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Original Article

Efficacy and Safety of Tenofovir and Entecavir in Patients with Chronic Hepatitis B - Comparative Cohort Study

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ABSTRACT

Background: *Hepatitis B virus (HBV) infection is a global problem and >350 million HBV carriers in the world. HBV infection causes chronic hepatitis and can lead to liver cirrhosis and hepatocellular carcinoma (HCC).*

Aim: *To evaluate safety and efficacy of Tenofovir and Entecavir medications in liver disease course in HBV-decompensated cirrhosis patients*

Patients & Methods: *The study was carried out in hepatology Out-Patient Clinic, Amiri hospital, Kuwait. Forty six HBV decompensated cirrhosis patients were classified into 2 groups; Tenofovir group (n=23) and Entecavir group (n=23). All patients underwent clinical examination, laboratory data (liver profile, HBV DNA, eGFR, Phosphate) and Assessment of Child-Pugh (CP) score, Model for end stage liver disease (M ELD) score before and after treatment.*

Results: *Baseline HBV DNA and liver enzymes of both groups showed no significant difference before treatment. 21 (91.3%) of patients of in each group had undetectable HBV DNA at 12 months. CP and MELD scores among the 2 groups showed improvement in both scores after treatment with similar changes in both scores between the 2 medications at any time. Comparison of eGFR among the 2groups showed no changes at any time in eGFR at each group and in between the 2 groups.*

Conclusion: *Both antivirals (Tenofovir and Entecavir) were well tolerated; none of the patients discontinued therapy, while eGFRs were not different between Tenofovir and Entecavir groups during the follow up period, the patients had excellent virological response without viral breakthrough and with improvement in severity of liver disease.*

Keywords: *Tenofovir, Entecavir, chronic hepatitis B, Decompensated cirrhosis.*

INTRODUCTION

Approximately one third of the world's population has serological evidence of past or present infection with hepatitis B virus (HBV). Chronic hepatitis B patients all over the world around 350 million persons. The prevalence of HBsAg in the area of middle eastranges from 3% to 11%.and genotype D is the most prevalent genotype and in

Kuwait is 4 %.The incidence is expected to decrease among children in countries as Egypt, where 90% immunization coverage has been achieved (Ismail s., et al 2014, Huang et al., 2015) [1,2].

HBV has different mode of transmission as perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in dense endemic areas (Mast et al., 2005) [3].

Up-to-date treatment choices for chronic HBV consist of nucleos (t) ide analogues and (pegylated) interferon. Antiviral treatment with nucleos(t)ide analogues aims at hindering viral polymerase activity. In the treatment of chronic HBV infection, tenofovir and entecavir provide more powerful viral inhibition and cause fewer chances of formation of resistant mutant HBV viruses than other anti-viral agents (Kwon et al 2015) [4].

Entecavir (ETV) and Tenofovir (TDF)] are strong antiviral mediators with a slime chance of resistance and so they exemplify the recommended first-line for the managing HBV-decompensated cirrhosis cases (Evangelos et al 2015) [5].

Liver transplantation should be considered for all cases of HBV decompensated cirrhosis, data showed that some cases improved, downgraded, or withdrawn from transplant list after receiving antiviral therapy and improvement of hepatic dysfunction or failure. However, a significant proportion of HBV-Decompensated cirrhosis patients die or require liver transplantation despite the use of antiviral treatment.

Since the last 40 years, Child-Turcotte-Pugh (CTP) score has been used frequently for assessing the prognosis of cirrhosis. (3) The Child-Pugh gain the acceptance because it is simple, and convinient as bed sideassesment. (4,5) The CP score consider presence and severity of ascites and encephalopathy, prothrombin time, albumin level and bilirubin. It ranges from 5 to 15. Patients are grouped into three classes. Patients with score 5-6 were named as CP class A, with 7-9 as class B and > 9 as class C (Shaikh et al 2010) [6].

