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Efficacy and Safety of Tenofovir Alafenamide in Treatment Naive Patients with Hepatitis B-Virus Related Decompensated Cirrhosis: A Prospective Observational Study

Sanjeev Jha*, Ravikant Kumar, Saurabh Kumar, Ravi Keshri, Aditya V. Singh, Gaurav Kumar and Samir S. Bhagwat

Department of Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India

Abstract

Background: The effect of Tenofovir Alafenamide (TAF) therapy on viral suppression and hepatic function in patients of Hepatitis B Virus (HBV) related decompensated cirrhosis is not known. Aim of this study was to evaluate the efficacy and safety of TAF therapy in these patients.

Methods: We analyzed 55 consecutive HBV-infected treatment naive patients with decompensated cirrhosis treated with 25 mg/day TAF and evaluated the treatment outcomes. Treatment efficacy was evaluated by measuring virological, serological, biochemical responses and changes in hepatic function over period of 6 month.

Results: At month 6, undetectable HBV-DNA level, HBeAg loss, HBeAg seroconversion and ALT normalization was seen in 65.2%, 22.2%, 5.5% and 74.5% patients respectively. Virological and biochemical responses were similar in HBeAg positive and negative patients. CTP (8.38 ± 1.56 vs. 6.73 ± 1.05), MELD-Na (16.00 ± 6.22 vs. 12.00 ± 4.50), bilirubin [1.65 (0.4-16.7) mg/dL vs. 1.20 (0.7-3.2) mg/dL], INR (1.45 ± 0.35 vs. 1.32 ± 0.32), albumin (2.88 ± 0.58 vs. 3.05 ± 0.39 g/dL), and ALT (68 IU/L (19-390) vs. 36 IU/L (11-94)) was significantly improved after 6 months of TAF treatment. 45.5% and 47.2% patients showed improvement in CTP and MELD-Na score by ≥ 2 points after 6 months. There was no significant difference in eGFR measured respectively at baseline and at month 6 (94.82 ± 38.66 vs. 92.93 ± 25.75 mL./minute, p=0.64).

Conclusion: TAF therapy is effective in decreasing HBV DNA levels, normalizing ALT, improving hepatic function and is well tolerated in decompensated cirrhosis patients.

Keywords: Hepatitis B virus • Tenofovir alafenamide • Naïve patients • Cirrhosis

Abbreviations: SD: Standard Deviation; CTP: Child Turcotte Pugh; MELD Na: Model for End-stage Liver Disease-sodium; SBP: Spontaneous Bacterial Peritonitis; ALT: Alanine Amino Transferase; gm: Gram; mg: Milligram; dL: Deciliter; IU: International Unit; meq: Milliequivalent; INR: International Normalized Ratio; eGFR: Estimated Glomerular Rate.

Introduction

Chronic Hepatitis B virus (CHB) infection is the major public health problem associated with significant morbidity and mortality due to complications of cirrhosis and development of Hepatocellular Carcinoma (HCC) [1]. 11% annual incidence of decompensation in patients with compensated chronic liver disease has been reported in a population based cohort study [2]. In patients with decompensated liver disease, the annual risk of HCC and mortality increases by 7%-8% and up to 20%-50% respectively [3]. Antiviral therapy has shown to reduce liver disease progression and mortality in patients with Decompensated Cirrhosis (DC) [4]. In fact, long term suppression of hepatitis B infection by antiviral therapy has been shown to regress fibrosis and cirrhosis [5]. Entecavir or Tenofovir Disoproxil (TDF) is recommended as preferred first line agents in patients with DC [6]. Both have been shown to be effective and well tolerated [7]. However, long term use of TDF may be associated with reduced bone mineral density and adverse renal profile [8,9]. In patients with advance decompensated cirrhosis, entecavir treatment may be associated with development of lactic acidosis [10]. Therefore, safer antiviral drug is needed in management of CHB related DC.

