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Original Article

Combining Telbivudine with Tenofovir in hepatitis B virus related acute on chronic liver failure reduce the risk of renal impairment.

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Abstract:

Introduction: *Chronic hepatitis B virus (HBV) infection is a major health problem because of its worldwide distribution and its potential adverse sequel, including acute-on-chronic liver failure (ACLF), liver cirrhosis and hepatocellular carcinoma. Short term prognosis of patients with spontaneous severe acute exacerbation of CHB leading to ACLF- like presentation is extremely poor, with mortality ranging from 30% to 70%. Therefore, early and rapid reduction of HBV DNA is the essence of therapy in ACLF-B.*

Methods: *Patients with spontaneous reactivation of HBV [(ALT >5 × upper limit of normal or >2 × baseline) and HBV DNA >20,000 IU/ml] were randomized to Tenofovir mono therapy (300 mg/day) or Tenofovir plus Telbivudine (600 mg/day) dual therapy along with standard medical treatment. Clinical and biochemical parameters were evaluated at baseline, 1 week, 4 weeks and at 3 months. Virological evaluation was done at baseline and at 3 months. Primary end point was reduction of HBV DNA. Secondary end point was reduction of liver related complication, therapy related adverse effects and survival at 3 months.*

Results: *27 patients were enrolled and 15 of them received mono therapy with Tenofovir and 12 patients received dual therapy (Tenofovir plus Telbivudine). Baseline parameters in two groups had no significant difference. Both groups significantly improve s. bilirubin, ALT, INR, CTP score and MELD score. Only MELD score showed significant improvement in patient with dual therapy at 3 months in comparison of mono therapy. 11 patient on Tenofovir mono therapy (n=15) showed undetected HBV DNA (91.7%) at 3 month and one patient had detectable HBV DNA (<2,000 IU/ml). 10 patients on dual therapy (n=12) had undetectable HBV DNA (100%). Patients receiving dual therapy showed significant improvement in AKI on follow up compared to those on Tenofovir mono therapy. Among 5 deaths, 3 had received mono therapy with Tenofovir and 2 had received dual therapy. Predictors of mortality were high S. bilirubin (25.8±7.8), HBV DNA (5.18±1.17 $\log_{10}$IU/ml), MELD score (33.0±4.2) and CTP score (12.2±0.8).*

Conclusion: *In spontaneous reactivation of hepatitis B presenting as acute on chronic liver failure, combination of Telbivudine plus Tenofovir is potentially safer with less risk of Tenofovir related nephrotoxicity and hence improved outcomes.*

Introduction:

Acute on Chronic Liver Failure (ACLF) is a serious acute insult of the liver on the background of underlying compensated chronic liver disease. In ACLF two simultaneous insults are operating, acute and chronic, which is a rather new disease entity and the term was first used in 1995 and later defined in 2009 by the Asian Pacific Association for the Study of the Liver (APASL). This is a clinical condition manifesting as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease.[1]

ACLF is characterized by a high mortality rate caused by multi organ failure.[2] The short term mortality may be as high as 65% at 3 months.[1] Early and rapid reduction in HBV DNA is the essence of therapy for ACLF-B. The high mortality can be managed in the wake of new potent antiviral therapy. Lamivudine and entecavir have shown short-term survival benefits, however, drug resistance is a concern with Lamivudine. Monotherapy with tenofovir is promising for improving survivals. At present, mono therapy is recommended for ACLF-B; however, information regarding potential benefit of combination therapy in the world literature is very sparse.

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Combining drugs may achieve synergistic or additive antiviral effects compared with single drug therapy. Combination therapies may achieve greater degrees of HBV DNA suppression, but this has not been associated with higher rates of seroconversion (hepatitis B e antigen or hepatitis B surface antigen) compared to single drug therapy. Undesirable aspects of combination therapy include higher treatment costs and possibly lower adherence rates (due to pill number or complexity of regimen). Potentially harmful effects of combination therapy include higher rates of side effect and the risk of multidrug-resistant hepatitis B virus (HBV) if combination therapy is insufficient to prevent resistance.[3] The renoprotective effect of telbivudine has been shown and its addition to tenofovir in managing ACLF-B may, therefore, be beneficial. Besides combination of a neucleoside analoge with a neocleotide analoge will ensure that there is no cross resistance to HBV.

Methods

Acute on Chronic Liver Failure (ACLF) patients were admitted in Hepatology Department of Bangabandhu Sheikh Mujib Medical University (BSMMU) was enrolled in the study if inclusion criteria were met. The study protocol was approved by The Institutional Review Board (IRB) of BSMMU.

Fifteen of them (Group-A) were selected for tenofovir and twelve (Group-B) were selected for telbivudine plus tenofovir. Group A patients received tenofovir 300 mg daily and group B received telbivudine 600 mg plus tenofovir 300 mg daily. Tenofovir was given on an empty stomach (at least 1 hour before or 2 hours after breakfast) and telbivudine at the same time of day along with standard medical therapy and followed at least 3 months. Biochemical and hematological tests were done during enrollment, at 1st week, 2nd week, at 1st month and then at 3rd month. HBV DNA was determined during enrollment and then at 3rd month.