In 1999 the Model for end stage liver disease (MELD) was introduced for assessing the risk of mortality and morbidity in patients with cirrhosis of liver. (9) MELD score calculation is based on the cause of cirrhosis and three laboratory variables, serum bilirubin, serum creatinine and prothrombin time expressed as international normalized ratio (INR). MELD and CP score are considered as a predictors of morbidity, and mortality in patients with decompensated liver cirrhosis (Shaikh et al 2010) [6].

The aim of this work to evaluate safety and efficacy of Tenofovir and Entecavir medications in liver disease course in HBV-decompensated cirrhosis patients.

PATIENTS AND METHODS

Study design and Setting

The study was carried out at the Out-Patient Clinic, Hepatology Department, Amiri Hospital, Kuwait .

Patients' eligibility and Sample size

Forty six decompensated HBV cirrhosis patients (with positive HBsAg and HBV DNA by RT-PCR) presenting at the hepatology outpatient Clinic of Amiri Hospital, Kuwait, between March 2013 and November 2013 were enrolled in this study.

The patients were divided into two groups: Group (1) 23 patients who received Tenofovir (TDE) and Group (2) 23 patients who received Entecavir (ETV).

Informed written consent was obtained from all subjects after explanation of the nature, purpose of the study and this study was approved by the Department committee and the Institution Review Board (IRB). This study was performed in accordance with the ethics guidelines of the 1975 Declaration of Helsinki.

We included patients who fulfilled the following: (1) Age 18 to 70 years old (1) Naïve decompensated HBV cirrhosis (with positive

HBsAg and HBV DNA by RT-PCR by any level). Decompansation was defined by the development of any complication of portal hypertension (ascites, variceal bleeding, or hepatic encephalopathy) and/or the Child-Pugh (CTP) score more than 7.

We excluded patients with (1) Combined hepatitis C virus-positive serology, (2) Hepatitis D coinfection, (3) Previous use of Lamivudine or any antiviral against HBV or (4) Use of nephrotoxic drugs (5) Presence or history alcohol intake.

Study protocol

All patients were treated with nucleotides (Tenofovir 300mg PO qday orEntecavir 1mg PO qday), starting from March 2012 till March 2013. The baseline was defined as the date of starting the nucleotides treatment.

All patients were subjected to (1) Thorough history taking including previous antiviral therapy, associated diseases (e.g. Diabetes mellitus, hepatocellular carcinoma) and clinical examination. (2) Laboratory data: liver and kidney profiles and INR, serum phosphate (3) Abdominal ultrasound for: diagnosis and staging of ascites, follow-up for HCC and following any renal changes (3) Child-Pugh (CTP) and model for end stage of liver disease (MELD) scores were recorded at baseline, at six and twelve months visits (4) HBV DNA by RT-PCR was recorded at baseline, at six and twelve months visits with a cutoff lower detection limit of 12 IU/ml.

Follow-up of patients for one year after recruitment, and included recording (1) Cirrhosis-related complications [variceal bleeding, ascites, spontaneous bacterial peritonitis (SBP), hepatorenal syndrome, hepatic encephalopathy, HCC] and its time of occurrence, (2) Deterioration of the liver profile whether related or unrelated to the treatment adverse effect. (3) The response to Tenofovir and Entecavir through Liver profile, CBC, viral load, HBV serology (HBsAg, HBsAb, HBeAg), and concomitant HDV infection) (4) Any associated adverse events related to Tenofovir or Entecavir (5) Assessment of renal function based on serum creatinine and estimated glomerular filtration rate (eGFR) using MDRD formula, serum phosphate at 3, 6 and 12 months follow up.

Virologic response was defined as a serum level of HBV DNA undetectable by polymerase chain reaction (PCR). Renal damage was defined as an increase in serum creatinine> 0.3 mg / dl.