Tenofovir Alafenamide (TAF) is a prodrug of tenofovir currently used in treatment for HIV and hepatitis B virus (HBV) infections [11]. TAF has pharmacology similar to TDF but with higher cell delivery to the hepatocytes and less systemic exposure [12]. In two multinational trials which included treatment naive and experienced patients with hepatitis B e antigen (HBeAg) positive or negative HBV infection, TAF provided effective and sustained viral suppression and was found to be well tolerated [13]. TAF was shown to be noninferior to TDF in terms of the proportion of patients achieving viral suppression but was associated with significantly higher Alanine Aminotransferase (ALT) normalization rates than TDF [13]. Given the bone and renal safety concerns associated with long-term TDF treatment, the more favourable pharmacological profile of TAF permits reduced systemic exposure to tenofovir and therefore, potentially improving the bone and renal safety profile [14]. Even in patients with severe hepatic impairment, TAF has shown only a modest decrease in hepatic exposure to tenofovir [15]. Currently, there is little information regarding treatment efficacy and safety with TAF in CHB related DC.

Methodology

This study was single centre prospective observational study conducted in a tertiary level institute in eastern India. Institutional ethics committee approved this study. Patients gave written consent for study participation. Study duration was in between April 2018 and July 2019. Patients of HBV related DC was enrolled in this study. Diagnosis of cirrhosis was based on clinical, biochemical or radiological imaging like Ultrasonography (USG) or Contrast Enhanced Computed Tomography (CECT). Decompensation is marked by the development of overt clinical signs like ascites, bleeding, encephalopathy, and jaundice. Following patients were excluded.

I. Undetectable level of Serum HBV DNA at baseline

***Address for Correspondence:** Sanjeev Jha, Department of Gastroenterology, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India, E-mail: drsanjeevjha2010@gmail.com*

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II. Estimated glomerular filtration rate (eGFR)<15 milliliter (mL)/minute

III. Hepatitis C virus positive serologies

IV. HIV positive serologies

V. History of active alcohol intake

VI. Uncontrolled diabetes

VII. Significant co-morbidities

VIII. Hepatic encephalopathy (HE) higher than Grade 2

IX. Hepatorenal syndrome (HRS)

X. Evidence of HCC.

XI. Pregnancy or lactation

Baseline evaluation

Baseline evaluation included detailed clinical assessment, complete blood count; Liver Function Tests (LFT), International Normalized Ratio (INR), Kidney Function Tests (KFT), blood sugar and electrolyte estimation. Serum hepatitis viral markers, including HBsAg, HBeAg, anti-HBe, IgM-antiHBc, anti-HCV and HIV were done using commercially available enzyme immunoassays. Serum HBV DNA level was quantified using the Roche Cobas TaqMan Real Time Polymerase Chain Reaction (RT-PCR) assay. Detection limit of virus by this technique was 3.8 IU/mL. eGFR was measured by using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Ascetic fluid examinations for cell count, SAAG (Serum ascites albumin gradient) and culture were done when indicated. Imaging data such as ultrasonography or CECT of abdomen was obtained for all subjects. All patients underwent Upper Gastrointestinal Endoscopy (UGIE) for assessment of gastro-esophageal varices. All included patients were treated with 25 mg oral tablet of TAF along with other standard form of treatment for DC.

Follow-up studies

Patients were followed-up every 3 months or when developed symptoms that required consultation. Clinical examination and counselling regarding treatment adherence were per-formed for all patients. LFT, KFT, INR, HBeAg, anti-HBe, and HBV DNA level were performed every 3 months. Ultrasound abdomen was repeated after 6 months. HBV-related outcomes like ALT flares, further hepatic decompensation and HCC were assessed. The occurrences of serious adverse events and deaths were also reported.

Treatment-efficacy analyses

The main objective of the study was to investigate the efficacy and clinical outcomes of antiviral therapy with TAF in patients with DC. Treatment efficacy was evaluated by measuring virological response, defined as HBV-DNA being undetectable (assessed by RT-PCR), and ALT normalization (≤ 1 × upper limit of normal which was 40 IU/mL in our study). The incidence of virological breakthrough was determined during follow-up. Virological breakthrough was defined as increase in serum HBV DNA by 1log above nadir after achieving virologic response, during continued treatment. Serological response was defined as the disappearance of HBeAg (HBeAg loss) and then appearance of HBeAb (HBeAg seroconversion). Clinical outcomes evaluated were changes in hepatic functions, episodes of liver decompensation, diagnosis of HCC and death. Hepatic functions were assessed by using Child-Turcotte-Pugh (CTP) and Model for End-stage Liver Disease Sodium (MELD-Na) score and Secondary objectives included safety and tolerability assessments of the drug.