Quantitative data was presented as mean ± SD and qualitative data was presented in percentage. Qualitative data were analyzed by Chi-square test and quantitative data were analyzed by student's t-test. Chi-square test was used to check the association between two qualitative variables. The Wilcoxon rank sum test was used to compare laboratory parameters and measurement obtained in 1st and last visit to assess the effectiveness of drug. A statistically significant result was considered when p-value was less than 0.05.

Results

The mean age was found 41.75±15.0 in tenofovir plus telbivudine group and 42.73±13.67 in tenofovir group. Majority of the patients were male in both tenofovir 14(93.3%) and telbivudine plus tenofovir 11(91.7%) group. Jaundice and ascites was present in all patients of both study groups. Hepatic encephalopathy was present in 2 (16.7%) cases of telbivudine plus tenofovir group and 3(20.0%) cases of tenofovir group. Study patient was distributed as organ failure during enrollment according to CLIF-SOFA (Chronic liver failure-Sequential Organ Failure Assessment) score.[4]

Table-1 shows organ failure between two groups (n=27)

Table 1

Physical examination	Tenofovir plus Telbivudine (n=12) No. (%)	Tenofovir (n=15) No. (%)	P value
Liver failure (bilirubin > 12mg/dl)	11(91.7%)	10(66.7%)	0.121
Coagulation failure (INR ≥ 2.5)	1(8.3%)	2(13.3%)	0.681
Cerebral failure (hepatic encephalopathy)	3(25.0%)	3(23.1%)	0.813
Kidney failure (s. creatinine > 2.0mg/d)	3(25.0%)	0(0.0%)	0.040
Circulatory failure (DBP < 70 mmHg)	1(8.3%)	2(13.3%)	0.681

Mean serum bilirubin were 19.30±7.45 in telbivudine plus tenofovir group and 17.43±8.41 in tenofovir group. S. creatinine was 1.53±0.92 in telbivudine plus tenofovir group and 0.97±0.27 in tenofovir group. The mean difference was only significant ($p<0.05$) for S. creatinine in both groups. Other baseline investigation (Total count, ALT, INR, Albumin, Electrolytes) were not statistically significant ($p>0.05$).

Telbivudine plus tenofovir group had 6 cases with >20000 IU/ml DNA and 6 cases with <20000 IU/ml DNA. Tenofovir group had 9(60.0%) cases >20000 IU/ml DNA and 6(40%) cases of <20000 IU/ml DNA.

Table-2 shows effect of Tenofovir plus Telbivudine dual therapy on liver function with CTP and MELD (Model for End-stage Liver disease) score at baseline and after 90 days (n=10).

Table 2

Variables	Before treatment (n=10) Mean±SD	After 90 days (n=10) Mean±SD	P value
Serum bilirubin (mg/dl)	18.9±8.06	3.61±2.05	<0.001
ALT (U/L)	207.2±163.9	45.2±21.13	0.014
INR	1.88±0.28	1.33±0.19	<0.001
Serum albumin (gm/L)	23.53±4.90	22.85±11.11	0.804
CTP score	11.33±1.23	8.40±1.26	<0.001
MELD score	30.42±5.07	20.70±4.37	<0.001

Table:3 shows effect of Tenofovir mono therapy on liver function with CTP and MELD score at baseline and after 90 days (n=10).

Table 3

Variables	Before treatment (n=12) Mean±SD	After 90 days (n=12) Mean±SD	P value
Serum bilirubin (mg/dl)	14.54±5.57	2.51±1.76	<0.001
ALT (U/L)	340.0±216.2	59.7±17.6	0.001
INR	1.74±0.16	1.31±0.15	<0.001
Serum albumin (gm/L)	24.28±4.45	28.36±9.16	0.206
CTP score	10.80±1.21	7.67±1.23	<0.001
MELD score	26.60±4.34	15.16±5.24	<0.001

Mono therapy with tenofovir and dual therapy with tenofovir plus telbivudine both reduced the LFT after 90 days and this was statistically significant. However, comparison of reduction of LFT in both study groups was not statistically significant. Comparison of CTP score was not statistically significant after 90 days among both groups. MELD score was significantly improved with tenofovir plus telbivudine dual therapy in comparison of tenofovir mono therapy.

Table:4 shows comparison of MELD score and CTP score between two study groups after 90 days (n=27).

Table 4

	Tenofovir plus Telbivudine (n=12) Mean±SD	Tenofovir (n=15) Mean±SD	P value
MELD score	20.70±4.37	15.17±5.24	0.015
CTP score	8.40±1.26	7.67±1.23	0.185

HBV DNA reduction was detected after 90 days of antiviral therapy in both groups. In only one patient of Tenofovir group, the HBV DNA was detectable after 90 days.

Fig: 1 shows HBV DNA level after 90 days' therapy in both study groups.