Ethical considerations

The aim of the study was explained to all participants. They were assured that refusing participation in this study will not affect their benefit from all services and treatment. A written consent was obtained from all the participants. Security and confidentiality of all the information obtained was observed. Data were collected from the medical records and by personal examinations with patients by one investigator.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS version 16.0, Inc., Chicago, IL, USA) was used for all statistical analysis. The values of continuous variables were presented as mean ± SD and of categorical variables as absolute number and percentages. Differences in variables between groups (patients with PCOS and controls) and subgroups were tested with Mann-Whitney "U" test and χ^2 test as appropriate. Multivariate logistic regression analysis was used to detect data predictability. The patient survival according to different antiviral agents was calculated using Kaplan-Meier analysis A $P < 0.05$ was considered statistically significant.

RESULTS

Patients' baseline characteristics

According to the exclusion criteria, we included a total of 46 patients with a mean age 58.21 years in Tenofovir group and 57.13 years in Entecavir group with 21 females and 15 males. The patients' characteristics were summarized in (Table 1).

Table (1): Demographic characteristics of study groups

	Tenofovir (N=23)	Entecavir (N=23)		P
Age	58.21 ± 1.42	57.13 ± 2.43	1.6 (t test)	0.965
Male **Female**	13(56.5%) 10 (43.5%)	12 (52.1%) 11(47.9%)	0.87 (Chi square)	0.767
Previous antiviral treatment (Lamivudine**)**	4 (17.3%)	6 (26%)	0.511	0.475
Diabetes Mellitus	4 (17.3%)	5 (21.7%)	0.138	0.710
Hepatocellular carcinoma	2 (8.6%)	1 (4.3%)	0.357	0.550

Baseline HBV DNA and liver enzymes of the two groups showed no statistically significant difference before treatment (Table 2).

Table (2): Baseline HBV DNA and liver enzymes of both groups

	Tenofovir (N=23)	Entecavir (N=23)	T test	P
HBVDNA IU/ml	58.21 ± 1.42	57.13 ± 2.43	1.6	0.965
AST IU/l	58.21 ± 1.42	57.13 ± 2.43	1.6	0.965
ALT IU/l	77.3± 7.35	80.2± 9.29	1.1	0.122

Virologic And Serological Response Of Both Drugs

21 (91.3%) patients in each group had undetectable serum HBV DNA at 12 months and there was no viral breakthrough in any patient throughout the follow-up period (Table 3). Naïve or experienced patients (previous Lamivudine treatment) did not show significant difference in the success rate or incidence of viral breakthrough in both groups.

Table (3) : Frequency of Undetectable HBV DNA serum level after 12 months treatment

HBV DNA serum level (<12IU/ml)	Tenofovir group	Entecavir group
Undetectable	21 (91.3%)	21 (91.3%)
Detectable	2 (8.7%)	2 (8.7%)

Clinical and Biochemical Responses

Child Pugh (CP) score was comparable between both groups before treatment. Clinical and biochemical evaluation for efficacy was done at 6 months and 12 months, the CP score of both groups showed improvement after treatment with similar changes in CP scores between the 2 medications of both groups at any time during follow-up. (Table 4)

Table (4): Comparison of Child-Pugh (CP) score among the 2 groups

CP score	Tenofovir (N=23)	Entecavir (N=23)	T test	P
Baseline	8 ± 1.1	8.2± 1.8	0.45	0.326
6 Months	7.5± 1.4	7.4± 1.2	0.26	0.601
12 Months	7.2± 1.6	7.3± 1.4	0.22	0.401

Also, the MELD score among the two groups showed improvement when comparing before and after treatment scores with similar changes in MELD scores between the two medications at different times during follow-up. (Table 5)

Table (5): Comparison of model for end stage liver disease (MELD) score among the two groups

MELD score	Tenofovir (N=23)	Entecavir (N=23)	T test	P
Baseline	13.2 ± 3.2	12.9± 1.9	0.387	0.649
6 Months	12.4± 1.9	12.3± 2.2	0.16	0.565
12 Months	11.2± 1.2	11.3± 1.8	0.22	0.413

Safety Of Tenofovir Versus Entecavir

By Comparing the effect of both medications on renal function, we found that the eGFR values among the two groups showed no changes at any time throughout the follow-up period at each group and in between the two groups. (Table 6)