Statistical analysis

Quantitative data were expressed as mean ± standard deviation or median (range). Comparisons between the two groups were done using independent sample t test for normally distributed and Mann-Whitney U test for no normally distributed continuous data. Qualitative data were expressed as percentage and were analyzed using Fisher's exact test. Effects of TAF on hepatic function, HBV-DNA level and e-GFR were evaluated by using Paired-Samples T Test. Logistic regression analyses were done to assess the factors independently correlated with virological response. A p value of <0.05 were considered significant.

Results

Eighty-five patients of HBV related DC was enrolled in this study. Fifteen patients were excluded due to causes mentioned in flow chart 1. Therefore, seventy patients were started treatment with TAF 25 mg per oral along with other standard form of treatment for DC. Median duration of disease presentation was 60 days (range: 4-120 days). 10 patients died during study period. 7 Patients died within 3 months after enrolment. Causes of death were acute on chronic liver failure (4 Patients), HRS (2 patients) and HE (1 patients). 3 patients died in between 3 and 6 months due to sepsis with multi-organ dysfunction (2 patients) and variceal rebleeding (1 patient). Five patients were lost to follow-up before evaluation at 6 months. We have excluded patients who have not completed the 6 months follow up period. Therefore, we analyzed clinical and laboratory data of the remaining 55 patients (Figure 1).

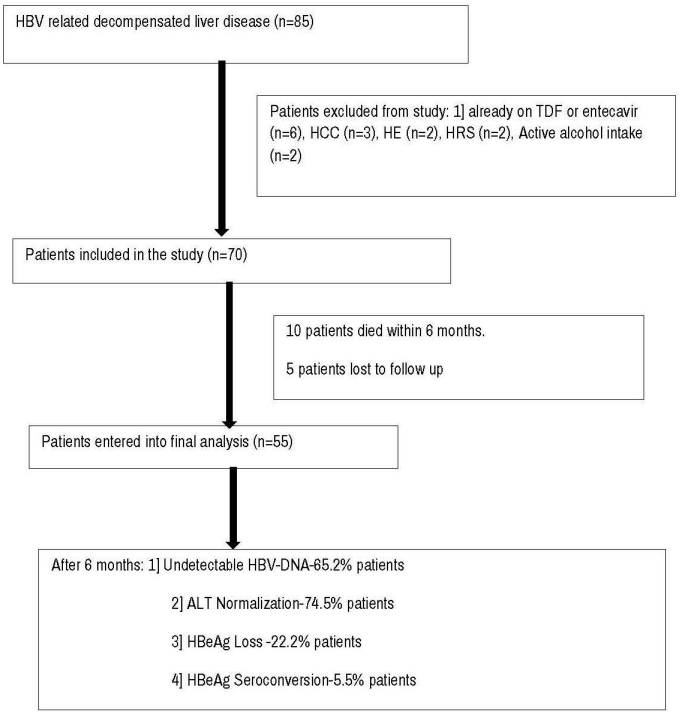

Figure 1. Flow chart of HBV related decompensated cirrhotic patients enrolled in the study.