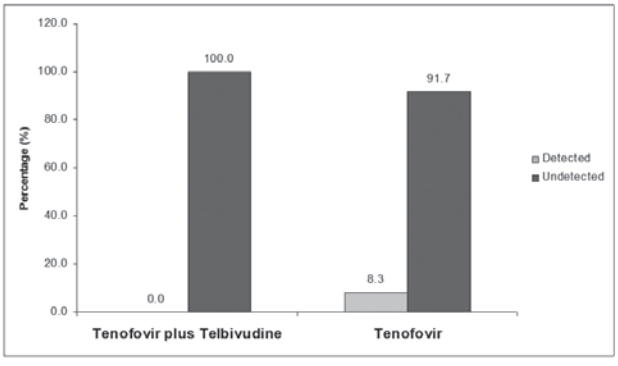

Fig: 1

Renal function improvement occurred after 90 days of dual therapy. Baseline creatinine was higher in Tenofovir plus Telbivudine group.

Table-5 shows S. creatinine levels after 90 days of Tenofovir plus Telbivudine and Tenofovir mono therapy (n=10).

Table 5

S. creatinine (mg/dl)	Before treatment No. (%)	After 90 days No. (%)	
Tenofovir plus Telbivudine (n=12)			
< 1.5	8(66.7%)	9(90.0%)	
> 1.5	4(33.3%)	1(10.0%)	
Mean±SD	1.49±0.97	1.12±0.34	0.266
Tenofovir (n=15)			
< 1.5	14(93.3%)	12(100.0%)	
> 1.5	1(6.7%)	0.0	
Mean±SD	0.91±0.17	0.81±0.13	0.143

After 90 days, a total of 22(81.4%) patients were alive. Out of them, 10(83.3%) patients were from the tenofovir plus telbivudine group, and 12(80.0%) patients were from tenofovir group. 2(16.7%) patients died among tenofovir plus telbivudine group and 3(20%) patients died from tenofovir group. Early death (within 7 days) occurred in 4(14.8%) cases and 1(3.8%) patient died after 2 months. ACLF with acute kidney injury was the predominant cause of death in this observation. One patient from each study group died due to septicemia and circulatory failure. One patient died of multiple causes (hepatorenal syndrome and septicemia).

Table 6 shows cause of death among two study groups (n=5).

Table 6

Cause of death	Tenofovir plus Telbivudine (n=2) No. (%)	Tenofovir (n=3) No. (%)
Acute kidney injury / hepatorenal syndrome	0 (0.0%)	2(33.3%)*
Hepatic encephalopathy	0(0.0%)	1(33.3%)
Septicemia & circulatory failure	1(50.0%)	1(33.3%)
Electrolyte imbalance (hyponatraemia)	1(50.0%)	0(0.0%)

* Multiple cause

Discussion

This observational study was carried out with an aim to determine the survival outcome of HBV related acute on chronic liver failure after 03 months of antiviral therapy (tenofovir mono therapy or tenofovir plus telbivudine dual therapy). Telbivudine, tenofovir and entecavir are currently preferred for the treatment of decompensated cirrhosis because of greater antiviral potency and a high genetic barrier to resistance.[4] In the present, it was observed that in tenofovir group, 15 patients had detectable HBV DNA during pretreatment and 11 patients (3 of whom died) had undetected HBV DNA after 90 days ($p<0.05$). Therefore, success rate of tenofovir in HBV DNA suppression was 91.7% after 90 days. Another study also reported that tenofovir significantly reduced HBV DNA levels from baseline 6.64 log to 4.07 ($P<0.05$) at day 15 and 3.04 at day 90 ($P<0.05$).[2] Tenofovir plus telbivudine dual therapy was more effective in viral suppression, and also cause improvement or stabilization in both scores. In the present study, tenofovir plus telbivudine dual therapy suppresses the HBV DNA 100.0% after 90 days. This is consistent with the findings of an Indian experience.[6]

In fact, various evolving therapies have been employed for the management of different forms of chronic liver diseases. [7-9] Combination of drugs has some additive or synergistic effect compared with single drug therapy. The renoprotective effects of telbivudine have been shown in a few studies to be useful in the presence of renal dysfunction. In the present study, tenofovir plus telbivudine study group pretreatment S. creatinine was 1.53±0.97 and after 90 days 1.12±0.34. Here combination of tenofovir with telbivudine lessened the risk of renal failure and improved the overall survival in ACLF and this finding is consistent with others.[10]

ACLF-B has been associated with extremely high short term mortality ranging from 30- 70% according to reports.[11] In the present study, it was observed that after 90 days, 83.3% patients in tenofovir plus telbivudine group were alive compared to 80.0% in tenofovir group, but this result was statistically not significant ($p>0.05$). Therefore, the present study clearly shows that combination therapy had no effect on overall mortality.

Combination therapy was well tolerated, with no safety related concerns. The present study did not observe any adverse effect in any of the groups.

Conclusion

It can be concluded that both groups significantly show improvement in bilirubin, ALT, INR, CTP score and MELD score. Both groups suppressed HBV DNA significantly. Combination therapy significantly improved MELD score and renal function than tenofovir mono therapy but there is no survival benefit between two groups. However, both protocols are safe and effective and there is no safety related concerns. Large study to compare many available high potency antiviral agents and their combination for ACLF-HBV need to be undertaken to clarify and produce standardized protocol.

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