–4]. In Asian, Hepatitis B virus (HBV) infection accounts for the majority of ACLF3. Recently, new diagnostic criteria for HBV-ACLF and a prognostic scoring system were developed in a prospective work conducted by the Chinese Group on the Study of Severe Hepatitis B-ACLF (COSSH-ACLF) (1322 patients in 13 liver centres were studied)[4]. Liver transplantation (LT) effectively treats HBV-ACLF patients who respond poorly to standard treatment, but is limited by organ scarcity. Over the past three decades, artificial liver support systems (ALSS) have been employed to treat liver failure. Previous studies found that ALSS improved short-term survival in those with acute-on-chronic liver failure[5, 6]. Some studies, including a prospective controlled study, found that ALSS was safe, well tolerated, and a useful bridge to LT in patients with ACLF[7–9]. However, another study found that HBV-ACLF patients with lower Model for End-stage Liver Disease scores (MELDs) enjoyed significantly better outcomes than did those with higher MELDs10. Other studies suggested that ALSS afforded survival benefits in specific groups[11, 12]. Thus, subgroups of patients who can benefit from HBV-ACLF, and factors affecting survival, must be identified. To guide and optimise targeted therapy for HBV-ACLF patients, a practical, accurate decision-making. 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 (Vizzutti et al. 2013).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) (Peng et al. 2012). It was estimated that more than 200,000 and 300,000 chronic HBV carriers worldwide die of liver cirrhosis and HCC, respectively, each year (Perz et al. 2006). 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%. (Tsubota et al. 2005).

II. Methodology

The study was carried out from January 2013 to December 2015. Randomized 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 $\geq$ 5 mg/dl, Coagulopathy (international normalized ratio $\geq$ 1.5), Complicated by ascites and/or encephalopathy within 4 weekspatients with chronic liver disease due to HBV infection.Acute insult by reactivation of HBV or HBV flares. Exclusioncriteria: 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.Coexistenthepatocellular 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 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.

III. Result

Time (days)	n=32		%
	Tenofovir	Entecavir	
7 days	7	6	86.66
8-15 days	5	1	60.00
16-28 days	1	0	14.28
Total	13	7	100

Table I: Intervention by antiviral at different time of survival rate after three month ofearly intervention by antiviral (Tenofovir or Entecavir) therapy in HBV-ACLF patients improves survival rate. (n=15)

Time (days)	n=32		%
	Tenofovir	Entecavir	
7 days	0	2	13.33
8-15 days	0	4	40.00
16-28 days	3	3	85.71
Total	3	9	100

Table II: Intervention by antiviral at different time of death rate after three month of early intervention by antiviral (Tenofovir or Entecavir) therapy in HBV-ACLF patients' death rate. (n=32)

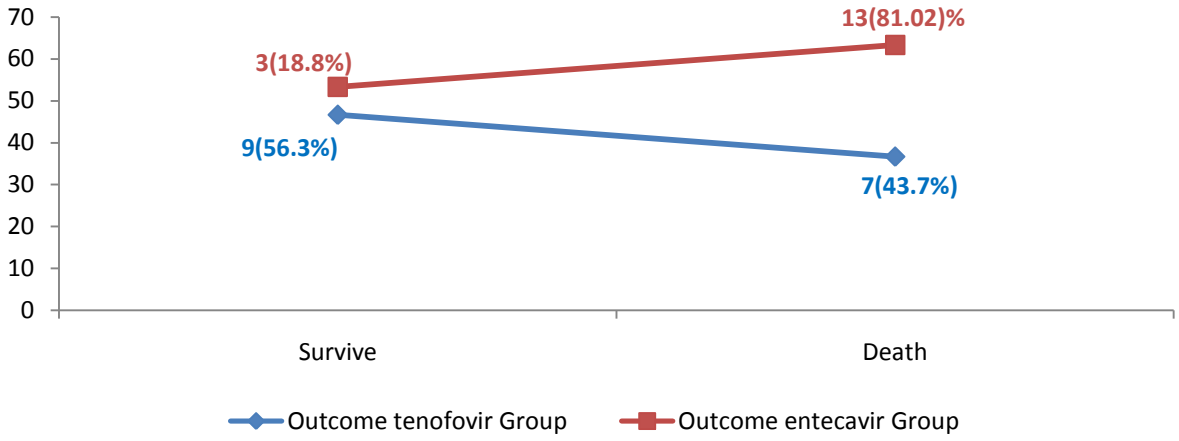

Figure I: Outcome of the ACLF patients three months after the antiviral therapy.

IV. 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 the 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. (2013) ,Garg et al.(2011). And Chang et al. (2006). 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. (2012), Garg et al. (2011), Bommel et al. (2010), Lai et al. (2013) and Chang et al. (2006).

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. (2011) and Chang et al. (2006). 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. (2011).In terms of the primary serological outcomes, Zuo et al. (2015) 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. (2015) 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 HBV-DNA levels<400 copies/ml. 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. (2011) 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

V. Limitations Of The Study

The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not be reflect the exact picture of the country. Due to the lack of availability of the liver transplantation facility in our institute, a decision for early enrollment for the life-saving treatment option could not be offered to the patients. A larger sample size could have helped in better identifying the predictors of mortality, especially in defining them with respect to disease course and respective organ failure.

VI. 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 improves survival rates of HBV-ACLF patients and early intervention by tenofovir improves more survival. There is no cure for hepatitis B. The good news is it usually goes away by itself in 4 to 8 weeks.

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