Baseline characteristics

The baseline characteristics of the study groups are shown in Table 1. Mean age of patients was 45.61 ± 15.89 years and 92.7% were male. 13 patients (23.6%) belonged to Child C status and 14 patients (25.5%) had MELD-Na score ≥ 20. Five patients were diagnosed as acute on chronic liver failure. Ascites, jaundice, HE, and Spontaneous Bacterial Peritonitis (SBP) were seen in 46 (83.6%), 15 (27.3%), 2 (3.6%) and 2 (3.6%) patients respectively. 18 (32.7%) patients experienced variceal bleeding. More than one form of decompensation seen in 26 (47.27%) patients (ascites plus variceal bleeding-10 patients, ascites plus jaundice-9 patients, ascites plus bleeding and jaundice-3 patients, ascites plus bleeding and HE-2 patients, ascites with SBP-2 patients). Baseline mean serum HBV-DNA level was 4.6 ± 1.5 log 10IU/mL. 18 Patients (32.7%) were positive for HBeAg. During UGIE, large and small esophageal varices were seen in 17 and 30 patients respectively. Gastric varices were seen in 5 patients. Eight patients did not show varices during endoscopy. No patients discontinued TAF during the study period.

Parameters	Results
Age (Mean ± SD)	45.61 ± 15.89
Sex (Male: Female) (%)	51:4 (92.7:7.3)
CTP score (Mean ± SD)	8.38 ± 1.56
MELD-Na score (Mean ± SD)	16.00 ± 6.22
Presence of Ascites (%)	46 (83.6%)
Presence of Hepatic encephalopathy (%)	2 (3.6%)
History of variceal bleeding (%)	18 (32.7%)
Presence of jaundice (%)	15 (27.3%)
Presence of SBP (%)	2 (3.6%)
Hemoglobin in g/dL (Mean ± SD)	9.51 ± 2.20
Platelet (× 109 cells/L) (Mean ± SD)	104.29 ± 52.36
Leukocytes (× 109 cells/L) (Mean ± SD)	6116 ± 3317
Median total S. Bilirubin in mg/dL (Range)	1.65 (0.4-16.7)
Median direct S. Bilirubin in mg/dL (Range)	0.70 (0.2-10.2)
Median ALT in IU/L (Range)	68 (19-390)
Protein in gm/dL (Mean ± SD)	6.58 ± 1.07
Albumin in gm/dL (Mean ± SD)	2.88 ± 0.58
INR (Mean ± SD)	1.45 ± 0.35
Creatinine in mg/dL (Mean ± SD)	0.99 ± 0.21
eGFR in ml/minute (Mean ± SD)	94.15 ± 39.17
Sodium in meq/L (Mean ± SD)	135.65 ± 5.16

Table 1. Baseline clinical and laboratory profile of patients (n=55).

We also compared the baseline profile of patients who succumbed to disease with survivors and found significantly high INR, bilirubin, CTP and MELD-Na score in non-survivor group. These two subgroups, however, did not differ in serum HBV DNA or HBeAg serostatus as shown in Table 2.

Virological, serological, and biochemical responses

Mean value of HBV-DNA measured at baseline, at month 3 and 6 were 4.6 ± 1.5 log 10IU/mL, 2.71 ± 1.47 log 10IU/mL and 1.02 ± 1.31 log 10IU/mL respectively (p<0.001). At month 3, more than 2 log reductions from baseline HBV-DNA were seen in 54.5% cases. At month 3 and 6, HBV-DNA level was undetectable in 9 (17.6%) and 32(65.2%) patients respectively. At month 6, HBeAg loss was seen in 4 (22.2%) patients and HBeAg seroconversion was seen in 1(5.55%) patient. At baseline normal level ALT<40 U/ml) was seen in 11 (20%) patients. 41 patients (74.5%) had normal ALT at month 6. We also analyzed virological and biochemical response of TAF according to HBeAg status of patients. We found virological and biochemical responses were similar in HBeAg positive and negative patients as shown in Table 3. Logistic regression analyses showed that none of the factors at baseline like age (p=0.47), sex (p=0.69), and HBeAg status (p=0.36) and baseline HBV DNA (p=0.53) levels independently affected virological response during TAF therapy. In the context of clinical antiviral resistance, virological breakthrough was not noted during the study period.