Table (6): Comparison of eGFR among the two groups

eGFR<60ml/min/1.73m2	Tenofovir (N=23)	Entecavir (N=23)	T test	P
Baseline	90.2 ± 4.2	89.9± 17	0.318	0.623
6 Months	89.3± 5.9	88.3± 1.1	0.799	0.786
12 Months	87.2± 1.8	88.1± 3.8	1.027	0.153

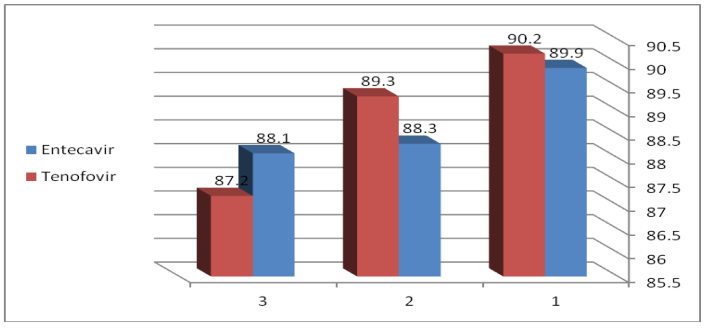

Figure (1) GFR values in both groups throughout different times. 1= basal, 2= 6 months, 3=12 months

Logistic regression analysis of different variables like age, duration of illness, CP score, MELD score, HBV DNA level for prediction of drug success (undetectable HBV DNA) showed that the viral load was the most determining factor for the outcome with high statistical significance (p value 0.031, 95%CI 1.1-1.3). Also, MELD and CP scores showed significant effect on the efficacy of Tenofovir or Entecavir in suppressing HBV (Table 7).

Table (7) Logistic regression analysis for Predictive factors for the outcome **(**undetectable serum HBV DNA**)**

	Coeffecient (B)	p-value	Odds Ratio	95% CI
Age	1.17	0.324	1.1	0.9-2.6
Duration of HBV	1.22	0.211	1.3	1.1-2.6
CP score	1.23	0.043	1.5	1.1-1.9
MELD score	1.43	0.031	1.9	1.1-1.3
Viral Load	3.65	0.012	3.1	2.1-4.1

DISCUSSION

Current guidelines support using oral antiviral in patients with HBV-decompensated cirrhosis. Tenofovir and Entecavirare recommended as first-line Nucleotides, because of their potency, and low possibility of resistance [7].

Entecavir (0.5 mg dose) is preferable and more recommended than lamivudine in treatment naïve hepatitis B e antigen (HBeAg)-positive and HBeAg-negative patients [7,8] and entecavir resistance is very low [9] However, entecavirnis is less successful in lamivudine-refractory patients even at 1.0 mg daily, with high resistance rate at 5 years of 51%.

Tenofovir is superior to adefovir in HBeAg-negative and HBeAg-positive treatment-naive patients [10]. Additionally, tenofovir confirmed potent antiviral activity in lamivudine-experienced HBeAg-positive patients [11], and in patients with lower response to adefovir [12]. No resistance recorded with tenofovir through 144 weeks of therapy but there are worries regarding the long-term safety of tenofovir in certain HBV patients as nephrotoxicity and metabolic bone disease [13].

Patients with decompensated cirrhosis are usually undernourished and may have low vitamin D levels [14].

Though Entecavir and tenofovir are better therapeutic alternatives now, but they have few restrictions and long term data is awaited.

We aimed at studying efficacy and safety of Entecavir and Tenofovir, in a cohort of 46 patients with decompensated HBV cirrhosis attending our hospital.

The current study showed no statistically significant differences in age, sex, diabetes mellitus and hepatocellular carcinoma between the two groups before treatment and this indicates good distribution of patients.

The current study showed that 91.2% of patients in both groups had undetectable serum HBV DNA at 12 months and there was no viral breakthrough in any patient of indicating similar efficacy of both drugs in suppressing HBV replication.

amulticenter randomized study by Liaw et al. 2011 [15], showed that both drugs have similar virologic efficacy in patients with HBV decompensated cirrhosis, they found no difference in virologic efficacy.