Changes in hepatic function

To evaluate the influence of TAF therapy on hepatic function, we measured the CTP score and its components (i.e., total bilirubin, albumin, and INR), along with MELD-Na score and compared these values at baseline and at month 6. As shown in Table 4, CTP score (8.38 ± 1.56 vs. 6.73 ± 1.05), MELD-Na score (16.00 ± 6.22 vs. 12.00 ± 4.50), total bilirubin [1.65 (0.4-16.7) vs. 1.20 (0.7-3.2) mg/dL], INR (1.45 ± 0.35 vs. 1.32 ± 0.32), albumin (2.88 ± 0.58 vs. 3.05 ± 0.39 g/dl), and ALT [68 (19-390) vs. 36 (11-94) IU/L] were significantly improved after 6 months of TAF treatment. Twenty-five patients (45.5%) showed an improvement of ≥ 2 points in CTP score. 13 patients (23.63%) showed improvement in CTP by more than 1 point but less than 2 points. 13 patients (23.63%) did not show any improvement in CTP and 4 (7.27%) experienced deterioration in CTP. 26 patients (47.27%) showed an improvement in MELD-Na score by ≥ 2 points whereas 7 patients (12.72%) experienced deterioration in MELD-Na score.

Parameters	Survivors (n=55)	Patients who succumbed (n=10)	p-Value
CTP Score (Mean ± SD)	8.38 ± 1.56	10.70 ± 1.63	<0.001
MELD-Na Score (Mean ± SD)	16 ± 6.22	24.80 ± 6.89	<0.001
INR (Mean ± SD)	1.45 ± 0.35	2.19 ± 0.83	<0.001
S. Bilirubin in mg/dL (Mean ± SD)	2.53 ± 3.12	9.79 ± 10.98	<0.001
Albumin in g/dL (Mean ± SD)	2.88 ± 0.58	2.70 ± 0.46	0.34
Presence of ascites	46(83.6%)	10(100%)	0.46
Hepatic encephalopathy	2(3.6%)	3(30%)	0.03
Presence of SBP	2(3.6%)	1(10%)	0.53
Presence of ACLF	5 (9.1%)	4(40%)	0.04
Presence of HBeAg	18 (32.7%	6(60%)	0.30
Median baseline HBV-DNA level (Range)	4.6 ± 1.5 log10 IU/mL	5 log10 IU/mL	0.63

Table 2. Comparison of baseline characteristics of patients who succumbed to disease versus survivors.

	HBeAg+(n=18)	HBeAg-(n=37)	p-value
Baseline DNA (log10 copies/ml)	5.11 ± 1.64	4.39 ± 1.50	0.11
DNA at month 6 (log10 copies/ml)	1.12 ± 1.48	0.80 ± 1.16	0.22
Undetectable DNA at month 6	55.6%	68.8%	0.23
Normal ALT at baseline	16.7%	22.2%	0.62
ALT normalization at month 6	66.7%	79.3%	0.58

Table 3. Virological and biochemical response of TAF based on HBeAg status of patients.

Parameters of hepatic functions	Baseline	At month 6	p-value
CTP Score (Mean ± SD)	8.38 ± 1.56	6.73 ± 1.05	<0.001
MELD-Na Score (Mean ± SD)	16.00 ± 6.22	12.00 ± 4.50	<0.001
Median total S. Bilirubin in mg/dl (Range)	1.65 (0.4-16.7)	1.20 (0.7-3.2)	0.012
INR (Mean ± SD)	1.45 ± 0.35	1.32 ± 0.32	<0.001
Albumin in gm/dL (Mean ± SD)	2.88 ± 0.58	3.05 ± 0.39	0.05
Median ALT in IU/L (Range)	68 (19-390)	36 (11-94)	<0.001

Table 4. Changes in hepatic function after 6 months of TAF therapy (n=55).

Out of 55 patients, six patients were readmitted during study period. Causes of readmission were ascites recurrence (n=3), variceal rebleeding (n=1), variceal rebleeding with SBP (n=1) and HE (n=1). All patients were improved on standard medical therapy.

Changes of creatinine clearance (eGFR)

eGFR was measured at baseline and at 6 months. There were no statistically significant differences in eGFR measured respectively at baseline and at month 6 (94.82 ± 38.66 mL/minute vs. 92.93 ± 25.75 mL/minute, p=0.64) during TAF therapy. Creatinine at baseline and at month 6 was 0.99 ± 0.21 and 1.03 ± 0.62 mg/dl (p=0.35) respectively.

Discussion

TAF is a novel prodrug formulated to deliver the active metabolite to target cells more efficiently than TDF at a lower dose, thereby reducing systemic exposure. In patients with HBeAg-positive HBV infection, TAF was shown to be non-inferior to TDF and had improved bone and renal effects [13]. Patients treated with TDF for 96 weeks and then switched to TAF, had shown improvements in renal and Bone Mineral Densitometry (BMD) measured only 24 weeks after switching [12]. It has been shown that the glomerular, tubular and bone safety parameters rapidly improved while virological suppression was maintained in patients switched to TAF after getting treatment with TDF for 96 weeks [16]. TAF has the potential advantages that dose adjustment is not required in patients with renal impairment, and monitoring can be less intense because of the better safety profile [17]. Recent studies have reported that CHB patients are aging with higher rates of comorbidities including chronic kidney disease and osteoporosis [18]. For patients with existing renal or bone diseases or high risk for such disorders, TAF would be preferable to TDF given the more favourable renal and bone safety profiles. Currently, there is little information regarding treatment efficacy and safety with TAF in CHB-related DC.

We examined the efficacy and safety of TAF for 24 weeks in treatment-naive DC patients. In our study, HBV-DNA level was undetectable in 9 (17.6%) and 32(65.2%) patients respectively at 3 and 6 months respectively. Miquel et al. in a retrospective study showed that undetectable HBV-DNA at month 3 and 6 in 60% and 70% respectively in patients with DC treated by either entecavir or TDF though the number of patients was only 10. Lee et al. in observational prospective study found that 51% and 70% patients of DC (n=57) had undetectable DNA level at 6 and 12 months respectively. The entecavir study reported by Shim et al. also showed that undetectable HBV DNA at 6 months in 58.2% cases which is similar to our study. ALT normalization occurred in 74.5% cases at month 6 in our study. Entecavir showed ALT normalization in similar proportion of patients (78.2%) while only 63% of patients receiving TDF showed normalization of ALT at month 6. Out of 18 HBeAg positive patients, 4 patients (22.5%) became negative at month 6 while seroconversion seen in one (5.55%) patient. Shim et al. in their entecavir study showed that HBeAg loss in 33.3% cases and seroconversion in 18.5% cases at 6 months. Lee et al. in TDF study also showed HBeAg loss in 10.7% cases and without seroconversion at 6 months [19,20].

In our study 10 patients died during study period of which 7 patients died within 3 months after starting TAF therapy. Patients who succumbed to disease while on TAF therapy showed significantly high INR, bilirubin, CTP and MELDNa score. Shim et al. in their entecavir study also showed that patients with early death or who underwent early liver transplantation had significantly high CTP score, INR, bilirubin level and low albumin level. Therefore, in patients with advance liver disease TAF therapy could not effectively prevent early mortality and thus liver transplantation should not be delayed in patients with higher CTP class or MELD score at baseline.

CTP and MELD scores, both of which reflect liver function and their components including serum albumin, bilirubin and INR dramatically improved during the period of TAF treatment in our patients with DC. In our study, twenty-five patients (45.5%) showed improvement of ≥ 2 points in CTP score after 6 months. 26 patients (47.27%) showed improvement in MELD-Na score by ≥ 2 points. SK et al. in TDF study also showed improvement of ≥ 2 points in CTP score after 12 months of therapy in 49.1% of patients. Entecavir also showed improvement in CTP by ≥ 2points in similar proportion of patients after 12 months. Improvement in the biochemical and clinical parameters of patients with HBV-related DC may be because of improvement in the functional capacity of underlying liver disease by antiviral therapy [21,22]. In HBV-infected advance liver disease patients, early treatment with TAF may possibly prevent clinical progression, taper complication risk, and even delay or avoid liver transplantation. Therefore, current practice guidelines suggest that antiviral treatment should be considered in DC patients regardless of HBV DNA levels.