Also, Evangelos et al. 2015 [5] reported better response rate as all patients had undetectable HBV DNA serum at end of treatment with Tenofovir and Entecavir.

Surude, et al. 2015[16] reported that undetectable HBV DNA at 24, 48 weeks in chronic HBV patients were (50%, 60% respectively) for tenofovir and (60%, 75% respectively) for entecavir with p value (0.71, 0.81 respectively).

However, Centeno et al., 2016 [17], treated 64 patients with chronic HBV, they found that at 48 weeks, Tenofovir was significantly more effective as 90.3% of patients achieved virological response vs. 67.7% in the ETV arm.

The current study showed improvement in severity of liver disease after treatment in Tenofovir and Entecavir groups as regard CP and MELD scores with similar efficacy in both groups.

Similarly, Evangelos et al. 2015[5] showed that MELD scores and CP scores at different time points were similar between Tenofovir and Entecavir groups.

Another study by Liaw et al. 2011[15] showed similar results with reduction in CP and MELD scores under Tenofovir and Entecavir patients.

Changes in CP score were observed in various studies after antiviral treatment for HBV, CP score mean reduction ≥2 was found in lamivudine in 39% of patients, adefovir in 27%, entecavir in (35-49%) and tenofovir in 26% [18, 19, 20, 15, 21].

Moreover, the decrease in MELD score is a good prognostic marker. Efficacy in reducing MELD score of various anti-HBV drugs was (-1.7 to -2.6) forentecavir and (-2) for tenofovir [22, 15, 19-21].

In a study done by Surude, et al. 2015[16] on tenofovir and entecavir (18 patients in each group), they found that the mean CP score reduction in 24, 48 weeks for tenofovir was (1.50, 1.94) and entecavir (1.56, 2) with p value (0.18, 0.13). Decrease in MELD score (24, 48 weeks) was (2, 2.4) for tenofovir and (2.4, 2.7) forentecavir with p value (0.09, 0.46).

Our study showed no reported side effects along the follow-up period with no deterioration in renal functions as estimated by eGFR in the both drugs used.

Evangelos et al. 2015 [5] showed similar safety profiles as eGFR was not different between Tenofovir and Entecavir groups of patients at baseline, at 6 months, at 12 months and at the end of follow up with no reported deterioration in renal function.

Similarly, Koklu et al. (2013) [23] reported that both antiviral agents had equivalent long-term safety and efficacy, but no specific details regarding HBV-decompensated cirrhosis patients were given. And it's worth mentioning that adefovir have been associated with renal impairment.

Also, in Surude, et al. 2015 [16] study, tenofovir and entecavir did not lead to changes of renal function in any patient and there was no recorded cases of lactic acidosis suggesting the safety of these drugs in HBV population.

Multivariate regression analysis, in our study, showed that the HBV viral load was the main predictors of outcome (undetectable HBV DNA serum), lower viral load showed increased 3.1 folds possibility of success of therapy, also, low MELD score showed 1.9 folds possibility of success of therapy and low CTP score showed 1.5 folds possibility of success of therapy.

In agreement with our study, Chiu et al. (2014) [24] used HBsAg titer ≤1000 IU/mL to predict HBsAg clearance and found that those with HBsAg titer ≤1000 IU/mL at enrollment during childhood have a higher rate of HBsAg clearance (hazard ratio = 5.23; P < .001).

Also, Myo et al. (2013) [25] reported that the baseline HBV DNA level determines the long-term clinical outcome and chronic hepatitis B CHB-related mortality; it also influences the virological response to antivirals.

In Conclusion, in this study of HBV decompensated cirrhosis patients, both antivirals (Tenofovir and Entecavir) were well tolerated with no reported side effects, eGFRs were not different between groups during the 12 month follow up period, none of the patients discontinued therapy. All patients had excellent virological response without viral breakthrough and with improvement in severity of liver disease as measured by CP and MELD scores.

Limitations of the present study: None reported

Conflict of interest: The authors declare that they have no conflicts of interest.

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