We analyzed the renal function change over time. At month 6, there were no significant changes in eGFR as compared to baseline. In our study the mean eGFR was 1.99% lower than baseline. In decompensated cirrhotic patients treated by entecavir and TDF, the mean eGFR was 5.57% and 4.13% respectively lower than at baseline as shown by Park et al. [23]. Kaneko et al. in the real-world study also showed significant decline in eGFR in TDF group as compared to patients treated by TAF.

In summary, our study suggests that TAF therapy improves the virological, serological and biochemical parameters in patients with DC. It also improves the liver function. Effects of TAF are comparable to that of TDF or entecavir. TAF therapy also showed no significant change in renal function over time.

This study had several limitations. First, the follow up period was 6 months, which is not sufficient. Second, the numbers of patients were small. Thus, data from a longer follow-up period is needed comprising larger number of patients. BMD was not measured during study period, is also one of the limitations. We have not done a comparative study of TAF with TDF, because many studies in the past have already assessed the efficacy and safety of TDF in patients with DC. Therefore, we have taken historical control for comparison.

Conclusion

In conclusion, we showed that TAF therapy is effective in decreasing HBV DNA levels, normalizing ALT, improving hepatic function and is well

tolerated in patients with decompensated cirrhosis. Thus, our findings may establish a rationale for the use of TAF as a first line therapeutic agent in decompensated cirrhotic patients.

Author Contributions

Sanjeev Kumar Jha drafted the manuscript, oversight the study, assisted with data analysis, performed statistical analysis and prepared the manuscript; Ravikant Kumar participated in design and oversight of the study; Saurabh Kumar, Ravi Keshari, Aditya Vardhan Singh, Gaurav Kumar and Samir Sandipan Bhagwat recruited the patients, involved with data collection and assisted with data analysis. All authors read and approved the final manuscript.

References

1. Fattovich, Giovanna. "Natural History and Prognosis of Hepatitis B". *Semin Liver Dis* 23(2003):47-58.
2. Fleming, Guruprasad Aithal, Timothy Card and Joe West. "The Rate of Decompensation and Clinical Progression of Disease in People with Cirrhosis: A Cohort Study." *Aliment Pharmacol Ther* 32(2010):1343-1350.
3. Fattovich, Giovanna, Giuliano Giustina, Solko Schalm and Stephanos Hadziyannis et al. "Occurrence of Hepatocellular Carcinoma and Decompensation in Western European Patients with Cirrhosis Type B. The Eurohep Study Group on Hepatitis B Virus and Cirrhosis." *Hepatology* 21(1995):77-82.
4. Tada, Toshifumi, Takashi Kumada, Hidenori Toyoda and Seiki Kiriyama et al. "Long-term Prognosis of Patients with Hepatitis B Infection: Causes of Death and Utility of Nucleos(t)ide Analogue Therapy." *J Gastroenterol* 50(2015):795-804.
5. Marcellin, Patrick, Edward Gane, Maria Buti and Nezam Afdhal et al. "Regression of Cirrhosis During Treatment with Tenofovir Disoproxil Fumarate for Chronic Hepatitis B: A 5-year Open-label Follow-up Study." *Lancet* 381(2013):468-475.
6. Terrault, Norah, Anna Lok, Brian McMahon and Kyong-Mi Chang, et al. "Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance." *Hepatology* 67(2018):1060-1599.
7. Miquel, Mireia, Oscar Nunez, Maria Trapero-Marugan and Antonio Diaz-Sanchez et al. "Efficacy and Safety of Entecavir and/or Tenofovir in Hepatitis B Compensated and Decompensated Cirrhotic Patients in Clinical Practice. Ann Hepatol 12 (2013):205-212.
8. Gill, Upkar, Alexandra Zissimopoulos, Safa Al-Shamma and Katherine Burke et al. "Assessment of Bone Mineral Density in Tenofovir-Treated Patients with Chronic Hepatitis B: Can the Fracture Risk Assessment Tool Identify Those at Greatest Risk?" *J Infect Dis* 211(2015):374–382.
9. Lange, Christian, Jörg Bojunga, Wolf Peter Hofmann and Katrin Wunder et al. "Severe Lactic Acidosis During Treatment of Chronic Hepatitis B with Entecavir in Patients with Impaired Liver Function. *Hepatology* 50(2009):2001-2006.
10. Murakami, Eisuke, Ting Wang, Yeojin Park and Jia Hao et al. "Implications of Efficient Hepatic Delivery by Tenofovir Alafenamide (GS-7340) for Hepatitis B Virus Therapy. *Antimicrob Agents Chemother.* 59(2015):3563-3569.
11. Basit, Syed Abdul, Altaf Dawood, John Ryan and Robert Gish. "Tenofovir Alafenamide for the Treatment of Chronic Hepatitis B Virus Infection." *Expert Rev Clin Pharmacol* 10(2017):707-716.
12. Chan, Henry, Scott Fung, Wai Kay Seto and Wan-Long Chuang et al. "Tenofovir Alafenamide versus Tenofovir Disoproxil Fumarate for the Treatment of HBeAg-positive Chronic Hepatitis B Virus Infection: A Randomized, Double-blind, Phase 3, Non-inferiority Trial." *Lancet Gastroenterol Hepatol* 1(2016):185-195.
13. Scott, Lesley and Henry Chan. "Tenofovir Alafenamide: A Review in Chronic Hepatitis B. Drugs." 77(2017):1017-1028.
14. Custodie, Gene Ma, Jennifer Cuvin and Lie Ting et al. "Pharmacokinetics and Safety of Tenofovir Alafenamide in Subjects with Severe Hepatic Impairment." J. Hepatol 64(2016):594-595
15. Viganò, Mauro, Alessandro Loglio, Glenda Grossi and Pietro Lampertico. "Tenofovir Alafenamide (TAF) Treatment of HBV, What are the Unanswered Questions?" *Expert Rev Anti Infect Ther*. 16(2018):153-161.
16. Buti, Maria, Mar Riveiro-Barciela and Rafael Esteban. "Tenofovir Alafenamide Fumarate: A New Tenofovir Prodrug for the Treatment of Chronic Hepatitis B Infection." *J Infect Dis*. 2016(2017):792-796.
17. Ogawa, Eiichi, Norihiro Furusyo and Mindie H Nguyen. "Tenofovir Alafenamide in the Treatment of Chronic Hepatitis B: Design, Development, and Place in Therapy. Drug Des Devel Ther 11(2017):3197-3204.
18. Kyu Lee, Soon, Myeong Jun Song, Seok Hyun Kim and Byung Seok Lee et al. "Safety and Efficacy of Tenofovir in Chronic Hepatitis B-Related Decompensated Cirrhosis." *World J Gastroenterol* 23(2017):2396-2403.
19. Ju Hyun Shim, Han Chu Lee, Kang Mo Kim, Young-Suk Lim, Young-Hwa Chung et al. "Efficacy of Entecavir in Treatment-Naive Patients with Hepatitis B Virus-related Decompensated Cirrhosis. *J Hepatol* 52(2010)176-182.
20. Yao, Francis and Nathan M Bass. "Lamivudine Treatment in Patients with Severely Decompensated Cirrhosis due to Replicating Hepatitis B Infection. *J Hepatol* 33(2000):301-307.
21. Kapoor, Dharmesh, Rajkumar Guptan, Salma Wakil and Syed Kazim et al. "Beneficial Effects of Lamivudine in Hepatitis B Virus-related Decompensated Cirrhosis. *J Hepatol* 33(2000):308-312.
22. Park, Jihye, Kyu Sik Jung, Hye Won Lee and Beom Kyung Kim et al. "Effects of Entecavir and Tenofovir on Renal Function in Patients with Hepatitis B Virus-Related Compensated and Decompensated Cirrhosis." *Gut Liver* 11(2017)828-834.
23. Kaneko, Shun, Masayuki Kurosaki and Nobuharu Tamaki et al. "Tenofovir Alafenamide for Hepatitis B Virus Infection Including Switching Therapy from Tenofovir Disoproxil Fumarate. *J Gastroenterol Hepatol*. 34(2019):2004-2010.

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